

Molecular mechanism, regulation, and therapeutic targeting of the STAT3 signaling pathway in esophageal cancer (Review)

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Abstract. Esophageal cancer (EC) is the seventh most common cancer globally, and the overall 5-year survival rate is only 20%. Signal transducer and activator of transcription 3 (STAT3) is aberrantly activated in EC, and its activation is associated with a poor prognosis. STAT3 can be activated by canonical pathways such as the JAK/STAT3 pathway as well as non-canonical pathways including the Wnt/STAT3 and COX2/PGE2/STAT3 pathways. Activated STAT3, present as phosphorylated STAT3 (p-STAT3), can be transported into the nucleus to regulate downstream genes, including VEGF, cyclin D1, Bcl-xL, and matrix metalloproteinases (MMPs), to promote cancer cell proliferation and induce resistance to therapy. Non-coding RNAs, including microRNAs (miRNAs/miRs), circular RNAs (circRNAs), and long non-coding RNAs (lncRNAs), play a vital role in regulating the STAT3 signaling pathway in EC. Several miRNAs promote or suppress the function of STAT3 in EC, while lncRNAs and circRNAs primarily promote the effects of STAT3 and the progression of cancer. Additionally, various drugs and natural compounds can target STAT3 to suppress the malignant behavior of EC cells, providing novel insights into potential EC therapies.

Contents

1. Introduction
2. STAT3 signaling pathway in EC
3. Pathological roles of STAT3 in EC
4. Regulation of STAT3 in EC
5. Conclusions and future perspectives

1. Introduction

Esophageal cancer (EC) is the seventh most common type of cancer in the world and the sixth leading cause of cancer-related deaths (1). At present, the morbidity and mortality rates of EC are exhibiting an increasing trend annually (2), and the overall 5-year survival rate is only 20% (3). There are two primary pathological types of EC: Esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). ESCC is the most common pathological type, accounting for ~84% of EC cases, whereas the rates of EAC are increasing in high-income countries (4). Significant geographical differences have been found in the incidence of EC; the incidence of EC is highest in East Asia, followed by South Africa and East Africa (1). It is worth mentioning that gastroesophageal reflux disease (GERD) can cause Barrett esophagus (BE), which is the precursor lesion to EAC (5). It is estimated that 10-15% of GERD patients will develop BE, and the existence and grading of dysplasia in BE are the most important predictors of EAC (6). There are also studies highlighting the involvement of sex (4), obesity (7), smoking (8), and alcohol consumption (9) in the development of EC. Due to the massive amount of lymphatic drainage into the submucosa of the esophagus, lymphatic metastasis occurs in the early stage of EC, which leads to a lower survival rate (10). Recent findings indicated that patients with EC exhibited metastasis to adjacent and distant tissues, such as the liver (11), lungs (12), and bones (13). Thus, the occurrence and metastasis of EC appear to be related to several factors. To improve the management of this life-threatening disease, the factors involved in the development of EC as well as those involved in its malignant transformation need to be determined.

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With the development of molecular biology research, a considerable body of evidence has indicated that several molecular pathways are involved in the acquisition of malignancy in EC, which may pave the way for effective EC therapies. The hedgehog family is highly conserved in mammals and consists of three proteins: Sonic hedgehog (Shh), Indian hedgehog, and Desert hedgehog (14). Hedgehog signaling is generally involved in the development and differentiation of embryonic tissues, hemostasis of normal adult cells, and carcinogenesis (15). Shh acts on the activity of the GLI family, including GLI1, GLI2, and GLI3, for regulating gene expression (16). In EC, GLI1 was overexpressed and linked to epithelial-mesenchymal transformation (EMT) and lymph node metastasis (17). Research has revealed that GLI1 can activate cyclin D2 and FOXM1, serving an oncogenic role (18). The Wnt signaling pathway is also confirmed to exert a carcinogenic effect in several types of tissues when aberrantly activated (19). Wnt binds to the cysteine-rich domain of the Frizzled (Fzd) family receptors, preventing β -catenin phosphorylation and ubiquitination by activating Dishevelled. β -Catenin then enters the nucleus, where it binds to the transcriptional complex consisting of the T-cell factor (TCF)-1, BCL-9, and Pygopus 2 to promote cancer cell development and metastasis (20). Upregulation of the Wnt signaling pathway has been demonstrated to enhance the proliferation and motility of EC cells (21-23). The NOTCH pathway is mediated through ligands binding to NOTCH receptors and regulating squamous differentiation in the skin and esophagus (24). In ESCC, the NOTCH pathway exerts a carcinogenic effect when aberrantly activated, which promotes EMT and tumorigenesis by mediating the expression of transforming growth factor- β and thus increasing the number of tumor stem cells (25).

