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Potential therapeutic targets of the JAK2/STAT3 signaling pathway in triple-negative breast cancer

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Triple-negative breast cancer (TNBC) poses a significant clinical challenge due to its propensity for metastasis and poor prognosis. TNBC evades the body's immune system recognition and attack through various mechanisms, including the Janus Kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling pathway. This pathway, characterized by heightened activity in numerous solid tumors, exhibits pronounced activation in specific TNBC subtypes. Consequently, targeting the JAK2/STAT3 signaling pathway emerges as a promising and precise therapeutic strategy for TNBC. The signal transduction cascade of the JAK2/STAT3 pathway predominantly involves receptor tyrosine kinases, the tyrosine kinase JAK2, and the transcription factor STAT3. Ongoing preclinical studies and clinical research are actively investigating this pathway as a potential therapeutic target for TNBC treatment. This article comprehensively reviews preclinical and clinical investigations into TNBC treatment by targeting the JAK2/STAT3 signaling pathway using small molecule compounds. The review explores the role of the JAK2/STAT3 pathway in TNBC therapeutics, evaluating the benefits and limitations of active inhibitors and proteolysis-targeting chimeras in TNBC treatment. The aim is to facilitate the development of novel small-molecule compounds that target TNBC effectively. Ultimately, this work seeks to contribute to enhancing therapeutic efficacy for patients with TNBC.

KEYWORDS

triple-negative breast cancer, receptor tyrosine kinase, Janus Kinase 2, signal transducer and activator of transcription 3, small molecule compounds

1 Introduction

Globally, breast cancer stands as the most prevalent malignant tumor (1). Among its subtypes, triple-negative breast cancer (TNBC), characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) expression, constitutes approximately 10%-15% of all breast cancer cases (2). The treatment of TNBC presents significant challenges, notably its propensity for early metastasis (3) and a comparatively poorer prognosis than other breast cancer subtypes (4). Current clinical strategies for TNBC primarily employ taxanes and anthracycline-based cytotoxic drugs. However, these approaches frequently encounter obstacles in the form of chemotherapy resistance, and the absence of effective small-molecule targeted therapies, constituting primary impediments in TNBC clinical management (5).

Reassessing classic drug targets is crucial for advancing new precision medicine strategies. The JAK2/STAT3 pathway, clinically validated as a therapeutic target for inflammation-related conditions, has shown promise through its inhibitors in treating inflammatory and autoimmune diseases. This success paves the way for novel clinical therapy developments (6, 7). Extensive research has established a strong association between aberrations in the JAK2/STAT3 signaling pathway and key oncogenic processes such as proliferation, invasion, and metastasis in various malignancies, including TNBC. Notably, activation of this pathway has been observed in multiple solid tumors, TNBC included (8–12). Targeted inhibition of the JAK2/STAT3 signaling has demonstrated efficacy in curtailing TNBC cell proliferation, invasion, and migration (13), knockdown of JAK2 or STAT3 in triple-negative breast cancer cells significantly reduced cell proliferation, invasion and migration (14–21), tumor volume and distant metastasis were significantly inhibited in a mouse model of triple-negative breast cancer with conditional knockout of JAK2 or STAT3 (22–25). Moreover, the downregulation of this pathway has been shown to counteract paclitaxel (PTX) resistance (26). Thus, targeting JAK2/STAT3 emerges as a promising therapeutic strategy for treating TNBC and overcoming challenges associated with PTX resistance.

Abbreviations: TNBC, Triple-negative breast cancer; JAK2, Janus Kinase 2; STAT3, Signal transducer and activator of transcription 3; ER, Estrogen receptor; PR, Progesterone receptor; HER-2, Human epidermal growth factor receptor 2; PTX, paclitaxel; RTKs, Receptor tyrosine kinases; EGFRs, Epidermal growth factor receptors; VEGFRs, Vascular endothelial growth factor receptors; IGFRs, Insulin-like growth factor receptors; PDGFRs, Platelet-derived growth factor receptors; FGFRs, Fibroblast growth factor receptors; LIFR, Leukemia inhibitory factor receptor; IL-6R, Interleukin-6 cell factor receptor; IL-13R, Interleukin-13 cell factor receptor; GP130, Glycoprotein 130 receptor; EGF, Epidermal growth factor; MEK, Mitogen-activated protein kinase; ERK, Extracellular signal-regulated kinase; PI3K, Phosphoinositide 3-kinase; AKT, Protein kinase B; VEGF, Vascular endothelial growth factor; PDGF, Platelet-derived growth factor; FGF, Fibroblast growth factor; TBx3, T-box transcription factor 3; TYK2, Tyrosine kinase 2; PROTAC, Proteolysis targeting chimera; PD-L1, Programmed death-ligand 1; c-MET, Cellular mesenchymal-epithelial transition; PARP, Poly ADP-ribose polymerase; AR, Androgen receptor; EZH2, Enhancer of zeste *homolog 2*; CDK, Cyclin-dependent kinases.

The signaling cascade of the JAK2/STAT3 pathway is predominantly mediated through receptor tyrosine kinases (RTKs), JAK2, and the transcription factor STAT3. RTKs are single-pass transmembrane proteins ubiquitously expressed across various cell types, including those within the tumor microenvironment. Characteristically, all RTKs possess a conserved structural composition: an extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain (27). Upon ligand binding, RTKs undergo dimerization on the cell membrane and phosphorylate tyrosine residues on the receptors, facilitating their recognition and binding by downstream proteins with SH2 domains, such as JAK2. RTK dimerization brings the associated JAK2 kinase into proximity, enabling their activation through reciprocal tyrosine phosphorylation. Activated JAK2 then stimulates the RTKs to generate binding sites for STAT3. STAT3 binds to RTKs through its SH2 domain and undergoes phosphorylation under the influence of JAK2. The phosphorylated STAT3 forms homodimers and enters the nucleus to induce downstream signal transduction, effectuating various physiological or pathological roles (28). Given the characteristics of this signaling pathway, targeting its components to treat TNBC represents an effective strategy for precision therapy (Figure 1).

Consequently, this review systematically summarizes the roles of the JAK/STAT3 pathway in the pathogenesis of TNBC and the current advances in research on small-molecule compounds targeting the JAK/STAT3 signaling pathway as a therapeutic approach for TNBC.

2 Receptor tyrosine kinases in TNBC

Receptor tyrosine kinases represent a diverse class of enzyme-linked cell surface receptors with a high affinity for growth factors, cytokines, and hormones. These receptors not only bind specific ligands but also function as protein kinases, phosphorylating tyrosine residues on target proteins. RTKs are categorized into 20 distinct families based on the types of ligands they bind (29). TNBC expresses various RTKs, including epidermal growth factor receptors (EGFRs) (30), vascular endothelial growth factor receptors (VEGFRs) (28), insulin-like growth factor receptors (IGFRs) (31), platelet-derived growth factor receptors (PDGFRs) (32), fibroblast growth factor receptors (FGFRs) (33), leukemia inhibitory factor receptor (LIFR) (34), interleukin-6 cell factor receptor (IL-6R) (35), interleukin-13 cell factor receptor (IL-13R) (36), and glycoprotein 130 receptor (GP130) (37). Before ligand binding, RTKs exist on the cell surface as inactive monomers. Homologous ligand binding induces receptor dimerization, activating their intrinsic kinase activity (38).

