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REVIEW

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STAT3 pathway in cancers: Past, present, and future

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Signal transducer and activator of transcription 3 (STAT3), a member of the STAT family, discovered in the cytoplasm of almost all types of mammalian cells, plays a significant role in biological functions. The duration of STAT3 activation in normal tissues is a transient event and is strictly regulated. However, in cancer tissues, STAT3 is activated in an aberrant manner and is induced by certain cytokines. The continuous activation of STAT3 regulates the expression of downstream proteins associated with the formation, progression, and metastasis of cancers. Thus, elucidating the mechanisms of STAT3 regulation and designing inhibitors targeting the STAT3 pathway are considered promising strategies for cancer treatment. This review aims to introduce the history, research advances, and prospects concerning the STAT3 pathway in cancer. We review the mechanisms of STAT3 pathway regulation and the consequent cancer hallmarks associated with tumor biology that are induced by the STAT3 pathway. Moreover, we summarize the emerging development of inhibitors that target the STAT3 pathway and novel drug delivery systems for delivering these inhibitors. The barriers against targeting the STAT3 pathway, the focus of future research on promising targets in the STAT3 pathway, and our perspective on the overall utility of STAT3 pathway inhibitors in cancer treatment are also discussed.

KEYWORDS
cancer hallmarks, cancer treatment, STAT3 pathway inhibitors, STAT3

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1 | INTRODUCTION

The incidence and mortality rates of cancer are rapidly increasing worldwide. An estimated 19.3 million new cancer cases and 10.0 million cancer-related deaths were recorded around the world in 2020. By 2040, the global cancer burden is expected to undergo a 47% rise from 2020.[1] According to World Health Statistics 2021 posted by the World Health Organization, there were 1.9 million new cases diagnosed in 2021. Even in high-income countries, cancer has been regarded as one of the leading causes of "premature death" defined as the death between the ages of 30 and 70.[2] Currently, most patients with cancer are treated with surgery combined with radiotherapy, chemotherapy, and/or immunotherapy, depending on the types of cancer.[3–5] Although these conventional therapies may achieve the significant tumor elimination effect initially, various barriers such as surgical trauma, high cost, drug resistance, and cytotoxicity in normal tissues are associated with the risk of treatment discontinuation and cancer recurrence and metastasis.[6–8] Therefore, searching for new therapeutic targets and treatment methods are crucial for improving the survival rate and quality of life of patients with cancer.

Signal transducer and activator of transcription (STAT) proteins are latent cytoplasmic transcription factors comprising seven members, including STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6.[9] Among them, STAT3 is involved in various basic cell functions including cell growth, survival, differentiation, regeneration, immune response, and cellular respiration. STAT3 can be strictly regulated by upstream signaling molecules, such as Janus kinase (JAK) and epidermal growth factor receptor (EGFR). It then localizes to the nucleus of cells and binds to target DNA to regulate the expression of downstream proteins.[10–14] However, in addition to its functions in the normal cells, STAT3 activation in the tumor microenvironment (TME) is regarded as an oncogenic event. High phospho-STAT3 expression is associated with poor prognosis in patients with various types of cancers such as non-small cell lung cancer, gastric cancer, and colorectal cancer.[15–17] Constitutive activation of STAT3 plays an important role in tumor formation, development, metastasis, and recurrence. These are strongly associated with cancer hallmarks and lead to poor patient outcomes. Therefore, the STAT3 pathway is a promising target for cancer therapy.[18–22]

In this review, we summarize the latest advances in STAT3 pathway in cancer. The mechanisms of STAT3 pathway regulation and the cancer hallmarks induced by the STAT3 pathway are also reviewed. We introduce the STAT3 pathway inhibitors and the novel drug delivery systems in preclinical studies and clinical trials for cancer treatment. Furthermore, the difficulties and prospects of targeting the STAT3 pathway in cancer are also discussed.

2 | HISTORY OF STAT3 PATHWAY INVESTIGATION

In 1990, interferon-stimulated gene factor 3 (ISGF3), the STAT protein complex activated by interferon α (IFNα), was purified and identified as a DNA-binding protein by Darnell et al. (Figure 1).[23] In 1992, Fu reported that the 113, 91, and 84 kDa (ISGF3α) proteins of the IFNα-induced primary transcription factor ISGF3 had conserved Src homology domains (SH2 and SH3). IFNα treatment stimulates the activating phosphorylation of ISGF3α by protein tyrosine kinase (PTK), which facilitates direct signal transduction from the cell membrane to the nucleus.[24] The discovery of JAK/STAT pathway was considered as one of the top 10 breakthroughs in 1993 by *Science*. Subsequently, an acute-phase response factor (APRF) was observed to bind to interleukin-6 (IL-6) responsive elements and was activated in the cytoplasm to achieve the IL-6 signal transduction.[25] After the purification and cloning of APRF, Akira et al. demonstrated that APRF is highly homologous to the ISGF3 family and is involved in the glycoprotein 130 (gp130)-mediated signaling pathway. And this APRF was regarded as the novel transcription factor named STAT3.[26] The structure of STAT3 contains several conserved domains, including an N-terminal domain, coiled-coil domain, DNA-binding domain (DBD), linker domain, SH2 domain, and C-terminal domain, which are critical for its functions (Figure 2A,B).[27,28] The N-terminal domain mediates tetramerization of two phosphorylated STAT3 dimers, dimerization of unphosphorylated STAT3, and binds other proteins to form functional complexes. These three main functions are associated with DNA binding, nuclear accumulation, and gene regulation

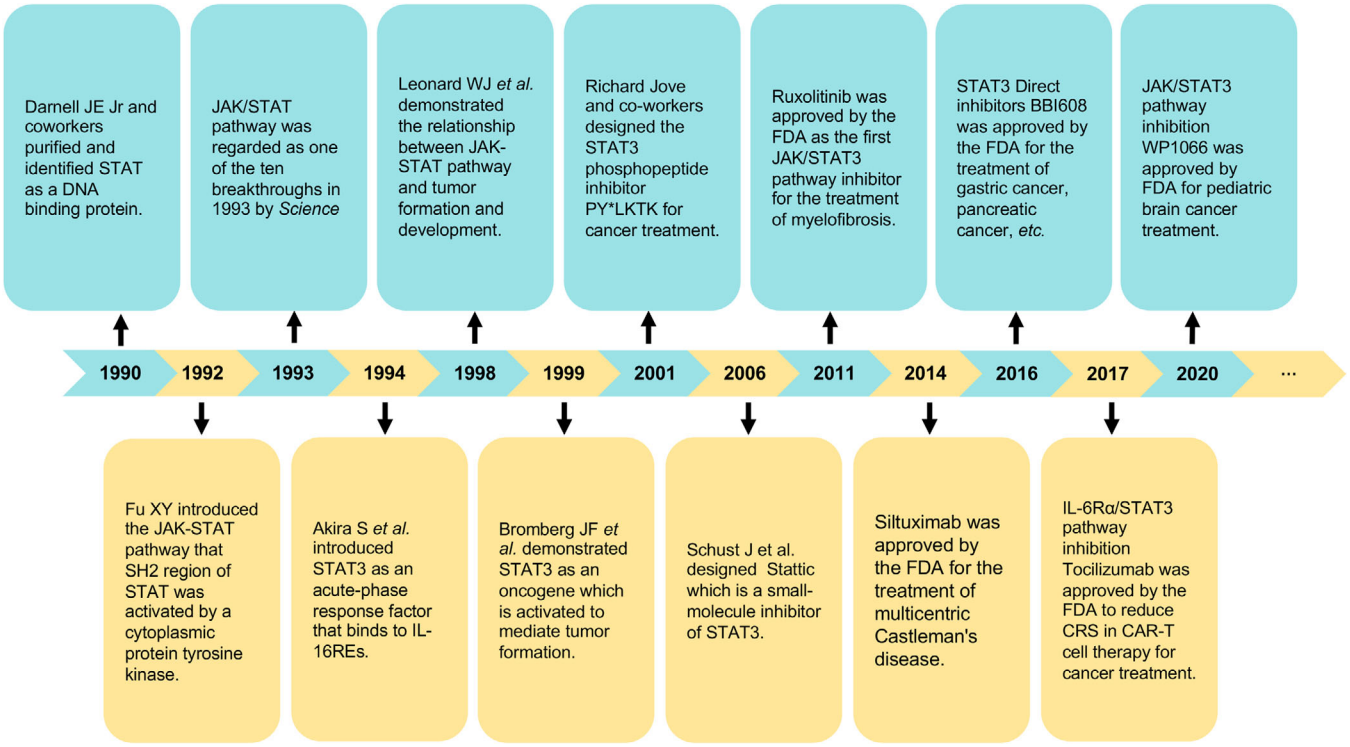

FIGURE 1 Brief history of signal transducer and activator of transcription 3 (STAT3) studies

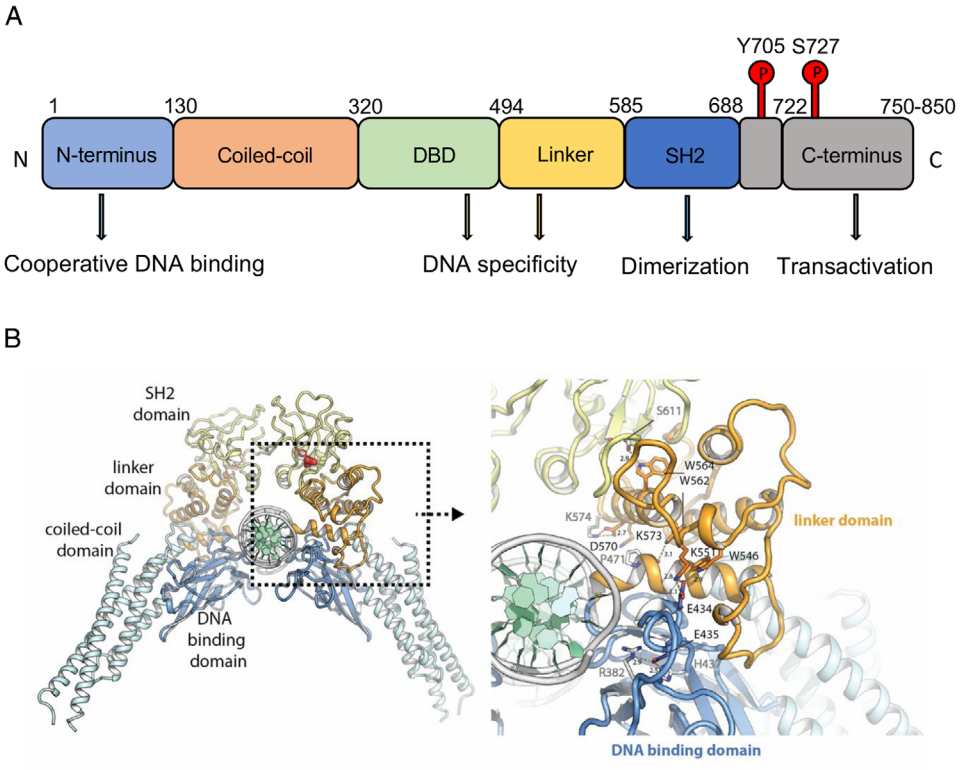

FIGURE 2 (A, B) Schematic and functional architecture of STAT3 protein. STAT3 has the construction, including N-terminus domain, coiled-coil domain, DNA-binding domain, linker, SRC homology 2 and C-terminus domain. Each of them plays a role such as DNA binding, dimerization, and transactivation. Reprinted with permission from Mertens et al.[28] Copyright 2015 by National Academy of Sciences

of STAT3.[29] The coiled-coil domain is essential for early events in STAT3 signal transduction, including STAT3 recruitment for the receptor binding, tyrosine phosphorylation, dimerization, and DNA binding.[30] The C-terminal domain, also known as the trans-activation domain (TDA), contains a specific tyrosine residue (Tyr705) that can be phosphorylated through the interaction of ligands with their receptors. STAT3 has an alpha-helical linker domain spanning amino acid residues 500 to 575 that is followed by a classical SH2 domain. The SH2 domain is the highly conserved region that interacts with specific phosphotyrosine motifs of cytoplasmic signaling molecules and plays an important role in the dimerization of two STAT3.[31]

