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Review

Pre-clinical investigation of STAT3 pathway in bladder cancer: Paving the way for clinical translation

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ABSTRACT

Effective cancer therapy requires identification of signaling networks and investigating their potential role in proliferation and invasion of cancer cells. Among molecular pathways, signal transducer and activator of transcription 3 (STAT3) has been of importance due to its involvement in promoting proliferation, and invasion of cancer cells, and mediating chemoresistance. In the present review, our aim is to reveal role of STAT3 pathway in bladder cancer (BC), as one of the leading causes of death worldwide. In respect to its tumor-promoting role, STAT3 is able to enhance the growth of BC cells via inhibiting apoptosis and cell cycle arrest. STAT3 also contributes to metastasis of BC cells via upregulating of MMP-2 and MMP-9 as well as genes in the EMT pathway. BC cells obtain chemoresistance via STAT3 overexpression and its inhibition paves the way for increasing efficacy of chemotherapy. Different molecular pathways such as KMT1A, EZH2, DAB2IP and non-coding RNAs including microRNAs and long non-coding RNAs can function as upstream mediators of STAT3 that are discussed in this review article.

Abbreviations: STAT3, signal transducer and activator of transcription 3; IL-6, interleukin-6; APRF, activator acute phase response factor; SH2, Src homology 2; ER, endoplasmic reticulum; miR, microRNA; BC, bladder cancer; EGF, epidermal growth factor; IFN, interferon; SOCS, suppressors of cytokine signaling; PIAS, protein inhibitors of activated STAT3; PTPass, protein tyrosine phosphatases; APR, acute phase response; BK, bradykinin; MMP-2, matrix metalloproteinase-2; KP, Kaempferia parviflora; TCC, transitional cell carcinoma; SCC, squamous cell carcinoma; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2; Pae, paeoniflorin; RPA, Radix Paeoniae alba; TME, tumor microenvironment; Gln, glutamine; TCA, tricarboxylic acid; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; Msi2, musashi-2; PLC, εphospholipase Cε; LDH, lactate dehydrogenase; RORC, receptor retinoic acid-related orphan receptor C; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; IDO1, indoleamine 2,3-dioxygenase 1; lncRNAs, long non-coding RNAs; circRNAs, circular RNAs; RACGAP1, Rac GTPase activating protein 1; ES1, estrogen receptor 1; ESR1, ES receptor 1; DANCR, differentiation antagonizing non-protein coding RNA; CCR7, C-C chemokine receptor.

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1. Introduction

The discovery of signal transducer and activator of transcription 3 (STAT3) goes back to 25 years ago when it was identified as a member of interleukin-6- (IL-6)-activated acute phase response factor (APRF) complex that mediates innate immune mediators in liver [1–4]. Consequently, STAT3 was recognized as a crucial member of STAT family due to size similarity, DNA binding activity, and antigenic and structural resemblance [4–7]. Notably, STAT3 demonstrates a unique structure that is vital for its action. STAT3 contains conserved Src homology 2 (SH2) domain and a C-terminal tyrosine residue (Y705 in mice) that are affected by JAK kinases during its signaling [8]. It seems that the most important structure of STAT3 that is important for signaling is SH2 domain that is involved in the formation of STAT3 homodimers. The transcriptional activity of STAT3 enhances via its phosphorylation at serine727 and tyrosine705 [9–11]. The interaction of STAT3 with DNA is directed by a central DNA-binding region. Post-transcriptional modifications such as acetylation and methylation also play a significant role in transcriptional activity of STAT3 [12–15].

STAT3 gene is located on chromosome 17q21 and encodes STAT3 protein with 89-kDa molecular weight [16]. The phosphorylation of STAT3 occurs on tyrosine705 residue between SH2 and carboxyl transactivation domain, resulting in homo- or hetero-dimerization of two STAT molecules reciprocal phosphotyrosine interactions between the SH2 domains of two monomers. This dimerization facilitates STAT3 binding with DNA by altering its conformation [17]. In addition to STAT3 dimerization, there are STAT3 and STAT3 heterodimers with transcriptional capabilities [18–20]. Moreover, DNA-binding fold consists of multiple ß-sheets that have resemblance to sheets present in DNA-binding domains of NF-κB1 and TP53. This shows that there are cross-talks among aforementioned pathways. For instance, during starvation, endoplasmic reticulum (ER) stress activates NF-κB1 signaling that in turn, induces IL-6. STAT3 is required for IL-6 induction by NF-κB1 that produces similar nuclear complexes on IL-6 promoter [21]. A similar scenario occurs for p53, so that STAT3 is vital for TP53-RELA to affect microRNA (miR)-21 expression [22]. These studies provide the complex nature of molecular pathways that STAT3 is involved in.

In respect to the involvement of STAT3 in various cellular events including cell proliferation, migration, angiogenesis, differentiation and so on, its role in development of different disorders has been investigated [23–27]. Cancer as one of the most lethal malignancies around the world is of importance [8,28–32], and it has been reported that STAT3 exerts a tumor-promoting role during cancer progression [33–36]. This review is allotted to explore the role of STAT3 in bladder cancer (BC), and how it is regulated by other upstream molecular pathways. Besides, we demonstrate that anti-tumor compounds can effectively target STAT3 in BCcells, making it apotential therapeutic target.

2. STAT3: activation and function

A variety of cytokines and growth factors are capable of activating STAT3 signaling pathway such as cytokines that target IL-6 signal-transducing receptor chain gp130 (IL-6, IL-11 and oncostatin M). Growth factors acting via protein tyrosine receptor kinase receptors such as epidermal growth factor (EGF) can also activate STAT3 signaling [3,4,37,38]. STAT3 can in turn trigger signaling cascades by recruiting intracellular proteins such as induced Ras or tyrosine kinase oncoproteins (Src kinase) [39–44]. In this section, we provide an explanation of STAT3 signaling, and its major functions.

