Role of STAT3 in cancer cell epithelial-mesenchymal transition (Review)

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Abstract. Since its discovery, the role of the transcription factor, signal transducer and activator of transcription 3 (STAT3), in both normal physiology and the pathology of numerous diseases, including cancer, has been extensively studied. STAT3 is aberrantly activated in different types of cancer, fulfilling a critical role in cancer progression. The biological process, epithelial-mesenchymal transition (EMT), is indispensable for embryonic morphogenesis. During the development of cancer, EMT is hijacked to confer motility, tumor cell stemness, drug resistance and adaptation to changes in the microenvironment. The aim of the present review was to outline recent advances in knowledge of the role of STAT3 in EMT, which may contribute to the understanding of the function of STAT3 in EMT in various types of cancer. Delineating the underlying mechanisms associated with the STAT3-EMT signaling axis may generate novel diagnostic and therapeutic options for cancer treatment.

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1. Introduction

The signal transducer and activator of transcription (STAT) family of transcription factors (TFs) coordinate cytokine and growth factor signaling pathways to transcriptionally regulate a diverse array of cellular processes, such as cellular and organismal development, proliferation, metabolism, infection, inflammation and cancer (1). STAT3, one of seven members of the STAT family (comprising STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6), has a key role in the growth and development of various types of human cancer (2). STAT3 is typically activated by a wide variety of cytokines [including interleukin (IL)-6, IL-10, IL-11, IL-31, IL-23, leukaemia inhibitory factor (LIF), ciliary neurotrophic factor and oncostatin M (OSM)] and growth factors [including epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor, fibroblast growth factor receptor, leptin, granulocyte colony-stimulating factor and peptide hormones that may be excessively secreted by tumor cells, tumor stromal cells or immune cells]. These factors bind to their cognate receptors, inducing conformational changes in the receptors, which enables the activation of intracellular kinases mainly of the Janus kinase (JAK) family of non-receptor tyrosine kinases. Once activated, JAKs transphosphorylate one another and the cytoplasmic tails of the receptor, forming a docking site for STAT3, which binds via its SRC homology 2 (SH2) domain. STAT3 is phosphorylated at Tyr-705 both by JAKs and by non-receptor tyrosine kinases, including the Src and Abl families of tyrosine kinases (3). Phosphorylated STAT3 undergoes dimerization via reciprocal interactions between phosphor-Tyr-705 and the SH2 domain, and the homodimer subsequently enters the nucleus (4) to bind to palindromic sequences in the genome, thereby initiating the transcription of hundreds of genes with diverse biological consequences (3). This pathway is tightly controlled by negative regulators, including protein inhibitor of activated STAT3 (PIAS3), protein tyrosine phosphatases, ubiquitin enzymes and suppressor of cytokine signaling 3 (SOCS3), which block STAT3 activation either by directly inhibiting JAK or through inducing its degradation (5) (Fig. 1). Hyperactivation of the STAT3 signaling pathway is common in diverse types of cancer, and this typically occurs through several mechanisms, including augmented cytokine secretion, mutation in upstream

kinases or inactivating mutations in (or epigenetic silencing of) other negative regulators, such as SOCS (2,3,6,7).

STAT3 is composed of 770 amino acids with six distinct domains (Fig. 2), including a conserved amino-terminal domain (NTD), a coiled-coil domain (CCD), the DNA-binding domain (DBD), a linker domain (LD), the SH2 domain for receptor binding and dimerization and a carboxy-terminal transactivation domain (TAD) for co-factor recruitment (3). The SH2 domain mediates the binding of STAT3 to phosphotyrosine residues in interacting proteins. The NTD and SH2 domain promote STAT dimerization; furthermore, together with the CCD, they mediate the majority of the STAT3 interactions with other proteins. The DBD and LD bind to DNA and mediate the transcription of STAT3 target genes. The TAD is currently considered to fulfil a major role in regulating the functions of STAT3, through protein-protein interactions with Tyr-705 and Ser-727, which, upon phosphorylation, mediate STAT3 dimerization within this region (8). The post-translational modifications (PTMs), along with the protein-protein interactions, are mainly responsible for controlling the functions of STAT3. In total, >80 PTMs of STAT3 have been identified, including phosphorylation, methylation, SUMOylation, acetylation and ubiquitination, although the roles of the majority these PTMs of STAT3 remain poorly understood (8).

Epithelial-mesenchymal transition (EMT) is a cellular program that drives plasticity during embryogenesis, wound healing and cancer progression (9). In various types of cancer, EMT has been shown to be associated with a large variety of cancer features, including tumor cell stemness (9), metastasis (9), cancer metabolism (10,11), immune evasion (9,12) and drug resistance (9), in addition to adaptation to the microenvironment (9,13-16). EMT is regulated at multiple levels; physical constraints, hypoxia, inflammation and oncogenic or metabolic stress act at the first level, whereas the activation of signaling pathways, including the WNT, hypoxia-inducible factor (HIF), Notch, transforming growth factor-β (TGF-β), Ras and nuclear factor-κB (NF-κB) pathways, operates at the second level. These pathways converge on a set of EMT-activating TFs (EMT-TFs), whose core set includes SNAI1 (Snail), SNAI2 (Slug), Twist1, zinc finger E-box binding homeobox 1 (ZEB1) and ZEB2. These TFs are also termed the 'master' regulators of EMT, and bind to EMT effector genes (such as E-cadherin, vimentin and N-cadherin), which promote the loss of epithelial features and the gain of mesenchymal properties (such as invasion and stem-cell phenotype) (17,18).

E-cadherin acts as the gatekeeper of epithelial cells and loss of E-cadherin expression is considered a crucial event in EMT. Snail, Slug and ZEB1 can directly suppress E-cadherin expression via binding to its promoter (19,20). Twist1 also suppresses E-cadherin expression but debates regarding its mechanism exist. While some studies report that Twist1 can directly bind to E-boxes within the E-cadherin promoter to reduce its expression (21,22), others suggest that Twist1 reduces expression in an indirect manner such as through PTM (20,23,24). Moreover, loss of E-cadherin expression is not only a marker of EMT, it also results in the induction of multiple TFs, including Twist and β-catenin, to promote EMT (25). Upregulation of N-cadherin, vimentin and fibronectin is also often observed during EMT.

In the present review, it is proposed that STAT3 signaling is an integral part of EMT, serving to facilitate the EMT process via interactions with EMT-TFs, microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs). The present review aims to provide both novel insights and a comprehensive basis for follow-up research.

2. Role of STAT3 signaling in EMT

IL-6/STAT3 signaling in EMT. IL-6 is secreted by multiple cell types within the tumor microenvironment, including tumor cells, tumor-infiltrating immune cells and stromal cells (2). There is some evidence to suggest that the IL-6/STAT3 signaling axis promotes EMT in different types of cancer. For example, Sullivan *et al* (26) demonstrated that MCF7, BT474, T47D and ZR-75-1 cells in a 3D model treated with IL-6 exhibited reduced expression levels of E-cadherin, a characteristic feature of EMT. Furthermore, MCF7 cells stably expressing IL-6 ($MCF7^{IL-6}$ cells), showed characteristics of EMT, including suppression of E-cadherin expression, induction of vimentin, N-cadherin, Snail and Twist, and increased invasiveness. Notably, $MCF7^{IL-6}$ cells also exhibited a reduced expression level of E-cadherin, and an increased expression of vimentin, in a mice model *in vivo*. Similarly, CAL27 cells, a type of head and neck squamous cell carcinoma (HNSCC) cell line, displayed a decreased level of E-cadherin expression and enhanced expression of vimentin when treated with IL-6 for 72 h, which was mitigated by the addition of a neutralizing anti-IL-6 antibody (27). Additionally, IL-6 overexpression in HNSCC and immortalized oral epithelial cells was shown to induce EMT, and these cells also showed higher levels of activation of STAT3 and Snail compared with the control cells. STAT3 knockdown in these cells, but not knockdown of AKT or ERK, led to a reversal of the IL-6-mediated EMT features, suggesting that STAT3 is responsible for IL-6-mediated EMT (27). In an attempt to understand the role of IL-6 signaling in prostate tumorigenesis, Rojas *et al* (28) treated the P69 and BPH-1 benign non-tumorigenic prostate epithelial cell lines with IL-6, which resulted in the induction of EMT, including changes in the levels of E-cadherin, vimentin, N-cadherin and Snail, and enhanced motility. Such effects were suppressed by addition of the JAK2 inhibitor, AG490. IL-6/STAT3-induced EMT has also been reported in human cervical carcinoma (29). However, there are also reports indicating IL-6 treatment could not induce EMT in cancer. For example, treatment of A549, H358 and cancer tissue-originated spheroid cells with 50 ng/ml IL-6 for 48 h did not lead to EMT (30). It is possible that this negative result may be due to an insufficient treatment time with IL-6. In summary, IL-6 may be effective in inducing EMT in several cancer models; however, more studies are required to elucidate the underlying mechanisms, especially with the use of constructed *in vivo* models.