Additionally, special attention should be paid to one member of the signal transducer and activator of transcription (STAT) family: STAT3. The STAT family was first discovered in 1994 when evaluating the molecular pathways involved in gene regulation triggered by interferon (IFN) molecules, which are mediators that transmit signals from the extracellular matrix to the nucleus (26,27). A total of seven STAT proteins have been identified to date: STAT1, 2, 3, 4, 5a, 5b, and 6, and they have been shown to mediate multiple cellular functions (28). STAT1 and STAT2 primarily take part in the inhibition of the development of cancer, whereas STAT3, STAT4, and STAT5 are commonly regarded as cancer promoters (29). Among these STAT subtypes, STAT3 has been confirmed to be activated in various types of cancer, promoting tumor cell proliferation, angiogenesis, and metastasis, thus attracting the attention of researchers (30,31). In recent years, an increasing number of researchers have begun to investigate the relationship between STAT3 and EC. Therefore, a comprehensive search of literature published until the end of March 2022 was conducted using PubMed. Various combinations of keywords were used for searching: 'Signal transducer and activator of transcription 3' or 'STAT3', 'phosphorylated signal transducer and activator of transcription 3' or 'p-STAT3', 'esophageal' or 'esophagus', and 'cancer' or 'carcinoma'. In addition, studies related to the epidemiology of EC, the molecular structure of STAT3, the role of STAT3 and its related molecules in various cancers, and other signaling pathways in EC were also searched for to fully present the topic. Duplicate data, research

not relevant to the topic of the present review, and non-English studies were excluded. As a result, a total of 211 studies were cited in the present review to summarize the research progress regarding STAT3 in EC.

2. STAT3 signaling pathway in EC

Canonical STAT3 signaling pathway. The STAT3 coding gene is located on chromosome 12 (q13-q14-1) in humans. The STAT3 protein has a unique secondary structure consisting of six primary domains (Fig. 1): i) An N-terminal domain (NTD), which has the functions of binding to DNA, nuclear translocation, interactions between proteins, and regulating transcription of downstream target genes (28); ii) a coiled-coil domain that is critical in recruitment of STAT3 to its receptor and in nuclear translocation (26,27). iii) a DNA-binding domain that plays an essential role in determining the DNA connection (32); iv) a linker domain (LD) that connects the DNA-binding domain with the SH2 domain; v) an Src Homology 2 (SH2) domain that can bind to and activate the JAK of the cytokine-receptor cytoplasmic domain to induce STAT3 protein recruitment to JAK, as STAT3 dimer formation relies on the interactions of the SH2 domain (31); and vi) a transactivation domain (TAD) which is a highly disordered and conserved domain that possesses phosphorylation sites essential for the activation of STAT3 and protein-protein interactions (33). Researchers have identified four STAT3 isoforms: STAT3 α , STAT3 β , STAT3 γ , and STAT3 δ (34). STAT3 α is a 92-kDa in length isoform expressed in most cells, which has two crucial phosphorylation sites (Yyr705 and Ser727) at the C-terminus (35). STAT3 β has different splice isoforms and only one phosphorylation site (Tyr705), whose TAD has only 7 residues, whereas the TAD in STAT3 α has 50 residues (33). STAT3 γ and STAT3 δ are truncated forms of STAT3 α and play a role in granulocytic differentiation (35).