2.1 Epidermal growth factor receptors: regulator of progression, metastasis, and cancer stem cells in TNBC

Epidermal growth factor receptors, the receptor for epidermal growth factor (EGF), is a key member of the HER family, which also

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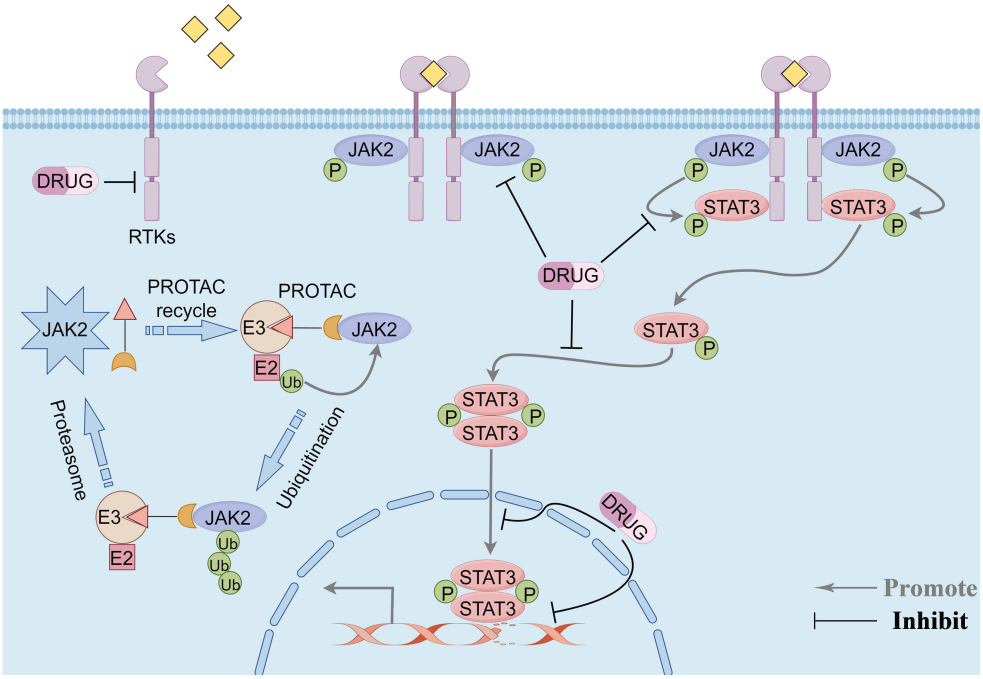

FIGURE 1
Overview of the JAK2/STAT3 pathway signaling modality and potential therapeutic targets of the pathway. Phosphorylation signaling blockade and protein-targeted degradation pathways. By Figdraw.

includes Her-2, Her-3, and Her-4 (39). EGF binding to EGFR induces receptor dimerization, a critical step leading to the autophosphorylation of tyrosine residues on the activated receptor. This activation allows the receptor to recruit various signal sequence proteins, transmitting biological signals from the extracellular milieu to the intracellular domain. These signaling cascades culminate in gene transcription, modulating key cellular processes such as proliferation, differentiation, and apoptosis. In cancer, EGFR contributes to tumor progression by promoting invasion and metastasis and stimulating tumor angiogenesis (40). EGFR activates complex signal transduction pathways with primary pathways including mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) (41), JAK2/STAT3 (42), and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) (43). Dysregulation of these pathways is intricately linked to tumor development, invasion, and metastasis. EGFR is overexpressed in several malignant tumors, including lung, colon, liver, and breast cancers (44–47). In the context of cancer prognosis, EGFR overexpression is associated with shorter recurrence times, increased recurrence rates, and reduced survival durations (48). In TNBC, the positive expression rate of EGFR is notably higher than in non-TNBC, with over 40% of patients with TNBC exhibiting EGFR overexpression, a factor closely correlated with TNBC prognosis (49, 50). Targeted inhibition of EGFR expression has demonstrated anti-cancer effects in TNBC (51). EGFR expression is also implicated in CD44+ cell aggregation, with its inhibition disrupting cancer stem cell assembly in TNBC. These lines of evidence suggest a link between EGFR expression and the progression of CD44+-mediated cancer stem cells (52).

2.2 Vascular endothelial growth factor receptors: regulator of angiogenesis and cancer stem cells in TNBC

Vascular endothelial growth factor receptors, the receptor for vascular endothelial growth factor (VEGF), comprises three primary types: VEGFR1, VEGFR2, and VEGFR3. VEGF induces angiogenesis by binding to VEGFR-2, enhancing the survival, proliferation, migration, and adhesion of endothelial cells (53). However, in pathological contexts, particularly in cancer, VEGFR expression is linked to the promotion of tumor angiogenesis and metastasis (54, 55). Numerous studies have documented the overexpression of VEGFR in a range of malignant tumors, including lung, colon, breast, liver, and ovarian cancers (56–60). In TNBC, elevated VEGF levels correlate with increased metastasis, poor treatment response, and decreased survival rates (61). Upregulation of VEGFR in TNBC is linked to heightened cell proliferation, while its downregulation inhibits this proliferation (62). A notable randomized cohort study has indicated a strong association between high VEGFR expression and 5-year and 10-year breast cancer-specific survival rates in patients (63). These findings underscore the potential of targeting the VEGF/VEGFR axis as a promising approach in the targeted therapy of TNBC. Research employing primary breast cancer mouse models and models of spontaneous breast cancer metastasis has revealed elevated VEGFR expression levels in metastatic breast cancer compared to non-metastatic forms (64). Additionally, VEGFR expression correlates with cancer stem cell characteristics. By activating the VEGFR2/STAT3 pathway, VEGF induces the

upregulation of Myc and Sox2 expression, thereby promoting the self-renewal of breast cancer stem cells. The autocrine action of VEGF can establish a positive feedback loop, diminishing the efficacy of anti-angiogenic drugs and enhancing cancer stem cell renewal (28). Consequently, targeting VEGFR expression emerges as a potentially effective therapeutic strategy for the regulation of breast cancer stem cells.

2.3 Platelet-derived growth factor receptors: regulator of endothelial cell differentiation and cancer stem cells in TNBC

Tumor blood vessel development is crucial to tumor growth, making angiogenesis a potential target in cancer therapy (65). Platelet-derived growth factor receptors, which binds to platelet-derived growth factor (PDGF), exists in two forms: PDGFRα and PDGFRβ. PDGFR activation, contingent upon PDGF interaction, initiates various intracellular signaling pathways. While PDGFR contributes to vascular repair after tissue damage (66), it also promotes cell proliferation within tumor tissues (67). Studies involving mouse models with differential PDGF gene expression have yielded insightful observations. Specifically, tumors in mice with PDGF gene deficiency exhibit reduced pericyte recruitment, whereas tumors in mice with PDGF overexpression demonstrate increased pericyte recruitment. These findings suggest that tumors recruit pericytes through paracrine PDGF secretion, interacting with PDGFR, facilitating blood vessel maturation, and synergizing with VEGF-mediated angiogenesis, contributing to tumor vascularization (68). Extensive research indicates that PDGFR is overexpressed in various malignant tumors, including lung, colon, breast, and ovarian (69–72). In TNBC, PDGFRβ plays a notable role in mediating endothelial cell differentiation and vasculogenic mimicry in tumor cells (32). Further studies have identified a link between PDGFRβ expression in TNBC, and cancer stem cells, where FOXC2 induces cancer stem cell characteristics and metastasis by upregulating PDGFRβ expression (73). These findings position PDGFR as a promising therapeutic target for TNBC.