2.1. Canonical STAT3 signaling

There is overall consensus about the fact that STAT3 exists in cytosol as a latent monomer, until it is activated by growth factors and cytokines that bind to cell surface receptors [45]. Receptor aggregation and changes in conformation occur upon ligand-receptor interaction that triggers signaling cascades. When the receptors do not possess tyrosine kinase activity, for instance, in case of IL-6 and interferon (IFN) family receptors, JAK kinases are brought into close proximity such that they enable transphosphorylation of each other and the cytoplasmic tail of receptors. Subsequently, phosphorylated tyrosine residues produce docking site for eliciting STAT3 through its SH2 domain. Phosphorylation of STAT3 on tyrosine705 is essential for its homodimerization, nuclear translocation and DNA-binding activity. STAT3 can also form heterodimers with other STAT members including STAT1 [46–48]. It is noteworthy that there are endogenous STAT3 inhibitors capable of suppressing STAT3 via ubiquitination and subsequent proteasomal-degradation. These endogenous inhibitors include suppressors of cytokine signaling (SOCS), protein inhibitors of activated STATs (PIAS), protein tyrosine phosphatases (PTPases) [49,50].

2.2. Non-canonical STAT3 signaling

Although canonical pathway of STAT3 includes its phosphorylation at tyrosine705, there is evidence showing that unphosphorylated STAT3 can shuttle between cytosol and nucleus and exerts it effects. However, it appears that STAT3 phosphorylation affects duration of its binding with DNA [51]. It has been reported that unphosphorylated STAT3 can affect gene transcription. Regardless of phosphorylation, STAT can target gene expression such as RANTES, IL-6, IL-8 and MET [18,52]. In addition to nuclear activities, there have been reports about non-genomic actions of STAT3. It seems that STAT3 can associate with cytosolic structures such as focal adhesions, microtubules, mitotic spindle, cell membrane, mitochondria and so on [43,53–55], demonstrating non-genomic functions of STAT3 (Fig. 1).

2.3. STAT3 function

Research suggests that STAT3 is crucial for development, and its knock-down is correlated with early embryonic lethal mice [56,57]. Through cell autonomous and non-autonomous mechanisms, STAT3 regulates vital functions in several tissues [58–60]. It is quite difficult to identify and categorize STAT3 target genes due to highly divergent binding sites, and pleiotropic effects of STAT3 in various tissues. Through STAT3 gene modulation, expression and chromatin profiling, as well as DNA binding assays, several hundreds of STAT3 target genes have been identified [61–66]. Although they belong to different studies, it seems that modulation of genes by STAT3 leads to regulation of cell proliferation, differentiation, survival, pluripotency, angiogenesis, wound healing, immunity, and metastasis. For instance, in case of immunity, STAT3 is necessary for normal expression of acute phase response (APR) genes in the liver [67,68]. STAT3 is also involved in epigenetic switching and subsequent regulation of metabolic reprogramming, inflammation and transformation [69–75]. It has been reported that STAT3 can regulate metabolism and survival via affecting mitochondrial DNA, and its electron transport chain [76–78]. These are examples of STAT3 function in cells and accordingly, any impairment in these functions provide condition for development of diseases, particularly cancer [79–82]. In the next section, we provide an overview of STAT3 role in cancer.

3. STAT3 in carcinogenesis: an overview

Before discussing the role of STAT3 in BC, it would be beneficial to give an introduction about involvement of STAT3 in tumorigenesis to shed light on its role in promoting proliferation and metastasis of cancer cells. Firstly, studies are in agreement with the fact that STAT3 is a tumor-promoting factor in different cancers, suppressing the expression makes its an effective candidate in cancer therapy. However, it would be beneficial to understand upstream and down-stream mediators of STAT3 signaling pathway in cancer. Experiments have demonstrated that various oncogene factors in cancer target STAT3 to exert their tumor-

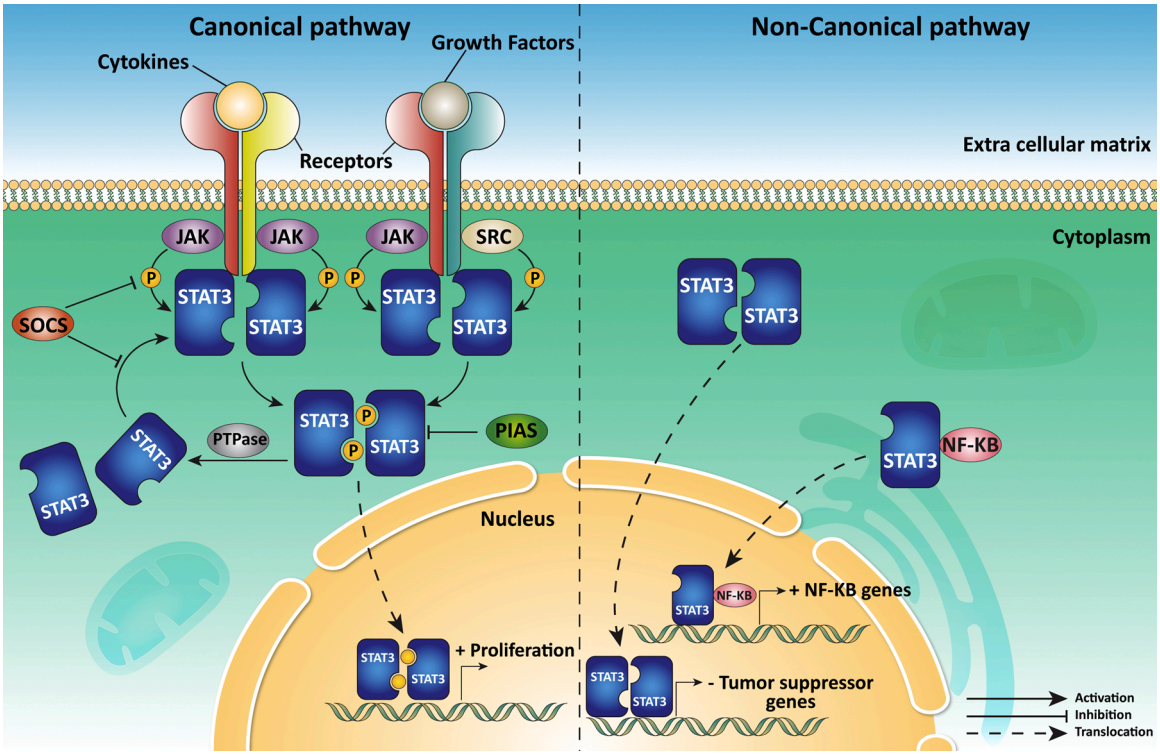

Fig. 1. Canonical and non-canonical pathways of STAT3.

promoting roles. For instance, bradykinin (BK) is suggested to be involved in cancer progression. A newly published study has revealed that BK is capable of enhancing proliferation and migration of cancer cells via STAT3 induction. By positively affecting STAT3 pathway, molecular pathways involved in migration of cancer cells such as matrix metalloproteinase-2 (MMP2) and MMP9 undergo upregulation to promote cancer invasion [83]. Suppressing phosphorylation (Y705) of STAT3 leads to suppressing liver metastasis of colorectal cancer cells [84].It is also noteworthy that in addition to cancer cells, STAT3 is able to promote cancer stem cell formation via IL-6 upregulation [85]. IL-6 is not only down-stream target of STAT3, it also functions as upstream mediator of STAT3 signaling pathway. It has been reported that STAT3 induction by IL-6 results in enhanced stemness of osteosarcoma cells [86].

