

Negative regulators of STAT3 signaling pathway in cancers

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Abstract: STAT3 is the most ubiquitous member of the STAT family and involved in many biological processes, such as cell proliferation, differentiation, and apoptosis. Mounting evidence has revealed that STAT3 is aberrantly activated in many malignant tumors and plays a critical role in cancer progression. STAT3 is usually regarded as an effective molecular target for cancer treatment, and abolishing the STAT3 activity may diminish tumor growth and metastasis. Recent studies have shown that negative regulators of STAT3 signaling such as PIAS, SOCS, and PTP, can effectively retard tumor progression. However, PIAS, SOCS, and PTP have also been reported to correlate with tumor malignancy, and their biological function in tumorigenesis and antitumor therapy are somewhat controversial. In this review, we summarize actual knowledge on the negative regulators of STAT3 in tumors, and focus on the potential role of PIAS, SOCS, and PTP in cancer treatment. Furthermore, we also outline the STAT3 inhibitors that have entered clinical trials. Targeting STAT3 seems to be a promising strategy in cancer therapy.

Keywords: cancer, STAT3 signaling, PIAS, SOCS, PTP, negative regulators

Introduction

STAT protein family members, including STAT1, STAT2, STAT3, STAT4, STAT5 (STAT5A and STAT5B), and STAT6, are important transducers of many cytokines and growth factors.¹ Of the seven members of the STAT protein family, STAT3 is the most common, and is constitutively activated or overexpressed in approximately 70% of human solid and hematological tumors compared with normal tissue.² STAT3 is activated by phosphorylation to form a homodimer and then translocates to the nucleus. The nuclear homodimer recognizes and binds to STAT3-specific DNA-binding elements that can regulate the expression of target genes associated with cell growth, proliferation, differentiation, apoptosis, and immunoresponse.³ Aberrant activation of STAT3 can induce malignant cell transformation and is associated with poor prognosis of some tumors.⁴⁻¹⁰ It has been reported that disruption of constitutively activated STAT3 can suppress tumor-cell growth and promote cell apoptosis, and the STAT3-signaling pathway has become an attractive target for cancer therapy.^{4-7,11} Therefore, great efforts have been made to discover new selective inhibitors targeting STAT3 signaling. Recent studies have shown that several negative regulators of STAT3 signaling, including PIAS, SOCS, and PTP, can effectively prevent cancer progression (Figure 1).¹²⁻¹⁷ However, these negative regulators have also been reported to correlate with tumor malignancy, and their biological functions in tumorigenesis and antitumor therapy are somewhat controversial. Here, we review actual knowledge on PIAS, SOCS, and PTP in cancer and

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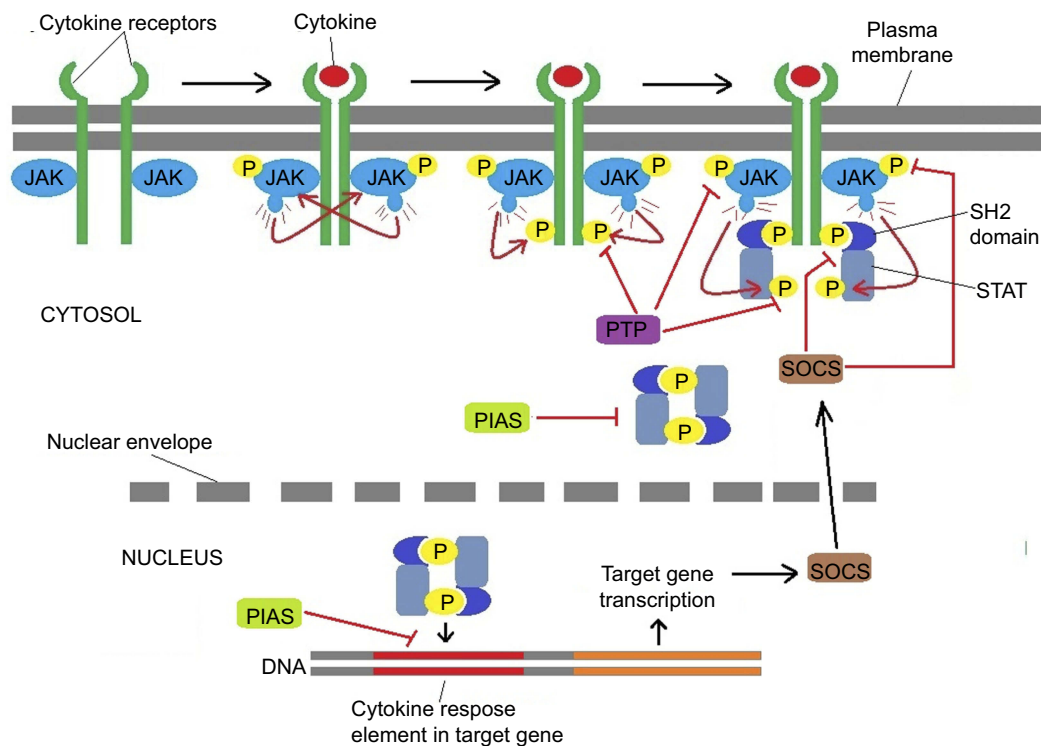