2.4 Fibroblast growth factor receptors: regulator of cell proliferation and cancer stem cells in TNBC

Fibroblast growth factor receptors, the receptor for fibroblast growth factor (FGF), comprises four subtypes: FGFR1, FGFR2, FGFR3, and FGFR4, collectively forming the FGFR family. Upon binding with FGF, FGFR is activated and modulates multiple intracellular signaling pathways crucial to various biological processes, including angiogenesis and lymphangiogenesis (74). Studies have highlighted the association of FGFR expression in various solid tumors with tumor cell proliferation (75–79). High-throughput sequencing has identified FGFR gene mutations in approximately 7.1% of malignant tumors, with breast cancer exhibiting the second-highest frequency after urothelial carcinoma (80). In TNBC, FGFR3 expression is observed, and inhibition of the FGFR3 signaling pathway reduces TNBC cell invasion and migration (81). Targeting and blocking the FGFR pathway can significantly enhance T cell infiltration and suppress tumor growth in TNBC (33). Some studies have revealed that estrogen can stimulate breast cancer stem cell proliferation via the paracrine FGF/FGFR/T-box transcription factor 3 (TBx3) signaling pathway, and inhibiting this pathway curtails cancer stem cell expansion in TNBC (82). These findings highlight the potential of targeting the FGFR pathway as a therapeutic approach in TNBC.

3 Activation of the JAK2/STAT3 signaling pathway in TNBC

Janus Kinase 2, a member of the JAK family of non-receptor tyrosine kinases, includes JAK1, JAK3, and tyrosine kinase 2 (TYK2). JAK3 is predominantly expressed in hematopoietic cells, while JAK1, JAK2, and TYK2 exhibit broader expression across various tissues (83). JAKs mediate a range of disease processes, including immune system disorders (84), hematologic conditions (85), and various malignancies (86, 87). Signal transducer and activator of transcription (STAT) protein family comprises members such as STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. Notably, STAT3 is implicated in the promotion of tumor growth and the induction of immunosuppression (88–90). The JAK2/STAT3 signaling pathway is ubiquitously expressed in cells and vital in physiological functions (91), such as cell proliferation, differentiation, apoptosis, and immune regulation (92). Beyond its physiological roles, this pathway is significantly implicated in various pathologies, notably in cancer and autoimmune disorders. In breast cancer, particularly TNBC, JAK2/STAT3 signaling is known for its excessive activation (93). Advanced research has facilitated a more precise molecular classification of TNBC, identifying the mesenchymal subtype characterized by heightened JAK2/STAT3 activity (8). This insight offers a new direction and foundation for the personalized clinical treatment of TNBC, focusing on targeting the JAK2/STAT3 signaling pathway. Research has elucidated that the JAK2/STAT3/Cyclin D2 signaling pathway is pivotal in promoting cancer stem cell proliferation (94). Specifically, in TNBC, studies have demonstrated that downregulating the JAK2/STAT3 pathway can significantly inhibit cancer stem cell proliferation (95). Furthermore, additional research has indicated that suppressing this pathway may reduce TNBC cell proliferation and migration (13).

4 The role of the JAK2/STAT3 signaling pathway in multidrug resistance in TNBC

The lack of effective targeted therapies, necessitating reliance on taxanes and anthracycline cytotoxic drugs significantly hinders the treatment of TNBC. However, the emergence of multidrug resistance during treatment poses a formidable challenge to this approach (5). For instance, the activation of the JAK2/STAT3

signaling pathway in nasopharyngeal carcinoma has been demonstrated to induce forkhead box M1 transcription, thereby enhancing resistance to PTX (96). Subsequent studies have revealed the contribution of the JAK2/STAT3 pathway to the development of PTX resistance by upregulating anti-apoptotic gene expression. Targeting this pathway has proven effective in reversing PTX resistance in ovarian cancer (97). In a model of PTX-resistant cells, researchers observed differential expression of the JAK2 gene, suggesting its potential role as a candidate gene linked to PTX resistance in ovarian cancer cell lines (98). Further studies indicate that the downregulation of JAK2/STAT3 signaling pathway can counteract PTX resistance in TNBC (26). Furthermore, a separate research effort found that JAK2 inhibitors can directly bind to the drug efflux protein P-gp in resistant cell lines, thus impeding P-gp-mediated drug efflux (99). Collectively, these studies underscore the significance of the JAK2/STAT3 signaling pathway in the development of multidrug resistance. Consequently, targeting this pathway, either as a standalone therapy or in combination with PTX, presents a promising strategy for the treatment of PTX-resistant TNBC.

5 Current therapeutic applications of the JAK2/STAT3 signaling pathway in TNBC

Recent research has elucidated the pivotal role of the JAK2/STAT3 signaling pathway in driving the proliferation, invasion, and migration of TNBC. These findings position the JAK2/STAT3 pathway as a promising therapeutic target for TNBC management. In response to these insights, numerous preclinical and clinical studies are actively exploring the development of inhibitors targeting RTKs, JAK2, and STAT3. These inhibitors are categorized based on their mode of action into traditional small molecule inhibitors in the occupation-driven mode and proteolysis targeting chimera (PROTAC) molecules based on ubiquitin-mediated protein degradation in an event-driven mode. Traditional small molecule inhibitors in the occupation-driven mode function by occupying the active site or binding site of the target protein with small molecule compounds. This action blocks its interaction with downstream signaling molecules, inhibiting its function. On the other hand, PROTAC molecules employ a ligand linker to bind the target protein with an E3 ubiquitin ligase, leveraging the ubiquitin-proteasome system to drive the degradation of the target protein (Figure 2).

5.1 Occupation driven mode: application of small molecule inhibitors in TNBC

5.1.1 RTKs inhibitors

Currently, the U.S. Food and Drug Administration (FDA) has not approved RTK inhibitors for the treatment of TNBC. Both monoclonal antibodies and small molecule inhibitors are progressing through preclinical and clinical research stages. Preclinical studies have shown that cetuximab can effectively reduce cancer stem cells in TNBC and inhibit tumor growth (100). However, clinical trials reveal a more complex picture. For instance, a study investigating the combination of cetuximab and cisplatin in metastatic TNBC reported benefits in fewer than 20% of patients. Genomic analyses revealed limited efficacy due to cetuximab-induced activation of alternative bypass pathways. Combining cetuximab with inhibitors targeting downstream elements of the EGFR pathway is proposed for enhanced benefits in patients with TNBC (101). Preclinical research has demonstrated that bevacizumab, a VEGFR inhibitor, effectively suppresses TNBC growth *in vivo* (102). However, the adjunctive use of bevacizumab with chemotherapy did not improve overall survival rates in early-stage patients with TNBC compared to chemotherapy alone. Similarly, tocilizumab, an interleukin-6 receptor (IL-6R) inhibitor, exhibits potential anti-TNBC properties in preclinical studies (103), but its clinical efficacy in TNBC treatment remains unreported and warrants further investigation.