STAT3 signaling promotes the activity of EMT-TFs. Another layer of evidence supporting the role of STAT3 in EMT is the close association between STAT3 signaling and the EMT-TFs (Fig. 3).

STAT3 and Snail. Snail is the most studied of the EMT-TFs. Numerous signaling pathways have been found to be associated with the induction of Snail expression, including

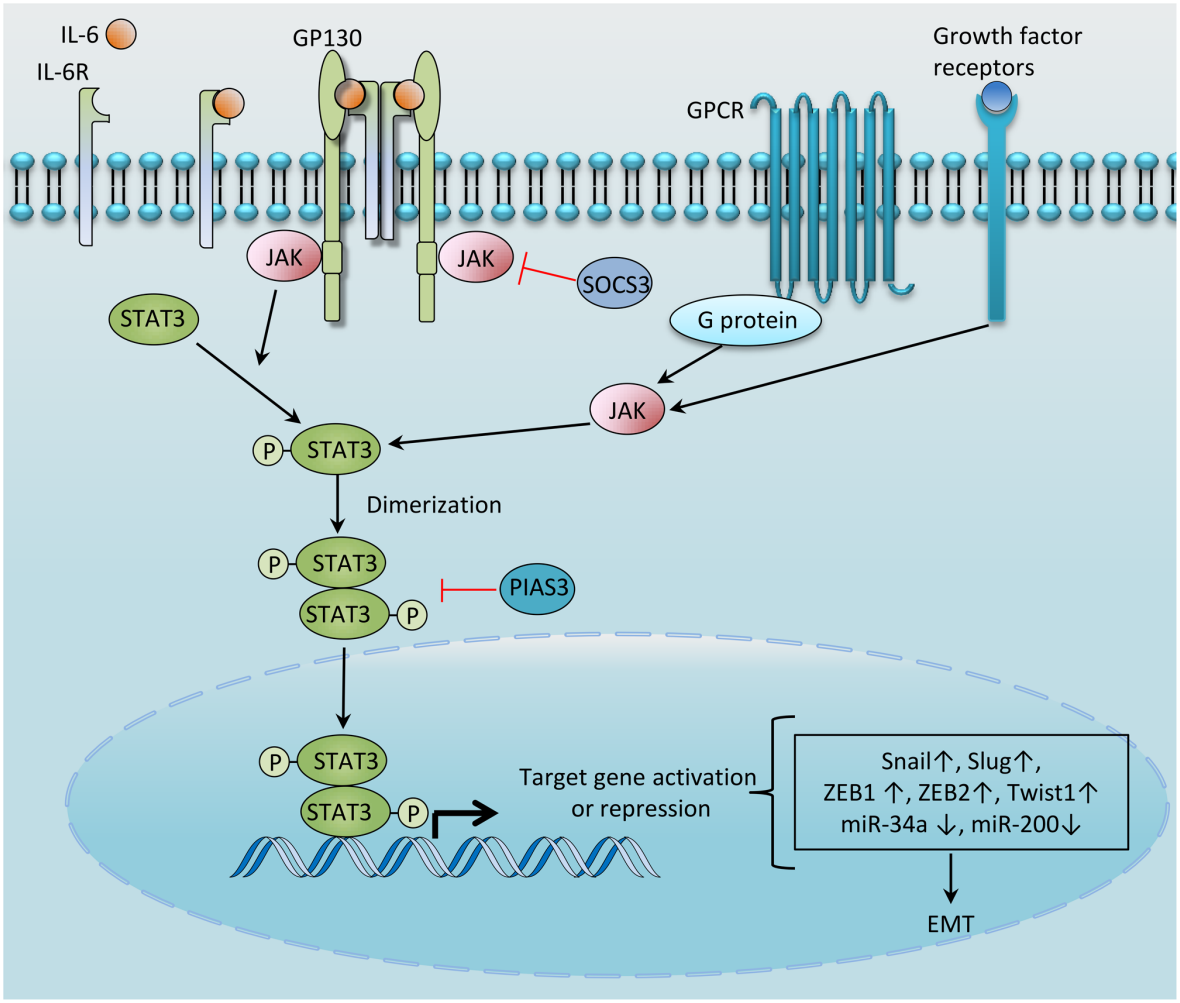

Figure 1. STAT3 signaling. IL-6 binds to its receptor (IL-6R), leading to receptor conformational changes and activation of intracellular kinases, mainly the JAK family of non-receptor tyrosine kinases. JAKs then activate STAT3, which dimerizes and is translocated to the nucleus, where it enhances the transcription of genes with diverse functions, including Snail, Slug, ZEB1, ZEB2 and Twist. STAT3 also suppresses the transcription of certain miRNAs, including miR-34a and miR-200. STAT3 signaling is tightly controlled by negative regulators such as SOCS3 and PIAS3. IL-6, interleukin-6; IL-6R, IL-6 receptor; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; ZEB1/2, zinc finger E-box binding homeobox 1/2; SOCS3, suppressor of cytokine signaling 3; PIAS3, protein inhibitor of activated STAT3; P, phosphorylated; miRNA, microRNA; GP130, glycoprotein 130; GPCR, G-protein coupled receptor; EMT, epithelial-mesenchymal transition.

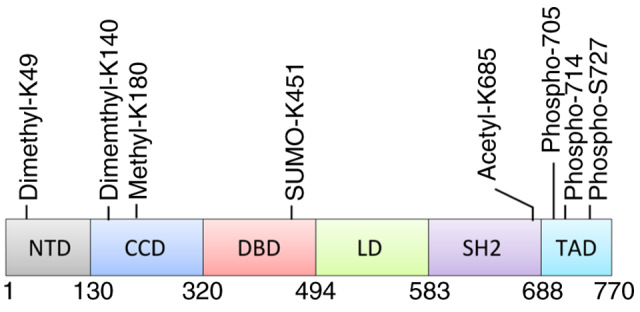

Figure 2. Structure of signal transducer and activator of transcription 3. The NTD, CCD, DBD, LD, SH2 and TAD domains are shown. The residues with post-translational modifications are indicated. NTD, amino-terminal domain; CCD, coiled coil domain; DBD, DNA-binding domain; LD, linker domain; SH2, SRC homology 2; TAD, transcription activation domain.

the TGF-β, NF-κB, HIF-1α, Notch and Wnt pathways, reactive oxygen species (ROS) and hypoxia stress [see the reviews (18,31) for further information]. Snail is also regulated by the IL-6/STAT3 signaling pathway. The first reports linking STAT3 and Snail were from studies on zebrafish and breast cancer. Solute carrier family 39 member 6 (SLC39A6; also termed LIV-1 or ZIP6), a member of the family of zinc transporter proteins, was revealed to be upregulated by STAT3 during zebrafish gastrulation (32) and in EMT in breast cancer induced by EGF (33). SLC39A6 facilitates the influx of zinc, which inactivates glycogen synthase kinase-3β (GSK-3β). Inactivated GSK-3β is unable to phosphorylate and destabilize Snail, which thereby increases the level of nuclear Snail (33) and promotes EMT. Therefore, STAT3 serves to regulate Snail in an indirect, post-transcriptional manner.

Treatment with IL-6, or IL-6 overexpression leads to Snail upregulation at both the mRNA and protein levels in various types of cancer *in vitro*, including pancreatic cancer (34), HNSCC (27), breast cancer (26) and colon cancer (35), and even non-tumorigenic prostate epithelium cells (28). Such effects were mediated by STAT3, as suppression of STAT3 led to a decrease in IL-6-induced Snail upregulation (27,34). In separate studies, TGF-β and H-Ras were shown to act

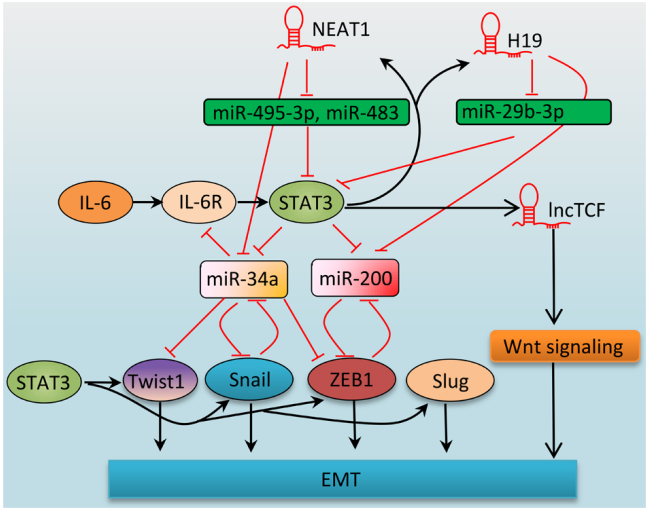

Figure 3. STAT3, EMT-TFs, miRNAs and lncRNAs form complex network to regulate EMT. STAT3 enhances EMT by transcriptionally increasing the expression of Twist1, Snail, ZEB1 and Slug. STAT3 also increases their expression by suppressing miR-34a and miR-200. lncRNAs such as NEAT1 and H19 facilitate EMT by upregulating STAT3 through miR-495-3p, miR-483 and mir-29b-3p. In addition, STAT3 promotes lncTCF, which stimulates the Wnt signaling pathway to trigger EMT. STAT3, signal transducer and activator of transcription 3; EMT, epithelial-mesenchymal transition; ZEB1, zinc finger E-box binding homeobox 1; NEAT1, nuclear paraspeckle assembly transcript 1; H19, H19 imprinted maternally expressed transcript; lncRNA, long non-coding RNA; miRNA, microRNA.

synergistically to increase Snail expression (36,37), in which STAT3 also had a role as STAT3 knockdown ameliorated Snail upregulation by TGF-β and H-Ras (37). STAT3 was shown to maintain Snail expression under normal culture conditions, and STAT3 knockdown or suppression by inhibitors decreased Snail expression in both breast and prostate cancer (38,39). In a study using hepatocellular carcinoma (HCC) cells, phosphorylated STAT3 was found to bind to the Snail promoter; moreover, inhibition of STAT3 by AG490 abrogated hepatitis virus C core-induced expression of Snail (40).