A variety of signals can activate STAT3, including cytokines such as interleukin (IL)-6 (36-38) and leptin (39-41); growth factors including epidermal growth factor (EGF) (42,43) and platelet-derived growth factor (PDGF) (44); other molecules such as cellular Src (c-Src) tyrosine kinase (45-47), and thyroid-stimulating hormone (TSH) (48); and environmental factors including nicotine (49), infections (50), and stress (51), amongst others. These signals activate STAT3 through phosphorylation of Ser727 or Tyr705 in the TAD via several signaling pathways, form dimers via the SH2 domain, then translocate into the nucleus to regulate gene transcription. The JAK/STAT3 pathway is a canonical pathway of signal transduction and transcriptional activation of STAT3 (Fig. 2). When activators bind to the corresponding receptors on the cell membrane, the conformational change in the receptors results in their dimerization or oligomerization and thus activation (35,36). Following activation, the cytoplasmic parts of the receptor bind to each other, and the receptor-coupled tyrosine kinases are activated by cross-phosphorylation. These tyrosine kinases are often Janus kinase (JAK) family members, including JAK1, JAK2, JAK3, and TYK2. Activated JAK kinase can phosphorylate a specific receptor in the cytoplasm and activate the receptor (35,52). The molecular configuration of the receptor changes to provide a binding site for activating STAT3 monomers in

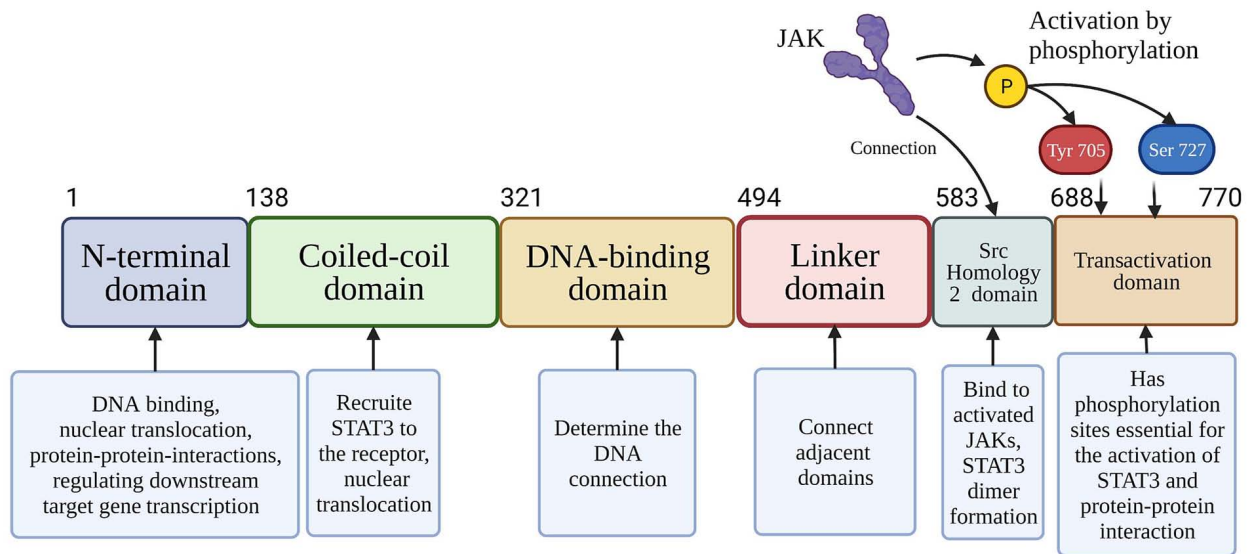


Figure 1. Secondary structure of STAT3. Each of the six domains plays a unique role in the functions of STAT3. STAT3 binds to JAK at the SH2 domain, and STAT3 can be activated by phosphorylation of Tyr 705 or Ser 727. STAT3, signal transducer and activator of transcription 3; SH2, Src homology 2.

