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STAT family of transcription factors in breast cancer: Pathogenesis and therapeutic opportunities and challenges

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Abstract

Breast cancer is the most commonly diagnosed cancer and second-leading cause of cancer deaths in women. Breast cancer stem cells (BCSCs) promote metastasis and therapeutic resistance contributing to tumor relapse. Through activating genes important for BCSCs, transcription factors contribute to breast cancer metastasis and therapeutic resistance, including the signal transducer and activator of transcription (STAT) family of transcription factors. The STAT family consists of six major isoforms, STAT1, STAT2, STAT3, STAT4, STAT5, and STAT6. Canonical STAT signaling is activated by the binding of an extracellular ligand to a cell-surface receptor followed by STAT phosphorylation, leading to STAT nuclear translocation and transactivation of target genes. It is important to note that STAT transcription factors exhibit diverse effects in breast cancer; some are either pro- or anti-tumorigenic while others maintain dual, context-dependent roles. Among the STAT transcription factors, STAT3 is the most widely studied STAT protein in breast cancer for its critical roles in promoting BCSCs, breast cancer cell proliferation, invasion, angiogenesis, metastasis, and immune evasion. Consequently, there have been substantial efforts in developing cancer therapeutics to target breast cancer with dysregulated STAT3 signaling. In this comprehensive review, we will summarize the diverse roles that each STAT family member plays in breast cancer pathobiology, as well as, the opportunities and challenges in pharmacologically targeting STAT proteins and their upstream activators in the context of breast cancer treatment.

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Conflict of interest

Authors declare no conflict of interest.

CRediT authorship contribution statement

Grace L. Wong: Conceptualized the manuscript, Selected the reviewed literature, Compiled the review tables and figures, Wrote the manuscript. **Sara G. Manore**: Contributed to manuscript editing. **Daniel L. Doheny**: Contributed to manuscript editing. **Hui-Wen Lo**: Supervised the design and writing of the manuscript, Edited the figures and manuscript, Obtained the funding for this publication.

Keywords

Breast cancer; Breast cancer stem cells (BCSCs); Signal transducer and activator of transcription (STAT); STAT inhibitors; Breast cancer therapeutics

1. Introduction

Breast cancer is the most frequently diagnosed cancer in women; an estimated 287,000 will be diagnosed with breast cancer in 2022 [1]. Despite advances in early detection and breast cancer therapeutics, breast cancer patients that present with distant metastases have poor prognoses and high probabilities of drug resistance resulting in tumor relapse [2–4]. Metastasis to distant organs is responsible for the majority of breast cancer-related deaths [5], underscoring the importance of identifying mechanisms or cell populations that drive and facilitate breast cancer metastasis.

Breast cancer stem cells (BCSCs) are a small percentage of cells within breast tumors that maintain the ability to self-renew and regenerate the heterogeneous tumor lesions, known as tumor relapse [2,6,7]. These BCSCs are few in number, often quiescent, express high levels of ATP-binding cassette transporters, maintain upregulated DNA-repair capacity, and retain resistance to high levels of reactive oxygen species (ROS) contributing to therapeutic resistance and poor patient prognoses [7–9]. Given that BCSCs are responsible for metastasis and contribute to therapeutic resistance, this supports the clinical need to study and therapeutically target these cell populations [6,7].

Transcription factors play essential roles in eukaryotic gene expression by binding specific DNA sites and regulating transcription of almost every gene in a cell's genome [10–12]. It is estimated that there are more than 1600 transcription factors in the human genome, nearly 20% have been associated with different disease phenotypes [10,13]. Multiple transcription factors have been identified as molecular markers and/or mediators of BCSCs that are correlated with breast cancer disease stage [14–18]. Since some transcription factors have been established to play important roles in promoting cancer progression [19], they often represent valid therapeutic opportunities.

Signal transducer and activator of transcription (STAT) family of transcription factors were originally discovered as ligand-induced transcription factors in interferon (IFN)-treated cells that mediate cytokine signaling pathways [20–22]. STATs play important roles in the regulation of cell proliferation, differentiation, apoptosis, and modulate the immune cell landscape [23,24]. In breast cancer, some members of the STAT family, particularly STAT3 and STAT5, are frequently hyperactivated by multiple cytokines leading to the enrichment of BCSCs and other malignant phenotypes of more aggressive breast cancer [25]. Thus, a deeper understanding of how these transcription factors modulate breast cancer progression remains essential in the development of novel breast cancer therapeutics in order to improve patient prognoses and reduce tumor relapse and metastasis.

2. Methods

Databases including open access journals, PubMed (Central), Scopus, Medline, Web of Science, and Google Scholar were utilized to obtain articles related to specific topics of interest. Key terms used during data collection include “STAT” with “breast cancer”, “treatment”, “inhibitors”, and “therapeutics”. Boolean logic (AND, OR) applied to connect the terms when searching databases. The comprehensive review included the most relevant or original articles for Sections 1–4. Section 5 (STAT proteins in breast cancer) includes all references that described individual STAT proteins in breast cancer and any tested STAT inhibitors in breast cancer.

3. Breast cancer, BCSCs, and transcription factors

3.1. Breast cancer

Breast cancer represents 31% of all diagnosed cancer cases in women and is the second leading cause of cancer-related deaths in women [1]. Though a large percentage of breast cancer cases are treatable, metastatic breast cancer patients have a dismal 5-year survival of 22%, with metastasis to distant organs causing the majority of breast cancer deaths [4,5]. Breast cancers can be categorized by intrinsic subtypes (PAM50), which are broadly named Luminal A, Luminal B, human epidermal growth factor receptor 2 (HER2)-enriched, and triple-negative breast cancer (TNBC), which encompasses claudin-low and basal-like TNBCs [26,27]. To make the breast cancer classifications more clinically relevant, the surrogate intrinsic subtypes are based on molecular and histological characteristics that are more widely used: Luminal A-like, Luminal B-like HER2-negative, Luminal B-like HER2-positive, HER2-enriched (non-luminal), and triple-negative [26]. Luminal A-like tumors are the least proliferative and tend to express high levels of specific hormone receptors: estrogen receptor (ER) and progesterone receptor (PR) [28]. Luminal B-like HER2-negative tumors express ER and PR, but at levels lower than in Luminal A-like and lack HER2 expression. Luminal B-like HER2-positive tumors are significantly more proliferative (indicated by a higher Ki-67 index) than Luminal A-like and Luminal B-like HER2-negative, which is partly attributed to expression of HER2. HER2-enriched (non-luminal) tumors lack expression of both hormone receptors and are considered one of the most aggressive breast cancer subtypes. While many HER2-enriched breast tumors respond to HER2-targeted therapies, it is not uncommon that these tumors become refractory to HER2-targeted therapies after 1–3 years [26,29]. TNBCs are characterized by the lack of ER, PR, and HER2 receptors excluding these patients from hormone- or HER2-targeted therapies. Due to the lack of these important receptors and incomplete knowledge of the mechanisms that drive TNBC, prognoses for TNBC patients are poor. Moreover, TNBC and HER2-enriched breast cancers also maintain the highest propensity to metastasize to distant organs [5,30]. The most common sites of metastasis for breast cancer patients include: bone, lungs, brain, and liver [4]. Despite advances in breast cancer therapeutics [29,31,32], there are limited FDA-approved therapies for TNBC patients and few options for HER2-enriched breast cancer patients who exhibit tumor relapse underscoring the clinical importance for further investigating the molecular mechanisms that drive metastatic breast cancer.

3.2. The discovery of cancer stem cells (CSCs) and BCSCs

Stem cell properties and the manipulation of “stemness” by cancer has been widely accepted for years [33]. The first “cancer stem cell” was discovered in the 1930 s when researchers identified a single cell from a mouse tumor initiates a new tumor in a recipient mouse [34]. Nearly 30 years later, single cells isolated from malignant teratocarcinomas have the ability to differentiate into multiple cell lineages and differentiate into non-tumorigenic tumor types [35]. Multiple findings led to the first definition of a cancer stem cell (CSC) that describes cancer cells as those that mimic tissue renewal, retain stemness properties, and contain malignant stem cells that maintain the ability to proliferate, but have limited ability to differentiate [33,36]. In 1995, multiple subtypes of acute myeloid leukemia were consistently engrafted into immunodeficient mice; engraftment was only successful when initiated from CD34-positive CD38-negative populations [37].

The first BCSCs were identified in 2003 when researchers established that breast cancer cells within a single breast tumor were incredibly heterogeneous [6]. Furthermore, as few as 100 $CD44^{high}/CD24^{low}$ cells could initiate tumors in a mouse xenograft assay. In contrast, thousands of cells with combinations of markers other than $CD44^{high}/CD24^{low}$ were unable to establish tumors in immunodeficient mice. Notably, the subpopulation of tumorigenic cells could be serially passaged and at each passage, the $CD44^{high}/CD24^{low}$ subpopulation could give rise to both $CD44^{high}/CD24^{low}$ cells, as well as, non-tumorigenic cells of differing phenotypes. Though specific subsets of markers have been identified to be expressed heterogeneously in numerous cancer types, combinations of markers are variable and remain to be fully understood as there are still conceptual and technological challenges within the CSC field [33,38]. However, since the discovery and isolation of BCSCs [6], an abundance of exciting BCSC research has flourished in the last two decades leading to the discovery of important factors known as transcription factors.

3.3. Transcription factors and breast cancer

Transcription factors are an essential class of proteins that control expression of nearly the entire cell genome, and have become a focus of cancer research and therapeutics following the discovery of oncogenes [19,39,40]. The main function of transcription factors is to bind specific sites on DNA and recruit transcriptional machinery to regulate gene expression [13]. Transcription factors typically act as the nuclear effectors of signal transduction pathways that starts with the binding of an extracellular ligand to a cell-surface receptor with an extracellular domain for that ligand [13,19]. This interaction may cause conformational, chemical, or biological changes that activate intracellular signaling. Here, latent transcription factors are activated by a host of modifications including phosphorylation or interactions with other factors. The activated transcription factors then translocate to the nucleus where they modulate the cell’s transcriptome. Given the critical regulatory control that transcription factors exhibit within cells, dysregulation of these gene expression networks often leads to cancer [41].

In breast cancer, there are numerous transcription factor families known to promote tumor malignancy including the STAT family of proteins. Since their discovery in 1994 [20–23], significant advances have been made in elucidating the roles of and mechanisms

for the STAT transcription factors in facilitating or suppressing breast cancer. In recent years, substantial efforts have been invested in developing STAT-targeted therapeutics with promising outcomes and challenges. This review will focus on the STAT family of transcription factors, their important roles in breast cancer, and the advancements made in STAT-targeted breast cancer therapeutics.

4. STAT family of transcription factors

4.1. STAT transcription factors and structure

The discovery of STAT proteins resulted from the examination of IFN-related pathways, which led to the identification of a previously unrecognized signal transduction pathway [20–22,42]. Since the discovery of the STAT family, STATs play essential roles in the regulation of a myriad of physiological and biological processes in cells [23]. Given that STATs regulate proliferation, metastasis, and chemoresistance, STAT function is often hyperactivated or dysregulated in many cancer types [24,43]. STAT transcription factors maintain the ability to transduce signals resulting in STAT translocation to the nucleus and subsequent gene expression modulation [23]. The STAT family consists of six major isoforms including STAT1, STAT2, STAT3, STAT4, STAT5, and STAT6, which have been identified at these chromosome locations within the human genome 2q32.2, 12q13.3, 17q21.2, 2q32.2, 17q21.2, 17q21.2, and 12q13.3, respectively [23,44,45]. Of note, multiple isoforms for each STAT protein have been identified, so full-length isoforms are denoted with α and the following isoforms named with β-δ [46].

STAT family members are ~740–900 amino acid residues in length and are mostly structurally conserved. In general, the canonical STAT members contain these common domains/regions including 1) the N-terminal domain (NTD; NH2), 2) the coiled-coil domain (CCD), 3) the DNA-binding domain (DBD), 4) the linker domain (LD), 5) the SRC homology 2 domain (SH2), 6) the tyrosine-phosphorylation site (pY), and 7) the C-terminal transactivation domain (TAD) [23,46–53] (Fig. 1).