Several RTK small molecule inhibitors have been reported in clinical studies for the treatment of TNBC (Table 1). Apatinib, a highly selective VEGFR inhibitor, has exhibited promising efficacy in a Phase II clinical trial for patients with TNBC combined with chemotherapy. The results highlighted not only its effectiveness but also a manageable safety profile (104). Furthermore, combining Apatinib with a programmed death-ligand 1 (PD-L1) inhibitor in another Phase II trial resulted in favorable outcomes with a controllable safety profile (105). Integration of Apatinib with a PD-L1 inhibitor and Eribulin in a multicenter Phase II trial demonstrated significant therapeutic benefits in treating advanced TNBC, notably extending its efficacy to PD-L1–negative patients (106). Anlotinib, identified as a small molecule inhibitor targeting the VEGFR, displayed promising results in advanced TNBC treatment. Specifically, a Phase Ib clinical trial revealed that Anlotinib, when employed in a chemotherapy-free regimen alongside a PD-L1 inhibitor, effectively treated previously advanced patients with TNBC. This combination not only demonstrated favorable efficacy but also maintained a manageable safety profile (107). Another Phase II clinical trial combining Anlotinib with standard chemotherapy for metastatic TNBC demonstrated therapeutic benefits with manageable safety (108).

Gefitinib, a small molecule EGFR inhibitor, along with neoadjuvant chemotherapy, showed a higher pathological complete response rate in a Phase II clinical trial for patients with TNBC, especially in the chemotherapy and Gefitinib combination group. However, it is critical to note that patients receiving Gefitinib exhibited a higher incidence of toxic reactions, consequently leading to the discontinuation of the trial for those patients (109). In another Phase II clinical trial, Erlotinib, a small molecule EGFR inhibitor, was evaluated for its efficacy in treating metastatic TNBC. Patients in this trial initially received treatment with albumin-bound PTX combined with bevacizumab, followed by a maintenance regimen comprising both bevacizumab and Erlotinib. Notably, a significant proportion of participants in this trial exhibited partial tumor responses (110).

Research on RTK inhibitors in TNBC is expanding to include natural products such as Salidroside extracted from Rhodiola (Table 2).

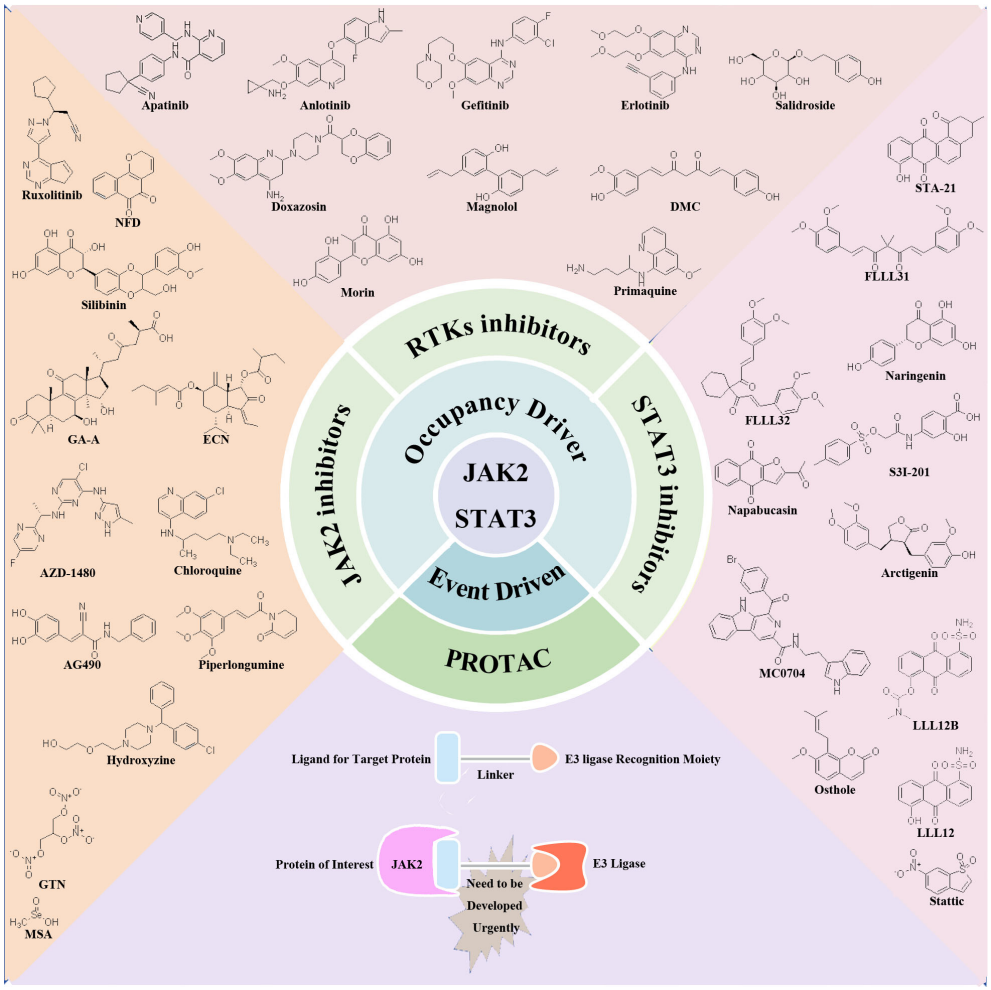

FIGURE 2
Potential therapeutic targets and inhibitors targeting JAK2/STAT3 signaling pathway for TNBC treatment. Occupation-driven mode: RTKs, JAK2 and STAT3-targeted inhibitors; event driven mode: small molecule compounds targeting JAK2 protein for ubiquitination degradation.

Preclinical studies have shown that Salidroside inhibits phosphorylation signaling pathways of EGFR/JAK2/STAT3, thereby impacting TNBC cell viability by binding to EGFR. Salidroside's therapeutic potential is highlighted by its selective efficacy, demonstrating minimal toxicity in normal breast epithelial cells (114). Doxazosin, primarily known as a vasodilator, has a dual-target mechanism, binding to cellular mesenchymal-epithelial transition factor (c-MET) and EGFR. This binding results in the inhibition of JAK2/STAT3 phosphorylation signaling. Research has demonstrated that doxazosin significantly affects TNBC cell proliferation, invasion, and migration, supported by *in vitro* and *in vivo* evidence. The efficacy of doxazosin in curbing TNBC lung metastasis was further substantiated through a mouse lung metastasis model (115).