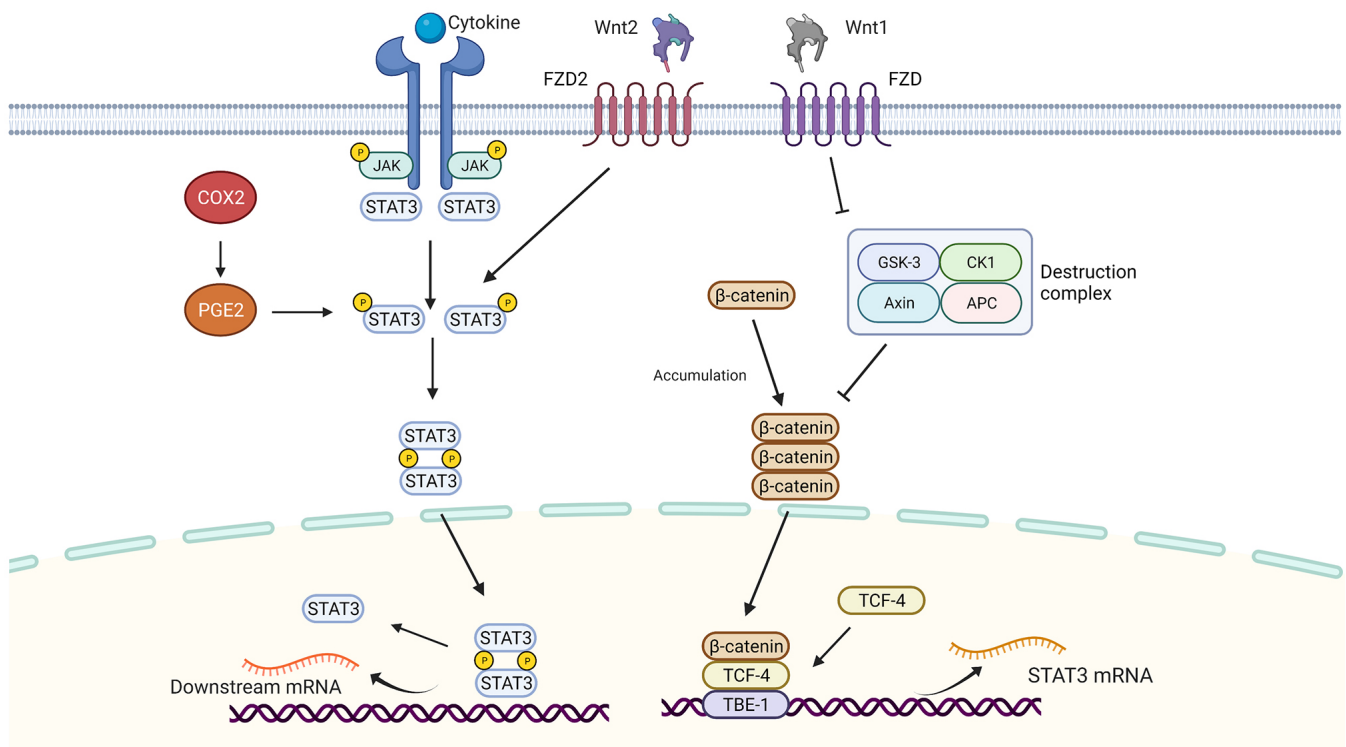


Figure 2. Several signaling pathways are closely related to STAT3. The canonical STAT3 signaling pathway is the JAK/STAT3 pathway, which can receive signals from cytokines or growth factors and transmits these signals to the nucleus to regulate downstream genes. Additionally, the COX2/PGE2/STAT3 pathways play a role in modifying the phosphorylation of STAT3. Wnt1 can inactivate the destruction complex for β -catenin transfer into the nucleus and form a complex with TCF-4, through binding of the TBE to the promoter region of STAT3, thereby increasing the transcription of STAT3. Wnt2/FZD2 phosphorylate STAT3 directly at Tyr705 to activate STAT3 signaling. STAT3, signal transducer and activator of transcription 3; COX2, cyclooxygenase-2; PGE2, prostaglandin E2; TCF-4, T-cell factor-4; TBE, TCF-4 binding element.

the cytoplasm. STAT3 molecules recognize and bind to the receptor through the SH2 domain. JAK or Src, using the STAT3 molecule recruited by the receptor as the substrate, phosphorylates the tyrosine (Tyr-705) residue of the STAT3 molecule. Two phosphorylated STAT3 (p-STAT3) monomers combine with the phosphorylated tyrosine residue of SH2 to

form a dimer and separate from the receptor, which is then transferred into the nucleus where they bind to specific DNA sequences, regulating downstream gene transcription (53). This transport process primarily relies on the coiled-coil and DNA binding domains. Nuclear protein tyrosine phosphatases such as TC45 are required for the dephosphorylation of

STAT3 in the nucleus. The inhibition of these enzymes can lead to the downregulation of dephosphorylation of STAT3, which results in continuous activation of STAT in the tumor cell nucleus (54).