The NTD is a hook-like structure made up of several alpha-helices [51,54]. Importantly, the NTD mediates critical protein-protein interactions between the STAT family members leading to dimerization and cooperative DNA-binding [47,51]. The CCD also consists of multiple alpha-helices, this time forming a rope-like structure [46]. In contrast to the NTD, the CCD facilitates STAT protein binding to other transcription factors or co-activators [46,55]. For example, STAT1 and STAT3-STAT6 interact with N-Myc interactor (Nmi), which is stimulated by the ligands interleukin-2 (IL-2) and IFNɣ [55]. In another example, downstream of IFNα, the STAT1-STAT2 heterodimer recruits and interacts with p48 to mediate STAT-driven transcription [56]. In addition, STAT5a and STAT5b interact with silencing mediator for retinoic acid receptor and thyroid hormone receptor, which suppresses STAT5-mediated transcription, demonstrating that the CCD also mediates interactions with co-repressors [57]. The CCD also contributes to nuclear translocation as the nuclear localization signal (NLS) interacts with importins to facilitate nuclear translocation [46,58,59]. The DBD contains an immunoglobulin fold that mediates recognition, binding to specific DNA sequences, and stabilization of DNA interacting elements [46,47,50]. The LD is an essential contact point that provides structural stability

for the STAT-driven complex [46,56]. The SH2 domain structure enables the protein the ability to bind specific phosphotyrosine-containing motifs, also referred to as tyrosine-phosphorylation sites (pY) [60–62]. This region is highly conserved in a variety of signaling molecules in order to mediate protein-protein interactions [61]. More specifically, the SH2 domains of STAT proteins can bind both pYs on receptor complexes and pYs on the same STAT protein leading to subsequent dimerization [46, 63]. Moreover, tyrosine phosphorylation is necessary for activation of a myriad of transcription factors including those in the STAT family [21, 44,64,65]. Finally, the C-terminal TAD facilitates STAT interactions with transcriptional co-factors [66,67]. For example, TAD enables STAT2 to bind p300/CREB-binding protein [68] and Brahma-related gene 1 in response to IFNα signaling [69]. Additionally, STAT6 can directly interact with p300/CBP and the nuclear coactivator 1 via the TAD to enhance transcriptional activation [70].

4.2. Canonical STAT functions

The canonical STAT pathway is evolutionarily conserved and activated by ligands, such as IFNs or ILs, binding to cell surface receptors [47,53]. Activation by ligand binding to its respective surface receptor initiates a cascade of signaling events leading to STAT translocation to the nucleus and regulation of downstream target genes (Fig. 2). Inactive (i.e. unphosphorylated) STAT proteins reside in the cytoplasm prior to ligand binding [47,53]. Once an extracellular ligand binds a cell surface receptor, it undergoes conformational changes leading to the recruitment of Janus kinases (JAKs), non-receptor tyrosine kinase family, and subsequent autophosphorylation of tyrosine residues within the receptor complex [21,44,53,71]. Activated JAKs now provide docking sites for a diverse number of signaling molecules with SH2 domains, such as STATs [72]. Given that multiple ligands can activate this JAK/STAT signal cascade to modulate many cell phenotypes, the pY-SH2 interaction is highly specific as a way of regulating STAT activation. When receptor-mediated STATs are recruited to the activated JAK complex, the JAKs phosphorylate a specific pY on the unactivated STAT molecule resulting in reciprocal binding of the pY on one phosphorylated STAT (pSTAT) to the SH2 domain of the pSTAT associated with the second receptor. This reciprocal binding leads to STAT homo- or heterodimerization releasing the complex from the extracellular receptor-JAK complex and allows the pSTAT dimer to translocate the nucleus, which is facilitated by importins and other helper proteins [73–75]. Unactivated STATs are also phosphorylated by tyrosine kinases that retain intrinsic kinase activity, which do not require JAKs (Fig. 2). In this mechanism, a growth factor or ligand binds its respective receptor tyrosine kinase, which phosphorylates STAT proteins, allows for STAT dimerization and translocation to the nucleus [43,76]. Though the physical STAT functions within the nucleus are relatively conserved, nuclear import of each STAT varies representing an important aspect of STAT regulation. However, the mechanistic findings of how STATs 1–6 are imported and exported from the nucleus go beyond the scope of this review [73,77–79].

Within the nucleus, the pSTAT dimer binds specific DNA sequences within promoter or regulatory regions of genes, often referred to as DNA regulatory elements, leading to robust transcriptional changes that alter expression of a multitude of target genes [44,47,80–82]. Though canonical STAT signaling involves STATs homo- or heterodimerizing following

phosphorylation by JAKs, multiple studies report non-canonical STAT signaling. For example, STAT1 and STAT3 can form homodimers prior to phosphorylation [83–86]. However, these non-phosphorylated STAT dimers are unable to translocate to the nucleus [84]. In another report, the majority of unactivated STAT3 (as well as other STATs) is detected in multimeric complexes, referred to as “statosomes”, indicating an alternate method of STAT3 activation that is retained in the cytoplasm [87]. In contrast to previous reports, unphosphorylated STAT1 translocates to the nucleus and upregulates immune regulatory genes in the absence of IFN stimulation [88]. Interestingly, STAT5 forms tetramers, which mediate IL-2-dependent transcriptional activation of a specific subset of genes involved in immune function that canonical STAT5 dimers are unable to activate [89, 90]. Alternative STAT activation also occurs through other proteins, such as non-receptor tyrosine kinases or G-protein coupled receptors (GPCRs) that facilitate STAT recruitment to JAKs as STAT proteins are unable to phosphorylate themselves or other proteins since they do not maintain any tyrosine kinase activity [23,82,91,92]. Though these reports shed some light on alternative STAT signaling, non-canonical mechanisms of STAT signaling remain largely unexplored.

There are main regulators of STAT signaling including suppressors of cytokine signaling (SOCS), which are expressed at the start of STAT signaling [93]. SOCS have the ability to bind and inhibit both STAT proteins and/or JAK kinases as they maintain an SH2 domain and kinase inhibitory regions to inhibit each, respectively [93,94]. For example, SOCS3 is an important JAK-STAT pathway inhibitor that specifically prevents STAT3 expression and pSTAT5 in breast cancer [95,96]. Moreover, treatment with isolinderalactone increases SOCS3 and subsequently suppresses pSTAT3 and apoptosis-inducing factors in TNBC [97]. Additionally, SOCS2, SOCS3, SOCS5, SOCS6, and SOCS7 are highly, constitutively expressed in breast cancer cells compared to normal breast epithelial cells [98]. Phosphatases are another category of proteins that can negatively regulate STAT pathway activation mediated by dephosphorylation of tyrosine residues [99]. Though regulation of STATs are important for understanding STAT pathways, further detail into the exact mechanisms of the negative regulators of STATs go beyond the scope of this review [53,93].

It is widely understood that STAT proteins play critical roles in many signal transduction pathways that are important in human physiology and biology. Furthermore, over 50 cytokines and growth factors can activate a combination of STAT signal cascades [21,44], suggesting that dysregulation of the extracellular activators (i.e. cytokines or growth factors), the intrinsic players (i.e. STATs or associated factors and kinases), the negative regulators of STAT proteins, or any combination of these events may lead to cancer [53]. More specifically, STAT3 contributes to breast cancer progression and chemoresistance with many of these findings leading to the development of natural compounds and drug inhibitors that target STAT3 for breast cancer treatment. While STAT proteins besides STAT3 are not as well understood in breast cancer, there are promising findings investigating all STAT family members in breast cancer. This review will summarize functions for all STAT proteins in breast cancer, discuss STAT inhibitors reported in breast cancer, and their clinical implications.

5. STAT proteins in breast cancer

5.1. STAT1

STAT1 signaling modulates pathways involved in cell growth, differentiation, homeostasis, immune signaling, and immune response [100]. Similar to other STAT family members, STAT1 is activated by both types of IFNs (I and II) [80,101]. Numerous reports demonstrate that STAT1 displays tumor suppressive functions in many cancer cell types, including breast cancer, with loss of STAT1 expression or activation leading to cancer progression [23,102,103]. Moreover, higher STAT1 activation, as indicated by both tyrosine phosphorylation and DNA binding, is associated with longer relapse-free survival and overall survival for breast cancer patients [104]. Furthermore, high STAT1 mRNA expression using a STAT1-immune-related gene signature correlates with longer distant metastasis-free survival (DMFS) in ER-negative/PR-negative and TNBC patients [105]. Additionally, chemotherapy-induced IFN target genes are associated with STAT1 phosphorylation and IFNγ secretion in treatment-sensitive breast cancers, suggesting that IFN/STAT1 activation predicts response of ER-negative breast cancers [106]. PR also suppresses IFN-activated pSTAT1 decreasing immune surveillance and increasing immune evasion in PR-positive breast tumors [107]. STAT1 inhibition decreases breast cancer cell proliferation, ERα protein levels and target gene expression [108]. Further investigation reveals that STAT1 directly binds the promoter region of ERα, suggesting an important role for STAT1 in ER activity [108].

Utilizing diverse transgenic and alternative mouse models, STAT1 exhibits anti-tumor function including inhibition of mammary gland tumorigenesis and promotion of tumor immune surveillance *in vivo* [102,109–113]. For example, STAT1 suppresses ErbB2/Neu (or Her2/Neu)-induced tumorigenesis in transgenic mice [110]. In another study, human breast tumors had little to no expression of STAT1; normal breast epithelial cells express significantly elevated levels of STAT1 compared to adjacent breast tumor tissue [102]. From the same study, STAT1-deficient transgenic mice develop spontaneous ER-positive/PR-positive mammary tumors whereas none of the wild-type mice developed tumors [102]. Moreover, STAT1 antagonizes the JAK2-STAT3/5 A/5B pathway, induced by the prolactin receptor, to inhibit ER-positive tumorigenesis [114]. STAT1 also downregulates NAD(P)H quinone dehydrogenase 1 resulting in increased oxidative stress in sensitized patient-derived xenografts for both HER2-positive and TNBCs [115].

In contrast to multiple studies demonstrating a tumor-suppressive role for STAT1, high STAT1 activity also correlates with poorer patient prognoses [116]. STAT1 is activated by CD95 (Fas), a receptor that mediates apoptosis by activating a caspase cascade, which promotes STAT1-dependent mammospheres [117]. Inhibition of DNA methyltransferase 3 beta by microRNA (miR)− 29c results in upregulated TIMP3/STAT1/FOXO1 signaling, which promotes breast cancer progression [118]. Phospholipid scramblase 1 directly binds and increases STAT3 interactions with the STAT1 promoter, leading to enhanced transactivation and breast cancer cell proliferation and invasion [119]. Overexpression of STAT1 also promotes myeloid-derived suppressor cell (MDSC) migration and suppresses both CD4-positive and CD8-positive T cells in mouse tumors [116]. STAT1 knockdown in

cancer-associated fibroblasts extends breast cancer progression and combination treatment of a STAT1 inhibitor with doxorubicin suppresses tumor progression in mouse mammary tumors [120]. STAT1 also interacts with ERα and STAT1 and ERα directly interact with the promoter region of interferon-induced transmembrane protein 1 (IFITM1) resulting in upregulated IFN-mediated gene expression to promote breast cancer cell survival [121]. In another example, STAT1 activation, in cooperation with mucin 1, associates with shortened recurrence-free survival and overall survival in breast cancer patients [122], suggesting that STAT1 functions in breast cancer still remain to be fully understood.

Given that BCSCs are major drivers of therapeutic resistance, STAT1's role in modulating BCSCs may be important in understanding how to utilize STAT1 in breast cancer treatment. Low levels of surface-CD24, concurrently with high levels of surface CD44, indicate cancer-initiating cells or BCSCs [6]. CD24-mediated inhibition of the Sonic Hedgehog (SHH) pathway and STAT1 activity suppresses breast cancer cell proliferation and invasion [123]. Similarly, sphingosine kinase 1 promotes breast cancer cell proliferation and mammosphere formation, while suppressing apoptosis, in part by downregulating STAT1 activation [124]. Following irradiation, an increase in STAT1 is attributed to a significant decrease in apoptosis of mammospheres [125]. In contrast, overexpressed and hyperactive STAT1 decreases CD44-expressing cells in breast cancer cells [126]. STAT1's role in modulating BCSCs and potential contribution to radioresistance highlight the need to further examine STAT1 mechanisms in breast cancer.

STAT1 and STAT3 have been reported to functionally interact, antagonize, and cooperate in cancer cells [127,128], suggesting these two STAT family members have complex networks. STAT1 is enriched by nuclear epidermal growth factor receptor (EGFR) and STAT3 binds to the STAT1 promoter to increase STAT1 expression in breast cancer cells [127]. EGFR is an important transcriptional regulator in breast cancer and nuclear EGFR staining is a predictive marker for patient prognosis [129]. Moreover, inhibition of EGFR and subsequent suppression of STAT3 activation with tannic acid promotes cell cycle arrest and apoptosis in breast cancer cells [130]. Further investigation reveals that tannic acid also increases pSTAT1, leading to increased expression of p21, a cyclin-dependent kinase inhibitor, leading to cell cycle arrest and apoptosis [130]. When comparing STAT expression in lymph nodes and primary breast tumors using a tissue microarray, the lymph nodes exhibit increased cytoplasmic STAT1, pSTAT3, and STAT5 and nuclear pSTAT3 [131].

