Brain Research Bulletin 201 (2023) 110702

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Chronic inflammation, neuroglial dysfunction, and plasmalogen deficiency as a new pathobiological hypothesis addressing the overlap between post-COVID-19 symptoms and myalgic encephalomyelitis/chronic fatigue syndrome

Adriano Maia Chaves-Filho [a], Olivia Braniff [a], Angelina Angelova [b], Yuru Deng [c,*], Marie-Ève Tremblay [a,d,e,f,g,**,1]

[a] Division of Medical Sciences, University of Victoria, Victoria, British Columbia, Canada
[b] Université Paris-Saclay, CNRS, Institut Galien Paris-Saclay, F-91400 Orsay, France
[c] Wenzhou Institute, University of Chinese Academy of Sciences, Wenzhou, China
[d] Department of Molecular Medicine, Université Laval, Québec City, Québec, Canada
[e] Neurology and Neurosurgery Department, McGill University, Montréal, Québec, Canada
[f] Department of Biochemistry and Molecular Biology, University of British Columbia, Vancouver, British Columbia, Canada
[g] Centre for Advanced Materials and Related Technology (CAMTEC) and Institute on Aging and Lifelong Health (IALH), University of Victoria, Victoria, British Columbia, Canada

ARTICLE INFO

Keywords:
Myalgic encephalomyelitis
Chronic fatigue syndrome
Post-COVID-19 syndrome

ABSTRACT

After five waves of coronavirus disease 2019 (COVID-19) outbreaks, it has been recognized that a significant portion of the affected individuals developed long-term debilitating symptoms marked by chronic fatigue, cognitive difficulties ("brain fog"), post-exertional malaise, and autonomic dysfunction. The onset, progression,

Abbreviations: AA, arachidonic acid; AD, Alzheimer's disease; AG, alkylglycerols; Aβ, amyloid-beta; APOE, apolipoprotein E; ARDS, adult respiratory disease syndrome; ASD, autism spectrum disorders; BAL, bronchoalveolar lavages; BBB, blood-brain barrier; BD, bipolar disorder; BOLD, blood oxygenation level-dependent; CAR, acylcarnitines; CBF, cerebral blood flow; CHR, clinical high risk; CM, cubic membrane; COVID-19, coronavirus disease 2019; CNS, central nervous system; COX-2, cyclooxygenase-2; DAMPs, danger-associated molecular patterns; DGs, diglycerides; DHA, docosahexaenoic acid; E2, 17β-estradiol; EBV, Epstein-Barr virus; EGFR, endothelial growth factor receptor; EPA, eicosapentaenoic acid; ER, endoplasmic reticulum; ERα, estrogen receptor-α; ERβ, estrogen receptor-β; FDG, fluorodeoxyglucose; FFA, free fatty acids; GDSSV-J, geriatric depression scale-short version-Japanese; GNPAT, glycerone phosphate O-acyltransferase; HDL, high-density lipoproteins; HexCer, hexosylceramides; HMGCR, HMG-CoA reductase; IL, interleukin; IFNs, interferons; ISGs, interferon-stimulated genes; IsoPs, isoprostanes; LAD, late-stage AD; LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LCPFAs, long chain polyunsaturated fatty acids; LDL, low-density lipoproteins; LPC, lysophosphatidylcholine; LPS, lipopolysaccharide; LT, leukotriene; LPCAT, lysophosphatidylcholine acyltransferase; lyso-PE, lysophosphatidylethanolamine; lyso-pPC, lysoplasmenylcholine; lyso-PS, lysophosphatidylserine; MAVS, mitochondrial antiviral signaling protein; MDD, major depressive disorder; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; MFP2, multifunctional protein-2; MMSE-J, mini mental state examination-Japanese; MRS, magnetic resonance spectroscopy; MS, multiple sclerosis; mtDNA, mitochondrial DNA; NAA, N-acetyl aspartate; NeuroP, neuroprostanes; NF-kB, nuclear factor kappa B; OG, oleoyl glycerol; PAF-AH, PAF-acetylhydrolase; PAF-R, PAF receptor; PAF, platelet-activating factor; PAMP, pathogen-associated molecular patterns; PANSS, positive and negative syndrome scale; PC, phosphatidylcholine; PCP, phencyclidine; PD, Parkinson's disease; PE, phosphatidylethanolamine; PEM, post-exertional malaise; PET, positron emission tomography; PEX, Peroxisome biogenesis factor; PI, phosphatidylinositol; PLA2, phospholipase A2; PS-ODNs, phosphorothioate oligonucleotides; Pls, plasmalogens; PPA, propionic acid; pPC, choline plasmalogen; pPE, ethanolamine plasmalogen; PRR, pattern recognition receptor; PRT, plasmalogen replacement therapy; PS, phosphatidylserine; PUFA, polyunsaturated fatty acid; PVFS, post-viral fatigue syndrome; PVN, paraventricular nucleus; RCDP, rhizomelic chondrodysplasia punctata type 1; RIG-I, retinoic-inducible gene-I; RLR, retinoic-inducible gene-I-like receptors; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCZ, schizophrenia; SERMs, selective estrogen receptor modulators; SK, sphingosine kinase; SM, sphingomyelin; SMases, sphingomyelinases; sPLA2-IIA, sPLA2 group IIA; sPLA2, secreted phospholipase A2; TAG, triacylglycerols; TBI, traumatic brain injury; TCA, tricarboxylic acid; TG, triglycerides; TLR, Toll-like receptor; TNFα, tumor necrosis factor alpha; TSPO, translocator protein; VLCFAs, very long-chain fatty acids; VLDL, very-low-density lipoprotein; WHO, World Health Organization; WMS-R, Wechsler memory scale-revised.

* Corresponding author.
** Corresponding author at: Division of Medical Sciences, University of Victoria, Victoria, British Columbia, Canada.
E-mail addresses: dengyr@wibe.ac.cn (Y. Deng), evetremblay@uvic.ca (M.-È. Tremblay).
[1] Present Address: Division of Medical Sciences, Medical Sciences Building, 3800 Finnerty Road, Victoria, British Columbia, V8P 5C2, Canada.

https://doi.org/10.1016/j.brainresbull.2023.110702
Received 10 March 2023; Received in revised form 13 May 2023; Accepted 6 July 2023
Available online 7 July 2023

SARS-CoV-2
Microglia
Plasmalogen

and clinical presentation of this condition, generically named post-COVID-19 syndrome, overlap significantly with another enigmatic condition, referred to as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Several pathobiological mechanisms have been proposed for ME/CFS, including redox imbalance, systemic and central nervous system inflammation, and mitochondrial dysfunction. Chronic inflammation and glial pathological reactivity are common hallmarks of several neurodegenerative and neuropsychiatric disorders and have been consistently associated with reduced central and peripheral levels of plasmalogens, one of the major phospholipid components of cell membranes with several homeostatic functions. Of great interest, recent evidence revealed a significant reduction of plasmalogen contents, biosynthesis, and metabolism in ME/CFS and acute COVID-19, with a strong association to symptom severity and other relevant clinical outcomes. These bioactive lipids have increasingly attracted attention due to their reduced levels representing a common pathophysiological manifestation between several disorders associated with aging and chronic inflammation. However, alterations in plasmalogen levels or their lipidic metabolism have not yet been examined in individuals suffering from post-COVID-19 symptoms. Here, we proposed a pathobiological model for post-COVID-19 and ME/CFS based on their common inflammation and dysfunctional glial reactivity, and highlighted the emerging implications of plasmalogen deficiency in the underlying mechanisms. Along with the promising outcomes of plasmalogen replacement therapy (PRT) for various neurodegenerative/neuropsychiatric disorders, we sought to propose PRT as a simple, effective, and safe strategy for the potential relief of the debilitating symptoms associated with ME/CFS and post-COVID-19 syndrome.

1. Introduction

After three years of worldwide pandemic, a significant and growing portion of patients with the coronavirus disease 2019 (COVID-19) were reported to develop long-lasting debilitating symptoms, often neurological, marked by the presence of fatigue, headache, cognitive dysfunction (”brain fog”), post-exertional malaise (PEM) and orthostatic intolerance (Campos et al., 2022). This condition has been recognized as a distinct clinical entity by the generical name of post-COVID-19 syndrome. The incidence of post-COVID syndrome is estimated at 10–35% for mild cases, while for hospitalized patients it may reach 85%. Fatigue was recognized as the most prevalent post-COVID-19 symptom, followed by residual dyspnea and psychiatric symptoms (Pavli et al., 2021).

There is significant overlap in the onset, symptom profile and progression of post-COVID-19 condition with an enigmatic disorder commonly associated with acute viral infections, named myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (Sukocheva et al., 2022). Several disease mechanisms have been proposed for ME/CFS, including immune abnormalities, central nervous system (CNS) inflammation, mitochondrial alterations, as well as endothelial and vascular disturbances (Holden et al., 2020; Mackay and Tate, 2018; Nelson et al., 2021). However, only recently, these mechanisms have been unified into a common pathophysiological hypothesis centered on the pathologically reactive neuroglia (mainly microglia and astrocytes) in stress-responsive brain regions, such as the hypothalamic nuclei and other parts of the limbic system. This hypothesis can efficiently explain not only the onset of ME/CFS symptoms but also the hallmark features of the disorder, such as PEM, and its progression over time (Renz-Polster et al., 2022).

On the other hand, acute systemic and CNS inflammation, reactive pro-inflammatory neuroglia, oxidative stress and abnormally elevated levels of pro-inflammatory cytokines have also been reported in patients with COVID-19 (Meinhardt et al., 2021; Poloni et al., 2021; Schwabenland et al., 2021). Further, the demonstration of several neurotropic and neuroinvasive properties of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) highlights the virus’s potential to impact the CNS in a long-term way (Meinhardt et al., 2021). In addition, inflammation and microglial reactivity are common hallmarks of several neurodegenerative diseases which were further associated with reduced brain plasmalogen levels (Hossain et al., 2017; Ifuku et al., 2012). Plasmalogens (Pls) are one of the major phospholipid components of biological membranes and play several relevant homeostatic functions, such as control of oxidative stress, inflammation and generation of several bioactive derived lipid mediators (Tremblay, 2022; Wu et al., 2019). Recently, metabolomic/lipidomic studies have shown evidence of significant depletion in Pls contents associated with dysfunction of their synthesis or metabolism in patients with ME/CFS (Che et al., 2022) and acute COVID-19 (Pike et al., 2022; Schwarz et al., 2021). These important bioactive lipids have increasingly attracted attention in the past couple of years, with their depletion emerging as a shared biological finding between aging and chronic CNS inflammatory conditions, such as neurodegenerative disorders [e.g., Alzheimer’s disease (AD), Parkinson’s disease (PD), multiple sclerosis (MS)] and neuropsychiatric disorders (e.g., depression, schizophrenia, bipolar disorder) (Paul et al., 2019a; Schoneveldt et al., 2022; Senanayake and Goodenowe, 2019; Udagawa and Hino, 2022). However, alterations of Pls levels have not yet been examined in individuals suffering from post-COVID-19 syndromes. In the present review, we comprehensively summarize the current clinical and preclinical literature in the field. We propose that neuroglial dysfunction is a pertinent pathophysiological model to explain post-COVID symptoms and their similarities with ME/CFS. In addition, we aim to discuss the contribution of Pls deficiency as a core biological factor underlying immunopathogenesis of both conditions. Further, based on promising data in other neuroinflammatory and neurodegenerative conditions, we speculate that plasmalogen replacement therapy (PRT) may offer an effective and safe therapeutic tool for the potential relief of debilitating symptoms associated with both ME/CFS and post-COVID-19.

2. Discussion

2.1. ME/CFS definition and hallmark features

ME/CFS is a complex, multi-system disorder presenting with debilitating and often lifelong symptoms. It has an estimated worldwide prevalence between 0.4% and 2.6%, making it up to 10-fold more prevalent than other fatigue-causing illnesses like MS (Deumer et al., 2021). Females are approximately three times more likely to be affected than males. The disorder has two peaks of incidence with no clear distinction related to sex: one in the late teen years and another between 30 and 40 years of age (Thomas et al., 2022). Clinically, the syndrome usually comprises self-reported symptoms including unrelenting fatigue persisting over more than 6 months, exertional intolerance, sleep disturbances, impairments in the cognitive, emotional and speech domains, hypersensitivity to light and noise, together with psychomotor slowness and orthostatic intolerance (Bateman et al., 2021; Deumer et al., 2021).

The most common risk factor for the disorder is exposure to acute viral infections (Thomas et al., 2022), although there are reports of ME/CFS cases triggered by non-infectious factors, such as vaccination, chemical toxins and emotional trauma/psychological stressors (Heim et al., 2009; Retornaz et al., 2022). Historically, however, the definition

and documentation of ME/CFS as a distinctive entity emerged from the observational evidence of 75 reported outbreaks of fatigue illnesses post-viral infection (Deumer et al., 2021; Rasa, 2018). The most publicized of these gave rise to the current definition of the condition: from the Royal Free Hospital outbreak in London in 1955 originated the term ME (Underhill and Baillod, 2020), and from the Incline Village, Nevada outbreak in 1984 originated the other term CFS (Strickland et al., 2001). In recent times, the condition is recognized by the World Health Organization (WHO) as ME/CFS, the combined name derived from both the European and American outbreaks (Bateman et al., 2021).

Since the definition of this syndrome, there has been no specific biomarker or pathognomonic finding to facilitate an accurate diagnostic, and despite several years of clinical investigation, the ME/CFS diagnosis remains an exclusion condition (Deumer et al., 2021). Despite this, the disease presents two hallmark features – one on the clinical level and one on the pathobiological level – that stand out for their characteristic and defining attributes. Both are well studied, unanimously accepted among researchers, and present in all patients with ME/CFS (if diagnosed according to the now internationally accepted Consensus Criteria) (Carruthers et al., 2011). The clinical core feature is PEM. While patients with ME/CFS have very different baseline levels of functionality, they all have one common clinical feature: a distinctly abnormal reaction to stressful events. PEM is described as an exacerbation of ME/CFS symptoms triggered both by physical or mental exertion and even sensory overload (Stussman et al., 2020). Each patient presents an individual and disease severity-dependent threshold for PEM development. The triggered clinical exacerbation often begins after a delay of at least several hours post-exercise and typically persists over several days (McManimen et al., 2019; Stussman et al., 2020).

Regarding the biological hallmark, many of the pathophysiological findings in ME/CFS are poorly replicable or found only in a subset of ME/CFS patients. However, a few pathophysiological findings appear uniformly present, including autonomous dysfunction, metabolic abnormalities and cerebral hypoperfusion. Among them, cerebral hypoperfusion or reduced cerebral blood flow (CBF) is objectively assessed and consistently reported in patients with ME/CFS (Van Campen et al., 2020). Also, exacerbation of cerebral hypoperfusion has been linked to relapses of PEM, which infers a potential common biological basis (Bond et al., 2021) [for further information about CBF findings in ME/CFS, please see the review (Wirth et al., 2021)].

2.2. *Post-viral fatigue and post-COVID-19 syndrome as shared representations of ME/CFS*

Long-COVID, also known as the post-COVID-19 condition, post-COVID-19 syndrome, or post-COVID conditions, includes a wide range of persistent or new symptoms that develop after SARS-CoV-2 infection and typically last for more than 12 weeks to months and up to 3 years, as reported so far. The most common symptoms can be broadly classified into neurological (fatigue, brain fog, and headache), respiratory (chest pain and shortness of breath), and diverse (heart palpitations, muscle pain, and neuropsychiatric symptoms) (Pavli et al., 2021; Townsend et al., 2020a). These symptoms are often debilitating enough to impair work capacity and cognitive abilities, and they have significant similarities to those of ME/CFS, including the most common trigger factor of acute viral infection (Mackay, 2021; Troyer et al., 2020).

It is noteworthy that while non-infectious etiologies are also reported, approximately 50–80% of diagnosed patients with ME/CFS start suddenly with a flu-like illness, from which they do not completely recover. Indeed, in some estimates, at least half of the ME/CFS cases emerged after identified viral infections, including those from Epstein-Barr virus (EBV), poliovirus, rhinovirus and coronaviruses, suggesting a virus-induced immunological dysfunction as the possible initiator of a multi-systemic immune impairment (Campos et al., 2022; Mackay, 2021), which is also influenced by a strong inter-individual predisposition, as shown in a twin analysis (Giloteaux et al., 2016). In this context, the current COVID-19 pandemic with 756,135,075 confirmed cases worldwide (retrieved from WHO: Coronavirus website, 15 February 2023), and globally still with an upward trend after five waves of infections will considerably impact this scenario. The number of post-COVID-19 patients is likely to be in the order of millions and with growing tendencies based on the most conservative projections. Indeed, around 10–30% of those million cases are suffering long-term effects of the disease (Pavli et al., 2021; Townsend et al., 2020). Among these effects, a substantial cohort of patients will experience independently or comorbidly ongoing “fatigue” or “post-viral fatigue” syndromes (Campos et al., 2022; Retornaz et al., 2022; Rogers et al., 2020).

In this context, considering the important similarities of COVID-19 post-viral fatigue syndrome (PVFS) with the definition of ME/CFS, the ongoing pandemic would likely already have added at least 75 million cases of COVID-19 associated-PVFS (based on the 22 January 2023 report of cumulative cases by WHO) to the already estimated 20 million cases of ongoing ME/CFS related to other causes. With the long-term prognosis still not clear, PVFS can add a highly significant health burden for COVID-19 (Mackay, 2021). The new WHO clinical case definition for COVID-19 PVFS is very similar to the most recent versions of the consensus definition for ME/CFS diagnosis. The main difference is that this condition has to persist for 3 months before confirmation of the diagnosis, while for ME/CFS it has to last for 6 months (WHO/COVID-19 Report, 2022).

Strong links between these two entities are becoming more evident with increasing publications of longitudinal studies tracking post-COVID-19 patient symptoms over 6 months or longer. The first illustrative one, a Chinese study including 1,733 patients with COVID-19 discharged from the hospital, found that 76% of them had at least one persistent symptom observed 6 months after their initial diagnosis (Huang et al., 2021). The most common symptoms reported were fatigue or muscle weakness (63%), followed by sleep difficulties (26%) and anxiety or depression (23%). Of the patient cohort, 75% had required supplemental oxygen, with 7% needing mechanical ventilation. This represents a considerable bias for a subset of patients, however, a significant fraction of mild symptomatic cases not requiring intensive support also showed PVFS symptoms (at least 25%), indicating that the spectrum of ME/CFS can emerge not only in severe but also in mild COVID-19 cases (Huang et al., 2021).

A second study consisted of an international web-based survey involving 3,762 adult participants, evaluating neurologic symptoms 6 months after the acute SARS-CoV-2 infection (Ziauddeen et al., 2022). Similarly, the most frequently reported symptoms were fatigue (>75%) and cognitive dysfunction (“brain-fog”) (>52%), all core symptoms of ME/CFS. Over 85% of the patients experienced symptom exacerbations, induced by physical or mental exercise, defining the PEM, a key characteristic of ME/CFS (6). Also, around 67% of the patients in the cohort were unable to work or were on a reduced work schedule at the time of the survey. Most of those surveyed (>90%) had not been hospitalized, reinforcing the assumption that even relatively mild COVID-19 cases could trigger long-term ME/CFS-like symptoms (Ziauddeen et al., 2022).

The last longitudinal study was a comprehensive German assessment of 42 patients with post-COVID-19, aged between 22 and 62 years, of which 29 were female, for the clinical diagnosis of ME/CFS (Kedor et al., 2022). All patients had only mild to moderate COVID-19 acute symptoms, and none required hospitalization. The most frequently reported symptoms were chronic fatigue in all 42 patients, PEM (n = 41), cognitive impairment (n = 40), headache (n = 38), and muscle pain (n = 35). The Canadian Consensus Criteria for ME/CFS diagnosis was applied and 19 of 42 patients met the full diagnostic criteria. The remaining patients (n = 23) shared many ME/CFS clinical features, but at a lesser severity, and they were categorized as having the closely-related fatigue syndrome (Kedor et al., 2022).

Interestingly, this association with PVFS is not exclusive to SARS-CoV-2 infection. Several studies of the first SARS pandemic (2003) indicated that up to 60% of patients experienced long-term symptoms,

including fatigue and cognitive abnormalities (Lam et al., 2009; Moldofsky and Patcai, 2011; Yang et al., 2020). When interviewed four years after the acute infection, 40% of the survivors of SARS-CoV (2003) in Hong Kong complained of ongoing fatigue and other complications (Lam et al., 2009). A Canadian study also reported that post-SARS acute infection, patients presented an elevated prevalence of persistent fatigue, diffuse myalgia, weakness, and depressive symptoms, along with difficulties to return to work, 1–3 years after the acute infection (Moldofsky and Patcai, 2011).

Despite reports of an alarming condition, no clear pathophysiological explanation has been proposed for the COVID-19 PVFS and related fatigue syndromes. Due to its significant clinical and originating similarities with ME/CFS, a novel etiological paradigm for COVID-19 PVFS has been proposed based on a unifying model for ME/CFS (Mackay, 2021; Sukocheva et al., 2022). Integral to this paradigm is a unique rationale to explain how SARS-CoV-2 infection might be triggering PVFS, in common with other known causes of ME/CFS (Yang et al., 2020). Also, this conceptual paradigm is developed to explain chronic fatigue and PEM, both of which are the key characteristics of ME/CFS (Mackay, 2021). For some pathobiological features, such as reduced CBF and CNS inflammation, the body of evidence for long-COVID or associated PVFS is just emerging, and most of the assumptions are extended based on the similarities with ME/CFS (Tate et al., 2022).

2.3. *Neuroglia failure: a unifying neuroinflammation-based model for COVID-19 post-viral fatigue syndrome and ME/CFS*

A wide range of pathobiological explanations have been proposed to explain COVID-19 PVFS and ME/CFS. While most hypotheses assume an immunological basis for ME/CFS, they differ in how the immunological dysfunction may translate into clinical manifestations. In this context, the investigation of inflammatory processes in the CNS has received increased attention in ME/CFS research (VanElzakker et al., 2019). Inflammation in the CNS sets off a well-orchestrated response, which includes the release of inflammatory mediators, such as cytokynes and chemokines, and activation of downstream signaling pathways that can temporarily disrupt the blood-brain barrier (BBB), thus increasing perfusion and facilitating the transit of peripheral immune cells (Glassford, 2017; Shao et al., 2022). These responses are tightly controlled by microglia, the CNS resident immune cells, in concert with astrocytes, microvascular endothelial cells and perivascular CNS macrophages (Santiago et al., 2017). Therefore, recent publications have highlighted the contribution of neuroglial dysfunction and mainly of microglia in the etiopathogenesis and progression of ME/CFS (Renz-Polster et al., 2022; VanElzakker et al., 2019).

Multiple causative mechanisms can mediate CNS inflammation and neuroglial reactivity after acute viral infection. These mechanisms include direct virus invasion and cytotoxic effects in the brain, reactivation of endogenous microbial reservoirs in CNS cells, glial reactivity caused by peripheral secreted inflammatory cytokines and chemokines, autoimmune reactivity triggered against specific neuronal or glial epitopes, recognition of danger-associated molecular patterns (DAMP), vagal dysfunction and sympathetic or angiotensin II overload (Acanfora et al., 2022; Kai and Kai, 2020; Klein et al., 2019). Moreover, the combined exposure to psychosocial stress and aggravated societal challenges, such as social isolation and poverty during the pandemic years, can further exacerbate the CNS inflammatory milieu and increase glial reactivity (Al Omran et al., 2022; Glassford, 2017; Penninx et al., 2022).

The rationale for a unifying pathophysiological model premises that the common triggers of ME/CFS, not only the infectious agents, but also vaccination, chemical toxins and emotional trauma, and COVID-19 by itself, share the same aspect: being a severe physiological stressor able to induce an acute neuroimmune response (Tate et al., 2022). A proposed target of this initial inflammatory response is the brain stress center, a cluster of neurons located in the hypothalamic paraventricular nucleus (PVN), which has been proposed as a key target site in ME/CFS pathophysiology. The hypothalamic PVN functions as a stress integrator, which processes and responds to a wide range of physiological stressors, playing an essential role in neuroendocrine and autonomic regulation (Mackay and Tate, 2018). Incoming stress signals from all types of infections (via inflammatory mediators, such as cytokines and chemokines), pain, emotional distress and cardiovascular changes from physical exertion, all converge onto the hypothalamic PVN, through a range of humoral and neural routes (Barson et al., 2020; Jiang et al., 2019). This single point of convergence, the hypothalamic PVN, is a potential vulnerable site in genetically susceptible people or those primed by previous environmental stressors (Mackay and Tate, 2018).

SARS-CoV-2 has been shown to provoke an acute pro-inflammatory response, at the initial site of infection, but also systemically leading to a surge in the release of chemokines and pro-inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor alpha (TNFα), and IL-1β. Studies indicate that a more severe COVID-19 infection leads to a greater cytokine storm (Tang et al., 2020). Pro-inflammatory cytokines released into systemic circulation act on the circumventricular organs – areas of the brain that have an incomplete BBB and can therefore detect blood chemical signals, for example, the area postrema, which then relays these signals onto the hypothalamic PVN (Akrout et al., 2009). Also, pro-inflammatory mediators released by immune cells in lymphoid tissue can communicate by ascending means through vagus nerve afferents. These afferents can activate another circumventricular organ, the nucleus tractus solitarius, which also relays neural stimuli and secreted factors onto the hypothalamic PVN (Daulatzai, 2012). Besides these routes able to induce CNS inflammation, some lines of evidence stated that SARS-CoV-2 has a neuroinvasive potential and can cause a direct pro-inflammatory microglial reactive state (Li et al., 2020; Yachou et al., 2020). Meinhardt and coworkers (2021) gave seminal evidence showing not only the presence of SARS-CoV-2 RNA and protein expression in anatomically distinct regions of the nasopharynx and brain, but also the ability of the virus to cross the neural–olfactory mucosa interface, ascend through the sensory nerve endings and penetrate defined brain areas, especially the brainstem (Meinhardt et al., 2021). Also, these researchers and others (Jeong et al., 2022; Poloni et al., 2021) reported increased markers of phagocytosis and pro-inflammatory reactivity on microglia/brain non-parenchymal macrophages, such as CD68 and human leukocyte antigen (HLA)-DR, which were often organized in so-called “microglial nodules” mainly inside the brainstem and hippocampus (Meinhardt et al., 2021; Poloni et al., 2021).

Nevertheless, an association between the severity of systemic inflammatory response induced by SARS-CoV-2 and the emergence of PVFS was not yet confirmed. A recent Irish study found no correlation between the severity of SARS-CoV-2 pro-inflammatory response (measured by blood levels of IL-6, sCD25, C-reactive protein and neutrophil-to-lymphocyte ratio) or of hospitalization with the incidence of fatigue symptoms, when examined 10 weeks after the viral infection. However, female sex and a pre-existing diagnosis of depression/anxiety significantly contributed to increasing PVFS severity (Townsend et al., 2020). These findings reinforced that mild SARS-CoV-2 infection can provoke a sufficient stress response in some patients to trigger ME/CFS symptoms. Also, they provided further evidence that possible host-vulnerability factors, such as female sex and previous mental disorders, can lower the susceptibility threshold to disease onset and symptom severity (Townsend et al., 2020).

In this context, the neuroglial failure model can greatly explain not only the PVFS onset, as stated, but also the PEM and relapses which are core features of ME/CFS (Renz-Polster et al., 2022). As above-mentioned, some recent longitudinal studies conducted over 6 months or more have highlighted the presence of PEM and relapses (Huang et al., 2021; Kedor et al., 2022). Also, in line with the many triggers of ME/CFS, these setbacks seem to occur despite the triggering event (SARS-CoV-2 acute infection) being no longer detectable. These triggering events for PEM and relapses encompass physical or mental overexertion, emotional or financial stress, sleep deprivation, and

environmental stressors (Stussman et al., 2020). These stressful events by themselves can result in dysfunctional glia, mainly microglia, and reactivate an innate immune memory, a phenomenon recently discussed in the context of chronic neurodegenerative disorders (Wendeln et al., 2018). However, based on the current evidence, this hypothesis should be experimentally verified.

The most supportive evidence for this association comes from findings in patients with ME/CFS. Of note, Nakatomi et al. (2014) using positron emission tomography (PET) with a translocator protein 18 kDa (TSPO) radiotracer, which notably labels reactive microglia and astrocytes, showed increased TSPO binding among the cingulate cortex, hippocampus, amygdala, thalamus, and midbrain of individuals with ME/CFS. These findings further correlated with the severity of fatigue sensation, cognitive impairment, pain, and depression symptoms (Nakatomi et al., 2014). Also, evidence for the neuroglial dysfunction in ME/CFS comes from magnetic resonance spectroscopy (MRS) studies describing altered levels of several metabolites related to CNS inflammation and glial dysfunction, such as lactate, choline, and N-acetylaspartate (NAA) (Godlewska et al., 2022; Mueller et al., 2020). Interestingly, Mueller et al. (2020) reported increased temperature in the right insula, thalamus, and cerebellum, which was paired with converged elevated lactate/choline ratio in the same brain regions (Mueller et al., 2020). More indirect evidence of glial dysfunction in ME/CFS have been provided by consistent findings of blood oxygenation level-dependent (BOLD) signal hyporesponsiveness to cognitive tasks in visual and auditory cortex of patients (Baraniuk et al., 2022; Rayhan and Baraniuk, 2021). Also, continued activation of task-dependent brain regions decreased the responsiveness of other brain regions not related to task trials in patients with ME/CFS, sugesting shared features with cortical spreading depression. Cortical spreading depression is a pronounced depolarization of neurons and glia that spreads slowly across the cortex followed by a period of depressed electrophysiological activity, and supports the notion of glial dysfunction (Tanaka et al., 2006). Reduced regional fluorodeoxyglucose (FDG) uptake in the right mediofrontal cortex, brain stem and orbitofrontal cortex of patients with ME/CFS (Siessmeier et al., 2003; Tirelli et al., 1998) also strengthens the body of evidence indicating hypometabolism in stress-responsive brain regions [for more details, please read (Shan et al., 2020)].

Therefore, PEM may reflect a stress-induced aggravation of CNS inflammation and/or neuroglial dysfunction initiated by acute viral infection (Mackay, 2021). Upon exposure to sequential pro-inflammatory stimuli (e.g., infections, vaccination, toxins and psychosocial stress), microglia and astrocytes can shift to a pro-inflammatory hyper-responsive state, named “primed” glia, where these cells respond exaggeratedly to subsequently similar or different stimuli even with a lower severity threshold, while displaying compromised physiological functions (Frank et al., 2016; Murta et al., 2020). This plasticity and adaptive response of glial cells may explain several aspects of PEM not only in the context of ME/CFS, but also in COVID-19 PVFS. For instance, the delayed onset of PEM symptoms relapse or exacerbation after exercise may reflect the temporal need for the stress response to reach the brain, especially the hypothalamic PVN through pro-inflammatory cytokines, chemokines, alarmins or stress-related neurotransmitters and neuropeptides (Renz-Polster et al., 2022). The duration of PEM may also correspond to the timeframe needed for the partial recovery of reactive glia to their homeostatic functions and reversion to a more homeostatic state. The individual PEM threshold and variable severity of induced symptoms can be related to the degree of glial reactivity and their pre-existing impaired or primed immune state, as well as the propagation of glial dysfunction into distant brain areas, such as the limbic regions, and regulatory centers along glial functional networks (Mackay, 2021; Renz-Polster et al., 2022). Therefore, the neuroglial dysfunction is pivotal for several functions disrupted in ME/CFS – including motor functions, autonomous regulation, sleep homeostasis, sensory gating, memory, mood and cognition. The involvement of neuroglia may explain the onset, the clinical course and relapses in ME/CFS (Renz-Polster et al., 2022). In the context of COVID-19 PVFS and other post-COVID fatigue syndromes, despite consistent evidence showing the neuroinvasive potential and related glial reactivity after acute SARS-CoV-2 infection, the direct association between neuroglial dysfunction and these long-term consequences of COVID-19 should be experimentally demonstrated.

2.4. Plasmalogens: small lipid molecules that matter

2.4.1. Role in lipid rafts and cubic membranes

Plasmalogens (Pls) are a special type of ether lipid containing a vinyl-ether linkage at the sn-1 position and a polyunsaturated fatty acid (PUFA) at the sn-2 position of their glycerol backbone (Fig. 1). Pls are not a trace nutrient, yet they constitute the building blocks of cell membranes. Approximately 1 in 5 phospholipids represent Pls in human tissues, where they are particularly enriched among the brain, heart, and immune cells (Braverman and Moser, 2012). Pls act as a reservoir for important PUFAs which can be released as omega-6 arachidonic acid (AA) and omega-3 docosahexaenoic acid (DHA) (i.e., the precursors of inflammatory/anti-inflammatory lipid mediators), through an enzymatic reaction of phospholipase A2 (PLA2) (Yang et al., 1996) . Pls are recognized as powerful antioxidants (Zoeller et al., 1999) in addition to their novel anti-inflammatory properties (Ifuku et al., 2012; Kong et al., 2020) as well as role as major structural components of lipoproteins (low-density lipoprotein: LDL, high-density lipoprotein: HDL) (Bozelli et al., 2021), myelin sheaths, and synaptic membranes (Braverman and Moser, 2012). Of note, choline plasmalogens (pPC) account for about 40% of all choline glycerophospholipids in the human heart, whereas ethanolamine plasmalogens (pPE) account for nearly 90% of ethanolamine glycerophospholipids in myelin sheaths (Bozelli et al., 2021).

The traditional view of cell membranes as flat-lamellar sheets of phospholipid bilayers dividing the cytoplasm or the organelles into multiple subcellular compartments was surpassed by the characterization of several spatial arrangements that the membranes can assume, such as hexagonal, micellar and cubic arrangements (Chong and Deng, 2012; Landh, 1995). These 3D membrane topologies can be provoked by changes in the membrane lipid composition, protein clustering, bilayer bending caused by embedded or anchored proteins, or membrane curvature altered under the influence of environmental factors, such as temperature or pH (Almsherqi et al., 2006). Among these factors, the lipid composition is one of the most important factors modulated by the cell to achieve the most adaptive membrane conformation. Whereas lipids with a cylindrical shape (like the typical pPC glycerophospholipids) favor the formation of lamellar structures, lipids with a cone molecular shape (such as pPE) tend to form curved membrane assemblies, such as bicontinuous cubic, bicontinuous sponge or inverted hexagonal structures (Angelova et al., 2021; West et al., 2020). Among them, the cubic membranes (CM) are characterized by periodic arrangement of bicontinuous lipid bilayers organized into cubic lattice networks. In this context, CM have been considered as part of an adaptation system against environmental changes or disease states usually associated with increased oxidative and cellular stress, such as pH and temperature changes, increased osmolarity, starvation or viral infection (Deng and Almsherqi, 2015).