Non-canonical STAT3 signaling pathway. In the canonical STAT3 signaling pathway, STAT3 is activated by JAK, but there are other STAT3 regulators that affect the regulation of STAT3 (Fig. 2).

The cyclooxygenase (COX2)/prostaglandin E2 (PGE2)/STAT3 pathway is typical of non-canonical STAT3 signaling pathways. COX is a rate-limiting enzyme that can catalyze arachidonic acid conversion to prostaglandins to induce the production of PGE2. COX2 expression is upregulated in ESCC. STAT3 has been indicated as the downstream target of COX2/PGE2 that is involved in the induction of proliferation and EMT in EC tumors (55,56).

The Wnt signal transduction pathway controls numerous biological processes. The Wnt pathway can be divided into canonical (β -catenin dependent) and non-canonical (β -catenin independent) signaling; and both can modulate the STAT3 signaling pathway.

In canonical Wnt/STAT3 signaling, Wnt-1 binds to its cognate receptors, inhibiting the activity of destruction complexes formed by Axin, APC, GSK3, and CK1, thus releasing and in turn increasing the accumulation of β -catenin in the plasma (57). In ESCC, Wnt-1 induces β -catenin accumulation and activates the TCF reporter gene (58). β -Catenin is transferred to the nucleus, where it forms complexes with TCF4, and it has DNA binding activity, regulating the transcription of genes. Further research indicated that STAT3 promoters have five putative TCF4 binding elements (TBEs). Among them, TBE1 specifically binds to TCF4 protein. Therefore, β -catenin/TCF4 increased STAT3 mRNA and protein expression levels by binding to TBE1 (59).

In non-canonical Wnt/STAT3 signaling, one of the Wnt2 transmembrane receptors from the frizzled (FZD) family, FZD2, plays a vital role. FZD2 is upregulated in several types of cancer, which is suggested to be a predictor of tumor recurrence (60). FZD2 was overexpressed in ESCC and promoted the migration and invasion of ESCC cells and was associated with a poor prognosis. FZD2 was revealed to directly activate STAT3 at the Tyr705 site in ESCC, activating downstream genes including TWIST1 and Slug (61).

3. Pathological roles of STAT3 in EC

By 2012, researchers determined that the activation of STAT3 induces abnormal proliferation and migration of ESCC (62). In subsequent studies, the roles of STAT3 in EC have been gradually revealed (Fig. 3).

Promoting proliferation, angiogenesis, and inhibiting apoptosis. Activating STAT3 signaling promotes proliferation and inhibits apoptosis in ESCC (63). The evidence from loss of function studies has also confirmed that STAT3 acts as an oncogene in EC cells. Inactivation of STAT3 in EC cells has been revealed to lead to cell apoptosis, cell cycle arrest, and inhibition of proliferation (64-67), confirming the crucial role

in the proliferation of EC from another perspective. The downstream genes of STAT3 play an essential role in this process.

The Bcl-2 protein family is closely related to apoptosis and consists of several antiapoptotic proteins including Bcl-xL, Bcl-2, Bcl-w, and Mcl. These proteins are critical factors in regulating apoptosis and the survival of cells. In EC, STAT3 acts as an upstream factor of Bcl-xL and enhances its expression, inhibiting the programmed death of tumor cells (68). Additionally, suppressing STAT3 activity leads to the downregulation of Bcl-2 and thus the induction of apoptosis (64,69).