In another study using breast cancer specimens, high STAT1 and STAT3 activation correlate with decreased tumor grade; high pSTAT1 associates with increased immune infiltration (inflammation-induced) whereas increased pSTAT3 associates with suppressed CD4-positive T-cell infiltrate [132]. The Shc1 scaffold activates STAT3 and inhibits STAT1 activation to promote immunosuppression while inhibiting anti-tumor immune surveillance in breast cancer cells, respectively [128]. Loss of Shc1-tyrosine kinase signaling increases IFNγ, while WT-Shc1-tyrosine kinase signaling represses IFNγ secretion [128]. Further investigation into the relationship between STAT1 and STAT3 in anti-tumor immunity reveals that STAT1 loss in high STAT3-activated mammary tumors suppresses tumor onset in mice. Interestingly, STAT1 loss in low STAT3-activated mammary tumors significantly

promotes tumor growth, suggesting that STAT3 activity may be critical in determining STAT1's pro- or anti-tumor roles [128].

The programmed cell death 1 (PD-1) and programmed death-ligand 1 (PD-L1) interaction, which inhibits hyperactivation of immune cells to balance normal immune homeostasis, is a common strategy for tumor cells to inhibit and evade anti-tumor immune cells [133,134]. IFNγ induces PD-L1 expression through the JAK1/2-STAT1 pathway in TNBC cells [135,136]. PD-L1 and pSTAT1 are positively correlated in breast tumor specimens [137]. Furthermore, upregulated PD-L1 in CSCs promotes immune evasion or suppression [138]. One study elucidating the mechanisms of PD-L1 in breast cancer utilizes dual inhibition of both STAT1 and STAT3, and found that combined inhibition abrogates expression of PD-L1; pSTAT1 and pSTAT3 form a heterodimer in the cytosol, translocate to the nucleus, and directly bind the promoter region of PD-L1 [139]. Taken together, STAT1 plays critical roles in modulating breast cancer cells, BCSCs, and the pro- and anti-tumor immune system. However, the major regulators or modulators that determine whether STAT1 will promote or antagonize breast cancer remain unclear, emphasizing the importance of continuing to investigate STAT1 in breast cancer.

Since the tumor suppressive role of STAT1 is highly reported, there are few STAT1 inhibitors currently used for the treatment of breast cancer (Table 1). Epigallocatechin gallate (EGCG), the main active component in green tea and a known STAT1 inhibitor, reduces cell proliferation and induces apoptosis in luminal A breast cancer cells [131,140]. Furthermore, EGCG decreases tumor volume and increases PARP expression to inhibit tumor growth *in vivo* [140]. EGCG also exhibits a dual impact by suppressing proliferation and migration and by modulating vascular endothelial growth factor (VEGF) in TNBC, suggesting an important role for angiogenesis in TNBC [141]. Another STAT1 inhibitor, Fludarabine [142,143], suppresses STAT1 expression, pSTAT1, and PD-L1 expression in breast cancer cells [139]. In conclusion, the pro- or anti-tumor roles may be dependent on the status of additional factors (i.e. STAT3) or other aspects in the tumor microenvironment, which warrants further investigation.

5.2. STAT2

STAT2 was discovered through investigation of IFN signaling pathways and relays important immunomodulatory and anti-viral functions of IFN-I [144–146]. STAT2 is the longest STAT family protein and is physically and functionally conserved; IFNɣ signaling is restored with mouse STAT2 in STAT2-deficient human cells [147,148]. Canonical STAT2 signaling involves IFN-I or –III activation of the heterotrimeric interferon-stimulated gene factor 3 (ISGF3) complex, which contains STAT1, STAT2, and interferon regulatory factor 9 (IRF9) [42,144]. The ISGF3 complex is unique to STAT2 activation as pSTAT2 molecules do not form homodimers despite the fact that alternative homo- and heterodimers of the other STAT proteins are identified to mediate IFN signaling [148]. Notably, the STAT2-mediated ISGF-3 complex can upregulate IL-6 gene expression leading to increased IL-6/STAT3 signaling [149,150], which is commonly dysregulated and hyperactivated in breast cancer [24].

PR suppresses IFN signaling in breast cancer cells by promoting an immunosuppressive microenvironment [151]. Further investigation reveals that STAT2 is critical for IFN-I pathway activation and that PR-mediated suppression of IFN signaling occurs by increasing ubiquitination and subsequent degradation of STAT2 in breast cancer cells [151]. STAT2-deficiency suppresses breast cancer cell proliferation, migration, and invasion, while STAT2 overexpression upregulates expression of IFITM1, contributing to aggressive inflammatory breast cancer phenotypes [152]. Covalent addition of ISG15 ubiquitin like modifier (ISG15), a ubiquitin-like protein tag, to STAT2 promotes secretion of chemokine ligands leading to a subsequent increase in CD8 + T cells and suppression of breast cancer growth and metastasis [153]. Analysis of breast cancer patient data reveals that high STAT2 mRNA expression correlates with worse post-progression survival, but better relapse-free survival [154,155]. Given that STAT2 is not as commonly studied, there are currently no published natural compounds or pharmacological inhibitors for STAT2 in breast cancer.

5.3. STAT3

In 1994, STAT3 was first described as a DNA-binding protein activated by IL-6 in hepatocytes [156,157]. A year later, the Src oncoprotein was reported to activate STAT3, making this publication the first to implicate STAT3 in cancer [158]. Nearly 20 years later, STAT3 is now the most widely studied STAT family member in breast cancer as it regulates networks of genes involved in oncogenesis [159], cancer cell proliferation [43], cell cycle progression [43], angiogenesis [160,161], metastasis, and evasion of apoptosis [162–164]. Moreover, STAT3 is the only STAT protein that is essential for embryonic development as homozygous genetic deletion is lethal in mice [165]. STAT3 activation is triggered by the largest and most diverse number of cytokines of all the STAT family members, underscoring its vast influence on many physiological pathways [53, 166, 167]. These ligands include the IL-6 cytokine family, IL-10 cytokine family, additional interleukins (i.e. IL-21), multiple IFNs, EGF, FGF, IGF, leptin, and granulocyte-colony stimulating factor (G-CSF) [21, 44, 53, 168, 169]. Additionally, there are multiple isoforms of STAT3, though most publications studying STAT3 in cancer refer to the full-length isoform (STAT3α) [170].

Though in normal conditions STAT3 is regulated by many molecular factors [23], STAT3 is dysregulated in multiple cancer types including breast cancer [171,172]. The IL-6 family of cytokines are the most predominant STAT3 activators, in particular, IL-6 is a major mediator of breast cancer cell growth, angiogenesis, tumor growth, metastasis, and immune evasion or modulation [24, 43, 169, 173–175]. Increased serum IL-6 upregulates STAT3 activity, which increases IL-6 expression through STAT3 directly binding and transactivating the IL-6 promoter region, further promoting this IL-6/JAK/STAT3 positive-feedback loop [173,174]. Hyperactivation of STAT3 enriches expression of genes involved in cancer stemness (CD44) [176], cell cycle (cyclin D1) [159, 177], apoptosis or cell survival (Bcl-2, Bcl-xL, and Mcl-1) [178–180], invasion and migration (matrix metalloproteases or MMPs, ERRα) [181, 182], angiogenesis (VEGF and HIF1α) [183,184], and immunosuppression (IL-10 and TGFβ) [174, 183, 185, 186]. Furthermore, pSTAT3 correlates with poor prognosis for breast cancer patients [187]. Though STAT3-mediated gene signatures are identified in most breast cancer subtypes, STAT3-mediated gene signatures are upregulated in basal-like compared to

luminal subtypes, suggesting STAT3 activity is more likely to be hyperactivated in TNBC subtypes of breast cancer [188].

Oncostatin M (OSM) upregulates STAT3-dependent expression of IL-6 and high OSM associates with worse patient survival [189,190]. Increased IL-6 secretion and pSTAT3 promote breast cancer progression resulting in shortened patient survival [189]. OSM activates STAT3/SMAD3 signaling in breast cancer cells, which leads to increased Snail and epithelial-to-mesenchymal transition (EMT) [191]. IFNβ antagonizes this OSM/STAT3/OSM pathway, thus inhibiting BCSC phenotypes and increasing STAT1 and pSTAT1 in breast cancer cells [191]. Increased IL-8 and growth-regulated oncogene in inflammatory breast cancer promotes BCSCs, which is enhanced by co-culture with macrophages [192]. On the other hand, IL-17 suppresses STAT3 activation [193].

In addition to cytokines and chemokines, proteins or other factors also activate STAT3 signaling in breast cancer. Long noncoding RNA (lncRNA) MAFG-antisense 1 (MAFG-AS1), whose expression is elevated in breast tumors compared to normal breast tissue, increases pJAK2 and pSTAT3; knockdown of MAFG-AS1 suppresses breast cancer cell proliferation and decreases tumor growth in mice [194]. Enhancer of zeste homolog 2 methylates STAT3 to increase nuclear localization of STAT3 and promote breast cancer progression [195]. Endogenous breast tumor kinase (Brk) leads to upregulated pSTAT3 and STAT3 transcriptional activation to promote breast cancer oncogenesis [196]. Furthermore, STAP-2 enhances STAT3 activation by directly binding and interacting with STAT3 and indirectly through Brk; increased STAT3 activation promotes breast cancer cell proliferation [197–199].

EGFR is highly upregulated and often constitutively activated in breast cancer [200–202]. Importantly, EGFR activation leads to JAK autophosphorylation and subsequent STAT activation [203,204]. EGFR and pSTAT3 promote breast cancer cell proliferation and invasion and are upregulated in TNBC tissues [203]. Growth factor receptor-binding protein 2 (Grb2), the adaptor protein that directly binds EGFR, downregulates EGF-mediated activation of STAT3, which decreases STAT3-mediated gene transcription [205].

Tropomyosin receptor tyrosine kinases (Trk), a family of tyrosine kinase receptors, bind neurotrophins and other ligands to regulate multiple cellular processes [206]. TrkA and phosphorylated-TrkA (pTrkA) levels are elevated in breast tumors compared to normal breast tissue; overexpression promotes breast cancer cell proliferation, migration, and invasion [207]. Our lab found that TrkA and JAK2/STAT3 are co-overexpressed and activated in HER2-enriched and TNBC [208]. TrkA and JAK2/STAT3 also physically and functionally interact in HER2-enriched and TNBC [208]. Moreover, TrkA interaction with STAT3 promotes STAT3 phosphorylation resulting in STAT3 translocation to the nucleus and increases STAT3 transcriptional activity. Additionally, co-activation of the TrkA-STAT3 pathway promotes BCSCs and correlates with poor patient prognosis [208].

Interestingly, STAT3 also physically and functionally interacts with truncated glioma-associated oncogene homolog 1 (tGLI1), a gain-of-function isoform of the transcription factor GLI1, increasing mammosphere forming ability of breast cancer cells [171,209].

tGLI1, originally discovered in glioblastoma [210], is tumor-specific [210,211], and can regulate GLI1 target genes as well as eight novel target genes, which include VEGF-A, VEGF-C, VEGFR2, TEM7, HPSE, CD24, CD44, and OCT4 [171, 212–218]. tGLI1 has also been shown to promote breast cancer brain metastasis (BCBM) by enriching BCSCs [214]. More recently we found that tGLI1-positive breast cancer cells upregulate extracellular vesicle-derived miR-1290 and miR-1246 to activate astrocytes to promote the progression of brain metastases; astrocytes overexpressing miR-1290 promoted the growth of co-implanted breast cancer cells in the brain *in vivo* [219].

There are also multiple negative regulators of STAT3 reported in breast cancer. Double PHD fingers 3 (DPF3 or CERD4) suppresses breast cancer cell proliferation and higher expression correlates with better patient prognoses; downregulation of DPF3 activates the JAK2/STAT3 pathway to promote breast cancer proliferation and migration [220]. WW domain-containing oxidoreductase (Wwox) is lost in TNBC compared to luminal breast cancer cells, while overexpression of Wwox suppresses cell proliferation and metastasis in TNBC [221]. Further investigation reveals Wwox inhibits pJAK2, pSTAT3, and STAT3 association with the IL-6 promoter region, implicating Wwox as an important negative regulator of STAT3 activity [221]. Gametogenetin-binding protein suppresses breast cancer cell proliferation, migration, invasion, BCSCs, and induces apoptosis partly through the inhibition of the IL-6/JAK/STAT3 pathway [222]. GRAM domain-containing protein 1B decreases breast cancer cell migration by modulating cell morphology and decreasing STAT3 signaling [223].