Based on the role of STAT3 in cancer malignancy [87,88], studies have focused on developing STAT3 inhibitors in cancer therapy. STAT3 inhibitors are able to prevent phosphorylation or directing it into degradation. A newly published study has shown that a small molecule known as SD-36 can promote degradation of STAT3, leading to apoptosis and cell cycle arrest in cancer cells [89]. STAT3 inhibitors can suppress DNA-protein interaction in cancer therapy [90]. In addition to synthetic drugs, natural compounds have demonstrated great potential in suppressing STAT3 signaling pathway in cancer therapy. *Kaempferia parviflora* (KP) inhibits STAT3 phosphorylation by IL-6 to induce anti-carcinogenesis effect in cancer cells [91]. Furthermore, phytochemicals with anti-tumor activity such as brusatol, corilagin and vitexin suppress cancer metastasis via STAT3 down-regulation [11,92,93].Taken collectively, it appears that: 1) STAT3 is a tumor-promoting factor in different cancers, 2) there are upstream and down-stream mediators of STAT3, and 3) STAT3′s expression can be inhibited using natural and synthetic agents. In the present review, these topics are discussed to shed some light on the role of STAT3 in BC.

4. Bladder cancer: epidemiology and pathogenesis

BC is also known as urinary bladder cancer or urological cancer, and is at the tenth place among most common cancers. The incidence rate of BC has an ascending trend, particularly in developed countries [94]. In 2018, based on GLOBOCAN data, up to 550,000 people were diagnosed with BC that comprises 3% of all new cases. Southern and Western Europe and North America are among the nations with highest incidence rate of BC. It is noteworthy that Greece and Lebanon are among countries that have the highest incidence rate of BC among men and women. BC is 10th most common cancer around the world. In term of mortality, BC is 13th most deadly cancer, and in 2018 alone, it caused 200,000 deaths that comprises 2.1 % of all cancer-related deaths [95]. The survival rate in patients with BC is different. For instance in US, BC patients have a 5-year survival rate of 77.1 %, and this number reduces in advanced stages, so that patients with metastatic BC have a 5-year survival rate of 4.6 % [94,96]. This reveals that early diagnosis of BC is of importance in ensuring survival of patients with BC.

The most common pathological subtype of BC is transitional cell carcinoma (TCC) [97]. Nested and micropapillary are two variants of TCC. Squamous cell carcinoma (SCC) and adenocarcinoma are other subtypes of BC, but their incidence rate is low (less than 5 %). Up to 90 % of patients are diagnosed with TCC [98]. Both genetic and environmental factors are involved in the development of BC [99]. Environmental factors are exposing to ionizing irradiation, presence of arsenic in drinking water, or smoking. [99]. Increasing evidence demonstrates that genetic mutations also plays a significant role in BC development [100,101]. Alterations in tyrosine receptor kinase FGFR3, HRAS, and PIK3CA genes are responsible for BC progression [102–105]. Besides, changes in expression of genes accounting for cell cycle such as *p53*, *p16* and *Rb* lead to BC malignancy [106–108]. Targeting these molecular pathways are of importance in BC therapy, as it has been shown in clinical studies. For instance, an initial phase II clinical trial has shown that using Bevacizumab as an anti-VEGF, is effective in patients with BC [109]. Furthermore, Everolimus as an inhibitor of mTOR is beneficial in BC therapy [110–112] as mTOR is involved in BC pathogenesis [113]. In the next sections, we specifically discuss the role of STAT3 in BC. Different aspects such as involvement of STAT3 in BC proliferation, metastasis and chemoresistance are discussed. Furthermore, upstream and

down-stream mediators of STAT3 in BC is examined. Subsequently, anti-cancer agents targeting STAT3 in BC are discussed with an emphasis on molecular pathways.

5. STAT3 and bladder cancer

5.1. Direct inhibition of STAT3

Considering the fact that STAT3 contributes to BC progression and aggressiveness [114,115], STAT3 inhibitors have been designed for effective BC therapy. Evidence suggests that STAT3/5 inhibitor is associated with a decrease in STAT3 phosphorylation and subsequently diminishes viability of BC cells, while inducing apoptosis and cyclin D1 expression. It is noteworthy that STAT3 inhibition promotes efficacy of oncolytic adenoviruses in BC therapy. After STAT3 inhibition, an increase occurs in viral replication and cell lysis that is in favor of BC therapy [116]. WP1066 is another suppressor of STAT3 signaling pathway and its role in BC treatment has been examined. WP1066 (2.5 μM) effectively reduces viability and proliferation of BC cells. WP1066 is able to prevent STAT3 phosphorylation, resulting in apoptosis induction [117]. Notably, WP1066 is also capable of suppressing STAT3 in mouse model of BC [118], showing that it can be further analyzed for using in clinical studies related to BC.

Metformin is an efficient anti-diabetic agent, but recently, its anti-tumor activity has been investigated, particularly in BC. Metformin induces apoptosis in BC cells, and induces AMPK to exert anti-proliferative activity [119,120]. On the other hand, cyclooxygenase-2 (COX-2) is a critical enzyme in biosynthesis of prostaglandin E2 (PGE2) with tumor-promoting role in various cancers, especially BC [121,122]. Administration of Metformin (0−20 mM) is associated with down-regulation of COX2, and subsequent decrease in PGE2 expression. This provides the condition for inhibition of STAT3 signaling pathway, and suppression of stem cell repopulation [123].

Natural products are potential inhibitors of STAT3 in cancer therapy [8]. Paeoniflorin (Pae) is the main component of Radix Paeoniae alba (RPA) with effectiveness in treatment of anti-inflammatory diseases [124]. Newly published studies have shed light on anti-tumor activity of Pae via affecting different molecular pathways such as Skp2 and NEDD4 [125–127]. It is noteworthy that Pae can modulate STAT3 in suppressing BC malignancy. It has been reported that Pae prevents nuclear translocation of STAT3 in BC cells that subsequently sensitizes cancer cells into apoptosis [128].