Caspase-3 is a critical factor in apoptosis, and it regulates tumor cell repopulation (70). Caspase-3 can be activated through cleavage of upstream caspases, including caspase-8 and caspase-9, which interact with promoters of various pro-angiogenic genes, such as the vascular endothelial growth factor (VEGF)A gene (71). In mice trials, p-STAT3 increased the levels of caspase-3, causing loss of muscle mass (72). In EC, after inhibition of the activation of STAT3, cleaved caspase-3 expression was upregulated, suggesting the correlation between p-STAT3 and cleaved caspase-3 (73).

Cyclins are cell-cycle-associated nuclear proteins. Cyclin D1, a member of the cyclin family, typically binds with its catalytic chaperone cyclin-dependent protein kinase (CDK)4 or CDK6 to form a complex, that controls the progression of the G1 phase of the cell cycle (74). Tumorigenesis is closely associated to the cell cycle. As an essential cell cycle regulator, cyclin D1 has been demonstrated to be a significant prognostic predictor of ESCC (75). Zhang *et al* (76) indicated that p-STAT3 upregulated cyclin D1 expression in ESCC and reduced the survival of patients. Additionally, Li *et al* (77) revealed that high levels of STAT3 and cyclin D1 were associated with a poorer prognosis after curative resection of ESCC, showing the potential application of STAT3 and cyclin D1 as molecular predictors of the curative effect of treatment.

Angiogenesis provides the essential nutrition for cancer cell growth and metastasis. Yang *et al* (78) demonstrated that metformin suppressed the JAK/STAT3 signaling pathway and tumor angiogenesis *in vivo*, highlighting the roles of STAT3 in angiogenesis and in the formation of the cancer microenvironment in EC. In other studies, AR-42, a pan-histone deacetylase (HDAC) inhibitor, decreased the levels of p-STAT3 in ESCC cells, resulting in an anti-angiogenic outcome both *in vitro* and *in vivo* (79). Moreover, as a gasotransmitter in ESCC cells, exogenous H₂S promoted angiogenesis via upregulating the activity of the STAT3 signaling pathway (80).

Promoting infiltration and metastasis. Infiltration and distant metastasis are manifestations of malignant esophageal tumors in which STAT3 is also involved. Research has shown that in EC, STAT3 was associated with infiltration degree (pT) and pTNM stage, and p-STAT3 was associated with pT, lymphatic metastasis (pN), and pTNM stage (76). The function of STAT3 in promoting cancer invasion and metastasis can be regulated by upstream proteins, and realized through the expression of downstream genes. T-LAK cell-originated protein kinase (TOPK) is a type of MAPKK-like kinase that can activate the Src/GSK3 β /STAT3 signaling pathway to promote the invasion and migration of ESCC cells (46).