Figure 1 The negative regulators of JAK-STAT signaling. Binding of the ligand to cytokine receptor induces receptor dimerization and activation of receptor associated JAK kinase, which in turn phosphorylates STAT proteins. After forming a homodimer, STAT proteins translocate to the nucleus to control gene expression. Negative regulation of the JAK-STAT pathway is provided by PTPs, SOCS and PIAS proteins.

summarize the STAT3 inhibitors that have entered clinical trials, in order to evaluate the role of targeting STAT3 in cancer therapy.

Protein inhibitor of activated STAT (PIAS) family

There are four PIAS genes in mammals: *PIAS1*, *PIAS2*, *PIAS3*, and *PIAS4*. These genes share 40% of sequence homology and a similar domain organization, and the protein corresponding to each gene has a Zn-binding ring-finger domain in the central portion (Figure 2).¹⁸ PIAS proteins were initially identified as inhibitors of STAT transcription factors (Figure 1),^{19,20} but in fact they can regulate a broader range of biological processes, including nuclear trafficking and DNA-damage repair by interacting with other transcription factors, such as NF- κ B and p53.²¹ PIAS proteins may regulate transcription through several mechanisms (Figure 1), eg, blocking the DNA-binding activity of transcription factors, recruiting transcriptional co-repressors, and promoting protein SUMOylation.²² It has been reported that PIAS proteins can bind to activated STAT dimers and prevent them from binding DNA (Figure 1). PIAS1 and PIAS3 bind to STAT1 and STAT3, respectively, and inhibit transcriptional activity of STAT1 and STAT3.^{19,20}

A basal amount of PIAS3 has been shown to exist in the nucleus in most normal human epithelial and endothelial cells.²³ Due to the inhibitory effect of PIAS3 on STAT3 activation, downregulation of PIAS3 expression may play a critical role in cancer development. As a matter of fact, many studies have demonstrated that PIAS3 expression is reduced in various cancers.^{24–27} For example, PIAS3 mRNA is undetectable in most lymphoma cells, and absence of PIAS3 partly contributes to the high levels of activated STAT3 in these cells.²⁴ The PIAS3 protein is also absent in most lung squamous-cell carcinoma (SCC).¹² Moreover, the association of low PIAS3 expression with increased STAT3 activation has been found in malignant mesothelioma.²⁷ Lastly, it has been shown that there is reduced PIAS3 expression in glioblastoma tissue that can promote glioblastoma-cell proliferation.^{25,26}

In contrast, a lot of studies have demonstrated that upregulation of PIAS3 expression can inhibit cell proliferation and increase drug chemosensitivity in various tumors. Inhibition of constitutively activated STAT3 by curcumin attenuates tumor-cell growth by upregulating PIAS3 in ovarian and endometrial cancer cells.¹³ Overexpression of PIAS3 contributes to suppression of lung cancer-cell growth and restores drug chemosensitivity.^{28–30} In prostate

