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Novel activators and small-molecule inhibitors of STAT3 in cancer

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ABSTRACT

Excessive activation of signal transducer and activator of transcription 3 (STAT3) signaling is observed in a subset of many cancers, making activated STAT3 a highly promising potential therapeutic target supported by multiple preclinical and clinical studies. However, early-phase clinical trials have produced mixed results with STAT3-targeted cancer therapies, revealing substantial complexity to targeting aberrant STAT3 signaling. This review discusses the diverse mechanisms of oncogenic activation of STAT3, and the small molecule inhibitors of STAT3 in cancer treatment.

1. Introduction

Signal transducer and activator of transcription 3 (STAT3) is a cytoplasmic transcription factor and a member of the STAT protein family [1]. STAT3 plays crucial roles in tumor cell proliferation, survival, angiogenesis, migration differentiation, invasion and immunosuppression [1,2]. Although targeting STAT3 signaling as a cancer therapeutic target has lagged behind that of receptor tyrosine kinases (RTKs), substantial evidence demonstrates that STAT3 is an attractive target for therapeutic intervention in cancer [3,4]. Inhibiting STAT3 activation is a burgeoning field. Clinical STAT3 inhibitors with various structural skeletons are being developed [5]. Reviews on STAT3 have recently focused on STAT3 activity and functions in cancer and other diseases [6]. In this review, we discuss recent scientific findings that provide insight into the variable therapeutic effects of targeting STAT3 therapy, review recent advances in diverse mechanisms of oncogenic STAT3 activation and focus on STAT3 inhibitors from clinical drugs and natural products.

Abbreviations: ADAM12, ADAM metallopeptidase domain 12; ADME, absorption distribution, metabolism and elimination; AKR1C1, aldo-keto reductase family 1 member C1; AKT, protein kinase B; BMX, bone marrow and X-linked; BRAF, V-raf murine sarcoma viral oncogene homolog B1; CCL2, C-C motif chemokine ligand 2; CDK7, cyclin dependent kinase 7; ceRNA, competing endogenous lncRNA; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; ERK, extracellular regulated protein kinases; FABP5, fatty acid binding protein 5; FEZF1, fasciculation and elongation protein zeta family zinc finger 1; FEZF1-AS1, FEZF1 antisense RNA 1; FGFR1, fibroblast growth factor receptor 1; GSC, glioma stem cell; HCC, hepatocellular carcinoma; HPV18, human papilloma virus 18; HSP110, heat shock protein 110; HUVECs, human umbilical vein endothelial cells; IL6, interleukin 6; JAK2, Janus kinase 2; KLF-11, Krüppel-like factor 11; lncRNA, long noncoding RNA; MALAT1, metastasis associated lung adenocarcinoma transcript 1; MEK, MAPK/Erk kinase; MET, mesenchymal to epithelial transition factor; miRNA, MicroRNA; MKK, MAPK kinase; MTD, maximum tolerated dose; MUC1, Mucin 1; NEAT1, nuclear enriched abundant transcript 1; NPCs, neural progenitor cells; NSCLC, non-small cell lung cancer; p38 MAPK, p38 mitogen activated protein kinases; PA28γ, proteasome activator 28 gamma; PBX1, PBX homeobox 1; PIAS3, rotein inhibitor of activated STAT 3; PVT1, plasmacytoma variant translocation 1; Rac1, ras-related C3 botulinum toxin substrate 1; RanBP6, RAN binding protein 6; Ras, rat sarcoma; RTKs, receptor tyrosine kinases; Smads, drosophila mothers against decapentaplegic proteins; SOCS3, suppressor of cytokine signaling 3; SOX2, SRY-box 2; Src, sarcoma gene proto-oncogene, non-receptor tyrosine kinase; STAT3, signal transducer and activator of transcription 3; TALE, three amino acid loop extension; TC45, T-cell protein-tyrosine phosphatase(45kd); TGF-β, transforming growth factor beta; TKI, tyrosine kinase inhibitor; TRIM, tripartite motif containing; USP22, ubiquitin specific peptidase 22; VEGFA, vascular endothelial growth factor A; XIST, X inactive specific transcript; YAP, yes associated protein

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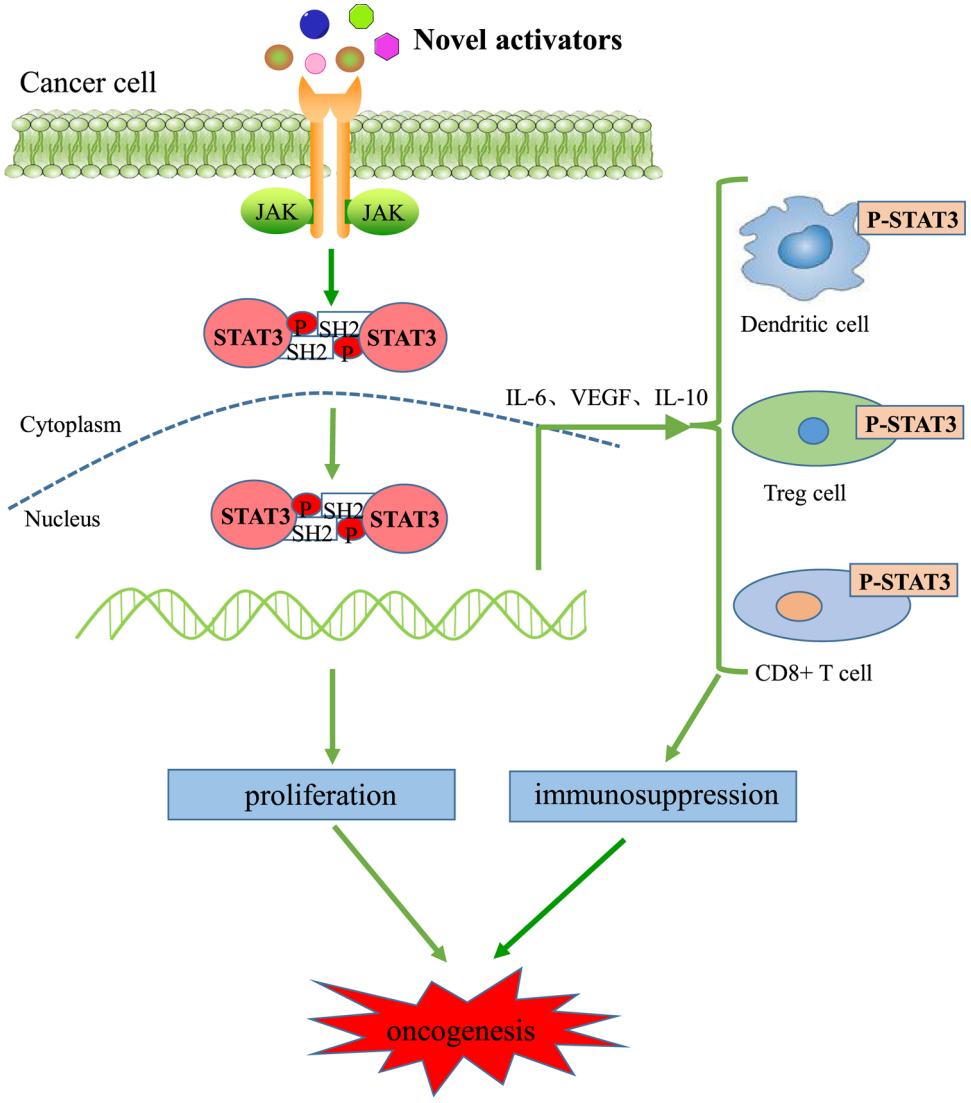