The biophysical and biochemical properties of Pls may play a major role in promoting non-lamellar hexagonal and cubic phase formation (Almsherqi, 2021; West et al., 2020). Glaser and Gross (1995) reported that, *in vitro*, vesicles with varying ratios of individual Pls could induce the formation of different non-lamellar structures, including hexagonal and cubic membrane phases (Glaser and Gross, 1995). Moreover, important data supporting the Pls contribution for CM formation came from simple organisms. Indeed, starvation induces the production of greater levels of free radicals in amoeba (*Chaos carolinense*) compared to fed conditions (Deng et al., 2002). Also, starvation induces CM formation in amoeba mitochondria (Deng and Mieczkowski, 1998). The transformed inner mitochondrial membranes into CM organization in

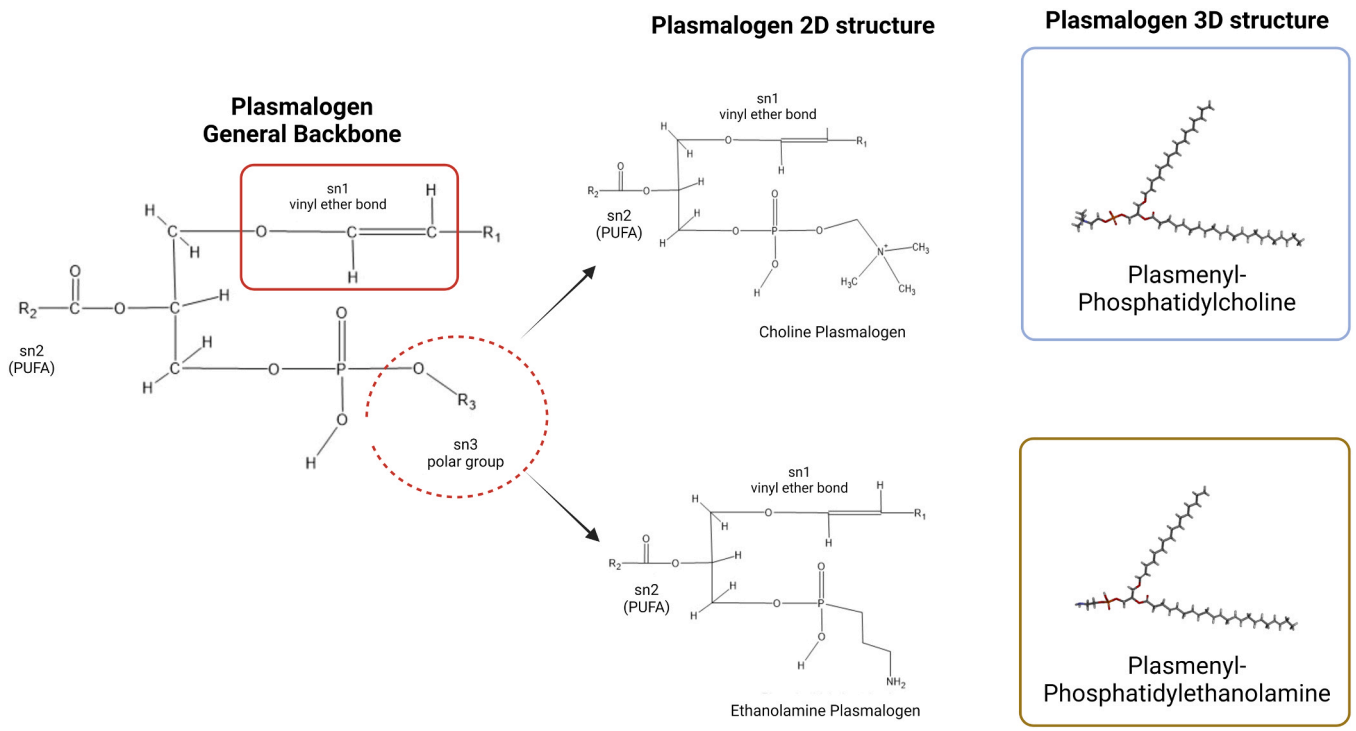

Fig. 1. The plasmalogen backbone and 2D/3D structural representation. The backbone structure of a typical plasmalogen is characterized by a vinyl ether linkage with 16:0, 18:0, and 18:1 hydrocarbon chains at sn-1 position (highlighted within red rectangular brackets to be the chemical distinctive feature of Pls), a ester bond linking PUFAs at sn-2 position, and a phosphate group at sn-3 position (R3 refers to a ethanolamine or a choline) of the glycerol backbone. The right panels show respectively the 2D and 3D structural representation of a choline plasmalogen (pPC) and ethanolamine plasmalogen (pPE) . The 2D chemical representations were drawn using the software ACD/ChemSketche, Freeware Version (for non-commercial use), while the 3D representations were build using the open-source software Discovery Studio, BIOVIA, Dassault Systèmes. Abbreviations: Pls: plasmalogens: pPC: choline plasmalogen; pPE: ethanolamine plasmalogen; PUFA: poly-unsaturated fatty acid; R: radical.

the starved amoeba *Chaos* exhibit a high abundance of Pls-containing very long-chain (VLC)-PUFAs, specifically the phosphatidylcholine Pls, phosphatidylethanolamine Pls and phosphatidylinositol species, which appear to be critical for developing and maintaining highly ordered yet curved interwoven CM structures (Chong et al., 2021; Deng et al., 2009).

Also, it was found that the CM isolated from starved amoeba interact with short segments of phosphorothioate oligonucleotides (PS-ODNs), which resemble RNA in more complex biological systems. Interestingly, Pls-containing VLC-PUFAs do not only facilitate spatial arrangements for the formation of CM, but also can interact with short segments of ODN (or RNA in mammalian cells) thereby protecting them against oxidative damage. This has been attributed to the vinyl-ether bond which is highly susceptible to the attack of free radicals, providing an efficient scavenger system compared to other lipids (Reiss et al., 1997). Therefore, CM and its derived Pls together have been proposed as a "protective shelter" mechanism for biological membranes, especially in mitochondria, to cope with conditions associated with increased oxidative stress (Deng and Almsherqi, 2015).

Cholesterol synthesis is tightly regulated through fine-tuned post-translational and transcriptional mechanisms. The third step of cholesterol synthesis catalyzed by HMG-CoA reductase (HMGCR) is generally accepted as a rate-limiting step. HMGCR activity is mainly regulated via a sterol-mediated feedback mechanism at the level of gene transcription and proteasomal degradation (Cerqueira et al., 2016). More recently, epoxidation of squalene catalyzed by the enzyme squalene monooxygenase (SQLE) was proposed as the second rate-limiting step in cholesterol biosynthesis (Chua et al., 2020; Yoshioka et al., 2020). In this context, it was demonstrated that Pls levels play a key role in mediating cholesterol homeostasis by regulating this step of the synthetic route (Honsho et al., 2015; Mankidy et al., 2010). Important evidence was reported by Honsho et al. (2015) demonstrating that in several cell lines, including murine fibroblasts and Chinese hamster ovary (CHO) cells, the elevation of cellular content in Pls causes suppression of cholesterol synthesis through an increased degradation of SQLE (Honsho et al., 2015). In mammals, SQLE expression is regulated by the E3 ubiquitin-protein ligase, MARCH6. This enzyme promotes ubiquitylation and proteasomal degradation of SQLE (Dang et al., 2009; Zelcer et al., 2014). The constitutive degradation of SQLE is stimulated by the elevation of Pls, through a cholesterol-independent mechanism, and is dependent on a facilitated interaction between SQLE with MARCH6 via Pls-modified transmembrane domain in the N-terminal region of SQLE (Honsho et al., 2015).

Also, the main lipoproteins involved in cholesterol transport and distribution, such as LDL and HDL, have comparable contents enriched in Pls (Bozelli et al., 2021). The circulating LDL levels are an indicator of the cellular cholesterol demand, whereas circulating HDL levels reflect cellular cholesterol export and constitute an indirect measure of membrane cholesterol. Cholesterol is one of the most important lipids in the body and 80–85% of body cholesterol is located within cell membranes as a non-esterified form. Due to its importance in regulating cell membrane fluidity, body cholesterol has sophisticated transport and homeostatic regulation systems to ensure that all cells have an adequate access. Therefore, Pls restoration or augmentation was proposed as a novel mechanism allowing for cholesterol reduction *in vitro*, serving as an alternative to statin therapy in achieving adequate cholesterol homeostasis (Mankidy et al., 2010).

Together with cholesterol, Pls are key lipid components of lipid raft microdomains (Pike et al., 2020), which are important for multiple cellular signaling pathways (Bozelli and Epand, 2021; Dorninger et al., 2020) with implications as potential targets for a plethora of human diseases (Siimons and Ehehalt, 2002). The pioneering work of atomistic molecular dynamics simulations by Rog and Koivuniemi (2016) showed

that Pls form more condensed and thicker lipid bilayers compared to the analogous diacyl phospholipid-based bilayer system (Rog and Koivuniemi, 2016). Of note, Pls are recognized as essential in highly ordered CM formation in amoeba *Chaos* upon cell starvation, as above-mentioned (Chong et al., 2021). Pls were further found to inhibit hippocampal neuron cell death upon nutrient deprivation in a mouse model (Hossain et al., 2013). These observations support the amoeba *Chaos* cell starvation study findings showing increased survival following pre-feeding with Pls-rich *Paramecium* compared to Pls-poor *Tetrahymena*. The Pls-rich food feeding could induce amoeba *Chaos* CM formation under starvation stress, while Pls-poor food failed to induce CM formation under the same starvation stress, thus significantly reducing the amoeba's lifespan (Chong et al., 2021). In summary, Pls next to cholesterol act as one of the major lipid components of rafts microdomain structures and are key for promoting intracellular hexagonal and/or CM formation, thus suggesting their importance in further cellular signaling pathways and processes.

2.4.2. Peroxisomes as the hub of plasmalogen biosynthesis and regulators of the innate immune responses

Pls are synthesized first in the cell organelle peroxisome followed by the endoplasmic reticulum (ER) (Nagan and Zoeller, 2001) . The body's ability to synthesize Pls is markedly impaired when peroxisome function is compromised, for instance with aging, and Pls become degraded due to inflammation and oxidative stress (Wanders, 2013). Of note, the decreased levels of Pls that normally allow to protect phospholipids in biomembranes from damage can support the view that cell membranes suffer from oxidative stress in patients with ME/CFS (Armstrong et al., 2015; Morris and Maes, 2014). The low Pls level measured in ME/CFS (Che et al., 2022) indicate dysfunctional peroxisomes due to overwhelming oxidative stress, which is also associated with alterations of mitochondria (Morris and Maes, 2014), the indispensable organelles with a dual role in both energy and free radical production. There is increasing evidence that Pls play important roles in these crucial organelles and that patients with deficit in Pls also have impairments in mitochondria accompanied by cellular energy defects (Kimura et al., 2019) (for an overall overview of Pls biosynthesis, please see Fig. 2).

Peroxisomes being the site of Pls biosynthesis in the cell, they also help supply the building block of cell membranes, reducing oxidative stress, in addition to breaking down the very long chain fatty acids (VLCFAs) to metabolic intermediates that the mitochondria can use for further ATP generation. Without peroxisomes breaking down those fatty acids, mitochondria lack the fuel to produce the cellular currency ATP. Peroxisomes appear to be damaged in ME/CFS, and the disrupted peroxisome/mitochondrial functional interaction most likely contributes to the fatigue and cognitive problems experienced in ME/CFS (Che et al., 2022).

Indeed, peroxisomes are dynamic, multifunctional, and ubiquitous organelles (Wanders, 2013). As above-mentioned, peroxisomes are crucial metabolic organelles for lipid metabolism, including Pls biosynthesis and reactive oxygen species (ROS) metabolism (Farooqui and Horrocks, 2001a, 2001b, 2001c; Kimura et al., 2019). The role of peroxisomes in innate immunity and inflammation has gained significant attention in the last years (Ferreira et al., 2019). The discovery of the localization of the mitochondrial antiviral signaling protein (MAVS) in these organelles highlighted its role especially for innate antiviral responses. MAVS is an essential adaptor protein of the retinoic-inducible gene-I (RIG-I)-like receptors (RLR), which can sense the presence of cytosolic viral RNA upon infection, and trigger the production of interferons (IFNs) and IFN-stimulated genes (ISGs) that act as direct antiviral effectors (Dixit et al., 2010). Deficiencies in peroxisomal functions were, therefore, implicated in abnormal immune responses against several viruses (HIV, CMV, Hepatitis viruses), increased viral escape from immune effectors, and abnormal virus-induced pathology (Bender et al., 2015; Magalhães et al., 2016; Xu et al., 2017).

Furthermore, peroxisomes have also been implicated in other innate immunity processes (Ferreira et al., 2019). Of note, during phagocytosis, in peritoneal macrophages, the number of peroxisomes increases, and they are relocated to the regions near phagosomes, where they discharge the antioxidant enzyme catalase (Calabrese and Canada, 1989; Li et al., 2017). This enzyme has important bactericidal effects in the presence of hydrogen peroxide, but also acts to limit oxidative damage related to the lysosomal-phagosomal activity (Ferreira et al., 2019; Kono, 1995). In *Drosophila* and murine macrophages, impaired peroxisome biogenesis factors (PEX)5 and PEX7 gene expression was associated with defective actin organization and compromised phagocytosis of intracellular pathogens, such as encapsulated bacteria, and reduced viability (Di Cara et al., 2017). Moreover, treatment of macrophages with peroxisome-derived lipids enhanced their capacity to phagocytose bacteria (Di Cara et al., 2017). Similarly, the same type of peroxisomal lipids was found to be essential for the full maturation of natural killer T cells in the thymus (Facciotti et al., 2012).

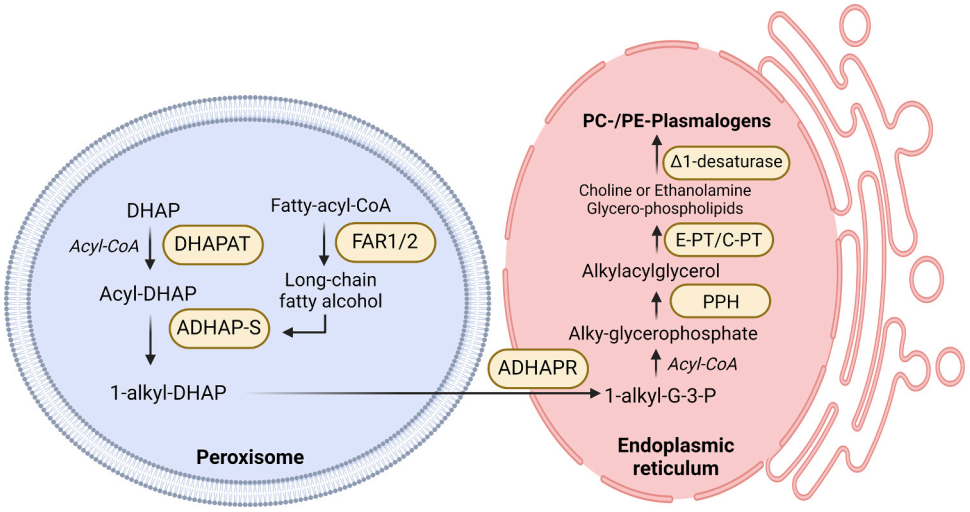

Fig. 2. Plasmalogens biosynthesis pathway. The biosynthesis of plasmalogens (Pls) is initiated in peroxisomes and terminated in the endoplasmic reticulum (ER) via seven-step subsequent reactions. The initial two steps of Pls synthesis are catalyzed by peroxisomal matrix enzymes, dihydroxyacetonephosphate acyltransferase (DHAPAT) and alkyl-dihydroxyacetonephosphate synthase (ADHAP-S) . ADHAP-S generates alkyl-acyl-dihydroxyacetonephosphate (1-alkyl-DHAP) by replacing the acyl chain of acyl-DHAP, the product of DHAPAT, with a long-chain fatty alcohol. Far1, fatty acyl-CoA reductase 1, is a peroxisomal C-tail anchored protein responsible for the rate-limiting step of Pls biosynthesis. The activity of Far1 is regulated by the endogenous levels of Pls sensed by Pls localized in the inner leaflet of plasma membranes. Following the metabolic route, Alkyl-DHAP is further reduced and Pls are synthesized via the remaining four steps in the ER. The enzymatic reactions of Pls *de novo* biosynthetic pathway are separated by the organelles where they take place. This illustration was generated using Biorender (©BioRender). Abbreviations: Pls: plasmalogens; ER: endoplasmic reticulum; DHAP: alkyl-acyl-dihydroxyacetonephosphate; DHAPAT: dihydroxyacetonephosphate acyltransferase; ADHAP-S: alkyl DHAP synthase .

Peroxisomes further play an important role in the control of inflammation-related ROS and reactive nitrogen species damage (Fransen et al., 2012). Indeed, peroxisomes can produce and deliver to other organelles, such as lysosomes, catalase and peroxiredoxins, that besides neutralizing ROS generated during β-oxidation of lipids, are also essential for maintaining cellular redox homeostasis (Fransen et al., 2012; Terlecky et al., 2012). Furthermore, peroxisomes were shown to metabolize leukotrienes and prostaglandins, important modulators of inflammation. The inactivation of these proinflammatory lipids through β-oxidation produces metabolites that can act as resolution mediators of inflammation (Di Cara et al., 2019). Indeed, in the murine macrophage cell line RAW264.7 stimulated with lipopolysaccharide (LPS), peroxisomal proliferation abrogated the hyper-production of pro-inflammatory cytokines, while the disruption of peroxisomal functions had the opposite effect. Therefore, the upregulation of peroxisomal number may serve as a homeostatic mechanism in macrophages, which renders protection against uncontrolled pro-inflammatory response. With this, peroxisomes may act as late-phase inflammation suppressors at the post-translational level to self-regulate inflammatory macrophages (Vijayan et al., 2017). In the brain, the loss of peroxisomal functions, namely peroxisomal β-oxidation, was associated with increased accumulation of arachidonic acid metabolites and pro-inflammatory reactivity of microglia (Bottelbergs et al., 2012; Verheijden et al., 2015).

2.5. Plasmalogens and related lipid mediators' abnormalities in ME/CFS

The environmental triggers associated with ME/CFS, such as psychological stress, bacterial toxins and viral infection, can severely affect lipid metabolism and consequently reduce Pls levels (Hossain et al., 2017). More recently, further evidence supported the involvement of impaired Pls and other lipids mediators in ME/CFS. Of note, previous metabolomic analysis of serum samples from patients with ME/CFS reported abnormalities in sphingolipid, phospholipid, cholesterol, branch chain amino acid, peroxisomal, and mitochondrial metabolism (Germain et al., 2022; Huth et al., 2020). This was corroborated by subsequent findings showing impaired acyl-phosphocholines, belonging to the fatty acid synthetic sub-pathway of lipids, and steroids (androgenic, progestin, and corticosteroids) metabolism in serum samples of women with ME/CFS (Germain et al., 2020). Considering the important sex differences in the incidence of ME/CFS, it is plausible that marked differences in metabolomic profile are sex-related in this disorder. Analyzing plasma samples, Naviaux et al. (2016) were able to stratify the metabolomic profiles of patients with ME/CFS according to their sex. They found decreased levels of eight metabolites, including some Pls species, able to discriminate men diagnosis, while decreased levels 13 metabolites, also including Pls derived-species, were highly predictive of women diagnosis. Regarding phospholipids, several plasma phosphatidylcholine (PC) phospholipids showed markedly reduced levels across sexes. By contrast, molecular species containing the essential omega-3 PUFA DHA (C22:6) and oleic acid (C18:1) were increased mainly in females (Naviaux et al., 2016). In accordance, (Nagy-Szakal et al., 2018) found that the most significant changes in plasma metabolites in both male and female patients with ME/CFS were the decreased levels of phospholipids and phospholipids-derived lipids, such as lysophosphatidylcholine (LPC) and PC, and sphingomyelin (SM) (Nagy-Szakal et al., 2018).

Further exploring the existing sex-related differences in the lipid mediators' signature in ME/CFS, Nkiliza et al. (2021) performed comprehensive lipidomics in the serum of male and female patients with ME/CFS. They showed a clear sex-related lipidic molecular signature, with the levels of total phosphatidylethanolamine (PE), omega-6 arachidonic acid-containing PE, and total hexosylceramides (HexCer) being significantly decreased in women, while the men lipidome was characterized by increased total levels of HexCer, monounsaturated PE, phosphatidylinositol (PI), omega-6 linoleic acid-derived oxylipins and saturated triglycerides (TG). Additionally, negative correlations between the levels of PC, PE and SM were negatively associated with headache and fatigue severity across the sexes. By contrast, negative correlations between oxylipins and *N*-acylethanolamine and the severity of headaches, fatigue and cognitive deficits were observed only in females (Nkiliza et al., 2021). These data highlight the potential impact of phospholipids and differences in lipid signatures across the sexes, with Pls depletion being more predominantly found in women (Naviaux et al., 2016; Nkiliza et al., 2021). Also, the association between some Pls-derived oxidized lipid mediators, such as oxylipins, and the symptom severity in women, suggests contribution of these species to the sex-specific factors in ME/CFS immunobiology. Interestingly, some Pls-derived oxidized lipids, such as chlorinated fatty acids, have also been involved in the leakage of the BBB in systemic inflammatory conditions (Pike et al., 2020), but their role in ME/CFS pathophysiology remains to be further investigated.

As previously mentioned, Pls are abundant ether phospholipids that protect cell membranes from oxidative stress and associated damage. Their biosynthesis starts in peroxisomes and is completed in the ER. A cross-talk between mitochondria and peroxisomes plays an important role in maintaining energy homeostasis, and its dysregulation can contribute to the fatigue and cognitive dysfunction which are hallmarks of ME/CFS (Berger et al., 2016; Demarquoy and Borgne, 2015). More recently, Che et al. (2022) added an important piece of evidence for this scenario. These researchers pioneeringly showed the participation of disturbed peroxisomal lipid metabolism in ME/CFS. They reported decreased levels Pls and other ether phospholipids, along with impaired levels of carnitines, in the serum of these patients. In line with previous studies, these findings indicate a marked dysregulation of peroxisomal metabolism, tricarboxylic acid (TCA) cycle and mitochondrial lipid oxidation (Che et al., 2022). Also, carnitine depletion can lead to the accumulation of long-chain triglycerides which become targets for lipid peroxidation and oxidative damage in peroxisomes (Bjørndal et al., 2018; Violante et al., 2013). Toxic lipid peroxidation products can promote mitochondrial membrane leakage and accentuate the metabolic unbalance involved in ME/CFS (Anderson et al., 2012). Interestingly, higher correlation coefficients were found in all peroxisome-related metabolites (Pls, carnitines, long-chain TG) with the energy Modified Fatigue Impact scales (general fatigue, physical fatigue, reduced activity), supporting the notion that dysregulated interactions between mitochondria and peroxisomes are important biological correlates of symptom severity in ME/CFS (Che et al., 2022).

A disturbed mitochondria-peroxisome interaction could be the underlying factor for the suggested immune system exhaustion in ME/CFS patients (Demarquoy and Borgne, 2015). Indeed, a recent study showed that circulating CD4 + and CD8 + T cells from patients with ME/CFS exhibited reduced mitochondrial membrane potential and metabolic remodeling capacity (Missailidis et al., 2021, 2020). Also, pPC are abundant phospholipids in the mitochondrial membranes. Most pPCs are synthesized via the cytidine 5'-diphosphocholine-choline pathway and may undergo substantial lipid remodeling via lipases and acyltransferases (Gibellini and Smith, 2010; Sperka-Gottlieb et al., 1988). pPCs are essential to the formation of intermediate structures in membrane fusion and fission events, for stabilizing membrane proteins into their optimal conformations, and for actin-filament disassembly at the end stage of cytokinesis (Furt and Moreau, 2009). pPC depletion demonstrated in the serum of patients with ME/CFS can specifically affect the function and stability of protein translocases in mitochondria, including the inner membrane translocase TIM23 complex and the outer membrane sorting and assembly machinery complex (Schuler et al., 2016, 2015). The destabilization of these complexes leads to a reduction in mitochondrial membrane potential and respiratory chain energy efficiency (Schuler et al., 2016). Therefore, the depletion of lipids specific to mitochondrial function, such as acylcarnitines (CAR) and some phospholipids species, is a putative underlying factor for the immuno-metabolic abnormalities seen in ME/CFS, including the

dysregulated adaptive immune response and immune exhaustion.

While COVID-19 and its long-term association with fatigue and cognitive dysfunction was recently linked to ME/CFS, notably based on shared mechanisms involving oxidative stress, inflammation, and energy metabolic deficits (Paul et al., 2021; Russell et al., 2016; Sukocheva et al., 2022), abnormalities in Pls levels and metabolism may underlie these common processes (Tremblay et al., 2022). Moreover, a similar pattern characterized by the depletion of circulating Pls and increased levels of fatty-acid derived lipid mediators as well as oxidized lipids, which have been described in ME/CFS populations, can also potentially be found in patients with post-COVID-19 syndromes. However, further investigation is needed to confirm the shared mechanisms for these alterations, including disturbed peroxisomes-mitochondria interactions and increased oxidative damage to Pls and other membrane phospholipids.

2.6. Plasmalogens and related lipid mediators' abnormalities in COVID-19 pathogenesis

Lipid synthesis and metabolism play important roles in determining COVID-19 outcomes. More generally, lipids play essential roles across the life cycle of a virus. The host cell membrane lipid composition can influence viral entry by facilitating its fusion with the viral envelope or affecting the membrane receptor conformation and interaction with viral proteins (Theken et al., 2021). Upon infection, viruses can remodel host lipid membranes and fuel the production of new virions through replicating membrane-enclosed replication organelles, which localize the viral replicase and cofactors nearby each other. In this context, Pls have been proposed to be fundamental for the necessary membrane adaptations, such as CM formation, that support virion production (Deng and Angelova, 2021). Furthermore, several classes of Pls-derived lipid mediators, including eicosanoids and chlorinated lipids, regulate the host immune response to viral infection (McCarthy and Weinberg, 2012).

Host resistance and disease tolerance are essential for a successful defense against infection including SARS-CoV-2 (Theken et al., 2021). Early studies suggested that the host response to COVID-19 may be associated with an excessive proinflammatory response caused by a cytokine storm syndrome (Booz et al., 2020; Tang et al., 2020). In addition to the cytokine storm previously documented, analyses of lung fluids from SARS-CoV-2-infected patients have indicated that a "lipid storm" also takes place (Rezaei et al., 2022). Several lung bioactive lipids have been detected in the course of SARS-CoV-2 infection, while the "lipid storm" in severe COVID-19 cases involves a particular lipidic metabolic signature (Archambault et al., 2021; Palmas et al., 2021).

In the context of SARS-CoV-2 infection, Pls can perform important functions in the host immune responses and in determining the infection outcomes (Deng and Angelova, 2021). Pls have been suggested to have important roles in biological membranes, which are due, in part, to their unique packing in membranes compared to diacyl phospholipids (Almsherqi, 2021). Pls likely have key roles in inflammation at several levels (Tremblay et al., 2022). Pls are membrane-borne antioxidants and have been shown to protect the endothelium from oxidative stress. The vinyl-ether bond of Pls is susceptible to attack by reactive species, suggesting that these lipids can protect cells by scavenging ROS (Dean and Lodhi, 2018; Engelmann, 2004). Additionally, Pls have been shown to have a key role in macrophage phagocytosis and in membrane adaptations that promote endocytosis (Rubio et al., 2018). Furthermore, Pls are enriched with AA, DHA and other PUFAs at the sn-2 position, and their metabolism by phospholipases (especially PLA2) leads to the mobilization of these fatty acids and their subsequent oxidation to bioactive eicosanoids and resolvins (Paul et al., 2019). Collectively, the roles of Pls in membrane molecular dynamics, as antioxidants and precursors of bioactive lipids, indicate their importance in host responses to acute SARS-CoV-2 infection.

Lipidomic studies examining COVID-19 patient samples have revealed specific lipid mediator profiles in mild and severe cases of COVID-19, and have highlighted the role of Pls. Indeed, evaluation of serum samples from 19 healthy patients, 18 mild COVID-19 patients, and 20 severe COVID-19 patients that required intensive care unit admission showed that both mild and severe disease groups were associated with lowered levels of Pls, specially PUFA-containing PC, PUFA-containing phosphatidylserine (PS), and PUFA-containing PE. On the other hand, these same groups showed increased levels of free fatty acids (FFA), PUFA-containing lyso-phospholipids, and PUFA-containing triacylglycerols (TAG)(Schwarz et al., 2021). Other studies also confirmed this pattern of mobilization of Pls stores and depletion toward fatty acids lipid mediators and their association with COVID-19 disease severity (Archambault et al., 2021; Ciccarelli et al., 2022; Wu et al., 2020). Of note, Wu et al. (2020) reported that serum PCs gradually reduced over the course of COVID-19 fatal cases, at the same time, primary lipid subclasses including diglycerides (DGs), FAAs, and TGs, were identified in higher abundance in the COVID-19 fatality group (Wu et al., 2020). Also, increased levels of fatty acids-derived lipid mediators, such as thromboxane A2, inflammatory leukotriene (LT)B4 and LTE4, eoxin E4 and monohydroxylated 15-lipoxygenase metabolites were detected in the bronchoalveolar lavages (BAL) of patients with severe COVID-19 requiring mechanical ventilation (Archambault et al., 2021). Further, Zaid et al. (2021) reported increased levels of selected pro-inflammatory eicosanoids (PGE2, TXBA2, 12-HHTrE) and LTB4 showing positive correlations with the levels of pro-inflammatory cytokines and chemokines (IL-1a, IL-6, TNFα, IL- 12p70, IL-22, IFN-a2, CCL2, CCL11, CXCL9, and CXCL10) and the presence of blood-derived immune cells, such as neutrophils, lymphocytes, and eosinophils in the BAL of patients with severe COVID-19 (Zaid et al., 2021) .

In this context, another important evidence was reported by Schuurman et al. (2022). These researchers showed that platelet lipidome of patients hospitalized for COVID-19 presented decreased levels of plasma pPC, lysoplasmenylcholine (lyso-pPC), and long-chain unsaturated TAG, compared to non-infected control subjects. Other phospholipid subclasses not containing a vinyl-ether bond did not display class-wide changes. Further, hospitalized patients had increased levels of bis-(monoacylglycerol)-phosphate and its biosynthetic precursor lysophosphatidylglycerol, which positively correlated with *ex vivo* platelet reactivity to thrombin (Schuurman et al., 2022).

Additional studies have replicated these findings of phospholipids abnormalities in animal models of SARS-CoV-2 infection and have established important comparisons with other sepsis-related models (Mayneris-Perxachs et al., 2021; Pike et al., 2022). In this context, Pike et al. (2022) compared the lipidome of serum samples from patients with bacterial sepsis, with an animal model of sepsis (cecal slurry) and SARS-CoV-2 intranasally-infected K-18-hACE2 mice (beta variant B.1.351). In the plasma of patients with sepsis and cecal-slurry-sepsis rats, several Pls species were depleted, such as pPC, pPE, and lyso-pPC levels. In the lungs of SARS-CoV-2 infected mice, multiple molecular species of pPC and pPE were also depleted. This was followed by a marked reduction of total pPC levels in the plasma of SARS-CoV-2 infected mice (Pike et al., 2022). Taken together, this evidence highlights the consequences of Pls depletion throughout the course of COVID-19 immunopathogenesis and suggests a potentially shared mechanism with other sepsis-related conditions.

This convergent evidence that COVID-19 modifies the circulating lipidome towards decreased levels of Pls and increases the quantities of lyso-phospholipids and fatty acid-derived lipids suggests the involvement of degrading mechanisms that cleave intact phospholipids in the cellular membranes (Pike et al., 2022; Schwarz et al., 2021). In this context, Snider et al. (2021) demonstrated that severe and deceased COVID-19 patients presented serum lipidic signatures compatible with the lipidic catalysis by secreted PLA2, such as increased levels of lyso-phosphatidylethanolamine (lyso-PE) and lysophosphatidylserine (lyso-PS), confirming the findings from previous studies. Also, these researchers reported higher levels of circulating and catalytically active

sPLA2 group IIA (sPLA2-IIA) in severe COVID-19 and a marked positive association between elevated sPLA2-IIA levels and several indices of disease severity (e.g., kidney dysfunction, hypoxia, multiple organ dysfunction) (Snider et al., 2021). Patients with severe COVID-19 and deceased from COVID-19 also showed elevations of short- and medium-chain acylcarnitines, as well as of mitochondrial DNA (mtDNA), pointing to defective fatty acid oxidation and mitochondrial dysfunction in COVID-19 severity and mortality (Snider et al., 2021).

Among phospholipases, the secreted phospholipase A2 (sPLA2) family includes 12 members with highly conserved structural characteristics and the need of high Ca^{2+} levels for catalytic activity (Boyanovsky and Webb, 2009). Elevated sPLA2 group IIA (sPLA2-IIA) levels have been associated with various other critical clinical conditions, including sepsis and systemic bacterial infections, adult respiratory disease syndrome (ARDS) and multiple organ failure (Berg et al., 2018; Hurley and McCormick, 2008; Letsiou et al., 2021). Previous studies have demonstrated associations between elevated circulating PLA2 activity in severe sepsis cases, whereas surviving patients showed a marked tapering of PLA2 levels/activity (Berg et al., 2018), mirroring the findings in COVID-19 cases, while the deceased ones presented consistently increased levels of PLA2. In the context of multi-organ dysfunction associated with COVID-19, it has been hypothesized that secreted PLA2 can hydrolyze Pls and other anionic phospholipids externalized by damaged cell membranes and mitochondria, resulting in the release of several lipid mediators, such as pro-inflammatory eicoisanoids, mtDNA and acetylcarnitines, which can have direct pro-inflammatory effects but also act as danger-associated molecular patterns (DAMPs) activating pattern recognition receptor (PPR) pathways, such as Toll-like receptor (TLR)4, mainly in macrophages and other monocytic cells, fueling abnormal inflammation and tissue damage (Boyanovsky and Webb, 2009; Snider et al., 2021). Also, PLA2 gene expression can be induced by pro-inflammatory cytokines, especially IL-6, through genomic induction mechanisms in macrophages and hepatocyte cells (Murakami et al., 2016; Ribardo et al., 2001). Additionally, the role of PLA2 in COVID-19 immunopathogenesis has also been supported by recent evidence showing that high levels of sPLA2 predict clinical disease severity in infected children, both in the acute phase of COVID-19 and following the development of a multisystem inflammatory syndrome (Kuypers et al., 2021). However, the profile of phospholipids and derived lipid mediators' abnormalities warrants further demonstration in this pediatric population.

As above-mentioned, Pls are particularly susceptible to attack by ROS, while oxidative stress has been proposed as an additional mechanism for the Pls depletion in septic-related conditions, such as in COVID-19 severe cases (Pike et al., 2022). Of note, in sepsis, the Pls vinyl ether bond can be targeted by neutrophil-derived hypochlorous acid (a product of myeloperoxidase activity, highly increased in acute systemic infection in neutrophils) resulting in 2-chlorofatty aldehyde and 2-chlorofatty acid production (Amunugama et al., 2021; Anbukumar et al., 2010). Increased 2-chlorofatty acid plasma levels associate with ARDS-induced mortality in human sepsis (Anbukumar et al., 2010) and several organ dysfunction in rats subjected to cecal slurry sepsis (Pike et al., 2020). In addition, *in vitro* and *in vivo* studies have shown that chlorinated lipids play an active role in the dysregulated host immune response in sepsis. For instance, 2-chlorofatty acid is a potent neutrophil chemotactic agent, which induces cyclooxygenase-2 (COX-2) expression in endothelial cells and lung alveolar cells (Anbukumar et al., 2010; Messner et al., 2008), and disrupts the endothelial-blood barrier, including the BBB (Pike et al., 2020b). Pls attacked by free radicals were proposed to generate precursors for chlorinated lipid production during sepsis with subsequent consequences on organ dysfunction, including in lung acute injury and ARDS (Pike et al., 2022).

Taken together, converging pieces of literature suggest a phospholipids depletion state in patients with COVID-19 and a marked shift in their lipidomic profile towards the predominance of products of Pls cleavage, such as lyso-lipids and fatty-acid derived eicosanoids, including pro-inflammatory prostaglandins and leukotrienes (Archambault et al., 2021; Schwarz et al., 2021; Zaid et al., 2021). The underlying mechanisms for the Pls metabolism toward these bioactive metabolites involves the upregulation of circulating levels of sPLA2-IIA (Snider et al., 2021), but also increased oxidative attack to the membrane lipid components and generation of toxic byproducts, such as oxidized lipids (Pike et al., 2022). The relevance of Pls and their relationship with other lipid mediators, such as chlorinated lipids, as putative outcome predictors and biomarkers during COVID-19 and sepsis-related conditions, should be explored in depth within future studies.

2.7. Gut dysbiosis and short-chain fatty acids (SCFA)-producing bacteria: a possible link to Pls depletion in ME/CFS and COVID-19

The gut microbiome can influence human health and can regulate immunity via the production of various immunomodulatory metabolites such as short-chain fatty acids (SCFAs) (Yatsunenko et al., 2012). Among them, butyrate plays an important probiotic role primarily through strengthening the intestinal barrier and interacting with the gut immune system. Most butyrate-producing bacteria in the human gut belong to the Firmicutes phylum, in particular clostridial clusters IV and XIVa (Rivière et al., 2016; Velasquez-Manoff, 2015).