MicroRNAs (miRNAs), small noncoding RNAs that regulate gene expression by targeting mRNAs, also modulate STAT3 activity in breast cancer [30, 224, 225]. Overexpression of miR-124 decreases mRNA and protein levels of STAT3; miR-124 directly binds to STAT3 mRNA leading to decreased breast cancer cell growth and invasion [226]. Moreover, lncRNA nuclear enriched abundant transcript 1, which is increased in breast cancer compared to normal breast tissues, promotes proliferation and cell cycle progression of breast cancer cells, potentially by downregulating the STAT3-inhibitor miR-124 [227]. miR-125a and miRNA let-7e directly target the 3’- untranslated regions of IL-6 receptor (IL-6R) and STAT3 to mediate breast cancer cell proliferation, chemosensitivity, and endothelial cell adhesion [228]. The cytokine resistin increases expression of LIN28A, which suppresses let-7a in breast cancer cells [229]. Furthermore, downregulation of let-7a increases expression of target genes STAT3 and IL-6 and overexpression of let-7a suppresses resistin-mediated breast cancer cell proliferation and mammosphere formation [229]. miR-93–5p also suppresses cell proliferation by downregulating STAT3 in breast cancer [230]. miR-519d negatively regulates STAT3 to suppress breast cancer cell proliferation and invasion while inducing apoptosis [231]. Similarly, miR-520c suppresses breast cancer cell migration, invasion, and EMT-associated markers by downregulating STAT3 [232]. miR-204 suppresses expression and subsequent activity of JAK2, decreasing pSTAT3 and breast cancer cell proliferation [233]. Similarly, miR-375 suppresses BCSCs and Adriamycin resistance by directly targeting JAK2 and subsequent STAT3 activation [234]. In contrast, miR-18a overexpression correlates with a decrease in protein inhibitor of activated signal transducer and activator of transcription 3 expression to counteract STAT3 downregulation [235].

Immune modulation is another way STAT3 promotes a pro-tumorigenic microenvironment for breast cancer. Macrophages play important roles in immune surveillance and the anti-tumor immune response. However, macrophages can be transformed into tumor-promoting cells (referred to as tumor-associated macrophages, TAMS) that facilitate cancer cell evasion of the immune response as well as promote tumor cell growth [236–239]. Breast cancer cell-derived chemokine C-C motif ligand 5 promotes the M2 macrophage phenotype through activating STAT3 from receptor C-C chemokine receptor type 5 [240]. TAM-secreted IL-6 also induces BCSCs by activating STAT3 signaling to promote migration and angiogenesis [241]. In contrast, overexpression of Kruppel-like family of transcription factor-14 (KLF14), which is downregulated in breast cancer, inhibits M2 macrophage polarization as well as suppresses breast cancer cell invasion *in vitro* and tumor growth *in vivo* [242]. Further investigation reveals that KLF14 reduces invasion of breast cancer cells by activating expression of SOCS3, leading to the suppression of RhoA/Rock/STAT3 signaling in breast cancer cells [242].

STAT3 signaling also upregulates immune evasion to promote breast cancer progression. STAT3-deficient mice developed early lesions, suggesting that STAT3 is not required for tumor initiation. However, the lesions regressed over time, which is attributed to an increase in immune infiltration including increased CD8 + T cells and macrophages resulting in tumor clearance [243]. Interestingly, STAT3-wild-type mice developed a high number of lung metastases, while STAT3-deficient mice did not develop any lung metastases [243]. These findings are consistent with additional reports of high STAT3 activity in BCSC-enriched TNBC cells increasing metastatic potential [244]. In addition, IL-35, secreted from breast cancer cells, suppresses canonical T cell proliferation and induces differentiation of regulatory T cells [245]. These induced-regulatory T cells activate both STAT1 and STAT3 activity to promote breast cancer cell proliferation and T cell-specific immune evasion [245].

STAT3 can also promote breast cancer progression through mediating resistance to breast cancer treatments. SIRT4 decreases pSTAT3 in breast cancer cells and increases sensitivity to tamoxifen [246]. Exosomal miR-378a-3p and miR-378d are highly secreted by breast cancer cells treated with doxorubicin or paclitaxel and increase drug resistance by upregulating Wnt and Notch pathways while downregulating Dickkopf WNT Signaling Pathway Inhibitor 3 and NUMB Endocytic Adaptor Protein [247]. Furthermore, STAT3 promotes a drug resistant phenotype by binding the promoter regions of both miR-378a-3p and miR-378d in the breast cancer cells. miR-124, previously reported to downregulate STAT3 [226], sensitizes doxorubicin-resistant BCSCs by downregulating STAT3 and hypoxia-inducible factor-1 (HIF-1) signaling pathways in breast cancer [248]. Consistent with these findings, pharmacological inhibition of STAT3 also sensitizes breast cancer cells to doxorubicin [249]. Higher expression of Bcl-2, a regulator of apoptosis, and STAT3 activity is elevated in metastatic breast cancer cell lines compared to their parental lines and additional functional assays reveal that constitutively active STAT3 upregulates Bcl-2 in a mechanism that promotes chemoresistance of metastatic breast cancer cells [250]. Inhibition of HER2 and subsequent STAT3 activity sensitizes HER2-positive breast cancer cells to radiotherapy [251]. JAK/STAT3 signaling also regulates fatty acid beta-oxidation (FAO) by activating CPT1B and JAK inhibition suppresses FAO-mediated BCSCs and chemoresistance in breast cancer cells [252]. Overexpression of leukemia inhibitory

factor receptor (LIFR)-mediated STAT3 activation promotes resistance to trastuzumab-emtansine (T-DM1), while STAT3 inhibition sensitizes T-DM1-resistant breast cancer cells [253]. Given that STAT3 promotes the progression of breast cancer by upregulating pro-tumorigenic pathways, STAT3 is a very favorable target for breast cancer therapeutics both pre-clinically and clinically [254].

As previously mentioned, STAT3 is the most widely studied STAT protein in breast cancer. Given STAT3's various roles contributing to breast cancer progression, there are over 60 STAT3 inhibitors published in breast cancer to date (Table 1). Since the early 2000 s, STAT3 inhibitors ranging from pharmacological small-molecule inhibitors to natural plant derivatives have been a major focus for breast cancer therapeutics. It is important to note that many synthetic or natural compound STAT3 inhibitors are not fully characterized in breast cancer as not every publication shows direct and specific STAT3 inhibition. This section will discuss STAT3 inhibitors for breast cancer listed in Table 1.

For example, novel platinum compounds, CPA-1/7, inhibit STAT3 activation and DNA-binding, resulting in a decrease in cell proliferation and increase in apoptosis in breast cancer cells [255]. S31–201 inhibits activated-STAT3 dimerization to suppress breast cancer cell proliferation and induce apoptosis [256]. An analog of S3I-201, referred to as BP-1–102, inhibits STAT3 activation, which results in a decrease in breast cancer cell proliferation, migration, invasion, and increase apoptosis [257]. Furthermore, BP-1–102 intravenously injected into mice bearing breast tumor xenografts suppresses tumor growth, tumoral pSTAT3, and additional STAT3-mediated gene expression [257]. Stattic (or 6-nitro-benzo[*b*]thiophene-1,1-dioxide 1), an important STAT3 inhibitor, acts by selectively inhibiting STAT3 activation by blocking the GP130 receptor and STAT3-SH2 domain interaction, STAT3 dimerization, and nuclear translocation [258]. In addition, Stattic induces apoptosis in highly activated STAT3 breast cancer cell lines. Though Stattic is highly selective for STAT3, Stattic can bind STAT1 and STAT5b, but with significantly reduced binding affinities [258]. Hydroamic and benzoic acid analogues SH5–07 or SH4–54 inhibit pSTAT3 and DNA-binding and both effectively suppress breast tumor growth *in vivo* [259]. Furthermore, pimozide, an antipsychotic drug originally synthesized to treat schizophrenia, suppresses pSTAT3, migration and invasion and induces apoptosis in multiple TNBC cell lines [260].

WP1066, originally discovered to inhibit STAT3 in human glioma cells [261], inhibits STAT3 activation and reduces macrometastases of brain-tropic breast cancer cells in the brain of nude mice [262]. Moreover, WP1066 suppresses breast cancer cell invasion and MMP9 expression and angiogenesis, implicating WP1066 as a potential therapeutic for BCBM [262]. Interestingly, STAT3 activation distinguishes a subpopulation of reactive astrocytes that promote BCBM; loss of STAT3 in reactive astrocytes abrogates brain metastases in mice, in part, by modulating both innate and adaptive immunity in the brain [263]. Silibinin (Legasil), a STAT3 inhibitor derived from a nutraceutical product extract from milk thistle seeds, crosses the blood-brain barrier [264, 265], and suppresses brain metastases in both mouse models and in patients [263].

In addition to silibinin, there are numerous natural compounds that exhibit anticancer effects in breast cancer. Curcumin, for example, is an important phytochemical derived from turmeric that is implicated in prevention and treatment of a multitude of diseases including cancer [266]. Furthermore, curcumin alone and with EGCG suppressed mammosphere formation, pSTAT3, and CD44-positive cells of TNBC and HER2-enriched breast cancer cells [267]. In another example, FLLL31/FLLL32, STAT3-specific small molecule inhibitors designed to biochemically mimic curcumin inhibit pSTAT3, DNA-binding, and subsequent transactivation in breast cancer cells; FLLL32 suppresses tumor growth in mouse xenografts [268]. Saikosaponin b2 (SSb2) is extracted from the root of Bupleurum plants and is traditionally used to treat inflammation [269]. SSb2 decreases pSTAT3 and suppresses proliferation and migration of breast cancer cells [270]. Additionally, Esculentoside A (EsA) is extracted from Phytolacca esculenta roots; the triterpene saponin suppresses cell proliferation and mammosphere formation of BCSCs as well as induces apoptosis [271]. Furthermore, treatment with EsA decreases tumor growth of mouse breast tumors *in vivo* [271].

Medicinal mushrooms can also exhibit pharmacological properties, including antitumor and immunotherapeutic effects [272,273]. *Hericium erinaceus* (*H. erinaceus*) water extract, a medicinal mushroom demonstrated to exhibit anticancer properties, inhibits cell viability, and induces apoptosis and cell cycle arrest in breast cancer cells [274]. Moreover, whole genome and transcriptome analysis revealed that the JAK-STAT pathway is significantly enriched in response to *H. erinaceus* treatment based on differential gene expression results [274]. Furthermore, Micotherapy U-care, which contains medicinal mushroom extracts from *Agaricus blazei, Ophiocordyceps sinensis, Ganoderma lucidum, Grifola frondosa*, and *Lentinula edodes*, has been shown to decrease pulmonary metastases and reduce NOS, COX2, and IL-6 expression in a TNBC mouse model [275]. Reduced IL-6 expression in metastatic and bronchial epithelial cells suggested that Micotherapy U-care could suppress STAT3 activation in TNBC.

There are over 60 STAT3 inhibitors published in breast cancer and more in clinical trials for the treatment of numerous cancers [276,277]. However, there are currently no FDA-approved STAT3 inhibitors for the treatment of breast cancer underscoring the clinical importance of these preclinical studies in breast cancer.

5.4. STAT4

The crystal structure of the NTD of multiple STATs and the specific characterization of the secondary structure of this NTD for STAT4 was discovered in 1998 [51]. STAT4 is not as commonly studied as other STAT proteins, which may be due to the fact that very few cytokines activate the STAT4-mediated immune pathways [23]. IL-12 is the main ligand that triggers JAK2-Tyk2 phosphorylation, STAT4 homodimerization, translocation to the nucleus, and subsequent modulation of STAT4-mediated genes [278,279]. IL-12 increases production of IFNγ, differentiation of T helper cells, and facilitates innate and adaptive immunity in a mainly tumor-suppressive manner [279–282]. Though few cytokines trigger STAT4 pathways, STAT4 has the ability to bind multiple target gene promoter regions including MYD88, IFNγ, TNF, IL18R1, Furin, and IL18RAP [280,283]. Additionally,

STAT4-deficient mice have underdeveloped immunity against both parasitic and bacterial infections [278]. Though IL-12 is the master regulator of STAT4 activation, IL-23, IFNα, IL-2, IL-27, and IL-35 also trigger STAT4 signaling [284–286].

STAT4's functions in breast cancer are not well understood. Immunohistochemical analysis of STAT4 expression reveals higher STAT4 expression in non-cancer breast tissues compared to the breast cancer tissue samples [287]. High STAT4 expression correlates with better overall survival and relapse-free survival in breast cancer patients [154]. High expression of STAT4 and IL12B1/2 also correlates with better survival in breast cancer patients [288]. Furthermore, pSTAT4 is upregulated by cryptotanshinone in CD4-positive T cells, which suppresses breast cancer cell growth *in vivo* [289]. STAT4 co-expressed genes are also enriched in adaptive immune responses, specifically T cell activation and signaling as well as cytokine regulation [290]. The role of STAT4 in breast cancer or specifically in the breast-immune microenvironment warrants further investigation. Given that there are limited studies and that most of breast cancer studies implicate STAT4 in a tumor suppressive role, there currently no published STAT4 inhibitors for breast cancer.