Fig. 1. Activators of STAT3 promote cancer growth through immunosuppression. STAT3 target genes, VEGF, IL-10, and IL-6 are transcriptionally regulated by STAT3 and are propagated from cancer cells to immune cells. Then, these tumor-associated factors activate STAT3 in the immune system.

2. STAT3 signaling and role in gene regulation and immune response

Constitutive activation of STAT3 promotes cancer by directly regulating oncogene expression, such as cyclin B1, CDC2, p53, MCL-1, survivin, VEGF, BCL2 and BAX [7,8]. In addition, more and more evidences show that the specific functions of STAT3 in immunosuppression and immunoregulatory effects is related to the occurrence of tumors [2,9]. Immune cells in the tumor microenvironment cannot produce effective antitumor immune response, but also interact closely with the transformed cells, thus promoting the occurrence of tumors [10]. STAT3 is constitutively activated both in tumor cells and immune cells in the tumor microenvironment. Constitutively activated STAT3 inhibits the expression of mediators necessary for immune activation against tumor cells [11–13]. In addition to this typical role, STAT3 is also essential in regulating tumor microenvironment, such as stromal and immune cells, to promote tumor progression [14]. STAT3 is considered to be an effective checkpoint for antitumor immune response. The amazing fusion of tumor promotion and immunosuppression in the STAT3 pathway makes STAT3 an important target for effective immunotherapy (Fig. 1).

STAT3 regulates the interaction between tumor cells and host immunity [15]. STAT3 transmits multiple levels of crosstalk between tumor cells and their immunological microenvironment, leading to tumor-induced immunosuppression. STAT3 expression in tumor microenvironment can recruit and promote the proliferation of regulatory T (Treg) cells, and then inhibit the activity of CD^{8+} effector T cells and other immune cell types [16]. The combination of IL-6 and G-CSF enhances the activation of STAT3 in bone marrow progenitor cells, induces the formation of neutrophils, enhances precancerous response, and inhibits the function of neutrophils associated with antitumor activity, suggesting that there is serious tumor immune crosstalk [17]. Targeting STAT3 can not only directly inhibit the growth of tumors, but also enhance antitumor immunity (Fig. 2). Therefore, rendering STAT3 a promising target with therapeutic potential for effective cancer treatment seems easier to achieve with the emergence of innovatively developed direct and/or no-specific small molecule inhibitors of STAT3.

3. STAT3 activation in cancer development

Similar with the biological function in immune response, STAT3 is also involved in the development and progression of many human cancers [7]. STAT3 regulates multiple biological functions in the initiation of malignant transformation and the pathogenesis of many cancers [13,18,19]. STAT3 may be the convergence point of several major oncogenic signaling pathways, including interleukin-6 receptor

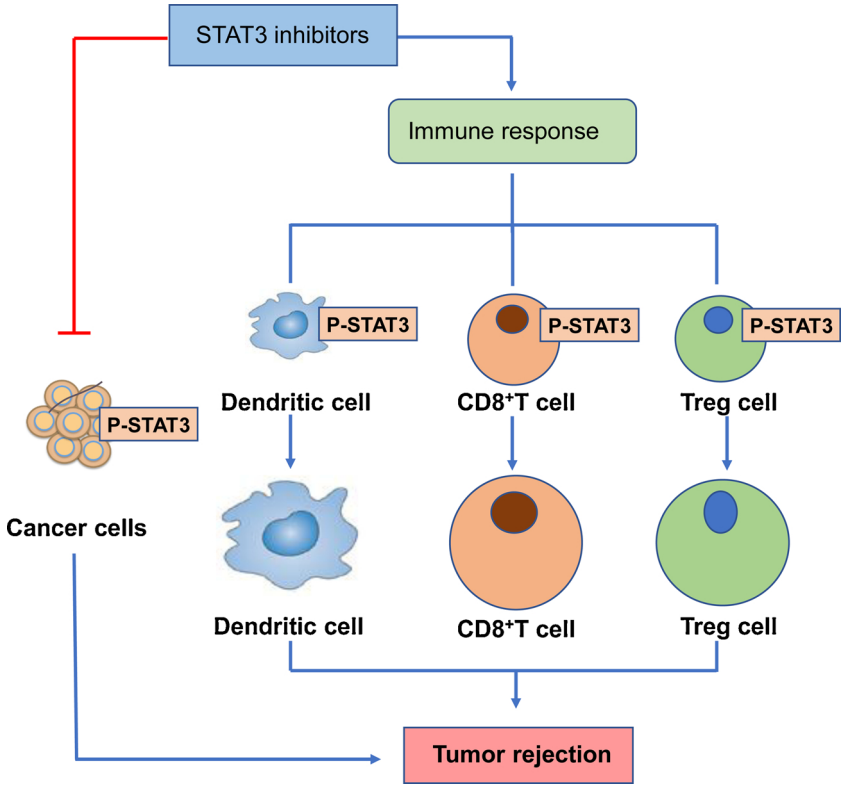


Fig. 2. Targeting STAT3 for cancer immunotherapy. Inhibiting STAT3 can significantly attenuate cancer cell proliferation and induce apoptosis. Moreover, STAT3 ablation in diverse immune cells may trigger a robust anti-tumor immune response.