Several studies have identified differences in the gut microbiome, indicative of gut dysbiosis, between patients with ME/CFS and healthy individuals (Nagy-Szakal et al., 2017; Sampson, 2023; Xiong et al., 2023). Of note, a recent study by Guo et al. (2023) performed an extensive metagenomic analysis of 106 patients with ME/CFS and 91 healthy controls, and found a common reduction in the abundance of the two major butyrate producers in the human gut: *Faecalibacterium prausnitzii* and *Eubacterium rectale*. Interestingly, the abundance of *Faecalibacterium prausnitzii* was inversely associated with fatigue severity symptoms (Guo et al., 2023). Regarding the association between Pls and gut dysbiosis in ME/CFS, the evidence is still preliminary but interesting findings have been published in recent years (Ding et al., 2020; Liebisch et al., 2021). It is well-known that Pls are produced by mammals and bacteria, and the aerobic biosynthetic pathway in mammals is well-established (Brites et al., 2004). However, more recently, a Pls biosynthetic pathway was also described for anaerobionts (Jackson et al., 2021). Indeed, two-gene operon (plasmalogen synthase, pls) responsible for Pls production was described in the anaerobic bacterium *Clostridium perfringens*. The pls operon is predicted to encode a multidomain complex similar to benzoyl-CoA reductase/hydroxylacyl-CoA dehydratase (BCR/HAD) enzymes. Versions of this operon were found in several human gut microbiome species, most notably in *Clostridium perfringens*, *Clostridium innocuum*, *Faecalibacterium prausnitzii* and *Eubacterium rectale* (Jackson et al., 2021). Reduction in clostridial species have been involved in gut dysbiosis described as part of a common metagenomic signature between patients with ME/CFS and proposed as an underlying factor for the deficiency of butyrate production in this disorder (Guo et al., 2023). However, it is still unclear whether this Pls endogenous production by gut microbiome species can be transferred to their host, thereby influencing human Pls circulating and plasma membrane contents. Despite additional evidence showing that Clostridium species, such as *Clostridium pasteurianum*, can use butyrate-derived structures, such as butanol and isobutyrate, to boost their endogenous production of Pls, especially pPE (Johnston and Goldfine, 1983; Kolek et al., 2015; Wegner and Foster, 1963), a direct association between butyrate production, Pls bacterial synthesis and Pls levels in human health is not fully understood.

Furthermore, there is growing evidence that the gut microbiota is significantly altered in patients with acute COVID-19 and, more recently, in post-COVID-19 syndrome (Wang et al., 2022). In this context, Zuo et al. (2020) revealed that in patients with COVID-19, the abundance of *Coprobacillus, Clostridium ramosum,* and *Clostridium hathewayi* was correlated with COVID-19 severity, and there was an

inverse correlation between the abundance of *Faecalibacterium prausnitzii* and the disease severity. Also, other symbiont species, such as the *Bacteroides thetaiotaomicron, Bacteroides massiliensis, and Bacteroides ovatus*, correlated inversely with SARS-CoV-2 load in fecal samples. Interestingly, depleted symbionts and gut dysbiosis persisted even after clearance of SARS-CoV-2 in throat swabs and resolution of respiratory symptoms (Zuo et al., 2020). Also, increased proportions of opportunistic fungal pathogens, *Candida albicans, Candida auris,* and *Aspergillus flavus*, were detected in fecal samples from COVID-19 patients, and they persisted after resolution of the acute symptoms (Zuo et al., 2020). As the microbiome composition has been associated with the disease course of COVID-19, Venzon et al. (2022) added an important shred of evidence, demonstrating that the gut dysbiosis profile in COVID-19 is associated with increased bacterial translocation into the blood of germ-free mice submitted to fecal transplantation from samples of patients with COVID-19 and of human infected patients (Venzon et al., 2021).

Regarding the post-COVID-19 syndrome, a recent prospective study analyzed the gut microbiome of 106 patients with post-COVID-19 followed up from admission to 6 months and 68 controls. Interestingly, at 6 months, 76% of patients showed PVFS symptoms, mainly fatigue, cognitive impairment and hair loss. Gut microbiome of patients with PVFS were characterized by higher levels of *Ruminococcus gnavus*, *Bacteroides vulgatus*, and mainly lower levels of *Faecalibacterium prausnitzii*. Butyrate-producing bacteria, including *Bifidobacterium pseudocatenulatum* and *Faecalibacterium prausnitzii*, showed the largest inverse correlations with PVFS symptoms at 6 months. Patients that did not develop fatigue symptoms presented a normalization in their microbiome profile compared to controls at 6 months of follow-up (Liu et al., 2022a; Liu et al., 2022b). A recent preprint study reported that the gut microbiota of patients with post-COVID (up to 4 months after initial positive testing) had a strong predominance of Enterobacteriaceae strains. Moreover, after fecal transplantation to germ-free mice, animals receiving samples from patients with post-COVID displayed higher lung inflammation and impaired cognitive performance (De Almeida et al., 2022) .

Therefore, considering that depletion of butyrate-producing bacteria, which is common between multiple metagenomic analyses of acutely-ill and post-COVID-19 patient samples (the same finding was consistently observed in patients with ME/CFS), we can hypothesize that it serves as a shared pathophysiological mechanism between these two conditions. Also, considering the association between the depletion of these species, which are the predominant Pls-producing ones in the gut microbiome, this mechanism also opens up new perspectives that can at least partially explain the Pls circulating abnormalities evidenced in patients with COVID-19, which need to be further explored.

2.8. Plasmalogen depletion as a common biological factor for brain pathology

Pls have different biological functions based on their physicochemical properties and interactions with several biological pathways, which make them interesting targets for therapeutic approaches (Paul et al., 2019b). Based on their biophysical and chemical properties, Pls are known to increase lipid packing in lipid rafts and membrane thickness, contribute to the formation and stabilization of curved membrane surfaces, act as membrane-born scavengers for free radical species, and store signaling molecules such as PUFAs as part of their structure (Braverman and Moser, 2012).

Pls degradation could occur either by non-enzymatic or enzymatic biochemical reactions (Fig. 2). The non-enzymatic mechanisms of Pls degradation are chemical in nature and depend on oxidation or hydrolysis. This pathway has been suggested as a main underlying factor for Pls depletion in several neurodegenerative and inflammatory conditions (Paul et al., 2019), such as ME/CFS (Paul et al., 2019). On the other hand, the enzymatic mechanisms are dependent on the cleavage by phospholipases, especially PLA2 (Farooqui and Horrocks, 2001a, 2001b, 2001c; Yang et al., 1996). In addition, it has been shown that cytochrome c upon oxidative stress can act as a plasmalogenase, releasing the alkyl chain at sn-1 position of the glycerol moiety (Jenkins et al., 2018). The increased degradation of Pls by circulating phospholipases has been proposed as an important mechanism behind COVID-19 progression into severe clinical outcomes (Snider et al., 2021).

Furthermore, Pls are precursors of another clinically relevant molecule, platelet-activating factor (PAF). Together, Pls and PAF regulate the balance of anti-inflammatory and pro-inflammatory signaling pathways to maintain homeostasis and appropriate immune responses (Tremblay et al., 2022). Pls deficiencies and excess PAF levels are most reported under pathophysiological conditions (Tremblay et al., 2022). The metabolic interconversion between Pls into PAF is thought to be a contributing factor for the pro-inflammatory action of PAF and potential anti-inflammatory role of Pls in response to acute and/or chronic inflammation (Rong et al., 2022) . Pls deficiency was also shown to decrease DHA- and increase AA-containing ethanolamine Pls, which may shift the immunological balance towards pro-inflammation through PAF upregulation (Dorninger et al., 2019).

PAF mainly exerts its pro-inflammatory effect by binding to the PAF receptor (PAF-R). Normal activity of PAF is important for the protection against infection. PAF-R blockade or deficiency in mice has resulted in more severe infection manifestations and mortality (Upton, 2022). PAF-R is expressed by many cell types, including T lymphocytes, monocytes and macrophages, platelets, lung alveolar cells, brain microglia and neurons, among others (Honda et al., 2002)). Upon binding to PAF-R, PAF can activate NF-κB and MAPK inflammatory signaling pathways in macrophages (Rong et al., 2022). These inflammatory cascades can lead to histamine release from basophils, activation and degranulation of mast cells, chemotaxis of mast cells and eosinophils, recruitment of neutrophils, as well as production of IL-4 by B lymphocytes (Upton, 2022). PAF also participates in synaptic transmission, long-term potentiation, memory formation, proliferation and differentiation of neural cells (Goracci et al., 2009). Further evidence supports the role of PAF as a key messenger in neuron-microglia interactions (Aihara et al., 2000).

Under pathological conditions, PAF contributes to allergic and nonallergic inflammatory diseases (Upton, 2022). Increased levels of PAF, due to upregulation of biosynthetic pathways or downregulation of its degradation enzyme PAF-acetylhydrolase (PAF-AH), have been observed in pathological conditions involving neuroinflammation, brain ischemia, and neurodegenerative diseases (Goracci et al., 2009). For example, PAF participates in the neuroinflammation and cerebral dysfunction during acute traumatic brain injury (TBI), as observed in a model of TBI by the rescue of morphological and behavioral abnormalities in PAF-R *knockout* mice (Yin et al., 2017). In addition, an excess of PAF has been implicated in AD pathology (Tremblay et al., 2022). Furthermore, high concentration of PAF may induce neuronal apoptosis , leading to neurotoxicity from excessive glutamate release and overloading post-synaptic Ca^{2+} (Ryan, 2007). PAF-R binding may lead to the activation of pro-inflammatory and prothrombotic pathways, which have been implicated in the onset and development of atherosclerotic cardiovascular disease (Harishkumar et al., 2022). PAF and its effects on the endothelium were also implicated in the pathology of COVID-19, which is further supported by the finding that drugs inhibiting viral entry into host cells also inhibit PAF synthesis (Theoharides et al., 2019). Blocking PAF signaling pathway may thus have therapeutic effects in numerous disease states. Given the metabolic interconversion of Pls and PAF, the plasmalogenic precursors of PAF have been suggested as modulators and potentially inhibitors of PAF-mediated pro-inflammatory effects (Rong et al., 2022).

Furthermore, aging, a common risk factor for several neurodegenerative, neuropsychiatric and metabolic disorders, has a notable association with progressive Pls reduction and increased pro-inflammatory Pls-derived lipid mediators (Bottino, 2012; Mohebali et al., 2014). Indeed, circulating Pls content increases gradually up to 40 years of age,

after which it tends to level off and, by the age of 70, decreases progressively (e.g., there is a 40% decrease in Pls levels in the serum of individuals over 70 years of age compared with younger individuals) (Maeba et al., 2007; Rouser and Yamamoto, 1968). A similar scenario was described for PAF abnormalities. A Chinese study described a progressive age-related increase in the plasma levels of PAF in healthy individuals older than 40 years (Zhang et al., 2003). Also, age-dependent increases in PAF levels were correlated with an increased incidence of coronary heart disease, blood stasis syndrome and stroke (Satoh et al., 1992; Zheng et al., 2012). Changes in cerebral microcirculation and leukocyte-brain endothelium interactions were additionally quantified in rat brains perfused with different PAF concentrations (1pM – 1 μM) for 20 min. The authors showed that higher PAF concentrations (≥ 0.1 μM) increased the number of rolling and adherent leukocytes in venules and caused a transient increase of arteriolar diameters (Uhl et al., 1999). Also, PAF induced a dose-dependent transitory arterial hypotension and caused irreversible circulatory shock at high concentration (0.1 μM) (Uhl et al., 1999). Moreover, in patients with cerebrovascular disorders (ischemic stroke and subarachnoid hemorrhage), increased plasma PAF levels were correlated with increased IL-6 levels and delayed neurological deficits weeks after the onset of the disorder (Hirashima et al., 1997; Mohebali et al., 2014).

Despite the multiple relevant biological functions displayed by Pls, some interesting findings have brought controversies regarding their main role in the neurodegeneration and neuroinflammation-associated with peroxisomal deficiency. In this context, mice with a selective peroxisome dysfunction in neural progenitor cells (controlled by Nestin promoter), named Nestin-Pex5 *knockout* mice, showed a marked developmental delay and progressive neurodegenerative changes starting at the age of 3 weeks (Bottelbergs et al., 2012; Krysko et al., 2007). These mice display a phenotype of progressive demyelination, macrophage activity, increased microglial density, and axonal loss occurring throughout the brain. This was followed by motor and later on cognitive deficits, aggravating with increasing age and evolving into immobility and death before the age of 6 months (Hulshagen et al., 2008; Krysko et al., 2007). In this context, Bottleberg et al. (2012) have shown that Nestin-Pex5 *knockout* mice present marked signs of chronic CNS inflammation, especially in the most demyelinated areas, including upregulation of pro-inflammatory genes (C1q, TNFα, and TLR2) and increased microglial phagocytic activity in the corpus callosum, spinal cord, and brain stem. Interestingly, to dissect the role of Pls deficiency in driving neurodegenerative changes induced by peroxisomal dysfunction, these researchers compared the Nestin-Pex5 *knockout* mice to glycerone phosphate O-acyltransferase (GNPAT) *knockout* mice, which specifically have Pls synthesis impairment (Bottelbergs et al., 2012). Contrary to other literature, Pls deficiency was not found in this study to impact CNS inflammation (no induction of proinflammatory genes or increased microglial phagocytosis), as well as demyelination aggravating with age (Bottelbergs et al., 2012).

Similarly, mice with peroxisomal dysfunction caused by the absence of the multifunctional protein-2 (MFP2), a pivotal enzyme in peroxisomal β-oxidation, develop a fatal disorder characterized by motor and cognitive abnormalities similar to the milder form of MFP2 deficiency in humans (Baes et al., 2000). The hallmark of this disease in mice is the chronic proliferation of microglia accompanied by abnormal inflammation in the brain (Verheijden et al., 2015, 2013). However, Beckers et al. (2019) selectively deleted MFP2 in microglia using Cx3cr1-Mfp2 *knockout* mice and found that despite these animals showing a basal microglial state marked by increased pro-inflammatory reactivity and proliferation, they exhibited normal neuronal transmission, clinical motor performance, and cognition (Beckers et al., 2019). Taken together, these studies raise questions about the single contribution of Pls deficiency to the neurodegeneration and CNS inflammatory changes induced by peroxisomal inactivity. More studies should be performed in the field to clarify the complex interactions between Pls synthesis and other peroxisomal functions in the context of health and CNS disease, as well as the specific contributions of different cell types, such as microglia, to the observed cellular and behavioral phenotypes.

Sphingolipids are another major constituent of cellular membranes in the human brain. Among the sphingolipids, SM occurs at higher concentrations in neuronal membranes and myelin sheaths. Besides its role as a signaling molecule, SM has a crucial function in modulating the structure of membranes (Kraft, 2017). Due to its highly intermolecular interactions, which are mediated by the 2-amide group, the 3-hydroxy group, and partially by the 4,5-*trans* double bond of the sphingoid-base, SM has an important role in forming the so-called lipid rafts, which are important for multiple homeostatic functions in the CNS, notably synaptic plasticity and receptor trafficking (Bieberich, 2018; Kraft, 2017). In addition to several lipid classes including Pls, PUFAs, trans-FAs, and phytosterols, sphingolipids are found altered in AD specimens, including blood samples and *post-mortem* brain. Indeed, in *post-mortem* brains of patients with AD, a reduction in SM and an elevation of ceramide have been reported (Alessenko et al., 2004; Grimm et al., 2017; He et al., 2010). Interestingly, SM is a precursor for ceramide, within a reaction that is catalyzed by the action of sphingomyelinases (SMases). A more recent report showed significantly increased SMases activity not only in human *post-mortem* brains, but also in plasma and fibroblasts derived from patients with AD (Lee et al., 2014). Mechanistically, it has been shown that amyloid-beta (Aβ) can directly activate SMases in the picomolar range. In return, inhibition of SMases leading to an increased SM level resulted in a decrease of Aβ production (Grimm et al., 2005). In addition, Koal et al. (2015) reported increased SM species [SM (d18:1/18:0)] to be significantly enhanced in cerebrospinal fluid (CSF) samples of patients with AD and suggested this could serve as a biomarker for AD with a specificity of 76% and a sensitivity of 66% with a cut-off of 546 nM (Koal et al., 2015). Another study showed that many other sphingolipids, including SM39:1, SM41:1, and SM42:1, are by contrast decreased. However, this study clearly pointed out that SM alone is not sufficient as a biomarker and has to be accompanied by other lipids to increase specificity and sensitivity (Olazarán et al., 2015). Another connection between AD, SM, and SMases can be indirectly drawn from the fact that SM is decreased in *post-mortem* brain samples and serum of patients with depression, accompanied by an increased SMase activity (Kornhuber et al., 2005). Additionally, in animal studies, it was shown that an inhibition of the acid sphingomyelinase/ceramide system mediates the effects of tri- and tetracyclic antidepressants in mice (Gulbins et al., 2013). Moreover, an accumulation of ceramide in the hippocampus results in depression-like symptoms and impaired hippocampal neurogenesis in mice (Sambolín-Escobales et al., 2022). For further details, please see some relevant reviews in the field (Grimm et al., 2017; Jernigan et al., 2015; Mühle et al., 2013).

2.9. Estrogens as master controllers of the brain immune responses and lipid metabolism: the case of post-menopausal hormonal depletion and increased risk of CNS pathology

The endocrine transition from the menacme phase (normal hormonal fluctuations in women) to the post-menopause, besides a loss of reproductive function and gonadal hormones depletion (Su and Freeman, 2009), is also associated with a rise in chronic low-grade inflammation (Dias et al., 2016). Along with this, the menopausal transition is characterized by decline in brain glucose metabolism and mitochondrial respiration (Lejri et al., 2018), myelin catabolism and loss of white matter volume (Klosinski et al., 2015) (and increased glial reactivity (Brinton et al., 2015)). Altogether, the menopausal transition has been associated to an increased risk of several neurodegenerative and inflammation-related disorders (Cheng et al., 2021). For example, post-menopausal women are at increased risk of developing sporadic AD (more than twice) compared to their male counterparts (Scheyer et al., 2018). Women with AD have lower endogenous estrogen levels than age-matched healthy women (Manly et al., 2000). Surgically induced

menopause prior to natural menopause is also associated with a rapid cognitive decline and an earlier onset of AD (Bove et al., 2014). Also, post-menopausal women are at higher risk of developing autoimmune disorders, such as rheumatoid arthritis, and obesity (Desai and Brinton, 2019). While ME/CFS in general is more prevalent in women, the highest incidence was detected around the ages of 40–49 in women, a period corresponding to the post-menopausal transition, while the symptom severity worsened significantly after menopause (Boneva et al., 2011; Reeves et al., 2007). Among the mechanisms by which post-menopausal women could be more prone to abnormal immune responses, the lack of ovarian hormones, especially estrogen, takes an important place (Brinton et al., 2015; Trenti et al., 2018). Indeed, the lack of steroidal hormones, especially estrogens, further potentiates inflammation, and creates a low-grade chronic inflammation state, which is reflected in levels of circulating cytokines and other mediators (Vegeto et al., 2008). For example, higher levels IL-6 and soluble IL-6 receptor (Kim et al., 2012), IL-4, IL-2 and IFN-γ were markedly increased in the blood of post-menopausal women compared to age-matched men and pre-menopausal women (Goetzl et al., 2010).

Regarding the brain immune responses, gene expression analysis in postmenopausal women revealed a pro-inflammatory gene expression profile in the post-central and superior frontal gyrus (Sárvári et al., 2012) and hippocampus (Sárvári et al., 2015). In comparison to pre-menopausal women, post-menopausal women presented an increase in pro-inflammatory markers, such as CD14, CD18, CD45, TLR4, MHC-II, CD74 and complement C3 (Sárvári et al., 2012). In animal studies, similar findings were observed. Ovariectomized middle-aged (13-month old) rats showed an upregulation of pro-inflammatory markers, such as CD11b, C18, CD45, and CD86, complement C3, and phagocytic markers Msr2 and CD32, in the frontal cortex (Sárvári et al., 2012). Also, in the hippocampus, a similar increase in pro-inflammatory markers (CD45, IBA1, CD68, CD11b, CD18, Fcgr1a, and Fcgr2b) was observed after ovariectomy in middle-aged rats (Sárvári et al., 2015). Despite that these markers are not exclusively expressed on microglia, usually they are upregulated in the face of pro-inflammatory and neurodegenerative conditions, therefore direct associations of these findings with possible microglial states should be taken cautiously (Muzio et al., 2021; Sousa et al., 2018). Additionally, these changes were rescued by treatment with estradiol and selective estrogen receptor-α (ERα) and estrogen receptor-β (ERβ) agonists (Sárvári et al., 2015).

In parallel, as well-known, aging is associated with a marked upregulation of genes associated with pro-inflammatory responses, such as TLRs (Shaw et al., 2011), and the complement pathway (Reichwald et al., 2009). This effect seems to be more pronounced in women and supports a sexual dimorphism of the immune system (Berchtold et al., 2008). The extent of microglial reactivity induced by ovariectomy is also exacerbated by aging. In fact, in 20–24-month old ovariectomized mice, the expression of brain pro-inflammatory markers, such as IL-6 and TNFα, was markedly higher than in age-matched controls (Lei et al., 2003). This indicates that low circulating estrogens increase the susceptibility of aged and possibly senescent microglia to assume pro-inflammatory and hyper-reactive states, which often are accompanied by neurodegenerative consequences (Villa et al., 2016). Interestingly, studies with a model reporting on the transcriptional activity of estrogen receptors (ERE-Luc mouse) (Della Torre et al., 2022) showed that it diminished significantly in the hippocampus with aging, although the synthesis of ERα mRNA was increased and circulating levels of estrogens remained constant (Baumgartner et al., 2019). It is therefore plausible that aging courses with an estrogen resistance that impairs the ability of microglia to resolve inflammation as they assume a pro-inflammatory phenotype, possibly leading to neurodegenerative consequences and an increased risk for dementia and brain pathology (Villa et al., 2016). Similar to estrogens, acute administration of the estrogen modulators tamoxifen and raloxifene to ovariectomized young and aged mice reduced microglial pro-inflammatory reactivity after LPS stimulation (Arevalo et al., 2012; Tapia-Gonzalez et al., 2008) and spinal cord injury (Tian et al., 2009). Long-term treatment with 17β-estradiol or raloxifene in old ovariectomized female mice also significantly decreased microglial density and ameboid morphology in the hippocampus (Lei et al., 2003), suggesting that estrogens and selective estrogen receptor modulators (SERMs) may be considered as protective treatments against post-menopausal exacerbation of age-related neuropathology (Lamas et al., 2015).

The lipid structure of cortical lipid rafts undergoes significant alterations of specific lipid classes and phospholipid-bound FAs correlated with aging. This “lipid raft aging” appears to be more pronounced in postmenopausal women during a decline of estrogen levels, which may help to explain why AD is more prevalent in this subgroup of patients (Mesa-Herrera et al., 2019). A decline in long chain polyunsaturated fatty acids (LCPFAs),mainly AA and DHA, in cortical lipid rafts was only apparent in women above age 80, which was also associated to the depletion in estrogen levels (Díaz et al., 2018). In the non-pathological brain, lipid raft aging is accompanied by increased sulphatide levels and decreased cholesterol. The authors suggest that these alterations, in conjunction with a decline in omega-3 and omega-6 PUFA and Pls, may determine the onset of neurodegeneration at the lipid raft level (Díaz et al., 2018), which can be even exacerbated in estrogen deficiency conditions, such as in post-menopausal women (Cheng et al., 2021).

A connection between estrogens and sphingolipids also exists. These bioactive molecules, namely ceramide, S1P, and sphingosine, modulate steroidogenesis by regulating the expression of steroidogenic genes and enzymes, acting as paracrine/autocrine regulators, and serving as ligands for steroid nuclear receptors, such as the estrogen receptors (Lucki and Sewer, 2010). Sphingolipids have been reported to mediate multiple actions of steroid hormones, especially estrogens (Sukocheva et al., 2009). Sphingosine kinase (SK) that metabolizes sphingosine in S1P was also shown to bridge the crosstalk between estrogens and growth factor signaling. 17β-estradiol-induced SK activity and the resulting production of S1P is essential for estrogen-dependent mitogenic effects and increased cell proliferation in breast cancer and epithelial cell lineages (Hahnefeld et al., 2020). In addition, SK mediates estrogen-stimulated endothelial growth factor receptor (EGFR) transactivation, Ca^{2+} mobilization, and ERK1/2 activation in breast and prostate cancer cells (Allam et al., 2018; Hahnefeld et al., 2020). However, despite this promising evidence, it is still not completely understood how ovarian hormones, especially estrogens, and their depletion in post-menopausal women, interact with lipid disturbances, notably in microglia, that course during the aging and brain pathology associated to neurodegenerative and neuropsychiatric disorders. Therefore, further research is needed to draw the link between lipid disturbances and Pls abnormalities, observed in conditions presenting CNS inflammation and abnormal glial reactivity, such as ME/CFS and post-viral syndromes, with the depletion of estrogens after the post-menopausal transition.

2.10. Plasmalogens and derived lipid mediators' abnormalities in neurodegenerative and neuropsychiatric disorders

In addition to their association with aging and the basic mechanisms of brain pathology and inflammation, abnormalities in Pls contents and metabolism have been described in several neurodegenerative and neuropsychiatric disorders (Udagawa and Hino, 2022). This section describes recent experimental and observational evidence of the association between abnormalities in ether phospholipids, mainly Pls species, and the clinical and pathobiological aspects of different neuropsychiatric and neurodegenerative disorders (summarized in Table 1). The investigation of the role of Pls and PAF in the neurobiology of these disorders has often relied on the use of accessible peripheral tissues for metabolic profiling. It should be noted, however, that the reported changes in lipids detected in peripheral cells may not necessarily be causative of the other underlying pathological mechanisms.

Table 1
Plasmalogens abnormalities and their therapeutic use in neurodegenerative and neuropsychiatric disorders.

Neurodegenerative/ Neuropsychiatric disorder	Reference	Study Design	Main Findings/Outcomes
Alzheimer's disease	Fujino et al. (2017)	Patients (aged 60–85 years) with mild Alzheimer's disease (AD) and mild cognitive impairment (MCI) were randomized to receive 24 weeks of treatment with either: 1 mg/d purified plasmalogens (Pls) extracted from scallops (n = 140) or placebo (n = 136).	Mild AD patients showed a significantly greater decrease in plasma ethanolamine plasmalogens (pPE) in the placebo group than in the treatment group. Oral administration of Pls significantly improved memory among female mild AD patients and those aged below 77 years as shown in Wechsler memory scale-revised (WMS-R) test.
	Wood et al. (2015a)	Serum samples of diagnosed patients with late-onset AD (LOAD) (n = 90), patients with MCI (n = 77), and controls (n = 51) were analyzed by lipidomics.	Three patient cohorts within each clinical diagnosis (LOAD and MCI were observed: lower circulating pPEs; higher circulating diacylglycerols (DAG); and neither of these two lipid alterations. More patients showed low levels of pPEs in advanced stage of disease.
	Yamashita et al. (2017)	Plasma and red blood samples of 28 patients with AD (age: 72.5 ± 1.4) and 28 normal control subjects (age: 74.1 ± 1.3) were analyzed. Plasma amyloid-beta (Aβ) was correlated with phosphatidylcholine (PC) - hydroperoxide (PCOOH), and pPE in the blood of patients with AD.	Plasma from AD patientsshowed lower concentrations of pPE species, especially docosahexaenoic acid (DHA) - containing pPE. Lower pPE and higher PCOOH levels were observed in erythrocytes of AD patients. In both AD and control blood samples, PCOOH levels in erythrocytes tended to correlate with plasma levels of Aβ.
	Wood et al. (2015)	*Post-mortem* cerebrospinal fluid (CSF), frontal cortex grey matter and white matter of patients with AD (n = 28), MCI (n = 19) and controls (n = 28) were submitted to lipidomic analysis.	DAG and fatty acid 26:0 were elevated in the grey matter of the MCI and old dementia (OD) cohorts. Pls were decreased in the grey matter of early dementia (ED) and OD patients while and PEs were lower in the MCI, ED, and OD patients compared to aged-matched controls.
	Wood et al. (2010)	The serum Pls of 40 patients with AD and 66 controls aged 67–89 years were analyzed and correlated with cognitive functions using AD assessment scale-cognitive (ADAS-Cog). Serum Pls levels in AD patients were retested 1 year later.	Only subjects with serum DHA-Pls ≤ 75% or less of normal levels exhibited cognitive decline over a 12-month period. There was no change in ADAS-Cog scores among participants with normal serum Pls levels at baseline (> 75%).
	Goodenowe et al. (2007)	The serum samples of 324 dementia subjects low, moderate, and severe stage) were analyzed and compared with 68 age-matched controls to investigate the relations between dementia severity and Pls levels. 209 healthy subjects were divided into 3 age groups (50–59, 60–69, and 70– 95 years) and their serum was analyzed to determine the effect of age on Pls levels. *Post-mortem* samples of subjects with AD (n = 20) and those without AD pathology (n = 19) were analyzed to compare the Pls levels. Serum from 50 clinically diagnosed AD subjects (3 stages), who were later confirmed to have AD upon *post-mortem* examination, was analyzed to determine the DHA-Pls levels.	The levels of Pls species were significantly reduced in all three groups of AD subjects, and the decrease was correlated with the severity of AD. Subjects with very low Pls in the 60–69-year cohort were more than twice as abundant compared to the other two groups. Increased mortality rate was evidenced in both AD subjects and peroxisomal disorders with low Pls levels. Serum Pls levels were significantly reduced in the *post-mortem* (55%) AD subjects, and clinically diagnosed AD subject (47%). The decrease was related to the severity of the disease. Serum DHA-Pls levels were significantly reduced in the AD subjects.
	Han et al. (2001)	*Post-mortem* human brain tissue (AD, n = 30, controls, n = 6) and brain tissues from two animal models of AD, APPV717F and APPsw mice, were analyzed using electrospray ionization mass spectrometry (ESI/ MS).	A dramatic decrease in Pls content (up to 40% of total Pls) in white matter at a very early stage of AD; a correlation of the deficiency in gray matter Pls content (10–30% deficiency) with the severity of AD (very mild to severe); no alterations of Pls content and molecular species in the cerebellum gray matter despite dramatic alterations in the cerebellum white matter. In mice, 10% deficiencies were present at age of 18 months in cerebral cortices but not in the cerebellum.
Parkinson's disease	Mawatari et al. (2022)	Analysis of the pattern of phospholipid composition of erythrocyte membrane through high-performance liquid chromatography (HPLC) in patients with AD (n = 146), Parkinson's disease (PD) (n = 45) and coronary artery disease (n = 30) compared with healthy individuals (n = 39).	A common pattern of changes among the three disorders was noticed: The decrease of erythrocyte pPE was accompanied by a decrease of PC although phosphatidylethanolamine (PE) remained unchanged. The decreases of PE and PC were associated with an increase of sphingomyelin (SM) in the total phospholipids.
	Fujino et al. (2020)	Retrospective analysis of a multicenter, randomized, double-blind, placebo-controlled trial of oral Pls supplementation (1 mg/day) for 24 weeks in patients with MCI (n = 178) and mild AD (n = 98). An open-label study of Pls supplementation (1 mg/day) for 12 weeks in moderate AD (n = 57) and severe AD (n = 18), and the same open-labeled design for patients with PD (n = 10) for 24 weeks. Plasma Pls were assessed before and after the intervention.	A significant improvement in cognitive function and other clinical symptoms with an elevation of the blood Pls levels. No adverse events were reported. The baseline levels of plasma pPE and erythrocyte pPE in MCI, AD, and PD were significantly lower than those of normal aging. The degree of reduction in the blood Pls levels was in the order of MCI ≺ mild AD ≺ moderate AD ≺ severe AD ≺ PD.
	Mawatari et al. (2020)	Open-labeled study where patients with PD (n = 10) received oral administration of 1 mg/day of purified Pls derived from scallop for 24 weeks. Clinical symptoms were assessed and blood tests were peformed at 0, 4, 12, 24, and 28 weeks. The blood Pls levels in patients with PD were compared with those of 39 age-matched normal controls.	Initial levels of Pls in plasma and erythrocytes from PD were lower than those of age-matched normal controls. Oral administration of 1 mg/day of the purified Pls increased plasma ether phospholipids in PD and increased the relative composition of ether phospholipids of erythrocyte membrane in PD. The levels of Pls in peripheral blood reached almost normal

(*continued on next page*)

Table 1 (*continued*)

Neurodegenerative/ Neuropsychiatric disorder	Reference	Study Design	Main Findings/Outcomes
			levels after 24 weeks. Some clinical symptoms of PD improved concomitantly.
	Fabelo et al. (2011)	Purified lipid rafts from the frontal cortex from healthy (n = 11), early motor stages of PD (n = 8) and incidental PD (n = 8) subjects were analyzed by lipidomics.	Lipid rafts from PD and incidental PD cortices exhibited dramatic reductions in their contents of omega-3 and omega-6 long-chain polyunsaturated fatty acids (PUFAs), especially DHA (22:6n-3) and arachidonic acid (20:4n-6). Saturated fatty acids (16:0 and 18:0) were significantly higher in PD and incidental PD patients than in control brains. Other lipid classes were also affected in PD and incidental PD lipid rafts: phosphatidylserine (PS) and phosphatidylinositol (PI) were increased in PD and incidental PD, whereas cerebrosides and sulfatides and Pls levels were considerably diminished in the same disease groups.
Multiple sclerosis	Ferreira et al. (2021)	The phospholipidomic signature of plasma samples of patients with multiple sclerosis (MS) in remission (n = 17) and relapse (n = 7) phases and healthy control (n = 30) was determined	Patients with MS had a plasma phospholipidomic signature different from that of healthy controls, especially the PE, PC, pPE and pPC species. pPC and pPE species showed significantly lower levels in patients undergoing both remission and relapse of MS. The lowest p-value were reached for pPC(34:3), pPC(36:6), pPE(40:10) and PC(38:1), proposing them as suitable biomarkers for clinical applications in MS.
Schizophrenia	Li et al. (2022)	Erythrocyte membrane lipid profiling of patients with schizophrenia (SCZ) (n = 80) and healthy controls (n = 40) using ultra-performance liquid chromatography-mass spectrometry to compare 812 quantified lipids.	Reduced total concentration of phospholipids, including Pls, in both pPE and pPC of the erythrocyte membrane lipidome. 244 lipids were significantly reduced in SCZ, and 154 of these were categorized as PEs or PCs. The total concentration of alkyl-acyl phospholipids was significantly decreased in both the PC and PE classes. The total concentration of Pls was also significantly reduced in SCZ.
	Wang et al. (2021)	Compared serum levels of 177 phospholipids and free fatty acids from 119 patients with SCZ (n = 119) and healthy controls (n = 109) using targeted liquid chromatography-mass spectrometry (LC-MS).	110 metabolites including 16 free fatty acids, 25 PCs, 23 lyso-PCs, 11 pPC, 7 PEs, 9 pPE, and 13 SM were significantly altered in the serum of SCZ patients, with reduced pPC and pPE compared to controls.
	Huang et al. (2017)	Unbiased metabolic profiling of fibroblasts from patients with SCZ (n = 10) and age- and sex-matched controls (n = 10) under normal growth conditions (25 mM glucose for 6 h) and under stressful *in vitro* perturbations: low-glucose media (1 mM for 6 h) and exposure to dexamethasone (1 μM for 6 h).	Levels of PCs and several pPC species were reduced in fibroblasts of SCZ compared to healthy controls, particularly under stressful conditions.
	Tessier et al. (2016)	Lipidomic analysis of phospholipid classes and fatty acids in erythrocyte membranes from antipsychotic-medicated and clinically stable outpatients with SCZ (n = 74) compared with matched controls (n = 40). Clinical manifestations were examined using the positive and negative syndrome scale (PANSS). Cognitive function was assessed using the Continuous Performance Test, Salience Attribution Test and Wisconsin Card Sorting Test.	pPE levels in erythrocyte membranes were reduced in SCZ patients, particularly in individuals with low SM levels. Patients with low SM membrane content were also characterized by more severe PANSS total, positive, disorganized/cognitive, and excited psychopathology. This group also displayed poorer cognitive performance.
	Wood and Holderman (2015)	Targeted lipidomic analysis of Pls, sulfatides, and *N*-acyl-PS in the frontal cortex of *post-mortem* SCZ (n = 10), bipolar disorder (BD) (n = 10), and amyotrophic lateral sclerosis (ALS) (n = 10) tissues and in the *post-mortem* cerebellum of patients with SCZ compared to controls (n = 10).	Levels of sulfatides, pPC, pPE, and N-acyl-PS were elevated in the frontal cortex of *post-mortem* SCZ and BD but not ALS tissues. These lipids were unchanged in the SCZ cerebellum compared to controls.
	Wood et al. (2015)	Lipidomic analysis of pPC and pPE in the plasma and platelets of patients with SCZ (n = 23) and age-matched controls (n = 27).	Plasma levels of both pPE and pPC were decreased by 23–45% in patients with SCZ. Platelet levels of pPE were also decreased while pPC levels were increased. Levels of DHA were decreased by 30% in both plasma and platelets.
	Wood et al. (2014)	Shotgun lipidomic analysis of over 700 lipids in the *post-mortem* frontal cortex of patients with SCZ (n = 10) compared to controls (n = 10) and hippocampus of G72/G30 transgenic mice (n = 11) compared to wild-type mice (n = 10).	Levels of sulfatides were elevated in the white and gray matter of the frontal cortex of *post-mortem* SCZ tissues and in the hippocampus of G72/G30 transgenic mice. Levels of polyunsaturated fatty acid (PUFA)-lacking pPC were elevated in the white matter of SCZ frontal cortex and the G72/G30 mouse hippocampus. PUFA-containing pPC were elevated in the frontal cortex gray matter in SCZ. Levels of PUFA-lacking pPE were elevated while PUFA-containing pPE were decreased in both the gray and white matter of SCZ frontal cortex.
	Kaddurah-Daouk et al. (2012)	Targeted metabolomics of plasma samples from drug free patients with first episode SCZ (n = 20), chronic patients with recurrent psychotic relapses (n = 20) and age- and body mass index-matched controls (n = 17).	Levels of total plasma Pls, pPC and pPE, and pPC- and pPE-containing fatty acids 16:0, 18:0 and 18:1n9 were lower in SCZ patients compared to controls. No significant differences were observed in Pls between first episode *vs* recurrent patients.
Psychosis	Dickens et al. (2021)	Serum lipidomic analysis of individuals with clinical high risk (CHR) (n = 263) compared with healthy controls	Serum ether phospholipids levels were reduced in CHR patients who subsequently developed psychosis compared to