5.5. STAT5

STAT5 often refers to two proteins: STAT5a and STAT5b [291]. Originally described as mammary gland factor (MGF), STAT5 was later renamed as it shared amino acid sequence homology with STAT1 and STAT2 [292]. Further investigation reveals that there are two STAT5 proteins, STAT5a and STAT5b, as the proteins share 94% structural homology, but originate from separate genes [293–295]. Structurally, the CCD, DBD, LD, and SH2 domain remain conserved throughout the STAT family; however, the NTD and TAD exhibit the most diversity and allow for different signaling activities [295]. STAT5 proteins are mainly activated by the IL-2 family of cytokines, which are characterized by signaling through the IL-2 receptor γ and includes IL-2, IL-4, IL-7, IL-9, and IL-15 [296–299]. The IL-2 family and receptors are critical for normal immune cell development as well as mediate lymphocyte activation and expansion during immune responses [291]. Importantly, STAT5a and STAT5b dimers bind to similar core consensus sequences, suggesting these STAT5 isoforms can regulate many of the same pathways and genes [291]. Moving forward, "STAT5" will be used to describe both STAT5 isoforms unless otherwise specified.

In normal mammary development, STAT5 transcription factors modulate genes involved in mammary tissue differentiation, development of alveolar progenitors, and lactation associated with pregnancy [300–303]. Dysregulated activation of STAT5 results in over-aggressive alveolar development, impaired mammary gland remodeling, and mammary tumor formation through upregulating Akt/phosphatidylinositol 3-kinase (PI3K) signaling components [304]. Constitutively active STAT5 also significantly promotes mammary tumor formation in mice with loss of phosphatase and tensin homolog, an important tumor suppressor in the PI3K pathway [304]. STAT5a and Nmi are downregulated in 70% of metastatic breast tissues compared to primary tumors, suggesting that these two cooperatively regulate normal breast tissue and that dysregulation may contribute to breast cancer metastasis [305]. N-α-Acetyltransferase 10 protein (Naa10p) decreases migration and invasion of breast cancer cells [306]. Furthermore, Naa10p physically and functionally

interacts with STAT5a and antagonizes STAT5a-JAK2 activity leading to suppression of breast cancer metastasis *in vitro* and *in vivo* [306].

Activation of STAT5 signaling has been reported to contribute to breast cancer. For example, 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase 4 (PFKFB4) promotes angiogenesis by upregulating IL-6 in breast cancer cells, which activates pSTAT5 in endothelial cells [307]. Pharmacological inhibition of PFKFB4 suppresses breast cancer tumor growth and decreases angiogenesis in mouse xenografts [307]. Fibroblast growth factor 2 (FGF2) activates STAT5, ERK, and AKT to increase breast cancer cell proliferation [308]. Additionally, breast cancer cells with constitutively active FGFR-2, the receptor for FGF that co-localizes in the nucleus with STAT5, promotes breast tumor growth in an orthotopic mouse model [308]. Signal-transducing adaptor protein-2 (STAP-2) promotes STAT5 activation through Brk phosphorylation of STAT5; knockdown of STAP-2 suppresses breast cancer cell proliferation [309]. In another study, parathyroid hormone-related protein overexpressed in mammary tissue promotes tumor growth in transgenic mice, in part, through the activation of STAT5 and subsequent downstream target genes [310]. FYN, a Src tyrosine kinase family member, promotes breast cancer cell migration and invasion through the activation of STAT5 and subsequent upregulation of Jagged-1 and Delta Like Canonical Notch Ligand 4 [300]. Consistent with *in vitro* findings, knockdown of FYN suppresses breast cancer lung metastases in mice [300]. ABL non-receptor tyrosine kinases upregulate pSTAT5 to promote STAT5-target gene-mediated osteolysis of breast cancer cells [311]. ABL kinase knockdown, and subsequent STAT5 downregulation, suppresses breast cancer bone metastasis *in vivo* [311].

Prolactin (PRL) signaling is implicated in breast cancer progression [312]. PRL-induced pSTAT5 directly upregulates heat shock protein-90α to promote breast cancer cell survival by evading apoptosis [313]. Further investigation into the mechanism by which PRL-induces STAT5 activation reveals that PRL promotes the dissociation of linker histone H1, which negatively regulates STAT5 signaling by limiting chromatin accessibility, thereby increasing breast cancer cell proliferation [314]. Moderate extracellular acidosis suppresses PRL-STAT5 signaling in breast cancer, but did not impact signaling triggered by other ligands, such as OSM [315]. Additionally, protein tyrosine phosphatase 1B (PTP1B) negatively regulates PRL-induced pSTAT5 by inhibiting JAK2 phosphorylation in breast cancer cells [316]. Given that PTP1B and pSTAT3 negatively correlate in breast cancer patient datasets [316], further investigation into PTP1B and additional modulators of the PRL-STAT5 signaling axis may inform breast cancer treatments.

On the other hand, STAT5 activation, not protein expression, is decreased or lost in breast cancers, especially those with lymph-node positive or metastasized breast cancers [317]. Moreover, PRL-STAT5 suppresses invasive phenotypes, such as migration, invasion, MMP secretion, and regulation of E-cadherin in breast cancer cells [318]. Stabilized and upregulated E-cadherin is recapitulated in breast cancer xenografts with STAT5 activation [318].

Breast cancer cells can modulate immune cells in the tumor microenvironment to create a pro-tumorigenic niche. In response, anti-tumor immune cells may activate pathways

associated with tumor clearance. For example, STAT5 activation by breast cancer cells secreting GM-CSF promotes expression of immune-related genes and loss of STAT5 in macrophages promotes breast cancer cell migration *in vitro* and breast cancer lung metastasis *in vivo* [319].

STAT5a exhibits dual roles in luminal breast cancer depending on which tyrosine residue is phosphorylated [320]. Where phosphorylation at one residue decreases cell proliferation, the other suppresses clonogenicity, suggesting STAT5a may be able to switch phosphorylation-dependent phenotypes. Prognostic assessment of STAT mRNA expression reveals that high STAT5a and high STAT5b expression associates with better overall survival and relapse-free survival in breast cancer patients [154,155]. Interestingly, an endogenous dominant-negative STAT5 isoform, identified in luminal A breast cancer cells, inhibits transcriptional activity of STAT5a, STAT5b, and both estrogen receptors [321]. The dominant-negative STAT5 also induces apoptosis in some luminal breast cancer cells, suggesting the full mechanism of action of this STAT5 isoform has yet to be elucidated.

Despite the abundance of studies focused on STAT5 in breast cancer, there are limited studies describing the role of STAT5 in therapeutic resistance. STAT5a expression is increased in chemoresistant patient breast tumors compared to chemosensitive breast tumors [322]. STAT5a also upregulates ABCB1 expression, which mediates chemoresistance in breast cancer cells [323].

STAT3 and STAT5 are activated in 29% of breast tumors stained [324,325]. STAT3 and STAT5 are upregulated by STAP-2 in breast cancer cells and knockdown of STAP-2 or STAT5 decreases proliferation of breast cancer cells [197,309]. Interestingly, STAT3 and STAT5 can exhibit antagonistic functions in breast cancer. For example, LIF-mediated STAT3 activation induces apoptosis in mammary epithelial cells whereas STAT5 activation inhibits apoptosis [326,327]. STAT5, with STAT3 or alone, plays important roles in breast cancer emphasizing the importance of studying STAT5 inhibitors for the treatment of breast cancer.

Despite STAT5's numerous roles in breast cancer, there are only a few STAT5 inhibitors published for the treatment of breast cancer (Table 1). A nicotinoyl hydrazine compound, CAS 285986–31–4, decreases pSTAT5 to reduce breast cancer cell proliferation [314]. Pimozide, an antipsychotic drug previously mentioned to target STAT3, inhibits cell proliferation and promotes cell cycle arrest and DNA damage in breast cancer cells [328,329]. Consistent with these findings, pimozide decreases pSTAT5 and ABCB1 and sensitizes doxorubicin-resistant luminal A breast cancer cells to doxorubicin treatment [322]. Interestingly, pharmacological inhibition of JAK2 and subsequent inactivation of STAT5 in combination with PI3K/mTOR inhibitors exhibits synergism. Combination treatment decreases cell proliferation and suppresses breast tumor growth and metastasis in an orthotopic mouse model [330]. This JAK2/STAT5 signaling pathway is induced by IL-8 suggesting that IL-8 mediated activation of JAK2/STAT5 signaling promotes breast cancer progression and metastasis and should be investigated further. Though few STAT5 inhibitors are reported in breast cancer, inhibition of STAT5-mediated pathways reveals promising results for breast cancer therapeutics.

5.6. STAT6

STAT6 was first discovered in B cells when researchers identified a transcription factor whose activation was upregulated by IL-4 [331, 332]. Further investigation reveals that IL-4 activation of STAT6 allows STAT6 to translocate to the nucleus and influence gene expression [333–335]. IL-13, which is structurally and functionally similar to IL-4 and shares the same receptor, also triggers canonical STAT6 signaling [332, 336, 337]. STAT6 activation promotes differentiation of macrophages and expansion and proliferation of B and T cells [332, 338, 339]. Though STAT6 is implicated in multiple cancer and disease types, the crystal structure was not solved until 2016, where researchers confirmed that only the activated STAT6 homodimer exhibits DNA-binding activity as opposed to the non-phosphorylated form [340].

STAT6 regulates G1/S cell cycle progression as STAT6 knockdown increases proliferation and decreases p21 and p27, G1 cyclin-dependent kinase (CDK) inhibitors, in breast cancer cells [341]. Furthermore, STAT6 interacts with transcription factor Sp1 to transcriptionally regulate p21 and p27 expression [341]. Interestingly, TNBC cells expressing low levels of STAT6 modulate expression of genes associated with decreased metastatic potential and apoptotic resistance as compared to the luminal A, STAT6-high expressing breast cancer cells [342]. STAT6 increases breast cancer cell resistance to apoptosis [342, 343]. STAT6-deficient mice challenged with 4T1 cells exhibit reduced primary breast tumor growth and decreased metastases, suggesting that loss of STAT6 may promote anti-tumor immunity *in vivo* [344].

Interestingly, reduction of IL-13 receptor subunit alpha 2 (IL13RA2) results in elevated pSTAT6 and suppresses migration of breast cancer cells [345]. Silencing IL13RA2 with IL-13 treatment increases expression of tumor protein 63, a tumor suppressor protein, and suppresses STAT6-mediated breast cancer lung metastasis [345]. Additionally, overexpression of IL-4 and subsequent STAT6 activation suppresses cell proliferation and increases apoptosis of breast cancer cells [346]. Suppression of STAT6 by miR-1207–5p decreases breast cancer cell proliferation and promotes cell cycle arrest [347]. Trastuzumab-resistant breast cancer cells express significantly decreased levels of STAT6 compared to trastuzumab-sensitive breast cancer cells [323]. Loss of STAT6 increases resistance to trastuzumab in HER2-positive breast cancer cells [348]. Moreover, STAT6 knockout modulates expression of genes associated with EMT, promotes mammosphere formation, and increases anchorage-independence of breast cancer cells [323,348]. In addition, loss of STAT6 transformed a non-tumorigenic breast cancer cell line to promote tumor formation in mice [348]. High STAT6 mRNA expression correlates with favorable overall survival relapse-free survival in breast cancer patients [154].

IL-4 and IL-13, STAT6 activators, also promote macrophage polarization [349,350]. In contrast to previous findings, STAT6 upregulates pro-tumorigenic, M2 phenotype associated genes [351,352], suggesting that inhibition of STAT6 may prevent TAM differentiation. M2 macrophages exhibit high levels of pSTAT6, while STAT6 knockdown or inhibition prevents M2 phenotype differentiation of mouse macrophages [353]. Furthermore, pharmacological inhibition of STAT6 suppresses tumor growth of 4T1 tumors and liver metastasis in mice [353]. Similarly, inhibition of both IL-4- and IL-13-induced pSTAT6 suppresses M2

macrophages in breast cancer [354]. Though STAT6 is not as widely studied in breast cancer compared to its other STAT family members, STAT6-mediated pathways could provide important therapeutic targets for breast cancer treatment.

Though STAT6 inhibitors are used in multiple cancer types, very few are published for breast cancer (Table 1) [254]. Notably, AS1517499, a potent STAT6 inhibitor originally synthesized to treat asthma and other allergic reaction-associated diseases [355,356], inhibits M2 macrophage polarization in mouse macrophages to suppress breast cancer tumor growth and liver metastasis [353]. To assess the clinical relevance of this STAT6 inhibitor in breast cancer, AS1517499 was used in a 4T1-orthotopic mouse model and found to suppress tumor growth and liver metastasis *in vivo* [353]. These findings suggest that STAT6-mediated signaling pathways may contain important therapeutic targets and warrant further investigation.