In 1999, Darnell et al. identified *STAT3* as an oncogene that could be constitutively activated and cause growth dysregulation in human tumor samples.[32] Thus, STAT3 inhibitors have been developed for a long time. In 2001, Turkson et al. designed a STAT3 inhibitor, the SH2 domain-binding phosphopeptide PY*LKTK, based on the key structural features of the STAT3 protein. PY*LKTK can bind to STAT3 in a manner similar to the Tyr(P)-SH2 interaction, block STAT3 dimerization, and selectively inhibits STAT3 activation.[33] Subsequently, the first non-peptidic small-molecule STAT3 inhibitor, Stattic, was developed. Stattic was reported to inhibit both the activation and dimerization of STAT3 by selectively inhibiting the binding of tyrosine-phosphorylated peptides to the STAT3 SH2 domain.[34] Moreover, the orally available direct STAT3 inhibitor napabucasin (BBI608) was approved by the United States Food and Drug Administration (FDA) for the treatment of two cancers, including gastric/gastroesophageal junction (GEJ) cancer and pancreatic cancer in 2016. In 2017 and 2020, the FDA approved tocilizumab and WP1066, respectively, to reduce cytokine release syndrome (CRS) induced by chimeric antigen receptor T (CAR-T) cell therapy and to treat pediatric brain cancer. These results indicate that the STAT3 pathway is indispensable for treatment strategies against cancer in the past, present, and future.

3 | *STAT3* AS AN ONCOGENE

Oncogenes are regarded as the viral or mutated cellular genes that play a decisive role in tumor formation. Activated oncogenes, such as K-*ras* and *src*, inducing malignant transformation in tumor cells were found.[35,36] Generally, *STAT3* is considered an oncogene because of the following reasons.

Aberrant phosphorylation of STAT3 accumulates in nearly 70% of cancers, such as non-small cell lung cancer and breast tumor. In human breast tissues, the level of STAT3-binding activity was significantly higher in carcinomas than in normal and benign lesions.[37] And STAT3 expression is 10.6-fold higher in head and neck squamous cell carcinoma (HNSCC) tissues, compared to normal mucosa tissues derived from non-HNSCC patients, leading to that activated *STAT3* is regarded as an oncogene.[38–42]

In addition to STAT3 overexpression in tumor tissues, cells bearing the activated STAT3 were transformed to form tumors in nude mice. Bromberg et al. replaced the C-terminal loop with two cysteine residues in the SH2 domain of STAT3 to develop a STAT3 molecule (STAT3-C) that can dimerize spontaneously without tyrosine phosphorylation. After transfection of immortalized fibroblasts with STAT3-C, colonies were observed in soft agar, and tumors were present in nude mice 2–4 weeks after the injection of STAT3-C clones.[32]

Aberrantly, phosphorylated STAT3 is also involved in tumor formation, development, and metastasis, which would influence the clinical outcome of patients. Lin et al. obtained tumor samples from 90 patients with glioblastoma (GBM) to examine the association between p-STAT3 expression levels and patient outcomes. Patients with a large percentage of p-STAT3 positive tumor cells had shorter progression-free survival years and overall survival years. In this study, p-STAT3 expression was considered an independent prognostic indicator in the outcome of patients with GBM.[43] Fei et al. reported that high plasma STAT3 levels with the high programmed death ligand 1 (PD-L1) expression induced by STAT3 led to the worst overall survival in patients with diffuse large B-cell lymphoma.[44]

Moreover, STAT3 pathway inhibitors are reported to be effective in cancer treatment. In 2000, Song et al. proposed that targeting STAT3 can inhibit tumor growth through downregulating Bcl-xL expression to increase apoptosis of HNSCC cancer cells, which supports the view of *STAT3* as an oncogene.[45] Moreover, there is a significant correlation between downstream proteins regulated by STAT3 and lymph node metastasis, cancer stages, recurrence, and death in patients with lingual squamous cell carcinoma. Knocking down the upstream molecule of STAT3 or inhibiting STAT3 expression can decrease the growth and metastasis of HNSCC.[18,46,47] The enhancer of zeste homolog 2/STAT3 signaling is demonstrated to play a promoting role in chemoresistance and chemo-related adverse events in prostate cancer treatment. Targeting this signaling can significantly block the neuroendocrine differentiation in prostate cancer and inhibit the growth of chemoresistant cancer in vivo.[48,49] Collectively, the above studies provide evidence that the high expression level and constitutive activation of STAT3 in the TME are strongly associated with cancer formation and poor prognosis of patients.

However, some researchers hold the converse view that *STAT3* is an oncosuppressor. Kenichi Shinagawa et al. showed that the clinicopathological factors are significantly associated with IL-6 expression rather than STAT3 expression levels. The expression of IL-6 and STAT3 in 116 patients with oral squamous cell carcinoma (OSCC) were independent, and only high IL-6 expression significantly promoted vascular invasion and decreased the 5-year disease-free survival rate.[50] Moreover, STAT3-positive cells are associated with favorable outcomes in some cancers. High nuclear STAT3 levels were associated with a 72.4% overall survival rate in patients with HNSCC at 5 years, compared to 38.3% in the low nuclear STAT3-level group. High STAT3 expression may contribute to the early stages of tumor formation and development by inhibiting apoptosis of tumor cells.[51] Tissue microarray-based study of both node-negative and node-positive breast tumors showed that overexpression of phospho-STAT3 (Tyr705) improved the short-term survival and long-term survival of patients with breast tumor, which indicated a better prognosis of patients with STAT3 positive breast cancer.[52,53] Pencik et al. reported that the ARF–Mdm2–p53 tumor suppressor axis is regulated by STAT3, and loss of STAT3 signal transduction increases the risk of prostate cancer metastasis and recurrence in mouse models, indicating a poor outcome after treatment with IL-6/STAT3 inhibitors.[48,54]

4 | REGULATORS OF THE STAT3 PATHWAY

4.1 | Activation of STAT3

STAT family proteins were first reported in the last three decades as the transcription factors that are activated in a ligand-dependent manner and promote the rapid induction of gene expression.[55–57] It is reported that more than 40 different polypeptide ligands, including cytokines, JAK kinases, and growth factors, are associated with STAT phosphorylation. As one of the most important members of the STAT family, STAT3 is activated through tyrosine phosphorylation in response to epidermal growth factor (EGF) and IL-6 and others to play an important role in regulating cell proliferation, differentiation, and apoptosis after DNA binding.[57,58] Once activated by JAK, STAT3 molecules start dimerizing mainly via the SH2 domain with the help of TDAs to form the reciprocal pY-SH2 interactions. Then, phosphorylated STAT3 can translocate into the nucleus and bind to specific DNA to activate the downstream proteins gene expression.[56,59,60]

4.2 | Positive regulators

As a transcription factor, STAT3 is expressed in almost all types of cells and is tightly activated by upstream regulatory molecules under normal conditions. However, the continuous release of upstream molecules causes the constitutive activation of STAT3 in the TME (Figure 3). JAK/STAT pathway is an important oncogenic signaling cascade activated by multiple adaptor proteins such as IL-6, EGF, and IFN-γ.[61] Persistent activation of STAT3 induced by cytokines and growth factors is associated with cell proliferation, differentiation, and apoptosis in cancer.[62,63] IL-6 is expressed at the high levels in the TME by immune cells, tumor cells, and stromal cells and acts as both pro- and anti-inflammatory cytokine. IL-6 binds to IL-6R on the cell membrane and subsequently forms a protein complex with IL-6Rβ (gp130 receptor), mediates the activation of STAT3, and promotes tumorigenesis.[64–66] IL-6 signaling can also be mediated by a trans-signaling pathway, wherein the interaction of IL-6 with the secreted from IL-6R (sIL-6R) can form the IL-6–sIL-6R complex and subsequently bind to gp130.[67] Moreover, activated STAT3 can induce IL-6 expression to generate a positive-feedback loop for STAT3 overexpression. The JAK family contains four non-receptor tyrosine kinases (RTKs) including JAK1, JAK2, JAK3, and TYK2. Except JAK3 expressed in hematopoietic cells, others are widely expressed in various cells. With the engagement of gp130, JAK is activated to phosphorylate STAT3 subsequently.[68]

In addition to the IL-6/JAK/STAT3 pathway, the activation of EGFR, fibroblast growth factor receptor, C-X-C chemokine receptor (CXCR), G-protein coupled receptor, and B7-H3, as well as the stimulation with carcinogenic (areca nut extract) and others, can also cause STAT3 phosphorylation via the JAK/STAT3 pathway.[69–73] It was reported that other classes of non-receptor PTKs could stimulate STAT3 activation. The Src family of kinases, including Src, Lck, Hck, Lyn, Fyn, and Fgr can mediate STAT3 activation. Among them, viral Src was reported to induce constitutive STAT3 activation in a JAK-independent manner. Cellular Src tyrosine kinase was later demonstrated to be a positive regulator of STAT3 activation via stimulation with platelet-derived growth factor and ligand of the human EGFR family.[74–76] EGFR, a receptor PTK, is upregulated in most epithelial cancers, and EGFR signaling contributes to cancer cell proliferation and survival. Activated EGFR can directly interact with SH2 domains to phosphorylate STAT3. Moreover, treatment by targeting both EGFR and STAT3 was demonstrated to play an important role in EGFR–STAT3 feedback loop blockade and restriction of pancreatic cancer volume.[77]