Magnolol, a multifunctional lignan compound derived from the traditional Chinese herb Houpo, has demonstrated notable anti-cancer properties against TNBC. *In vitro* studies reveal that Magnolol effectively reduces the viability of TNBC cells. This inhibitory effect is primarily attributed to the suppression of phosphorylation signaling in the EGFR/JAK2/STAT3 pathway (116). The lead compound APP has also shown promising results in TNBC treatment. *In vitro* analyses indicate that APP induces apoptosis in TNBC cells. This apoptotic effect is mediated through the inhibition of EGFR/JAK2/STAT3 phosphorylation signaling, coupled with the regulation of apoptotic proteins (117). Demethoxycurcumin (DMC), a principal variant of curcumin predominantly found in the rhizomes of turmeric, has garnered attention in the context of TNBC research. *In vitro* studies have illuminated its potential in modulating TNBC cell viability. DMC achieves this by inhibiting EGFR protein expression levels. Furthermore, its mechanism involves the inhibition of specific phosphatases, thereby sustaining EGFR activation. This suggests that DMC's influence on TNBC cells might result from its regulation of multiple signaling pathways (118). Morin, a flavonoid compound derived from plants, has shown potential in the treatment of TNBC. Studies indicate that Morin, particularly when used in conjunction with doxorubicin, promotes apoptosis in TNBC cells. This synergistic effect is attributed to the inhibition of EGFR/STAT3 phosphorylation signaling (119, 120).

Primaquine, an antimalarial drug, has been observed to inhibit TNBC cell viability and migration *in vitro*. This inhibition is linked

TABLE 1 Targeting JAK2/STAT3 signaling pathway for TNBC in preclinical studies.

Compd.	Target	Effects/ Adverse Reactions	Citation
Apatinib	VEGFR	Combined with chemotherapy in a phase II clinical trial study, excellent results were achieved in patients with TNBC and were safe and manageable; Combination with a PD-L1 inhibitor in a phase II clinical trial study showed favorable results with a manageable safety profile in patients with advanced TNBC; Combination of PD-L1 inhibitors and eribulin shows promising results in the treatment of advanced TNBC in a multicenter phase II clinical trial study.	(104–106)
Anlotinib	VEGFR	Combination with a PD-L1 inhibitor in a phase Ib clinical trial showed favorable efficacy in previously treated patients with advanced TNBC with a manageable safety profile; Combination chemotherapy for treatment of metastatic TNBC achieves efficacy and is safe and controlled in phase II clinical trial studies.	(107, 108)
Gefitinib	EGFR	Efficacy achieved in combination with neoadjuvant chemotherapy in TNBC patients in a randomized phase II clinical trial study, but the trial was terminated due to toxic events.	(109)
Erlotinib	EGFR	Combined bevacizumab maintenance therapy reduces tumor load in most patients in a phase II clinical trial study.	(110)
Ruxolitinib	JAK2	In a phase II clinical trial study, treatment of TNBC as a single agent did not meet efficacy endpoints; Combination capecitabine has no benefit over capecitabine alone for TNBC in a phase II clinical trial study; Combined PTX is better than PTX alone for TNBC in a phase I clinical trial study.	(111–113)

TABLE 2 Targeting RTKs to modulate the JAK2/STAT3 signaling pathway in preclinical studies for the treatment of TNBC.

Compd.	Target	*In Vivo* Or *In Vitro*	Citation
Salidroside	EGFR	*In vitro*	(114)
Doxazosin	EGFR/ c-MET	*In vitro* and *in vivo*	(115)
Magnolol	EGFR	*In vitro*	(116)
4-(adamantan-1-yl)-2-(3-(2,4-dichlorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl) thiazole (APP)	EGFR	*In vitro*	(117)
Demethoxycurcumin	EGFR	*In vitro*	(118)
Morin	EGFR	*In vitro*	(119, 120)
Primaquine	EGFR	*In vitro* and *in vivo*	(121)
Centipeda minima Extract (CME)	EGFR	*In vitro* and *in vivo*	(122)
CAPE-*p*NO2	EGFR	*In vitro* and *in vivo*	(123)
Phospho-aspirin-2 (PA-2)	EGFR	*In vitro* and *in vivo*	(124)
Deguelin	EGFR/ c-MET	*In vitro* and *in vivo*	(125, 126)
Picrasidine G	EGFR	*In vitro*	(127)
Regorafenib	VEGFR/ PDGFR	*In vitro* and *in vivo*	(128)
Bazedoxifene	GP130	*In vitro* and *in vivo*	(129, 130)
Raloxifene	GP130	*In vitro*	(131)
EC359	LIFR	*In vitro* and *in vivo*	(34, 132)
Chikusetsusaponin IVa Butyl Ester (CS-IVa-Be)	IL-6R	*In vitro*	(133)

to the suppression of EGFR/STAT3 phosphorylation signaling. However, the specific mechanisms by which Primaquine impedes TNBC growth *in vivo* remain to be explored further (121). Additionally, Centipeda minima Extract (CME), an extract from the Centipeda minima, has demonstrated efficacy in regulating TNBC cell behavior by modulating the phosphorylation signaling of multiple pathways, notably the STAT3 pathway. This modulation occurs through the inhibition of EGFR expression, thereby promoting apoptosis in TNBC cells (122). CAPE-pNO2 has also been identified as a potent inhibitor of proliferation and migration in TNBC by suppressing EGFR phosphorylation and the regulation of STAT3 and AKT phosphorylation signaling. This dual effect has been observed in both *in vitro* and *in vivo* studies (123).

Similarly, PA-2, another compound under investigation, has demonstrated its ability to promote apoptosis in TNBC cells. It achieves this through the inhibition of EGFR phosphorylation and by modulating the phosphorylation signaling of the PI3K/AKT and STAT3 pathways (124). Deguelin also contributes to this growing field of TNBC therapeutics. It influences the expression of both EGFR and c-Met, leading to the downregulation of phosphorylation signaling across several pathways, including STAT3, AKT, ERK, and NFκB. This comprehensive action results in a marked impact on the viability of TNBC cells (125, 126). Picrasidine G, a naturally derived dimeric alkaloid, has shown efficacy in inhibiting the vitality

of TNBC cells *in vitro* by suppressing the EGFR/STAT3 phosphorylation signaling pathway (127). Regorafenib, another compound under study, exerts its anti-cancer effects by inhibiting key receptors such as VEGFR and PDGFR. This inhibition impacts the STAT3 phosphorylation signaling (128).

Bazedoxifene presents a different angle in TNBC treatment. By targeting GP130, it influences the STAT3 phosphorylation signaling pathway. This strategic inhibition inhibits TNBC both *in vitro* and *in vivo* (129, 130). Raloxifene, a compound known for its influence on the GP130 receptor, has been shown to inhibit the vitality of TNBC cells *in vitro*. This effect is achieved through the modulation of the STAT3 phosphorylation signaling pathway (131). EC359, another promising agent, binds to the leukemia inhibitory factor receptor (LIFR), inhibiting the LIFR/STAT3 phosphorylation signaling, thereby curbing TNBC proliferation both *in vitro* and *in vivo* (34, 132). Similarly, CS-IVa-Be targets cancer cells through the inhibition of IL-6R, impacting the JAK2/STAT3 phosphorylation signaling pathway. This specific action has been observed to inhibit TNBC *in vitro* (133).