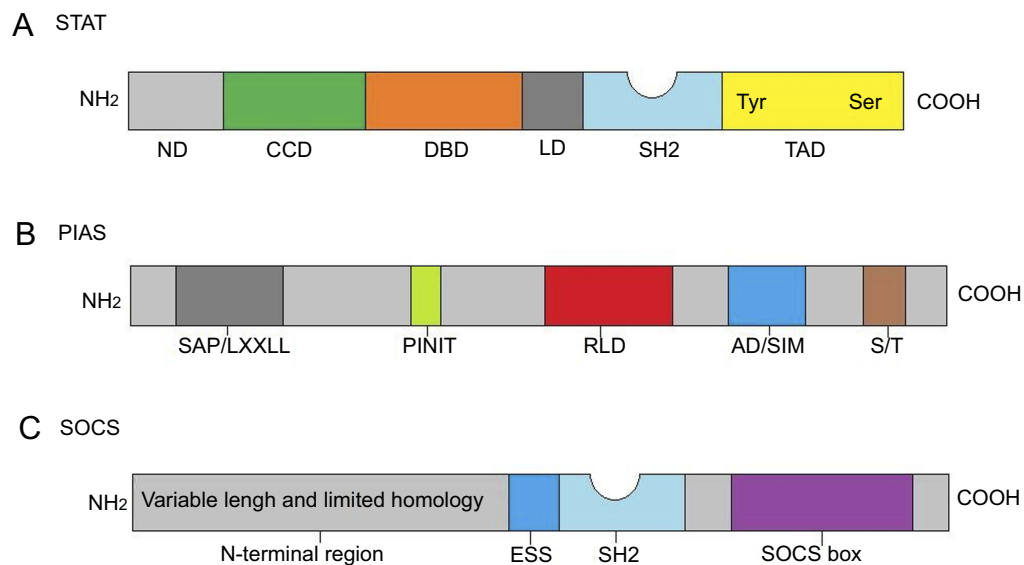


Figure 2 Structure characteristics of STATs, PIAS and SOCS. **(A)** Structure of STAT. ND, N domain; CCD, coiled coil domain; DBD, DNA-binding domain; LD, linker domain; SH2, Src homology 2 domain; TAD, transactivation domain. **(B)** The domain structure of PIAS proteins. SAP/LXXLL, SAF (scaffold attachment factor A and B) -A/B, Acinus and PIAS domain (it can recognize and bind to AT-rich DNA sequences), Within the SAP domain, there is a conserved LXXLL (it mediates interactions between nuclear receptors and their co-regulators) signature motif; PINIT, Pro-Ile-Asn-Ile-Thr motif (a highly conserved region of PIAS proteins and it may be involved in the nuclear retention of PIAS3); RLD, RING finger-like zinc binding domain; AD/SIM, acidic domain (AD), Within the AD, there is a putative SUMO1 interaction motif (SIM) in all PIASs except PIASy; S/T, serine-threonine rich region (in all PIASs except PIASy). **(C)** Structure of SOCS proteins. All eight members are characterized by their N-terminal region with variable length and limited homology, an extended SH2 domain (ESS), a central SH2 domain and a conserved SOCS box at the C-terminus.

cancer, overexpression of PIAS3 induces cancer-cell apoptosis both in vitro and in nude mice.³¹ In addition, PIAS3 overexpression can reduce STAT3 transcription and inhibit glioblastoma-cell proliferation.²⁶ All these findings indicate that PIAS3 may be an attractive candidate for targeting the JAK–STAT signaling pathway and restoring sensitivity to chemotherapeutic drugs in cancer therapy.

However, overexpression of PIAS genes has also been observed in some cancers.^{23,32} *PIAS1* is overexpressed in human prostate cancer, and enhances cancer-cell growth through inhibition of p21.^{33,34} High *PIAS1* expression is associated with adverse patient outcomes in multiple myeloma.³⁵ Additionally, *PIAS3* is overexpressed in colorectal cancer.³⁶ The mechanism of the PIAS proteins promoting tumorigenesis may be related to their SUMO-ligase activity. Through SUMOylation, PIAS proteins can interact with several tumor suppressors and oncogenes including *TP53*, *PML*, *AKT*, *MYC*, and *FAK*.³⁶ This field needs to be further explored in the near future.

In conclusion, the biological function of PIAS in tumorigenesis and antitumor therapy is somewhat controversial. Therefore, much more detailed genetic and functional analyses of PIAS should be performed to clarify the inconsistencies and thus better to understand the role of PIAS in cancer therapy.

Suppressor of cytokine–signaling proteins

The mammalian SOCS family consists of eight members: SOCS1–7 and the cytokine-inducible SH2-containing protein. They all are negative-feedback regulators of the JAK–STAT signaling pathway.³⁷ Structures of SOCS family members are characterized by an N-terminal region of variable length and limited homology, a central SH2 domain, and a conserved SOCS box at the C-terminus (Figure 2).³⁸ SOCS proteins inhibit JAK–STAT signaling by mechanisms (Figure 1) of blocking STAT recruitment to the cytokine receptor by shielding the STAT-binding sites of the receptor, binding to JAKs and inhibiting their kinase activities, and targeting receptor proteins or JAKs for proteosomal degradation via ubiquitination.^{39,40} A positive correlation has been proven between SOCS dysregulation and tumor progression. Several members of the SOCS family have been identified as tumor suppressors, and dysregulation of their biological roles in controlling cytokine and growth-factor signaling may contribute to the development of many human cancers.^{41,42}