(IL-6R/gp130), cytoplasmic enzymes in the Janus family of kinases (JAK), epithelial growth factor receptor (EGFR), c-Met, platelet-derived growth factor receptor (PDGFR), heregulin-2/neuregulin receptor (Her2/Neu), the Abelson leukemia protein (ABL) family of kinases and the Src family of kinases [20,21]. More importantly, the feedback activation of STAT3 would emerge as a cancer drug-resistance mechanism in failure of tyrosine kinase inhibitor (TKI)-mediated therapies [22] (Fig. 3A).

Advances in new STAT3 activators and biological functions reveal many unexpected new roles and potential mechanisms of STAT3 in cancer. These findings provide comprehensive evidence that STAT3 is constitutively activated in a variety of tumors as a junction of multiple oncogenic signaling pathways. Moreover, aberrant activation of STAT3 induced by these novel activators plays key roles in tumor progression, drug-resistance and recurrence. These findings continue to demonstrate that STAT3 is a promising molecular target for cancer therapy (Fig. 3B).

4. Novel activators of STAT3 in cancer

STAT3 signaling mediates tumor protective functions in different contexts [7]. Identifying of the active mechanisms of STAT3 will be important to understanding how STAT3 signaling can be most appropriately therapeutically targeted and to developing novel inhibitors [5] (Table 1). Long noncoding RNA (LncRNA) PVT1 can increase protein stability of phospho-STAT3 (P-STAT3) in the nucleus to mediate angiogenesis. In addition, the PVT1 promoter could combine with STAT3 to stimulate its transcription. The association between STAT3 and PVT1 shows synergetic oncogenic effects [23]. LncRNA NEAT1 promotes STAT3 levels by sponging miR-485 as a competing endogenous lncRNA (ceRNA) [24]. LncRNA FEZF1-AS1 promotes migration and invasion of hepatocellular carcinoma cells by upregulating the JAK2/STAT3 signaling-mediated epithelial-mesenchymal transition (EMT) [25]. A novel positive feedback regulation between lncRNA UICC and IL6/STAT3 signaling promotes cervical cancer progression [26]. Moreover, lncRNA MALAT1 and XIST can regulate STAT3 expression, which is a direct target of miR-124 in non-small cell lung cancer (NSCLC) and retinoblastoma [27,28]. Mir-30d is a microRNA that upregulates Krüppel-like factor 11 (KLF-11) and P-STAT3 in breast cancer cell lines [29].

CD109, a novel pro-metastatic gene, promotes tumor metastasis by activating the JAK/STAT3 signaling pathway. Thus, CD109-JAK/STAT3 maybe a new critical, pharmacologically targetable effector for metastatic cancer [30]. CD146 is an inducible signaling receptor that concurrently inhibits E-cadherin expression and upregulates N-cadherin expression in response to TGF-β via the STAT3/Twist and ERK-activation pathways. Therefore, simultaneously targeting both CD146 and TGF-β signaling could have better efficacy in cancer therapy [31]. SOX2 and CD24 overexpression can lead to Src and STAT3 activity. Furthermore, SOX2 and CD24 are upregulated upon BRAF inhibitor treatment in melanoma [32]. CDK7 activity is necessary for STAT3 dependent transcription, an approach that could benefit patients with tumors that present interleukin- or mutation-driven activation of STAT3 programs such as those in peripheral T-cell lymphomas or other malignances [33].

Smads, which form a trimer of two receptor-regulated Smads (R-Smads), such as Smad2 and Smad3, with the co-Smad, Smad4, act as transcription factors to regulate gene expression. The Smad family includes two inhibitory Smads (Smad6 and Smad7). Smad6 reduces PIAS3-mediated STAT3 inhibition and promotes glioma cell growth and stem-like cell initiation [34]. Smad7 activates STAT3 by directly binding to the cytokine receptor upstream of STAT3 activation and promotes pluripotency independent of TGF-β signaling. Thus, Smad7 may have a broader role in bridging the collaborative functions of the TGF-β-Smad and gp130-STAT3 signaling pathways in other pathophysiological processes such as inflammation and tumorigenesis [35].

TRIM24 functions as a transcriptional co-activator and recruits STAT3, leading to stabilized STAT3-chromatin interactions subsequently activating of STAT3 downstream signaling [36]. TRIM27 also