In summary, RTK inhibitors can inhibit the signaling of the JAK2/STAT3 pathway. However, due to the activation of bypass pathways, clinical trial results suggest that combining these inhibitors with chemotherapy may be more beneficial for patients with TNBC.

5.1.2 JAK2 inhibitors

Directly targeting JAK2 emerges as a strategic approach for modulating the JAK2/STAT3 signaling pathway in TNBC treatment. However, to date, JAK2 inhibitors have not received FDA approval for use in TNBC therapy. Ruxolitinib, a JAK1/JAK2 inhibitor, is being evaluated for its clinical efficacy in treating TNBC in several clinical trials. In a Phase II clinical trial, Ruxolitinib monotherapy did not meet its efficacy endpoint for TNBC treatment (111). Further research explored the potential of Ruxolitinib in combination with chemotherapy drugs. While combining Ruxolitinib with Capecitabine did not enhance overall survival, another trial pairing it with PTX showed improved clinical efficacy, outperforming PTX monotherapy (112, 113) (Table 1).

In preclinical TNBC studies, several small molecules exhibit promise as JAK2 inhibitors (Table 3). For instance, Glyceryl Trinitrate (GTN), a vasodilator, inhibits STAT3 activation by blocking JAK2 phosphorylation, suppressing TNBC cell viability (134). Additionally, a range of compounds, including Withaferin A (WA) (135), Naphtho[1,2-b]furan-4,5-dione (NFD) (136), Ganoderic acid A (GA-A) (137), Methylseleninic Acid (MSA) (138), and AZD1480 (139), have been identified to inhibit the phosphorylation and signal transduction of the JAK2/STAT3 pathway, reducing the viability of TNBC cells. Recent research findings highlight the efficacy of JAK2 small molecule inhibitors in TNBC. For instance, the JAK2 inhibitor AG490 has been shown to reduce TNBC cell viability by modulating the phosphorylation and signal transduction of STAT3 and AKT (140, 141). Additionally, 3-Deoxy-2β,16-dihydroxynagilactone E (B6) interacts with the FERM-SH2 domain of JAK2, inhibiting downstream STAT3 phosphorylation and reducing TNBC cell viability (142). Another study highlights the effectiveness of ECN in suppressing TNBC cell viability by targeting the JAK2/STAT3 signaling pathway. ECN has also demonstrated the ability to inhibit TNBC tumor growth *in vivo* (143).

TABLE 3 Targeting the JAK2 for TNBC in preclinical studies.

Compd.	Target	*In Vivo* Or *In Vitro*	Citation
Glyceryl Trinitrate (GTN)	JAK2	*In vitro* and *in vivo*	(134)
Withaferin A (WA)	JAK2	*In vitro*	(135)
Naphtho[1,2-b]furan-4,5-dione (NFD)	JAK2	*In vitro*	(136)
Ganoderic acid A (GA-A)	JAK2	*In vitro*	(137)
Methylseleninic Acid (MSA)	JAK2	*In vitro* and *in vivo*	(138)
AZD1480	JAK2	*In vitro*	(139)
AG490	JAK2	*In vitro*	(140, 141)
3-Deoxy-2β,16-dihydroxynagilactone E (B6)	JAK2	*In vitro*	(142)
7β-(3-Ethyl-*cis*-crotonoyloxy)-1α-(2-methylbutyryloxy)-3,14-dehydro-Z-notonipetranone (ECN)	JAK2	*In vitro* and *in vivo*	(143)
Chloroquine	JAK2	*In vitro* and *in vivo*	(95)
Silibinin	JAK2	*In vitro*	(144, 145)
Piperlongumine	JAK2	*In vitro* and *in vivo*	(146)
Hydroxyzine	JAK2	*In vitro*	(147)

Chloroquine enhances PTX therapeutic efficacy in TNBC by inhibiting JAK2/STAT3 pathway phosphorylation, impacting autophagy processes (95). Additionally, Silibinin suppresses TNBC cell invasive and migratory capabilities *in vitro* by downregulating JAK2/STAT3 pathway phosphorylation (144, 145). Piperlongumine, a bioactive alkaloid known for its antioxidant and anti-tumor properties, has been found to inhibit TNBC cell proliferation and migration by inhibiting JAK2/STAT3 pathway phosphorylation (146). Similarly, Hydroxyzine, primarily recognized as a histamine H1 receptor antagonist, has demonstrated the capability to induce apoptosis in TNBC cells through the inhibition of JAK2/STAT3 phosphorylation (147).

JAK2 inhibitors have shown significant efficacy in inhibiting TNBC *in vitro*. Clinical trial data *in vivo* also suggest that a combination of these inhibitors with the chemotherapy drug paclitaxel could be a promising therapeutic approach for TNBC. However, concerns about the safety of JAK2 inhibitors, as evidenced by FDA warnings, underscores the necessity for alternative therapeutic strategies targeting the JAK2/STAT3 pathway.

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5.1.3 STAT3 inhibitor

Several STAT3 small molecule inhibitors have been reported in preclinical studies for the treatment of TNBC (Table 4). The therapeutic strategy to inhibit STAT3 involves targeting multiple stages of its functional cycle, including phosphorylation, dimerization, nuclear translocation, and DNA binding activities. This approach leverages the nuclear translocation signal of STAT3.

Stattic, a non-peptidic small molecule, has demonstrated notable anti-TNBC effects by selectively targeting STAT3, inhibiting its activation, dimerization, and nuclear translocation. This inhibition is facilitated through Stattic's binding to the SH2 functional domain of STAT3 (148, 149). Similarly, STA-21, another small molecule inhibitor, induces apoptosis in TNBC cells by inhibiting DNA binding activity and dimerization of STAT3 (150). FLLL31 and FLLL32, derivatives of curcumin, have been identified as selective inhibitors of STAT3. They achieve this by binding to the SH2 functional domain of STAT3, thereby inhibiting its phosphorylation and DNA binding activities. Notably, these compounds have shown potential in synergistically inhibiting TNBC cell proliferation when combined with doxorubicin. *In vivo* studies further indicate that FLLL32 can effectively suppress TNBC growth by downregulating STAT3 phosphorylation levels (151). Pyrrolidine sulfonamide derivative **6a** selectively inhibits STAT3 activation at phosphorylation and transcription levels, reducing TNBC cell viability in response to IL-6 stimulation (152). LLL12, a non-peptidic, cell-permeable small molecule, selectively targets STAT3 by inhibiting its DNA binding activity and phosphorylation through SH2 domain binding. It induces apoptosis in TNBC cells and suppresses TNBC growth *in vivo* by downregulating STAT3 phosphorylation levels (153). LLL12B, a prodrug of LLL12, is activated in the tumor microenvironment by tumor-associated plasmin, which cleaves its aminoformate bond to release active LLL12. LLL12B exhibits improved pharmacokinetic properties compared to its parent compound, LLL12. However, additional research is required to fully elucidate the comparative *in vivo* and *in vitro* pharmacology of these compounds, particularly their respective abilities to bind to STAT3 (15).