STAT3-binding sites have been identified in the Snail promoter (36,41,42), although the exact binding sites reported in different models are different. A region (TTACTCTGAA; -909 to -900) was reported to be the binding site for STAT3 in atypical teratoid/rhabdoid tumor cells, and mutation of the last 'AA' to 'GG' led to reduced binding (41). Another study (40) revealed that the identical region was also the binding site for STAT3 in HepG2 cells, which mediates hepatitis virus C core-induced Snail expression. However, in temozolomide-resistant glioblastoma (GBM) cells, the binding sites may be located between -484 to -82 of the snail promoter (42). In MDA-MB-231 (38), HCC and LM3 (43) cell lines, GTTCCGGGGATC (+325 to +336) appears to be the binding site, as demonstrated by chromatin immunoprecipitation (ChIP) assays. However, the explanation for this inconsistency is unknown at present.

Snail also regulates STAT3 signaling; for example, in ARCaP and MCF-7 cells, ectopic overexpression of Snail was shown to induce further activation of STAT3 (39). Overexpression of Snail also led to an increase in lactate-induced STAT3 activation in A549 and H1299 cells, whereas Snail knockdown reduced STAT3 activation (44). The underlying mechanism has yet to be elucidated; however, lactate was demonstrated to induce the formation of a Snail-enhancer of zeste homolog 2 (EZH2)-STAT3 complex, which enhanced STAT3 activation (44). EZH2 has also been shown to activate STAT3 via methylation in GBM stem-like cells (45) and in breast cancer cells (46), and therefore, it may be interesting to investigate whether EZH2 may be required for Snail-induced STAT3 activation. In hepatitis B virus (HBV)-associated HCC, the HBV-induced overproduction of ROS was shown to increase the expression level of Snail, which binds to E-boxes of the SOCS3 promoter, thereby decreasing SOCS3 expression via hypermethylation of the SOCS3 promoter, and causing constitutive activation of STAT3 (47).

Therefore, taken together, the results from several studies have shown that a positive and mutual regulatory relationship exists between STAT3 and Snail. STAT3 is able to increase Snail expression both transcriptionally and post-transcriptionally, whereas Snail is able to increase the activation of STAT3 via interacting with STAT3 or suppressing SOCS3 expression.

STAT3 and Slug. Slug is another EMT-TF that is important for the EMT process in cancer. Radiation-resistant A549 cells exhibited enhanced expression of Slug, which mediated tumor invasion and resistance. STAT3 small interfering (si)RNA and the STAT3 inhibitor, WP1006, reduced Slug expression and partly restored tumor cell sensitivity to radiation (48). In HBV-associated HCC, small-surface antigens promote HCC progression via STAT3-induced Slug. Treatment with either STAT3 siRNAs or the JAK2 inhibitor, AG490, was found to reduce the small-surface antigen-induced upregulation of Slug (49).

STAT3 suppression in brain tumor stem cells (BTSCs) decreased Slug expression. Furthermore, treatment with EGF, LIF or OSM led to Slug upregulation, which was reduced by a STAT3 inhibitor, suggesting that these effects were mediated by STAT3. A ChIP assay revealed that STAT3 bound to the Slug promoter, but not to the promoters for Snail, Twist, ZEB1 or ZEB2, in BTSCs (50). Lin *et al* (51) showed that STAT3 binds to the -472 to -463 (TTTTTCAAAA) region of the slug promoter, thereby increasing Slug expression and enhancing GBM radioresistance.

Plasmacytoma variant translocation 1 (PVT1) is a well-studied lncRNA that is located at the 8q24.21 region near the c-Myc oncogene. PVT1 is upregulated by copy number amplification and is able to promote cancer progression (52,53). Zhao *et al* (54) showed that PVT1 enhances STAT3 recruitment to the Slug promoter, and transcriptionally enhances Slug expression in gastric cancer. Treatment with a STAT3 inhibitor led to a reduction in PVT1-induced Slug upregulation.

Taken together, these results demonstrated that STAT3 acts as a positive regulator of Slug expression through binding to its promoter and increasing its transcription.

STAT3 and Twist. The Twist protein is a highly conserved TF that belongs to the family of basic helix-loop-helix proteins. Twist fulfils a critical role in both embryogenesis and tumorigenesis (55,56), and its upregulation has been shown to be associated with numerous types of aggressive tumors, executing multiple roles in cancer initiation and progression (56). Several signaling pathways have been shown to upregulate Twist1 expression in various types of cancer (56),

including NF-κB, Src, HIF-1α and STAT3. Knockdown of STAT3 protein by RNA interference in mouse breast cancer cells was shown to block the expression of Twist and to prevent metastases (57). STAT3 also mediates the IL-6-, EGF- and Notch-induced upregulation of Twist (58-60). When upregulated, mesoderm-specific transcript promotes the invasion of breast cancer, and has been shown to induce Twist-mediated EMT through STAT3 activation (61). Therefore, diverse signaling pathways converge on STAT3 to increase Twist expression. Furthermore, immunohistochemical (IHC) analysis of breast carcinoma (58,59) and HCC (62) samples revealed that a positive correlation exists between phosphorylated STAT3 and Twist. Mechanistically, STAT3 was shown to bind to the promoter of Twist (58-60), leading to an increase in Twist expression. Moreover, these studies suggested the same STAT3 binding site in the Twist promoter (-95 to -116).

STAT3 and ZEB1. ZEB1 is not only an EMT-TF, but it is increasingly being recognized as a crucial regulator of fundamental biological processes, including stemness vs. differentiation, cell proliferation vs. senescence and survival vs. apoptosis (63,64). STAT3 is a direct regulator of ZEB1 in various types of cancer. For example, in colon cancer, which often features STAT3 hyperactivation (65), AG490, an inhibitor of JAK2, was shown to suppress the expression of ZEB1, but not of ZEB2, Snail, Slug, Twist1 or Twist2. Similarly, STAT3 knockdown was found to suppress both ZEB1 expression and the migration of colon cancer cells (66). STAT3 has also been shown to bind to the ZEB1 promoter, and mutation of the binding sites led to a marked reduction both of STAT3 binding and of ZEB1 promoter activity (66). Another example was provided in a study by Avtanski *et al* (67), where it was shown that the constitutively activated form of STAT3 was able to bind to the ZEB1 promoter and to increase the mRNA expression of ZEB1. In addition, the STAT3 inhibitors, Stattic and honokiol, were shown to reduce both STAT3 binding and the mRNA expression of ZEB1, and to suppress EMT in breast cancer (67). The STAT3/ZEB1 signaling axis was also investigated in gefitinib-resistant A549 and PC9 cells, wherein increased activation of STAT3 and the characteristic features of EMT were displayed, including increased expression levels of ZEB1, N-cadherin and vimentin, and a decreased expression of E-cadherin, compared with the parental cells. STAT3 knockdown by siRNA in these resistant cells led to a reversal of EMT, including ZEB1 downregulation (68). Taken together, these results support the hypothesis that STAT3 binds directly to the promoter of ZEB1, enhancing ZEB1 expression to promote EMT.

STAT3 and E-cadherin. Loss of E-cadherin is a hallmark of EMT, and this phenomenon is associated with increased tumor cell invasion and spread. In a study by Zhang *et al* (62), IHC analysis revealed that activation of STAT3 was conversely correlated with E-cadherin expression in HCC. In addition, it has been demonstrated that IL-6 treatment leads to E-cadherin downregulation in HCT116 colorectal carcinoma cells (69). Although there are two putative STAT3-binding sites in the E-cadherin promoter region, STAT3 may not directly bind to the E-cadherin promoter; instead, it may function via regulating the major EMT-TFs, including Snail, Slug, Twist and ZEB1, to influence E-cadherin expression (66,69).