Chrysin belongs to large family of flavonoids and flavone category with excellent pharmacological activities. The most important therapeutic effect of chrysin is anti-tumor activity against different cancer cells with capacity of suppressing proliferation and metastasis of cancer

Table 1
Anti-tumor compounds targeting STAT3 in bladder cancer therapy.

Anti-tumor compound	*In Vitro*/ *In Vivo*	Cell line/Animal model	Dosage	Remarks	Refs
Metformin	*In Vitro*	Human bladder cancer cell lines T24 and J82	10, 20, 40 and 60 mM	Inhibiting carcinogenesis Suppressing transformation of normal cells into tumoral ones Reducing STAT3 phosphorylation	[134]
Metformin	*In Vitro*	Human bladder cancer cells (T24 and RT4)	20 mM	Suppressing stem cell repopulation Stimulating cell cycle arrest at G1/S phase STAT3 activation	[123]
Cucurbitacin E	*In Vitro*	T24 cells	0−2000 nM	Inducing cell cycle arrest via activating STAT3/p53/p21 axis Suppressing EMT and proliferation	[135]
Resveratrol	*In Vitro*	Human normal bladder cell line (SV-HUC-1)	50 μM	Down-regulation of STAT3/Twist1 axis Preventing tumor development	[136]
AG490 and methylsulfomethane	*In Vitro* *In Vivo*	T24 and 253J-BV cells	25 μM AG490 300 mM methylsulfomethane	Reducing viability, proliferation and migration of cancer cells Down-regulation of STAT3 signaling pathway	[137]
SYD007	*In Vitro*	T24 and MB49 cells	0−10 μM	Reducing IGF-1R levels Preventing STAT3 phosphorylation at tyrosine705 Suppressing proliferation of cancer cells STAT3 down-regulation	[138]
WP1066	*In Vitro*	Human bladder cancer cell lines T24 and UMUC-3	0−10 μM	Impairing survival of cancer cells Apoptosis induction via Bcl-2 and Bcl-xL down-regulation Reducing migratory capacity via MMP-2 and MMP-9 inhibition	[117]
Paeoniflorin	*In Vitro* *In Vivo*	RT4 cells	0−400 μM	Reducing STAT3 expression Induction apoptosis via activating caspase-3, -8 and -9	[128]
Chrysin	*In Vitro*	Human bladder cancer cell lines T-24 and 5637 and the non-malignant immortalized urothelial SV-HUC-1 cells	0−80μM	Repressing STAT3 signaling Triggering apoptosis and cell cycle arrest	[131]
δ-tocotrienol	*In Vitro*	Bladder cancer cell lines T24, 5637, J82 and UMUC-3	0−200 μM	Suppressing STAT3 expression Inducing apoptosis and cell cycle arrest Promoting chemosensitivity	[132]
Tanshinone IIA	*In Vitro*	Human BCa cell lines 5637 (grade II carcinoma), BFTC (BFTC 905, papillary transitional cell carcinoma), and T24 (transitional cell carcinoma)	0−4 μg/mL	Reducing metastasis of cancer cells via EMT inhibition Preventing STAT3 phosphorylation at tyrosine705 and subsequent inhibition of CCL2	[139]
Chaetocin	*In Vitro*	Cell lines SV-HUC-1 and T24	0−100 nM	Abrogating self-renewal capacity of bladder cancer stem cells Down-regulation of STAT3	[140]

cells [129,130]. Administration of chrysin (0−80 μM) is associated with an increase in ROS generation that subsequently reduces STAT3 expression, leading to apoptosis induction in BC cells [131]. Anti-tumor compounds targeting STAT3 pathway not only induce apoptosis in BC cells, but also are able to enhance sensitivity of BC cells to chemotherapy [132]. These studies demonstrate multifaceted role of STAT3 in BC [133] and how its regulation by anti-tumor agents is of importance (Table 1).

5.2. Upstream mediators of STAT3

Increasing evidence shows that tumor microenvironment (TME) plays a significant role in BC progression and malignancy [141,142]. TME can meet needs of BC cells to energy. Glutamine (Gln) is one of the abundant amino acids in TME with involvement in physiological mechanisms such as energy synthesis, biosynthesis, and cell signaling [143,144]. Gln is able to induce tricarboxylic acid (TCA) cycle for energy production [145]. A transporter on the cell membrane transfers Glnto cell. Then, glutaminase changes Glnto glutamate for entering to TCA cycle [146]. Furthermore, Gln can reduce generation of ROS [147,148]. This suggests that the effects of Gln are vital for enhancing BC proliferation. In BC cells, Gln substantially reduces levels of ROS and is applied as a fuel in the TCA cycle. Further analyses demonstrate that Gln metabolism has a direct relationship with STAT3 expression. It seems that Gln promotes cancer metabolism via providing ATP, and decreases ROS levels to induce STAT3 signaling pathway as a tumor-promoting factor for elevating aggressiveness behavior of BC cells [149].

The enhancer of Zeste 2 Polycomb Repressive Complex 2 subunit (EZH2) belongs to polycomb group of proteins with critical roles in embryonic stem cell pluripotency and self-renewal [150–152]. It has been reported that upregulation of EZH2 is correlated with an increase in proliferation and metastasis of BC cells, and results in unfavorable prognosis [153,154]. Identification of down-stream targets of EZH2 is key in treatment of BC cells, and STAT3 is one of them. Both *in vitro* and *in vivo* experiments demonstrate association of EZH2 with proliferation and apoptosis resistance of BC cells. EZH2 inhibition significantly reduces growth and metastasis of BC cells. Mechanistically, EZH2 induces JAK2/STAT3 pathway to promote migration and proliferation of BC cells [155]. Hence, suppressing EZH2/JAK2/STAT3 axis can be considered as a promising target in BC therapy.

Musashi-2 (Msi2) is a member of Musashi family and has two isoforms due to alternative splicing [156]. Msi2 gene is located on chromosome 17q22 with length of 987 bp [157], and is considered an oncogene factor in cancer, promoting both migration and proliferation. Msi2 is able to exert control over other molecular pathways such as TGF-β and is a prognostic factor [158–160]. In BC cells, Msi2 promotes growth and invasion of cancer cells and is associated with lymph node metastasis. This is performed via upregulation of JAK2/STAT3 that provides poor prognosis [161]. This shows that silencing STAT3 is a key factor in suppressing BC malignancy [162].