(*continued on next page*)

Table 1 (*continued*)

Neurodegenerative/ Neuropsychiatric disorder	Reference	Study Design	Main Findings/Outcomes
		(n = 51) who were then clinically monitored for up to 5 years. Machine learning discriminated between groups and subjects with distinct clinical outcomes.	CHR individuals who did not. Compared to healthy controls, CHR individuals had higher levels of lipids in general, with higher levels of triacylglycerols (TAG) with a low acyl carbon number and double bond count.
Bipolar disorder	Beasley et al. (2020)	Gas liquid chromatography analysis of phospholipids (including pPC and pPE) from dorsolateral prefrontal cortex grey matter (*post-mortem* tissue) from controls (n = 35), SCZ (n = 35), and patients with BD (n = 34).	From the 15 quantified individual fatty acid or Pls species, no significant differences were observed in the dorsolateral cortex between *post-mortem* tissues from patients with SCZ, BD and controls.
	Ogawa et al. (2020)	Compared pPE and PE levels in blood plasma between patients with BD (n = 34) and age-, sex-, and ethnicity-matched controls (n = 38). The relationship between plasma pPE and PE levels with clinical symptoms was also examined.	Plasma pPE levels were significantly reduced in patients with BD, particularly in BD type 1, compared to healthy controls. Plasma PE levels were also significantly lower in BP type I than controls and BD type 2. There were no significant correlations between plasma pPE or pPC levels with depression or manic symptoms.
	Ghosh et al. (2017)	Phospholipids PE and PC were quantified in white matter adjacent to the dorsolateral prefrontal cortex in patients with BD (n = 34), SCZ (n = 35), and controls (n = 35) using HPLC.	Levels of PC were significantly lower in subcortical white matter in BD *post-mortem* samples compared to controls, but not statistically significant in patients with SCZ. No change in PE or PC was observed in prefrontal cortex or hippocampus.
	Tabarés-Seisdedos et al. (2006)	Analysis of two genomic regions: lissencephaly critical region (chromosome 17p) encompassing the LIS1 gene and which is involved in human lissencephaly; and the genes related to the platelet-activating factor (PAF), functionally related to LIS1, in patients with SCZ (n = 52), BD I (n = 36), and controls (n = 65). Groups were also assessed for neuropsychological battery.	14.8% patients with SCZ or BD type I displayed genetic variations in either two markers implicated in lissencephaly or in the PAF receptor gene, and these individuals performed worse in the Wisconsin Card Sorting Test.
Depression/anxiety	Brydges et al. (2022)	Melancholia and anxious distress were characterized in patients (n = 158) who participated in the Predictors of Remission to Individual and Combined Treatments study. Biochemical profiles were also determined by targeted metabolomics analysis of serum samples.	Melancholia severity was significantly inversely correlated with several PCs, including lyso-PC. Anxious distress severity inversely correlated with both saturated and polyunsaturated free fatty acids, SM, as well as several amino acids and bile acids.
	Dorninger, Gundacker et al. (2019)	Examined the behavioral phenotype of ether lipid-deficient mice GNPAT *knockout* (KO) as it relates to human depression and anxiety.	GNPAT KO mice showed strongly impaired social interaction, nestlet shredding, and marble burying. In addition, KO mice displayed behavioral patterns of anxiety and depression in the elevated plus maze test, light/dark box test, and forced swim test.
	Knowles et al. (2017)	Mass spectrometry lipidomic analysis of people with major depression disorder (MDD) (n = 567) from 37 extended pedigrees, including analysis of 23 biologically distinct lipid classes and their shared genetic etiology with MDD.	Arachidonic acid-containing alkyl-PC and alkenyl-PC species had the largest endophenotype ranking value and genetic overlap with MDD determined by cluster analysis.
	Liu et al. (2016)	Non-targeted lipidomic analysis of differential lipids between MDD (n = 60) and healthy controls (n = 60) using ultra performance liquid chromatography coupled with quadruple time-of-flight mass spectrometry. Validation of changed lipid species was also performed (MDD n = 75; controls: n = 52).	Decreased plasma levels of ether PCs and PEs in patients with MDD. Levels of lyso-PC, lyso-PE, pPC, pPE, PI, and TG were significantly increased in MDD and correlated positively with depression severity. 1-O-alkyl-2-acyl-PE and SM significantly decreased in MDD and correlated negatively with depression severity.
	Liu et al. (2015)	Nontargeted metabolomics analysis of differential metabolites in plasma samples from first-episode drug-naïve patients with MDD (n = 60) and healthy controls (n = 59). Validation analysis was done using targeted metabolomics on the candidate metabolites in patients with MDD (n = 75) (including moderate and severe, and drug-naïve and drug-treatment) and healthy controls (n = 52).	Levels of acyl carnitines, ether phospholipids, and tryptophan were significantly decreased, whereas PC, PE, lyso-PC, and lyso-PE were markedly increased in the plasma of patients with MDD compared to healthy controls.
	Demirkan et al. (2013)	The relationships between 148 different plasma phospho- and sphingolipid species and depression/anxiety symptoms as measured by the Hospital Anxiety and Depression Scales and the Centre for Epidemiological Studies Depression Scale in a family-based study (n = 742).	The plasma SM 23:1/16:0 ratio was inversely correlated with symptoms of depression and anxiety. A similar trend was observed for plasma PC, particularly the PC 36:4/ceramide (CER) 20:0 ratio.
	Pettegrew et al. (2001)	Measured rat brain phospholipid levels after acute (n = 20/group) and chronic (n = 10/group) *myo*-inositol administration using nuclear magnetic resonance and quantitative high-performance thin-layer chromatography.	Chronic oral *myo*-inositol administration increased the rat brain PE Pls by 10% and decreased brain PE by 5%, thereby increasing the ratio of PE Pls/PE by 15%.
Autism spectrum disorders	Zandl-Lang et al. (2022)	LC-MS/MS lipidomic analysis of the CSF and plasma composition of patients with Rett syndrome (RTT) (CSF: n = 7; plasma: n = 13) compared to healthy controls (CSF: n = 13; plasma: n = 18).	Levels of PE, PC and SM species were decreased in CSF of patients with RTT compared to controls. Various ether-linked phospholipids including PE Pls were also decreased in CSF of patients with RTT compared to controls. The lipidome of plasma was unchanged.
	Dorninger, König et al. (2019)	Behavioral tests (wheel, open field, social interaction, contextual fear conditioning) were performed using GNPAT KO mice (n = 6).	GNPAT KO mice displayed hyperactivity and impaired social interactions. GNPAT KO mice also had significantly reduced

(*continued on next page*)

Table 1 (*continued*)

Neurodegenerative/ Neuropsychiatric disorder	Reference	Study Design	Main Findings/Outcomes
			ether lipids, which may have contributed to the increased metabolite/monoamine neurotransmitter ratio in the brain.
	Thomas et al. (2010)	Intraventricular infusion of propionic acid (PPA) in rats (n = 6) was evaluated for alterations in brain lipids associated with autism-like behavioral changes.	PPA-infused rats had significantly reduced total pPE brain levels and significantly increased locomotor activity (total distance travelled and stereotypy).
	Wiest et al. (2009)	Lipid profiling was performed on fatty acids of plasma samples obtained from children of the Childhood Autism Risk from Genetics and the Environment study.	From plasma samples, children with autism had significantly decreased DHA, PE and PC.
	Bell et al. (2004)	Eritrocytes fatty acid composition was measured in patients with classical autism/Asperger's syndrome (ASP), regressive autism, or controls.	Patients with autism and ASP had significantly higher fatty acid deficiency scores compared to controls based on questionnaire results. Patients with both regressive autism and ASP had a significantly higher AA/eicosapentaenoic acid (EPA) ratio compared to controls. Patients with both regressive autism and classical autism/ASP had significantly higher concentrations of erythrocyte type IV phospholipase A2 compared to controls.

Abbreviations: AA: arachidonic acid; AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; APP: apolipoprotein; ASP: Asperger's syndrome; BD: bipolar disorder; CER: ceramide; CHR: clinical high risk; CSF: cerebrospinal fluid; DAG: diacylglycerols; DHA: docosahexaenoic acid; ED: early dementia; EPA: eicosapentaenoic acid; GNPAT: glyceronephosphate O-acyltransferase; HPLC: high-performance liquid chromatography; KO: *knockout*; LC-MS: liquid chromatography-mass spectrometry; MCI: mild cognitive impairment; MDD: major depressive disorder; MS: multiple sclerosis; OD: old dementia; PCOOH: phosphatidylcholine hydroperoxide: Pls: plasmalogens; PPA: propionic acid; SCZ: schizophrenia; PUFA: poly-unsaturated fatty acid; PC: phosphatidylcholine; PE: phosphatidylethanolamine; PI: phosphatidylinositol; pPC: choline plasmalogens; pPE: ethanolamine plasmalogens; PS: phosphatidylserine; PANSS: positive and negative syndrome scale; PAF: platelet-activating factor; PI: phosphatidylinositol; RTT: Rett syndrome; TAG: triacylglycerol; WMS-R: Wechsler Memory Scale – Revised.

2.10.1. Alzheimer's disease

In the last two decades, compelling evidence has highlighted the implication of Pls deficiency in AD pathology (Chew et al., 2020; Wood, 2012). A pioneering study in this field comes from Ginsberg et al. (1995) who firstly showed a significant deficiency of pPE in *post-mortem* brain samples (mid-temporal cortex) of patients with AD (Ginsberg et al., 1995). In the last years, subsequent studies have demonstrated that depleted levels of Pls are not only found in *post-mortem* brain samples from patients with AD, but also in plasma, erythrocytes and cerebrospinal fluid of living patients with AD (Su et al., 2019). Of note, a consistent finding across studies is the reduction of Pls contents measured across different types of AD specimens (Chew et al., 2020; Su et al., 2019). Interestingly, in the brain, Pls abnormalities have been detected only in AD-related primary sites of neurodegeneration, such as the hippocampus, temporal cortex and frontal cortex, but not in the cerebellum of patients with AD (Ellison et al., 1987; Ginsberg et al., 1995; Wood et al., 2015a). Also, reductions in some Pls species and their brain regional distributionhave been specifically associated with different stages of severity of the disorder. For example, a temporal lobe white matter decrease in pPE levels was observed in the early stage of the disease, while a dramatic reduction of pPE in the gray matter of the same region showed a positive progressive correlation with disease severity in very mild to severe cases (Goodenowe et al., 2007; Han, 2005; Han et al., 2001). There is also consistent evidence showing that DHA is closely related to brain functions impaired in AD (Song et al., 2016; Wood et al., 2010a). In this context, previous studies reported the decreased levels of Pls-containing DHA or free DHA in the brain, liver and plasma samples from patients with AD (Astarita et al., 2010; Chu et al., 2022; Wood et al., 2010b), and described strong correlations between these findings and the degree of cognitive deficit manifested by these patients (Chu et al., 2022; Su et al., 2019).

The cause of Pls deficiency in the AD brain is unclear. It is also not known whether the decrease of Pls in patients with AD is a cause or consequence of the disease. Some possible mechanistic explanations have been proposed, including peroxisome dysfunction and neuroinflammation-induced abnormal oxidative stress (Chew et al., 2020; Senanayake and Goodenowe, 2019). Indeed, peroxisome dysfunctions have been described in the brain and liver of individuals living with AD (Grimm et al., 2011; Kou et al., 2011). Increased levels of VLCFAs (behenic acid C22:0, lignoceric acid C24:0 and hexacosanoic acid C26:0), mainly metabolized in peroxisomes, were correlated with deficient Pls, mainly pPC and pPE, contents in the *post-mortem* brain of patients with AD, as well accompanied by degenerative structural changes in neuronal peroxisomes (Kou et al., 2011). Oxidative stress is a well-known hallmark of the disorder (Tamagno et al., 2021). As established, Pls are very susceptible species to oxidative stress and may act as scavengers to protect other lipids and lipoproteins from oxidative damage (Senanayake and Goodenowe, 2019). Increased secondary by-products of lipid peroxidation have been reported in the AD brain, which indicates direct damage to lipidic membranes, and potentially Pls. Among the oxidized lipids, isoprostanes (IsoPs) are derived from AA-containing species, while neuroprostanes (NeuroP) are derived from DHA and eicosapentaenoic acid (EPA) species (Bradley-Whitman and Lovell, 2015). Several IsoPs were found elevated in CSF and in the *post-mortem* frontal and temporal cortices of patients with late-stage AD (LAD) compared to age-matched controls (Pratico et al., 1998; Reich et al., 2001; Yao et al., 2003). Elevated IsoPs in CSF were associated with cortical atrophy as rated by Braak staging scores, and apolipoprotein E 4 (APOE) genotype (Montine et al., 2002, 1999). Similarly, levels of NeuroPs were elevated in the temporal cortex and occipital cortex of individuals with LAD (Musiek et al., 2004; Nourooz-Zadeh et al., 1999; Reich et al., 2001). Comparing both groups of oxidized lipids, higher levels of NeuroP isomers were found within the same cohort suggesting that DHA-containing lipids are preferentially oxidized in the AD brain, also offering a putative cause for its depleted levels in AD pathology (Nourooz-Zadeh et al., 1999; Reich et al., 2001).

Additionally, abnormal PAF signaling has been elected as a potential biomarker for AD and a target closely related to inflammation involved in this disorder (Dorninger et al., 2020). Previously, it was shown that an increased PAF binding to platelets was positively correlated with the degree of cognitive impairment in patients with AD (Hershkowitz and Adunsky, 1996). Also, individuals with higher platelet response and PAF levels were found to have a higher risk of dementia in late life during a 20-year follow-up, reinforcing the role of platelet function in conferring AD risk (Ramos-Cejudo et al., 2022). More recently, a pathobiological link between PAF and neuroinflammation involved in AD was provided by Liu et al. (2022a) and Liu et al. (2022b). The authors screened the Gene Expression Omnibus database and found that between the highly

differentially expressed genes, PAF-R was the most promising biomarker upregulated in brain tissues, peripheral blood, and cerebrospinal fluid of patients with AD. PAF-R could mediate the exaggerated inflammatory responses of microglia against Aβ oligomers through the upregulation of IL6-STAT3 pathway (Liu et al., 2022a; Liu et al., 2022b).

Taken together, these findings indicate that the depletion of Pls and generation of lipid mediators, such as oxidized lipids and PAF, are putative biological mechanisms behind AD neuropathology (Dorninger et al., 2020; Su et al., 2019). Considering other biological hallmarks of the disorder, such as peroxisomal dysfunction and oxidative stress, an intricated relationship between Pls and these factors is suggested, where possibly one factor positively feedbacks onto the other, favoring the disease progression.

2.10.2. Parkinson's disease

PD is a neurodegenerative disease characterized by the presence of fibrillar aggregates of α-synuclein and the associated loss of dopaminergic neurons within the basal ganglia (Poewe et al., 2017). PD progression is associated with dysfunctional mitochondria, increased oxidative stress, and neuroinflammation (Borsche et al., 2021; Subramaniam and Chesselet, 2013). Although the body of evidence is not as extensive as for AD, there is convergent data supporting the role of Pls deficiency in PD neurobiology. Indeed, a study conducted by Fujino et al. (2020) compared the baseline Pls levels in the plasma of patients with mild cognitive impairment, mild to severe AD, and late-stage PD. They showed the deficiency in Pls levels was higher in specimens from PD compared to all the other conditions. Also, a significant improvement in cognitive function and other clinical symptoms was associated with higher blood Pls levels among patients with PD (Fujino et al., 2020). In addition, a longitudinal study conducted by the same research group assessed the blood Pls levels and clinical symptoms of PD over 28 weeks. They showed that oral supplementation of Pls (1 mg/day) increased pPE levels in the plasma and erythrocyte membrane of these patients, which was paired with a significant reduction in the severity of PD symptoms (Mawatari et al., 2022). Also, it was reported that patients with PD, AD and coronary artery disease shared the same pattern of Pls changes in their erythrocyte membrane, characterized by reduction of pPE and PC, and increase of SM levels (Mawatari et al., 2022). Regarding the analysis of *post-mortem* brain samples, only one study showed a marked reduction of Pls levels, especially species containing DHA- and AA-Pls , along with reduction in cerebrosides and sulfatides lipid species, in the purified lipid rafts of the frontal cortex from patients with early motor stages of PD and incidental PD (Fabelo et al., 2011).

2.10.3. Multiple sclerosis

MS is a chronic neurodegenerative disease that occurs at least partially due to the infiltration of autoreactive lymphocytes across the BBB, leading to localized inflammation, demyelination, axonal loss, and gliotic scarring (Podbielska et al., 2021). In MS, mitochondrial dysfunction contributes to neuroinflammation, likely via an oxidative stress related mechanism (Morris et al., 2015). While the Pls-specific literature surrounding MS is currently very limited, there was a recent characterization of the phospholipidome of plasma from patients with MS (in both remission and relapse phases) compared to healthy controls. MS samples showed a marked reduction in the PE, PC, pPE, ether-linked PE and ether-linked PC, with the lowest p-values for the following phospholipid species: PC(34:3), PC(36:6), PE(40:10) and PC(38:1) (Ferreira et al., 2021). Older evidence using *post-mortem* samples already showed reduced levels of pPE species in the white matter of demyelinating brain lesions (17 patients with MS and 1 with subacute sclerosing panencephalitis) compared to age-matched controls (Boggs et al., 1982). In accordance, increased PLA2 activity in the brain's white matter was also reported in *post-mortem* samples from patients with MS and in monkeys submitted to a demyelination model induced by B12 deficiency (Ansell and Spanner, 1968). Despite promising, the contribution of Pls to MS etiopathogenesis and progression, as well as their possible application as candidate biomarkers, should be further investigated in future studies.

2.10.4. Schizophrenia & psychosis

In schizophrenia (SCZ), there is accumulating evidence that abnormal phospholipid and fatty acid structure or metabolism may influence its pathophysiology. In the clinical setting, significantly lower plasma pPC and pPE levels were reported in drug-naïve patients experiencing first psychotic episodes and in patients with recurrent disease compared to healthy controls (Kaddurah-Daouk et al., 2012), suggesting that this phenotype may appear at the onset of psychotic illness and after multiple psychotic relapses. In another study, lipidomic analysis of patients with SCZ compared to age-matched controls revealed a 23–45% decrease in both plasma pPC and pPE levels (Wood et al., 2015b). In platelets, pPE were also decreased while pPC were increased (Wood et al., 2015b). DHA levels were correspondingly decreased in both plasma and platelets of patients with SCZ (Wood et al., 2015b). Similarly, Dickens et al. (2021) investigated the serum levels of lipids related to adverse clinical outcomes in individuals at clinical high risk for psychosis (CHR). At baseline, CHR individuals who later developed psychosis presented lower levels of ether phospholipids than non-CHR individuals, suggesting that lipidomic abnormalities arise before the onset of psychosis. In addition to blood cells, unbiased metabolic profiling revealed reduced levels of several Pls species and PCs in fibroblasts from patients compared to healthy controls, particularly under stressful conditions, suggesting that SCZ disease phenotypes can also be observed in peripheral cells (Huang et al., 2017). Tessier et al. (2016) performed lipid data analysis using liquid chromatography-tandem mass spectrometry (LC-MS/MS) of erythrocyte membranes from blood samples of SCZ patients and identified a significant decrease in pPE. This was observed particularly in individuals presenting with low SM erythrocyte content, which also correlated with more severe psychotic symptoms, disorganized thoughts and cognitive impairment, as measured using the positive and negative syndrome scale (PANSS), the Continuous Performance Test, Salience Attribution Test, and Wisconsin Card Sorting Test. Furthermore, reduced erythrocyte Pls levels were associated with a compensatory PE increase. These authors speculated that this membrane lipid abnormality may contribute to an aberrant presynaptic dopamine signaling in SCZ. Li et al. (2022) also performed LC-MS/MS to quantify erythrocyte membrane lipids and found significantly reduced pPE and pPC in patients with SCZ compared to healthy controls. In addition, there was an increased accumulation of membrane oxidized lipids. Further investigation revealed that the excessive oxidative stress may cause activated phospholipid remodeling, as observed by increased PLA2 and lysophosphatidylcholine acyltransferase (LPCAT) gene expression, thus impairing membrane lipid homeostasis (Li et al., 2022). Wang et al. (2021) also used a targeted LC-MS/MS approach to detect alterations in serum levels of over one hundred lipid metabolites, including Pls species, from patients with SCZ and healthy controls. Overall, patients with SCZ had a significantly higher total serum level of free fatty acids, but lower lyso-PCs, pPC, and pPE, compared to healthy controls, which is consistent with other SCZ studies showing reduced blood Pls (Kaddurah-Daouk et al., 2012; Wang et al., 2022; Wood et al., 2015b). Wang et al. (2021) further demonstrated that a decline in Pls is a characteristic of the disease and not a marker varying with treatment or recurrent psychotic episodes. Levels of glycosphingolipids and pPC, structural components of myelin, were significantly elevated in *post-mortem* frontal cortex samples of patients with SCZ and in the hippocampus of G72/G30 transgenic mice (model of SCZ-like symptoms) (Wood et al., 2014; Wood and Holderman, 2015). Additionally, one preclinical study investigated the role of PAF-R in the phencyclidine (PCP)-induced mouse model of SCZ and found that PAF-R upregulation was associated with exacerbated SCZ-like behaviors (Tran et al., 2018). Another study in patients with SCZ and bipolar disorder (BD) suggested that genetic variations in the PAF-R gene may predict the severity of the prefrontal cortex-associated cognitive deficits in both

disorders (Tabarés-Seisdedos et al., 2006).

2.10.5. Bipolar disorder

ER stress and mitochondrial dysfunction have been implicated in BD, although there is limited evidence regarding the role of Pls specifically. One study investigated whether familial BD is associated with peroxisomal dysfunction, but no significant alterations in peroxisomal biomarkers were observed to correlate with symptom severity (McNamara et al., 2016). In a recent study, Ogawa et al. (2020) found differential ethanolamine phospholipid profiles in patients with BD type 1 (BD I; associated with an episode of mania) and BD type 2 (BD II; associated with a hypomanic episode, which is less severe than a full manic episode), with reduced plasma pPE and PE levels being detected in patients with BD I compared to healthy controls and patients with BD II. However, no significant correlations were found between pPE or PE and specific depression or mania symptoms (Ogawa et al., 2020). In a *post-mortem* study, prefrontal white matter PC content was significantly lower in both patients wth SCZ and BD, though total levels of analyzed Pls did not differ significantly among the control, SCZ and BD groups (Ghosh et al., 2017). The authors noted potential confounding demographic variables, such as alcohol use and lifetime antipsychotic dose, however, which were negatively correlated with the Pls levels (Ghosh et al., 2017). Another study found no significant difference in phospholipids and fatty acids composition in the dorsolateral cortex of patients with SCZ, BD and controls (Beasley et al., 2020).

2.10.6. Depression & anxiety

Multi-omic studies have also been conducted for major depressive disorder (MDD) aiming to improve biomarker discovery. Through non-targeted metabolomics, Liu et al. (2015) identified a reduction of several ether-bonded phospholipid species in the plasma of patients with MDD compared to matched controls. In particular, the authors noted a decrease in alkyl-acyl PC and alkyl-acyl PE, which are important for Pls synthesis (Liu et al., 2015). Another study found an inverse correlation between symptoms of depression and anxiety and levels of PC O 36:4, an alkyl-acyl PC and potential target for PLA2 (Demirkan et al., 2013). Consistent with these findings, a study by Knowles et al. (2017) demonstrated a shared genetic etiology between MDD and ether-linked PC species containing AA, suggesting that the AA inflammation pathway could serve as a potential diagnostic marker and/or treatment for MDD. This study also found in samples from individuals with a familial history of MDD that the ether-PC lipid class had the largest endophenotype ranking value, while further cluster analysis revealed that species containing AA had the greatest degree of genetic overlap with MDD. A recent study by Brydges et al. (2022) found an inverse correlation between ether-linked PCs and PEs in serum samples and depression symptoms, mainly melancholia. In contradiction, however, another non-targeted lipidomics study found that lyso-PC, lyso-PE, PC, and PE were significantly increased in the plasma of patients with MDD (Liu et al., 2016).

In placebo-controlled studies, administration of oral inositol revealed beneficial effects in MDD, panic disorder, and obsessive-compulsive disorder (Mukai et al., 2014). A pre-clinical study investigating the effects of myo-inositol oral supplementation (12–18 g/day) on membrane phospholipid alterations also showed increased pPE in the rat brain (Pettegrew et al., 2001), suggesting a potential mechanism by which antidepressants may act to increase vesicle fusion in the processes of synaptic transmission, hormone release, and membrane trafficking. Lipid deficiencies were reported in other mouse studies, leading to severe disruptions of neurotransmitter homeostasis, and associated behavioral abnormalities. For instance, a study by Dorninger, Gundacker et al. (2019) showed that Pls-deficient mice,GNPAT) *knockout,* strongly displayed features associated with human mood disorders, including impaired social interaction as well as nestlet shredding and marble burying, indicating disturbed execution of inborn behavioral patterns. GNPAT *knockout* mice also displayed a poorer passive coping strategy in the tail suspension and forced swim tests (Dorninger et al., 2019).

2.10.7. Autism spectrum disorders

Recent evidence further suggests the involvement of peroxisomal function and ether lipids in neurodevelopmental disorders such as autism spectrum disorders (ASD). Earlier studies have reported reduced levels in Pls species and DHA in erythrocyte phospholipids of subjects with autism and Asperger's syndrome (Bell et al., 2004; Wiest et al., 2009). These studies in the clinical setting have been further supported by findings in rodent models. Intraventricular infusions of propionic acid (PPA) was shown to produce brain and behavioral changes associated with ASD. Thomas et al. (2010) found that PPA resulted in increased locomotor activity (total distance travelled and stereotypy) along with reduced levels of pPE in the rat brain. Pls-deficient mice (GNPAT *knockout*) showed reduced release of norepinephrine upon high-intensity stimulation in the hippocampal and cortical regions (Dorninger et al., 2019) . Pls deficiency in these animals further manifested as multiple neurobehavioral deficits, such as increased stereotypy, impaired social interaction, and abnormal marble burying (Dorninger et al., 2019a,b) . Altered phospholipid metabolism was also reported in patients with the neurodevelopmental disorder Rett syndrome . Specifically, decreased levels of Pls in the CSF, but not in the plasma, were found in patients with Rett syndrome (Zandl-Lang et al., 2022).

2.11. Plasmalogens replacement therapy as a useful approach to recover the debilitating symptoms of ME/CFS and post-COVID-19 syndromes

As above-mentioned, compelling literature posits that depletion of the content of Pls and derived molecular species represents a common biological substrate between several metabolic and neurodegenerative disorders (Paul et al., 2019b). There is also convergent literature reporting Pls depletion as an underlying biological factor for both COVID-19 and ME/CFS pathogenesis (Che et al., 2022; Pike et al., 2022; Snider et al., 2021). Based on this, it is plausible that therapies centered on the replacement of these lipid species could provide promising therapeutic strategies for these disorders (Bozelli and Epand, 2021). Based on this, a modern and innovative therapeutic approach that started to emerge is membrane lipid replacement. A replacement therapy is a pharmacological intervention aimed at restoring the levels of a biological molecule that is deficient in some pathophysiological conditions (Sultanov et al., 2022). PRT is a type of membrane lipid replacement strategy that relies on the use of small molecules to increase Pls biosynthesis or availability with the final goal of improving health outcomes (Bozelli and Epand, 2021).

The first PRT attempt was through dietary supplementation of Pls and their precursors, mainly, alkylglycerols (AG), intermediates of the Pls biosynthesis pathway, found to be enriched in marine animals (e.g., shark liver, krill, mussels, sea squirt/urchin/cucumber, and scallops) as well as in land animal meat (e.g., pork, beef, and chicken) (Iannitti and Palmieri, 2010; Paul et al., 2021a; Pugliese et al., 1998). This strategy offers several advantages, including convenient oral administration as dietary intake, without reported toxicity in humans even at high doses. Also, the AG from marine organisms have a lower omega-6/omega-3 fatty acid ratio than livestock ones, being proposed as a stable source of omega-3 fatty acids (Deniau et al., 2010; Paul et al., 2021b; Zakrzewska et al., 2021). However, despite these advantages, the decreased bioavailability and the enormous amount of raw material required to reach therapeutical doses for clinical use make it impractical (Bozelli and Epand, 2021).

Purified or synthetic compounds are also an attractive alternative to implement PRT as they can be administered at a high dosage. Synthetic AG of different chain lengths have been used, the most common ones being 1-O-hexadecyl-sn-glycerol (HG, 16:0-AG), 1-O-octadecyl-sn-glycerol (OG, 18:0-AG), and 1-O-octadecenyl-sn-glycerol (OeG, 18:1-

AG) (Das and Hajra, 1988; Paltauf, 1972). In mammals, oral administration of purified Pls shows an extensive breakdown in the intestinal mucosal cells, while administration of AG leads to complete absorption by the intestine without cleavage of the ether bond, likely because the vinyl-ether bond in plasmalogens is more acid/oxidation labile than the ether bond in AG. In the intestinal mucosal cells, the majority of AG is metabolized into Pls (specifically pPE), while a small fraction is transported to the liver, where it is catabolized (Iannitti and Palmieri, 2010).

More recently, another approach has been the use of synthetic analogs of Pls in PRT, e.g., PPI-1011 (an alkyl-diacyl plasmalogen precursor with DHA at the sn-2 position), PPI-1025 (an alkyl-diacyl precursor of Pls with oleoyl at the sn-2 position), and PPI-1040 (a pPE analog with a proprietary cyclic PE head-group) (Fallatah et al., 2019; Miville-Godbout et al., 2017; Wood et al., 2011). They are bioavailable in rodents and lead to an increase in pPE levels in circulation. Also, some of their metabolites can cross both the blood-retina and the BBB, circumventing a major problem of CNS penetrance with most previous PRT strategies (Wood et al., 2011).

The most direct evidence of PRT benefits comes from animal models of peroxisomal dysfunction. For instance, in the mouse models of rhizomelic chondrodysplasia punctata type 1 (RCDP) induced by GNPAT and Pex7 *knockout*, PRT using synthetic AGs, such as oleoyl glycerol (OG), and novel Pls synthetic analogs, such as PPI-1040, were able to replenish the depleted levels of pPE in several organs, tissues and fluids, such as plasma, erythrocytes, liver, small intestine, skeletal muscle and heart, as well as to alleviate the progression of neurodegenerative changes, such as cognitive impairment and retina degeneration (Brites et al., 2011; Fallatah et al., 2019; Malheiro et al., 2019). Based on this

Table 2
Plasmalogen abnormalities in models of neuroinflammation and glia proinflammatory reactivity.

Authors	Plasmalogen Intervention	Plasmalogen Source	Organism or Cell Model	Disease Model	Main Findings
Gu et al. (2022)	Intragastric administration of Pls in water (300 mg/kg), once a day, 5 days per week for 2 months.	Ascidian	Aged female C57BL/6 J mice (starting at 16 months of age)	Aging model	Pls-fed intervention improved memory and cognition, alleviated age-associated hippocampal synaptic loss, and promoted synaptogenesis and synaptic vesicles formation. Pls treatment also enhanced hippocampal synaptic plasticity and neurogenesis and normalized dystrophic microglia and inflammatory cytokine expression.
Hossain et al. (2018)	Oral ingestion of Pls (0.1 μg/ml and 10 μg/ml) in normal drinking water. Water was replaced every two days and continued for 3 months followed by lipopolysaccharide (LPS) injection.	Chicken breast meat	Male C57BL/6 J mice (7 months old)	Chronic LPS injection model	Oral intake of Pls inhibited LPS-mediated memory loss associated with a reduction of glial reactivity and accumulation of amyloid beta (Aβ) proteins in the hippocampus.
Ifuku et al. (2012)	Intraperitoneal injections of Pls (20 mg/kg) after daily LPS injections for 7 days.	Chicken breast meat	Male C57BL/6 J mice (10 months old)	LPS injection model of Alzheimer's disease (AD) pathology	Administration of Pls after daily LPS injections attenuated LPS-mediated glial reactivity and accumulation of Aβ proteins. Co-administration of Pls also suppressed the LPS-mediated reduction of Pls in the prefrontal cortex and hippocampus.
Youssef et al. (2019)	Cells were treated with Pls (1 μg/ml) in fetal bovine serum (FBS) 2% Dulbecco's Modified Eagle Medium (DMEM) for 6 h followed by LPS treatment (1 μg/ml).	Scallop	MG6 and BV2 mouse microglial cell lines	LPS-challenged microglial cell lines *in vitro*	Pls inhibited nitric oxide production in LPS-treated microglial cells lines. Polyunsaturated DHA-Pls were more effective than monounsaturated oleic acid-Pls. Pls also blocked the activation of nuclear factor kappa B (NF-kB), p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) pathways.
Ali et al. (2019)	Mice were subjected to Pls drinking (0.1 μg/ml) for 15 months. BV2 cells were treated with Pls (5 μg/ml) for 6 h followed by LPS (1 μg/ml) for 3 and 6 h.	Scallop	BV2 microglial cell line and primary mouse microglial cells; AD pathology mouse model (APP/PS1/Tau) (18 months old); C57BL/6 J mice (2 and 18 months old)	LPS-challenged microglial cell lines *in vitro*; Aging and AD pathology model	Pls inhibit LPS-mediated Toll-like receptor (TLR)4 endocytosis and the downstream caspases activation. *Knockdown* of GNPAT enhanced TLR4 endocytosis and caspase-3 activation, resulting in pro-inflammatory cytokine expression. Endocytosis of TLR4 was enhanced in the cortex of aged and AD pathology mice, while Pls drinking in AD pathology mice significantly reduced TLR4 endocytosis.
Sejimo et al. (2018)	BV2 cells were pretreated with Pls (5 μg/ml) for 12 h. C57BL/6 J mice were subjected to Pls drinking (1 μg/ml) for 2 months and LPS was injected daily for one week. 3 Tg mice were given Pls drinking (1 μg/ml) for 15 months before euthanasia.	Scallop	BV2 cells; AD model Tg mice (APP/PS1/Tau) (3 months old); male C57BL/6 J mice; human *post-mortem* AD brain tissue	Neuroinflammation model and AD pathology mice; human *post-mortem* AD brain tissue	Pls attenuated microglial expression of LPS-mediated PKCδ in neuroinflammation and AD pathology murine brain. Human *post-mortem* AD brains had increased levels of PKCδ. Pls inhibited p38 MAPK and JNK protein expression in microglia.
Rubio et al., (2018)	RAW.108 cells incubated with lyso-Pls (10 μM) for 10 min before phagocytosis was analyzed.	Exogenous lyso- Pls	RAW264.7 macrophage-like cells and Pls-deficient RAW.108 cells	Macrophage-like cells *in vitro*	Pls-deficient cells had reduced capacity to phagocytose opsonized zymosan particles. Incubation with lyso-Pls resulted in an increased phagocytic ability.