STAT3 is activated and required for TGF-β1-induced EMT. The TGF-β superfamily comprises structurally related growth factors, including TGF-β, activins and bone morphogenetic proteins. These factors fulfil important roles in morphogenesis during embryonic development and tissue homeostasis in adults (70,71). Among them, TGF-β1 is a well-established potent EMT inducer (72), and adding TGF-β1 to epithelial cell culture has been shown to be an effective way of inducing EMT. TGF-β1 activates signaling by binding to and promoting the formation of the single-span transmembrane TGF-β receptor (TβR)I-TβRII heterocomplex (Fig. 4), which leads to the phosphorylation and activation of the receptor-regulated Smad (R-Smad) proteins, Smad2 and Smad3. The activated R-Smad proteins subsequently form a complex with co-Smad (Smad4), and the complex then translocates to the nucleus, where it regulates the transcription of a broad range of genes. In addition to the canonical Smad signaling pathway, TGF-β1 activates other signaling pathways, including the AKT, ERK, p38/MAPK, GTPase and STAT3 signaling pathways (71). These pathways all contribute to the effects elicited by TGF-β1 in both a context and cell type-dependent manner. In the present review, the role of STAT3 signaling in TGF-β1-induced EMT is specifically summarized.

The association between STAT3 and TGF-β1 signaling is context-dependent in cancer [refer to (71,73) for further information]. During the early phase of tumorigenesis, STAT3 and TGF-β1 are mutually antagonistic. Although STAT3 is oncogenic even in the onset of tumorigenesis (74,75), TGF-β functions both as a tumor suppressor in pre-malignant cells and as a tumor promoter in late-stage tumors (76).

TGF-β-induced EMT and Snail expression has been shown to be enhanced by Ras signaling (77). Through screening a library of siRNAs, Saitoh *et al* (37) identified STAT3 as the mediator molecule that markedly enhances the Snail promoter activity induced by TGF-β and Ras signaling. Knockdown or inhibition of STAT3 attenuates TGF-β-induced Snail upregulation and EMT; moreover, STAT3 mutants that either cannot be phosphorylated at Tyr-705 or lack transcriptional activity fail to activate Snail expression. Mechanistically, Smad3 activated by TGF-β signaling both interacts with and sequesters PIAS3 in the presence of Ras signaling, thereby causing STAT3 to be released from its inhibition of PIAS3 and allowing it to positively regulate Snail expression. Notably, the presence of a PIAS3-Smad3-p300 ternary complex was found to be significantly enhanced in response to TGF-β, which subsequently increased the activity of Smad3 (78); therefore, PIAS3, upon dissociation from STAT3, forms the PIAS3-Smad3-p300 ternary complex, and this represents one of the mechanisms underlying TGF-β-induced STAT3 activation (Fig. 4).

TGF-β has also been shown to activate STAT3 in colon cancer, in which TGF-β signaling was inactivated by mutations (79), suggesting that TGF-β may activate STAT3 via a mechanism not involving intracellular signaling. Indeed, IL-11 was revealed to be the mediator (Fig. 5); TGF-β induces stromal cells to secrete IL-11, which in turn activates STAT3 in colon cancer cells through binding to the transmembrane receptor protein, glycoprotein 130 (79). The TGF-β/IL-11/STAT3 signaling axis was also shown to be required for colon cancer metastasis (79). In addition to IL-11, in non-small cell lung cancer (NSCLC), HCC and normal human lung fibroblast

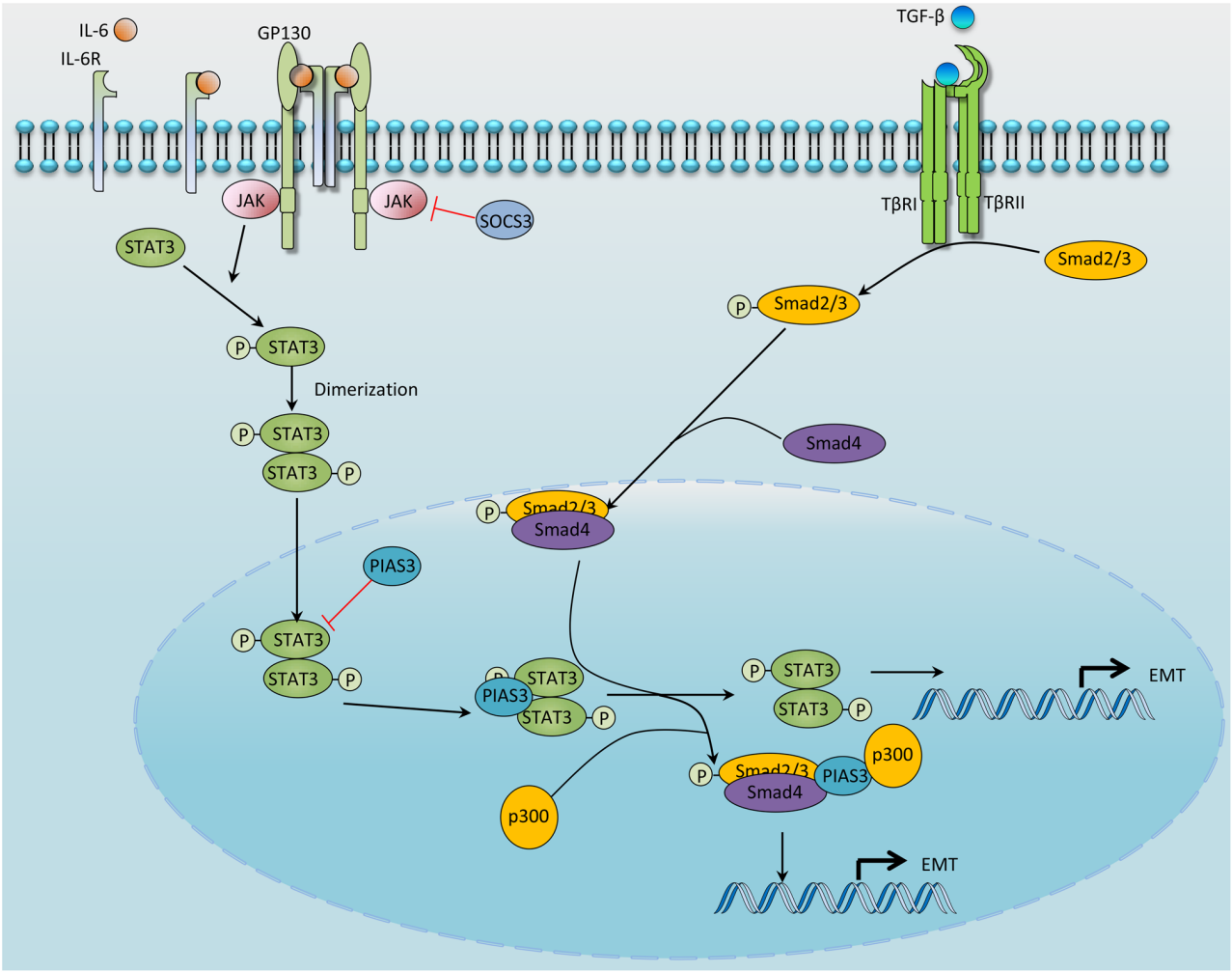

Figure 4. PIAS3 links TGF-β and STAT3 signaling. TGF-β activates Smad2/3, which binds to PIAS3 and dissociates it from STAT3, releasing the inhibitory effect of PIAS3 on STAT3. PIAS3 then binds to and enhances Smad3 transactivation activity. STAT3, signal transducer and activator of transcription 3; PIAS3, protein inhibitor of activated STAT3; TGF-β, transforming growth factor-β; IL-6, interleukin-6; IL-6R, IL-6 receptor; JAK, Janus kinase; TβR, TGF-β receptor; P, phosphorylated; GP130, glycoprotein 130; EMT, epithelial-mesenchymal transition.

cells, TGF-β treatment led to increased secretion of IL-6. Treatment with either an IL-6 receptor neutralizing antibody or a JAK/STAT3 inhibitor was found to reduce TGF-β-mediated STAT3 activation and EMT (80-82). Taken together, these results suggest that IL-6 is also a mediator of TGF-β-mediated STAT3 activation and EMT (Fig. 5).

Src homology 2-b3 protein (SH2B3; also known as lymphocyte adapter protein) belongs to the SH2B family of adaptor proteins and is a negative regulator of JAK/STAT signaling. Mutations in SH2B3 have been identified in a range of hematological and inflammatory diseases (83). Although SH2B3 is considered to act as a negative regulator in hematological cancer, its role in solid tumors remains controversial. SH2B3 was reported to act as a tumor promoter in ovarian (84), breast (85) and anaplastic thyroid cancer (86) cancer. However, compared with matched adjacent normal tissues, SH2B3 was found to be downregulated in colon cancer, and its overexpression led to a decrease in the invasion rate of colon cancer cells (87). Wang *et al* (88) also showed that the expression of SH2B3 is decreased in lung cancer, whereas its overexpression led to a suppression of malignant phenotypes, including reduced rates of cell proliferation and invasion. Furthermore, TGF-β was shown to both reduce SH2B3 expression and activate JAK2/STAT3 and EMT, which was attenuated by SH2B3 overexpression. Therefore, SH2B3 downregulation may represent an additional mechanism underlying TGF-β-induced STAT3 activation and EMT.