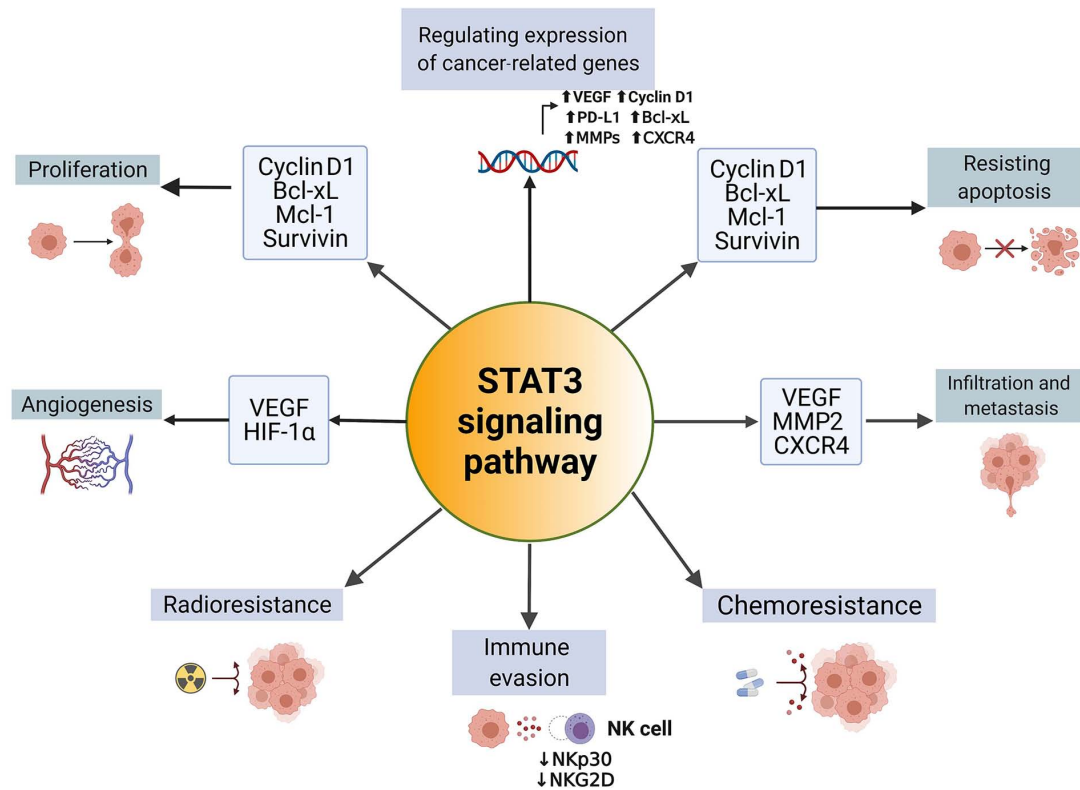


Figure 3. STAT3 plays varying roles in EC, such as promoting proliferation, infiltration, metastasis, and angiogenesis; inducing immune evasion, chemoresistance, and radioresistance; and upregulating the expression of cancer-related genes. Taken together, these properties explain the poor prognosis of patients with EC with upregulated levels of STAT3. STAT3, signal transducer and activator of transcription 3; EC, esophageal cancer; VEGF, vascular endothelial factor; MMPs, matrix metalloproteinases; CXCR4, CXC chemokine receptor 4; NK, natural killer.

VEGF has been revealed to stimulate endothelial cell proliferation and migration, in addition to promoting the malignant progression of tumors. p-STAT3 was demonstrated to increase VEGF expression in EC and induce infiltration and metastasis of tumors (76).

MMPs are proteolytic enzymes that degrade the extracellular matrix (ECM), promoting migration and invasion of tumors. MMP2 is overexpressed in ESCC samples and this is significantly associated with tumor invasion depth, clinical stage, and lymph node metastasis (81). p-STAT3 can bind to the MMP2 promoter at 648-641 bp (TTCTCGAA) to induce MMP2 expression in a dose-dependent manner (82). In addition, tumor necrosis factor receptor-associated protein 1 (TRAP1), a member of the mitochondrial heat shock protein 90 family acts as an upstream protein of the STAT3/MMP2 pathway, where it is involved in mediating migration and invasion via STAT3/MMP2 (83).

CXC chemokine receptor 4 (CXCR4) belongs to the G-protein coupled receptor (GPCR), which is the co-receptor of HIV-1 (84). In EC, CXCR4 expression was revealed to be significantly upregulated, and the levels of CXCR4 were downregulated after using STAT3 inhibitors (85), indicating that CXCR4 is a downstream molecule regulated by STAT3, providing another piece of evidence that STAT3 promotes infiltration and metastasis.

Inducing immune evasion, therapeutic resistance, and a poor prognosis. Although the primary treatment for EC is surgery; immunity, radiotherapy, and chemotherapy also serve an

essential role in the treatment regimen and in improving the prognosis of patients with EC.