Phospholipase Cε (PLCε) belongs to phospholipase C family that generates second messenger via catalyzing polyphosphoinositol [163]. PLCε is involved in BC development [164,165], and may induce STAT3 signaling pathway [166]. On the other hand, lactate dehydrogenase (LDH) is upregulated in different cancers and participates in enhancing glucose metabolism and uptake [167,168]. As an upstream mediator, PLCε induces STAT3 signaling pathway that in turn, promotes expression of LDH, leading to enhanced growth and glucose metabolism of BC cells [169]. These studies are in line with that fact that not only STAT3, but also its upstream mediators can be targeted in effective BC therapy [170].

Increasing evidence demonstrates the role of B7-H3 in disease severity and progression of cancer. However, the exact role ofB7-H3 is not certain, such that there are experiments showing overexpression of B7-H3 is associated with desirable prognosis [171–173]. On the other hand, it has been reported that 42 % of patients with BC have mutations in PI3K/Akt signaling pathway [174]. This axis is capable of regulating both proliferation and invasion of BC cells [175,176]. Interaction between B7-H3 and PI3K/Akt pathways is important for promoting aggressive behavior of BC cells. B7-H3 is overexpressed in BC cells and is able to stimulate PI3K/Akt signaling pathway. As an upstream mediator, PI3K/Akt activates STAT3 to promote migration (MMP-2 and MMP-9 upregulation) and proliferation of BC cells [177]. STAT3 induction by Akt prevents cell cycle arrest and apoptosis in enhancing proliferation and viability of BC cells [170].

CXC chemokines are a family of small secreted proteins with molecular weight of 8−11 kDa. They interact with G protein-coupled receptors to regulate immune and inflammatory responses [178]. CXCL12 is a ligand that binds to CXCR4 in promoting proliferation and invasion of cancer cells [179–181]. In BC cells, CXCL12 is capable of enhancing growth and migratory abilities. It appears that CXCL12, first, induces CXCR4 that in turn, activates STAT3, resulting in enhanced invasion of BC cells [182]. Targeting aforementioned axis can be beneficial in suppressing BC metastasis (Table 2, Fig. 2).

6. STAT3 and drug resistance of bladder cancer cells

Brining more hope to cancer therapy occurs when signaling networks involved in drug resistance of cancer cells are identified [186–190]. Thanks to experiments conducted in recent years, the molecular pathways involved in chemoresistance of cancer cells have been revealed [191,192]. It has been reported that signaling networks that promote growth and metastasis of BC cells, and provide their recurrence, are able to induce drug resistance in these cells [193–195]. In this section, we discuss molecular pathways that are involved in drug resistance of BC cells, and in which STAT3 is the key player.

Receptor retinoic acid–related orphan receptor C (RORC) is a DNA-binding transcription factor and a member of nuclear orphan receptors [196]. Experiments demonstrate the role of RORC in different cancers. For instance, down-regulation of RORC undergoes in breast cancer cells and has a negative association with histologic grade in multiple human cohorts [197]. The expression of RORC reduces during progression of melanoma cells with lowest expression at advanced stages [198]. These studies demonstrate the antitumor activity of RORC. The role of RORC in BC and its relationship with STAT3 signaling have been investigated. The expression of RORC is downregulated in BC cells and tissues. Enhancing expression of RORC is correlated with proliferation inhibition, glucose metabolism suppression and enhanced sensitivity to

Table 2
STAT3 signaling and its upstream and down-stream mediators in bladder cancer.

Signaling network	Effect on STAT3	Remarks	Refs
KMT1A/ GATA3/ STAT3	Upregulation	Inhibition of GATA3 by KMT1A STAT3 induction Promoting self-renewal capacity of bladder cancer stem cells	[183]
DAB2IP/ STAT3/ Twist1	Down-regulation	Reducing STAT3 phosphorylation Promoting Twist1 expression Enhancing P-glycoprotein activity Suppressing chemoresistance	[184]
STAT3	Upregulation	Enhanced expression of STAT3 is correlated with progression of urothelial stem cells to invasive bladder cancer	[185]
Glutamine/ STAT3	Upregulation	Enhancing ATP production Neutralizing ROS STAT3 induction	[149]
EZH2/JAK2/ STAT3	Upregulation	Promoting proliferation Promoting metastasis and growth via JAK2/STAT3 activation	[155]
PLCε/STAT3/ LDHA	Upregulation	Promoting STAT3 phosphorylation Subsequent activation of LDHA Enhancing bladder cancer growth	[169]