3. miRNAs and the STAT3-EMT axis

miRNAs in cancer. miRNAs are small (~22-nucleotide) non-protein-coding RNAs that regulate gene expression by associating with complementary sequences in the 3'-untranslated region (UTR) of their target genes, thereby blocking translation. In the field of cancer, miRNAs can be functionally divided into oncogenic miRNAs and tumor-suppressor miRNAs (89). Several miRNAs has been shown to be critical regulators of EMT (18,90,91), including miR-200, miR-34 and miR-30a, and herein only those miRNAs that are associated with STAT3-induced EMT are discussed (see Table I).

STAT3 suppresses miR-34a to promote EMT. The miR-34 family members (miR-34a, miR-34b and miR-34c), and miR-34a in particular, are recognized as master tumor

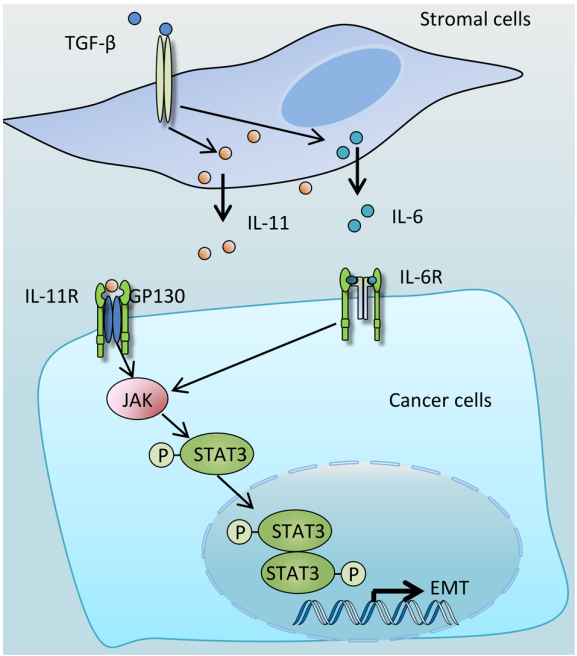

Figure 5. TGF-β enhances IL-6 and IL-11 secretion in stromal cells to activate STAT3 signaling in cancer cells to promote EMT. TGF-β signaling in tumor stromal cells increases the expression and secretion of IL-11 and IL-6, both of which activate STAT3 signaling in tumor cells, thereby enhancing tumor EMT. TGF-β, transforming growth factor-β; IL, interleukin; STAT3, signal transducer and activator of transcription 3; EMT, epithelial-mesenchymal transition; IL-6/11R, IL-6/11 receptor; JAK, Janus kinase; P, phosphorylated; GP130, glycoprotein 130.

suppressors (92). Loss of miR-34a expression occurs in a wide range of tumors, and this miRNA has been validated as a promising prognostic indicator. To date, >200 miR-34a targets have been reported, and through these target genes, miR-34a has been shown to regulate multiple cancer processes, including the cell cycle, EMT, metastasis, stemness of cells, apoptosis, senescence and tumor immunity (92,93).

It has been demonstrated that miR-34a suppresses EMT in various cancer types through targeting a number of key EMT genes. For instance, miR-34a inhibits EMT through directly downregulating the expression of the EMT-TFs, Snail (94), ZEB1 (95) and Twist (95), by binding to their 3'-UTRs. Moreover, Snail and ZEB1 are able to bind to the E-box sequences in the miR-34a promoter, thereby decreasing miR-34a expression and forming a double-negative feedback loop maintaining the EMT state (94). In addition, miR-34a suppresses several critical EMT signaling pathways, including the TGF-β [via targeting Smad4 (96) and TβRII (97)], STAT3 [via targeting IL-6R (35)], Wnt (98,99) [via targeting Wnt1 (100,101), transcription factor 7 (TCF7) (102) and lymphoid enhancer binding factor 1 (103)], Notch [via targeting Notch1 (104) and Notch2 (105)] and AXL [via targeting AXL (106)] pathways. All of these signaling molecules and pathways act as enhancers of EMT (9,17,107,108).

Rokavec *et al* (35) demonstrated that IL-6 suppresses the expression of miR-34a in a STAT3-dependent manner; knockdown of STAT3 attenuated the downregulation of miR-34a that was induced by IL-6. IL-6 treatment led to binding of STAT3 to a conserved site located at the first intron of miR-34a, thereby suppressing its transcription. Furthermore, ectopic expression of miR-34a was shown to prevent IL-6-induced EMT and block IL-6-induced invasion (35). This STAT3/miR-34a signaling axis was subsequently confirmed in a study by Avtanski *et al* (109), which showed that leptin and IL-6 could induce the binding of STAT3 to the promoter of miR-34a and reduce its expression. These effects could be suppressed by honokiol, a bioactive polyphenol obtained from *Magnolia grandiflora*. Taken together, these studies have shown that STAT3 may directly suppress miR-34a to enhance EMT.

STAT3 suppresses miR-200 to promote EMT. The miR-200 family of miRNAs, including miR-200a, miR-200b, miR-200c, miR-141 and miR-429, are encoded by two clusters of hairpin precursors located on human chromosomes 1p36.33 (miR-200b, miR-200a and miR-429 are termed the 'miR-200b/200a/429 cluster') and 12p13.31 (miR-200c and miR-141 are termed the 'miR-200c/141 cluster'). Each of these miRNAs produces a mature-5p and -3p miRNA (110).

miR-200 is highly expressed in epithelial cancer cells, and minimally expressed in mesenchymal cancer cells (110). Overexpression or knockdown of miR-200 causes changes in the EMT state of cancer cells by directly targeting ZEB1 and ZEB2 (110-113), which leads to an alteration in E-cadherin expression, thereby promoting EMT (114-116). Downregulation of miR-200 expression is observed during TGF-β-induced EMT, and overexpression of miR-200 hinders TGF-β-induced EMT, implying that miR-200 is an integral component of TGF-β-induced EMT (115,116).

The promoters of both of the aforementioned miR-200 clusters contain ZEB-type E-box elements, and their activities were shown to be repressed by ZEB1 and ZEB2 (117,118). Therefore, ZEB1/2 and miR-200, which exert opposite functions on EMT, reciprocally regulate each other in a double negative feedback loop. There is also evidence to suggest that STAT3 suppresses miR-200 expression. For instance, treatment with OSM has been shown to reduce miR-200b and miR-200c expression in a STAT3-dependent manner to promote EMT (119). Additionally, treatment with the STAT3 inhibitor, Stattic, leads to a significant upregulation of miR-200a, miR-200b and miR-429, and a reversal of EMT (120). By contrast, overexpression of STAT3 leads to a reduction in the expression of these miRNAs, and an enhancement of EMT (120). Further study showed that this effect is dependent on EZH2, which itself is a direct target of STAT3 (121). Therefore, disrupting the EZH2/miR-200 axis has the effect of attenuating the EMT-promoting effects of STAT3 (120). Another study (122) on bladder cancer also found that EZH2 was able to reduce miR-200 expression and promote cancer progression, thereby adding a further line of evidence in support of the existence of a STAT3/EZH2/miR-200 signaling axis in cancer. However, whether STAT3 directly binds to the promoter of miR-200b/-a/-429 or miR-200c/-141 requires further study.

STAT3 suppresses miR-30 to enhance EMT. miR-30 is a tumor suppressor that inhibits EMT by directly binding to Snail and downregulating its expression (123,124). As reported in AML12 murine hepatocytes (124) and HNSCC (125), TGF-β1 treatment led to the induction of EMT concomitant with the downregulation of miR-30. The ectopic expression

Table I. miRNAs involved in the STAT3-EMT axis.

miRNA	Information
miR-34a (tumor suppressor)	IL-6 inhibits miR34a via STAT3 binding to the promoter of miR34a. In addition, ectopic expression of miR-34a was shown to prevent IL-6-induced EMT (35,109).
miR-200 (tumor suppressor)	OSM decreases miR-200b and miR-200c expression in a STAT3-dependent manner (119). The STAT3 inhibitor, Stattic, upregulates miR-200a, miR-200b and miR-429, and reverses EMT. Overexpression of STAT3 decreases the expression of these miRNAs and enhances EMT (120).
miR-30 (tumor suppressor)	TGF-β1 activates STAT3, which then binds to the promoter of MALAT1 and increases its expression. Upregulated MALAT1 sponges miR-30a, causing a decrease in its expression, thereby mediating EMT induced by TGF-β1 (125).
miR-21 (oncogenic miRNA)	STAT3 directly binds to the promoter of miR-21 and enhances its expression (131). LIF enhances EMT via STAT3-dependent upregulation of miR-21. Blocking the function of miR-21 leads to a marked inhibition of the ability of LIF to promote EMT (133).

miRNA, microRNA; IL, interleukin; STAT3, signal transducer and activator of transcription 3; EMT, epithelial-mesenchymal transition; OSM, oncostatin M; TGF-β1, transforming growth factor-β1; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; LIF, leukaemia inhibitory factor.

of miR-30 mimics inhibited both the EMT phenotype (125) and TGF-β1-induced EMT (124,125). miR-30 was also shown to negatively regulate the expression of Snail though direct targeting of its 3'-UTR sites (124). STAT3 activated by TGF-β1 binds to the promoter of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), thereby increasing its expression. Upregulated MALAT1 sponges miR-30a, leading to a decrease in miR-30a expression (125). Therefore, it has been shown that TGF-β1 is also able to promote EMT through the STAT3/MALAT1/miR-30 signaling axis.