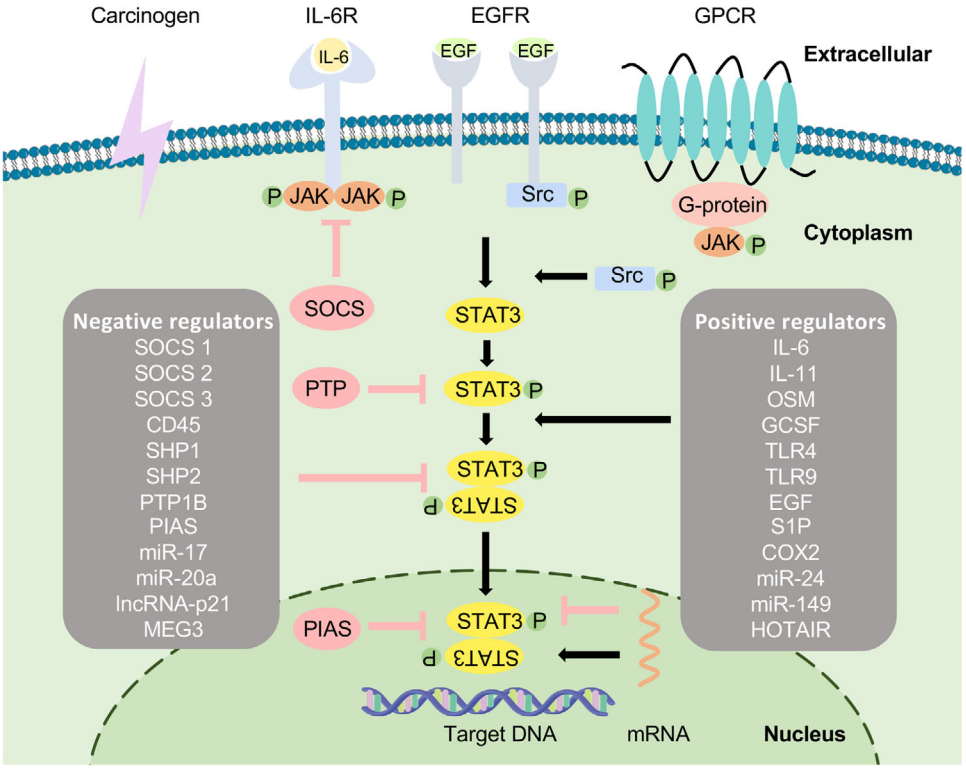

FIGURE 3 Schematic of pathways activating STAT3 signaling. Once cytokines and growth factors such as interleukin-6 (IL-6), epidermal growth factor (EGF) and G-proteins as positive regulators bind to their receptors, ligand-bound receptors undergo conformational changes and activate Janus kinase (JAK) family. STAT3 molecules are phosphorylated on Y705 by intracellular non-receptor tyrosine kinases (RTKs) such as JAK and RTKs such as EGF receptor, or STAT3 can also be activated directly by Src and Abl. While PTP, suppressor of cytokine signaling and protein inhibitor of activated STAT as the negative regulators can inhibit the activity of STAT3. The dimerization of two activated STAT3 molecules binding via SH2 domain enters the nucleus and then binds to target gene

Long non-coding RNAs (lncRNAs) with a length of more than 200 nucleotides can induce or reduce STAT3 expression.[78] MicroRNA (miRNA), as one of the non-coding endogenous RNA, can also induce or reduce STAT3 expression by regulating mRNA degradation or translational inhibition via binding to targeting mRNA molecules.[79,80] Plenty of studies have found that lncRNAs such as HOX Transcript Antisense RNA (HOTAIR), Gastric Cancer Associated Transcript 3 (GACAT3), Nuclear Paraspeckle Assembly Transcript 1(NEAT1), Forkhead Box D2 Adjacent Opposite Strand RNA 1 (FOXD2-AS1), and Inter-Alpha-Trypsin Inhibitor Heavy Chain 4 Antisense RNA 1 (ITIH4-AS1), as well as miRNAs including miR-24, miR-629, miR-149, miR-495-3p, and miR-34a can act as the positive regulators of the STAT3 pathway.[81–86]

4.3 | Negative regulators

STAT3 is temporarily activated and tightly regulated by negative regulators that can silence the STAT3 pathway in normal tissues. However, these negative regulators are inhibited in tumor cells. These negative regulators either block the STAT3 signaling pathway or directly act on the STAT3 protein and, thus, may inspire new ideas for cancer treatment (Figure 3).

Due to the significance of tyrosine phosphorylation in STAT3 activation, tyrosine phosphatases can negatively regulate STAT3.[87] The protein tyrosine phosphatase (PTP) family, which includes PTP receptor-type D (PTPRD), PTP receptor-type T, PTP receptor-type K, SH2-domain-containing PTP1 (SHP1), SHP2, PTP-non-receptor type 9, and T-cell PTP, is essential for the negative regulation of JAK-STAT3 signaling through STAT3 dephosphorylation.[88–93] Pertinently, PTPRD is downregulated in nasopharyngeal carcinoma (NPC), and PTPRD overexpression can promote the sensitivity of NPC cells to radiotherapy owing to STAT3 dephosphorylation.[94] Gupta et al. reported that morin-induced SHP1 expression abrogated the effect of STAT3 and promoted chemosensitization of HNSCC cells.[88]

The suppressor of cytokine signaling (SOCS) proteins family has eight members including SOCS 1–7 and cytokine-inducible SH2-containing protein. Each of them

inhibits STAT3 phosphorylation via different mechanisms: directly binding its kinase inhibitory region and SH2 domains to JAK kinase domain to block STAT3 phosphorylation; binding its SH2 domain to JAK-phosphorylated cytokine receptors to prevent STAT3 recruitment.[95] Considering SOCS1, Yoshikawa et al. showed that silencing of SOCS1 induced the constitutive activation of the JAK2/STAT3 pathway in hepatocellular carcinoma (HCC). The growth of SOCS1 restoration cancer was suppressed with the same efficacy as treatment with the JAK2 inhibitor AG490, which indicated the negative regulation of SOCS in the JAK/STAT3 pathway.[96] Moreover, SOCS1 expression inhibits the growth and metastasis of prostate cancer by decreasing levels of cyclins D1 and E and cyclin-dependent kinases (CDK) 2 and 4.[97]

Activated STAT3 is also regulated in the nucleus to regulate gene expression. It was reported that the protein inhibitor of activated STAT (PIAS) can bind to activated STAT dimers and prevent them from binding to DNA.[98] The most important negative regulator in the PIAS family is PIAS3, and many studies demonstrated that upregulation of PIAS3 expression can inhibit cell proliferation and increase drug chemosensitivity in various tumors.[99–101] Jiang et al. identified that JAK/STAT hyperactivation induced by SOCS3 and PIAS3 deficiency is associated with the development of early-stage myeloid-derived suppressor cells (eMDSCs) and immunosuppression in breast cancer.[102]

Moreover, various lncRNAs were demonstrated to induce the STAT3 gene expression and were downregulated in cancer tissues, which were associated with the tumor progression and poor prognosis. This negative correlation between STAT3 and specific lncRNAs indicated that lncRNAs could work as the negative regulators of STAT3 pathway.[103–105] It was reported that lncRNAs such as lncRNA-p21, MEG3, and PTCSC3, as well as miRNAs such as miR-548d-3p and miR-17 cluster family members, can directly target STAT3 and thereby regulate E-cadherin expression.[103,106–110]

5 | REGULATION OF CANCER HALLMARKS BY THE STAT3 PATHWAY

In 2000, Hanahan et al. proposed hallmarks of cancer, which contained six essential alterations inducing malignant cell growth.[111] Later in 2011, because of the advancement in cancer research, "energy metabolism" and "immune suppression" were also considered cancer hallmarks. A new generation of cancer hallmarks has been enumerated and includes "sustaining proliferative signaling," "evading growth suppressors," "avoiding immune destruction," "enabling replicative immortality," "tumor-promoting inflammation," "activating invasion and metastasis," "inducing angiogenesis," "genome instability and mutation," "resisting cell death," and "deregulating cellular energetics."[112] Recently, the number of cancer hallmarks increased from 10 to 14. "Unlocking phenotypic plasticity," "senescent cells," "non-mutational epigenetic reprogramming," and "polymorphic microbiomes" were considered as the emerging cancer hallmarks.[113] STAT3, as a multifunctional regulator in cancer formation, development, and metastasis, can influence all cancer hallmarks through the following five ways (Figure 4).

5.1 | Cell proliferation and apoptosis

Cancer is considered a cell cycle disease, and many studies suggest that connections between oncogenes and an abnormal cell cycle are caused by mutations or abnormalities in the expression of cyclins and cyclin-CDKs in a variety of cancers.[114–116] The activated cyclin-CDK complex formed by the binding of the cyclin box from cyclins with a well-conserved family of protein kinases regulates the progression of cells through the division cycle.[114] Cyclin D1 (CCND1) protein, which is one of the major isoforms of D-type cyclins, can interact with CDK4/6 and accelerate the progression of the cell cycle through the G1 phase. CCND1 was reported to be overexpressed and accumulated in association with p-STAT3 in gastric and oral cancer cells. Moreover, after treatment with STAT3 pathway inhibitors, cyclin expression was significantly reduced.[117,118] Luo et al. showed that upregulation of CCND1 by STAT3 enhanced the proliferation of gastric cancer cells. JAK/STAT3 blockade by AG490 could significantly decrease the CCND1 protein levels to inhibit cancer cells proliferation.[118] Yang et al. reported that icaritin can be used to inhibit OSCC cell proliferation via the regulation of the the STAT3 pathway.[119]

Additionally, the STAT3 pathway is reported to promote cell survival and inhibit apoptosis by modulating the apoptotic regulatory proteins including Bcl-2 family.[45,120] As regulator of programmed cell death, Bcl-2 family members are categorized into three subfamilies including prosurvival proteins, BH3-only proapoptotic proteins and multidomain proapoptotic proteins. Cell apoptosis can be evaluated through the expression ratio of proapoptotic to prosurvival factors.[121] Pro-survival proteins such as Bcl-X_L, Bcl-2, and MCL-1 are overexpressed in many cancers and contribute to tumor initiation, progression, and therapeutic resistance.[122–124] Catlett-Falcone et al. demonstrated that the growth and survival of multiple myeloma depended on IL-6 receptor signaling, which is associated with STAT3-induced Bcl-X_L expression. Consequently, blockade of gene regulation mediated by STAT3 could inhibit Bcl-X_L expression and induce apoptosis in cancer