6. Clinical trials targeting STAT family members in breast cancer

All of the STAT protein family members are implicated in breast cancer, either in pro-tumorigenic or anti-cancer roles. As previously mentioned, STAT3 is the most commonly studied STAT protein in breast cancer and contributes to breast cancer by promoting breast cancer cell and tumor growth, metastasis, and immune evasion [43]. TTI-101, an orally available STAT3 inhibitor, is currently in Phase I clinical trials (NCT03195699) for patients with advanced cancers. These include breast cancer, head and neck squamous cell carcinoma, non-small cell lung cancer, hepatocellular cancer, colorectal cancer, gastric adenocarcinoma, and melanoma. This Phase I clinical trial, which started recruiting as early as 2017, aims to determine compound administration safety, patient response (if any), and will focus on pharmacodynamics by measuring pSTAT3, PD1 and PD-L1 expression. Though there are additional clinical trials also directly targeting STAT3, many do not include breast cancer patients or are no longer recruiting patients due to adverse effects.

Though inhibition of STAT proteins has been demonstrated to be effective in suppressing breast cancer in preclinical models, there are numerous challenges to targeting transcription factors in the clinic. Transcription factors are reported to be “intrinsically disordered”, which not only effects the structure of potential binding pockets, but also means that the rate, frequency, and affinity for protein-protein or protein-nucleic acid interactions is highly variable [13,357]. Therefore, to target STAT3, JAK1/2 inhibitors are currently being utilized in clinical trials instead [24,358]. Ruxolitinib is a JAK1/2 receptor tyrosine kinase inhibitor and is currently approved to treat patients with myelofibrosis or polycythemia [359–361]. Ruxolitinib was evaluated in a non-randomized phase II clinical trial for patients with metastatic TNBC (NCT01562873). Patients were enrolled on the basis of tumoral-pSTAT3 IHC staining, and while pharmacodynamic analysis of ruxolitinib indicates that the proportion of pSTAT3-positive cells decreased, the study was terminated as other objective responses were not met [359]. In a randomized, phase II study designed for patients with advanced HER2-negative breast cancer (NCT02120417), ruxolitinib or placebo was evaluated in combination with capecitabine, a fluorouracil prodrug that is approved for metastatic breast cancer [362, 363]. Patients were enrolled based on prior chemotherapy treatments for hormone receptor positivity, advanced, or metastatic disease and patient

prognosis (overall survival and progression-free survival) was the main objective [363]. Though the overall response rate to the combination treatment was increased, the primary endpoint (overall survival) did not improve compared to capecitabine and placebo so the study was terminated. Combination of ruxolitinib and paclitaxel (NCT02041429), a chemotherapeutic approved to treat node-positive breast cancer, was evaluated in HER2-negative breast cancer patients and demonstrates promise as the combination treatment was well tolerated [364]. Similarly, the same combination was evaluated for TNBC patients with inflammatory Brca, though those results are still ongoing (NCT02041429, NCT02876302). A phase I/II clinical trial investigating the safety and efficacy of ruxolitinib in combination with trastuzumab (NCT02066532), a monoclonal antibody approved for the treatment of HER2-positive breast cancer, yielded less than successful results as there was no improvement in progression-free survival and hematologic-related adverse events were observed [365].

To improve upon current, FDA-approved treatments, ruxolitinib in combination with pembrolizumab, an anti-PD-1 immunotherapy, is being evaluated in a phase I study for patients with advanced or metastatic TNBC (NCT03012230). This study, which is still recruiting patients, aims to determine the safety and efficacy and examine PD-1, PD-L1, JAK2, and pSTAT3 tumoral expression. Interestingly, there is also a randomized phase II study evaluating ruxolitinib in the treatment of premalignant breast cancer cells with objectives focused on apoptosis and pSTAT5 levels (NCT02928978). Given that numerous clinical trials utilizing ruxolitinib alone or in combination have been terminated or completed, an open-label study for patients with breast cancer, colorectal cancer, pancreatic cancer or lung cancer is currently recruiting with the purpose of continuing ruxolitinib treatment alone or with a previously administered chemotherapy (NCT02955940). In summary, targeting STAT3 activity by directly or indirectly targeting STAT3 activity, such as JAK1/2 inhibitors, is a major focus for breast cancer treatment.

7. Conclusion

Since the discovery of the first STAT protein over 20 years ago, all of the STAT family members are considered mediators of multiple cellular processes leading to the progression or suppression of breast cancer. In this review, we discussed the STAT family of transcription factors, their many roles in breast cancer, and therapeutic strategies to target them for breast cancer treatment. Each STAT signaling pathway is activated by a set of cytokines or ligands and that dysregulation of the ligands, cell-surface receptors, STATs, negative regulators, or downstream target genes can lead to breast cancer. Further investigation reveals that understanding how one STAT member acts in a specific setting may not be enough to determine a patient's outcome, but that focusing on the balance between two or more STATs is incredibly beneficial. Though most studies focus on the role of STATs within breast cancer cells, emphasis on STAT signaling in tumor microenvironmental cells and the immune cell populations is gaining more attention. Insight into the communication between breast cancer cells and immune cells or stromal cells has led to clinical trials utilizing combination therapies yielding promising results.

Despite these promising findings, many of the mechanisms reported to date are still incomplete as STAT signaling is clearly complex in breast cancer. Furthermore, breast cancer is an incredibly heterogeneous malignancy and current understanding of breast cancer subtypes are constantly being modified. A better understanding of STAT expression and activation in different subtypes of breast cancer is critical in developing more effective STAT inhibitors for breast cancer treatment. Even with hundreds of published articles describing STAT mechanisms and dozens of STAT3 inhibitors in breast cancer, there are still no FDA-approved STAT inhibitors for the treatment of breast cancer. Moreover, the limited number of STAT inhibitors in clinical trials further underscores the need to continue to study STAT proteins in breast cancer to advance treatment for breast cancer patients. Though individual STAT proteins correlate with different patient outcomes, it is clear that a better understanding of the balance between the STAT family members is critical for breast cancer diagnoses and treatments. Important future tasks may include 1) the development or manipulation of current diagnostic tools to detect multiple STAT proteins simultaneously, 2) development of reliable, predictive biomarkers to determine STAT activity, 3) utilization of multiple methods to stratify patients for treatment, and 4) counteract or resolve issues in current STAT-targeted or JAK1/2-targeted treatments that are responsible for adverse events.

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Data availability

No data was used for the research described in the article.

Abbreviations:

BCSCs	breast cancer stem cells
CCD	coiled-coil domain
CDK	cyclin-dependent kinase
CSC	cancer stem cell
DBD	DNA-binding domain
DMFS	distant metastasis-free survival
DPF3	double PHD fingers 3
EGCG	epigallocatechin gallate
EGFR	epidermal growth factor receptor
EMT	epithelial-to-mesenchymal transition
ER	estrogen receptor

EsA	Esculentoside A
FAO	fatty acid beta-oxidation
FGF2	fibroblast growth factor 2
G-CSF	granulocyte-colony stimulating factor
GPCRs	G-protein coupled receptors
Grb2	growth factor receptor-binding protein 2
HER2	human epidermal growth factor receptor 2
HIF-1	hypoxia-inducible factor-1
IFITM1	interferon-induced transmembrane protein 1
IFN	interferon
IL13RA2	interleukin 13 receptor subunit alpha 2
IL-2	interleukin-2
IRF9	interferon regulatory factor 9
ISG15	ISG15 ubiquitin like modifier
ISGF3	interferon-stimulated gene factor 3
JAK	Janus kinase
KLF14	Kruppel-like family of transcription factor-14
LIF	leukemia inhibitory factor
LIFR	leukemia inhibitory factor receptor
MAFG-AS1	MAFG-antisense 1
MDSC	myeloid-derived suppressor cell
MGF	mammary gland factor
Naa10p	N-α-Acetyltransferase 10 protein
NLS	nuclear localization signal
NMI	N-Myc and STAT interactor
NTD	N-terminal domain
OSM	oncostatin M
PD-1	programmed cell death 1
PD-L1	programmed death-ligand 1

PFKFB4	6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase 4
PI3K	phosphatidylinositol 3-kinase
PR	progesterone receptor
PRL	prolactin
pSTAT	phosphorylated STAT
PTP1B	protein tyrosine phosphatase 1B
pY	tyrosine-phosphorylation site
ROS	reactive oxygen species
SHH	Sonic Hedgehog
SIRT4	sirtuin 4
SOCS	suppressors of cytokine signaling
SSb2	saikosaponin b2
STAP-2	signal-transducing adaptor protein 2
STAT	signal transducer and activator of transcription
TAD	transactivation domain
TAMS	tumor-associated macrophages
T-DM1	trastuzumab-emtansine
TNBC	triple-negative breast cancer
Trk	Tropomyosin receptor tyrosine kinases
VEGF	vascular endothelial growth factor
Wwox	WW domain-containing oxidoreductase

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Fig. 1. STAT structure.

The signal transducer and activator of transcription (STAT) family members are ~740–900 amino acids in length and maintain relatively conserved regions in their structures. Each STAT protein contains these functionally conserved domains: 1) N-terminal domain (NTD) capped with NH2, 2) coiled-coiled domain (CCD), 3) DNA-binding domain (DBD), 4) linker domain (LD), 5) SRC homology 2 domain (SH2), 6) tyrosine phosphorylation site (pY), and 7) C-terminal transactivation domain (TAD) containing COOH. STAT4 is the shortest STAT protein (748), while STAT2 is the longest (851). Additionally, there is another conserved phospho-serine residue in the TAD of STAT1, STAT3, STAT5a, STAT5b, and STAT6.

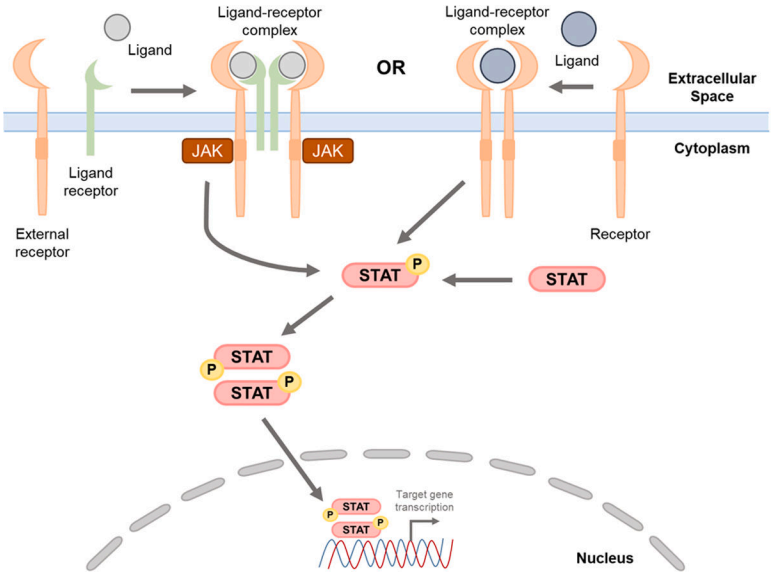

Fig. 2.

Canonical STAT pathway activation. STAT proteins are activated by a myriad of cytokines or growth factors (i.e. ligands), which bind to extracellular domains on cell-surface receptors (i.e. receptors) to form ligand-receptor complexes. The canonical IL-6/IL-6Ralpha/STAT3 pathway (left), for example, involves the IL-6 cytokine (ligand) binding to the IL-6Ralpha, which activates gp130 association with IL-6/IL-6Ralpha. Two trimeric IL-6/IL-6Ralpha/STAT3 complexes interact, recruit JAKs, phosphorylate the intracellular domains of gp130, activate STAT3 via phosphorylation, pSTAT3 dimers then translocate to the nucleus where they modulate gene expression of downstream target genes. Additional receptors, such as EGF or FGF receptors (right), retain intrinsic kinase activities and can directly phosphorylate STAT proteins leading to STAT phosphorylation, dimerization, and subsequent translocation to the nucleus. Though there are reports of alternative STAT activation including methods where STAT proteins form dimers without phosphorylation, this pathway describes the most common STAT pathway activation.

Table 1

Preclinical STAT inhibitors in breast cancer.