STAT3 and other miRNAs. miR-21 is a potent oncogenic miRNA that targets several tumor-suppressor genes (126,127). miR-21 enhances EMT (128-130), and has been shown to be directly regulated by STAT3 (131); moreover, several conserved STAT3-binding motifs upstream of the miR-21 gene promoter have been identified (132). miR-21 has an important role in STAT3-induced EMT. For instance, in breast cancer (133), LIF enhances EMT via STAT3-dependent upregulation of miR-21. Furthermore, blocking the function of miR-21 leads to a marked suppression of the ability of LIF to promote EMT, whereas STAT3 inhibition leads to a reduction in LIF-induced miR-21 upregulation. miR-21 has been shown to target multiple genes, including phosphatase and tensin homolog, T-cell lymphoma invasion and metastasis-inducing factor 1, programmed cell death 4 and maspin (133). The products of these genes are all associated with the inhibition of cell migration, invasion and metastasis. Collectively, these studies have supported the notion that miR-21 is one of the networks responsible for mediating STAT3-induced EMT.

miR-218, acting as a tumor suppressor, was shown to be downregulated in various cancer types compared with the normal surrounding cells (134). miR-218 suppress EMT in several cancer models, including lung cancer [via targeting of roundabout guidance receptor 1, EGFR-coamplified and overexpressed protein (135) and Slug/ZEB2 (136)], cervical cancer (via targeting of Scm-like with four MBT domains 1 and defective in cullin neddylation 1, domain containing 1) (137), HCC (via targeting of serpin mRNA-binding protein 1) (138), glioma cells (via targeting of lipoma HMGIC fusion partner-like 3) (139), colorectal cancer (CRC; via targeting of connective tissue growth factor) (140) and gastric cancer (via targeting of WASP family member 3) (141). STAT3 directly interacts with a locus downstream of the miR-218 gene, inhibiting its expression by recruiting the transcriptional repressor, BCL2-associated transcription factor 1 (142). Therefore, it seems plausible that STAT3 enhances EMT by directly inhibiting miR-218 expression; however, to date, this has not been confirmed experimentally.

4. lncRNAs and the STAT3-EMT axis

lncRNAs comprise a large class of regulatory RNA molecules, are generally >200 nucleotides in length and are considered to lack evident protein-coding potential (143-145). lncRNAs fulfil crucial roles in diverse biological processes, including EMT (144,145), and perform their functions through modifying gene expression at either the transcriptional or the post-transcriptional level, or by interacting with DNA, RNA (by complementary base-pairing) or proteins (by adapting specific secondary structures) (143).

A growing body of evidence has shown that STAT3 signaling is regulated by, and also regulates an increasing number of, lncRNAs (146-148). A dual relationship exists between lncRNAs and STAT3 signaling as they influence each other to promote cancer progression. STAT3 regulates the expression of lncRNAs to enhance EMT; however, lncRNAs also modulate STAT3 expression or activity to coordinate EMT (Fig. 3 and Table II). For instance, nuclear paraspeckle assembly transcript 1 (NEAT1), the most extensively studied lncRNA, which is abnormally expressed in numerous types of cancer, has been shown to drive tumor initiation, progression

Table II. lncRNAs involved the in STAT3-EMT axis.

lncRNA	Information
NEAT1	STAT3 enhances NEAT1 expression by binding to its promoter (153). NEAT1 increases STAT3 expression by sponging miR-483 (154), miR-361 (155) and miR-495-3p (156) to promote EMT.
H19	H19 promotes EMT by increasing STAT3 expression through targeting miR-29b-3p (165). H19 also positively modulates STAT3-EMT through SOCS5 suppression by miR-675-3p (166). STAT3 upregulates H19 transcriptionally to enhance EMT (167).
lncTCF7	IL-6 increases lncTCF7 expression by STAT3 binding to the lncTCF promoter, and knockdown of lncTCF7 expression impairs EMT induced by IL-6 in HCC (168).
KIAA0087	KIAA0087 prevents the growth, metastasis and EMT of osteosarcoma, concomitant with reduced JAK2/STAT3 activation. Moreover, such effects could be relieved by miR-411-3p mimics through targeting the SOCS1/JAK2/STAT3 pathway (171).
CSAC11	CSAC11 stimulates HCC cell EMT and invasion. STAT3 and CSAC11 expression were found to be positively correlated in HCC tumors. STAT3 overexpression or knockdown increased or decreased CSAC11, respectively, by binding to the promoter of CSAC11 (174). Additionally, CSAC11 enhances EMT and STAT3 activation in bladder cancer (173). However, whether or not STAT3 is required for CSAC11-induced EMT requires further study.
CHRF	Evidence suggests that lncRNA CHRF promotes EMT in prostate cancer (250), HCC (251), ovarian cells (170), colorectal cancer (252) and gastric cancer (253). Another study also revealed that CHRF activates STAT3 (170). However, whether or not STAT3 is required for CHRF-induced EMT has yet to be investigated.
AB073614	AB073614 promotes EMT in glioma cells (179) and colon cancer (181). In colon cancer, this effect was at least partly mediated by STAT3, as a JAK2 inhibitor blocked the effect of AB073614 (181). More details are required concerning the mechanisms underlying the AB073614/STAT3/EMT axis.
PVT1	lncRNA PVT1 induces EMT in several tumor models (173-178). PVT1 facilitates EMT by physically interacting with activated STAT3, which then enhances STAT3 binding to the Slug promoter and increases Slug expression to facilitate EMT (54). Additionally, STAT3 regulates PVT1 by binding to its promoter (14).
FEZH1-AS1	FEZF1-AS1 knockdown reduces EMT, concomitant with decreased activation of STAT3. Furthermore, JAK2 overexpression restores the attenuation of EMT mediated by FEZF1-AS1 knockdown, suggesting that JAK2/STAT3 signaling mediates the effect of FEZF1-AS1 on EMT (194).
DLGAP1-AS1	DLGAP1-AS1 sponges miR-26a/b-5p, which directly targets IL-6, promoting STAT3 signaling. STAT3 reciprocally enhances DLGAP1-AS1, thereby forming a positive feedback loop, which facilitates EMT in HCC. DLGAP1-AS1 knockdown inhibits EMT of HCC, although IL-6 treatment could partly restore EMT suppressed by DLGAP1-AS1 knockdown (183).

lncRNA, long non-coding RNA; NEAT1, nuclear paraspeckle assembly transcript 1; STAT3, signal transducer and activator of transcription 3; EMT, epithelial-mesenchymal transition; H19, H19 imprinted maternally expressed transcript; CASC11, cancer susceptibility 11; SOCS, suppressor of cytokine signaling; IL, interleukin; HCC, hepatocellular carcinoma; JAK2, Janus kinase 2; FEZF1-AS1, FEZ family zinc finger antisense 1; PVT1, plasmacytoma variant translocation 1; miR, microRNA.

and drug resistance (149), and is also an enhancer of EMT in different types of cancer (150-152). STAT3 enhances NEAT1 expression by binding to its promoter (153). In osteosarcoma cells, NEAT1 was found to increase STAT3 expression by sponging miR-483 to promote EMT (154). Additionally, NEAT1 has been shown to sponge miR-361 (155) and miR-495-3p (156), leading to the upregulation of STAT3. Therefore, a positive loop exists between NEAT1 and STAT3, as they mutually enhance each other's oncogenic function.

H19 imprinted maternally expressed transcript (H19) is another widely studied potent EMT enhancer (157-159). Several mechanisms have been suggested to explain the effects of H19 (158,159). For instance, H19 sponges miR-200 to upregulate ZEB1 and it sponges miR-138 to increase the level of SRY-box transcription factor 4 to enhance EMT (160,161). Additionally, H19 has been shown to associate with EZH2 to both enhance β-catenin expression and decrease E-cadherin expression (162). Moreover, studies have revealed that STAT3 is an important downstream mediator of the EMT-promoting function of H19. miR-29b-3p targets STAT3, leading to a decrease in its expression (163,164), and H19 has been shown to promote EMT by targeting miR-29b-3p to increase STAT3 expression (165). In prostate cancer cells, miR-675-3p, a non-coding RNA transcribed from the first exon of H19, was reported to mediate the EMT function of H19 by down-regulating the STAT3 inhibitor, SOCS5 (166). Considering that STAT3 also upregulates H19 transcriptionally (167), STAT3/H19 may constitute a positive loop to induce EMT.