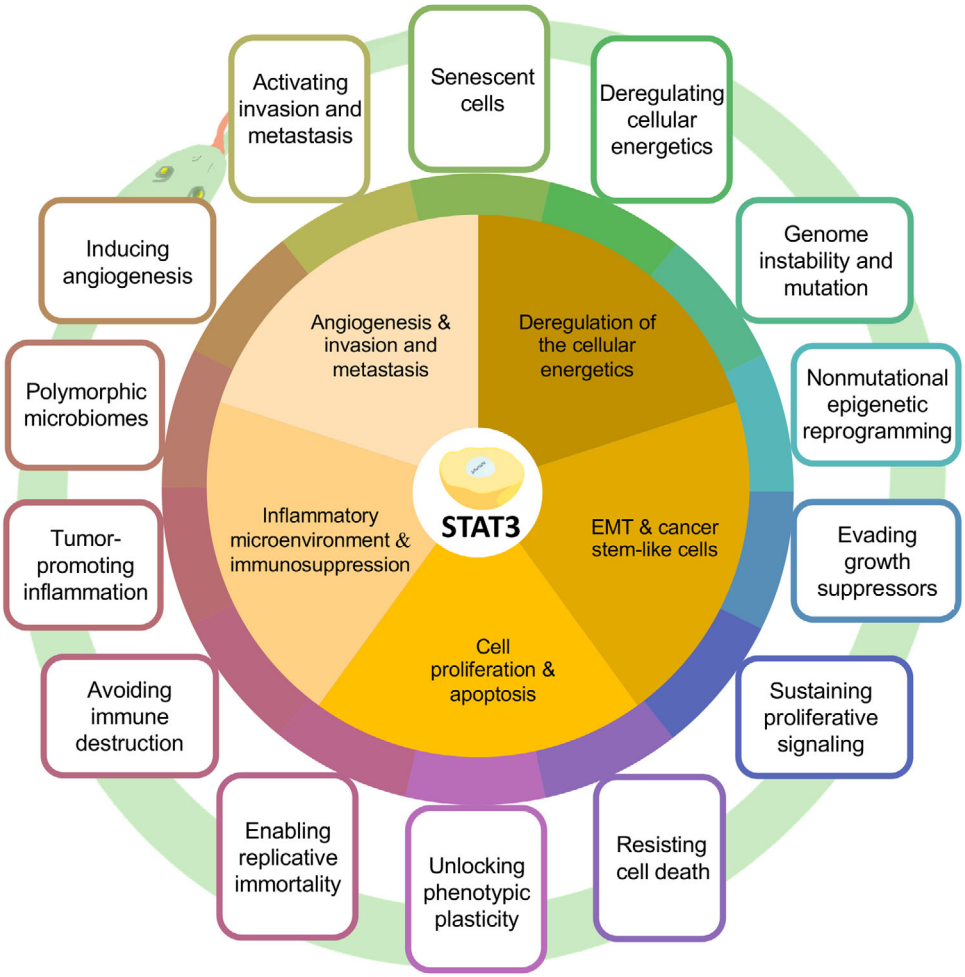

FIGURE 4 Schematic of the relationship between STAT3 and cancer hallmarks. STAT3 improve the representation of tumor hallmarks through the following five aspects: inflammatory microenvironment and immunosuppression; cell proliferation and apoptosis; epithelial-mesenchymal transition and cancer stem-like cells; deregulation of the cellular energetics; angiogenesis and invasion and metastasis

cells.[125] Oh et al. used licochalconce (LC) H for OSCC treatment, and their results showed that the JAK2/STAT3 pathway and STAT3 target genes such as Bcl-2 were suppressed by LCH, which caused the cell apoptosis and inhibited cell proliferation and colony formation in OSCC cells.[126]

In addition to cancer cells, STAT3 expression in senescent cancer-associated fibroblasts (CAFs) can improve the viability of cancer cells, which is associated with the senescence-associated secretory phenotype. Yasuda et al. demonstrated that the senescence of CAFs induced by pro-inflammatory cytokines was blocked after the treatment with JAK/STAT3 pathway inhibitors. The JAK/STAT3 inhibitor effectively blocks the peritoneal tumor formation in a mouse model.[127] Thus, constitutive activation of STAT3 can upregulate the expression of anti-apoptotic proteins and cyclins to regulate cell cycle, promote cell proliferation, and inhibit cell apoptosis.

5.2 | Chronic inflammatory microenvironment and immunosuppression

Tumors are also considered "wounds that do not heal," and many similarities can be found between the microenvironment of chronic inflammatory conditions and tumors. Chemokines and cytokines in TME interact with cancer cells.[20,128] Dynamic participants in the TME, including tumor-associated macrophages (TAMs), neutrophils, dendritic cells, and regulatory T-cells (Tregs) induce an immunosuppressive TME and enhance the evasion of tumor from immune surveillance, which are associated with cancer progression.[129–131] PD-L1, an immune checkpoint, plays an important role in delivering pro-survival signals to cancer cells to protect them from tumor-specific immunity.[132] The over-expressions of PD-L1 in cancer cells

and PD-1 in stromal cells were reported to be associated with the phosphorylation of STAT3, which demonstrated the immunosuppressive roles of the STAT3 pathway.[133] Xu et al. observed an effective cytotoxicity of natural killer (NK) cells after blockade of the IL-6/JAK/STAT3 pathway and PD-L1, which indicated that NK cell-mediated recognition and cytotoxicity against tumor cells were inhibited via STAT3 pathway-induced PD-L1 expression in tumor cells.[134] In addition to tumor cells, PD-L1 is also overexpressed via the STAT3 pathway on the surface of neutrophils with the engagement of PD-1 to block the activation of T-cells and NK cells. CAFs derived from HCC are reported to protect neutrophils from apoptosis and promote neutrophils activation via the IL-6/JAK/STAT3 pathway. Once activated, neutrophils inhibit T-cell immunity through the STAT3/PD-L1 axis.[135] Tumor-derived granulocyte colony stimulating factor (G-CSF) can also activate the STAT3 pathway in neutrophils and show pro-tumor effects involving dysfunction of NK cells via PD-L1/PD-1 interactions.[136]

Macrophages, which are regarded as the tissue sentinels, can eliminate or repair damaged cells and matrices to maintain tissue integrity. After the stimulation with different activation programs, macrophages are polarized into two different modes with their own metabolic functions, including M1-like macrophages that produce pro-inflammatory cytokines and M2-like macrophages that have anti-inflammatory and wound healing characteristics.[137] IL-6-dependent STAT3 activation induces M2 polarization while inhibiting M1 activation, and this promotes cancer progression and reduces patient survival.[138–140] Besides inducing M2 polarization, the STAT3 pathway also upregulates PD-L1 expression in cancer cells induced by TAMs. Zhang et al. conducted a study to demonstrate how TAMs suppress immune activation and promote the invasive capacity of cancer cells via the STAT3 pathway. The results showed that IFN-γ produced by TAMs enhances the constitutive activation of STAT3 in cancer cells, which is associated with PD-L1 expression.[141] Simultaneously, MDSCs play an immunosuppressive role in many cancers, and IL-10/STAT3 signaling in MDSCs suppresses $CD8^+$ T-cell proliferation and promotes the development of Tregs in tumors.[142–144]

Additionally, p-STAT3 in the TME can induce the production of IL-6, IL-10, and vascular endothelial growth factor (VEGF) and transform dendritic cells (DCs) into regulatory DCs that contribute to immune tolerance.[20,130,145] Kortylewski et al. ablated *STAT3* in hematopoietic cells of adult mice with the *Mx1-Cre-loxP* system via injection of poly(I:C), and the anti-tumor immunity was evaluated. The results showed that *STAT3* deletion in hematopoietic cells enhanced the ability of DCs to present antigens and activate T-cells, improved the ability of granulocytes and NKs to eliminate targeting tumor cells, increased T-cell responses to tumor antigens, and inhibited tumor growth in tumor-bearing mice.[146] Constitutive STAT3 activation decreases the expression of T-cell chemotactic factors (such as RANTES and IP-10) to inhibit T-cell chemotaxis. Further, S1PR1 promotes STAT3 activation in $CD4^+$ T-cell associated with Tregs accumulation at tumor sites.[147,148] However, some studies reported contradictory results. Hanna et al. showed that IL-10R/STAT3 pathway correlated with the accumulation of a PD-1^{int} $CD8^+$ T-cell subset, which plays an important role in tumor elimination, and the loss of IL-10R/STAT3 signaling enhanced the accumulation of functionally impaired PD-1^{hi} $CD8^+$ T-cells associated with the progression of tumors in a chronic lymphocytic leukemia model.[149] Taken together, constitutive activation of STAT3 regulates the adaptive immune response in the chronic inflammatory TME and mediates immunosuppression in cancers (Figure 5).

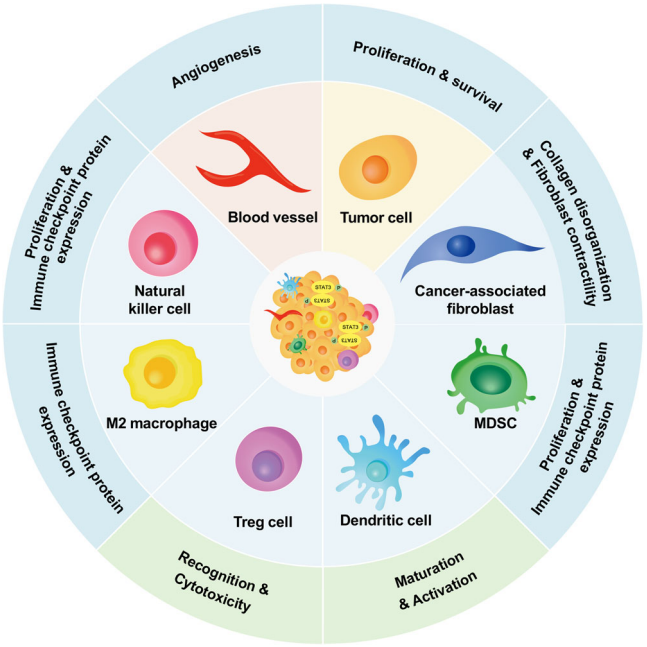

FIGURE 5 Schematic of STAT3 signaling in tumor microenvironment (TME). STAT3 activation has the ability in affecting TME via up- or downregulating downstream molecules and promoting tumor cell proliferation and survival, angiogenesis, immune evasion as the result. The functions of natural killer cell and dendritic cell in antigen presentation and target cell recognition are inhibited. While macrophage polarization toward M2-like endotype and the immune checkpoint expression and proliferation of myeloid-derived suppressor cell, cancer-associated fibroblasts, and regulatory T-cell are promoted by phosphorylated STAT3