Naringenin, a naturally occurring compound, reduces TNBC cell viability by binding to the SH2 domain of STAT3, suppressing STAT3 phosphorylation. In combination with cyclophosphamide, naringenin has demonstrated enhanced efficacy in inducing apoptosis in TNBC cells (154). S3I-201, a selective STAT3 inhibitor probe, targets the SH2 functional domain of STAT3, inhibiting its DNA binding activity and dimerization. *In vitro* studies have revealed that S3I-201 significantly diminishes the TNBC cell viability and inhibits tumor growth by reducing STAT3 phosphorylation (155). Napabucasin, a targeted therapeutic agent, selectively inhibits the DNA binding activity and phosphorylation of STAT3 by binding to its SH2 functional domain. *In vitro* studies have demonstrated Napabucasin's capability to reduce TNBC cell viability (156). Additionally, a series of compounds, such as 7a (157), SLSI-1216 (158), H182 (159), SMY002 (160), MC0704 (161), ZSW (162), and Acetyl-cinobufagin (163), have been identified to selectively inhibit STAT3 phosphorylation by binding to its SH2 domain and

TABLE 4 Targeting STAT3 for TNBC in preclinical studies.

Compd.	Target	*In Vivo* Or *In Vitro*	Citation
Stattic	STAT3	*In vitro*	(148, 149)
STA-21	STAT3	*In vitro*	(150)
FLLL31	STAT3	*In vitro*	(151)
FLLL32	STAT3	*In vitro* and *in vivo*	(151)
Pyrrolidinesulphonylaryl molecules (6a)	STAT3	*In vitro*	(152)
LLL12	STAT3	*In vitro* and *in vivo*	(153)
LLL12B	STAT3	*In vitro* and *in vivo*	(15)
Naringenin	STAT3	*In vitro*	(154)
S3I-201	STAT3	*In vitro*	(155)
Napabucasin	STAT3	*In vitro*	(156)
Coumarin-benzothiophene1, 1-dioxide conjugates compound(7a)	STAT3	*In vitro* and *in vivo*	(157)
SLSI-1216	STAT3	*In vitro*	(158)
H182	STAT3	*In vitro* and *in vivo*	(159)
SMY002	STAT3	*In vitro* and *in vivo*	(160)
MC0704	STAT3	*In vitro* and *in vivo*	(161)
ZSW	STAT3	*In vitro* and *in vivo*	(162)
Acetyl-cinobufagin	STAT3	*In vitro* and *in vivo*	(163)
Arctigenin	STAT3	*In vitro* and *in vivo*	(164)
KYZ3	STAT3	*In vitro* and *in vivo*	(165)
Dihydrotanshinone	STAT3	*In vitro* and *in vivo*	(166)
DT-13	STAT3	*In vitro* and *in vivo*	(167)
Cucurbitacin E	STAT3	*In vitro*	(168–170)
Niclosamide	STAT3	*In vitro* and *in vivo*	(171–173)
SG-1709	STAT3	*In vitro*	(174)
SG-1721	STAT3	*In vitro* and *in vivo*	(174)
Nifuroxazide	STAT3	*In vitro* and *in vivo*	(175, 176)
LLY17	STAT3	*In vitro* and *in vivo*	(177)

(Continued)

TABLE 4 Continued

Compd.	Target	*In Vivo* Or *In Vitro*	Citation
6Br-6a	STAT3	*In vitro* and *in vivo*	(178)
Pyrimethamine	STAT3	*In vitro* and *in vivo*	(179, 180)
Pectolinarigenin	STAT3	*In vitro* and *in vivo*	(181)
Flubendazole	STAT3	*In vitro* and *in vivo*	(182, 183)
Eupalinolide J	STAT3	*In vitro*	(184, 185)
Betulinic acid	STAT3	*In vitro* and *in vivo*	(186)
Carfilzomib	STAT3	*In vitro* and *in vivo*	(187)
WP1066	STAT3	*In vitro*	(188)
Rhus coriaria extract	STAT3	*In vitro* and *in vivo*	(189)
FZU-03,010	STAT3	*In vitro*	(190)
Disulfiram	STAT3	*In vitro*	(191)
Schisandrin B	STAT3	*In vitro* and *in vivo*	(192)
Osthole	STAT3	*In vitro* and *in vivo*	(193)
Brevilin A	STAT3	*In vitro* and *in vivo*	(194)
Arnicolide D	STAT3	*In vitro* and *in vivo*	(195)
Eucannabinolide	STAT3	*In vitro* and *in vivo*	(196)
Pulvomycin	STAT3	*In vitro* and *in vivo*	(197)
R001	STAT3	*In vitro* and *in vivo*	(198)
Salinomycin	STAT3	*In vitro*	(199, 200)
Ethanolic extract of Origanum syriacum	STAT3	*In vitro*	(201)
Apigenin	STAT3	*In vitro* and *in vivo*	(202)
AG-014699	STAT3	*In vitro*	(203)

suppressing TNBC cell viability *in vitro*. Arctigenin, a bioactive lignan isolated from the seeds of Arctium lappa, inhibits STAT3 in TNBC cells by binding to its SH2 domain, thereby disrupting hydrogen bond connections between DNA and STAT3. This disruption prevents STAT3's binding to genomic DNA, effectively reducing TNBC cell viability (164). Similarly, KYZ3, a derivative of cryptotanshinone, binds to the SH2 domain of STAT3, inhibiting its DNA binding activity and phosphorylation, leading to decreased TNBC cell viability *in vitro* (165). Research has identified a wide array of small molecules that exhibit the potential to inhibit TNBC cell viability. This includes Dihydrotanshinone (166), DT-13 (167), Cucurbitacin E (168–170), Niclosamide (171–173), SG-1709 (174), SG-1721 (174), Nifuroxazide (175, 176), LLY17 (177), 6Br-6a (178), Pyrimethamine (179, 180), Pectolinarigenin (181), Flubendazole (182, 183), Eupalinolide J (184, 185), Betulinic acid (186), Carfilzomib (187), WP1066 (188), Rhus coriaria extract (189), FZU-03,010 (190), Disulfiram (191), Schisandrin B (192), Osthole (193), Brevilin A (194), Arnicolide D (195), Eucannabinolide (196), Pulvomycin (197), R001 (198), Salinomycin (199, 200), the ethanolic extract of origanum syriacum (201), Apigenin (202), and AG-014699 (203). This inhibition is attributed to their ability to suppress STAT3 phosphorylation. However, direct evidence demonstrating their binding to STAT3 is currently lacking.

While preclinical studies have identified various small molecule compounds as potential STAT3 inhibitors, TTI-101 stands out as the sole compound advancing into Phase I clinical trials. Various groups of researchers are investigating the efficacy and safety of TTI-101 in patients with advanced breast cancer and those with inoperable solid tumors.

5.1.4 Adverse effects of JAK2/STAT3 pathway inhibition

Because the biological processes of normal cells also depend on the JAK2/STAT3 pathway, the long-term use of JAK2/STAT3 pathway inhibitors has certain toxic side effects. JAK2 inhibitors inevitably inhibit the normal hematopoietic function of the body, which can cause anemia, thrombocytopenia, and other adverse effects (including dizziness, headache, abdominal pain, diarrhea, and the secondary tumor).