IL-6 has been shown to increase the level of lncTCF7 expression via STAT3 binding to the lncTCF promoter, and

knockdown of lncTCF7 expression impaired EMT induced by IL-6 in HCC (168), suggesting the involvement of lncTCF7 in IL-6-induced EMT. KIAA0087 is a recently identified tumor suppressor lncRNA, the expression of which is reduced in endometrial carcinoma (169) and is associated with overall survival in NSCLC (170). Gong *et al* (171) demonstrated that KIAA0087 was also downregulated in osteosarcoma compared with normal tissues, and its downregulation was found to promote cell growth, metastasis and EMT through releasing the sponging effect of miR-411-3p, which mediates reductions in the level of SOCS1 and activation of the JAK2/STAT3 pathway.

The lncRNA cancer susceptibility 11 (CASC11; also known as CARLo-7, LINC00990 and MYMLR) was also found to be upregulated in various types of cancer (172), and functions as a oncogene to promote cancer progression, including EMT. CASC11 has also been shown to be associated with poor prognosis (172,173) and to enhance bladder cancer cell proliferation, invasion and EMT through activating the Wnt/β-catenin and STAT3 signaling pathways (173). Additionally, CASC11 knockdown was shown to reduce EMT in HCC (174). Notably, four STAT3 binding sites exist in the CASC11 promoter, and deletion of the first site significantly decreases CASC11 promoter activity. In addition, manipulation of STAT3 expression changes CASC11 expression accordingly (174). Therefore, these studies have collectively shown that STAT3 acts as a TF, promoting CASC11 expression to enhance cancer EMT. Additionally, STAT3 signaling appears to operate downstream of CASC11, mediating CASC11-induced EMT. However, the detailed underlying mechanisms of this requires further investigation.

The expression of lncRNA AB073614 was found to be significantly higher in the tumor tissues of various cancer types compared with that in the surrounding normal tissues, including ovarian cancer (175,176), cervical cancer (177), glioma (178,179) and CRC (180,181), and has been shown to facilitate invasion, proliferation and EMT (179,181). AB073614 knockdown in colon cancer cells reversed EMT, along with decreased STAT3 activation. Furthermore, a JAK2 inhibitor, AT9283, blocked the effects of AB073614, suggesting that STAT3 may be involved in the EMT-inducing role of AB073614 (181). DLGAP1-AS1, an oncogenic lncRNA, that has been identified in several types of cancer, and it was shown to be upregulated in tumor tissues, where it enhanced tumor progression, EMT and drug resistance (182). Lin *et al* (183) showed that DLGAP1-AS1, through sponging miR-26a/b-5p which directly targets IL-6, promoted STAT3 signaling. STAT3 reciprocally increased the expression of DLGAP1-AS1, thereby forming a positive feedback loop that facilitates EMT in HCC. DLGAP1-AS1 knockdown inhibits EMT in HCC, and treatment with IL-6 is able to partially restore EMT suppressed by knockdown of DLGAP1-AS1.

The lncRNA, PVT1, has been shown to facilitate EMT by physically interacting with activated STAT3, which then enhances STAT3 binding to the Slug promoter, increasing Slug expression to facilitate EMT (54). Indeed, several studies have revealed that PVT1 is an EMT inducer (52,53,184-187). Furthermore, STAT3 was also shown to upregulate PVT1 expression through binding to its promoter (14) and therefore, PVT1 and STAT3 form a positive regulatory loop to enhance cancer progression. Taken together, PVT1 has been demonstrated to participate in the regulation of the STAT3-EMT signaling axis.

FEZ family zinc finger antisense 1 (FEZF1-AS1) is a novel oncogenic lncRNA that is upregulated in various types of human cancer, and is associated with various aspects of carcinogenesis, including cell proliferation, invasion, metastasis and EMT (188-191). It was reported that FEZF1-AS1 could activate STAT3 in ovarian cancer and CRC (192,193). Conversely, Knockdown of FEZF1-AS1 was found to reduce cell proliferation and EMT, and to enhance apoptosis, concomitant with a decreased activation of STAT3 (194). Furthermore, JAK2 overexpression notably restored the attenuated EMT following FEZF1-AS1 knockdown, suggesting that the JAK2/STAT3 signaling axis participates in mediating the effect of FEZF1-AS1 on EMT (194).

5. circRNAs and the STAT3-EMT axis

circRNAs are a class of RNAs that are single-stranded and circular, lacking 5'-caps and 3'-tails. circRNAs are stable, difficult to cleave and resistant to RNA exonuclease or RNase degradation (195-197), and function through modulating transcription and splicing, regulating the stability and translation of cytoplasmic mRNAs, interfering with signaling pathways and serving as templates for translation (198). With the rapid development of sequencing technology, novel circRNAs have been discovered, and their characteristics and functions are being revealed (198). Dissecting the roles and mechanisms of circRNAs is a cancer research 'hotspot', and are also promising targets for cancer therapy (199-201).

An increasing number of studies have reported that circRNAs regulate EMT by targeting EMT-TFs or EMT-associated signaling pathways (195,202,203). Unfortunately, at present and to the best of our knowledge, no study has surveyed the role of circRNAs in the STAT3-EMT signaling axis or the role of STAT3 in the circRNA-EMT axis in any great detail. Previously published studies (204-207) have shown that certain circRNAs are able to induce or reduce EMT, concomitant with enhanced or reduced activation of STAT3. However, whether or not STAT3 is required for these circRNA-induced EMT changes has not yet been studied; therefore, at present, the STAT3-circRNA-EMT axis requires further investigation.

6. Targeting the STAT3 pathway in cancer

STAT3 pathway as a therapeutic target. Due to the critical tumor-promoting role, the STAT3 pathway has been intensely pursued as a therapeutic target. The inhibitors of the STAT3 pathway can be divided into direct STAT3 inhibitors, JAK inhibitors and IL-6/IL-6R inhibitors.

Direct STAT3 inhibitors. STAT3 itself is a TF that lacks enzymatic activity, and therefore the development of inhibitors has been difficult. Generally, direct inhibitors of STAT3 can be classified into three categories: peptides, small molecules and oligonucleotides (208,209).

Peptide STAT3 inhibitors. STAT3 activation requires an interaction between the SH2 domain and phosphorylated

Tyr-705; therefore, it is plausible that a peptide mimicking the sequence containing phosphorylated Tyr-705 would be able to bind to the SH2 domain of STAT3 and inhibit its activation and activity (209). Indeed, a 6-amino acid Tyr-phosphorylated peptide (PY*LKTK) can bind to the STAT3 SH2 domain, thus blocking STAT3 dimerization, DNA binding and gene regulation (210). Mimics or modification of PY*LKTK such as peptidomimetic ISS-610 (211) and PM-73G (212), also suppress STAT3 activity. However, these agents are challenged by potency, cellular permeability, stability and potential immunogenicity, which hinder their clinical development (2,209,213).

Small molecule inhibitors. Another group of STAT3 inhibitors are small molecules mainly targeting the SH2 domain (209). The number of inhibitors reported is large; however, only a few have entered into early phase clinical trials. For instance, C188-9 (also termed TTI-101), which targets the STAT3 SH2 domain, inhibits STAT3 activation *in vitro* (214) and alleviates inflammation and the severity of colitis in a T-cell transfer colitis model *in vivo* (215). C188-9 also suppressed HNSCC growth in a nude mice xenograft model (216). The clinical trial of this inhibitor in humans (NCT03195699) is still ongoing. Another two STAT3 SH2 domain inhibitors, OPB-31121 and OPB-51602, highly suppress STAT3 activation and display potent cancer suppression *in vitro* and in mouse models (217-220). However, early phase clinical trials of OPB-31121 and OPB-51602 showed very limited clinical activity (2), and the reasons for this failure are not currently known. A lack of specificity due to a high similarity of the SH2 domain of STAT3 and other STAT family members may be involved.

STAT3 antisense oligonucleotide (ASO) inhibitors. ASOs are short oligonucleotides that can base-pair with complementary RNA and trigger post hybridization mechanisms to modulate gene expression (221). One example is AZD9150 (danvatirsen), which targets the 3'-UTR region of the STAT3 gene (222). Clinical studies have shown that it is well tolerated (223-225), decreased the tumor-initiating potential of neuroblastoma cells (222) and suppressed leukemic cell growth (226). The tumor-suppressive effect of danvatirsen may be related to tumor stromal cells, which preferentially uptake danvatirsen and suppress tumor growth (227). Clinical trials for HCC (NCT01839604), HNSCC (NCT05814666), CRC (NCT02983578) and NSCLC (NCT02983578) are ongoing to evaluate the safety and activity of danvatirsen.