SOCS1, SOCS2, and tumors

Hypermethylation and silencing of SOCS1 have been commonly reported in various kinds of tumors, including

cervical cancer, esophageal SCC (ESCC), hepatocellular carcinoma, breast cancer, ovarian cancer, glioblastoma multiforme, acute myeloid leukemia, and chronic myeloid leukemia.^{43–49} Methylation of SOCS1-promoter CpG islands contributes to the transformation of liver cirrhosis to hepatocellular carcinoma.⁵⁰ The *SOCS1* gene has been found to be frequently mutated in both classical Hodgkin's lymphoma and primary mediastinal B-cell lymphoma.^{51,52} Restoration of *SOCS1* gene expression suppresses cell growth in acute myeloid leukemia,⁵³ breast cancer,⁵⁴ ovarian cancer, and hepatocellular carcinoma.^{46,55} Hypermethylation of *SOCS1* is reversed to an unmethylated state during chronic myeloid leukemia patients' remission phase.⁴⁹ In gastric cancer, loss of the SOCS1 protein is involved in tumor progression and lymph-node metastasis.⁵⁶ Spontaneous colorectal cancer is also found in SOCS1-knockout mice.⁵⁷ In addition, SOCS1 expression is correlated with the clinical stages of some tumors. The SOCS1 level at stages II–IV is lower than at stage I in colorectal tumors. Meanwhile, the SOCS1 protein is highly expressed in well-differentiated adenocarcinomas.⁵⁸ High mRNA levels of SOCS1 are also associated with early tumor stages, and can improve clinical outcomes in breast cancer.⁵⁹ Breast cancer patients with positive SOCS1 expression exhibit decreased incidence of detectable circulating tumor cells in peripheral blood.⁶⁰ In glioblastoma multiforme, hypermethylation-mediated silencing of SOCS1 enhances tumor radioresistance.⁴⁷

In light of these findings, SOCS1 displays a role as a tumor suppressor in most tumors through inhibiting tumor proliferation and invasion, as well as reducing the sensitivity of tumor cells to cytokines or hormones. Molecular mechanisms underlying the antiproliferative effect of SOCS1 on tumor cells are inhibition of JAK–STAT3 and other signaling pathways. In non-small-cell lung cancer, SOCS1 presents its potent antiproliferative effects through blockage of the JAK–STAT signaling and FAK-dependent signaling pathways.⁶¹ SOCS1 also exerts its growth-inhibitory function through downregulation of cyclin D1, CDK2, and CDK4 in prostate cancer.⁶² In addition, SOCS1 has been reported to inhibit the invasion and migration of colorectal cancer by preventing epithelial–mesenchymal transition and promotes mesenchymal–epithelial transition by increasing E-cadherin and decreasing ZEB1 observed in cell cultures and mouse-xenograft models.⁶³

Similarly, hypermethylation of SOCS2 has been detected in ovarian cancer.⁴⁶ SOCS2 CpG islands were found to be hypermethylated in 14% of primary ovarian cancers, but not in normal tissue. Furthermore, high SOCS2 expression is closely associated with favorable prognosis in primary breast cancer, and survival time also shows an evident positive correlation with SOCS2 expression in breast cancer patients.⁶⁴

SOCS3 and tumors

In various human cancers, reduced expression or silencing of SOCS3 is associated with constitutive STAT3 activation,¹⁵ and hyperactivation of STAT3 can contribute to tumorigenesis by inducing multiple tumor-promoting genes.⁶⁵ Hypermethylation of SOCS3 is mostly found in head-and-neck cancer,⁶⁶ lung cancer,⁶⁷ glioma,⁶⁸ cholangiocarcinoma,⁶⁹ prostate cancer (but not in benign prostate hyperplasia),⁷⁰ Barrett esophagus carcinoma, and ulcerative colitis-related colorectal cancer.^{71,72} Reduced SOCS3 expression has been detected in human malignant melanoma.⁷³ In hepatocellular carcinoma, level of SOCS3 expression is inversely correlated with STAT3 activation.⁷⁴ Loss of SOCS3 activates STAT3, promotes cell proliferation, and leads to enhanced hepatitis-induced hepatocarcinogenesis.⁷⁵ Moreover, restoration or upregulation of SOCS3 expression can suppress tumor growth and metastasis in some malignancies.^{76–78} For example, exogenous SOCS3 can inhibit cell growth and enhance cell sensitivity to radiotherapy in human non-small-cell lung cancer.⁷⁹ The antitumor mechanism of SOCS3 may involve its negative regulation of the JAK–STAT and other signaling pathways.^{80–82} In prostate cancer, SOCS3 antagonizes the proliferative and migratory effects of FGF2 by inhibiting p44/p42 MAPK signaling.⁸⁰ Other studies have also demonstrated that SOCS3 can inhibit the proliferation of mesothelioma cells via multiple signaling pathways, including JAK–STAT3, ERK, Fak, and p53.⁸¹ In addition, SOCS3 has also been found to inhibit inflammation-associated tumorigenesis in the colon through both STAT3 and NFκB pathways.⁸²