Abbreviations: Aβ: amyloid beta; AD: Alzheimer's disease; DMEM: Dulbecco's Modified Eagle Medium; FBS: fetal bovine serum; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; NF-kB: nuclear factor kappa B PKCδ: protein kinase C-delta; Pls: plasmalogens; LPS: lipopolysaccharide; TLR4: Toll-like receptor 4.

and additional clinical findings, in 2019 the Food and Drug Administration granted PPI-1040 orphan drug designation for the treatment of RCDP.

Further, considering a potential common pathophysiological basis involving neuroglial dysfunction for both ME/CFS and the long-term neuropsychiatric consequences of COVID-19, especially the PVFS, there is compelling *in vitro* and *in vivo* evidence showing the ability of PRT to protect neurons and glial cells against multiple injury models (Farooqui and Horrocks, 2001a, 2001b, 2001c; Hossain et al., 2013). In this context, it has been proposed that Pls halt neuroinflammation by modulating microglial responses (Ifuku et al., 2012; Hossain et al., 2018; Sejimo et al., 2018; Ali et al., 2019; Youssef et al., 2019). Of note, Hossain et al. (2017) demonstrated that several inflammatory stimuli, including PAMPs such asLPS and polyinosinic:polycytidylic acid (poly I:C), and the pro-inflammatory cytokine IL1β, reduced the content of Pls in murine microglial cells and in cell lines by a mechanism dependent on nuclear factor kappa B (NF-kB) activation-induced c-Myc gene suppression of the Pls-synthesizing enzyme GNPAT. Similarly, in mice, environmental contingencies associated with neuroinflammation, such as systemic LPS injection, chronic restraint stress, and aging, also induced the same profile of glial reactivity and suppression of Pls synthesis in the hippocampus and frontal cortex (Hossain et al., 2017). Interestingly, direct blockade of Pls synthesis by GNPAT *knockdown* in the murine cortex also induced a similar pro-inflammatory microglial

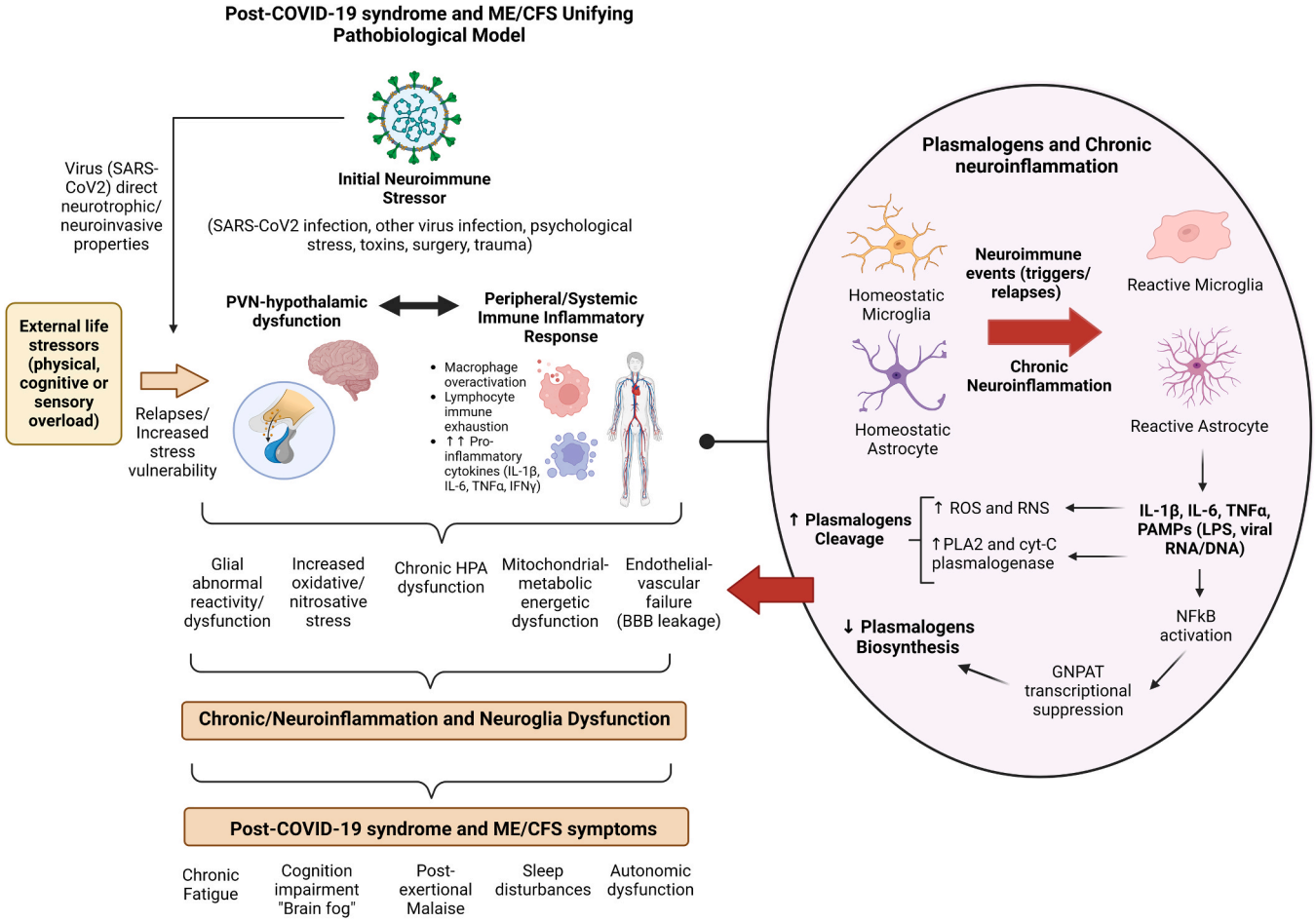

Fig. 3. Unifying bio-pathological model for post-COVID-19 syndromes and ME/CFS, and implications of chronic inflammation for plasmalogens levels. In the left panel, we propose an unifying model to explain both the post-COVID-19 and ME/CFS onset and progression toward a chronic sustained illness with relapse phases. Following an initial neuroimmune stressor, such as SARS-CoV-2 acute infection, a systemic inflammatory response is triggered, with the increased release of pro-inflammatory cytokines, recruitment of peripheral macrophages and lymphocytes, and activation of neural afferents at the sites of inflammation. All these mechanisms communicate with the central nervous system (CNS) via the circumventricular organs and through blood-brain-barrier (BBB) leakage induced by the endothelial-vascular inflammation. These inflammatory stress signals are processed mainly in the stress center of the hypothalamus, the paraventricular nucleus (PVN). The PVN activates other related brain areas, such as those of the limbic system, as well as feedbacks to the periphery via the hypothalamic–pituitary–adrenal (HPA) axis. In this model, the initial neuroimmune events together with daily life stressors induce a state of chronic CNS inflammation and neuroglial dysfunction (mainly affecting astrocytes and microglia) in the PVN and limbic system, which leads to a wide range of debilitating neurological symptoms, such as chronic fatigue, "brain fog" and post-exertional malaise (PEM). The systemic physiology is also chronically affected through important altered cellular functions, such as mitochondrial energetic dysfunction, increased oxidative and nitrosative stress, and endothelial vascular failure (associated with chronic BBB impairment). In the right panel, we summarize the current evidence that CNS inflammation induced by chronic stress as well as bacterial and viral PAMPs is able to induce the transcriptional activation of nuclear factor kappa B (NF-kB), which promotes through a Myc-related mechanism the genomic suppression of the glyceronephosphate O-acyltransferase (GNPAT) enzyme involved in plasmalogens (Pls) biosynthesis. Also, the increased production of reactive oxygen species (ROS) and potential stimulation of phospholipases, especially phospholipase A2 (PLA2), induced by pro-inflammatory cytokines, increased the cleavage of Pls. These two main mechanisms together could contribute to the depletion of Pls observed in several CNS disorders, as well as in ME/CFS and acute COVID-19 patient samples. This illustration was generated using Biorender (©BioRender). Abbreviations: BBB: blood-brain-barrier; CNS: central nervous system; COVID-19: Coronavirus disease 2019; GNPAT: glyceronephosphate O-acyltransferase; Pls: plasmalogens; ROS: reactive oxygen species; ME/CFS: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; NF-kB: nuclear factor kappa B; PAMPs: pathogen associated molecular patterns; PVN: paraventricular nucleus; HPA: hypothalamic–pituitary–adrenal; PEM: post-exertional malaise; PLA2: phospholipase A2.

transformation and increased the expression of pro-inflammatory cytokines (Hossain et al., 2017). Additionally, previous studies reported that treatment with different Pls formulations (e.g., scallop, chicken skin and ascidian derived) inhibited *in vitro* microglial pro-inflammatory reactivity induced by LPS, and related pro-inflammatory signaling pathways, such as NF-kB, JNK-p38 MAPK and TLR-4-induced caspase-3 activation (Ali et al., 2019; Youssef et al., 2019). A similar protective effect was found with Pls supplementation in a mouse model of systemic LPS-induced neuroinflammation and Aβ plaques accumulation (Hossain et al., 2018; Ifuku et al., 2012; Sejimo et al., 2018) (for further details, please see Table 2). Important evidence was recently added by Gu et al. (2022) showing that 2 months of ascidian-derived Pls intragastric administration to aged female C57BL/6 J mice reversed the aging-associated cognitive deficits, synaptic loss and promoted synaptogenesis and neurogenesis in the hippocampus. Interestingly, these findings were associated with the ability of Pls to reduce aging-induced microglial reactivity and neuroinflammation (Gu et al., 2022). Taken together, this evidence points to the key role of Pls depletion in mediating neuroinflammation-induced behavioral and neuroglial pathology including microglial dysfunction and its outcomes on synaptic loss. It also highlights the promising application of PRT to mitigate the deleterious effects associated with aging, chronic stress, and systemic responses against microbial toxins. We summarize the main findings into a unifying model of neuroglial dysfunction for ME/CFS and potentially post-COVID-19 pathobiology with our current hypothesis of Pls deficiency for the genesis of both conditions in Fig. 3.

Besides these prominent glia modulatory and anti-inflammatory actions, complementary evidence also highlights the action of PRT in additional neural functions *in vitro* and *in vivo*. For instance, in primary neurons, chicken-derived pPE has anti-apoptotic properties by activation of PI3K/AKT and MAPK/ERK signaling pathways (Hossain et al., 2013). Likewise, EPA-enriched pPE also showed anti-apoptotic properties against oxidative stress-induced damage in primary cultured hippocampal neurons (Zhu et al., 2021). In a mouse model of AD pathology, oral administration or intraperitoneal injection of purified pPE promoted activation of the brain-derived neurotrophic factor/tropomyosin receptor B/cAMP response element-binding protein (BDNF/TrkB/CREB) signaling pathway and an inhibition of oxidative stress (Che et al., 2020). In addition, in a rat model of AD pathology induced by intracerebroventricular infusion of Aβ, oral administration of purified pPE led to an increase in plasma pPE levels, as well as improved the reference and working memory-related learning abilities (Yamashita et al., 2017). In a mouse model of PD pathology induced using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, oral administration of Pls synthetic precursors further increased pPE levels in serum, displayed neuroprotective and anti-inflammatory properties, reversed dopamine and serotonin loss, and showed an anti-dyskinetic activity (Miville--Godbout et al., 2016).

Despite the compellingbody of evidence indicating PRT benefits for neurodegenerative disorders, few studies have investigated PRT outcomes against the behavioral and cellular effects of chronic stress. In this context, Trofimiuk and Braszko (2011) demonstrated that supplementation with cod liver oil, a rich source of EPA and DHA-containing Pls, alleviates the negative impact of prolonged restraint stress (2 h/day, for 21 days) on spatial, working, and fear-related memory in male rats (Trofimiuk and Braszko, 2011). This is in line with several previous studies showing protective effects of omega-3 PUFAs supplementation on behavioral consequences (cognitive impairment, anxiety- and depression-like behavior) in animal models of chronic stress (Di Miceli et al., 2022; Hennebelle et al., 2014; Zhu et al., 2021). However, until now, few studies have directly investigated the potential of PRT strategies, particularly in treating stress-related disorders, such as mood and anxiety disorders.

In humans, PRT has been investigated in subjects with peroxisomal, neurodegenerative, and metabolic disorders. Two independent early studies of PRT conducted in humans showed that oral administration of the Pls synthetic analog OG to individuals with peroxisomal disorders, such as the RCDP, led to the restoration of erythrocyte pPE content and clinical (growth, muscle/motor tone, general state of awareness, liver function, and retinal pigmentation) improvement (Das et al., 1992; Holmes et al., 1987). Oral administration of scallop-purified pPE to individuals with mild AD and mild cognitive impairment did not show a significant difference from the control (placebo) group in primary (Mini mental state examination-Japanese, MMSE-J) or secondary (Wechsler Memory Scale-revised, WMS-R, Geriatric depression scale-short version-Japanese, GDSSV-J, and plasma erythrocyte pPE levels) outcomes (Fujino et al., 2017). However, in another study from the same research group, oral administration of scallop-purified PE-Pls to individuals with mild cognitive impairment, mild-to-severe AD, and PD led to significant increases in plasma and erythrocyte PE-Pls levels as well as improved cognitive performance (Fujino et al., 2020). Likewise, in subjects with mild forgetfulness, sea-squirt-purified pPE showed improved cognitive function as evaluated by visual and verbal memory scores (Fujino et al., 2017). Individuals with PD treated with scallop-purified pPE displayed increased pPE content in the plasma and erythrocyte membranes (Mawatari et al., 2020). Improvement was also noted in PD clinical symptoms (Mawatari et al., 2020). In individuals with metabolic syndrome and obesity, oral administration of shark liver oil-purified AG led to increased levels of pPE in plasma and circulatory white blood cells, as well as decreased the total cholesterol, triglycerides, and C-reactive protein contents in the plasma (Paul et al., 2021b).

In the context of ME/CFS and COVID-19 immunopathogenesis, despite shared features of Pls depletion, neuroinflammation and lipid metabolism dysfunction, PRT approaches were not yet tested in clinical samples or animal models of these conditions. Also, considering the putative pathophysiological interplay involving neuroglial dysfunction and neuroinflammation between ME/CFS and the development and progression of COVID-19-associated PVFS (Renz-Polster et al., 2022), PRT could represent a valuable therapeutic tool against this emerging health condition affecting millions worldwide.

3. Conclusions and perspectives

After the worldwide COVID-19 outbreak, the disease has proven to be a serious and multifactorial problem for both acutely ill and recovering patients. A significant number of post-COVID-19 patients experience debilitating symptoms, marked by fatigue, brain fog, and post-exertional malaise, which has led to the recognition of a new pathological entity generically named post-COVID-19 syndrome or PVFS (Pavli et al., 2021; Tate et al., 2022). Importantly, many of the clinical and pathological observations of this condition have overlap with those described in ME/CFS (Sukocheva et al., 2022). While promising antiviral and immunization strategies were developed to prevent and treat acute viral infection, they do not seem to significantly reduce the risk of post-COVID symptoms (Notarte et al., 2022), and no available therapeutic strategies have proven to be effective against these debilitating symptoms. This reflects the knowledge gap regarding the causes and mechanisms of this post-COVID-19 condition. Recent advances in the understanding of ME/CFS pathophysiology have led to the development of the neuroglial failure hypothesis as central to explain ME/CFS pathophysiology. This hypothesis proposes that a glial dysfunction, mainly of microglia and astrocytes, takes place in stress-responsive brain regions due to the abnormal integration of central and peripheral responses to neuroimmune stressors (Renz-Polster et al., 2022). In this context, recent convergent evidence has postulated that samples from patients with COVID-19 (Pike et al., 2022; Schwarz et al., 2021; Snider et al., 2021) and ME/CFS (Che et al., 2022) are marked by the depletion and/or altered metabolism of Pls. These Pls exert key physiological roles required for maintaining health at the organism, system, as well as cell and subcellular organelle levels. Also, Pls depletion has been proposed as a causative factor for the neuroinflammation and abnormal neuroglial reactivity involved in several neurodegenerative and neuropsychiatric

conditions (Paul et al., 2019a; Tremblay et al., 2022). PRT has a favorable safety profile and has shown promising benefits for neurodegenerative, metabolic and inflammatory conditions (Bozelli and Epand, 2021). Taken together, Pls are likely central in the mechanism of neuroinflammation and neuroglial dysfunction underlying chronic debilitating post-viral symptoms, including post-COVID-19 syndrome, while their therapeutic replacement may be key in treating these disorders.

Furthermore, future pre-clinical and translational research will be fundamental to identify the cellular and molecular mechanisms by which specific Pls species modulate the function of neuroglial cell, including microglia and astrocytes, across various contexts of health and disease. Determining the beneficial outcomes of restored Pls levels, notably through the administration of precursors, naturally derived and synthetic analogs of Pls, in combination with other nutraceuticals such as dietary antioxidants and multimodal lifestyle interventions (e.g., acting on stress resilience, thermoregulation, metabolism), is expected to be critical for the prevention, management, and treatment of multifactorial diseases including ME/CFS and post-COVID-19 syndromes.

Funding information

Marie-Ève Tremblay is a Tier 2 Canada Research Chair in *Neurobiology of Aging and Cognition*. Yuru Deng was supported by the National Natural Science Foundation of China (Grant No. 31670841) and Wenzhou Institute, University of Chinese Academy of Sciences (Grant No. WIUCASQD2019005). Adriano Chaves-Filho is supported by the Aspiration 2030 Postdoctoral Fellowship from the University of Victoria, Canada (2023-2025).

CRediT authorship contribution statement

AMC, OB, YD and MET conceived the ideas and drafted the manuscript to which all authors contributed. AMC and OB created the figures and tables. AA, YD and MET carefully revised the overall manuscript, tables, and figures. All the authors read and approved the final version of this manuscript.

Declaration of Competing interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Data Availability

Non applicable.

References

Acanfora, D., Nolano, M., Acanfora, C., Colella, C., Provitera, V., Caporaso, G., Rodolico, G.R., Bortone, A.S., Galasso, G., Casucci, G., 2022. Impaired vagal activity in long-COVID-19 patients. Viruses 14 (5), 1035. https://doi.org/10.3390/v14051035.

Aihara, M., Ishii, S., Kume, K., Shimizu, T., 2000. Interaction between neurone and microglia mediated by platelet-activating factor. Genes Cells 5, 397–406. https://doi.org/10.1046/j.1365-2443.2000.00333.x.

Akrout, N., Sharshar, T., Annane, D., 2009. Mechanisms of brain signaling during sepsis. Curr. Neuropharmacol. 7 (4), 296–301. https://doi.org/10.2174/157015909790031175.

Al Omran, A.J., Shao, A.S., Watanabe, S., Zhang, Z., Zhang, J., Xue, C., Watanabe, J., Davies, D.L., Shao, X.M., Liang, J., 2022. Social isolation induces neuroinflammation and microglia overactivation, while dihydromyricetin prevents and improves them. J. Neuroinflamm. 19 (1), 2. https://doi.org/10.1186/s12974-021-02368-9.

Alessenko, A.V., Bugrova, A.E., Dudnik, L.B., 2004. Connection of lipid peroxide oxidation with the sphingomyelin pathway in the development of Alzheimer's disease. Biochem. Soc. Trans. 32 (1), 144–146. https://doi.org/10.1042/bst0320144.

Ali, F., Hossain, Md.S., Sejimo, S., Akashi, K., 2019. Plasmalogens inhibit endocytosis of toll-like receptor 4 to attenuate the inflammatory signal in microglial cells. Mol. Neurobiol. 56 (5), 3404–3419. https://doi.org/10.1007/s12035-018-1307-2.

Allam, R.M., Al-Abd, A.M., Khedr, A., Sharaf, O.A., Nofal, S.M., Khalifa, A.E., Mosli, H.A., Abdel-Naim, A.B., 2018. Fingolimod interrupts the cross talk between estrogen metabolism and sphingolipid metabolism within prostate cancer cells. Toxicol. Lett. 291, 77–85. https://doi.org/10.1016/j.toxlet.2018.04.008.

Almsherqi, Z.A., 2021. Potential role of plasmalogens in the modulation of biomembrane morphology. Front. Cell Dev. Biol. 9, 673917 https://doi.org/10.3389/fcell.2021.673917.

Almsherqi, Z.A., Kohlwein, S.D., Deng, Y., 2006. Cubic membranes: a legend beyond the Flatland* of cell membrane organization. J. Cell Biol. 173 (6), 839–844. https://doi.org/10.1083/jcb.200603055.

Amunugama, K., Jellinek, M.J., Kilroy, M.P., Albert, C.J., Rasi, V., Hoft, D.F., Shashaty, M.G.S., Meyer, N.J., Ford, D.A., 2021. Identification of novel neutrophil very long chain plasmalogen molecular species and their myeloperoxidase mediated oxidation products in human sepsis. Redox Biol. 48, 102208 https://doi.org/10.1016/j.redox.2021.102208.

Anbukumar, D.S., Shornick, L.P., Albert, C.J., Steward, M.M., Zoeller, R.A., Neumann, W. L., Ford, D.A., 2010. Chlorinated lipid species in activated human neutrophils: lipid metabolites of 2-chlorohexadecanal. J. Lipid Res. 51 (5), 1085–1092. https://doi.org/10.1194/jlr.M003673.

Anderson, E.J., Katunga, L.A., Willis, M.S., 2012. Mitochondria as a source and target of lipid peroxidation products in healthy and diseased heart: lipid peroxidation products in the heart. Clin. Exp. Pharmacol. Physiol. 39 (2), 179–193. https://doi.org/10.1111/j.1440-1681.2011.05641.x.

Angelova, A., Angelov, B., Drechsler, M., Bizien, T., Gorshkova, Y.E., Deng, Y., 2021. Plasmalogen-based liquid crystalline multiphase structures involving docosapentaenoyl derivatives inspired by biological cubic membranes. Front. Cell Dev. Biol. 9, 617984 https://doi.org/10.3389/fcell.2021.617984.

Ansell, G.B., Spanner, S., 1968. Plasmalogenase activity in normal and demyelinating tissue of the central nervous system. Biochem. J. 108 (2), 207–209. https://doi.org/10.1042/bj1080207.

Archambault, A., Zaid, Y., Rakotoarivelo, V., Turcotte, C., Doré, É., Dubuc, I., Martin, C., Flamand, O., Amar, Y., Cheikh, A., Fares, H., El Hassani, A., Tijani, Y., Côté, A., Laviolette, M., Boilard, É., Flamand, L., Flamand, N., 2021. High levels of eicosanoids and docosanoids in the lungs of intubated COVID-19 patients. FASEB J. 35 (6) https://doi.org/10.1096/fj.202100540R.

Arevalo, M.A., Diz-Chaves, Y., Santos-Galindo, M., Bellini, M.J., Garcia-Segura, L.M., 2012. Selective oestrogen receptor modulators decrease the inflammatory response of glial cells: oestrogens decrease the inflammatory response of glial cells. J. Neuroendocrinol. 24 (1), 183–190. https://doi.org/10.1111/j.1365-2826.2011.02156.x.

Armstrong, C.W., McGregor, N.R., Lewis, D.P., Butt, H.L., Gooley, P.R., 2015. Metabolic profiling reveals anomalous energy metabolism and oxidative stress pathways in chronic fatigue syndrome patients. Metabolomics 11, 1626–1639. https://doi.org/10.1007/s11306-015-0816-5.

Astarita, G., Jung, K.-M., Berchtold, N.C., Nguyen, V.Q., Gillen, D.L., Head, E., Cotman, C.W., Piomelli, D., 2010. Deficient liver biosynthesis of docosahexaenoic acid correlates with cognitive impairment in Alzheimer's disease. PLoS ONE 5 (9), e12538. https://doi.org/10.1371/journal.pone.0012538.

Baes, M., Huyghe, S., Carmeliet, P., Declercq, P.E., Collen, D., Mannaerts, G.P., Van Veldhoven, P.P., 2000. Inactivation of the peroxisomal multifunctional protein-2 in mice impedes the degradation of not only 2-methyl-branched fatty acids and bile acid intermediates but also of very long chain fatty acids. J. Biol. Chem. 275 (21), 16329–16336. https://doi.org/10.1074/jbc.M001994200.

Baraniuk, J.N., Amar, A., Pepermitwala, H., Washington, S.D., 2022. Differential effects of exercise on fMRI of the midbrain ascending arousal network nuclei in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and gulf war illness (GWI) in a model of postexertional malaise (PEM). Brain Sci. 12 (1), 78. https://doi.org/10.3390/brainsci12010078.

Barson, J.R., Mack, N.R., Gao, W.-J., 2020. The paraventricular nucleus of the thalamus is an important node in the emotional processing network. Front. Behav. Neurosci. 14, 598469 https://doi.org/10.3389/fnbeh.2020.598469.

Bateman, L., Bested, A.C., Bonilla, H.F., Chheda, B.V., Chu, L., Curtin, J.M., Dempsey, T. T., Dimmock, M.E., Dowell, T.G., Felsenstein, D., Kaufman, D.L., Klimas, N.G., Komaroff, A.L., Lapp, C.W., Levine, S.M., Montoya, J.G., Natelson, B.H., Peterson, D. L., Podell, R.N., Yellman, B.P., 2021. Myalgic encephalomyelitis/chronic fatigue syndrome: essentials of diagnosis and management. Mayo Clin. Proc. 96 (11), 2861–2878. https://doi.org/10.1016/j.mayocp.2021.07.004.

Baumgartner, N.E., Grissom, E.M., Pollard, K.J., McQuillen, S.M., Daniel, J.M., 2019. Neuroestrogen-dependent transcriptional activity in the brains of ERE-luciferase reporter mice following short- and long-term ovariectomy. ENEURO.0275-19.2019 Eneuro 6 (5). https://doi.org/10.1523/ENEURO.0275-19.2019.

Beasley, C.L., Honer, W.G., Ramos-Miguel, A., Vila-Rodriguez, F., Barr, A.M., 2020. Prefrontal fatty acid composition in schizophrenia and bipolar disorder: association with reelin expression. Schizophr. Res. 215, 493–498. https://doi.org/10.1016/j.schres.2017.05.033.

Beckers, L., Geric, I., Stroobants, S., Beel, S., Van Damme, P., D'Hooge, R., Baes, M., 2019. Microglia lacking a peroxisomal β-oxidation enzyme chronically alter their inflammatory profile without evoking neuronal and behavioral deficits. J. Neuroinflamm. 16 (1), 61. https://doi.org/10.1186/s12974-019-1442-3.

Bell, J.G., MacKinlay, E.E., Dick, J.R., MacDonald, D.J., Boyle, R.M., Glen, A.C.A., 2004. Essential fatty acids and phospholipase A2 in autistic spectrum disorders. Prostaglandins, Leukot. Essent. Fat. Acids 71 (4), 201–204. https://doi.org/10.1016/j.plefa.2004.03.008.

Bender, S., Reuter, A., Eberle, F., Einhorn, E., Binder, M., Bartenschlager, R., 2015. Activation of Type I and III interferon response by mitochondrial and peroxisomal MAVS and inhibition by hepatitis C virus. PLoS Pathog. 11 (11), e1005264 https://doi.org/10.1371/journal.ppat.1005264.

Berchtold, N.C., Cribbs, D.H., Coleman, P.D., Rogers, J., Head, E., Kim, R., Beach, T., Miller, C., Troncoso, J., Trojanowski, J.Q., Zielke, H.R., Cotman, C.W., 2008. Gene expression changes in the course of normal brain aging are sexually dimorphic. Proc. Natl. Acad. Sci. 105 (40), 15605–15610. https://doi.org/10.1073/pnas.0806883105.

Berg, E., Paukovits, J., Axelband, J., Trager, J., Ryan, D., Cichonski, K., Kopnitsky, M., Zweitzig, D., Jeanmonod, R., 2018. Measurement of a novel biomarker, secretory phospholipase A2 group IIA as a marker of sepsis: a pilot study. J. Emergencies, Trauma, Shock 11 (2), 135. https://doi.org/10.4103/JETS.JETS_29_17.

Berger, J., Dorninger, F., Forss-Petter, S., Kunze, M., 2016. Peroxisomes in brain development and function. Biochim. Et. Biophys. Acta (BBA) - Mol. Cell Res. 1863 (5), 934–955. https://doi.org/10.1016/j.bbamcr.2015.12.005.

Bieberich, E., 2018. Sphingolipids and lipid rafts: novel concepts and methods of analysis. Chem. Phys. Lipids 216, 114–131. https://doi.org/10.1016/j.chemphyslip.2018.08.003.

Bjørndal, B., Alterås, E.K., Lindquist, C., Svardal, A., Skorve, J., Berge, R.K., 2018. Associations between fatty acid oxidation, hepatic mitochondrial function, and plasma acylcarnitine levels in mice. Nutr. Metab. 15 (1), 10. https://doi.org/10.1186/s12986-018-0241-7.

Boggs, J.M., Stamp, D., Moscarello, M.A., 1982. Comparison of two molecular species of ethanolamine plasmalogen in multiple sclerosis and normal myelin. Neurochem. Res. 7 (8), 953–964. https://doi.org/10.1007/BF00965135.

Bond, J., Nielsen, T., Hodges, L., 2021. Effects of post-exertional malaise on markers of arterial stiffness in individuals with myalgic encephalomyelitis/chronic fatigue syndrome. Int. J. Environ. Res. Public Health 18 (5), 2366. https://doi.org/10.3390/ijerph18052366.

Boneva, R.S., Maloney, E.M., Lin, J.-M., Jones, J.F., Wieser, F., Nater, U.M., Heim, C.M., Reeves, W.C., 2011. Gynecological history in chronic fatigue syndrome: a population-based case-control study. J. Women's Health 20 (1), 21–28. https://doi.org/10.1089/jwh.2009.1900.

Booz, G.W., Altara, R., Eid, A.H., Wehbe, Z., Fares, S., Zaraket, H., Habeichi, N.J., Zouein, F.A., 2020. Macrophage responses associated with COVID-19: a pharmacological perspective. Eur. J. Pharmacol. 887, 173547 https://doi.org/10.1016/j.ejphar.2020.173547.

Borsche, M., Pereira, S.L., Klein, C., Grünewald, A., 2021. Mitochondria and Parkinson's disease: clinical, molecular, and translational aspects. J. Parkinson's Dis. 11 (1), 45–60. https://doi.org/10.3233/JPD-201981.

Bottelbergs, A., Verheijden, S., Van Veldhoven, P.P., Just, W., Devos, R., Baes, M., 2012. Peroxisome deficiency but not the defect in ether lipid synthesis causes activation of the innate immune system and axonal loss in the central nervous system. J. Neuroinflamm. 9 (1), 61. https://doi.org/10.1186/1742-2094-9-61.

Bottino, C.M.D.C., 2012. Lessons from the epidemiology of neuropsychiatric disorders in older people. Arq. De. Neuro-Psiquiatr. 70 (3), 165–166. https://doi.org/10.1590/S0004-282X2012000300001.

Bove, R., Secor, E., Chibnik, L.B., Barnes, L.L., Schneider, J.A., Bennett, D.A., De Jager, P. L., 2014. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. Neurology 82 (3), 222–229. https://doi.org/10.1212/WNL.0000000000000033.

Boyanovsky, B.B., Webb, N.R., 2009. Biology of secretory phospholipase A2. Cardiovasc. Drugs Ther. 23 (1), 61. https://doi.org/10.1007/s10557-008-6134-7.

Bozelli, J.C., Epand, R.M., 2021. Plasmalogen replacement therapy. Membranes 11 (11), 838. https://doi.org/10.3390/membranes11110838.

Bradley-Whitman, M.A., Lovell, M.A., 2015. Biomarkers of lipid peroxidation in Alzheimer disease (AD): An update. Arch. Toxicol. 89 (7), 1035–1044. https://doi.org/10.1007/s00204-015-1517-6.

Braverman, N.E., Moser, A.B., 2012. Functions of plasmalogen lipids in health and disease. Biochim. Et. Biophys. Acta (BBA) - Mol. Basis Dis. 1822 (9), 1442–1452. https://doi.org/10.1016/j.bbadis.2012.05.008.

Brinton, R.D., Yao, J., Yin, F., Mack, W.J., Cadenas, E., 2015. Perimenopause as a neurological transition state. Nat. Rev. Endocrinol. 11 (7), 393–405. https://doi.org/10.1038/nrendo.2015.82.

Brites, P., Waterham, H.R., Wanders, R.J.A., 2004. Functions and biosynthesis of plasmalogens in health and disease. Biochim. Et. Biophys. Acta (BBA) - Mol. Cell Biol. Lipids 1636 (2–3), 219–231. https://doi.org/10.1016/j.bbalip.2003.12.010.

Brites, P., Ferreira, A.S., Ferreira Da Silva, T., Sousa, V.F., Malheiro, A.R., Duran, M., Waterham, H.R., Baes, M., Wanders, R.J.A., 2011. Alkyl-glycerol rescues plasmalogen levels and pathology of ether-phospholipid deficient mice. PLoS One 6 (12), e28539. https://doi.org/10.1371/journal.pone.0028539.

Brydges, C.R., Bhattacharyya, S., Dehkordi, S.M., Milaneschi, Y., Penninx, B., Jansen, R., Kristal, B.S., Han, X., Arnold, M., Kastenmüller, G., Bekhbat, M., Mayberg, H.S., Craighead, W.E., Rush, A.J., Fiehn, O., Dunlop, B.W., Kaddurah-Daouk, R., 2022. Metabolomic and inflammatory signatures of symptom dimensions in major depression. Brain, Behav. Immun. 102, 42–52. https://doi.org/10.1016/j.bbi.2022.02.003.

Calabrese, E.J., Canada, A.T., 1989. Catalase: Its role in xenobiotic detoxification. Pharmacol. Ther. 44 (2), 297–307. https://doi.org/10.1016/0163-7258(89)90069-7.

Campos, M.C., Nery, T., Starke, A.C., De Bem Alves, A.C., Speck, A.E., S Aguiar, A., 2022. Post-viral fatigue in COVID-19: a review of symptom assessment methods, mental, cognitive, and physical impairment. Neurosci. Biobehav. Rev. 142, 104902 https://doi.org/10.1016/j.neubiorev.2022.104902.

Carruthers, B.M., Van De Sande, M.I., De Meirleir, K.L., Klimas, N.G., Broderick, G., Mitchell, T., Staines, D., Powles, A.C.P., Speight, N., Vallings, R., Bateman, L., Baumgarten-Austrheim, B., Bell, D.S., Carlo-Stella, N., Chia, J., Darragh, A., Jo, D., Lewis, D., Light, A.R., Stevens, S., 2011. Myalgic encephalomyelitis: International Consensus Criteria. J. Intern. Med. 270 (4), 327–338. https://doi.org/10.1111/j.1365-2796.2011.02428.x.

Cerqueira, N.M.F.S.A., Oliveira, E.F., Gesto, D.S., Santos-Martins, D., Moreira, C., Moorthy, H.N., Ramos, M.J., Fernandes, P.A., 2016. Cholesterol biosynthesis: a mechanistic overview. Biochemistry 55 (39), 5483–5506. https://doi.org/10.1021/acs.biochem.6b00342. https://pubmed.ncbi.nlm.nih.gov/27604037/.