Studies have shown that anemia and thrombocytopenia are the most common hematologic adverse effects when JAK2 inhibitors are used to treat myelofibrosis (204–210); in another study of Ruxolitinib as a drug treatment for true erythrocytosis, headache and diarrhea were the most common non-hematologic adverse effects (211); the immunosuppressive effects of JAK2 inhibitors are important in inducing infections, and in the JUMP study, the most common infection was pneumonia, followed by urinary tract infections and nasopharyngitis (205), and another study showed that 30 of 31 patients treated with Ruxolitinib developed infections, including several opportunistic infections (212); although JAK inhibitors can be used to treat hematologic cancers and inflammatory diseases, during treatment with these drugs, studies have found that some patients suffer from lymphomas and other malignancies, with a statistically significant 16-fold increase in the risk of B-cell malignancies in patients with myeloproliferative neoplasms treated with JAK1/2 inhibitors, and skin cancers being the most common secondary tumor (213); in addition to these symptoms, Ruxolitinib can also cause other adverse reactions such as abdominal pain, drowsiness, acute renal failure (211), and even some studies have reported that patients have died from cardiac arrest (204).

Since the JAK family mediates signaling of multiple cytokines and different receptors are associated with different JAKs, and comprehensive inhibition of the JAK family can result in a variety of side effects, the design and development of new targeted JAK2 inhibitors could provide a solution to these adverse effects.

5.2 Event-driven mode: application of PROTAC molecules based on ubiquitin-mediated protein degradation in TNBC

The regulation of the JAK2/STAT3 signaling pathway can be strategically achieved through the targeted degradation of the JAK2 protein employing PROTACs. These molecular constructs consist of a linker connecting two ligands, with one ligand binding to the target JAK2 protein and the other engaging with the ubiquitin E3 ligase. This dual binding facilitates the formation of a ternary complex, bringing the JAK2 protein and E3 ligase into close proximity. Subsequently, the target JAK2 protein undergoes ubiquitination, marking it for recognition by the proteasome system. This leads to the proteasomal degradation of JAK2 into peptide fragments, effectively nullifying its protein activity (214). Recent studies underscore the promising role of PROTAC molecules in TNBC treatment. MZ1, a small molecule PROTAC, targets BRD4 protein for degradation. Compared to JQ1, a conventional inhibitor targeting the protein domain, MZ1 exhibits superior anti-TNBC activity both *in vitro* and *in vivo*, which is attributed to its specific action in targeting BRD4 protein degradation (215). Another notable PROTAC molecule, NN3, is designed to target PARP1 protein degradation. Experimental findings indicate that NN3 demonstrates effective anti-TNBC activity *in vitro* and *in vivo*. Remarkably, NN3 retains its efficiency in degrading PARP1 protein even in the presence of point mutations, further underscoring its potential as an anti-tumor agent (216). Emerging research sheds light on the efficacy of PROTAC molecule 6n, designed to target the degradation of the AXL protein. Demonstrating a significant advantage over traditional AXL kinase inhibitors, 6n has shown superior anti-TNBC activity *in vitro* and *in vivo* (217). Similarly, YX-02-030, a PROTAC molecule targeting the MDM2 protein degradation, exhibits enhanced anti-tumor activity compared to specific MDM2 inhibitors. Notably, YX-02-030 achieves this therapeutic efficacy without causing harm to normal cells (218). TEP, a PROTAC molecule engineered to target c-Myc protein degradation, effectively inhibits the proliferation of TNBC cells by facilitating the specific degradation of the endogenous c-Myc/Max complex. Additionally, TEP enhances the sensitivity of TNBC cells to palbociclib, a cyclin-dependent kinase inhibitor (219). Another PROTAC molecule, CT-4, designed to target HDAC8 protein degradation, promotes apoptosis in TNBC cells through the targeted degradation of HDAC8 protein (220). The small molecule compound A4, a PROTAC developed based on DCAF16, specifically targets CDK4/6 protein degradation. Research demonstrates that A4 exhibits potent inhibitory activity against CDK4/6, offering a favorable safety profile in normal cells, which is considered superior to the established CDK4/6 inhibitor, palbociclib (221). The small molecule compounds 7f and PP-C8, which also function as PROTAC molecules, also target CDK12/13 degradation. Studies have indicated that these compounds effectively reduce TNBC cell viability by inhibiting the expression of CDK12/13 (222, 223). PROTAC molecules MS8815 and U3i, designed to target EZH2 protein degradation, induce ubiquitination and subsequent proteasome-dependent degradation of EZH2, effectively inhibiting TNBC cell growth (224, 225). Similarly, androgen receptor (AR)-PROTAC has shown efficacy in targeting AR-positive TNBC cells by mediating the ubiquitination and degradation of the AR, thereby inhibiting cell growth (226). Furthermore, C8, a PROTAC molecule developed based on the PARP1/2 inhibitor Olaparib, exhibits promising therapeutic potential against TNBC. It promotes PARP2 protein degradation, demonstrating effectiveness *in vitro* and *in vivo* (227).

Currently, PROTAC small molecules targeting the degradation of JAK2 protein have been reported. However, research indicates that the E3 ligase CUL5 mediates JAK2 protein degradation (228). Developing PROTAC small molecules that facilitate the binding of JAK2 protein to the E3 ligase CUL5 could be a feasible strategy for treating TNBC.

6 Conclusion

The JAK2/STAT3 signaling pathway, activated by cytokines, is central in governing fundamental cellular processes, including growth, differentiation, apoptosis, and immune responses. In TNBC, excessive activation of this pathway contributes to immune evasion by TNBC cells. This aberrant activation promotes tumor growth, facilitates metastasis, and develops drug resistance in TNBC. Therefore, the strategic therapeutic targeting of the JAK2/STAT3 signaling pathway emerges as a promising strategy for the effective treatment of TNBC. The JAK2/STAT3 signaling pathway presents multiple targets for therapeutic intervention in TNBC. Inhibition strategies focusing on RTKs, JAK2, and STAT3 effectively suppresses TNBC cell growth. Despite these promising results, clinical trials of inhibitors that bind to the active sites of these proteins have encountered challenges. These limitations can be attributed to several factors, including the activation of compensatory bypass pathways, overexpression of target proteins, emergence of point mutations within these targets, and the heightened expression of competitive ligands. Unlike conventional inhibitors, PROTAC molecules do not rely on sustained binding to the target protein to exert their inhibitory effect. This unique characteristic enables them to remain effective even in the presence of mutations in the protein's active binding site. A key advantage of PROTACs lies in their catalytic mechanism; following the facilitation of ubiquitination and degradation of the target protein, PROTAC molecules can be recycled. This recycling ability potentially allows for lower drug dosages, enhancing both the safety profile and therapeutic potential of these molecules. Consequently, employing PROTACs to target the JAK2/STAT3 pathway emerges as an exceptionally promising strategy for TNBC treatment. By developing PROTACs that specifically target JAK2 protein degradation, not only is TNBC growth inhibited through the downregulation of the JAK2/STAT3 pathway, but the typical toxic side effects associated with traditional JAK2 inhibitors are also likely to be mitigated.

Author's note

During the preparation of this work authors did not used any AI tool/service, and takes full responsibility for the content of the publication.

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