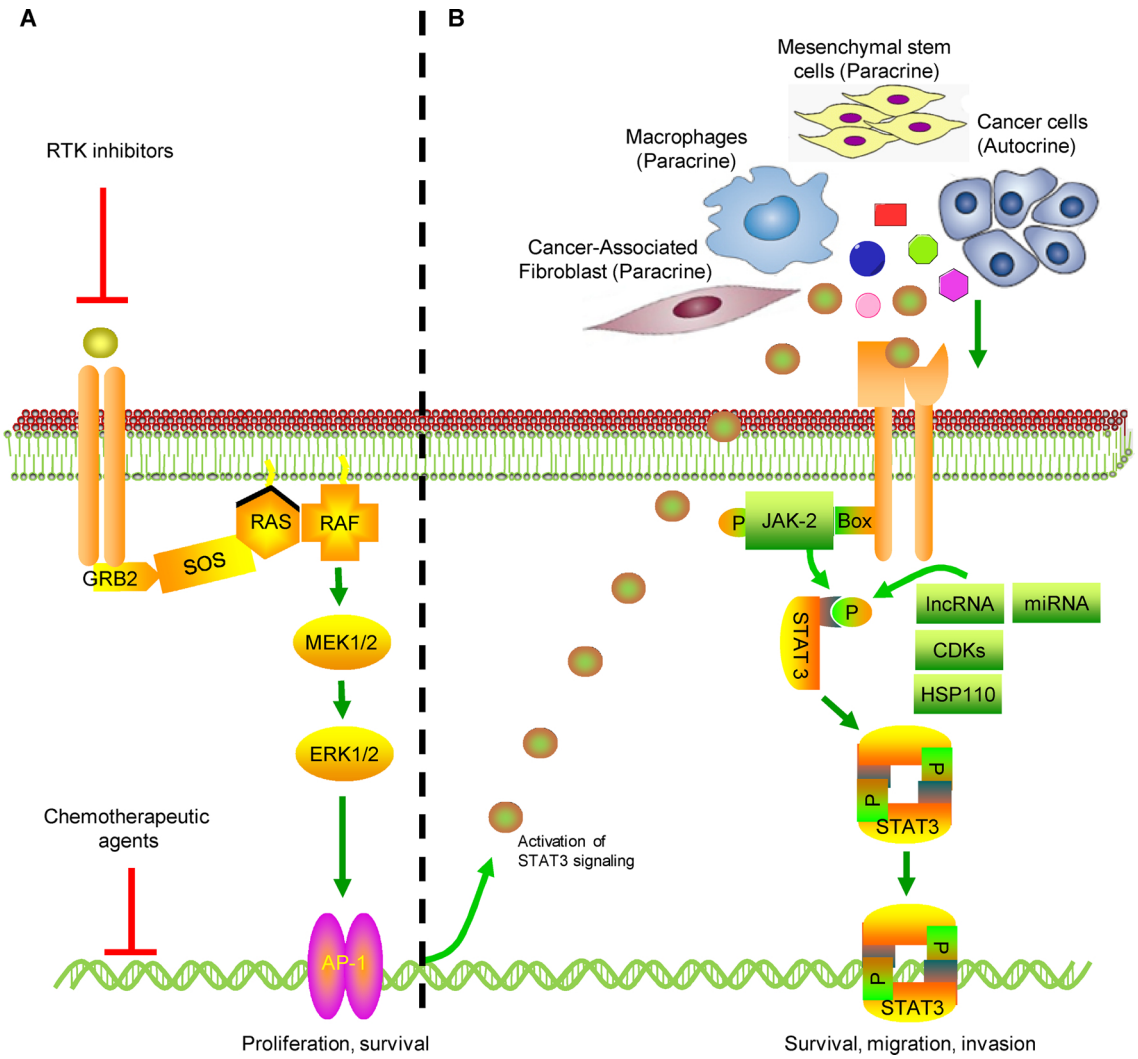


Fig. 3. Activation of STAT3 in cancer cells. a. Inhibition of cancer signaling activates STAT3 pathways. b. Novel activators of STAT3 secreted by mesenchymal stem cells, cancer cells, macrophages or cancer-associated fibroblast cells.

mediates STAT3 activation at retromer-positive structures to promote colitis and colitis-associated carcinogenesis [37]. However, TRIM59 promotes glioma genesis by inhibiting TC45 dephosphorylation of STAT3 [38].

Bone marrow and X-linked (BMX) nonreceptor tyrosine kinase mediated activation of STAT3 is relevant to maintaining glioblastoma and harbors glioma stem cell (GSC) regeneration and oncogenesis. BMX can bypass the suppressor of cytokine signaling 3 (SOCS3)-mediated inhibition of JAK2, whereas neural progenitor cells (NPCs) restrain the activation of JAK2-mediated STAT3 via negative correlation with SOCS3 [39]. AKR1C1 belongs to the human aldo-keto reductase family, which facilitates lung cancer metastasis as a key participant in the STAT3 pathway. AKR1C1 promotes phospho-STAT3 by incorporting with STAT3, which increases the binding of STAT3 to the target genes to activate these genes. Further, AKR1C1 can stimulate STAT3 to interact with its upstream kinase JAK2 [40]. Centrosomal P4.1-associated protein (CPAP) [41] and PRMT1 plays a crucial role in tumor progression and metastasis in hepatocellular carcinoma (HCC) by activating phosphorylation of STAT3 and the STAT3 pathway [42]. PBX1, a member of three amino acid loop extension (TALE) family of typical homeodomain transcription factors, plays an oncogenic role in renal clear cell carcinoma via upregulating the JAK2/STAT3 pathway [43].

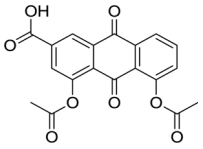
HSP110 expression contributes to colorectal cancer growth by activating STAT3 [44]. RanBP6 promotes nuclear translocation of STAT3 [45]. RAC1-GTP, a member of the Rac family, directly interacts with STAT3 to promote STAT3 phosphorylation, thus promoting EMT among colorectal cancer cells [46]. PA28γ, a member of the 11S proteasome activator family, binds and activates 20S proteasomes. P-STAT3 and P-AKT, downstream of the IL6 and CCL2 signaling pathway, are down-regulated in human umbilical vein endothelial cells (HUVECs) co-cultured with PA28γ-silenced supernatant and are upregulated with PA28γ-overexpressing supernatant [47]. E6-mediated activation of STAT3 induces the transcription of STAT3 responsive genes and is essential for the differentiation-dependent HPV18 life cycle [48]. Fatty acid binding protein 5 (FABP5), which is highly expressed in HCC, can promote angiogenesis and activate the IL6/STAT3/VEGFA pathway [49]. Disintegrin and metalloproteinase domain-containing protein 12 (ADAM12) and USP22 are novel regulators of tumor angiogenesis via STAT3 signaling [50,51]. ZDHHC19, ZFP42 zinc finger protein (REX1) and Mesoderm-specific transcript (MEST) are key regulators of IL-6/STAT3 signal pathway [52–54]. Groundbreaking understanding of STAT3 signaling activations at the molecular level has led to major advances in the last few years. However, the great diversity among STAT3-activating mechanisms has challenged the clinical translation of STAT3 inhibitors, and preclinical and clinical evidence exemplify the importance of considering individual aberrations.

Table 1
Novel activators of STAT3 in cancer cells.