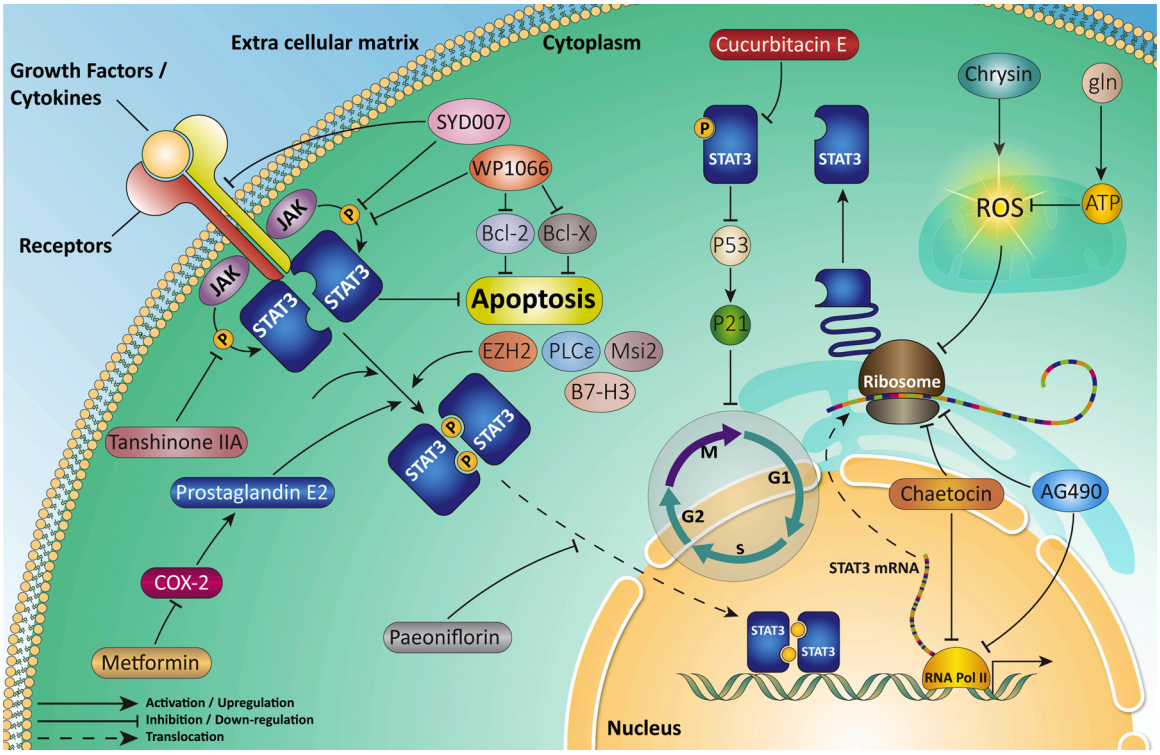

Fig. 2. Upstream mediators of STAT3 signaling in BC, and regulating STAT3 pathway by anti-tumor compounds.

cisplatin chemotherapy. RORC reduces expression of PD-L1 via binding to the promoter. PD-L1 induces ITGB6/FAK axis via interacting with ITGB8. It has been reported that RORC is able to suppress chemoresistance in BC cells via down-regulating PD-L1/TGB8 axis, and subsequent inhibition of STAT3 nuclear translocation [199].

Further, epidermal growth factor receptor (EGFR) is overexpressed in different cancers, and has been suggested as a promising therapeutic target [200]. EGFR monoclonal antibodies such as cetuximab and panitumumab are already well-studied in cancer therapy [201]. Increasing evidence has shown that STAT3 hyperactivation leads to resistance of cancer cells to EGFR inhibitors [202,203], thus affecting STAT3's role in chemosensitivity. STAT3 down-regulation using STAT3 decoys enhances anti-tumor activity of EGFR inhibitors against BC [204]. It is noteworthy that STAT3 increases expressions of MMP-2 and cyclin D1, factors involved in proliferation and metastasis and drug resistance in BC cells [205]. Therefore, inhibition of STAT3 signaling can be considered as a promising strategy in BC therapy.

7. STAT3 and EMT in bladder cancer cells

Loss of E-cadherin due to upregulation of E-cadherin-repressing transcription factors such as Twist1, Snail, and ZEB leads to epithelial-to-mesenchymal (EMT) induction [206]. Regardless of physiological roles of EMT during embryonic development, wound healing and so on, EMT is responsible for metastasis of cancer cells to distant sites, and reseeding primary tumors [207–209]. Identification of molecular pathways involved in EMT and their suppression are key in BC therapy, because EMT induction can provide aggressive behavior and chemoresistance of BC cells [210]. Furthermore, EMT is associated with undesirable prognosis of BC [211]. Targeting EMT can significantly reduce metastasis of BC cells [212]. Different molecular pathways accounting for EMT induction have been investigated, and it seems that STAT3 can be considered as an upstream mediator of EMT [213–215]. In this section, we provide a brief discussion about EMT regulation by STAT3 in BC cells.

The p27 is a CDK inhibitor that can drive metastasis and migration of cancer cells via EMT induction [216]. In BC cells, p27 induces STAT3 signaling pathway that in turn, upregulates expression of Twist1. p27 is involved in reducing E-cadherin levels and paving the road for EMT induction via enhancing N-cadherin levels. In fact, p27 affects Twsit1/EMT axis via targeting STAT3 to promote invasion of BC cells [217]. Indoleamine 2,3-dioxygenase 1 (IDO1) is another factor suggested to be involved in EMT regulation in BC cells. IDO1is a vital enzyme for accelerating breakdown of tryptophan to kynurenine. Experiments have shown that IDO1 undergoes upregulation in different cancers, particularly BC [218–220]. IDO1 enhances expression of IL-1 to induce STAT3 expression in BC cells. This remarkably promotes migratory ability of BC cells via PD-L1 induction and subsequent activation of EMT [221]. These studies are in agreement with the fact that different molecular pathways can regulate STAT3/EMT in BC, and their understanding can be considered as a milestone progress in providing therapeutic targets (Fig. 3) [136].

8. Non-coding RNAs and STAT3 signaling in bladder cancer

Non-coding RNAs are protein-free RNAs that comprise most parts of the genome [222]. Long non-coding RNAs (lncRNAs), circular RNAs (circRNAs) andmiRs are major types of non-coding RNAs that regulate gene expression at transcription, post-transcription and epigenetic levels [223–227]. In human genome, there are up to 20,000–25,000 genes and 40–90 % of them are modulated by miRs [228]. On the other hand, it has been reported that miRs play a significant role in regulation of STAT3 signaling pathway in cancer [229,230]. Thus, understanding the association of miR with STAT3 pathway can be of therapeutic importance in BC therapy. MiR-4324 is an onco-suppressor and its role in cancer has been studied. Reduced expression of miR-4324 provides conditions for upregulation of FAK and an increase in invasion of cancer cells via EMT induction [231]. Furthermore, miR-4324 upregulation is associated with decreased growth of cancer cells and inhibition of their aggressive behavior [232]. In BC cells, miR-4324 reduces expression of Rac GTPase activating protein 1 (RACGAP1) to suppresses STAT3 phosphorylation. There are feedbacks among aforementioned factors such that estrogen