SOCS4, SOCS5, and tumors

Some studies have proven that SOCS4 can suppress tumor growth.^{59,83–85} In human breast cancer, SOCS4 expression is inversely associated with TNM stage, and high SOCS4 expression predicts a favorable prognosis.⁵⁹ Meanwhile, an inverse relationship between SOCS4 and EGFR expression

has also been found in aggressive hepatocellular carcinoma.⁸³ Compared with noncancerous gastric tissues, gastric cancer elicits much lower SOCS4 expression, accompanied by hypermethylation of SOCS4-promoter CpG sites.⁸⁴ Moreover, in vivo studies using several mouse models have demonstrated that SOCS4 is able to suppress tumors derived from epithelial cells and that RUNX1 mediates repression of the SOCS4 promoter to reduce SOCS4 level and increase STAT3 activity, thereby promoting tumor development.⁸⁵

Similarly to SOCS4, SOCS5 is also able to suppress tumor development.^{43,86,87} SOCS5 expression is higher in normal human cervical tissue than in neighboring cervical tumors.⁴³ Significant reduction of SOCS5 is detected in the thyroid-gland cancer tissue than normal tissue,⁸⁶ and exogenous SOCS5 in the highly aggressive anaplastic thyroid cancer cells can reduce or abolish phosphorylation of the STAT3 protein and activation of the PI3K–AKT pathway, which can cause an altered balance between proapoptotic and antiapoptotic molecules and increase sensitivity to chemotherapeutic drugs.⁸⁷

SOCS6, SOCS7, and tumors

SOCS6 has also been reported to be downregulated in many cancers.^{88–92} Moreover, exogenous or upregulated SOCS6 can inhibit cancer-cell growth in gastric cancer, prostate cancer, medulloblastoma, glioblastoma, and cervical cancer.^{88,90,93,94} The role of SOCS6 in tumor suppression is associated with cKit (SCF receptor). The abnormality of SCF–cKit signaling is closely related to certain tumors.⁹⁵ SOCS6 can interact with cKit via its SH2 domain, which suppresses cKit-dependent pathways.⁹⁶ Overexpression of SOCS6 in a Ba/F3-Kit cell line causes a decrease in SCF-dependent cell proliferation and a parallel reduction in ERK1, ERK2, and p38 signaling.⁹⁷

Few data are currently available with regard to the tumor-suppression activity of SOCS7. SOCS7 is downregulated in colon cancer.⁹⁸ On the other hand, increased expression of SOCS7 can reduce aggressive ability of prostate cancer cells by blocking activation of the JAK–STAT3 pathway.⁹⁹ Importantly, high levels of SOCS7 predict good disease-free survival and overall survival in breast cancers.⁵⁹

Upregulated expression of SOCSs in tumors

Many SOCS types are considered tumor suppressors, and upregulation or activation of these proteins is associated with the inhibition or suppression of many malignant tumors. However, SOCSs are also upregulated in some tumors. Constitutive expression of SOCS1 has been

detected in chronic myeloid leukemia and correlates with poor response to IFN treatment.¹⁰⁰ Expression of SOCS2 is significantly higher in papillary thyroid cancer than in patients with benign disease.¹⁰¹ Additionally, expression of SOCS3 is significantly elevated in human breast cancer.¹⁰² In the human melanoma cell line 1286, constitutive SOCS3 can stimulate tumor-cell growth.¹⁰³ Increased SOCS in tumors can contribute to tumor development, and that is possibly mediated by its negative control of other SOCSs that normally suppress tumor development. For instance, in patients with active acromegaly and colonic polyps, SOCS2 is significantly increased, which causes a reduction in SOCS1 expression and leads to elevated STAT5B levels and consequently exaggerated GH-mediated proliferation of colonic epithelial cells.¹⁰⁴

As such, it is suggested that increased expression of SOCS proteins may be a consequence rather than a cause of their antitumor activities. Tumor cells are sustained by several cytokines that can activate JAK–STAT signaling and other molecules to support cell proliferation and survival within the tumor microenvironment. Dysregulation of oncogene expression and function, as well as any other loss of function changes in negative regulation of the JAK–STAT pathway, may overwhelm the capacity of SOCS proteins to inhibit JAK–STAT signaling activation. Therefore, the inhibitory action of SOCS proteins may not have a significant impact on proliferation and survival of tumor cells, even if they are overexpressed.