Che, H., Zhang, L., Ding, L., Xie, W., Jiang, X., Xue, C., Zhang, T., Wang, Y., 2020. EPA-enriched ethanolamine plasmalogen and EPA-enriched phosphatidylethanolamine enhance BDNF/TrkB/CREB signaling and inhibit neuronal apoptosis in vitro and in vivo. Food Funct. 11 (2), 1729–1739. https://doi.org/10.1039/C9FO02323B.

Che, X., Brydges, C.R., Yu, Y., Price, A., Joshi, S., Roy, A., Lee, B., Barupal, D.K., Cheng, A., Palmer, D.M., Levine, S., Peterson, D.L., Vernon, S.D., Bateman, L., Hornig, M., Montoya, J.G., Komaroff, A.L., Fiehn, O., Lipkin, W.I., 2022. Metabolomic evidence for peroxisomal dysfunction in myalgic encephalomyelitis/chronic fatigue syndrome. Int. J. Mol. Sci. 23 (14), 7906. https://doi.org/10.3390/ijms23147906.

Cheng, Y.-J., Lin, C.-H., Lane, H.-Y., 2021. From menopause to neurodegeneration—molecular basis and potential therapy. Int. J. Mol. Sci. 22 (16), 8654. https://doi.org/10.3390/ijms22168654.

Chew, H., Solomon, V.A., Fonteh, A.N., 2020. Involvement of lipids in Alzheimer's disease pathology and potential therapies. Front. Physiol. 11, 598. https://doi.org/10.3389/fphys.2020.00598.

Chong, K., Deng, Y., 2012. The Three Dimensionality of Cell Membranes: Lamellar to Cubic Membrane Transition as Investigated by Electron Microscopy. In: Methods in Cell Biology, Vol. 108. Elsevier, pp. 317–343. https://doi.org/10.1016/B978-0-12-386487-1.00015-8.

Chong, K., Almsherqi, Z.A., Zhuo, R., Deng, Y., 2021. Plasmalogen-rich foods promote the formation of cubic membranes in amoeba *Chaos* under stress conditions. FEBS Open Bio 11 (8), 2319–2328. https://doi.org/10.1002/2211-5463.13241.

Chu, C.-S., Hung, C.-F., Ponnusamy, V.K., Chen, K.-C., Chen, N.-C., 2022. Higher serum DHA and slower cognitive decline in patients with Alzheimer's disease: two-year follow-Up. Nutrients 14 (6), 1159. https://doi.org/10.3390/nu14061159.

Chua, N.K., Coates, H.W., Brown, A.J., 2020. Squalene monooxygenase: a journey to the heart of cholesterol synthesis. Prog. Lipid Res. 79, 101033 https://doi.org/10.1016/j.plipres.2020.101033.

Ciccarelli, M., Merciai, F., Carrizzo, A., Sommella, E., Di Pietro, P., Caponigro, V., Salviati, E., Musella, S., Sarno, V.D., Rusciano, M., Toni, A.L., Iesu, P., Izzo, C., Schettino, G., Conti, V., Venturini, E., Vitale, C., Scarpati, G., Bonadies, D., Campiglia, P., 2022. Untargeted lipidomics reveals specific lipid profiles in COVID-19 patients with different severity from Campania region (Italy). J. Pharm. Biomed. Anal. 217, 114827 https://doi.org/10.1016/j.jpba.2022.114827.

Dang, H., Liu, Y., Pang, W., Li, C., Wang, N., Shyy, J.Y.-J., Zhu, Y., 2009. Suppression of 2,3-oxidosqualene cyclase by high fat diet contributes to liver X receptor-α-mediated improvement of hepatic lipid profile. J. Biol. Chem. 284 (10), 6218–6226. https://doi.org/10.1074/jbc.M803702200.

Das, A.K., Hajra, A.K., 1988. High incorporation of dietary 1- *O* -heptadecyl glycerol into tissue plasmalogens of young rats. FEBS Lett. 227 (2), 187–190. https://doi.org/10.1016/0014-5793(88)80895-0.

Das, A.K., Holmes, R.D., Wilson, G.N., Hajra, A.K., 1992. Dietary ether lipid incorporation into tissue plasmalogens of humans and rodents. Lipids 27 (6), 401–405. https://doi.org/10.1007/BF02536379.

Daulatzai, M.A., 2012. Dysfunctional nucleus tractus solitarius: its crucial role in promoting neuropathogentic cascade of Alzheimer's dementia—a novel hypothesis. Neurochem. Res. 37 (4), 846–868. https://doi.org/10.1007/s11064-011-0680-2.

De Almeida, V.M., Engel, D.F., Ricci, M.F., Cruz, C.S., Lopes, I.S., Alves, D.A., Auriol, M. D., Magalhães, J., Zuccoli, G.S., Smith, B.J., Carregari, V.C., Machado, E.C., Rocha, V.M., Carvalho, T.G., Lacerda, L.D.S.B., Pimenta, J.C., Galvão, I., Silva, M.A., Rosa, E.D.S., … Vieira, A.T. (2022). *Gut microbiota from patients with mild COVID-19 cause alterations in mice that resemble post-COVID syndrome* (Preprint). in preparation. ⟨https://doi.org/10.21203/rs.3.rs-1756189/v1⟩.

Dean, J.M., Lodhi, I.J., 2018. Structural and functional roles of ether lipids. Protein Cell 9 (2), 196–206. https://doi.org/10.1007/s13238-017-0423-5.

Della Torre, S., Vegeto, E., Ciana, P., 2022. The Use of ERE-luc reporter mice to monitor estrogen receptor transcriptional activity in a spatio-temporal dimension. In: Eyster, K.M. (Ed.), *Estrogen Receptors*, Vol. 2418. Springer US, pp. 153–172. https://doi.org/10.1007/978-1-0716-1920-9_10.

Demarquoy, J., 2015. Crosstalk between mitochondria and peroxisomes. World J. Biol. Chem. 6 (4), 301. https://doi.org/10.4331/wjbc.v6.i4.301.

Demirkan, A., Isaacs, A., Ugocsai, P., Liebisch, G., Struchalin, M., Rudan, I., Wilson, J.F., Pramstaller, P.P., Gyllensten, U., Campbell, H., Schmitz, G., Oostra, B.A., Van Duijn, C.M., 2013. Plasma phosphatidylcholine and sphingomyelin concentrations are associated with depression and anxiety symptoms in a Dutch family-based lipidomics study. J. Psychiatr. Res. 47 (3), 357–362. https://doi.org/10.1016/j.jpsychires.2012.11.001.

Deng, Y., Mieczkowski, M., 1998. Three-dimensional periodic cubic membrane structure in the mitochondria of amoebae Chaos carolinensis. Protoplasma 203 (1–2), 16–25. https://doi.org/10.1007/BF01280583.

Deng, Y., Almsherqi, Z.A., 2015. Evolution of cubic membranes as antioxidant defence system. Interface Focus 5 (4), 20150012. https://doi.org/10.1098/rsfs.2015.0012.

Deng, Y., Angelova, A., 2021. Coronavirus-induced host cubic membranes and lipid-related antiviral therapies: a focus on bioactive plasmalogens. Front. Cell Dev. Biol. 9, 630242 https://doi.org/10.3389/fcell.2021.630242.

Deng, Y., Kohlwein, S.D., Mannella, C.A., 2002. Fasting induces cyanide-resistant respiration and oxidative stress in the amoeba Chaos carolinensis: Implications for the cubic structural transition in mitochondrial membranes. Protoplasma 219 (3–4), 160–167. https://doi.org/10.1007/s007090200017.

Deng, Y., Almsherqi, Z.A., Shui, G., Wenk, M.R., Kohlwein, S.D., 2009. Docosapentaenoic acid (DPA) is a critical determinant of cubic membrane formation in amoeba *Chaos* mitochondria. FASEB J. 23 (9), 2866–2871. https://doi.org/10.1096/fj.09-130435.

Deniau, A.-L., Mosset, P., Pédrono, F., Mitre, R., Bot, D.L., Legrand, A.B., 2010. Multiple beneficial health effects of natural alkylglycerols from shark liver oil. Mar. Drugs 8 (7), 2175–2184. https://doi.org/10.3390/md8072175.

Desai, M.K., Brinton, R.D., 2019. Autoimmune disease in women: endocrine transition and risk across the lifespan. Front. Endocrinol. 10, 265. https://doi.org/10.3389/fendo.2019.00265.

Deumer, U.-S., Varesi, A., Floris, V., Savioli, G., Mantovani, E., López-Carrasco, P., Rosati, G.M., Prasad, S., Ricevuti, G., 2021. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): an overview. J. Clin. Med. 10 (20), 4786. https://doi.org/10.3390/jcm10204786.

Di Cara, F., Sheshachalam, A., Braverman, N.E., Rachubinski, R.A., Simmonds, A.J., 2017. Peroxisome-mediated metabolism is required for immune response to microbial infection. Immunity 47 (1), 93–106.e7. https://doi.org/10.1016/j.immuni.2017.06.016.

Di Cara, F., Andreoletti, P., Trompier, D., Vejux, A., Bülow, M.H., Sellin, J., Lizard, G., Cherkaoui-Malki, M., Savary, S., 2019. Peroxisomes in immune response and inflammation. Int. J. Mol. Sci. 20 (16), 3877. https://doi.org/10.3390/ijms20163877.

Di Miceli, M., Martinat, M., Rossitto, M., Aubert, A., Alashmali, S., Bosch-Bouju, C., Fioramonti, X., Joffre, C., Bazinet, R.P., Layé, S., 2022. Dietary long-chain n-3 polyunsaturated fatty acid supplementation alters electrophysiological properties in the nucleus accumbens and emotional behavior in naïve and chronically stressed mice. Int. J. Mol. Sci. 23 (12), 6650. https://doi.org/10.3390/ijms23126650.

Dias, J.A., Fredrikson, G.N., Ericson, U., Gullberg, B., Hedblad, B., Engström, G., Borgquist, S., Nilsson, J., Wirfält, E., 2016. Low-grade inflammation, oxidative stress and risk of invasive post-menopausal breast cancer—a nested case-control study from the malmö diet and cancer cohort. PLOS ONE 11 (7), e0158959. https://doi.org/10.1371/journal.pone.0158959.

Díaz, M., Fabelo, N., Ferrer, I., Marín, R., 2018. "Lipid raft aging" in the human frontal cortex during nonpathological aging: Gender influences and potential implications in Alzheimer's disease. Neurobiol. Aging 67, 42–52. https://doi.org/10.1016/j.neurobiolaging.2018.02.022.

Dickens, A.M., Sen, P., Kempton, M.J., Barrantes-Vidal, N., Iyegbe, C., Nordentoft, M., Pollak, T., Riecher-Rössler, A., Ruhrmann, S., Sachs, G., Bressan, R., Krebs, M.-O., Amminger, G.P., De Haan, L., Van Der Gaag, M., Valmaggia, L., Hyötyläinen, T., Orešič, M., McGuire, P., Van Os, J., 2021. Dysregulated lipid metabolism precedes onset of psychosis. Biol. Psychiatry 89 (3), 288–297. https://doi.org/10.1016/j.biopsych.2020.07.012.

Ding, L., Zhang, L.-Y., Shi, H.-H., Wang, C.-C., Jiang, X.-M., Xue, C.-H., Yanagita, T., Zhang, T.-T., Wang, Y.-M., 2020. Eicosapentaenoic acid-enriched phosphoethanolamine plasmalogens alleviated atherosclerosis by remodeling gut microbiota to regulate bile acid metabolism in LDLR $^{-/-}$ mice. J. Agric. Food Chem. 68 (19), 5339–5348. https://doi.org/10.1021/acs.jafc.9b08296.

Dixit, E., Boulant, S., Zhang, Y., Lee, A.S.Y., Odendall, C., Shum, B., Hacohen, N., Chen, Z.J., Whelan, S.P., Fransen, M., Nibert, M.L., Superti-Furga, G., Kagan, J.C., 2010. Peroxisomes are signaling platforms for antiviral innate immunity. Cell 141 (4), 668–681. https://doi.org/10.1016/j.cell.2010.04.018.

Dorninger, F., Forss-Petter, S., Wimmer, I., Berger, J., 2020. Plasmalogens, platelet-activating factor and beyond – ether lipids in signaling and neurodegeneration. Neurobiol. Dis. 145, 105061 https://doi.org/10.1016/j.nbd.2020.105061.

Dorninger, F., Gundacker, A., Zeitler, G., Pollak, D.D., Berger, J., 2019. Ether lipid deficiency in mice produces a complex behavioral phenotype mimicking aspects of human psychiatric disorders. Int. J. Mol. Sci. 20 (16), 3929. https://doi.org/10.3390/ijms20163929.

Dorninger, F., König, T., Scholze, P., Berger, M.L., Zeitler, G., Wiesinger, C., Gundacker, A., Pollak, D.D., Huck, S., Just, W.W., Forss-Petter, S., Pifl, C., Berger, J., 2019. Disturbed neurotransmitter homeostasis in ether lipid deficiency. Hum. Mol. Genet. 28 (12), 2046–2061. https://doi.org/10.1093/hmg/ddz040.

Ellison, D.W., Beal, M.F., Martin, J.B., 1987. Phosphoethanolamine and ethanolamine are decreased in Alzheimer's disease and Huntington's disease. Brain Res. 417 (2), 389–392. https://doi.org/10.1016/0006-8993(87)90471-9.

Engelmann, B., 2004. Plasmalogens: targets for oxidants and major lipophilic antioxidants. Biochem. Soc. Trans. 32 (1), 147–150. https://doi.org/10.1042/bst0320147.

Fabelo, N., Martín, V., Santpere, G., Marín, R., Torrent, L., Ferrer, I., Díaz, M., 2011. Severe alterations in lipid composition of frontal cortex lipid rafts from parkinson's disease and incidental Parkinson's disease. Mol. Med. 17 (9–10), 1107–1118. https://doi.org/10.2119/molmed.2011.00119.

Facciotti, F., Ramanjaneyulu, G.S., Lepore, M., Sansano, S., Cavallari, M., Kistowska, M., Forss-Petter, S., Ni, G., Colone, A., Singhal, A., Berger, J., Xia, C., Mori, L., De Libero, G., 2012. Peroxisome-derived lipids are self antigens that stimulate invariant natural killer T cells in the thymus. Nat. Immunol. 13 (5), 474–480. https://doi.org/10.1038/ni.2245.

Fallatah, W., Smith, T., Cui, W., Jayasinghe, D., Di Pietro, E., Ritchie, S.A., Braverman, N., 2019. Oral administration of a synthetic vinyl-ether plasmalogen normalizes open field activity in a mouse model of Rhizomelic chondrodysplasia punctata. dmm.042499 Dis. Models Mech.. https://doi.org/10.1242/dmm.042499.

Farooqui, A.A., Horrocks, L.A., 2001a. Plasmalogens, phospholipase A_2, and docosahexaenoic acid turnover in brain tissue. J. Mol. Neurosci. 16 (2–3), 263–272. https://doi.org/10.1385/JMN:16:2-3:263.

Farooqui, A.A., Horrocks, L.A., 2001b. Book review: plasmalogens: workhorse lipids of membranes in normal and injured neurons and glia. Neuroscientist 7 (3), 232–245. https://doi.org/10.1177/107385840100700308.

Farooqui, A.A., Horrocks, L.A., 2001c. Book review: plasmalogens: workhorse lipids of membranes in normal and injured neurons and glia. Neuroscientist 7 (3), 232–245. https://doi.org/10.1177/107385840100700308.

Ferreira, A.R., Marques, M., Ribeiro, D., 2019. Peroxisomes and Innate Immunity: antiviral Response and Beyond. Int. J. Mol. Sci. 20 (15), 3795. https://doi.org/10.3390/ijms20153795.

Ferreira, H.B., Melo, T., Monteiro, A., Paiva, A., Domingues, P., Domingues, M.R., 2021. Serum phospholipidomics reveals altered lipid profile and promising biomarkers in multiple sclerosis. Arch. Biochem. Biophys. 697, 108672 https://doi.org/10.1016/j.abb.2020.108672.

Frank, M.G., Weber, M.D., Watkins, L.R., Maier, S.F., 2016. Stress-induced neuroinflammatory priming: a liability factor in the etiology of psychiatric disorders. Neurobiol. Stress 4, 62–70. https://doi.org/10.1016/j.ynstr.2015.12.004.

Fransen, M., Nordgren, M., Wang, B., Apanasets, O., 2012. Role of peroxisomes in ROS/RNS-metabolism: Implications for human disease. Biochim. Et. Biophys. Acta (BBA) - Mol. Basis Dis. 1822 (9), 1363–1373. https://doi.org/10.1016/j.bbadis.2011.12.001.

Fujino, T., Hossain, M.S., Mawatari, S., 2020. Therapeutic efficacy of plasmalogens for Alzheimer's disease, mild cognitive impairment, and parkinson's disease in conjunction with a new hypothesis for the etiology of Alzheimer's disease. In: Lizard, G. (Ed.), Peroxisome Biology: Experimental Models, Peroxisomal Disorders and Neurological Diseases, Vol. 1299. Springer International Publishing, pp. 195–212. https://doi.org/10.1007/978-3-030-60204-8_14.

Fujino, T., Yamada, T., Asada, T., Tsuboi, Y., Wakana, C., Mawatari, S., Kono, S., 2017. Efficacy and blood plasmalogen changes by oral administration of plasmalogen in patients with Mild Alzheimer's disease and mild cognitive impairment: a multicenter, randomized, double-blind, placebo-controlled trial. EBioMedicine 17, 199–205. https://doi.org/10.1016/j.ebiom.2017.02.012.

Furt, F., Moreau, P., 2009. Importance of lipid metabolism for intracellular and mitochondrial membrane fusion/fission processes. Int. J. Biochem. Cell Biol. 41 (10), 1828–1836. https://doi.org/10.1016/j.biocel.2009.02.005.

Germain, A., Barupal, D.K., Levine, S.M., Hanson, M.R., 2020. Comprehensive circulatory metabolomics in ME/CFS reveals disrupted metabolism of acyl lipids and steroids. Metabolites 10 (1), 34. https://doi.org/10.3390/metabo10010034.

Germain, A., Giloteaux, L., Moore, G.E., Levine, S.M., Chia, J.K., Keller, B.A., Stevens, J., Franconi, C.J., Mao, X., Shungu, D.C., Grimson, A., Hanson, M.R., 2022. Plasma metabolomics reveals disrupted response and recovery following maximal exercise in myalgic encephalomyelitis/chronic fatigue syndrome. JCI Insight 7 (9), e157621. https://doi.org/10.1172/jci.insight.157621.

Ghosh, S., Dyer, R.A., Beasley, C.L., 2017. Evidence for altered cell membrane lipid composition in postmortem prefrontal white matter in bipolar disorder and schizophrenia. J. Psychiatr. Res. 95, 135–142. https://doi.org/10.1016/j.jpsychires.2017.08.009.

Gibellini, F., Smith, T.K., 2010. The Kennedy pathway-De novo synthesis of phosphatidylethanolamine and phosphatidylcholine (n/a-n/a). IUBMB Life. https://doi.org/10.1002/iub.337.

Giloteaux, L., Hanson, M.R., Keller, B.A., 2016. A pair of identical twins discordant for myalgic encephalomyelitis/chronic fatigue syndrome differ in physiological parameters and gut microbiome composition. Am. J. Case Rep. 17, 720–729. https://doi.org/10.12659/AJCR.900314.

Ginsberg, L., Rafique, S., Xuereb, J.H., Rapoport, S.I., Gershfeld, N.L., 1995. Disease and anatomic specificity of ethanolamine plasmalogen deficiency in Alzheimer's disease brain. Brain Res. 698 (1–2), 223–226. https://doi.org/10.1016/0006-8993(95)00931-F.

Glaser, P.E., Gross, R.W., 1995. Rapid plasmenylethanolamine-selective fusion of membrane bilayers catalyzed by an isoform of glyceraldehyde-3-phosphate dehydrogenase: discrimination between glycolytic and fusogenic roles of individual isoforms. Biochemistry 34 (38), 12193–12203. https://doi.org/10.1021/bi00038a013.

Glassford, J.A.G., 2017. The neuroinflammatory etiopathology of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Front. Physiol. 8 https://doi.org/10.3389/fphys.2017.00088.

Godlewska, B.R., Williams, S., Emir, U.E., Chen, C., Sharpley, A.L., Goncalves, A.J., Andersson, M.I., Clarke, W., Angus, B., Cowen, P.J., 2022. Neurochemical abnormalities in chronic fatigue syndrome: a pilot magnetic resonance spectroscopy study at 7 Tesla. Psychopharmacology 239 (1), 163–171. https://doi.org/10.1007/s00213-021-05986-6.

Goetzl, E.J., Huang, M., Kon, J., Patel, K., Schwartz, J.B., Fast, K., Ferrucci, L., Madara, K., Taub, D.D., Longo, D.L., 2010. Gender specificity of altered human immune cytokine profiles in aging. FASEB J. 24 (9), 3580–3589. https://doi.org/10.1096/fj.10-160911.

Goodenowe, D.B., Cook, L.L., Liu, J., Lu, Y., Jayasinghe, D.A., Ahiahonu, P.W.K., Heath, D., Yamazaki, Y., Flax, J., Krenitsky, K.F., Sparks, D.L., Lerner, A., Friedland, R.P., Kudo, T., Kamino, K., Morihara, T., Takeda, M., Wood, P.L., 2007. Peripheral ethanolamine plasmalogen deficiency: a logical causative factor in Alzheimer's disease and dementia. J. Lipid Res. 48 (11), 2485–2498. https://doi.org/10.1194/jlr.P700023-JLR200.

Goracci, G., Balestrieri, M.L., Nardicchi, V., 2009. Metabolism and Functions of Platelet-Activating Factor (PAF) in the Nervous Tissue. In: Lajtha, A., Tettamanti, G., Goracci, G. (Eds.), Handbook of Neurochemistry and Molecular Neurobiology: Neural Lipids. Springer US. https://doi.org/10.1007/978-0-387-30378-9_13.

Grimm, M.O.W., Michaelson, D.M., Hartmann, T., 2017. Omega-3 fatty acids, lipids, and apoE lipidation in Alzheimer's disease: a rationale for multi-nutrient dementia prevention. J. Lipid Res. 58 (11), 2083–2101. https://doi.org/10.1194/jlr.R076331.

Grimm, M.O.W., Grimm, H.S., Pätzold, A.J., Zinser, E.G., Halonen, R., Duering, M., Tschäpe, J.-A., Strooper, B.D., Müller, U., Shen, J., Hartmann, T., 2005. Regulation

of cholesterol and sphingomyelin metabolism by amyloid-β and presenilin. Nat. Cell Biol. 7 (11), 1118–1123. https://doi.org/10.1038/ncb1313.
Grimm, M.O.W., Kuchenbecker, J., Rothhaar, T.L., Grösgen, S., Hundsdörfer, B., Burg, V. K., Friess, P., Müller, U., Grimm, H.S., Riemenschneider, M., Hartmann, T., 2011. Plasmalogen synthesis is regulated via alkyl-dihydroxyacetonephosphate-synthase by amyloid precursor protein processing and is affected in Alzheimer's disease: dysregulation of plasmalogen synthesis in AD. J. Neurochem. 116 (5), 916–925. https://doi.org/10.1111/j.1471-4159.2010.07070.x.
Gu, J., Chen, L., Sun, R., Wang, J.-L., Wang, J., Lin, Y., Lei, S., Zhang, Y., Lv, D., Jiang, F., Deng, Y., Collman, J.P., Fu, L., 2022. Plasmalogens eliminate aging-associated synaptic defects and microglia-mediated neuroinflammation in mice. Front. Mol. Biosci. 9, 815320 https://doi.org/10.3389/fmolb.2022.815320.
Gulbins, E., Palmada, M., Reichel, M., Lüth, A., Böhmer, C., Amato, D., Müller, C.P., Tischbirek, C.H., Groemer, T.W., Tabatabai, G., Becker, K.A., Tripal, P., Staedtler, S., Ackermann, T.F., Van Brederode, J., Alzheimer, C., Weller, M., Lang, U.E., Kleuser, B., Kornhuber, J., 2013. Acid sphingomyelinase–ceramide system mediates effects of antidepressant drugs. Nat. Med. 19 (7), 934–938. https://doi.org/10.1038/nm.3214.
Guo, C., Che, X., Briese, T., Ranjan, A., Allicock, O., Yates, R.A., Cheng, A., March, D., Hornig, M., Komaroff, A.L., Levine, S., Bateman, L., Vernon, S.D., Klimas, N.G., Montoya, J.G., Peterson, D.L., Lipkin, W.I., Williams, B.L., 2023. Deficient butyrate-producing capacity in the gut microbiome is associated with bacterial network disturbances and fatigue symptoms in ME/CFS. Cell Host Microbe 31 (2), 288–304. e8. https://doi.org/10.1016/j.chom.2023.01.004.
Hahnefeld, L., Gruber, L., Schömel, N., Fischer, C., Mattjus, P., Gurke, R., Beretta, M., Ferreirós, N., Geisslinger, G., Wegner, M.-S., 2020. Ether lipid and sphingolipid expression patterns are estrogen receptor-dependently altered in breast cancer cells. Int. J. Biochem. Cell Biol. 127, 105834 https://doi.org/10.1016/j.biocel.2020.105834.
Han, X., 2005. Lipid alterations in the earliest clinically recognizable stage of Alzheimers disease: implication of the role of lipids in the pathogenesis of Alzheimers disease. Curr. Alzheimer Res. 2 (1), 65–77. https://doi.org/10.2174/1567205052772786.
Han, X., Holtzman, D.M., McKeel, D.W., 2001. Plasmalogen deficiency in early Alzheimer's disease subjects and in animal models: molecular characterization using electrospray ionization mass spectrometry: plasmalogen deficiency in Alzheimer's disease. J. Neurochem. 77 (4), 1168–1180. https://doi.org/10.1046/j.1471-4159.2001.00332.x.
Harishkumar, R., Hans, S., Stanton, J.E., Grabrucker, A.M., Lordan, R., Zabetakis, I., 2022. Targeting the Platelet-Activating Factor Receptor (PAF-R): Antithrombotic and Anti-Atherosclerotic Nutrients. Nutrients 14, 4414. https://doi.org/10.3390/nu14204414.
He, X., Huang, Y., Li, B., Gong, C.-X., Schuchman, E.H., 2010. Deregulation of sphingolipid metabolism in Alzheimer's disease. Neurobiol. Aging 31 (3), 398–408. https://doi.org/10.1016/j.neurobiolaging.2008.05.010.
Heim, C., Nater, U.M., Maloney, E., Boneva, R., Jones, J.F., Reeves, W.C., 2009. Childhood trauma and risk for chronic fatigue syndrome: association with neuroendocrine dysfunction. Arch. Gen. Psychiatry 66 (1), 72. https://doi.org/10.1001/archgenpsychiatry.2008.508.
Hennebelle, M., Champeil-Potokar, G., Lavialle, M., Vancassel, S., Denis, I., 2014. Omega-3 polyunsaturated fatty acids and chronic stress-induced modulations of glutamatergic neurotransmission in the hippocampus. Nutr. Rev. 72 (2), 99–112. https://doi.org/10.1111/nure.12088.
Hershkowitz, M., Adunsky, A., 1996. Binding of platelet-activating factor to platelets of Alzheimer's disease and multiinfarct Dementia patients. Neurobiol. Aging 17 (6), 865–868. https://doi.org/10.1016/S0197-4580(96)00073-5.
Hirashima, Y., Nakamura, S., Endo, S., Kuwayama, N., Naruse, Y., Takaku, A., 1997. Elevation of platelet activating factor, inflammatory cytokines, and coagulation factors in the internal jugular vein of patients with subarachnoid hemorrhage. Neurochem. Res. 22 (10), 1249–1255. https://doi.org/10.1023/a:1021985030331.
Holden, S., Maksoud, R., Eaton-Fitch, N., Cabanas, H., Staines, D., Marshall-Gradisnik, S., 2020. A systematic review of mitochondrial abnormalities in myalgic encephalomyelitis/chronic fatigue syndrome/systemic exertion intolerance disease. J. Transl. Med. 18 (1), 290. https://doi.org/10.1186/s12967-020-02452-3.
Holmes, R.D., Wilson, G.N., Hajra, A., 1987. Oral ether lipid therapy in patients with peroxisomal disorders. J. Inherit. Metab. Dis. 10 (S2), 239–241. https://doi.org/10.1007/BF01811415.
Honda, Z., Ishii, S., Shimizu, T., 2002. Platelet-activating factor receptor. J. Biochem. 131, 773–779. https://doi.org/10.1093/oxfordjournals.jbchem.a003164.
Honsho, M., Abe, Y., Fujiki, Y., 2015. Dysregulation of plasmalogen homeostasis impairs cholesterol biosynthesis. J. Biol. Chem. 290 (48), 28822–28833. https://doi.org/10.1074/jbc.M115.656983.
Hossain, Md.S., Tajima, A., Kotoura, S., Katafuchi, T., 2018. Oral ingestion of plasmalogens can attenuate the LPS-induced memory loss and microglial activation. Biochem. Biophys. Res. Commun. 496 (4), 1033–1039. https://doi.org/10.1016/j.bbrc.2018.01.078.
Hossain, Md.S., Ifuku, M., Take, S., Kawamura, J., Miake, K., Katafuchi, T., 2013. Plasmalogens rescue neuronal cell death through an activation of AKT and ERK survival signaling. PLoS One 8 (12), e83508. https://doi.org/10.1371/journal.pone.0083508.
Hossain, Md.S., Abe, Y., Ali, F., Youssef, M., Honsho, M., Fujiki, Y., Katafuchi, T., 2017. Reduction of ether-type glycerophospholipids, plasmalogens, by NF-κB signal leading to microglial activation. J. Neurosci. 37 (15), 4074–4092. https://doi.org/10.1523/JNEUROSCI.3941-15.2017.
Huang, C., Huang, L., Wang, Y., Li, X., Ren, L., Gu, X., Kang, L., Guo, L., Liu, M., Zhou, X., Luo, J., Huang, Z., Tu, S., Zhao, Y., Chen, L., Xu, D., Li, Y., Li, C., Peng, L., Cao, B., 2021. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 397 (10270), 220–232. https://doi.org/10.1016/S0140-6736(20)32656-8.
Huang, J.H., Park, H., Iaconelli, J., Berkovitch, S.S., Watmuff, B., McPhie, D., Öngür, D., Cohen, B.M., Clish, C.B., Karmacharya, R., 2017. Unbiased metabolite profiling of schizophrenia fibroblasts under stressful perturbations reveals dysregulation of plasmalogens and phosphatidylcholines. J. Proteome Res. 16 (2), 481–493. https://doi.org/10.1021/acs.jproteome.6b00628.
Hulshagen, L., Krysko, O., Bottelbergs, A., Huyghe, S., Klein, R., Van Veldhoven, P.P., De Deyn, P.P., D'Hooge, R., Hartmann, D., Baes, M., 2008. Absence of functional peroxisomes from mouse CNS causes dysmyelination and axon degeneration. J. Neurosci. 28 (15), 4015–4027. https://doi.org/10.1523/JNEUROSCI.4968-07.2008.
Hurley, B.P., McCormick, B.A., 2008. Multiple roles of phospholipase a 2 during lung infection and inflammation. Infect. Immun. 76 (6), 2259–2272. https://doi.org/10.1128/IAI.00059-08.
Huth, T.K., Eaton-Fitch, N., Staines, D., Marshall-Gradisnik, S., 2020. A systematic review of metabolomic dysregulation in chronic fatigue syndrome/myalgic encephalomyelitis/systemic exertion intolerance disease (CFS/ME/SEID). J. Transl. Med. 18 (1), 198. https://doi.org/10.1186/s12967-020-02356-2.
Iannitti, T., Palmieri, B., 2010. An update on the therapeutic role of alkylglycerols. Mar. Drugs 8 (8), 2267–2300. https://doi.org/10.3390/md8082267.
Ifuku, M., Katafuchi, T., Mawatari, S., Noda, M., Miake, K., Sugiyama, M., Fujino, T., 2012. Anti-inflammatory/anti-amyloidogenic effects of plasmalogens in lipopolysaccharide-induced neuroinflammation in adult mice. J. Neuroinflamm. 9 (1), 197. https://doi.org/10.1186/1742-2094-9-197.
Jackson, D.R., Cassilly, C.D., Plichta, D.R., Vlamakis, H., Liu, H., Melville, S.B., Xavier, R. J., Clardy, J., 2021. Plasmalogen biosynthesis by anaerobic bacteria: identification of a two-gene operon responsible for plasmalogen production in *Clostridium perfringens*. ACS Chem. Biol. 16 (1), 6–13. https://doi.org/10.1021/acschembio.0c00673.
Jenkins, C.M., Yang, K., Liu, G., Moon, S.H., Dilthey, B.G., Gross, R.W., 2018. Cytochrome c is an oxidative stress–activated plasmalogenase that cleaves plasmenylcholine and plasmenylethanolamine at the sn-1 vinyl ether linkage. J. Biol. Chem. 293 (22), 8693–8709. https://doi.org/10.1074/jbc.RA117.001629.
Jeong, G.U., Lyu, J., Kim, K.-D., Chung, Y.C., Yoon, G.Y., Lee, S., Hwang, I., Shin, W.-H., Ko, J., Lee, J.-Y., Kwon, Y.-C., 2022. SARS-CoV-2 infection of microglia elicits pro-inflammatory activation and apoptotic cell death [Preprint]. Microbiology. https://doi.org/10.1101/2022.01.04.475015.
Jernigan, P.L., Hoehn, R.S., Grassmé, H., Edwards, M.J., Müller, C.P., Kornhuber, J., Gulbins, E., 2015. Sphingolipids in Major Depression. Neurosignals 23 (1), 49–58. https://doi.org/10.1159/000442603.
Jiang, Z., Rajamanickam, S., Justice, N.J., 2019. CRF signaling between neurons in the paraventricular nucleus of the hypothalamus (PVN) coordinates stress responses. Neurobiol. Stress 11, 100192. https://doi.org/10.1016/j.ynstr.2019.100192.
Johnston, N.C., Goldfine, H., 1983. Lipid composition in the classification of the butyric acid-producing clostridia. Microbiology 129 (4), 1075–1081. https://doi.org/10.1099/00221287-129-4-1075.
Kaddurah-Daouk, R., McEvoy, J., Baillie, R., Zhu, H., K. Yao, J., Nimgaonkar, V.L., Buckley, P.F., Keshavan, M.S., Georgiades, A., Nasrallah, H.A., 2012. Impaired plasmalogens in patients with schizophrenia. Psychiatry Res. 198 (3), 347–352. https://doi.org/10.1016/j.psychres.2012.02.019.
Kai, H., Kai, M., 2020. Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors—lessons from available evidence and insights into COVID-19. Hypertens. Res. 43 (7), 648–654. https://doi.org/10.1038/s41440-020-0455-8.
Kedor, C., Freitag, H., Meyer-Arndt, L., Wittke, K., Hanitsch, L.G., Zoller, T., Steinbeis, F., Haffke, M., Rudolf, G., Heidecker, B., Bobbert, T., Spranger, J., Volk, H.-D., Skurk, C., Konietschke, F., Paul, F., Behrends, U., Bellmann-Strobl, J., Scheibenbogen, C., 2022. A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity. Nat. Commun. 13 (1), 5104. https://doi.org/10.1038/s41467-022-32507-6.
Kim, O.Y., Chae, J.S., Paik, J.K., Seo, H.S., Jang, Y., Cavaillon, J.-M., Lee, J.H., 2012. Effects of aging and menopause on serum interleukin-6 levels and peripheral blood mononuclear cell cytokine production in healthy nonobese women. AGE 34 (2), 415–425. https://doi.org/10.1007/s11357-011-9244-2.
Kimura, T., Kimura, A.K., Ren, M., Monteiro, V., Xu, Y., Berno, B., Schlame, M., Epand, R. M., 2019. Plasmalogen loss caused by remodeling deficiency in mitochondria. Life Sci. Alliance 2 (4), e201900348. https://doi.org/10.26508/lsa.201900348.
Klein, R.S., Garber, C., Funk, K.E., Salimi, H., Soung, A., Kanmogne, M., Manivasagam, S., Agner, S., Cain, M., 2019. Neuroinflammation During RNA Viral Infections. Annu. Rev. Immunol. 37 (1), 73–95. https://doi.org/10.1146/annurev-immunol-042718-041417.
Klosinski, L.P., Yao, J., Yin, F., Fonteh, A.N., Harrington, M.G., Christensen, T.A., Trushina, E., Brinton, R.D., 2015. White matter lipids as a ketogenic fuel supply in aging female brain: implications for Alzheimer's disease. EBioMedicine 2 (12), 1888–1904. https://doi.org/10.1016/j.ebiom.2015.11.002.
Knowles, E.E.M., Huynh, K., Meikle, P.J., Göring, H.H.H., Olvera, R.L., Mathias, S.R., Duggirala, R., Almasy, L., Blangero, J., Curran, J.E., Glahn, D.C., 2017. The lipidome in major depressive disorder: Shared genetic influence for ether-phosphatidylcholines, a plasma-based phenotype related to inflammation, and disease risk. Eur. Psychiatry 43, 44–50. https://doi.org/10.1016/j.eurpsy.2017.02.479.
Koal, T., Klavins, K., Seppi, D., Kemmler, G., Humpel, C., 2015. Sphingomyelin SM(d18:1/18:0) is significantly enhanced in cerebrospinal fluid samples dichotomized by pathological amyloid-β42, Tau, and Phospho-Tau-181 levels. J. Alzheimer's Dis. 44 (4), 1193–1201. https://doi.org/10.3233/JAD-142319.