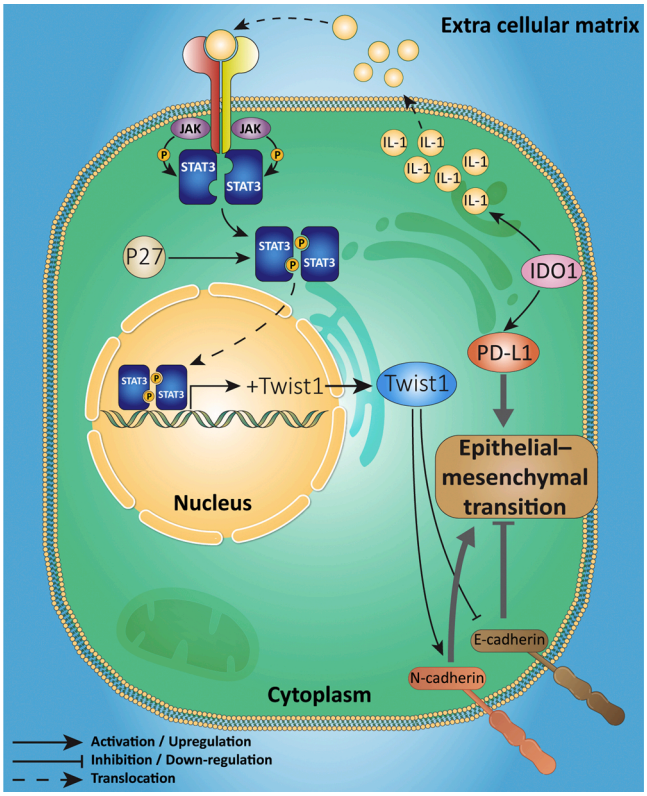

Fig. 3. STAT3 and its association with drug resistance and EMT in BC cells.

receptor 1 (ES1) enhances miR-4324 expression via binding to its promoter. Subsequently, STAT3 induces promoter methylation of ES receptor 1 (ESR1) via enrichment of DNMT3B to down-regulate expression of miR-4324. On the other hand, RACGAP1 promotes nuclear translocation of STAT3. MiR-4324 as an upstream mediator suppresses RACFAP1/STAT3 axis to induce apoptosis and increase sensitivity of BC cells to doxorubicin chemotherapy [233]. Preventing nuclear translocation of STAT3 is not the only pathway mediated by miRs. It seems that in order to induce apoptosis and suppress proliferation of BC cells, miR-124 binds to 3′-UTR of STAT3 to inhibits its expression [234].

Addiyionally, miRs can be targeted by circRNAs in cancer cells [235,236]. MiR-181a-5p is another onco-suppressor factor in cancer with potential roles in apoptosis induction and stimulating chemosensitivity [237,238]. A newly published experiment has shown that circRNA hsa-circ-0068871 is upregulated in BC cells, while miR-181a-5p is downregulated. Through reducing expression of miR-181-a-5p, hsa--circ-0068871 induces STAT3 signaling pathway that is in favor of cancer progression and proliferation. This suggests that downregulating hsa-circ-0068871 or upregulating miR-181a-5p can suppress BC malignancy [239].

LncRNAs are other types of non-coding RNAs capable of regulating STAT3 in cancer cells [240,241], also investigated in BC cells. LncRNA Differentiation antagonizing non-protein coding RNA (DANCR) increases proliferation of cancer cells via induction of angiogenesis [242]. Furthermore, it is able to promote migration of cancer cells via affecting genes such as MMP16 [243]. In BC cells, lncRNA DANCR functions as an oncogene factor. It elevates expression of IL-11 to induce STAT3 signaling, leading to an increase in proliferation and invasion [244]. This study demonstrates that STAT3 signaling and its upstream mediator can be affected by lncRNAs in BC cells.

C-C chemokine receptor (CCR7) is a receptor of chemokine CCL21 with potential role in different cancers. It has been shown that CCR7 can promote proliferation and metastasis of BC cells [245,246]. STAT3 is an upstream mediator of CCR7 in BC cells, and can upregulate its expression. It has been reported that miR-4500 as an onco-suppressor factor, binds to 3′-UTR of STAT3 to suppress CCR7, leading to a decrease in both growth and invasion of cancer cells [247]. Interestingly,lncRNAs are able to regulate miR/STAT3 axis in BC cells. This significantly promotes complexity of these signaling networks, urging scientists to explore the identification of more non-coding RNAs capable of regulating STAT3 signaling pathway. It has been shown that lncRNA SNHG16 reduces expression of miR-98 to enhance proliferation and migration of BC cells. Down-regulation of miR-98 by SNHG16 is vital for activation of STAT3 signaling pathway and exerts BC growth and malignancy [248]. In addition to targeting miRs, lncRNAs can directly target STAT3. Inducing STAT3 phosphorylation by lncRNAs is necessary for increasing aggressive behavior of BC cells. In contrast, lncRNAsexert inhibitory effects on BC cells, for example BRE-AS1 prevents phosphorylation of STAT3 [249].

As it was mentioned earlier, glycolysis as a hallmark of cancer is key in providing enough energy for cancer cells with high metabolism [250]. LncRNAs that promote proliferation of BC cells, may exert stimulatory effect on glycolysis. In this way, due to its role in enhancing glucose metabolism [251], STAT3 is a potential target. It is suggested that lncRNA UCA1 induces mTOR signaling pathway that in turn, activates STAT3. Subsequently, STAT3 down-regulates expression of miR-143 to induce HK2, leading to an increase in glycolysis and proliferation of BC cells [252]. Identification of such molecular pathways is of importance for targeting and impairing uncontrolled growth and migration of cancer cells (Fig. 4, Table 3) [253,254].

9. Conclusion and remarks

To date, there has been no certain cure for BC. Exposing BC cells to chemotherapeutic agents reduces their survival and stimulates apoptosis. However, these anti-tumor compounds are not sufficient in completely suppressing of BC cells. Besides, BC cells are capable of obtaining resistance for anti-tumor drugs. A question arises on why BC treatment is still a challenge? There are different answers for this question, but the most important one can be that molecular pathways involved in BC malignancy have not been completely understood. In fact, mutations and amplifications in a certain pathway can be responsible for uncontrolled growth and invasion of BC cells. STAT3 is one of the well-known oncogenic signaling pathways in different cancers, and its role in BC has been investigated. In the present review, we collected experiments related to STAT3 and its role and regulation in BC cells.

It has been shown that STAT3 hyperactivation can substantially promote proliferation and metastasis of cancer cells. Inhibiting apoptosis and cell cycle arrest is mediated by STAT3 to promote aggressive behavior of BC cells. Furthermore, metastasis of BC cells via EMT is induced by STAT3 signaling pathway. Interestingly, anti-tumor compounds with inhibitory effects on proliferation and invasion of BC cells reduce expression of STAT3 or suppress its phosphorylation. Nuclear translocation of STAT3 can be inhibited in suppressing BC.

The story is more complicated when STAT3 is regulated by different upstream mediators. In order to provide better understanding of signaling networks in which STAT3 is the key player, we discussed regulation of STAT3 by non-coding RNAs, and other molecular pathways. MiRs, lncRNAs and circRNAs are capable of regulating STAT3 in BC, and there is still a long way in identification of more non-coding RNAs with capability of STAT3 regulation. We also discussed other molecular pathways as upstream mediators of STAT3. This complex signaling networks demonstrate that in addition to STAT3, the upstream mediators can also be targeted.