STAT	Drug/Therapeutic Inhibitor	Main Function	Cancer and/or Cell Type	Ref.
STAT1	EGCG	Suppresses cell proliferation of breast cancer cells	Breast cancer (MCF-7) cells	[131]
STAT1	Fludarabine	Suppresses STAT1, pSTAT1, and PD-L1 expression in breast cancer cells	Breast cancer (MCF-7, MDA-MB-231 and MDA-MB-468) cells	[139]
STAT1	Fludarabine and doxorubicin	Decreased STAT1-positive cells and suppressed mammary tumor growth of murine mammary tumor cells	Breast cancer (MDA-MB-231 and PNA.Met1) cells; PNA.Met1 (murine mammary tumor line derived from spontaneous mammary tumors from MMTV-PyMT model)	[120]
STAT3	10,11-dehydrocurvularin (DCV)	Macrolide, derived from marine fungus, inhibits pSTAT3 without impacting upstream JAK1 or JAK2, leading to decreased breast cancer cell proliferation, migration, and invasion; DCV suppressed tumor growth through inhibited pSTAT3	Breast cancer (MDA-MB-231 and MDA-MB-468) and mammary epithelial (MCF-10A) cells; MDA-MB-231 cells in mouse xenografts	[366]
STAT3	17o	Decreases pSTAT3 in breast cancer cells	Breast cancer (MDA-MB-468) and multiple myeloma cells	[367]
STAT3	6Br-6a	Induces cell cycle arrest and apoptosis by blocking activation of STAT3; decreases tumor growth and size in mouse xenografts	Breast cancer (MDA-MB-231 and MCF-7) cells; MDA-MB-231 in right flank of nude mice	[368]
STAT3	7β-(3-Ethyl-cis-crotonoyloxy)– 1α-(2-methylbutyryloxy)–3,14-dehydro-Z-notonipetranone (ECN)	A sesquiterpenoid (from Farfarae Flos, traditional medicine used to treat inflammation) suppresses pSTAT3, pJAK1/2, pSrc and induces apoptosis in breast cancer cells	Breast cancer (MDA-MB-231) cells	[369]
STAT3	Alantolactone	A sesquiterpene lactone induces apoptosis and ROS levels; activates caspases and decreases mitochondrial membrane potential and pSTAT3 in breast cancer cells	Breast cancer (MDA-MB-231 and MCF-7) cells	[370]
STAT3	Bazedoxifene	Suppresses pSTAT3, cell proliferation, migration and invasion of breast cancer cells; induces apoptosis in breast cancer cells	Breast cancer (SUM159, MDA-MB-231, and MDA-MB-468) cells	[371]
STAT3	Betulinic acid	Inhibits proliferation, migration, and invasion of breast cancer cells; decreases tumor growth, volume, and lung metastasis *in vivo*	Breast cancer (MCF-7, 4T1, and MDA-MB-231) cells; subcutaneous 4T1 cells in BALB/C mice	[372]
STAT3	Bisindole-PBD (5b)	Suppresses angiogenesis by suppressing expression of VEGF and STAT3 in breast cancer cells	Breast cancer (MDA-MB-231 and MCF-7) and human endothelial cells	[373]
STAT3	BP-1–102	Analog of S31–201.1066; blocks pSTAT3 and STAT3 activation, suppresses growth, migration, and invasion of tumor cells and suppresses expression of STAT3-target genes; inhibits growth of human breast tumor xenografts in mice	Breast cancer (MDA-MB-231), prostate, non-small cell lung cancer, and pancreatic cancer cells; MDA-MB-231 xenografts in mice	[374]
STAT3	Cantharidin	Decreases cell growth in breast cancer cells, inhibited adhesion of breast cancer cells to platelets	Breast cancer (MCF-7) cells	[375]
STAT3	Cantharidin	Inhibits cell proliferation, migration, and invasion and induces cell cycle arrest in TNBC cells; inhibits tumor growth in xenograft mouse model	Breast cancer (MDA-MB-231) cells; MDA-MB-231 cells in breast xenograft mouse model	[376]
STAT3	Cantharidin	Inhibits cell proliferation and autophagy and induced apoptosis of TNBC cells; inhibited growth of TNBC xenografts in nude mice	Breast cancer (MDA-MB-231 and MDA-MB-468) cells; MDA-MB-231 and MDA-MB-468 cells in nude mice	[377]

STAT	Drug/Therapeutic Inhibitor	Main Function	Cancer and/or Cell Type	Ref.
STAT3	Caffeic acid p-nitro-phenethyl ester (CAPE-pNO2)	CAPE-pNO2 decreases pEGFR, pSTAT3, pAkt, MMP2, MMP9, and VEGFA; suppresses breast cancer cell proliferation, migration, and invasion; suppresses tumor growth and induces apoptosis in xenograft mouse model	Breast cancer (MDA-MB-231) cells; subcutaneous injection of MDA-MB-231 cells in nude mice	[378]
STAT3	Carfilzomib	Decreases proliferation and mitosis in breast cancer cell lines; decreases serum IL-6 in mice with MDA-MB-231 tumor	Breast cancer (MDA-MB-231 and MDA-MB-468) cells; MDA-MB-231 cells in nude mice	[379]
STAT3	Catechol	Inhibits proliferation and mammosphere formation (and $CD44^{high}/CD24^{low}$ subpopulation) of breast cancer cells	Breast cancer (MDA-MB-231 and MCF-7) cells	[380]
STAT3	CDDO-Methyl Ester (CDDO-ME)	Inhibits IL-6-induced and constitutive JAK1 activity, and inhibits IL-6-induced STAT3 activation and dimerization	Breast cancer (MDA-MB-468) and cervical cancer cells	[381]
STAT3	Compound 6b	Curcumin-benzo[*b*]thiophene 1, 1-dioxide (Curcumin-BTP) hybrids as STAT3 inhibitors; Compound 6B suppressed pSTAT3, nuclear translocation, and DNA-binding activity in breast cancer cells; Compound 6B induces apoptosis in breast cancer cells, but not normal breast epithelial cells; inhibits IL-6-mediated pSTAT3; suppresses tumor growth of breast cancer cells in mice with reduced pSTAT3 in tumors	Breast cancer (MCF-7), normal breast epithelial (MCF-10A), and normal liver cells; MCF-7 cells subcutaneously injected in BALB/C mice	[382]
STAT3	Coumarin-benzo[*b*]thiophene 1, 1-dioxide	Decreases pSTAT3 and cell proliferation and induced apoptosis and ROS generation of breast cancer cells; decreased tumor growth and pSTAT3 *in vivo*	Breast cancer (MDA-MB-231, MCF-7, and 4T1), mammary epithelial (MCF-10A), hepatocellular carcinoma, and colonic carcinoma cells; 4T1 mouse xenograft model	[383]
STAT3	CPA-1, CPA-7	Inhibition of constitutive STAT3 activation and decrease in pSTAT3 and cell viability and induces apoptosis in breast cancer cells	Breast cancer (MDA-MB-231, MDA-MB-435, MDA-MB-453, MCF-7, and MDA-MB-468), melanoma, prostate cancer, lung carcinoma and colon cancer cells	[384]
STAT3	Cucurbitacin E	(CuE) inhibits growth and pSTAT3 and induces apoptosis and cell cycle arrest of breast cancer cells	Breast cancer (MDA-MB-231 and Bcap-37) cells	[385]
STAT3	Curcumin alone and curcumin with EGCG	Curcumin and epigallocatechin gallate (EGCG) reduced pSTAT3, STAT3 interaction with NFkB, CD44-positive cells, and mammospheres	Breast cancer (MDA-MB-231 and MCF-7) cells	[267, 386]
STAT3	Cyanidin-3-glucoside (C3G)	C3G, an anthocyanin in many fruits, reduced angiogenesis by inhibiting VEGF expression and secretion in breast cancer cells	Breast cancer (MDA-MB-231 and Hs-578 T) cells	[387]
STAT3	Deguelin	Decreases pSTAT3 and expression of EGFR-downstream target proteins and cell proliferation of breast cancer cells; inhibits growth of MDA-MB-231 cells in dorsal flank of nude mice	Breast cancer (MDA-MB-231, MDA-MB-468, BT-20 and BT-549) cells; MDA-MB-231 cells in dorsal flank of nude mice	[388]
STAT3	Dihydrotanshinone (DHTS)	Decreases mammosphere formation of breast cancer cells; inhibits tumor growth in mouse xenograft model	Breast cancer (MDA-MB-231 and MCF-7) cells; MCF-7 in tumor xenografts in mice	[389]
STAT3	DT-13	Inhibits migration via suppression of pSTAT3 and PLOD2 expression in breast cancer cells; DT-13 had little effect on tumor growth, but decreased lung and liver metastasis burden in mice	Breast cancer (MDA-MB-231 and MD-MB-468) and pre-adipocyte cells; MDA-MB-231 in orthotopic xenograft tumor model	[390]
STAT3	Esculentoside A	Derived from root of Phytolacca esculenta; inhibits proliferation and mammospheres and induces apoptosis in breast cancer cells; suppresses breast CSC initiated tumor growth in mice	Breast cancer (EMT6, MCF-7), normal mammary epithelial (MCF10A), and normal liver cells	[271]
STAT3	Eupalinolide J	Suppresses pSTAT3, proliferation and induces apoptosis and cell cycle arrest of TNBC cells; suppresses tumor growth *in vivo*	Breast cancer (MDA-MB-231 and MDA-MB-468) and mammary epithelial (MCF-10A) cells; MDA-MB-231 cells in nude mouse xenograft model	[391]

STAT	Drug/Therapeutic Inhibitor	Main Function	Cancer and/or Cell Type	Ref.
STAT3	Evista (Raloxifene-HCl)	(Raloxifene-HCl) Inhibits pSTAT3 and IL-6-induced pSTAT3, decreases cell viability, and increases caspase-3 activity in breast cancer cells	Breast cancer (MCF-7, MDA-MB-231, and SUM159), colon cancer, multiple myeloma, and Hela cells	[392]
STAT3	FLLL31/FLLL32	Derived from curcumin (main compound in turmeric); designed to bind JAK2 and STAT3 SH2 domain; downregulates pSTAT3, DNA-binding activity, cell viability, and invasion of breast cancer cells; induces apoptosis of breast cancer cells; FLLL32 suppresses tumor growth and vascularization in mouse xenografts	Breast cancer (MDA-MB-231, SK-BR-3, MDA-MB-468, MDA-MB-453, and SUM159), pancreatic cancer, and human embryonic kidney cells; MDA-MB-231 mouse xenografts	[268]
STAT3	Flubendazole	Inhibits pSTAT3 and cell viability and induces apoptosis in TNBC cells; suppresses BCSC-enriched TNBC tumor growth, angiogenesis, and metastasis *in vivo*	Breast cancer (MDA-MB-231, Hs578T, BT-549, and 4T1) cells; 4T1 cells in MFP of BALB/C mice	[393]
STAT3	Galiellalactone, SG-1709, and SG-1721	Galiellalactone and two analogues (SG-1709 and SG-1721) block pSTAT3 and suppress cell viability and proliferation in TNBC cells; SG-1721 induces cell cycle arrest and apoptosis; SG-1721 inhibits tumor growth of TNBC cells *in vivo*	Breast cancer (BT-549, BT-20, MDA-MB-468, MCF-7, T47D, SK-BR-3, MDA-MB-453) and mammary epithelial (MCF-10A) cells; TNBC cells (exact cell line not stated) subcutaneous implantation in nude mice	[394]
STAT3	Ganoderic acid A	Decreases pJAK2, pSTAT3 and suppresses invasion and induces apoptosis of breast cancer cells	Breast cancer (MDA-MB-231) cells	[395]
STAT3	Genistein	Phytotherapeutic Genistein suppresses breast cancer cell proliferation	Breast cancer (MDA-MB-453) cells	[396]
STAT3	GO-Y030	Suppresses pSTAT3, STAT3 transcriptional activity, cell viability and induces apoptosis in breast cancer cells	Breast cancer (MDA-MB-231) and pancreatic cancer cells	[397]
STAT3	HJC0123	Inhibits pSTAT3 and STAT3-mediated luciferase reporter activity and induced apoptosis in TNBC cells; inhibits tumor growth in TNBC xenograft mouse model	Breast cancer (MCF-7 and MDA-MB-231) and pancreatic cancer cells; MDA-MB-231 cells in xenograft mouse model	[398]
STAT3	HJC0416	(5-chloro-N-(1,1-dioxo-1 H-1λ6-benzo[*b*]thiophen-6-yl)–2-hydroxybenzamide) HJC0416 inhibits cell cycle progression and promotes apoptosis in breast cancer cells; HJC0416 reduces tumor volume in breast cancer murine xenografts *in vivo*	Breast cancer (MDA-MB-231) cells; MDA-MB-231 tumor xenografts in mice	[399]
STAT3	Hydrazinocurcumin	(Analog of curcumin) inhibits pSTAT3, downstream STAT3 target genes, cell migration and invasion and induces apoptosis in breast cancer cells	Breast cancer (MDA-MB-231 and MCF-7) cells	[400]
STAT3	Ilamycin C	Ilamycins are cyclic peptides produced by (isolated from) Streptomyces; Increased toxicity against TNBC cells vs. LumA cells; suppresses pSTAT3, proliferation, migration and invasion and induces apoptosis in TNBC cells	Breast cancer (MDA-MB-231, BT-549, and MCF-7) and normal breast (MCF10A) cells	[180]
STAT3	IS3 295	Decreased cell proliferation and constitutive STAT3 activation in breast cancer cells; induced apoptosis and promoted cell cycle arrest in breast cancer cells	Breast cancer (MDA-MB-231, MDA-MB-435, MDA-MB-453, and MDA-MB-468), prostate cancer, melanoma, pancreatice cancer, and fibroblast cells	[401]
STAT3	Isoharringtonine (IHT)	IHT decreases pSTAT3 and suppresses proliferation, migration, and BCSCs in breast cancer cells	Breast cancer (HCC1937, HCC1806 and MCF-7) cells	[402]
STAT3	LLL12	Inhibits STAT3 phosphorylation, DNA binding activity, STAT3-dependent luciferase activity, cell viability and migration in breast cancer cells; decreased tumor volume in mouse tumor xenografts	Breast cancer (MDA-MB-231, MDA-MB-453, and SK-BR-3), pancreatic cancer, glioblastoma, human hepatocytes, and human lung fibroblast cells; MDA-MB-231 tumors in mice	[403]