Activators	Category	Mechanism	Functions	Cancer
PVT1	lncRNA	PVT1 promoter combine with STAT3 to stimulate its transcription	Promote angiogenesis	Gastric cancer
NEAT1	lncRNA	Sponge miR-485 and enhancing the expression of the STAT3	Promote cell growth, migration, and invasion capacity	Hepatocellular carcinoma
FEZF1-AS1	lncRNA	Activate the JAK2/STAT3 signaling pathway	Promote cell invasion and EMT	Hepatocellular carcinoma
UICC	lncRNA	Regulate the IL-6 transcription through binging to IL-6 promoter.; Directly interact with the phospho-STAT3	Promote tumor growth and metastasis	Cervical cancer
MALAT1	lncRNA	Modulate the miR-124/STAT3 axis	Promote cell proliferation and cycle progression	NSCLC
XIST	lncRNA	Modulate the miR-124/STAT3 axis	Promote cell proliferation and cycle progression	Retinoblastoma
miR-30d	microRNA	Targeted KLF-11 regulation of P-STAT3 expression	Promote cell invasion, migration, and EMT	Breast cancer
CD109	protein	Regulate CD109/Janus kinase/STAT axis	Promote metastasis	Lung cancer
CD146	protein	Through STAT3/Twist and ERK pathway	Promote migration and EMT	Ovarian cancer
CD24	protein	Induces activation of Src and STAT3	Promote cell proliferation and survival	Melanoma
CDK7	kinase	Activation of STAT signaling pathways	Promote survival	T-cell lymphomas
SOX	protein	Bind to the CD24 promoter resulting in an upregulation of CD24 leading to an increased activity of Src and STAT3.	Promote cell proliferation and survival	Melanoma
Smad6	protein	Regulate STAT3 activation through PIAS3 inhibition	Promotes tumor sphere formation, cell proliferation and tumorigenesis	Gliomas
Smad7	protein	Direct bind to the cytokine receptor upstream of STAT3 activation	Promoting self-renewal	
TRIM24	protein	As a transcriptional co-activator and recruits STAT3	Promote cell proliferation	Glioblastoma
TRIM27	protein	Recruit gp130, JAK1, and STAT3	Rromote cancer cell growth	Colitis and colitis-associated carcinogenesis
TRIM59	protein	Inhibit TC45 dephosphorylation of STAT3	Promote cell proliferation, migration	Glioblastoma
ADAM12	protein	Activate of EGFR, STAT3 and Akt signaling	Increase angiogenesis	Breast cancer
USP22	enzyme	Increase phosphorylation of STAT3	Regulate cell proliferation and G1/S transition	Lung adenocarcinoma
BMX	tyrosine kinase	Bypass the SOCS3-mediated negative regulation of JAK2 to sustainably activate STAT3	Promote cell proliferation and angiogenesis	Glioblastoma
AKR1C1	enzyme	Interacted with STAT3 and facilitated its phosphorylation	Promote the Metastasis	NSCLC
PRMT1	enzyme	Activate the phosphorylation of STAT3 and the STAT3 pathway	Promoted growth, colony formation and migration	Hepatocellular carcinoma
PBX1	transcription factor	Upregulate JAK2/STAT3 pathway	Promote cell viability, Proliferation and cell cycle progression	Renal clear cell carcinoma
HSP110	protein	HSP110 directly binds to STAT3 and promotes its phosphorylation	Promote cell proliferation	CRC
RanBP6	protein	Promote nuclear translocation of STAT3	Repress EGFR transcription	Glioblastoma
RAC1-GTP	protein	Interact with STAT3 to promote its phosphorylation	Promote EMT	CRC
PA28γ	protein	Through IL6 and CCL2 signaling pathway	Promote tumor angiogenesis	Oral squamous cell carcinoma
E6	protein	Promotes the dual phosphorylation and activation of STAT3	Delay differentiation and increased keratinocyte proliferation in stratified epithelia; Promote cell cycle progression	HPV-associated cancers
FABP5	protein	Activate the IL6/STAT3/VEGFA pathway	Promote angiogenesis	Hepatocellular carcinoma

Table 2
Novel Small molecule inhibitors of STAT3.

STAT3 inhibitors discovery using drug repositioning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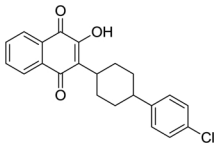
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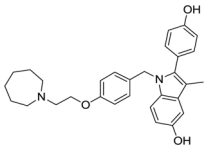
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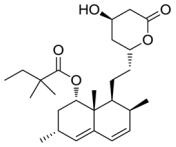
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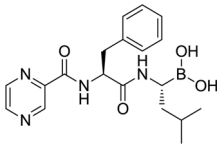
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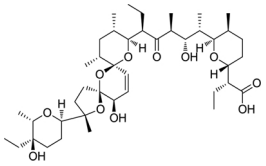
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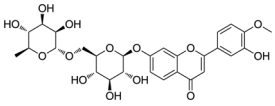
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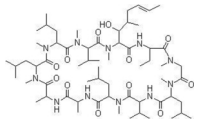
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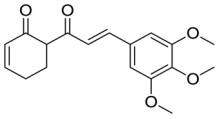
STAT3 inhibitors discovery in natural products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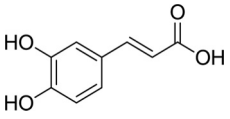
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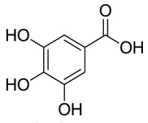
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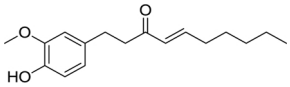
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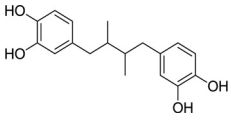
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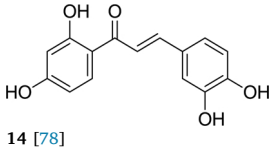
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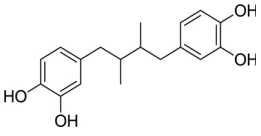
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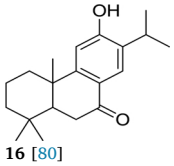
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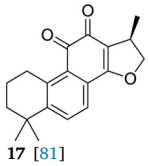
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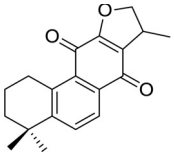
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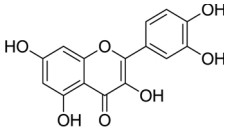
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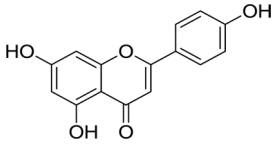
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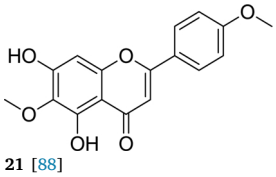
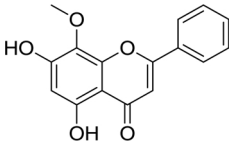
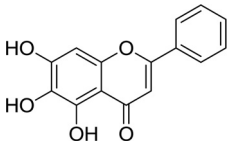