5.3 | Angiogenesis, invasion, and metastasis

Angiogenesis, which refers to the formation of new blood vessels, is activated by hypoxia and nutrient deprivation to meet the metabolic demands, to remove the waste products from solid tumors, and is involved in initiation, progression, and metastasis of cancer.[150,151] Tumor angiogenesis is mediated by tumor-secreted angiogenic cytokines, growth factors, and integrins expressed both on angiogenic endothelium and tumor cells. Integrins can integrate signals between the extracellular matrix (ECM) and cellular and chemokines, such as CCL4, to coordinate the migration of circulating endothelial progenitor cells to the hypoxic area.[152] VEGF is associated with vascular development and is regarded as one of the most important factors for the induction of angiogenesis. VEGF can be activated by hypoxic TME and directly upregulated by constitutive activation of STAT3.[153,154] STAT3 directly regulates VEGF expression via its promoter, and mutations in the STAT3 binding site in the VEGF promoter abrogate this regulation.[153] VEGF expression can also be indirectly induced by the hypoxic TME through a STAT3/hypoxia-inducible factor 1 alpha (HIF-1α)-dependent pathway. Hypoxia-induced pSTAT3 accelerates the accumulation of HIF-1α protein and prolongs its half-life in solid tumor cells, which subsequently enhances VEGF expression.[155,156] The study by Liu et al. employing sulforaphane to block angiogenesis in HCC demonstrated this indirect mechanism. After sulforaphane treatment, the STAT3/HIF-1α/VEGF pathway was blocked and the angiogenesis and tumor growth were inhibited.[157] High expression levels of STAT3 and VEGF are also associated with lymph node involvement in esophageal squamous cell cancer, indicating that STAT3/VEGF pathway promotes cancer cell lymphatic metastasis and is correlated with pTNM stage.[158]

Moreover, ECM remodeling induced by matrix metalloproteinases (MMPs), which can degrade ECM components is also involved in tumor angiogenesis.[159] In normal tissues, the function of MMPs is counteracted by tissue inhibitors of metalloproteinases (TIMPs) to maintain the balance between angiogenic and anti-angiogenic effects. However, the effect of MMPs is increased in tumor tissues, which break this balance and promote angiogenesis by remodeling the basement membrane and promoting pericyte recruitment.[152,160] Overexpression of MMPs is also reported to be induced by pSTAT3. Considering MMP-9, Roy et al. identified the mechanisms by which A Disintegrin and Metalloproteinase domain-containing protein 12 (ADAM12) induces angiogenesis in breast cancer. The results showed that ADAM12-regulated angiogenesis was correlated with the upregulation of the proangiogenic factors including VEGF and MMP-9 and the anti-angiogenic factors including TIMP2. The silencing of ADAM12 inhibited STAT3 activation, which demonstrated that angiogenesis can be promoted by activating MMP-9 in a STAT3-dependent manner.[161] The elevated gene transcription of MMP-9 was demonstrated to be associated with activation of the STAT3 in tumor-associated myeloid cells.[162] Additionally, MMP overexpression contributes to cancer cell invasion and metastasis, and IL-8/STAT3 signaling in HNSCC can also upregulate the expression of MMP-2 and -9 and play a key role in cancer invasion and metastasis.[163,164] Further, the migration of endothelial cells (ECs) during angiogenesis can be facilitated with the help of MMP-2/9 overexpression. In addition to important features of STAT3 pathway-related angiogenesis including cell migration, invasion, and tube formation, constitutive activation of STAT3 in CAFs and tumor cells can regulate collagen fibrogenesis and collagen disorganization and fibroblast contractility resulting in increased cancer invasion and metastasis.[20,165,166] Thus, constitutive activation of STAT3 promotes angiogenesis, invasion, and metastasis of cancer cells.

5.4 | Epithelial-mesenchymal transition (EMT) and cancer stem-like cells (CSCs)

EMT is a general phenomenon observed in embryonic development, tissue remodeling, and wound repair. However, the loss of intracellular adhesion and the transition from an epithelial to the mesenchymal phenotype are correlated with tumor progression and can be observed in cancer lesion area by the loss of E-cadherin and gain of vimentin, N-cadherin, and fibronectin.[167,168] In cancer tissues, the unlocking of the phenotypic plasticity of cancer cells concurs with EMT, and the EMT-related regulators including STAT3 are associated with cancer cell dedifferentiation.[169] Studies have demonstrated that downstream of STAT3, estrogen-regulated zinc transporter LIV-1, miR-21, IL-6, HIF, and VEGFR2 can repress E-cadherin and modulate EMT in many cancers.[170–174] Dysregulation of the STAT3 pathway in CAFs in pancreatic ductal adenocarcinoma (PDAC) samples was reported to be associated with transforming growth factor beta 1 secretion and the significant single-cell population shifts toward EMT, leading to the aggressive behavior of PDAC.[175]

CSCs are a heterogeneous population of cancer cells that play an important role in cell self-renewal and differentiation. CSCs are associated with tumor regeneration and metastasis and are considered indicators for the prognosis of patients with cancer.[176–178] Activation of the STAT3-dependent pathways including the STAT3/FAK/ERK

pathway, STAT3/Oct-4 pathway in various cancer cells, and the IL-8/STAT3 pathway and EGFR/STAT3/Sox-2 pathways in TAMs are shown to contribute to the cancer stemness.[179–182] Moreover, a link between EMT and CSCs is demonstrated.[183,184] The CSCs are associated with EMT exhibit and maintain EMT after cancer treatment. EMT phenotypes promote the metastatic proliferation of CSCs among cancer cells. This is crucial for treatment resistance and occurrence, progression, and recurrence of various tumor types.[151,185] STAT3 pathway is reported to regulate the EMT and CSC in cancer development. Oncostatin M (OSM), a crucial inducer of JAK/STAT3 pathway activation, promotes EMT and generates cells with CSC properties in a STAT3-dependent manner.[186,187] To further explore the mechanism by which the OSM/STAT3 pathway induces EMT and CSCs, Junk et al. infected epithelial/non-CSCs with retroviruses encoding shSMAD2, SMAD3, SMAD4 to inhibit SMAD proteins. SMAD3 knockdown significantly reduced mesenchymal/CSC expansion, compared to other treatment groups, which implicated the OSM/JAK/STAT3/SMAD3 pathway in EMT induction and CSCs generation.[188] Recent studies also demonstrated that STAT3 activation is involved in cisplatin chemotherapy resistance through the STAT3/Snail pathway, which is associated with the EMT-like phenotype and stem-like properties acquisition. Besides, resistance to 5-fluorouracil, temozolomide, and sorafenib treatment is also related to the enrichment of CSCs caused by p-STAT3 upregulation.[189–193] Thus, activated STAT3 can promote EMT and maintain the stemness of cancer stem cells, thereby affecting the prognosis of patients with cancer.

5.5 | Deregulation of the cellular energetics

Cancer cells convert pyruvate into lactate irrespective of the presence of oxygen via aerobic glycolysis, also known as the "Warburg effect," and metabolism in cancer cells can accelerate adenosine triphosphate (ATP) synthesis and maintain rapid cell proliferation.[194] An increased glycolytic rate and concomitant limitation of the tricarboxylic acid cycle (TCA cycle), even in the presence of completely functional mitochondria and sufficient oxygen, typify the Warburg effect.[195,196] The mechanism underlying the Warburg effect and its association with cancer cell proliferation is not fully understood, but the STAT3 pathway is demonstrated to contribute to Warburg's vicious circle. Studies show that STAT3 activation is associated with the M2 isozyme of pyruvate kinase (PKM2)/HIF-1α positive feedback loop and promotes proliferation of many types of cancer cells, such as human HCC cells, breast cancer cells, and colorectal cancer cells. PKM2 is typically present in tumor cells and can be activated by HIF-1α in response to oxygen deprivation, cytokines, and oncogenes in the TME. Activated PKM2 can promote HIF gene transcription and STAT3 activation, and pSTAT3 can induce the expression of HIF-1α and MEK5 and, thereby, enhance the Warburg effect.[197–201] The expression of hexokinase 2 (HK2), which is accelerated by the STAT3 pathway, is also involved in the Warburg effect. Pu et al. showed that circCUL3 was upregulated in gastric cancer tissues and activated HK2 expression by targeting the miR-515-5p/STAT3 pathway. The results demonstrated molecular interactions between activated STAT3 and HK2.[202] Thus, STAT3 signaling promotes the Warburg effect in cancer tissues by upregulating downstream glycolytic proteins; it also promotes cancer cell proliferation related to glycolysis through mechanisms that are not completely understood.

6 | STAT3 AS A THERAPEUTIC TARGET IN CANCER TREATMENT

Considering that aberrantly activated STAT3 is characteristic of cancer formation, progression, and metastasis, recent studies highlighted the effectiveness of blocking STAT3 signaling in cancer treatment (Table 1). In general, constitutive activation of STAT3 signaling can be disrupted by the following mechanisms: (1) indirect STAT3 inhibition by targeting upstream molecules, including IL-6, EGFR, and JAK; (2) direct STAT3 inhibition by blocking dimerization, preventing target gene transcription, or decreasing total STAT3 expression (Figure 6).

6.1 | Targeting the STAT3 pathway for cancer treatment

6.1.1 | Targeting upstream receptors

Targeting JAK

JAKs are the key activator of the STAT3 pathway. The JAK/STAT pathway is activated by various cytokines, and many JAK inhibitors focus on the potential treatment of chronic inflammatory disorders and CRS.[262–264] The efficacy and safety of several JAK inhibitors are evaluated in clinical trials. Additionally, some orally available, ATP-competitive, small-molecule JAK inhibitors are considered for treating solid tumors.[265]

Lestaurtinib (CEP-701), the "first generation" FMS-like tyrosine kinase-3 (FLT3) inhibitor that also inhibits JAK2, is reported to inhibit the growth and migration of cancer cells and prevent colony formation of various cancer,

TABLE 1 Inhibitors targeting signal transducer and activator of transcription 3 (STAT3) in cancers