The main challenge is that different down-stream targets have been identified for STAT3, and new experiments are going to reveal more down-stream targets. It is impossible to target all of these pathways to suppress BC malignancy, and based on the fact that STAT3 is a major player, modulation of STAT3 expression (i.e. downregulation) is of great importance in BC therapy.

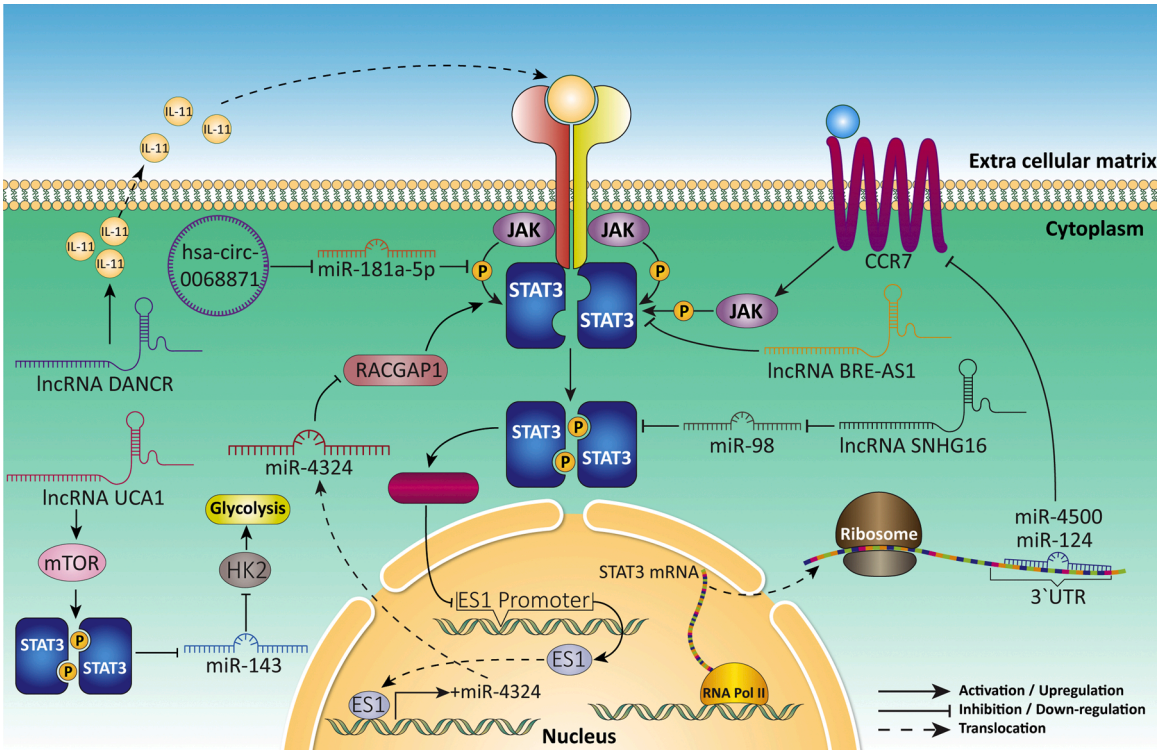

Fig. 4. Non-coding RNAs as modulators of STAT3 in BC.

Table 3
Role of non-coding RNAs in regulation of STAT3 in bladder cancer.

Non-coding RNA	Signaling network	Effect on STAT3	Remarks	Refs
Hsa-circ-0068871	MiR-181a-5p/STAT3	Upregulation	Reducing miR-181a-5p expression Inducing STAT3 signaling Promoting migration and growth of cancer cells	[239]
MiR-4324	RACGAP1/STAT3/ESR1	Down-regulation	Presence of a feedback loop Reducing RACGAP1 expression Preventing STAT3 phosphorylation Suppressing metastasis and proliferation	[233]
MiR-124	STAT3	Upregulation	Enhancing STAT3 expression Reducing apoptosis in bladder cancer cells	[234]
MiR-4500	STAT3/CCR7	Down-regulation	Binding to 3′-UTR of STAT3 and repressing its expression Suppressing proliferation and invasion	[247]
SNHG16	MiR-98/STAT3/Wnt-β-catenin	Upregulation	Decreasing miR-98 expression Promoting STAT3 expression Activating Wnt signaling Elevating progression of bladder cancer	[248]
BRE-AS1	STAT3	Down-regulation	Preventing STAT3 phosphorylation Apoptosis induction	[249]
DANCR	IL-11/STAT3	Upregulation	Promoting IL-11 expression and subsequent activation of STAT3 Increasing bladder cancer survival and metastasis	[244]
UCA1	mTOR/STAT3/miR-143/hexokinase 2	Upregulation	Activating mTOR/STAT3 axis Reducing miR-143 expression Promoting glycolysis via HK2 upregulation	[252]

In this review, we showed that pharmacological compounds are able to repress STAT3 expression in BC cells. Genetic tools such as CRISPR/Cas9 system, siRNA, or nano-vehicles can be applied in suppressing STAT3 expression and providing effective BC therapy. Furthermore, aforementioned technologies can be used in revealing upstream and down-stream mediators of STAT3 in BC. Further studies can focus on this topic.

One of the challenges in BC therapy and other types of cancer is that therapies suffer from off-targeting features. Tumor microenvironment, acidic pH and blood-tumor barriers and other impediments reduce efficiency of pharmacological and genetic interventions in BC therapy. Nano-scale delivery systems can be developed for targeted delivery of anti-tumor compounds and genetic tools that significantly enhance their efficiency in BC therapy. The most important therapy for BC suppression can be inhibiting nuclear translocation of STAT3, since in nucleus, STAT3 can stimulate signaling networks enhancing BC progression. It is impossible to provide an absolute mechanism of action for STAT3 in BC. EMT and MMP are the most important factors that are upregulated by STAT3 in increasing BC metastasis. In terms of proliferation, a variety of complicated molecular pathways and mechanisms are involved, but glycolysis induction appears the most important one. In addition to direct prevention of STAT3 nuclear translocation, upstream mediators of STAT3 can be modulated. However, we are still at the beginning points and more studies are needed to investigate the role of STAT3 in BC.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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