STAT	Drug/Therapeutic Inhibitor	Main Function	Cancer and/or Cell Type	Ref.
STAT3	LLY17	Inhibits pSTAT3 in breast cancer cells; suppresses cell viability and migration and induces apoptosis in TNBC cells, not Luminal A breast cancer cells; suppresses tumor growth of 4T1 cells *in vivo*	Breast cancer (MDA-MB-468, MDA-MB-231, SUM159, BT-549, and 4T1) cells; 4T1 in MFP mouse model in BALB/C mice	[404]
STAT3	LYR71	6-methyl-2-propylimino-6, 7-dihydro-5 H-benzo [1,3]-oxathiol4-one (LYR71), a derivative of trimeric resveratrol, suppresses pSTAT3, MMP9 expression and activity, migration and invasion of breast cancer cells; inhibits growth of MDA-MB-231 tumors in mice	Breast cancer (MDA-MB-231) cells; MDA-MB-231 subcutaneously injected in flank of nude mice	[405]
STAT3	Napabucasin	(BBI608) Decreases pSTAT3, cell viability, and sternness of breast cancer cells	Breast cancer (MCF-7) cells	[406]
STAT3	Naringenin	Decreases pSTAT3, cell viability and induces apoptosis of breast cancer cells; increases caspase 3 and 9 activity	Breast cancer (MDA-MB-231) cells	[407]
STAT3	Niclosamide	Inhibits proliferation, migration, and invasion and induces apoptosis in breast cancer cells; decreased IL-6 and pSTAT3 in breast cancer cells	Breast cancer (MDA-MB-468 and MCF-7) cells	[408]
STAT3	Nifuroxazide	Reduces pSTAT3 and expression of MMP2 and MMP9, decreases cell viability, migration and invasion and induces apoptosis of breast cancer cells; suppressed tumor growth of 4T1 cells *in vivo*	Breast cancer (MDA-MB-231, MCF-7, and 4T1) cells; 4T1 cells in BALB/C mice	[409]
STAT3	Pectolinarigenin	Suppresses proliferation, migration and invasion and induces apoptosis of breast cancer cells; had no effect on tumor growth of subcutaneously injected 4T1 cells, but decreased spontaneous lung metastases; increased CD8 + T cells in peripheral blood and in lung metastatic tissue	Breast cancer (4T1, MDA-MB-231, and MCF-7) cells; subcutaneous 4T1 cells in mice	[410]
STAT3	Picrasidine G	Decreases pSTAT3 and STAT3-regulated gene expression and induced apoptosis in TNBC cells	Breast cancer (MCF-7, T47D, MDA-MB-361, SKBR3, Hs578T, MDA-MB-231 and MDA-MB-468) and mammary epithelial (MCF10A) cells	[411]
STAT3	Pimozide	Decreases pSTAT3, suppresses migration and invasion and increases apoptosis in TNBC cells	Breast cancer (BT-549, MDA-MB-231, MDA-MB-468, and HCC1806) cells	[260]
STAT3	Piperlongumine (PL)	PL, a natural alkaloid, decreases pSTAT3 and pJAK2, suppresses breast cancer cell proliferation, colony formation, and induces apoptosis	Breast cancer (MDA-MB-231 and MDA-MB-453) cells	[412]
STAT3	PM-73 G	Phosphopeptidomimetic prodrug blocks constitutive pSTAT3, but not Akt or Tyr861 phosphorylation in MDA-MB-468 cells (first ref). Treatment inhibits orthotopic MDA-MB-468 human breast tumor xenograft tumor proliferation in nude mice (second ref)	Breast cancer (MDA-MB-468) cells; MDA-MB-468 human breast tumor xenografts in nude mice	[413, 414]
STAT3	Pyrimethamine	Decreases pSTAT3 in breast cancer cells and mouse tumors; decreases proliferation and invasion of breast cancer cells and decreases T reg cells in mice	Breast cancer (TUBO) cells	[415]
STAT3	Resveratrol (RES)	(aka RES, aka trans-3,4′,5-trihydroxystilbene) Blocks Src tyorisine kinase activity, thereby inhibiting constitutive STAT3 activation (pSTAT3), cell proliferation, cell cycle progression and induces apoptosis in breast cancer cells	Breast cancer (MDA-MB-231 and MDA-MB-468), pancreatic cancer, prostate cancer, and mouse fibroblast cells	[416, 417]
STAT3	rPP-C8	Recombinant STAT3-specific inhibitor (rPP-C8) suppresses STAT3 target gene expression and proliferation, and induced apoptosis of breast cancer cells	Breast cancer (SKBR3, MDA-MB-468, MCF-7, T47D, and 4T1), glioblastoma, melanoma, and prostate cancer cells	[418]
STAT3	S3I-1757	Disrupts STAT3-STAT3 dimerization, which is required for nuclear translocation; inhibits pSTAT3, nuclear accumulation of P-Y705-STAT3, STAT3 DNA-binding and suppresses expression of STAT3 target genes (BCL2L1, BIRC5, CCND1, and MMP9); suppresses migration and invasion of breast cancer cells	Breast cancer (MDA-MB-468, MDA-MB-231, and MDA-MB-453), lung cancer, mammary epithelial (MCF10A), and embryonic kidney cells	[419]

STAT	Drug/Therapeutic Inhibitor	Main Function	Cancer and/or Cell Type	Ref.
STAT3	S3I-201	(NSC #74859) Chemical probe inhibitor of STAT3 activity; binds to STAT3 phosphotyrosine peptide derived from the x-ray crystal structure of the STAT3beta homodimer; inhibits growth and induces apoptosis preferentially in tumor cells; inhibits expression of stat3-regulated genes (cyclin D1, Bcl-xl, and survivin) and inhibits growth of human breast tumors *in vivo*	Breast cancer (MDA-MB-231, MDA-MB-435, and MDA-MB-468) and other (NIH 3T3/v-Src) cells; MDA-MB-231 breast tumor xenografts in mice	[256]
STAT3	Sabutoclax	Pan-active BCL-2 protein antagonist; induces apoptosis and caspase activity, and decreases pSTAT3 and CD44high/CD24low subpopulation in breast cancer cells; increased apoptosis, decreases CD44 and ALDH1 cells and decreases pSTAT3 in fresh human breast tumors	Breast cancer (MCF-7 and Cal51) cells; human breast tumor samples	[420]
STAT3	Saikosaponin b2 (SSb2)	Saikosaponin b2 (SSb2) decreases pSTAT3, VASP, MMP2, and MMP9; suppresses breast cancer cell proliferation and migration; limited to no liver and kidney toxicity in mice	Breast cancer (MCF-7) cells	[270]
STAT3	Satraplatin	A tetravalent platinum derivative decreases pSTAT3 and increases apoptosis of breast cancer cells	Breast cancer (MCF-7 and MDA-MB-231) cells	[249]
STAT3	Schisandrin A	Inhibits P-gp mRNA and protein expression in breast cancer cells; decreased pSTAT3 in breast cancer cells	Breast cancer (MCF-7) and DOX-resistant (BEL-7402 and K-562) cells	[421]
STAT3	SH48	SH48 inhibits STAT3 dimerization and translocation into the nucleus; induces autophagy of mammary epithelial cells transformed by H-ras oncogene	Mammary epithelial cells transformed by H-ras oncogene (MCF10A-ras), prostate cancer, and cervical cancer cells	[422]
STAT3	SH5–07, SH4–54	Hydroxamic acid (SH5–07) and benzoic acid (SH4–54) analogues inhibit STAT3 activation and DNA binding activity; suppressed breast cancer cell proliferation to greater extent when the cells exhibit constitutive STAT3 activity; both compounds (individually) suppressed growth of breast cancer cells and decreased expression of STAT3-target genes *in vivo*	Breast cancer (MDA-MB-231 and MCF7), pancreatic, prostate, and normal mouse fibroblast cells; MDA-MB-231 cells injected into left flank athymic mice	[259]
STAT3	PMMB-187	PMMB-187 (a shikonin derivative) inhibits constitutive STAT3 activation, nuclear translocation, DNA binding activity, and subsequent target gene expression in breast cancer cells; induces breast cancer cell apoptosis; inhibits breast tumor growth in mouse xenografts	Breast cancer (MCF-7, MDA-MB-231 and MDA-MB-468) and non-tumor breast epithelial (MCF-10A) cells; MDA-MB-231 cells in mouse xenografts	[423]
STAT3	Silibinin	(Legasil), Made from flavonoid extracts from milk thistle seeds; blocks STAT3 signaling in reactive astrocytes resulting in decreased brain metastases from multiple cancers (including breast cancer) in mice	Brain-tropic breast cancer (MDA-MB-231-BrM2) and melanoma cells	[263]
STAT3	SPI	Potent and selective inhibitor of the STAT3 SH2 domain; blocks constitutive pSTAT3, DNA binding and activity, and transcriptional function in multiple cancers	Breast cancer (MDA-MB-231, MDA-MB-435, MCF-7), pancreatic cancer, prostate cancer, non-small cell lung cancer, and normal mouse fibroblast cells	[424]
STAT3	STA-21	(NSC #628869) STA-21 inhibits STAT3 DNA binding activity, dimerization, and STAT3-dependent luciferase activity; inhibits survival of breast cancer cells with constitutive STAT3 signaling	Breast cancer (MDA-MB-231, MDA-MB-435S, MDA-MB-453, MDA-MB-468, and MCF-7), human ovarian carcinoma, and human skin fibroblast cells	[425]
STAT3	Stattic	(6-nitro-benzo[*b*]thiophene-1,1-dioxide 1) Retains STAT3 in cytosol by inhibiting binding of a phosphotyrosine-containing peptide derived from the gp130 receptor to the STAT3 SH2 domain	Breast cancer (MDA-MB-231 and MDA-MB-435S) and HepG2 cells	[258]
STAT3	STX-0119	Inhibited STAT3 promoter binding and pSTAT3 in breast cancer cells	Breast cancer (MDA-MB-468) cells	[426]

STAT	Drug/Therapeutic Inhibitor	Main Function	Cancer and/or Cell Type	Ref.
STAT3	WP1066	(modified structure of AG490) WP1066 decreases pSTAT3 in breast cancer cells; decreases breast cancer brain metastases in intracardiac mouse model; reduces proliferation, MM9 expression, and VEGF expression in brain metastatic cells	Breast cancer (MDA-MB-231BR and BT-474BR) cells; MDA-MB-231BR brain metastases in mice	[261, 262]
STAT3	XZH-5	Decreases pSTAT3, STAT3 downstream target genes, colony formation and migration and induces apoptosis in breast cancer cells, inhibits IL-6-induced pSTAT3 and nuclear accumulation in breast cancer cells	Breast cancer (MDA-MB-231, SUM159 and MCF-7) and pancreatic cancer cells	[427]
STAT3 and STAT5	SH-4–54	Suppressed breast cancer cell proliferation; decreases TNBC cell plasma membrane antiporter system (xC) and cystine import, both of which are essential for cancer cells to adapt to increased levels of ROS	Breast cancer (MDA-MB-231 and T47D) cells	[428]
STAT3 and STAT5	Withacnistin	Blocks EGF- or IL-6-stimulated STAT3 and STAT5 binding to EGFR and gp130; suppresses pSTAT3 nuclear nuclear translocation and DNA binding activity resulting in decreased transactivation and STAT3-target gene expression and induces apoptosis in breast cancer cells; treatment suppresses breast tumor growth	Breast cancer (MDA-MB-468), lung cancer, and mouse fibroblast cells	[429]
STAT5	CAS 285986–31-4	Nonpeptidic nicotinoyl hydrazine compound STAT5 inhibitor; decreases pSTAT5 and proliferation in breast cancer cells	Breast cancer (T47D) cells	[314]
STAT5a	Pimozide	Pimozide sensitives DOX-resistant cells through the suppression of STAT5a; decreases tumor growth in subcutaneous xenograft mouse model	Breast cancer (MCF-7) cells	[322, 328]
STAT6	AS1517499	Inhibits pSTAT6 and M2 macrophage differentiation of mouse macrophages; suppresses tumor growth and liver metastasis of orthotopic 4T1 breast cancer mouse model	Breast cancer (4T1) and mouse macrophage cells; 4T1 cells in orthotopic mouse model	[353]