Inhibitor	Target	Type	Cancer type	Clinical trials
Inhibitors targeting upstream receptors				
Dasatinib[203–208]	Src	Small molecule	Breast cancer, head and neck squamous cell carcinoma (HNSCC), leukemia, non-small-cell lung carcinoma (NSCLC), prostate cancer	NCT00924352 NCT00826449 NCT02744768 NCT00385580
Cetuximab[209–213]	Epidermal growth factor receptor	Antibody	Colorectal cancer, HNSCC	NCT02928224 NCT02164916 NCT02358031
AZD1480[214,215]	Janus kinase (JAK)	Small molecule	HNSCC, colorectal cancer	-
Ruxolitinib[216–218]	JAK	Small molecule	Breast cancer, pancreatic cancer, NSCLC	NCT01423604 NCT01594216 NCT02155465
Tofacitinib[219]	JAK	Small molecule	Lymphocytic leukemia	-
8αTGH	JAK	Natural compound	HNSCC	-
Curcumin[221,222]	JAK	Natural compound	Lung cancer, HNSCC, breast cancer	NCT01160302 NCT01740323
WP1066[223–225]	JAK	Small molecule	HNSCC, gastric cancer, melanoma	-
Tocilizumab[226–228]	IL-6R	Antibody	HNSCC, breast cancer, lymphocytic leukemia	NCT03135171 NCT02906371
Siltuximab[229,230]	IL-6R	Antibody	Prostate cancer, NSCLC	NCT00433446 NCT00841191
Bazedoxifene[231]	IL-6R	Small molecule	Pancreatic cancer	-
Metformin[232,233]	IL-6R	Small molecule	HNSCC, ovarian cancer, breast cancer	NCT01579812 NCT01340300
Inhibitors blocking STAT3 dimerization				
S3I-M2001[234]	SH2	Peptidomimetic	Breast cancer	-
S3I-201[235–237]	SH2	Small molecule	AdCC, HNSCC, ASCC	-
STA-21[238]	SH2	Small molecule	Breast cancer	-
Stattic[239]	SH2	Small molecule	Nasopharyngeal carcinoma	-
OPB-51602[240–242]	SH2	Small molecule	Hematological malignancie, refractory solid malignancies	NCT01344876 NCT01184807
OPB-111077[243]	SH2	Small molecule	Hepatocellular carcinoma (HCC), acute myeloid leukemia	NCT01711034 NCT03197714
TTI-101[244,245]	SH2	Small molecule	HCC, HNSCC	-
CJ-1383[246]	SH2	Small molecule	Breast cancer	-
Inhibitors targeting STAT3 DNA-binding domain (DBD)				
STAT3 decoy[247,248]	DBD	Oligodeoxynucleotides (ODNs)	HNSCC, NSCLC	NCT00696176
G-quartet ODN[249,250]	DBD	ODNs	HNSCC, NSCLC	-
InS3-54A18[251]	DBD	Small molecule	Lung cancer, breast cancer	-
InS3-54[252]	DBD	Small molecule	NSCLC, breast cancer	-
BBI608[253–255]	DBD	Small molecule	Colorectal cancer, gastric cancer, glioblastoma	NCT01830621 NCT02315534 NCT02178956
MMPP[256,257]	DBD	Small molecule	NSCLC, ovarian cancer	-

(Continues)

TABLE 1 (Continued)

Inhibitor	Target	Type	Cancer type	Clinical trials
Inhibitors decreasing STAT3 expression				
AZD9150[258,259]	STAT3 mRNA	Antisense oligonucleotides	Lymphoma, lung cancer, HCC HNSCC	NCT01839604 NCT01563302 NCT03394144 NCT02549651
MiR-124-3p[260]	STAT3 mRNA	MicroRNA	Nasopharyngeal carcinoma	-
SD-36[261]	STAT3 protein	Small molecule	Lymphocytic leukemia	-

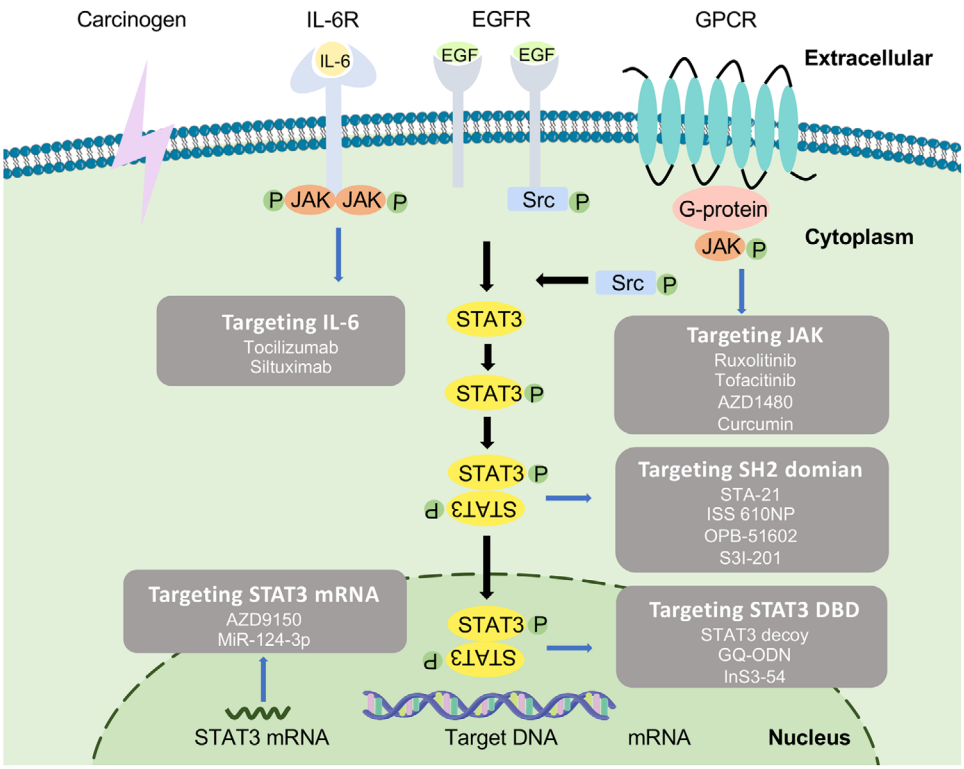

FIGURE 6 Schematic of STAT3 signaling inhibitors. The principle of STAT3 inhibitors in tumor treatment is based on targeting upstream proteins of the STAT3 signaling or directly targeting STAT3; inhibition of upstream cytokine such as IL-6 and tyrosine kinases JAK with small-molecule inhibitors and natural compound such as tocilizumab, siltuximab, curcumin, ruxolitinib. As for inhibiting STAT3 in direct way, NH2-terminal, DNA-binding and SH2 domains can be targeted with OPB-51602, S3I-201, STAT3 decoy, G-quartet oligodeoxynucleotide, AZD9150. Negative regulators of STAT3 can also play a role as STAT3 inhibitors (Figure 3)

including anaplastic thyroid cancer, human neuroblastomas, and mutated acute myeloid leukemia (AML).[266–268] However, Knapper et al. conducted a prospective randomized assessment to evaluate the efficacy of lestaurtinib administered after each cycle of chemotherapy in FLT3-AML treatment. The results showed that, compared to chemotherapy alone, the combination therapy of lestaurtinib and chemotherapy with concomitant anti-fungal prophylaxis promoted survival, while no other statistically significant clinical benefit was reported, indicating that lestaurtinib may not be the optimal drug for further AML clinical trials.[269]

Sen et al. showed that AZD1480 abrogated STAT3 phosphorylation induced by IL-6 and exhibited anti-tumor activity in HPV-HNSCC in vivo mouse model (in two patient-derived HNSCC xenograft models, the tumor volume derived from Patient 1 in the AZD1480 administration group was less than 1/2 compared with the vehicle treatment group).[214] Although AZD1480 is demonstrated to have a potential anti-cancer effect, its adverse events in clinical administration remain a problem. In a Phase 1 clinical trial, dose-limiting toxicities were observed after the administration of AZD1480 in patients with solid tumors.[270]

As a small-molecule inhibitor of JAK2 phosphorylation, WP1066 shows highly anti-tumor effectiveness in the treatment of AML, melanoma, and bladder cancer. Besides, WP1066 could improve the chemo-sensitivity in various tumor models.[271–273] For instance, WP1066 sensitizes OSCC cells to cisplatin by targeting the STAT3/miR-21 axis. Zhang et al. reported that after the combination of WP1066 and cisplatin in the treatment of Tca8113/DDP xenograft tumor models, the growth rate was significantly less than the untreated group.[223] Liu et al. demonstrated that AG490 plays a suppressing role in angiogenesis and reducing MDSCs in TME of HNSCC by inhibiting the JAK2/STAT3 pathway.[274]

Ruxolitinib (INC424) is an FDA-approved drug that targets JAK1/2 to treat inflammatory diseases. Although it is not approved for cancer treatment by FDA, clinical trials have been conducted. Dao et al. conducted a Phase II study of ruxolitinib to test its safety and efficacy in the treatment of chronic neutrophilic leukemia and atypical chronic myeloid leukemia. It was well-tolerated, with an overall hematologic response rate of 32% among treated patients.[275]

Natural compounds have also been reported to suppress JAK/STAT3 pathway.[276] Chen et al. introduced a betulinic acid derivative, SH479, which can target the JAK/STAT3 pathway to inhibit arthritis.[277] Lee et al. demonstrated the function of arctiin in abrogating JAK and Src activation as well as inhibiting the constitutive activation of pSTAT3.[278] Pouyfung et al. showed that 8α-tigloyloxyhirsutinolide-13-O-acetate (8αTGH), a compound from *Vernonia cinerea*, has anti-tumor activity in an HNSCC mouse model through inhibiting the JAK/STAT3 pathway.[220] JAK inhibitors were mainly designed for autoimmune dysfunction treatment. Although some of them demonstrated anti-tumor utility, the results of clinical trials for cancer treatment were still modest. Further studies using JAK inhibitors in combination therapies may provide more promising results.

Targeting IL-6 and IL-6R

As mentioned, IL-6 is an inflammatory cytokine that activates the JAK1 and JAK2 pathways, leading to STAT3 phosphorylation. IL-6 is elevated in the serum of cancer patients and has diagnostic and/or prognostic significance.[64,65] The blockade of IL-6 activity by IL-6 and IL-6R neutralizing antibodies is already used to treat rheumatoid arthritis (RA).[279] Moreover, it was reported that tocilizumab, an IL-6R blocking antibody that is FDA-approved for RA treatment, can sensitize tumor cells to radiation and overcome erlotinib resistance. Tocilizumab in combination with erlotinib is used to treat SQ20B xenograft tumor models. After 40 days of combination therapy, the survival rate of mice was 40%, compared with 0%, in the erlotinib only group, which suggests that this combinatorial approach may improve the treatment response and survival rate of patients.[226,280]

Siltuximab (CNTO-328) is a monoclonal antibody that can specifically target IL-6 and prevent its binding to IL-6R. IL-6 is upregulated in cholangiocarcinoma and non-small cell lung cancer, and treatment with siltuximab alters the IL-6/STAT3 pathway and suppresses the growth and invasion of tumor.[281,282] The results of Phase I/II and II clinical trials conducted by Angevin et al. and Coward et al., respectively, indicated that siltuximab was safe in ovarian and Kirsten rat sarcoma-2-mutant cancers treatment.[283,284] However, these several clinical trials of siltuximab in treating patients with cancer was still in their early stage such as Phases I or II due to the adverse events during the cancer treatment. For instance, in a Phase II trial that evaluated mitoxantrone/prednisone with or without siltuximab in prostate cancer treatment, the combination group presented higher percentages of patients with severe adverse events, grade P3 adverse events. Three patients in the combination-treated group were dead due to siltuximab side effects.[285] Although siltuximab was regarded as a promising drug in cancer treatment, the way to reduce adverse events associated with siltuximab still need to be explored.