Protein tyrosine phosphatases

Protein phosphorylation and dephosphorylation occur mainly at tyrosine residues and are catalyzed by PTKs and PTPs, respectively. Tyrosine phosphorylation of STAT3 by specific PTKs is critical for its activation. Therefore, PTPs are very important in the negative regulation of STAT3 activity. There are seven types of PTPs targeting STAT3 (Figure 1): PTPRD, PTPRT, PTPRK, SHP1, SHP2, PTPN9, and TC-PTP.²

Protein tyrosine phosphatase receptor-type D (PTPRD) and tumors

PTPRD belongs to the highly conserved family of receptor PTPs. Capable of interacting directly with STAT3, it negatively regulates STAT3-mediated signaling and thus functions as a tumor suppressor.^{105–107} The *PTPRD* gene is frequently inactivated in a number of cancers, such as glioblastoma multiforme, colon cancer, breast cancer, neuroblastoma, lung

cancer, and SCC.^{105,106,108–113} Loss of *PTPRD* enhances the tumor-forming capacity of immortalized human astrocytes in mouse-xenograft models.¹⁰⁵ Heterologous loss of *PTPRD* leads to a significant increase in STAT3 phosphorylation and expression of the STAT3 target genes within glioblastoma multiforme.¹⁰⁶ Loss-of-function mutations in *PTPRD* also promote cell growth and phosphorylation of STAT3 (Y705) in head-and-neck SCC cells.¹¹² Interestingly, head-and-neck SCC cells with a *PTPRD* mutation are more sensitive to a STAT3 inhibitor, providing an important clue to treatment of head-and-neck SCC patients.¹¹² Additionally, exogenous *PTPRD* significantly decreases tumor-cell proliferation and induces increased apoptosis in *PTPRD*-deficient primary melanoma cells.¹¹¹

Protein tyrosine phosphatase–receptor type T and tumors

PTPRT is also a member of the PTP-receptor family. Like *PTPRD*, *PTPRT* can act as a tumor suppressor, mainly through inhibition of STAT3 signaling via directly dephosphorylating STAT3 at Y705.^{114,115} *PTPRT* is inactivated by mutations in many cancers, including colorectal cancer, lung cancer, gastric cancer, and head-and-neck SCC.^{114–117} It has been reported that *PTPRT* mutations enhance STAT3 activation and promote cell survival in head-and-neck SCC.¹¹⁷ Many human tumors exhibit aberrant hypermethylation of the *PTPRT* promoter, which is associated with decreased expression of *PTPRT*.¹¹⁸ Reduction in *PTPRT* correlates with an increase in phosphorylated STAT3 and sensitivity to STAT3 inhibition in head-and-neck SCC.¹¹⁸ Therefore, it is possible that *PTPRT* hypermethylation can function as a biomarker for evaluating the efficacy of STAT3 inhibitors against cancer.

Protein tyrosine phosphatase–receptor type K and tumors

PTPRK is another member of the PTP-receptor family. In 2015, Chen et al firstly reported that *PTPRK* can interact directly with STAT3 by dephosphorylating phosphorylated STAT3 at Y705.¹¹⁹ In addition, they found that expression of *PTPRK* decreased in NKTCL cells. Furthermore, restored *PTPRK* dephosphorylates phospho-STAT3 at Y705, which can inhibit the proliferation, migration, and invasion of NKTCL cells. Low expression of *PTPRK* is related to its promoter's hypermethylation.¹¹⁹ Finally, *PTPRK* is able to inhibit EGFR signaling to suppress tumor growth.^{120–122}