21 [88]


22 [89]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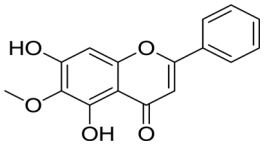
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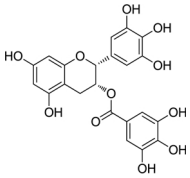
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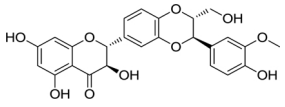
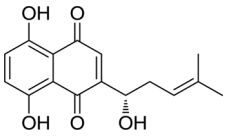

26 [93]

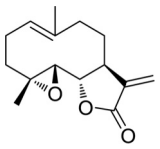
(*continued on next page*)

Table 2 (*continued*)

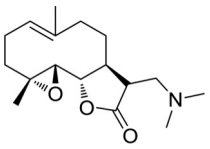
STAT3 inhibitors discovery in natural products



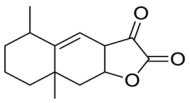
27 [94]



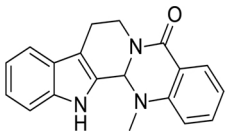
28 [95]



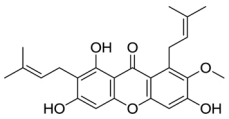
29 [96]



30 [97]



31 [98]



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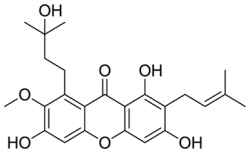

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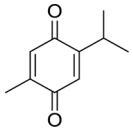
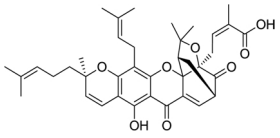
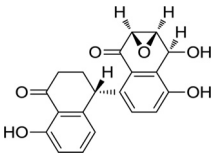


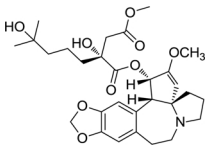
34 [101,102]



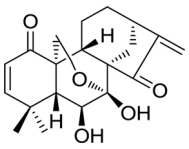
35 [103]



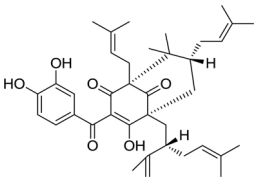
36 [104]



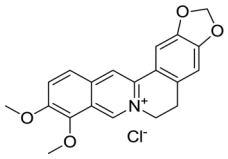
37 [105]



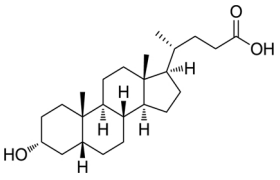
38 [106]



39 [107]



40 [108]



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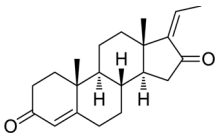
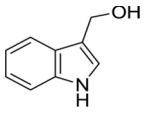


42 [110]



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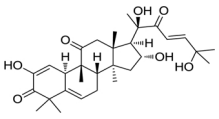
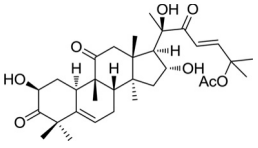


44 [112]



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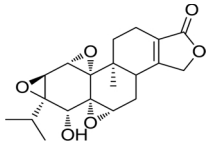

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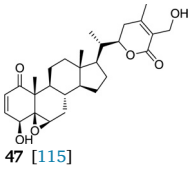
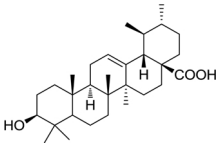
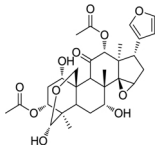


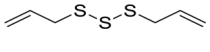
47 [115]



48 [116]



49 [117]



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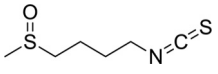

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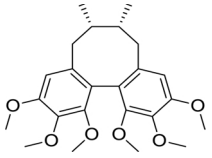
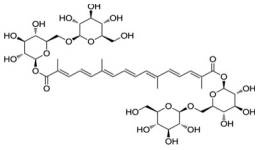


52 [120]



53 [121]

5. STAT3 activation-a mechanism of resistance to chemotherapies

Substantial evidences suggest that feedback activation of STAT3 plays a prominent role in mediating drug resistance to a broad range of targeted cancer therapies and chemotherapies (Fig. 3A) [22]. Ras pathway inhibition can immediately activate STAT3 in pancreatic ductal adenocarcinoma and glioblastoma. These findings demonstrate that resistance to MEK or MET inhibitors is mediated via STAT3 activation [55,56]. The FGFR1 V561M gatekeeper mutation also drives AZD4547 resistance through STAT3 activation [57]. This separation drives acquired resistance to the FGFR inhibitor by activating STAT3 via its cognate receptors [58]. Gefitinib can activate YAP-MKK3/6-p38

Table 3
Overview of benefits and adverse events in clinical trials involving STAT3 inhibitors.