6.1.2 | Targeting STAT3 directly

Blocking dimerization

SH2 domains recognize and bind to select phosphotyrosine residues on receptors and other proteins to form the multiprotein complexes and mediate the intracellular protein–protein interactions.[286] There are two ways to inhibit STAT3 directly by targeting SH2: blocking the recruitment of activated RTKs or non-receptor kinases that phosphorylate Tyr705 of STAT3 to the plasma membrane and blocking the dimerization of two activated STAT3 molecules. Two types of inhibitors, including peptides and small molecules targeting the SH2 domain of STAT3, have been reported to reduce the tumor cells proliferation.[286,287]

Peptidomimetic inhibitors, which are designed via amino acid residues in a STAT3 structure-based manner, can directly interact with the SH2 domain. PY*LKTK can form inactive STAT3:PY*LKTK complexes and effectively reduces levels of active STAT3:STAT3 dimers in vivo.[33] ISS 610, which is based on PY*L, was reported to induce the apoptosis of STAT3-dependent transformed cancer cells without affecting normal cells. S3I-M2001, an oxazole-based peptidomimetic, can inhibit the growth of tumors in mice with breast cancer.[234,288] Ac-pTyr-Leu-Pro-Gln-Thr-Val-NH2, BP-PM6, BP-PM7, and PMM-172 are all STAT3 inhibitors that target the SH2 domain to reduce

constitutive STAT3 phosphorylation in cancer cells such as HNSCC and breast cancer cells.[289–291]

Non-peptidic small-molecule inhibitors also block STAT3 activation. Genini et al. investigated the mechanism by which OPB-51602 interferes with STAT3 function in cancer cells. Binding of OPB-51602 to the SH2 domain disrupts intradomain interactions and promotes STAT3 aggregation, and this causes mitochondrial dysfunction and ultimately leads to cancer cell death.[240] Kim et al. assessed another inhibitor targeting the SH2 domain of STAT3 called ODZ10117. It can inhibit tyrosine phosphorylation and STAT3 dimerization and thereby reduce tumor growth and lung metastasis in patients with breast cancer.[292] Song et al. identified STA-21 as the best-match small-molecule inhibitor targeting the SH2 domain of STAT3 among nearly 429,000 compounds selected through serial functional evaluation based on their established cell-based assays. The breast cancer-bearing mouse was used to evaluate its anti-tumor effect, and STAT3 phosphorylation and dimerization were presented to be abrogated.[238] Moreover, studies have shown that STA-21 treatment can inhibit cell growth, induce apoptosis in bladder cancer cell lines, and improve psoriasis lesions.[293,294] Schust et al. introduced a small-molecule inhibitor of STAT3 activation and dimerization called Stattic, which also targets the SH2 domain. Stattic treatment with 10 μM resulted in the apoptosis of approximately 18% of STAT3-dependent MDA-MB-435S breast cancer cells.[34] Chen et al. reported a novel small-molecule inhibitor, N4, which can bind to the SH2 of STAT3 and abolish p-STAT3 (Tyr705). N4 suppresses tumor growth and metastasis in animal models of pancreatic cancer. After 20 days of treatment with 20 μM/kg N4 in pancreatic cancer-bearing mice, the tumor weights of the mice were significantly lower than those of the control group ($p < 0.0001$, $n = 6$).[295] Wang et al. reported that HJC0152, designed as an O-alkylamino-tethered derivative of niclosamide, can inhibit p-STAT3 (Tyr705) and decrease the invasion and migration ability of HNSCC cells.[296] LY5 was designed as a small-molecule inhibitor that blocks the phosphotyrosine-binding site of the SH2 domain at nanomolar concentrations. However, Yu et al. showed that the anti-tumor effects of LY5 were not due to the inhibition of STAT3 phosphorylation.[297] Bu et al. found that S3I-201 reduced MDSCs and improved CSC eradication, which enhanced the efficacy of conventional chemotherapy in an HNSCC mouse model. Six weeks after treatment with S3I-201 in this mouse model, tumor growth was significantly reduced, compared to that in the PBS control group ($p < 0.001$, $n = 6$). Further research has shown that S3I-201 can inhibit STAT3 activation and thereby impair cancer cell proliferation and immunosuppression without appreciable side effects in a mouse model of HPV-negative anal squamous cell carcinoma.[236,237,298]

Targeting the STAT3 *DBD*

As mentioned previously, the function of activated STAT3 in cancer cell proliferation, migration, and invasion relies on the physical interaction between the DBD and DNA after translocation into the nucleus. Inhibitors targeting the STAT3 DBD may also decrease STAT3 activity by disrupting its binding to the target DNA.[299] Previously, the DBD of STAT3 was considered undruggable because of its potentially limited selectivity.[300] Turkson et al. reported that platinum-containing compounds can selectively block STAT3, and it has been shown that platinum (IV)-containing complexes, CPA-1 and CPA-7, disrupt the DNA-binding capacity of STAT3 and induce tumor regression.[301] Recently, a novel small-molecule lead compound called (E)-2-methoxy-4-(3-(4-methoxyphenyl)prop-1-en-1-yl)phenol (MMPP) was synthesized by Son et al., and it can suppress cancer growth by directly interacting with the DBD of STAT3.[256] Compared to the bioactive compound (E)-2,4-bis(p-hydroxyphenyl)-2-butenal (BHPB), which was synthesized previously, MMPP circumvented the problem caused by the presence of α, β-unsaturated carbonyl groups in BHPB that form a non-selective covalent bond, which is conducive to side effects.[256,302] Leong et al. showed that the using of a STAT3 decoy is an alternative approach for targeting the activated STAT3. Treatment of HNSCC cells with the STAT3 decoy suppresses cancer cells growth and STAT3-mediated gene expression.[247] Moreover, the decoy can also block STAT3 activation in vivo, induce apoptosis, and decrease the proliferation of HNSCC cells. After treatment with the STAT3 decoy combined with cisplatin for 10 days in an HNSCC xenograft model, there was a 7.4-fold increase in the number of apoptotic cells compared to that in the control group ($p = 0.002$).[303] Jing et al. developed a series of G-quartet oligodeoxynucleotides (GQ-ODNs) as STAT3 inhibitors that can block its DNA-binding activity. Treatment with GQ-ODN plus paclitaxel in nude mice with HNSCC tumors over 21 days showed potent efficacy. The mean tumor size decreased by 35%, compared to the 9.4-fold increase in the untreated control group.[250]

Decreasing STAT3 expression

Antisense oligonucleotides (ASOs) can selectively inhibit the translation of STAT3 mRNA by binding to single-stranded RNA sequences in a complementary fashion.[304,305] Li et al. showed that treatment with a specific 2-O-methoxyethyl-modified ASOs, used to knock down STAT3 expression in HCC cells can decrease circulating VEGF, reduce neovascularization, and inhibit

metastasis and growth of cancer cells.[306] Oweida et al. demonstrated that treatment with STAT3 ASOs in combination with radiotherapy can increase the anti-tumor effect and decrease radioresistance. After treatment for LY2 and MOC2 tumor-bearing mice with STAT3 ASOs and radiation, the average tumor volumes were 53.0 (5.6) mm^3 and 254.8 (81.6) mm,^{3} respectively, compared to 277.4 (53.8) mm^3 and 1042.9 (326.8) mm^3 in mice treated with STAT3 ASOs alone.[307] AZD9150, a second-generation ASO, inhibited STAT3 expression and downstream signaling targets by reducing STAT3 mRNA in lymphoma and lung cancer models.[258] Treatment with AZD9150 combined with cisplatin in mice can significantly sensitize tumors to cisplatin and improve the survival rate, compared to treatment with either agent alone, which demonstrates a potential clinical benefit to overcome chemoresistance in HNSCC.[259] Moreover, in addition to ASOs, miR-124-3p was reported to downregulate the transcription of STAT3 by interfering with its 3′untranslated region, and this was associated with apoptosis of NPC cells as well as inhibition of proliferation, migration, and invasion.[260]

6.2 | STAT3 pathway inhibitors in clinical trials against cancer

To date, several STAT3 pathway inhibitors are approved by the FDA for clinical cancer treatment. However, various other STAT3 pathway inhibitors have been used in clinical trials. As mentioned above, lestaurtinib (NCT00557193), AZD1480, ruxolitinib (NCT02092324), and siltuximab have been evaluated for their safety and anti-tumor effects in cancer treatment in clinical trials.[269,270,275,283,308,309] EGFR, an activator of the STAT3 pathway, is targeted in clinical trials. Cetuximab is a monoclonal antibody against EGFR that can inhibit STAT3 activation. Carter et al. conducted a Phase 1 trial (NCT01445405) to explore the effect of bortezomib and cetuximab in combination with radiation therapy for advanced HNSCC. The median progression-free survival of patients treated with combination therapies was just 4.8 months, which indicated limited anti-tumor efficacy.[310] However, a Phase 2 trial (NCT00084318) showed that delivery of postoperative chemoradiotherapy (using cisplatin or docetaxel) with cetuximab for HNSCC treatment achieved 69% and 79% 2-year overall survival and 57% and 66% 2-year disease-free survival.[311]

Besides the inhibitors of STAT3 pathway activators, including JAK, IL-6, and EGFR, the results of drugs directly targeting STAT3 in early-phase clinical trials demonstrated their potential in clinical use. Grandis et al. conducted an early Phase 0 trial (NCT00696176) of a STAT3 decoy for HNSCC treatment, and results demonstrated that none of the patients suffered Grade 3/4 or dose-limiting toxicities. Moreover, patients with HNSCC received intratumoral injections of the STAT3 decoy before surgery, and levels of STAT3 target genes, including cyclin D1 and Bcl-XL, were reduced, compared to those in the control group (saline).[312] Owing to the promising anti-tumor effect of AZD9150 in preclinical studies, Hong et al. conducted a Phase I dose-escalation clinical trial. A total of 25 patients with lymphoma and lung cancer was included in this study; 5% of them experienced drug-related adverse events, and 11 of the 25 evaluated patients had stable disease or partial response. Moreover, three of six patients had refractory diffuse large B-cell lymphoma (DLBCL), and two presented with a durable partial response.[258] Subsequently, AZD9150 was demonstrated to be well-tolerated, and four of 30 patients with DLBCL achieved a response for at least 4 months associated with a 13% of clinical benefit rate in a Phase 1b clinical trial (NCT01563302).[313] In 2016, BBI608, a small molecule that directly targets the STAT3 DBD to inhibit STAT3 activation, was approved by the FDA for GEJ and pancreatic cancer treatment. Later, Jonker et al. conducted a Phase III clinical trial (NCT01830621) to test the efficacy of BBI608 for the treatment of refractory advanced colorectal cancer, and the results showed that BBI608 can prolong overall survival to 5.1 months in patients with pSTAT3-positive tumors, compared to 3 months in the placebo group.[253]