Kolek, J., Patáková, P., Melzoch, K., Sigler, K., Řezanka, T., 2015. Changes in membrane plasmalogens of clostridium pasteurianum during butanol fermentation as determined by lipidomic analysis. PLoS One 10 (3), e0122058. https://doi.org/10.1371/journal.pone.0122058.

Kong, D., Liu, R., Liu, J., Zhou, Q., Zhang, J., Li, W., Bai, H., Hai, C., 2020. Cubic membranes formation in synchronized human hepatocellular carcinoma cells reveals a possible role as a structural antioxidant defense system in cell cycle progression. Front. Cell Dev. Biol. 8, 617406 https://doi.org/10.3389/fcell.2020.617406.

Kono, Y., 1995. Apparent antibacterial activity of catalase: role of lipid hydroperoxide contamination. J. Biochem. 117 (1), 42–46. https://doi.org/10.1093/oxfordjournals.jbchem.a124718.

Kornhuber, J., Medlin, A., Bleich, S., Jendrossek, V., Henkel, A.W., Wiltfang, J., Gulbins, E., 2005. High activity of acid sphingomyelinase in major depression. J. Neural Transm. 112 (11), 1583–1590. https://doi.org/10.1007/s00702-005-0374-5.

Kou, J., Kovacs, G.G., Höftberger, R., Kulik, W., Brodde, A., Forss-Petter, S., Hönigschnabl, S., Gleiss, A., Brügger, B., Wanders, R., Just, W., Budka, H., Jungwirth, S., Fischer, P., Berger, J., 2011. Peroxisomal alterations in Alzheimer's disease. Acta Neuropathol. 122 (3), 271–283. https://doi.org/10.1007/s00401-011-0836-9.

Kraft, M.L., 2017. Sphingolipid organization in the plasma membrane and the mechanisms that influence it. Front. Cell Dev. Biol. 4 https://doi.org/10.3389/fcell.2016.00154.

Krysko, O., Hulshagen, L., Janssen, A., Schütz, G., Klein, R., De Bruycker, M., Espeel, M., Gressens, P., Baes, M., 2007. Neocortical and cerebellar developmental abnormalities in conditions of selective elimination of peroxisomes from brain or from liver. J. Neurosci. Res. 85 (1), 58–72. https://doi.org/10.1002/jnr.21097.

Kuypers, F.A., Rostad, C.A., Anderson, E.J., Chahroudi, A., Jaggi, P., Wrammert, J., Mantus, G., Basu, R., Harris, F., Hanberry, B., Camacho-Gonzalez, A., Manoranjithan, S., Vos, M., Brown, L.A., Morris, C.R., 2021. Secretory phospholipase A2 in SARS-CoV-2 infection and multisystem inflammatory syndrome in children (MIS-C). Exp. Biol. Med. 246 (23), 2543–2552. https://doi.org/10.1177/15353702211028560.

Lam, M.H.-B., 2009. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. Arch. Intern. Med. 169 (22), 2142. https://doi.org/10.1001/archinternmed.2009.384.

Lamas, A.Z., Caliman, I.F., Dalpiaz, P.L.M., De Melo, A.F., Abreu, G.R., Lemos, E.M., Gouvea, S.A., Bissoli, N.S., 2015. Comparative effects of estrogen, raloxifene and tamoxifen on endothelial dysfunction, inflammatory markers and oxidative stress in ovariectomized rats. Life Sci. 124, 101–109. https://doi.org/10.1016/j.lfs.2015.01.004.

Landh, T., 1995. From entangled membranes to eclectic morphologies: cubic membranes as subcellular space organizers. FEBS Lett. 369 (1), 13–17. https://doi.org/10.1016/0014-5793(95)00660-2.

Lee, J.K., Jin, H.K., Park, M.H., Kim, B., Lee, P.H., Nakauchi, H., Carter, J.E., He, X., Schuchman, E.H., Bae, J., 2014. Acid sphingomyelinase modulates the autophagic process by controlling lysosomal biogenesis in Alzheimer's disease. J. Exp. Med. 211 (8), 1551–1570. https://doi.org/10.1084/jem.20132451.

Lei, D.-L., Long, J.M., Hengemihle, J., O'Neill, J., Manaye, K.F., Ingram, D.K., Mouton, P. R., 2003. Effects of estrogen and raloxifene on neuroglia number and morphology in the hippocampus of aged female mice. Neuroscience 121 (3), 659–666. https://doi.org/10.1016/S0306-4522(03)00245-8.

Lejri, I., Grimm, A., Eckert, A., 2018. Mitochondria, estrogen and female brain aging. Front. Aging Neurosci. 10, 124. https://doi.org/10.3389/fnagi.2018.00124.

Letsiou, E., Htwe, Y.M., Dudek, S.M., 2021. Secretory phospholipase A2 enzymes in acute lung injury. Cell Biochem. Biophys. 79 (3), 609–617. https://doi.org/10.1007/s12013-021-01003-x.

Li, G., Li, J., Hao, R., Guo, Y., 2017. Activation of catalase activity by a peroxisome-localized small heat shock protein Hsp17.6CII. J. Genet. Genom. 44 (8), 395–404. https://doi.org/10.1016/j.jgg.2017.03.009.

Li, M., Gao, Y., Wang, D., Hu, X., Jiang, J., Qing, Y., Yang, X., Cui, G., Wang, P., Zhang, J., Sun, L., Wan, C., 2022. Impaired membrane lipid homeostasis in schizophrenia. Schizophr. Bull. 48 (5), 1125–1135. https://doi.org/10.1093/schbul/sbac011.

Li, Y., Bai, W., Hashikawa, T., 2020. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J. Med. Virol. 92 (6), 552–555. https://doi.org/10.1002/jmv.25728.

Liebisch, G., Plagge, J., Höring, M., Seeliger, C., Ecker, J., 2021. The effect of gut microbiota on the intestinal lipidome of mice. Int. J. Med. Microbiol. 311 (3), 151488 https://doi.org/10.1016/j.ijmm.2021.151488.

Liu, J., Jiao, L., Zhong, X., Yao, W., Du, K., Lu, S., Wu, Y., Ma, T., Tong, J., Xu, M., Jiang, W., Wang, Y., He, M., Xin, W., Liu, M., 2022a. Platelet activating factor receptor exaggerates microglia-mediated microenvironment by IL10-STAT3 signaling: a novel potential biomarker and target for diagnosis and treatment of Alzheimer's disease. Front. Aging Neurosci. 14, 856628 https://doi.org/10.3389/fnagi.2022.856628.

Liu, Q., Mak, J.W.Y., Su, Q., Yeoh, Y.K., Lui, G.C.-Y., Ng, S.S.S., Zhang, F., Li, A.Y.L., Lu, W., Hui, D.S.-C., Chan, P.K., Chan, F.K.L., Ng, S.C., 2022b. Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome. Gut 71 (3), 544–552. https://doi.org/10.1136/gutjnl-2021-325989.

Liu, X., Zheng, P., Zhao, X., Zhang, Y., Hu, C., Li, J., Zhao, J., Zhou, J., Xie, P., Xu, G., 2015. Discovery and validation of plasma biomarkers for major depressive disorder classification based on liquid chromatography–mass spectrometry. J. Proteome Res. 14 (5), 2322–2330. https://doi.org/10.1021/acs.jproteome.5b00144.

Liu, X., Li, J., Zheng, P., Zhao, X., Zhou, C., Hu, C., Hou, X., Wang, H., Xie, P., Xu, G., 2016. Plasma lipidomics reveals potential lipid markers of major depressive disorder. Anal. Bioanal. Chem. 408 (23), 6497–6507. https://doi.org/10.1007/s00216-016-9768-5.

Lucki, N.C., Sewer, M.B., 2010. The interplay between bioactive sphingolipids and steroid hormones. Steroids 75 (6), 390–399. https://doi.org/10.1016/j.steroids.2010.01.020.

Mackay, A., 2021. A paradigm for post-covid-19 fatigue syndrome analogous to ME/CFS. Front. Neurol. 12, 701419 https://doi.org/10.3389/fneur.2021.701419.

Mackay, A., Tate, W.P., 2018. A compromised paraventricular nucleus within a dysfunctional hypothalamus: a novel neuroinflammatory paradigm for ME/CFS, 205873841881234 Int. J. Immunopathol. Pharmacol. 32. https://doi.org/10.1177/2058738418812342.

Maeba, R., Maeda, T., Kinoshita, M., Takao, K., Takenaka, H., Kusano, J., Yoshimura, N., Takeoka, Y., Yasuda, D., Okazaki, T., Teramoto, T., 2007. Plasmalogens in human serum positively correlate with high- density lipoprotein and decrease with aging. J. Atheroscler. Thromb. 14 (1), 12–18. https://doi.org/10.5551/jat.14.12.

Magalhães, A.C., Ferreira, A.R., Gomes, S., Vieira, M., Gouveia, A., Valença, I., Islinger, M., Nascimento, R., Schrader, M., Kagan, J.C., Ribeiro, D., 2016. Peroxisomes are platforms for cytomegalovirus' evasion from the cellular immune response. Sci. Rep. 6 (1), 26028. https://doi.org/10.1038/srep26028.

Malheiro, A.R., Correia, B., Ferreira Da Silva, T., Bessa-Neto, D., Van Veldhoven, P.P., Brites, P., 2019. Leukodystrophy caused by plasmalogen deficiency rescued by glyceryl 1–myristyl ether treatment. Brain Pathol. 29 (5), 622–639. https://doi.org/10.1111/bpa.12710.

Mankidy, R., Ahiahonu, P.W., Ma, H., Jayasinghe, D., Ritchie, S.A., Khan, M.A., Su-Myat, K.K., Wood, P.L., Goodenowe, D.B., 2010. Membrane plasmalogen composition and cellular cholesterol regulation: a structure activity study. Lipids Health Dis. 9 (1), 62. https://doi.org/10.1186/1476-511X-9-62.

Manly, J.J., Merchant, C.A., Jacobs, D.M., Small, S.A., Bell, K., Ferin, M., Mayeux, R., 2000. Endogenous estrogen levels and Alzheimer's disease among postmenopausal women. Neurology 54 (4), 833–837. https://doi.org/10.1212/WNL.54.4.833.

Mawatari, S., Ohara, S., Taniwaki, Y., Tsuboi, Y., Maruyama, T., Fujino, T., 2020. Improvement of blood plasmalogens and clinical symptoms in Parkinson's disease by oral administration of ether phospholipids: a preliminary report. Parkinson's Dis. 2020, 1–7. https://doi.org/10.1155/2020/2671070.

Mawatari, S., Fukata, M., Arita, T., Maruyama, T., Kono, S., Fujino, T., 2022. Decreases of ethanolamine plasmalogen and phosphatidylcholine in erythrocyte are a common phenomenon in Alzheimer's, Parkinson's, and coronary artery diseases. Brain Res. Bull. 189, 5–10. https://doi.org/10.1016/j.brainresbull.2022.08.009.

Mayneris-Perxachs, J., Moreno-Navarrete, J.M., Ballanti, M., Monteleone, G., Alessandro Paoluzi, O., Mingrone, G., Lefebvre, P., Staels, B., Federici, M., Puig, J., Garre, J., Ramos, R., Fernández-Real, J.-M., 2021. Lipidomics and metabolomics signatures of SARS-CoV-2 mediators/receptors in peripheral leukocytes, jejunum and colon. Comput. Struct. Biotechnol. J. 19, 6080–6089. https://doi.org/10.1016/j.csbj.2021.11.007.

McCarthy, M.K., Weinberg, J.B., 2012. Eicosanoids and respiratory viral infection: coordinators of inflammation and potential therapeutic targets. Mediat. Inflamm. 2012, 1–13. https://doi.org/10.1155/2012/236345.

McManimen, S.L., Sunnquist, M.L., Jason, L.A., 2019. Deconstructing post-exertional malaise: an exploratory factor analysis. J. Health Psychol. 24 (2), 188–198. https://doi.org/10.1177/1359105316664139.

McNamara, R.K., Moser, A.B., Jones, R.I., Jandacek, R., Patino, L.R., Strawn, J.R., Strakowski, S.M., DelBello, M.P., 2016. Familial risk for bipolar disorder is not associated with impaired peroxisomal function: dissociation from docosahexaenoic acid deficits. Psychiatry Res. 246, 803–807. https://doi.org/10.1016/j.psychres.2016.10.042.

Meinhardt, J., Radke, J., Dittmayer, C., Franz, J., Thomas, C., Mothes, R., Laue, M., Schneider, J., Brünink, S., Greuel, S., Lehmann, M., Hassan, O., Aschman, T., Schumann, E., Chua, R.L., Conrad, C., Eils, R., Stenzel, W., Windgassen, M., Heppner, F.L., 2021. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat. Neurosci. 24 (2), 168–175. https://doi.org/10.1038/s41593-020-00758-5.

Mesa-Herrera, Taoro-González, Valdés-Baizabal, Diaz, Marín, 2019. Lipid and lipid raft alteration in aging and neurodegenerative diseases: a window for the development of new biomarkers. Int. J. Mol. Sci. 20 (15), 3810. https://doi.org/10.3390/ijms20153810.

Messner, M.C., Albert, C.J., Ford, D.A., 2008. 2-chlorohexadecanal and 2-chlorohexadecanoic acid induce COX-2 expression in human coronary artery endothelial cells. Lipids 43 (7), 581–588. https://doi.org/10.1007/s11745-008-3189-y.

Missailidis, D., Sanislav, O., Allan, C.Y., Smith, P.K., Annesley, S.J., Fisher, P.R., 2021. Dysregulated provision of oxidisable substrates to the mitochondria in ME/CFS lymphoblasts. Int. J. Mol. Sci. 22 (4), 2046. https://doi.org/10.3390/ijms22042046.

Missailidis, D., Annesley, S.J., Allan, C.Y., Sanislav, O., Lidbury, B.A., Lewis, D.P., Fisher, P.R., 2020. An isolated complex V inefficiency and dysregulated mitochondrial function in immortalized lymphocytes from ME/CFS patients. Int. J. Mol. Sci. 21 (3), 1074. https://doi.org/10.3390/ijms21031074.

Miville-Godbout, E., Bourque, M., Morissette, M., Al-Sweidi, S., Smith, T., Jayasinghe, D., Ritchie, S., Di Paolo, T., 2017. Plasmalogen precursor mitigates striatal dopamine loss in MPTP mice. Brain Res. 1674, 70–76. https://doi.org/10.1016/j.brainres.2017.08.020.

Miville-Godbout, E., Bourque, M., Morissette, M., Al-Sweidi, S., Smith, T., Mochizuki, A., Senanayake, V., Jayasinghe, D., Wang, L., Goodenowe, D., Di Paolo, T., 2016. Plasmalogen augmentation reverses striatal dopamine loss in MPTP mice. PLoS One 11 (3), e0151020. https://doi.org/10.1371/journal.pone.0151020.

Mohebali, D., Kaplan, D., Carlisle, M., Supiano, M.A., Rondina, M.T., 2014. Alterations in platelet function during aging: clinical correlations with thromboinflammatory

disease in older adults. J. Am. Geriatr. Soc. 62 (3), 529–535. https://doi.org/10.1111/jgs.12700.
Moldofsky, H., Patcai, J., 2011. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. BMC Neurol. 11 (1), 37. https://doi.org/10.1186/1471-2377-11-37.
Montine, T.J., Markesbery, W.R., Zackert, W., Sanchez, S.C., Roberts, L.J., Morrow, J.D., 1999. The magnitude of brain lipid peroxidation correlates with the extent of degeneration but not with density of neuritic plaques or neurofibrillary tangles or with APOE genotype in Alzheimer's disease patients. Am. J. Pathol. 155 (3), 863–868. https://doi.org/10.1016/S0002-9440(10)65185-1.
Montine, T.J., Neely, M.D., Quinn, J.F., Beal, M.F., Markesbery, W.R., Roberts, L.J., & Morrow, J.D. (2002). Lipid peroxidation in aging brain and Alzheimer's disease1,2 1Guest Editors: Mark A. Smith and George Perry 2This article is part of a series of reviews on "Causes and Consequences of Oxidative Stress in Alzheimer's Disease". The full list of papers may be found on the homepage of the journal. Free Radical Biology and Medicine, 33(5), 620–626. https://doi.org/10.1016/S0891–5849(02)00807–9.
Morris, G., Maes, M., 2014. Oxidative and nitrosative stress and immune-inflammatory pathways in patients with myalgic encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS). Curr. Neuropharmacol. 12, 168–185. https://doi.org/10.2174/1570159X11666131120224653.
Morris, G., Berk, M., Walder, K., Maes, M., 2015. Central pathways causing fatigue in neuro-inflammatory and autoimmune illnesses. In: BMC Medicine, 13, p. 28. https://doi.org/10.1186/s12916-014-0259-2.
Mueller, C., Lin, J.C., Sheriff, S., Maudsley, A.A., Younger, J.W., 2020. Evidence of widespread metabolite abnormalities in Myalgic encephalomyelitis/chronic fatigue syndrome: assessment with whole-brain magnetic resonance spectroscopy. Brain Imaging Behav. 14 (2), 562–572. https://doi.org/10.1007/s11682-018-0029-4.
Mühle, C., Reichel, M., Gulbins, E., Kornhuber, J., 2013. Sphingolipids in Psychiatric Disorders and Pain Syndromes. In: Gulbins, E., Petrache, I. (Eds.), Sphingolipids in Disease, Vol. 216. Springer, Vienna, pp. 431–456. https://doi.org/10.1007/978-3-7091-1511-4_22.
Mukai, T., Kishi, T., Matsuda, Y., Iwata, N., 2014. A meta-analysis of inositol for depression and anxiety disorders: inositol and depression and anxiety disorders. Hum. Psychopharmacol.: Clin. Exp. 29 (1), 55–63. https://doi.org/10.1002/hup.2369.
Murakami, M., Yamamoto, K., Miki, Y., Murase, R., Sato, H., Taketomi, Y., 2016. The roles of the secreted phospholipase A2 gene family in immunology. In: Advances in Immunology, Vol. 132. Elsevier, pp. 91–134. https://doi.org/10.1016/bs.ai.2016.05.001.
Murta, V., Villarreal, A., Ramos, A.J., 2020. Severe acute respiratory syndrome coronavirus 2 impact on the central nervous system: are astrocytes and microglia main players or merely bystanders?, 175909142095496 ASN Neuro 12. https://doi.org/10.1177/1759091420954960.
Musiek, E., Cha, J., Yin, H., Zackert, W., Terry, E., Porter, N., Montine, T., Morrow, J., 2004. Quantification of F-ring isoprostane-like compounds (F4-neuroprostanes) derived from docosahexaenoic acid in vivo in humans by a stable isotope dilution mass spectrometric assay. J. Chromatogr. B 799 (1), 95–102. https://doi.org/10.1016/j.jchromb.2003.10.036.
Muzio, L., Viotti, A., Martino, G., 2021. Microglia in neuroinflammation and neurodegeneration: from understanding to therapy. Front. Neurosci. 15, 742065 https://doi.org/10.3389/fnins.2021.742065.
Nagan, N., Zoeller, R.A., 2001. Plasmalogens: biosynthesis and functions. Prog. Lipid Res. 40, 199–229. https://doi.org/10.1016/s0163-7827(01)00003-0.
Nagy-Szakal, D., Williams, B.L., Mishra, N., Che, X., Lee, B., Bateman, L., Klimas, N.G., Komaroff, A.L., Levine, S., Montoya, J.G., Peterson, D.L., Ramanan, D., Jain, K., Eddy, M.L., Hornig, M., Lipkin, W.I., 2017. Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome. Microbiome 5 (1), 44. https://doi.org/10.1186/s40168-017-0261-y.
Nagy-Szakal, D., Barupal, D.K., Lee, B., Che, X., Williams, B.L., Kahn, E.J.R., Ukaigwe, J. E., Bateman, L., Klimas, N.G., Komaroff, A.L., Levine, S., Montoya, J.G., Peterson, D. L., Levin, B., Hornig, M., Fiehn, O., Lipkin, W.I., 2018. Insights into myalgic encephalomyelitis/chronic fatigue syndrome phenotypes through comprehensive metabolomics. Sci. Rep. 8 (1), 10056. https://doi.org/10.1038/s41598-018-28477-9.
Nakatomi, Y., Mizuno, K., Ishii, A., Wada, Y., Tanaka, M., Tazawa, S., Onoe, K., Fukuda, S., Kawabe, J., Takahashi, K., Kataoka, Y., Shiomi, S., Yamaguti, K., Inaba, M., Kuratsune, H., Watanabe, Y., 2014. Neuroinflammation in patients with chronic fatigue syndrome/myalgic encephalomyelitis: An ^{11}C-(*R*)-PK11195 PET study. J. Nucl. Med. 55 (6), 945–950. https://doi.org/10.2967/jnumed.113.131045.
Naviaux, R.K., Naviaux, J.C., Li, K., Bright, A.T., Alaynick, W.A., Wang, L., Baxter, A., Nathan, N., Anderson, W., Gordon, E., 2016. Metabolic features of chronic fatigue syndrome. Proc. Natl. Acad. Sci. 113 (37) https://doi.org/10.1073/pnas.1607571113.
Nelson, T., Zhang, L.-X., Guo, H., Nacul, L., Song, X., 2021. Brainstem abnormalities in myalgic encephalomyelitis/chronic fatigue syndrome: a scoping review and evaluation of magnetic resonance imaging findings. Front. Neurol. 12, 769511 https://doi.org/10.3389/fneur.2021.769511.
Nkiliza, A., Parks, M., Cseresznye, A., Oberlin, S., Evans, J.E., Darcey, T., Aenlle, K., Niedospial, D., Mullan, M., Crawford, F., Klimas, N., Abdullah, L., 2021. Sex-specific plasma lipid profiles of ME/CFS patients and their association with pain, fatigue, and cognitive symptoms. J. Transl. Med. 19 (1), 370. https://doi.org/10.1186/s12967-021-03035-6.
Notarte, K.I., Catahay, J.A., Velasco, J.V., Pastrana, A., Ver, A.T., Pangilinan, F.C., Peligro, P.J., Casimiro, M., Guerrero, J.J., Gellaco, Ma.M.L., Lippi, G., Henry, B.M., Fernández-de-las-Peñas, C., 2022. Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: a systematic review. EClinicalMedicine 53, 101624. https://doi.org/10.1016/j.eclinm.2022.101624.
Nourooz-Zadeh, J., Liu, E.H.C., Yhlen, B., Änggård, E.E., Halliwell, B., 1999. F4—isoprostanes as specific marker of docosahexaenoic acid peroxidation in Alzheimer's disease. J. Neurochem. 72 (2), 734–740. https://doi.org/10.1046/j.1471-4159.1999.0720734.x.
Ogawa, S., Hattori, K., Ota, M., Hidese, S., Miyakawa, T., Matsumura, R., Yokota, Y., Ishida, I., Matsuo, J., Yoshida, S., Yamazaki, Y., Goodenowe, D., Kunugi, H., 2020. Altered ethanolamine plasmalogen and phosphatidylethanolamine levels in blood plasma of patients with bipolar disorder. Psychiatry Clin. Neurosci. 74 (3), 204–210. https://doi.org/10.1111/pcn.12967.
Olazarán, J., Gil-de-Gómez, L., Rodríguez-Martín, A., Valentí-Soler, M., Frades-Payo, B., Marín-Muñoz, J., Antúnez, C., Frank-García, A., Acedo-Jiménez, C., Morlán-Gracia, L., Petidier-Torregrossa, R., Guisasola, M.C., Bermejo-Pareja, F., Sánchez-Ferro, Á., Pérez-Martínez, D.A., Manzano-Palomo, S., Farquhar, R., Rábano, A., Calero, M., 2015. A blood-based, 7-metabolite signature for the early diagnosis of Alzheimer's disease. J. Alzheimer's Dis. 45 (4), 1157–1173. https://doi.org/10.3233/JAD-142925.
Palmas, F., Clarke, J., Colas, R.A., Gomez, E.A., Keogh, A., Boylan, M., McEvoy, N., McElvaney, O.J., McElvaney, O., Alalqam, R., McElvaney, N.G., Curley, G.F., Dalli, J., 2021. Dysregulated plasma lipid mediator profiles in critically ill COVID-19 patients. PLOS ONE 16 (8), e0256226. https://doi.org/10.1371/journal.pone.0256226.
Paltauf, F., 1972. Intestinal uptake and metabolism of alkyl acyl glycerophospholipids and of alkyl glycerophospholipids in the rat biosynthesis of plasmalogens from [3H] alkyl glycerophosphoryl [14c]ethanolamine. Biochim. Et. Biophys. Acta (BBA) - Lipids Lipid Metab. 260 (3), 352–364. https://doi.org/10.1016/0005-2760(72)90049-5.
Paul, B.D., Lemle, M.D., Komaroff, A.L., Snyder, S.H., 2021. Redox imbalance links COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome. Proc. Natl. Acad. Sci. 118 (34), e2024358118 https://doi.org/10.1073/pnas.2024358118.
Paul, S., Lancaster, G.I., Meikle, P.J., 2019. Plasmalogens: a potential therapeutic target for neurodegenerative and cardiometabolic disease. Prog. Lipid Res. 74, 186–195. https://doi.org/10.1016/j.plipres.2019.04.003.
Paul, S., Rasmiena, A.A., Huynh, K., Smith, A.A.T., Mellett, N.A., Jandeleit-Dahm, K., Lancaster, G.I., Meikle, P.J., 2021a. Oral supplementation of an alkylglycerol mix comprising different alkyl chains effectively modulates multiple endogenous plasmalogen species in mice. Metabolites 11 (5), 299. https://doi.org/10.3390/metabo11050299.
Paul, S., Smith, A.A.T., Culham, K., Gunawan, K.A., Weir, J.M., Cinel, M.A., Jayawardana, K.S., Mellett, N.A., Lee, M.K.S., Murphy, A.J., Lancaster, G.I., Nestel, P.J., Kingwell, B.A., Meikle, P.J., 2021b. Shark liver oil supplementation enriches endogenous plasmalogens and reduces markers of dyslipidemia and inflammation. J. Lipid Res. 62, 100092 https://doi.org/10.1016/j.jlr.2021.100092.
Pavli, A., Theodoridou, M., Maltezou, H.C., 2021. Post-COVID syndrome: incidence, clinical spectrum, and challenges for primary healthcare professionals. Arch. Med. Res. 52 (6), 575–581. https://doi.org/10.1016/j.arcmed.2021.03.010.
Penninx, B.W.J.H., Benros, M.E., Klein, R.S., Vinkers, C.H., 2022. How COVID-19 shaped mental health: from infection to pandemic effects. Nat. Med. 28 (10), 2027–2037. https://doi.org/10.1038/s41591-022-02028-2.
Pettegrew, J.W., Panchalingam, K., Levine, J., McClure, R.J., Gershon, S., Yao, J.K., 2001. Chronicmyo-inositol increases rat brain phosphatidylethanolamine plasmalogen. Biol. Psychiatry 49 (5), 444–453. https://doi.org/10.1016/S0006-3223(00)00953-7.
Pike, D.P., Vogel, M.J., McHowat, J., Mikuzis, P.A., Schulte, K.A., Ford, D.A., 2020. 2-Chlorofatty acids are biomarkers of sepsis mortality and mediators of barrier dysfunction in rats. J. Lipid Res. 61 (7), 1115–1127. https://doi.org/10.1194/jlr.RA120000829.
Pike, D.P., McGuffee, R.M., Geerling, E., Albert, C.J., Hoft, D.F., Shashaty, M.G.S., Meyer, N.J., Pinto, A.K., Ford, D.A., 2022. Plasmalogen Loss in Sepsis and SARS-CoV-2 Infection. Front. Cell Dev. Biol. 10, 912880 https://doi.org/10.3389/fcell.2022.912880.
Podbielska, M., O'Keeffe, J., Pokryszko-Dragan, A., 2021. New insights into multiple sclerosis mechanisms: lipids on the track to control inflammation and neurodegeneration. Int. J. Mol. Sci. 22 (14), 7319. https://doi.org/10.3390/ijms22147319.
Poewe, W., Seppi, K., Tanner, C.M., Halliday, G.M., Brundin, P., Volkmann, J., Schrag, A.-E., Lang, A.E., 2017. Parkinson disease. Nat. Rev. Dis. Prim. 3 (1), 17013. https://doi.org/10.1038/nrdp.2017.13.
Poloni, T.E., Medici, V., Moretti, M., Visonà, S.D., Cirrincione, A., Carlos, A.F., Davin, A., Gagliardi, S., Pansarasa, O., Cereda, C., Tronconi, L., Guaita, A., Ceroni, M., 2021. COVID-19–related neuropathology and microglial activation in elderly with and without dementia. Brain Pathol. 31 (5) https://doi.org/10.1111/bpa.12997.
Pratico, D., Lee, V.M.-Y., Trojanowski, J.Q., Rokach, J., Fitzgerald, G.A., 1998. Increased F_2-isoprostanes in Alzheimer's disease: evidence for enhanced lipid peroxidation in vivo. FASEB J. 12 (15), 1777–1783. https://doi.org/10.1096/fasebj.12.15.1777.
Pugliese, P.T., Jordan, K., Cederberg, H., Brohult, J., 1998. Some biological actions of alkylglycerols from shark liver oil. J. Altern. Complement. Med. 4 (1), 87–99. https://doi.org/10.1089/acm.1998.4.1-87.
Ramos-Cejudo, J., Johnson, A.D., Beiser, A., Seshadri, S., Salinas, J., Berger, J.S., Fillmore, N.R., Do, N., Zheng, C., Kovbasyuk, Z., Ardekani, B.A., Pomara, N., Bubu, O.M., Parekh, A., Convit, A., Betensky, R.A., Wisniewski, T.M., Osorio, R.S., 2022. Platelet function is associated with dementia risk in the framingham heart study. J. Am. Heart Assoc. 11 (9), e023918 https://doi.org/10.1161/JAHA.121.023918.