Drug	Clinical trial identifier	Study disign	Intervention/ treatment	Tumor types	Phase	Primary Endpoint	Status
AZD9150	NCT01839604	58 participants, Single group assignment, Open label	AZD9150	Advanced/metastatic hepatocellular carcinoma	I	safety, tolerability, pharmacokinetics and preliminary anti-tumour activity	Completed
	NCT03394144	11 participants, Single group assignment, Open label	AZD9150 monotherapy and AZD9150 in combination with Durvalumab	Advanced solid malignancies	I	safety, tolerability, pharmacokinetics and preliminary anti-tumor activity	Active, not recruiting
	NCT03421353	110 participants, Randomized, Parallel assignment, Open label	AZD9150 monotherapy and AZD9150 in combination Durvalumab, cisplatin, 5-Flourouracil, Carboplatin, Gemcitabine, Nab-paclitaxel	Advanced solid Tumors	Ib/II	safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of AZD9150 plus durvalumab alone or in combination with chemotherapy in patients with advanced	Recruiting
	NCT02983578	75 participants, Non-Randomized, Parallel assignment, Open label	AZD9150 in combination with durvalumab	Malignant neoplasm of digestive organs intestinal tract; Primary malignant neoplasm of respiratory and intrathoracic organ carcinoma	II	ORR	Recruiting
Napabucasin (BBI608)	NCT03525405	8 participants, Single group assignment, Open label	napabucasin	healthy adult male volunteers	I	absorption, metabolism, and excretion of napabucasin	Completed
	NCT03411122	30 participants, Single group assignment, Open label	Napabucasin and cytochrome P450 (CYP450) probe drugs or BCRP transporter substrate	healthy adult male volunteers	I	safety, tolerability, pharmacokinetics and drug interaction potential of Napabucasin	Completed
	NCT02993731	1132 participants, Randomized, Parallel assignment, Open label	napabucasin plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine	Metastatic pancreatic adenocarcinoma	III	OS	Active, not recruiting
	NCT03522649	668 participants, Randomized, Parallel assignment, Open label	Napabucasin in combination with FOLFIRI versus Napabucasin	Previously treated metastatic colorectal cancer	III	OS	Recruiting
	NCT02753127	1250 participants, Randomized, Parallel assignment, Open label	napabucasin plus standard bi-weekly FOLFIRI versus standard bi-weekly FOLFIRI	Colorectal cancer	III	OS	Recruiting
	NCT01325441	570 participants, Single group assignment, Open label	napabucasin in combination with paclitaxel	Advanced malignancies	I/II	safety and DLTs	Recruiting
	NCT03721744	230 participants, Randomized, Parallel assignment, Open label	Napabucasin in combination with weekly paclitaxel and low-dose Gemcitabine	Metastatic pancreatic cancer	III	OS	Recruiting
	NCT02178956	714 participants, Randomized, Parallel assignment, Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Napabucasin plus weekly Paclitaxel vs. Placebo plus weekly Paclitaxel	Gastric cancer; Gastroesophageal junction cancer	III	OS	Active, not recruiting
	NCT02432326	147 participants, Single group assignment, Open label	Napabucasin and BBI503 in combination	Advanced solid tumors	I	safety, tolerability and DLTs	Active, not recruiting
	NCT02279719	99 participants, Randomized, Parallel assignment, Open label	Napabucasin in combination with sorafenib, or BBI503 in combination with sorafenib	Hepatocellular carcinoma	I/II	safety, tolerability and DLTs	Active, not recruiting
	NCT02315534			Glioblastoma	Ib/II	DLTs and PFS	

(*continued on next page*)

Table 3 (*continued*)

Drug	Clinical trial identifier	Study disign	Intervention/ treatment	Tumor types	Phase	Primary Endpoint	Status
		34 participants, Non-Randomized, Parallel assignment, Open label	Napabucasin in combination with temozolomide				Active, not recruiting
	NCT01776307	203 participants, Non-Randomized, Parallel assignment, Open label	Napabucasin in combination with either cetuximab, or panitumumab, or capecitabine	Colorectal cancer	II	DCR	Active, not recruiting
	NCT02352558	15 participants, Non-Randomized, Parallel assignment, Open label	Napabucasin	Hematologic malignancy	I	safety, tolerability and DLTs	Active, not recruiting
	NCT02851004	56 participants, Single group assignment, Open label	Napabucasin in combination with pembrolizumab	Metastatic colorectal cancer	Ib/II	ORR	Recruiting
	NCT01775423	87 participants, Single group assignment, Open label	Napabucasin	Advanced malignancies	I	safety and tolerability	Active, not recruiting
	NCT02024607	495 participants, Non-Randomized, Single group assignment, Open label	Napabucasin in combination with either FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, or regorafenib, or irinotecan.	Advanced gastrointestinal cancer	I/II	safety, tolerability and ORR	Active, not recruiting
	NCT02467361	104 participants, Non-Randomized, Parallel assignment, Open label	Napabucasin in combination with immune checkpoint inhibitors	Advanced cancers	I/II	safety, tolerability and DLTs	Active, not recruiting
	NCT02231723	139 participants, Non-Randomized, Parallel assignment, Open label	Napabucasin in combination with Gemcitabine and nab-Paclitaxel, mFOLFIRINOX, FOLFIRI, or MM-398 with 5-FU and leucovorin.	Metastatic pancreatic adenocarcinoma	Ib	safety and DLTs	Active, not recruiting
	NCT02358395	12 participants, Single group assignment, Open label	Napabucasin in combination with Sorafenib	Hepatocellular carcinoma	I	safety, tolerability, pharmacokinetics and DLTs	Completed
	NCT01830621	282 participants, Randomized, Parallel assignment, Triple (Participant, Care Provider, Investigator)	Napabucasin and best supportive care versus Placebo and best supportive care	Colorectal carcinoma	III	OS	Completed
	NCT02347917	24 participants, Single group assignment, Open label	Napabucasin in combination with Pemetrexed and Cisplatin	Malignant pleural mesothelioma	I/II	safety, pharmacokinetics and DLTs	Completed
	NCT02641873	4 participants, Single group assignment, Open Label	Napabucasin with FOLFIRI + Bevacizumab	Metastatic colorectal cancer	I	safety, tolerability, pharmacokinetics and DLTs	Completed
TTI-101	NCT03195699	30 participants, Single group assignment, Open label	TTI-101	Advanced cancers	I	MTD and pharmacokinetics	Recruiting

Overall Survival, OS; Disease Control Rate, DCR; Objective Response Rate, ORR; Maximum Tolerated Dose, MTD.