STAT3 decoy oligonucleotide inhibitors. TF decoy oligonucleotides are short double-stranded DNA molecules that bind to TFs, thus blocking the interaction between TFs and DNA. Leong *et al* (228) designed a STAT3 decoy composed of a 15-bp double-stranded oligonucleotide representing the STAT3 responsive element within the c-Fos promoter. The decoy inhibited STAT3 transcriptional activity by competitively interfering with phosphorylated STAT3 dimers binding to the promoter region of STAT3 target genes, thereby inhibiting STAT3-mediated gene regulation. Further studies showed that the decoy suppressed growth of HNSCC (229) and lung cancer (230) cells in xenograft models via daily intratumoral injection. Additionally, a phase 0 clinical trial (NCT00696176) demonstrated that this STAT3 decoy abrogated target gene expression in HNSCC tumors. Although encouraging effects were observed, the decoy was unstable in serum and short-lived, which restricted its usage (231). To overcome this barrier, Sen *et al* (231) designed a cyclic STAT3 decoy by linking the oligonucleotide strands using hexaethylene glycol spacers. This modified decoy had a long half-life in serum (~12 vs. ~1.5 h, compared with the parental decoy), making it suitable for intravenous (IV) administration. Indeed, in HNSCC (231) and NSCLC (232) xenograft mice, daily IV injections of the modified decoy significantly prevented tumor growth, concomitant with decreased expression of STAT3 target genes. Other modifying strategies have also been applied. For instance, Zhang *et al* (233) linked the same STAT3 decoy to the Toll-like receptor 9 (TLR9) ligand. This STAT3 decoy conjugate also had a long half-life and targeted $TLR9^+$ immune cells (dendritic cells and B cells) and the majority of acute myeloid leukemia cells from patients, including leukemia stem/progenitor cells preferentially. In preclinical studies, daily IV injections of the STAT3 decoy conjugate markedly reduced myeloid leukemia progression in a mouse model (233).

Although oligodeoxynucleotides inhibitors of STAT3 provide great specificity and potency, their poor cell membrane penetration, rapid degradation and the lack of effective targeted delivery carriers remain the major obstacles that impede their use against solid tumors clinically.

STAT3 suppression by proteolysis targeting chimera (PROTAC) technology. PROTAC technology has emerged as a promising strategy for developing novel drugs, and acts by inducing targeted protein degradation through ubiquitination-mediated proteasomal degradation (234,235). A STAT3-targeting PROTAC molecule can bind to STAT3 specifically on one side and to an E3 ligase on the other side, thus inducing specific degradation of STAT3.

Bai *et al* (236) developed SD-36, a novel STAT3 PROTAC inhibitor, which was designed by linking the STAT3 inhibitor, SI-109 (responsible for binding to STAT3), and lenalidomide, an analog of cereblon ligand (responsible for binding to cereblon E3 ligase). SD-36 was well tolerated and potently degraded STAT3, which led to complete tumor regression in mouse models (236). Notably, SD-36 is more potent than SI-109, on which SD-36 was based. This suggests that the PROTAC strategy may be more efficient than the suppression strategy. Another study (237) used toosendanin as the bait to target STAT3 and lenalidomide as the ligand for cereblon E3 ubiquitin ligase. This PROTAC molecule exhibited robust antitumor effects in HNSCC and CRC *in vivo*.

In addition to selective small molecules used as the STAT3 bait, Shih *et al* (238) used a decoy oligonucleotide as the STAT3 bait. The decoy oligonucleotide was the same as that used by Grandis *et al* in their STAT3 decoy (228,231,232). Shih *et al* (238) found that this oligonucleotide-based STAT3 inhibitor reduced STAT3 expression and suppressed cancer cell viability *in vitro*.

Since 2015, the field of PROTAC technology has grown rapidly and currently at least 20 PROTACs have entered clinical trials, including KT-333, which targets STAT3 (235,239). PROTAC technology provide routes to target proteins once considered 'undruggable', and some of these PROTACs exhibit superior potency and efficacy against cancer. For instance it was reported that SD-36 induced complete and long-term tumor regression at doses of either 100 mg/kg weekly or

50 mg/kg twice weekly for 4 weeks in animal models (236). However, there are several challenges to overcome, especially the adverse effects caused by protein degradation in healthy tissues when PROTACs are administered orally or intravenously (239).

Indirect STAT3 inhibitors. Indirect inhibitors of STAT3 target the upstream or downstream components of the STAT3 signaling pathway, for which hundreds of compounds have been identified, mainly JAK (2,6) and IL-6/IL-6R (2,6,240) inhibitors.

JAK inhibitors. The JAK family consists of four non-receptor tyrosine protein kinases (JAK1, JAK2, JAK3 and TYK2). JAKs incorporate signals from various cytokines and growth factor receptors and principally activate STATs. Targeting JAKs to interfere with the signaling of the JAK/STAT pathway has been successful, which is best illustrated by the fact that eight pan-JAKs or selective JAK inhibitors have been approved to treat rheumatoid arthritis (RA), atopic dermatitis and myeloproliferative neoplasm (MPN) (241). These inhibitors are tofacitinib, baricitinib, delgocitinib, peficitinib, ruxolitinib, upadacitinib, filgotinib and abrocitinib. Several JAK inhibitors, including the aforementioned eight inhibitors, are in clinical trials to evaluate their efficacy and safety in leukemia (242) and solid tumors. However, no JAK inhibitors are currently approved to treat these diseases. A clinical investigation showed an inadequate clinical response and serious adverse events following the treatment of solid tumors with the JAK inhibitor, AZD1480 (243).

IL-6/IL-6R inhibitors. Another strategy to suppress STAT3 signaling is targeting IL-6 and its receptor, IL-6R. Indeed, there have been several such antibody drugs used in the clinic including siltuximab, tocilizumab and sarilumab. Siltuximab, a chimeric antibody against IL-6, is currently used in the clinic to treat multicentric Castleman disease, which was approved in 2014 (244). Tocilizumab, a humanized anti-IL-6R inhibitor, has already successfully entered the clinic to treat RA. Sarilumab, an anti-IL-6R antibody, was also approved in 2017 for the treatment of RA. In addition, these inhibitors were widely evaluated in clinical trials for solid and hematological malignancies. However, anti-IL6 or anti-IL-6R antibodies do not demonstrated clinical efficacy in various types of cancer (245). For instance siltuximab monotherapy has not shown significant activity in pretreated castration-resistant prostate cancer (CRPC) (246), NSCLC (247), HNSCC (247), CRC (247) or multiple myeloma (245). Additionally, siltuximab plus mitoxantrone/prednisone (M/P) treatment did not show a more superior effect than M/P treatment alone in patients with metastatic CRPC (248). A number of clinical trials using tocilizumab to treat patients with cancer are ongoing, most of which are combination therapies; however, no results have been published. Sarilumab is also currently in the preclinical stages.

There are several possible explanations for this lack of efficacy of IL-6/IL-6R inhibitors. First, the large number of tumor-promoting cytokines in the tumor microenvironment may limit efficacy of therapeutically targeting a single one. Second, cancer plasticity and heterogeneity could enable tumor cell resistance to IL-6 and IL-6R therapies.

7. Conclusion

In conclusion, the STAT3 pathway is a central signaling node that regulates a plethora of cancer hallmarks. The hyperactivation of STAT3 facilitates cancer progression, drug resistance, metastasis and EMT. Various newly identified mechanisms and regulatory proteins, miRNAs, lncRNAs and circRNAs have been shown to be integral members of the STAT3/EMT axis. A great effort has already been made to develop inhibitors that suppress the IL-6/STAT3 axis via targeting IL-6, IL-6R, JAKs or STAT3 itself (2,3), some of which have been approved for the treatment of inflammatory diseases or MPN. There have also been several preclinical studies that demonstrated that some compounds suppress EMT through the STAT3 pathway (66,67). However, no inhibitors have yet been approved for solid tumors. In contrast to monotherapy, combination therapies involving STAT3 pathway inhibitors with chemotherapy, radiotherapy and immune checkpoint inhibitors could be considered to enhance efficacy and reduce side effects. Furthermore, if we consider that tens of thousands of non-coding RNAs have been identified by high-throughput RNA sequencing, but only a small percentage of these have been functionally characterized (159), we may anticipate that the number of known non-coding RNAs involved in the STAT3-EMT axis will increase in the future. This rapidly expanding area will provide increasing therapeutic targets for STAT3 signaling suppression. For instance, miR34, a molecule downstream of STAT3 that also acts as a regulator of STAT3 signaling, has also been evaluated for its potential as a cancer therapeutic agent in a clinical Phase I study (NCT01829971) (249). In addition, biomarkers to predict therapy responders are urgently needed. Technological advances such as single cell profiling, may increase the understanding of the response of cancer to STAT3 inhibitors at the single cell level and provide opportunities to stratify patients.

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GZ, SH and SL performed the literature review and wrote the manuscript. YW and WC revised the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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