6.3 | Drug delivery systems for STAT3 inhibitors

In cancer therapy, STAT3 inhibitors play a significant role in improving anti-tumor efficacy and can augment conventional chemotherapeutic effects.[314,315] However, conventional STAT3 inhibitors have some limitations, including the lack of anti-tumor effects, low selectivity, and high toxicity. To overcome these barriers, many studies have introduced novel drug delivery systems for STAT3 inhibitors to overcome these limitations. In nanomaterial-based drug delivery systems, STAT3 inhibitors described above are encapsulated into nanomaterials including biomimetic materials, liposomes, polymers, and inorganic materials (Table 2). Compared to the conventional STAT3 inhibitors, nanomaterial-based drug delivery systems have the following advantages: (1) biocompatibility and tumor targeting that reduce cytotoxicity to normal tissues; (2) efficient drug-loading capacity that can be used as a carrier for more than one drug; and (3) protection of loaded drugs from clearance during blood circulation.[316,317]

Liposomes, which are cell membrane-like structures, have an efficient drug-loading ability as well as biocompatibility; hydrophobic drugs can be readily loaded inside the

TABLE 2 Drug delivery system of STAT3 inhibitors in cancer treatment

Material	Drug	Delivery routes	Cells/Tissues Specificity	Ref
Liposomes	Curcumin-loaded liposomes-STAT3 siRNA	Intratumoral administration	Skin cancer	318
	Hyaluronic acid/TN-CCLP	Intravenous administration	Breast cancer	319
	Rop-DPRL and calorie restriction	Intraperitoneal injection	Melanoma	320
	Stattic	–	Melanoma cells	321
Polymers	Gel- NSC74859-ICG	Intravenous administration	HNSCC	322
	Ritonavir derivative	Intravenous administration	HNSCC	323
	Cucurbitacin-D; doxorubicin	Intravenous administration	Breast cancer	324
	HA/^{siSTAT3}PPL$_{PTX}$	Intravenous administration	Breast cancer	325
Biomimetic material	Exo-JSI124	Intranasal delivery	Glioblastoma tumor	326
	Tumor-derived exosomes- miR-34a	–	Colorectal cancer cells	327
	Corosolic acid-long-circulating liposomes-αCD163	–	Tumor-associated macrophages	328
	NPs-αIL6R Ab-CD44	Intravenous administration	Breast cancer	329
	CaP-cored low-density lipoprotein nanovehicle-STAT3 decoy ODNs	Intravenous administration	HCC cells	330
Inorganic material	AuNP-NUAP-STAT3d	–	HNSCC cells	331
	AIRISE-02(STAT3 siRNA-CpG-mesoporous silica nanoparticle)	Intratumoral administration	Breast cancer	332
	Layer-by-layer assembled gold nanoparticles-STAT3 siRNA -imatinib	Intratumoral administration	Melanoma	333
	SPION-TMC-ChT-TAT-H NPs	Intravenous administration	Colorectal cancer	334

lipid bilayer membranes.[335] Shi et al. designed a calcium phosphate-cored low-density lipoprotein nanovehicle as a Trojan horse to load STAT3 decoy ODNs to overcome tumor necrosis factor-related apoptosis-inducing ligand resistance.[330] Wu et al. introduced PEGylated liposomal FLLL32, a specific STAT3 inhibitor that binds to the SH2 domain. It enhanced anti-tumor efficacy and reduced toxicity through intravenous administration in treating pancreatic cancer.[336] Exosomes that are liposomes with antigens, mRNAs, and miRNAs derived from various cells are promising vehicles for cancer treatment to overcome the tumor barrier to drug delivery. Zhuang et al. introduced a non-invasive method to deliver a STAT3 inhibitor loaded into exosomes via an intranasal route. This inhibitor can be taken up by microglial cells, and it can prolong the survival time of GL26 tumor-bearing mice to 44.5 days, compared to the control group.[326]

Zheng et al. introduced poly lactic-co-glycolic acid (PLGA) nanoparticles to co-deliver the cancer drug doxorubicin (Dox) and the STAT3 inhibitor nifurate (DNNPs) and achieve long-term drug release. After 2 h of treatment with DNNPs, the fluorescence intensity of Dox, which reflected DNNP uptake by BGC-823 gastric tumors in mice, was approximately three-fold that of the Dox control group ($p < 0.001$).[337] Tavares et al. introduced HPMA-based copolymers containing cucurbitacin-D (CuD), a STAT3 inhibitor, and Dox. In this drug delivery system, CuD can be released in a sustained, controlled manner and can effectively target breast cancer. After treatment with linear-CuD in combination with micellar-Dox in 4T1 tumor-bearing mice, the tumor volume decreased significantly, compared to that in the linear-CuD control group.[324] Additionally, drug delivery systems introduced by Lavasanifar and colleagues including PEO-b-P(CL-JSI-124) conjugates, the PLGA-JSI-124 conjugate, PEO-b-PBCL micelles are demonstrated to be efficacy in cancer treatment.[338–340]

In addition to enhancing the anti-tumor efficacy of STAT3 inhibitors through different drug delivery systems. STAT3 inhibitors can also be combined with other therapies to enhance the efficacy and safety of tumor treatment strategies. The immune checkpoint protein blockade is a promising immunotherapy for cancer treatment. However, resistance to durvalumab (the anti-PD-L1 antibody) and tremelimumab (the anti-CTLA4 antibody) associated with STK11 gene mutations is reported in non-small-cell lung carcinoma (NSCLC) treatment, and this has impacted the efficacy of immune blockade. It was demonstrated that

STAT3 ASOs reversed this resistance, and STAT3 ASOs administration in combination with immune checkpoint blockade significantly enhanced the anti-tumor efficacy, compared to immunotherapy alone.[341]

CAR-T cell therapy is a novel immunotherapy that demonstrated excellent efficacy in the treatment of hematological malignancies. However, overexpression of cytokines, such as IL-6 and IL-10, caused by STAT3 hyperactivation is associated with the occurrence of CRS. Therefore, treatment with the STAT3 signaling pathway inhibitor tocilizumab in combination with CAR-T cell therapy can reduce adverse events without impeding CAR-T cell expansion.[342] Guha et al. demonstrated that STAT3 inhibitors of liver-associated MDSCs (STATTIC or BBI608) can enhance the anti-tumor efficacy of CAR-T cells. In the murine liver metastasis model, STAT3 inhibition did not decrease CAR-T cell cytotoxicity nor cause the death of CAR-T cells, and apoptosis of tumor cells dose-dependently increased, compared to the control group.[343] Because STAT3 is associated with upregulation of PD-L1 expression, STAT3 inhibitors play a role in immunotherapy, and STAT3 inhibition combined with photothermal therapy based on gelatinase-sensitive gelatin nanoparticles was reported to enhance anti-tumor efficacy in HNSCC cancer treatment.[133] On the 15th day after combination therapy, levels of immunosuppressive MDSCs and PD-1 in the blood, tumor, and spleen were significantly reduced, and the growth of tumor volume was limited in the *Tgfbr1/Pten* double conditional knockout (2cKO) mice model, compared to the untreated group.[322]

As mentioned, STAT3 inhibitors loaded into organic materials, inorganic materials, and unique biomimetic materials have demonstrated great tumor-targeting, biocompatibility, and anti-tumor efficacy.

7 | CONCLUSION AND PERSPECTIVES

The STAT3 pathway plays a physiological role in normal cell growth, differentiation, and survival. Meanwhile, as the "Achilles' heel" of many cancers, owing to the association of constitutive STAT3 activation with cancer hallmarks as well as the relationship between STAT3 pathway and poor patient outcomes, many researchers believe that STAT3 acts as an oncogene and that blockade of STAT3 activity is a viable strategy for cancer treatment. Additionally, based on clinical trial results, various STAT3 inhibitors are well-tolerated and potentially improve the overall survival of patients with cancer.

Despite improvements in STAT3 targeting therapeutics, the conventional view is that STAT3 is "undruggable" owing to its ubiquitous expression. Only a few clinically available STAT3 inhibitors for cancer treatment are approved by the FDA, and there are several concerns that remain worthy of attention and consideration. First, STAT3 inhibitors should not affect the functions of structurally similar proteins, such as STAT1, and the side effects of STAT3 inhibitors, including hematologic toxicity, are still major problems to be addressed. Further efforts should be made to clarify the mechanisms of selectivity for STAT3 inhibition and to explore the novel delivery of STAT3 inhibitors to reduce toxicity, increase local concentrations, enhance cellular internalization, and achieve long-term release. Second, the development of STAT3 inhibitors is focused on STAT3:STAT3 dimerization, which is a dilemma because of the lack of a reliable off-target biomarker. Thus, in addition to the SH2 domain, further research should explore the targeting of other STAT3 domains. Recently, with the development of purchasable chemical databases and computer-aided drug discovery, the undruggable STAT3–DNA interface is targeted via artificial intelligence, which can virtually screen (VS) billions of molecular structures.[344] For example, inS3-54, an inhibitor of STAT3 that targets its DBD, was designed via a VS of 200,000 compounds that excluded molecules predicted to bind STAT1. Moreover, to prevent off-target side effects, inS3-54 analogs were searched in the virtual Chemdiv database, and analog A18 was demonstrated to specifically bind to the DBD of STAT3 and inhibit its activity.[251,252] Third, the drug delivery system and the combination of STAT3 inhibitors with other anti-tumor therapies can greatly enhance cancer treatment. For instance, STAT3 inhibitors in combination with CAR-T cell therapy can reduce adverse events, STAT3 inhibitors loaded into nanocarriers have enhanced serum stability to promote anti-cancer efficacy, and STAT3 inhibitors in combination with radiation can overcome radiotherapy resistance. In summary, with the progress of research on STAT3 pathway and advances in clinical trials of STAT3 inhibitors, the significance of STAT3 pathway in anti-tumor activity is evident. In the future, multimodal delivery of drugs targeting STAT3 pathway and other conventional therapies could be a promising strategy for cancer treatment.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ETHICS STATEMENT

No ethical approval was required for this study.

AUTHOR CONTRIBUTION

L.L.B., L.L.C., and B.L. conceived the idea; H.Q.W., Q.W.M., and F.Y.H. performed the literature search and drafted the manuscript; X.G., H.L., S.R.L., J.W., F.C.S., Y.S. revised and edited the manuscript; L.L.B., L.L.C., and B.L. supervised and revised the manuscript. The authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Not applicable.

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