Src homology region 2 domain–containing phosphatase 1 and tumors

SHP1, also known as PTPN6, is a member of the nonreceptor PTP family and encoded by the *PTPN6* gene. The tumor-suppressive activity of SHP1 is mediated by its negative regulation of JAK and STAT. Downregulation or loss of SHP1 protein is often detected in human lymphoma and leukemia, and inhibition of SHP1 expression is proven to correlate with methylation of the *PTPN6* promoter in anaplastic large-cell lymphoma, multiple myeloma, T-cell lymphoma, and B-cell lymphoma.^{123–129} Another study demonstrated that overexpression of SHP1 is able to decrease STAT3 activity in non-Hodgkin's lymphoma cells with loss of SHP1.¹²³ It has also been reported that guggulsterone can induce apoptosis and suppress the proliferation of multiple cancer types, such as head-and-neck SCC, leukemia, and melanoma, by induction of SHP1 expression, which significantly decreases activities of JAK2 and STAT3.¹³⁰ In sorafenib-resistant HCC, dovitinib, a receptor-kinase inhibitor, can induce apoptosis and overcome sorafenib resistance through SHP1-mediated inhibition of STAT3 signaling.¹³¹ Sorafenib derivatives have been reported to be able to block STAT3 activity and suppress sorafenib-resistant HCC-cell growth through promoting SHP1 activity.¹³² Plumbagin, a vitamin K₃ analogue, has also been found to induce SHP1 expression in human myeloma cells, leading to inhibition of STAT3 phosphorylation by inactivation of cSrc, JAK1, and JAK2.¹³³ These findings further suggest that activity of STAT3 is vital to tumorigenesis and drug resistance, and SHP1-activating agents may be valuable in cancer therapy.

Src homology region 2 domain–containing phosphatase 2 and tumors

SHP2 is another member of the non-receptor PTP family, and is encoded by *PTPN11*. Studies have revealed that the tumor-suppressive capabilities of SHP2 occur mainly through its inactivation of STAT3. For example, SHP2-deficient mice present increased STAT3 activity, increased spontaneous hepatocellular adenomas, and chemically induced HCCs.¹³⁴ Accordingly, Bard-Chapeau et al reported that SHP2 is downregulated in a small number of human HCCs.¹³⁴ Moreover, SHP2 expression is depressed in human ESCC, and SHP2 knockdown enhances ESCC-cell proliferation in vitro and in vivo, along with a significant increase in phosphorylated STAT3.¹³⁵ More importantly, low SHP2 expression and high phosphorylated STAT3 correlate with poor prognosis

and vice versa in colorectal cancer.¹³⁶ However, SHP2 was initially established as an oncogenic protein, and *PTPN11* the first identified proto-oncogene to encode a tyrosine phosphatase.¹³⁷ Germline gain-of-function mutations of *PTPN11* are associated with increased risk of solid tumors and leukemia.^{138–141} Promotion of cancer by SHP2 is associated with activation of Ras GTPase–ERK signaling and the PI3K–AKT pathway mediated by SHP2.^{138–140}

MEG2/protein tyrosine phosphatase–nonreceptor type 9 and tumors

PTPN9 (PTP-MEG2 or MEG2) is a cytosolic nonreceptor PTP encoded by *PTPN9*. In 2012, PTP-MEG2 was first reported to dephosphorylate STAT3 and suppress tumor growth in breast cancer.¹⁴² This study also demonstrated that MEG2 can interact directly with STAT3 in vitro and in vivo by dephosphorylating STAT3 at Y705 in a time- and dose-dependent manner.¹⁴² Other

research has revealed that upregulated expression of MEG2 can effectively inhibit tumor-cell growth and induce cell apoptosis by reducing STAT3 activity in prostate carcinoma cells.¹⁴³ In addition, MEG2 is able to dephosphorylate the NGF receptor TrkA, the insulin receptor, and VEGFR2,^{144–146} while the detailed mechanisms need to be further explored.

T-cell protein tyrosine phosphatase and tumors

TC-PTP, encoded by *PTPN2*, also belongs to the nonreceptor PTP family. STAT3 is one of several substrates of TC-PTP.¹⁴⁷ TC-PTP has been reported to be tumor-suppressive through its modulation of STAT3 signaling. For instance, deletion of the *PTPN2* gene is present in some T-cell acute lymphoblastic leukemia cells and results in increased JAK–STAT signaling.¹⁴⁸ Biallelic inactivation of *PTPN2* correlates with activation of the JAK–STAT pathway in the Hodgkin's