MAPK-STAT3 signaling and induce tetraploidization in gefitinib-resistant cells [59]. USP22 or MUC1 sustained activation of STAT3 signaling pathways contributes to EGFR-TKI resistance [51,60]. Stratifin regulates RTK stabilization by interacting with ubiquitin-specific protease 8 and P-STAT3 in lung adenocarcinoma [61]. Preclinical and early clinical data demonstrate that targeting the STAT3 signaling pathway is a promising therapeutic strategy as a monotherapy as well as combined with other agents [22].

6. Novel small-molecule inhibitors of STAT3 in cancer

No small-molecular STAT3 inhibitors are available in clinical application, and traditional drug design and screening lack efficiency [5,8]. To overcome the high rate of losses in current drug discovery, as well as to reduce costs and shorten the development cycle, testing the thousands to millions of compound libraries at once would be impractical [3]. To solve this impracticality, determining STAT3 small-molecule inhibitors in clinical drugs and natural products is rapid and efficient, because the pharmacokinetics and safety, such as absorption,

distribution, metabolism and elimination (ADME), of these clinical drugs and natural products have been previously confirmed [62]. In this review, we report the typical clinical drugs and natural products that inhibit STAT3 (Table 2) with the hope that the inhibitory STAT3 antitumor substances found in clinical drugs and natural products can quickly progress phase II clinical evaluations, to save research and development costs, shorten the development cycle, and provide new drugs or drug combinations for clinically treating tumors.

7. Progress in clinical trials of STAT3 small molecule inhibitors

Although no STAT3-targeted therapies have yet been approved to treat cancer, the results of many early-phase therapeutic trials have revealed important information on targeting STAT3 clinically [5,8]. Table 3 presents the major STAT3 inhibitors that have entered clinical trials (http://clinicaltrials.gov/), some of which show promising results. For example, some clinical trials have assessed the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of AZD9150 in patients with advanced/metastatic carcinoma (NCT01839604, NCT03394144, NCT03421353). Another clinical research study is being conducted to determine whether AZD9150 given in combination with durvalumab can help control advanced pancreatic, lung, or colorectal cancer (NCT02983578). Napabucasin [122] recently underwent a series of clinical trials to determine its safety and efficacy in patients with metastatic pancreatic adenocarcinoma (NCT02993731, NCT03721744, NCT02231723), colorectal cancer (NCT03522649, NCT02753127, NCT01776307, NCT02851004, NCT01830621, NCT02641873), gastric cancer (NCT02178956, NCT02024607), glioblastoma (NCT02315534), hematologic malignancy (NCT02352558), malignant pleural mesothelioma (NCT02347917) and hepatocellular carcinoma (NCT02279719, NCT02358395). The maximum tolerated dose (MTD) and pharmacokinetics of TTI-101 are being evaluated in a Phase I trial in advanced cancers (NCT03195699).

Although the current task of developing small-molecule STAT3 inhibitors is highly interdisciplinary, the most useful type of STAT3 inhibitor must be determined from the accumulated clinical data. To date, only modest efficacy has been demonstrated with single-agent STAT3 inhibitor therapy [5,22]. Improved understanding of the pathogenesis of STAT3-amplified tumors, particularly factors that modify sensitivity and mediate resistance to STAT3 inhibitors, are essential to better select patients and increase the clinical success rate of STAT3 inhibitors [8].

8. Conclusions

Clinical studies have shown that many human cancers are correlated with STAT3 overexpression or over activation. Thus, STAT3 represents a new class of pharmaceutical targets [5]. The past decade has seen a dramatic increase in our understanding of the relevance of STAT3 and its activators to cancer biology [7,8]. Aberrant STAT3 signaling can activate different functions based on cellular context. Of the novel STAT3 activators, either CREB/ATF bZIP transcription factor CREBZF, LIF, CDK1/9, CD109, HSP110, lncRNA or miRNA currently holds the most potential as an attractive therapeutic target [123–125]. In addition, more tumor types and mechanisms driven by STAT3 signaling will likely emerge in the next few years to further strengthen the role of STAT3 signaling in cancer biology and provide more possibility for therapeutic applications of STAT3 inhibitors.

Several STAT3 inhibitors are now entering clinic trials or preclinical development [5]. However, compared with RTKs, clinical research on selective STAT3 inhibitors remains in its infancy [3], some significant challenges must be resolved. First, adverse reactions and toxicity of STAT3 inhibitors remain as challenges that must be addressed. STAT3 inhibitors that have entered clinical trials can generate nausea, weakness, and elevated blood pressure, thereby limiting their clinical efficacy. Moreover, novel STAT3 inhibitors or their combinations, which may overcome the side effects and toxicity raised by multitarget inhibition, must be planned in advance of clinical application. The key challenge will be to the discover high-quality targeted selective agents against STAT3 that do not affect the functions of healthy cells. A major challenge in the clinical use of STAT3 inhibitors is identifying patients who are likely to respond to the treatment. Additional work is therefore required to identify and confirm predictive biomarkers of constitutive/acquired resistance and sensitivity to each drug in large-scale clinical trials using homogeneous patient populations. These future studies could also benefit from more thoroughly analyzing of the entire STAT3 pathway in cancer patients and its crosstalk with other signal transduction networks aberrantly activated in cancers.

Future directions have been proposed that may lead to discovering small-molecule STAT3 inhibitors with novel functional mechanisms, new therapeutic indications, distinct structures, and different selectivity and pharmacological profiles. Currently, development of inhibitors of the STAT3-RTK interaction looks promising because concomitant use of these inhibitors with RTK inhibitors may slow the onset of drug resistance [22]. STAT3-based therapies remain relatively new to clinics and have yet to be fully exploited in treating of human diseases. Many new developments are expected, in further elucidating of STAT3 biology and its pharmacological applications.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Authors' contribution

LHY, LYX and SCL collected the related literature and drafted the manuscript. JL and XYH participated in the design of the review. CGZ revised and edited the manuscript. XYH and CGZ supervised the review process. All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests

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