Rasa, S., et al., 2018. Chronic viral infections in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). J. Transl. Med. 16, 268.
Rayhan, R.U., Baraniuk, J.N., 2021. Submaximal exercise provokes increased activation of the anterior default mode network during the resting state as a biomarker of postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome. Front. Neurosci. 15, 748426 https://doi.org/10.3389/fnins.2021.748426.
Reeves, W.C., Jones, J.F., Maloney, E., Heim, C., Hoaglin, D.C., Boneva, R.S., Morrissey, M., Devlin, R., 2007. Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. Popul. Health Metr. 5 (1), 5. https://doi.org/10.1186/1478-7954-5-5.
Reich, E.E., Markesbery, W.R., Roberts, L.J., Swift, L.L., Morrow, J.D., Montine, T.J., 2001. Brain regional quantification of F-ring and D-/E-ring isoprostanes and neuroprostanes in Alzheimer's disease. Am. J. Pathol. 158 (1), 293–297. https://doi.org/10.1016/S0002-9440(10)63968-5.
Reichwald, J., Danner, S., Wiederhold, K.-H., Staufenbiel, M., 2009. Expression of complement system components during aging and amyloid deposition in APP transgenic mice. J. Neuroinflamm. 6 (1), 35. https://doi.org/10.1186/1742-2094-6-35.
Reiss, D., Beyer, K., Engelmann, B., 1997. Delayed oxidative degradation of polyunsaturated diacyl phospholipids in the presence of plasmalogen phospholipids in vitro. Biochem. J. 323 (3), 807–814. https://doi.org/10.1042/bj3230807.
Renz-Polster, H., Tremblay, M.-E., Bienzle, D., Fischer, J.E., 2022. The pathobiology of myalgic encephalomyelitis/chronic fatigue syndrome: the case for neuroglial failure. Front. Cell. Neurosci. 16, 888232 https://doi.org/10.3389/fncel.2022.888232.
Retornaz, F., Rebaudet, S., Stavris, C., Jammes, Y., 2022. Long-term neuromuscular consequences of SARS-Cov-2 and their similarities with myalgic encephalomyelitis/chronic fatigue syndrome: results of the retrospective CoLGEM study. J. Transl. Med. 20 (1), 429. https://doi.org/10.1186/s12967-022-03638-7.
Rezaei, A., Neshat, S., Heshmat-Ghahdarijani, K., 2022. Alterations of lipid profile in COVID-19: a narrative review. Curr. Probl. Cardiol. 47 (3), 100907 https://doi.org/10.1016/j.cpcardiol.2021.100907.
Ribardo, D.A., Crowe, S.E., Kuhl, K.R., Peterson, J.W., Chopra, A.K., 2001. Prostaglandin levels in stimulated macrophages are controlled by phospholipase A2-activating protein and by activation of phospholipase C and D. J. Biol. Chem. 276 (8), 5467–5475. https://doi.org/10.1074/jbc.M006690200.
Rivière, A., Selak, M., Lantin, D., Leroy, F., De Vuyst, L., 2016. Bifidobacteria and butyrate-producing colon bacteria: importance and strategies for their stimulation in the human gut. Front. Microbiol. 7 https://doi.org/10.3389/fmicb.2016.00979.
Rog, T., Koivuniemi, A., 2016. The biophysical properties of ethanolamine plasmalogens revealed by atomistic molecular dynamics simulations. Biochim. Biophys. Acta 1858, 97–103.
Rogers, J.P., Chesney, E., Oliver, D., Pollak, T.A., McGuire, P., Fusar-Poli, P., Zandi, M.S., Lewis, G., David, A.S., 2020. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry 7 (7), 611–627. https://doi.org/10.1016/S2215-0366(20)30203-0.
Rong, P., Wang, J.-L., Angelova, A., Almsherqi, Z.A., Deng, Y., 2022. Plasmalogenic Lipid Analogs as Platelet-Activating Factor Antagonists: A Potential Novel Class of Anti-inflammatory Compounds. Front. Cell Dev. Biol. 10, 859421 https://doi.org/10.3389/fcell.2022.859421.
Rouser, G., Yamamoto, A., 1968. Curvilinear regression course of human brain lipid composition changes with age. Lipids 3 (3), 284–287. https://doi.org/10.1007/BF02531202.
Rubio, J.M., Astudillo, A.M., Casas, J., Balboa, M.A., Balsinde, J., 2018. Regulation of phagocytosis in macrophages by membrane ethanolamine plasmalogens. Front. Immunol. 9, 1723. https://doi.org/10.3389/fimmu.2018.0172.
Russell, L., Broderick, G., Taylor, R., Fernandes, H., Harvey, J., Barnes, Z., Smylie, A., Collado, F., Balbin, E.G., Katz, B.Z., Klimas, N.G., Fletcher, M.A., 2016. Illness progression in chronic fatigue syndrome: a shifting immune baseline. BMC Immunol. 17 (1), 3. https://doi.org/10.1186/s12865-016-0142-3.
Ryan, S.D., et al., 2007. Platelet activating factor-induced neuronal apoptosis is initiated independently of its G-protein coupled PAF receptor and is inhibited by the benzoate orsellinic acid. J. Neurochem. 103, 88–97.
Sambolín-Escobales, L., Feliciano-Quiñones, A., Tirado-Castro, L., Suárez, C., Pacheco-Cruz, D., Irizarry-Méndez, N., Fonseca-Ferrer, W., Hernández-López, A., Colón-Romero, M., Porter, J.T., 2022. Infusion of C20:0 ceramide into ventral hippocampus triggers anhedonia-like behavior in female and male rats. Front. Behav. Neurosci. 16, 899627 https://doi.org/10.3389/fnbeh.2022.899627.
Sampson, T.R., 2023. Revealing gut microbiome associations with CFS. Cell Host Microbe 31 (2), 171–172. https://doi.org/10.1016/j.chom.2023.01.011.
Santiago, A.R., Bernardino, L., Agudo-Barriuso, M., Gonçalves, J., 2017. Microglia in health and disease: a double-edged sword. Mediat. Inflamm. 2017, 1–2. https://doi.org/10.1155/2017/7034143.
Sárvári, M., Hrabovszky, E., Kalló, I., Solymosi, N., Likó, I., Berchtold, N., Cotman, C., Liposits, Z., 2012. Menopause leads to elevated expression of macrophage-associated genes in the aging frontal cortex: rat and human studies identify strikingly similar changes. J. Neuroinflamm. 9 (1), 773. https://doi.org/10.1186/1742-2094-9-264.
Sárvári, M., Kalló, I., Hrabovszky, E., Solymosi, N., Rodolosse, A., Vastagh, C., Auer, H., Liposits, Z., 2015. Hippocampal gene expression is highly responsive to estradiol replacement in middle-aged female rats. Endocrinology 156 (7), 2632–2645. https://doi.org/10.1210/en.2015-1109.
Satoh, K., Imaizumi, T., Yoshida, H., Hiramoto, M., Takamatsu, S., 1992. Increased levels of blood platelet-activating factor (PAF) and PAF-like lipids in patients with ischemic stroke. Acta Neurol. Scand. 85 (2), 122–127. https://doi.org/10.1111/j.1600-0404.1992.tb04010.x.
Scheyer, O., Rahman, A., Hristov, H., Berkowitz, C., Isaacson, R.S., Diaz Brinton, R., Mosconi, L., 2018. Female sex and Alzheimer's risk: the menopause connection. J. Prev. Alzheimer's Dis. 1–6. https://doi.org/10.14283/jpad.2018.34.
Schooneveldt, Y.L., Paul, S., Calkin, A.C., Meikle, P.J., 2022. Ether lipids in obesity: from cells to population studies. Front. Physiol. 13, 841278 https://doi.org/10.3389/fphys.2022.841278.
Schuler, M.-H., Di Bartolomeo, F., Mårtensson, C.U., Daum, G., Becker, T., 2016. Phosphatidylcholine affects inner membrane protein translocases of mitochondria. J. Biol. Chem. 291 (36), 18718–18729. https://doi.org/10.1074/jbc.M116.722694.
Schuler, M.-H., Di Bartolomeo, F., Böttinger, L., Horvath, S.E., Wenz, L.-S., Daum, G., Becker, T., 2015. Phosphatidylcholine affects the role of the sorting and assembly machinery in the biogenesis of mitochondrial β-barrel proteins. J. Biol. Chem. 290 (44), 26523–26532. https://doi.org/10.1074/jbc.M115.687921.
Schuurman, A.R., Léopold, V., Pereverzeva, L., Chouchane, O., Reijnders, T.D.Y., Brabander, J.D., Douma, R.A., Weeghel, M.V., Wever, E., Schomaker, B.V., Vaz, F. M., Wiersinga, W.J., Veer, C.V., Poll, T.V.D., 2022. The platelet lipidome is altered in patients with COVID-19 and correlates with platelet reactivity. Thromb. Haemost. 122 (10), 1683–1692. https://doi.org/10.1055/s-0042-1749438.
Schwabenland, M., Salié, H., Tanevski, J., Killmer, S., Lago, M.S., Schlaak, A.E., Mayer, L., Matschke, J., Püschel, K., Fitzek, A., Ondruschka, B., Mei, H.E., Boettler, T., Neumann-Haefelin, C., Hofmann, M., Breithaupt, A., Genc, N., Stadelmann, C., Saez-Rodriguez, J., Bengsch, B., 2021. Deep spatial profiling of human COVID-19 brains reveals neuroinflammation with distinct microanatomical microglia-T-cell interactions. Immunity 54 (7), 1594–1610.e11. https://doi.org/10.1016/j.immuni.2021.06.002.
Schwarz, B., Sharma, L., Roberts, L., Peng, X., Bermejo, S., Leighton, I., Casanovas-Massana, A., Minasyan, M., Farhadian, S., Ko, A.I., Yale IMPACT Team, Dela Cruz, C. S., Bosio, C.M., 2021. Cutting edge: severe SARS-CoV-2 infection in humans is defined by a shift in the serum lipidome, resulting in dysregulation of eicosanoid immune mediators. J. Immunol. 206 (2), 329–334. https://doi.org/10.4049/jimmunol.2001025.
Sejimo, S., Hossain, M.S., Akashi, K., 2018. Scallop-derived plasmalogens attenuate the activation of PKCδ associated with the brain inflammation. Biochem. Biophys. Res. Commun. 503 (2), 837–842. https://doi.org/10.1016/j.bbrc.2018.06.084.
Senanayake, V., Goodenowe, D.B., 2019. Plasmalogen deficiency and neuropathology in Alzheimer's disease: Causation or coincidence? Alzheimer's Dement.: Transl. Res. Clin. Interv. 5 (1), 524–532. https://doi.org/10.1016/j.trci.2019.08.003.
Shan, Z.Y., Barnden, L.R., Kwiatek, R.A., Bhuta, S., Hermens, D.F., Lagopoulos, J., 2020. Neuroimaging characteristics of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a systematic review. J. Transl. Med. 18 (1), 335. https://doi.org/10.1186/s12967-020-02506-6.
Shao, F., Wang, X., Wu, H., Wu, Q., Zhang, J., 2022. Microglia and neuroinflammation: crucial pathological mechanisms in traumatic brain injury-induced neurodegeneration. Front. Aging Neurosci. 14, 825086 https://doi.org/10.3389/fnagi.2022.825086.
Shaw, A.C., Panda, A., Joshi, S.R., Qian, F., Allore, H.G., Montgomery, R.R., 2011. Dysregulation of human Toll-like receptor function in aging. Ageing Res. Rev. 10 (3), 346–353. https://doi.org/10.1016/j.arr.2010.10.007.
Siessmeier, T., 2003. Observer independent analysis of cerebral glucose metabolism in patients with chronic fatigue syndrome. J. Neurol., Neurosurg. Psychiatry 74 (7), 922–928. https://doi.org/10.1136/jnnp.74.7.922.
Simons, K., Ehehalt, R., 2002. Cholesterol, lipid rafts, and disease. J. Clin. Invest. 110 (5), 597–603. https://doi.org/10.1172/JCI16390. Sep; PMID: 12208858 PMCID: PMC151114 DOI: 10.1172/JCI16390.
Snider, J.M., You, J.K., Wang, X., Snider, A.J., Hallmark, B., Zec, M.M., Seeds, M.C., Sergeant, S., Johnstone, L., Wang, Q., Sprissler, R., Carr, T.F., Lutrick, K., Parthasarathy, S., Bime, C., Zhang, H.H., Luberto, C., Kew, R.R., Hannun, Y.A., Chilton, F.H., 2021. Group IIA secreted phospholipase A2 is associated with the pathobiology leading to COVID-19 mortality. J. Clin. Investig. 131 (19), e149236 https://doi.org/10.1172/JCI149236.
Song, C., Shieh, C.-H., Wu, Y.-S., Kalueff, A., Gaikwad, S., Su, K.-P., 2016. The role of omega-3 polyunsaturated fatty acids eicosapentaenoic and docosahexaenoic acids in the treatment of major depression and Alzheimer's disease: acting separately or synergistically? Prog. Lipid Res. 62, 41–54. https://doi.org/10.1016/j.plipres.2015.12.003.
Sousa, C., Golebiewska, A., Poovathingal, S.K., Kaoma, T., Pires-Afonso, Y., Martina, S., Coowar, D., Azuaje, F., Skupin, A., Balling, R., Biber, K., Niclou, S.P., Michelucci, A., 2018. Single-cell transcriptomics reveals distinct inflammation-induced microglia signatures. EMBO Rep. 19 (11) https://doi.org/10.15252/embr.201846171.
Sperka-Gottlieb, C.D.M., Hermetter, A., Paltauf, F., Daum, G., 1988. Lipid topology and physical properties of the outer mitochondrial membrane of the yeast, Saccharomyces cerevisiae. Biochim. Et. Biophys. Acta (BBA) - Biomembr. 946 (2), 227–234. https://doi.org/10.1016/0005-2736(88)90397-5.
Strickland, P.S., Levine, P.H., Peterson, D.L., O'Brien, K., Fears, T., 2001. Neuromyasthenia and chronic fatigue syndrome (CFS) in northern nevada/california: a ten-year follow-up of an outbreak. J. Chronic Fatigue Syndr. 9 (3–4), 3–14. https://doi.org/10.1300/J092v09n03_02.
Stussman, B., Williams, A., Snow, J., Gavin, A., Scott, R., Nath, A., Walitt, B., 2020. Characterization of post–exertional malaise in patients with myalgic encephalomyelitis/chronic fatigue syndrome. Front. Neurol. 11, 1025. https://doi.org/10.3389/fneur.2020.01025.
Su, H.I., Freeman, E.W., 2009. Hormone changes associated with the menopausal transition. Minerva Ginecol. 61 (6), 483–489.
Su, X.Q., Wang, J., Sinclair, A.J., 2019. Plasmalogens and Alzheimer's disease: a review. Lipids Health Dis. 18 (1), 100. https://doi.org/10.1186/s12944-019-1044-1.

Subramaniam, S.R., Chesselet, M.-F., 2013. Mitochondrial dysfunction and oxidative stress in Parkinson's disease. Prog. Neurobiol. 106–107, 17–32. https://doi.org/10.1016/j.pneurobio.2013.04.004.

Sukocheva, O., Wadham, C., Xia, P., 2009. Role of sphingolipids in the cytoplasmic signaling of estrogens. Steroids 74 (7), 562–567. https://doi.org/10.1016/j.steroids.2008.12.014.

Sukocheva, O.A., Maksoud, R., Beeraka, N.M., Madhunapantula, S.V., Sinelnikov, M., Nikolenko, V.N., Neganova, M.E., Klochkov, S.G., Amjad Kamal, M., Staines, D.R., Marshall-Gradisnik, S., 2022. Analysis of post COVID-19 condition and its overlap with myalgic encephalomyelitis/chronic fatigue syndrome. J. Adv. Res. 40, 179–196. https://doi.org/10.1016/j.jare.2021.11.013.

Sultanov, R., Ermolenko, E., Poleshchuk, T., Kasyanov, S., 2022. Alkyl glycerol ethers as adaptogens. Mar. Drugs 21 (1), 4. https://doi.org/10.3390/md21010004.

Tabarés-Seisdedos, R., Escámez, T., Martínez-Giménez, J.A., Balanzá, V., Salazar, J., Selva, G., Rubio, C., Vieta, E., Geijó-Barrientos, E., Martínez-Arán, A., Reiner, O., Martínez, S., 2006. Variations in genes regulating neuronal migration predict reduced prefrontal cognition in schizophrenia and bipolar subjects from mediterranean Spain: a preliminary study. Neuroscience 139 (4), 1289–1300. https://doi.org/10.1016/j.neuroscience.2006.01.054.

Tamagno, E., Guglielmotto, M., Vasciaveo, V., Tabaton, M., 2021. Oxidative stress and beta amyloid in Alzheimer's disease. which comes first: the chicken or the egg? Antioxidants 10 (9), 1479. https://doi.org/10.3390/antiox10091479.

Tanaka, M., Sadato, N., Okada, T., Mizuno, K., Sasabe, T., Tanabe, H.C., Saito, D.N., Onoe, H., Kuratsune, H., Watanabe, Y., 2006. Reduced responsiveness is an essential feature of chronic fatigue syndrome: a fMRI study. BMC Neurol. 6 (1), 9. https://doi.org/10.1186/1471-2377-6-9.

Tang, Y., Liu, J., Zhang, D., Xu, Z., Ji, J., Wen, C., 2020. Cytokine storm in COVID-19: the current evidence and treatment strategies. Front. Immunol. 11, 1708. https://doi.org/10.3389/fimmu.2020.01708.

Tapia-Gonzalez, S., Carrero, P., Pernia, O., Garcia-Segura, L.M., Diz-Chaves, Y., 2008. Selective oestrogen receptor (ER) modulators reduce microglia reactivity in vivo after peripheral inflammation: potential role of microglial ERs. J. Endocrinol. 198 (1), 219–230. https://doi.org/10.1677/JOE-07-0294.

Tate, W., Walker, M., Sweetman, E., Helliwell, A., Peppercorn, K., Edgar, C., Blair, A., Chatterjee, A., 2022. Molecular mechanisms of neuroinflammation in ME/CFS and Long COVID to sustain disease and promote relapses. Front. Neurol. 13, 877772 https://doi.org/10.3389/fneur.2022.877772.

Terlecky, S.R., 2012. Peroxisomes, oxidative stress, and inflammation. World J. Biol. Chem. 3 (5), 93. https://doi.org/10.4331/wjbc.v3.i5.93.

Tessier, C., Sweers, K., Frajerman, A., Bergaoui, H., Ferreri, F., Delva, C., Lapidus, N., Lamaziere, A., Roiser, J.P., De Hert, M., Nuss, P., 2016. Membrane lipidomics in schizophrenia patients: a correlational study with clinical and cognitive manifestations. e906–e906 Transl. Psychiatry 6 (10). https://doi.org/10.1038/tp.2016.142.

Theken, K.N., Tang, S.Y., Sengupta, S., FitzGerald, G.A., 2021. The roles of lipids in SARS-CoV-2 viral replication and the host immune response. J. Lipid Res. 62, 100129 https://doi.org/10.1016/j.jlr.2021.100129.

Theoharides, T.C., Antonopoulou, S., Demopoulos, C.A., 2020. Coronavirus 2019, microthromboses, and platelet activating factor. Clin. Ther. 42, 1850–1852.

Thomas, N., Gurvich, C., Huang, K., Gooley, P.R., Armstrong, C.W., 2022. The underlying sex differences in neuroendocrine adaptations relevant to myalgic encephalomyelitis chronic fatigue syndrome. Front. Neuroendocrinol. 66, 100995 https://doi.org/10.1016/j.yfrne.2022.100995.

Thomas, R.H., Foley, K.A., Mepham, J.R., Tichenoff, L.J., Possmayer, F., MacFabe, D.F., 2010. Altered brain phospholipid and acylcarnitine profiles in propionic acid infused rodents: further development of a potential model of autism spectrum disorders. J. Neurochem. 113 (2), 515–529. https://doi.org/10.1111/j.1471-4159.2010.06614.x.

Tian, D.-S., Liu, J.-L., Xie, M.-J., Zhan, Y., Qu, W.-S., Yu, Z.-Y., Tang, Z.-P., Pan, D.-J., Wang, W., 2009. Tamoxifen attenuates inflammatory-mediated damage and improves functional outcome after spinal cord injury in rats. J. Neurochem. 109 (6), 1658–1667. https://doi.org/10.1111/j.1471-4159.2009.06077.x.

Tirelli, U., Chierichetti, F., Tavio, M., Simonelli, C., Bianchin, G., Zanco, P., Ferlin, G., 1998. Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. Am. J. Med. 105 (3), 54S–58S. https://doi.org/10.1016/S0002-9343(98)00179-X.

Townsend, L., Dyer, A.H., Jones, K., Dunne, J., Mooney, A., Gaffney, F., O'Connor, L., Leavy, D., O'Brien, K., Dowds, J., Sugrue, J.A., Hopkins, D., Martin-Loeches, I., Ni Cheallaigh, C., Nadarajan, P., McLaughlin, A.M., Bourke, N.M., Bergin, C., O'Farrelly, C., Conlon, N., 2020. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One 15 (11), e0240784. https://doi.org/10.1371/journal.pone.0240784.

Tran, T.-V., Park, S.J., Shin, E.-J., Tran, H.-Q., Jeong, J.H., Jang, C.-G., Lee, Y.J., Nah, S.-Y., Nabeshima, T., Kim, H.-C., 2018. Blockade of platelet-activating factor receptor attenuates abnormal behaviors induced by phencyclidine in mice through down-regulation of NF-κB. Brain Res. Bull. 137, 71–78. https://doi.org/10.1016/j.brainresbull.2017.11.004.

Tremblay, M., Almsherqi, Z.A., Deng, Y., 2022. Plasmalogens and platelet-activating factor roles in chronic inflammatory diseases. BioFactors 48 (6), 1203–1216. https://doi.org/10.1002/biof.1916.

Trenti, A., Tedesco, S., Boscaro, C., Trevisi, L., Bolego, C., Cignarella, A., 2018. Estrogen, angiogenesis, immunity and cell metabolism: solving the puzzle. Int. J. Mol. Sci. 19 (3), 859. https://doi.org/10.3390/ijms19030859.

Trofimiuk, E., Braszko, J.J., 2011. Long-term administration of cod liver oil ameliorates cognitive impairment induced by chronic stress in rats. Lipids 46 (5), 417–423. https://doi.org/10.1007/s11745-011-3551-3.

Troyer, E.A., Kohn, J.N., Hong, S., 2020. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. Brain, Behav., Immun. 87, 34–39. https://doi.org/10.1016/j.bbi.2020.04.027.

Udagawa, J., Hino, K., 2022. Plasmalogen in the brain: effects on cognitive functions and behaviors attributable to its properties. Brain Res. Bull. 188, 197–202. https://doi.org/10.1016/j.brainresbull.2022.08.008.

Uhl, E., Pickelmann, S., Röhrich, F., Baethmann, A., Schürer, L., 1999. Influence of platelet-activating factor on cerebral microcirculation in rats: part 2. local application. Stroke 30 (4), 880–886. https://doi.org/10.1161/01.STR.30.4.880.

Underhill, R., Baillod, R., 2020. Myalgic encephalomyelitis/chronic fatigue syndrome: organic disease or psychosomatic illness? A re-examination of the royal free epidemic of 1955. Medicina 57 (1), 12. https://doi.org/10.3390/medicina57010012.

Upton, J.E.M., et al., 2022. Platelet-activating factor acetylhydrolase is a biomarker of severe anaphylaxis in children. Allergy 77, 2665–2676.

Van Campen, C., (Linda), M.C., Verheugt, F.W.A., Rowe, P.C., Visser, F.C., 2020. Cerebral blood flow is reduced in ME/CFS during head-up tilt testing even in the absence of hypotension or tachycardia: a quantitative, controlled study using Doppler echography. Clin. Neurophysiol. Pract. 5, 50–58. https://doi.org/10.1016/j.cnp.2020.01.003.

VanElzakker, M.B., Brumfield, S.A., Lara Mejia, P.S., 2019. Neuroinflammation and cytokines in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a critical review of research methods. Front. Neurol. 9, 1033. https://doi.org/10.3389/fneur.2018.01033.

Vegeto, E., Benedusi, V., Maggi, A., 2008. Estrogen anti-inflammatory activity in brain: a therapeutic opportunity for menopause and neurodegenerative diseases. Front. Neuroendocrinol. 29 (4), 507–519. https://doi.org/10.1016/j.yfrne.2008.04.001.

Velasquez-Manoff, M., 2015. The peacekeepers. Nature 518 (7540), S3–S5. https://doi.org/10.1038/518S3a.

Venzon, M., Bernard-Raichon, L., Klein, J., Axelrad, J.E., Zhang, C., Hussey, G.A., Sullivan, A.P., Casanovas-Massana, A., Noval, M.G., Valero-Jimenez, A.M., Gago, J., Putzel, G., Pironti, A., Wilder, E., Yale IMPACT Research Team, Thorpe, L.E., Littman, D.R., Dittmann, M., Stapleford, K.A., Schluter, J., 2021. Gut microbiome dysbiosis during COVID-19 is associated with increased risk for bacteremia and microbial translocation [Preprint]. Microbiology. https://doi.org/10.1101/2021.07.15.452246.

Venzon, M., Bernard-Raichon, L., Klein, J., Axelrad, J.E., Zhang, C., Hussey, G.A., Sullivan, A.P., Casanovas-Massana, A., Noval, M.G., Valero-Jimenez, A.M., Gago, J., Putzel, G., Pironti, A., Wilder, E., Yale IMPACT Research Team, Thorpe, L.E., Littman, D.R., Dittmann, M., Stapleford, K.A., Shopsin, B., Torres, V.J., Ko, A.I., Iwasaki, A., Cadwell, K., Schluter, J., 2022. Gut microbiome dysbiosis during COVID-19 is associated with increased risk for bacteremia and microbial translocation. bioRxiv 2021.07.15.452246. https://doi.org/10.1101/2021.07.15.452246.

Verheijden, S., Beckers, L., Casazza, A., Butovsky, O., Mazzone, M., Baes, M., 2015. Identification of a chronic non-neurodegenerative microglia activation state in a mouse model of peroxisomal β-oxidation deficiency: microglia Signature in Peroxisomal Mfp2 Deficiency. Glia 63 (9), 1606–1620. https://doi.org/10.1002/glia.22831.

Verheijden, S., Bottelbergs, A., Krysko, O., Krysko, D.V., Beckers, L., De Munter, S., Van Veldhoven, P.P., Wyns, S., Kulik, W., Nave, K.-A., Ramer, M.S., Carmeliet, P., Kassmann, C.M., Baes, M., 2013. Peroxisomal multifunctional protein-2 deficiency causes neuroinflammation and degeneration of Purkinje cells independent of very long chain fatty acid accumulation. Neurobiol. Dis. 58, 258–269. https://doi.org/10.1016/j.nbd.2013.06.006.

Vijayan, V., Srinu, T., Karnati, S., Garikapati, V., Linke, M., Kamalyan, L., Mali, S.R., Sudan, K., Kollas, A., Schmid, T., Schulz, S., Spengler, B., Weichhart, T., Immenschuh, S., Baumgart-Vogt, E., 2017. A new immunomodulatory role for peroxisomes in macrophages activated by the TLR4 ligand lipopolysaccharide. J. Immunol. 198 (6), 2414–2425. https://doi.org/10.4049/jimmunol.1601596.

Villa, A., Vegeto, E., Poletti, A., Maggi, A., 2016. Estrogens, neuroinflammation, and neurodegeneration. Endocr. Rev. 37 (4), 372–402. https://doi.org/10.1210/er.2016-1007.

Violante, S., IJlst, L., Te Brinke, H., Koster, J., Tavares De Almeida, I., Wanders, R.J.A., Ventura, F.V., Houten, S.M., 2013. Peroxisomes contribute to the acylcarnitine production when the carnitine shuttle is deficient. Biochim. Et. Biophys. Acta (BBA) - Mol. Cell Biol. Lipids 1831 (9), 1467–1474. https://doi.org/10.1016/j.bbalip.2013.06.007.

Wanders, R.J.A., 2013. Peroxisomes in human health and disease: metabolic pathways, metabolite transport, interplay with other organelles and signal transduction. In: Del Río, L.A. (Ed.), *Peroxisomes and their Key Role in Cell*ular Signaling *and Metabolism*, Vol. 69. Springer Netherlands, pp. 23–44. https://doi.org/10.1007/978-94-007-6889-5_2.

Wang, B., Zhang, L., Wang, Y., Dai, T., Qin, Z., Zhou, F., Zhang, L., 2022. Alterations in microbiota of patients with COVID-19: Potential mechanisms and therapeutic interventions. Signal Transduct. Target. Ther. 7 (1), 143. https://doi.org/10.1038/s41392-022-00986-0.

Wang, D., Sun, X., Maziade, M., Mao, W., Zhang, C., Wang, J., Cao, B., 2021. Characterising phospholipids and free fatty acids in patients with schizophrenia: a case-control study. World J. Biol. Psychiatry 22 (3), 161–174. https://doi.org/10.1080/15622975.2020.1769188.

Wegner, G.H., Foster, E.M., 1963. Incorporation of isobutyrate and valerate into cellular plasmalogen by bacteroides succinogenes. J. Bacteriol. 85 (1), 53–61. https://doi.org/10.1128/jb.85.1.53-61.1963.

Wendeln, A.-C., Degenhardt, K., Kaurani, L., Gertig, M., Ulas, T., Jain, G., Wagner, J., Häsler, L.M., Wild, K., Skodras, A., Blank, T., Staszewski, O., Datta, M., Centeno, T.

P., Capece, V., Islam, Md.R., Kerimoglu, C., Staufenbiel, M., Schultze, J.L., Neher, J. J., 2018. Innate immune memory in the brain shapes neurological disease hallmarks. Nature 556 (7701), 332–338. https://doi.org/10.1038/s41586-018-0023-4.

West, A., Zoni, V., Teague, W.E., Leonard, A.N., Vanni, S., Gawrisch, K., Tristram-Nagle, S., Sachs, J.N., Klauda, J.B., 2020. How do ethanolamine plasmalogens contribute to order and structure of neurological membranes? J. Phys. Chem. B 124 (5), 828–839. https://doi.org/10.1021/acs.jpcb.9b08850.

Wiest, M.M., German, J.B., Harvey, D.J., Watkins, S.M., Hertz-Picciotto, I., 2009. Plasma fatty acid profiles in autism: a case-control study. Prostaglandins, Leukot. Essent. Fat. Acids 80 (4), 221–227. https://doi.org/10.1016/j.plefa.2009.01.007.

Wirth, K.J., Scheibenbogen, C., Paul, F., 2021. An attempt to explain the neurological symptoms of myalgic encephalomyelitis/chronic fatigue syndrome. J. Transl. Med. 19 (1), 471. https://doi.org/10.1186/s12967-021-03143-3.

Wood, P.L., 2012. Lipidomics of Alzheimer's disease: current status. Alzheimer's Res. Ther. 4 (1), 5. https://doi.org/10.1186/alzrt103.

Wood, P.L., Holderman, N.R., 2015. Dysfunctional glycosynapses in schizophrenia: disease and regional specificity. Schizophr. Res. 166 (1–3), 235–237. https://doi.org/10.1016/j.schres.2015.05.017.

Wood, P.L., Filiou, M.D., Otte, D.M., Zimmer, A., Turck, C.W., 2014. Lipidomics reveals dysfunctional glycosynapses in schizophrenia and the G72/G30 transgenic mouse. Schizophr. Res. 159 (2–3), 365–369. https://doi.org/10.1016/j.schres.2014.08.029.

Wood, P.L., Barnette, B.L., Kaye, J.A., Quinn, J.F., Woltjer, R.L., 2015a. Non-targeted lipidomics of CSF and frontal cortex grey and white matter in control, mild cognitive impairment, and Alzheimer's disease subjects. Acta Neuropsychiatr. 27 (5), 270–278. https://doi.org/10.1017/neu.2015.18.

Wood, P.L., Unfried, G., Whitehead, W., Phillipps, A., Wood, J.A., 2015b. Dysfunctional plasmalogen dynamics in the plasma and platelets of patients with schizophrenia. Schizophr. Res. 161 (2–3), 506–510. https://doi.org/10.1016/j.schres.2014.11.032.

Wood, P.L., Smith, T., Lane, N., Khan, M.A., Ehrmantraut, G., Goodenowe, D.B., 2011. Oral bioavailability of the ether lipid plasmalogen precursor, PPI-1011, in the rabbit: A new therapeutic strategy for Alzheimer's disease. Lipids Health Dis. 10 (1), 227. https://doi.org/10.1186/1476-511X-10-227.

Wood, P.L., Mankidy, R., Ritchie, S., Heath, D., Wood, J.A., Flax, J., Goodenowe, D.B., 2010. Circulating plasmalogen levels and Alzheimer Disease assessment scale–cognitive scores in alzheimer patients. J. Psychiatry Neurosci. 35 (1), 59–62. https://doi.org/10.1503/jpn.090059.

Wu, D., Shu, T., Yang, X., Song, J.-X., Zhang, M., Yao, C., Liu, W., Huang, M., Yu, Y., Yang, Q., Zhu, T., Xu, J., Mu, J., Wang, Y., Wang, H., Tang, T., Ren, Y., Wu, Y., Lin, S.-H., Zhou, X., 2020. Plasma metabolomic and lipidomic alterations associated with COVID-19. Natl. Sci. Rev. 7 (7), 1157–1168. https://doi.org/10.1093/nsr/nwaa086.

Wu, Y., Chen, Z., Darwish, W.S., Terada, K., Chiba, H., Hui, S.-P., 2019. Choline and ethanolamine plasmalogens prevent lead-induced cytotoxicity and lipid oxidation in HepG2 cells. J. Agric. Food Chem. 67 (27), 7716–7725. https://doi.org/10.1021/acs.jafc.9b02485.

Xiong, R., Gunter, C., Fleming, E., Vernon, S.D., Bateman, L., Unutmaz, D., Oh, J., 2023. Multi-'omics of gut microbiome-host interactions in short- and long-term myalgic encephalomyelitis/chronic fatigue syndrome patients. Cell Host Microbe 31 (2), 273–287.e5. https://doi.org/10.1016/j.chom.2023.01.001.

Xu, Z., Asahchop, E.L., Branton, W.G., Gelman, B.B., Power, C., Hobman, T.C., 2017. MicroRNAs upregulated during HIV infection target peroxisome biogenesis factors: implications for virus biology, disease mechanisms and neuropathology. PLOS Pathog. 13 (6), e1006360 https://doi.org/10.1371/journal.ppat.1006360.

Yachou, Y., El Idrissi, A., Belapasov, V., Ait Benali, S., 2020. Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: Understanding the neurological manifestations in COVID-19 patients. Neurol. Sci. 41 (10), 2657–2669. https://doi.org/10.1007/s10072-020-04575-3.

Yamashita, S., Hashimoto, M., Haque, A.Md, Nakagawa, K., Kinoshita, M., Shido, O., Miyazawa, T., 2017. Oral administration of ethanolamine glycerophospholipid containing a high level of plasmalogen improves memory impairment in amyloid β-infused rats. Lipids 52 (7), 575–585. https://doi.org/10.1007/s11745-017-4260-3.

Yang, H.-C., Farooqui, A.A., Horrocks, L.A., 1996. Plasmalogen-selective phospholipase A2 and its role in signal transduction. J. Lipid Mediat. Cell Signal. 14 (1–3), 9–13. https://doi.org/10.1016/0929-7855(96)01502-7.

Yang, Y., Peng, F., Wang, R., Guan, K., Jiang, T., Xu, G., Sun, J., Chang, C., 2020. The deadly coronaviruses: the 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. J. Autoimmun. 109, 102434 https://doi.org/10.1016/j.jaut.2020.102434.

Yao, Y., Zhukareva, V., Sung, S., Clark, C.M., Rokach, J., Lee, V.M.-Y., Trojanowski, J.Q., Pratico, D., 2003. Enhanced brain levels of 8,12-iso-iPF2 -VI differentiate AD from frontotemporal dementia. Neurology 61 (4), 475–478. https://doi.org/10.1212/01.WNL.0000070185.02546.5D.

Yatsunenko, T., Rey, F.E., Manary, M.J., Trehan, I., Dominguez-Bello, M.G., Contreras, M., Magris, M., Hidalgo, G., Baldassano, R.N., Anokhin, A.P., Heath, A.C., Warner, B., Reeder, J., Kuczynski, J., Caporaso, J.G., Lozupone, C.A., Lauber, C., Clemente, J.C., Knights, D., Gordon, J.I., 2012. Human gut microbiome viewed across age and geography. Nature 486 (7402), 222–227. https://doi.org/10.1038/nature11053.

Yin, X.-J., Chen, Z.-Y., Zhu, X.-N., Hu, J.-J., 2017. Loss of PAFR prevents neuroinflammation and brain dysfunction after traumatic brain injury. Sci. Rep. 7, 40614.

Yoshioka, H., Coates, H.W., Chua, N.K., Hashimoto, Y., Brown, A.J., Ohgane, K., 2020. A key mammalian cholesterol synthesis enzyme, squalene monooxygenase, is allosterically stabilized by its substrate. Proc. Natl. Acad. Sci. 117 (13), 7150–7158. https://doi.org/10.1073/pnas.1915923117.

Youssef, M., Ibrahim, A., Akashi, K., Hossain, M.S., 2019. PUFA-plasmalogens attenuate the LPS-induced nitric oxide production by inhibiting the NF-kB, p38 MAPK and JNK pathways in microglial cells. Neuroscience 397, 18–30. https://doi.org/10.1016/j.neuroscience.2018.11.030.

Zaid, Y., Doré, É., Dubuc, I., Archambault, A.-S., Flamand, O., Laviolette, M., Flamand, N., Boilard, É., Flamand, L., 2021. Chemokines and eicosanoids fuel the hyperinflammation within the lungs of patients with severe COVID-19. J. Allergy Clin. Immunol. 148 (2), 368–380.e3. https://doi.org/10.1016/j.jaci.2021.05.032.

Zakrzewska, K., Oszajca, K., Zep, W., Piekarska, A., Sidorkiewicz, M., 2021. The impact of short-term shark liver oil supplementation on the fatty acid composition of erythrocyte membranes. Nutrients 13 (10), 3329. https://doi.org/10.3390/nu13103329.

Zandl-Lang, M., Züllig, T., Trötzmüller, M., Naegelin, Y., Abela, L., Wilken, B., Scholl-Buergi, S., Karall, D., Kappos, L., Köfeler, H., Plecko, B., 2022. Changes in the cerebrospinal fluid and plasma lipidome in patients with rett syndrome. Metabolites 12 (4), 291. https://doi.org/10.3390/metabo12040291.

Zelcer, N., Sharpe, L.J., Loregger, A., Kristiana, I., Cook, E.C.L., Phan, L., Stevenson, J., Brown, A.J., 2014. The E3 ubiquitin ligase MARCH6 degrades squalene monooxygenase and affects 3-hydroxy-3-methyl-glutaryl coenzyme a reductase and the cholesterol synthesis pathway. Mol. Cell. Biol. 34 (7), 1262–1270. https://doi.org/10.1128/MCB.01140-13.

Zhang, X., Yuan, C.-L., Zhang, H.-Z., Huang, R.-X., 2003. Age-related increase of plasma platelet-activating factor concentrations in Chinese. Clin. Chim. Acta 337 (1–2), 157–162. https://doi.org/10.1016/j.cccn.2003.08.010.

Zheng, G.-H., Xiong, S.-Q., Mei, L.-J., Chen, H.-Y., Wang, T., Chu, J.-F., 2012. Elevated plasma platelet activating factor, platelet activating factor acetylhydrolase levels and risk of coronary heart disease or blood stasis syndrome of coronary heart disease in Chinese: a case control study: a case–control study. Inflammation 35 (4), 1419–1428. https://doi.org/10.1007/s10753-012-9455-4.

Zhu, Y., Zhang, T., Ding, L., Shi, H., Xue, C., Xie, W., Che, H., Wang, Y., 2021. A comparative study about the neuroprotective effects of EPA-enriched phosphoethanolamine plasmalogen and phosphatidylethanolamine against oxidative damage in primary hippocampal neurons. J. Ocean Univ. China 20 (5), 1207–1214. https://doi.org/10.1007/s11802-021-4764-6.

Ziauddeen, N., Gurdasani, D., O'Hara, M.E., Hastie, C., Roderick, P., Yao, G., Alwan, N. A., 2022. Characteristics and impact of Long Covid: findings from an online survey. PLoS One 17 (3), e0264331. https://doi.org/10.1371/journal.pone.0264331.

Zoeller, R.A., Lake, A.C., Nagan, N., Gaposchkin, D.P., Legner, M.A., Lieberthal, W., 1999. Plasmalogens as endogenous antioxidants: somatic cell mutants reveal the importance of the vinyl ether. Biochem. J. 338 (Pt 3) (Pt 3), 769–776.

Zuo, T., Zhan, H., Zhang, F., Liu, Q., Tso, E.Y.K., Lui, G.C.Y., Chen, N., Li, A., Lu, W., Chan, F.K.L., Chan, P.K.S., Ng, S.C., 2020. Alterations in fecal fungal microbiome of patients with COVID-19 during time of hospitalization until discharge. Gastroenterology 159 (4), 1302–1310.e5. https://doi.org/10.1053/j.gastro.2020.06.048.