Table I Direct inhibitors of STAT3

Molecules	Targets	Effects	Indications (clinical trial phase)	Refs
Peptide and peptidomimetics				
PY*LKTK	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Not applicable	151
ISS-610	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Not applicable	152
SPI	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Not applicable	153
CJ-1383	STAT3 SH2 domain	Inhibition of STAT3 phosphorylation	Not applicable	154
PM-73G	STAT3 SH2 domain	Inhibition of STAT3 phosphorylation	Not applicable	155
DBD-1	STAT3 DNA-binding domain	Inhibition of STAT3 DNA-binding	Not applicable	156
Non-peptide small molecules				
Stattic	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Not applicable	157
STA-21	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Psoriasis (phase I/II trial)	158
LLL-3	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Not applicable	159
LLL-12	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Not applicable	160
S3I-201	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Not applicable	161
SF-1-066	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Not applicable	162
SF-1-087	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Not applicable	162
SF-1-121	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Not applicable	162
S3I-1757	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Not applicable	163
S3I-M2001	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Not applicable	164
S3I-201.1066	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Not applicable	165
BP-1-102	STAT3 SH2 domain	Inhibition of STAT3 dimerization	Not applicable	166
OPB-51,602	STAT3 SH2 domain	Inhibition of STAT3 phosphorylation	Advanced malignancies (phase I trial)	167, 168
CPA-1	STAT3 DNA-binding domain	Inhibition of STAT3 DNA-binding	Not applicable	169
CPA-7	STAT3 DNA-binding domain	Inhibition of STAT3 DNA-binding	Not applicable	169
Platinum(IV) tetrachloride	STAT3 DNA-binding domain	Inhibition of STAT3 DNA-binding	Not applicable	169
InS3-54	STAT3 DNA-binding domain	Inhibition of STAT3 DNA-binding	Not applicable	170
InS3-54A18	STAT3 DNA-binding domain	Inhibition of STAT3 DNA-binding	Not applicable	171

lymphoma cell line SUPHD1 and T-cell non-Hodgkin's lymphoma tissue.¹⁴⁹ In addition, TC-PTP deficiency in triple-negative primary breast cancer leads to increased cell proliferation via elevated STAT3 signaling and SFK.¹⁵⁰ Restoration of TC-PTP expression in human breast cancer cell lines apparently suppresses cell proliferation in vitro and xenograft growth in vivo.¹⁵⁰ These findings suggest that TC-PTP can act as a suppressor of human tumors.

Direct inhibitors of STAT3

Given the critical role of constitutively active STAT3 in human tumors, STAT3 has become an attractive target for small-molecule therapeutics. Since the first peptide inhibitor of STAT3, PY*LKTK (where Y* represents phosphotyrosine) was reported,¹⁵¹ a number of small molecules (Table 1) have been developed to inhibit directly the function of STAT3 for cancer therapies.^{152–171} The mechanisms of direct STAT3 inhibition include disruption of phosphorylation, dimerization, nuclear translocation, and/or DNA binding of STAT3. Both peptides/peptidomimetics and small nonpeptidic molecules are able to target the STAT3 SH2 domain/STAT3 DNA-binding domain (details shown in Table 1). Because peptides/peptide-mimics have poor membrane permeability and stability,¹⁷² small nonpeptidic molecules have become attractive candidates of STAT3 inhibitors for tumor treatment. In this regard, STA21 has completed a phase I/II trial for psoriasis, and OPB51602 has completed a phase I trial for refractory hematologic and solid malignancies.^{158,167,168} However, it will take a long time to transfer these molecules to the clinic. One of the major reasons is that STAT3:STAT3 dimerization is a protein–protein interaction involving a large surface area and difficult to be influenced by small molecules.¹⁶³ Additionally, high concentrations of small-molecule inhibitors are required to counteract STAT3 activity, and in this case off-target toxicity is very likely increased. Up to now, although significant progress has been made in preclinical trials, few small-molecule inhibitors have been used in clinical cancer therapies.

Conclusion

STAT3 is an ideal target for tumor therapy, because of its pivotal biological functions in tumors. So far, various STAT3 inhibitors have been developed for tumor therapy, including peptides, small nonpeptidic molecules and natural-product inhibitors.¹⁷³ Some STAT3 inhibitors are currently in clinical trials; however, few are suitable for clinical application,^{172,173} so a new strategy for STAT3 inhibitors needs to be further explored. PIAS, SOCS, and PTP can effectively prevent tumor progression; therefore, negative regulation of STAT3 signaling

would be a valuable strategy. These studies showed that PIAS proteins can inhibit STAT3-transcription activity by binding to active STAT dimers and blocking the DNA-binding activity of STAT. SOCSs are known as a negative-feedback loop of STAT3 signaling, and interact with JAK domains or intracellular portions of cytokine receptors to reduce STAT3 activation. STAT3 is also inactivated through dephosphorylation of Tyr705 by such PTPs as PTPRD, SHP1, SHP2, and TC-PTP. The data presented in this review prove the important role of negative regulators of STAT3 signaling in tumor suppression, which will pave a new avenue for cancer treatment.

Abbreviation list

ESCC, esophageal squamous-cell cancer; HCC, hepatocellular carcinoma; NKTCL, NK/T-cell lymphoma; SCC, squamous-cell carcinoma.

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Disclosure

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