Natural killer (NK) cells are crucially involved in innate immunity. ESCC cells secrete IL-6 and IL-8 to activate the STAT3 signaling pathway of NK cells and decrease the activation of receptors (NKp30 and NKG2D) on NK cells (86), which may be the mechanism by which EC cells escape from innate immune cell surveillance. Additionally, STAT3 can induce chemoresistance in EC cells. Activating transcription factor 4 transactivates STAT3 to mediate multidrug resistance in ESCC (87), highlighting the critical role of STAT3 in drug resistance. In addition, suppressing the activation of STAT3 was demonstrated to enhance the sensitivity to cisplatin (88). For commonly used chemotherapeutic drugs such as 5-fluorouracil (5-FU), cisplatin, and paclitaxel, the IC_{50} values in EC cells were reduced when these drugs were combined with STAT3 inhibitors such as niclosamide (89). In addition to resistance to chemotherapy, STAT3 is involved in radioresistance as well. Zang *et al* (90) demonstrated that STAT3 activation is a critical event involved in ionizing radiation-induced EMT and radioresistance, and inhibiting the activation of STAT3 prevents these processes. Additionally, after being treated with the STAT3 inhibitor Stattic, the levels of p-STAT3, HIF-1 α , and VEGF in EC cells decreased, resulting in an increase in the radiosensitivity of EC cells both *in vitro* and *in vivo* (91), indicating the potential for the combined use of STAT3 inhibitors with radiotherapy in improving the curative effects in patients with EC.

Therefore, it is not surprising that the high levels of STAT3 and p-STAT3 are closely associated with reduced survival

rates in patients with EC. The 5-year survival rate of patients with ESCC was revealed to be significantly associated with p-STAT3 expression, and p-STAT3 was a relevant independent factor of a poor prognosis and an independent prognostic factor for progression-free survival (PFS) in ESCC (76).

4. Regulation of STAT3 in EC

miRNA-mediated regulation of STAT3. miRNAs, lncRNAs, circRNAs, small nucleolar RNAs (snoRNAs), and transfer RNAs (tRNAs) are non-coding RNAs (ncRNAs) that are transcribed from DNA but are not translated into proteins (92). An increasing body of literature supports the theory that ncRNAs play an important role in cancer development (93,94). STAT3 is an upstream mediator of multiple transcription factors, but it can also be modulated by ncRNAs themselves (95). miRNAs are small molecules 18-25 nucleotides in length and are generally transcribed by type II RNA polymerases (96,97), and they play a crucial role in modulating the translation of downstream genes by binding the 3'untranslated regions (UTRs) of mRNAs (98). Certain miRNAs have been revealed to downregulate or upregulate STAT3 expression. Thus, these miRNAs can be categorized into two types: Onco-suppressor miRNAs that suppress STAT3 expression, and onco-promotor miRNAs that enhance the expression of STAT3 (Fig. 4; Table I).

Tumor suppressor miRNAs. Most miRNAs associated with STAT3 signaling play tumor-suppressive roles, and some of them directly target STAT3 in EC, including miR-125a-3p, miR-296-5p and miR-874-3p.

miR-125 is a highly conserved miRNA family that consists of two sub-types, miR-125a and miR-125b. miR-125a is further subdivided into miR-125a-3p, and miR-125a-5p, which are derived from the 3' (passenger strand) and 5' (leading strand) ends of pre-miR-125a, respectively. The miR-125 family is closely associated with the STAT3 signaling pathway. For example, miR-125b was demonstrated to regulate the levels of STAT3 in T cells (99). In osteosarcoma, miR-125b was revealed to be downregulated and negatively associated with STAT3 expression (100). In ESCC tissues and cells, the expression of miR-125a-5p was identified to be low. Downregulation of miR-125a-5p increased cell proliferation, accelerated cell cycle progression, inhibited apoptosis, and improved the migratory and invasive capacities of ESCC cells, which were linked to EMT in ESCC, resulting in the progression of cancer to more advanced tumor stages and a shorter survival duration as a result. In ESCC cells, STAT3 was discovered to be a direct target of miR-125a-5p, and overexpression of miR-125a-5p significantly decreased STAT3, p-STAT3, and VEGF protein levels (88).

The miR-296 family consists of miR-296-5p and miR-296-3p and is involved in tumorigenicity (101). In hepatocellular carcinoma, miR-296 suppressed cell proliferation and increased apoptosis by modulating fibroblast growth factor receptor 1 (FGFR1) (102). Additionally, miR-296 inhibited colorectal cancer metastasis and EMT by targeting S100A (103). Wang *et al* (104) demonstrated that the levels of miR-296-5p in ESCC are downregulated, and miR-296-5p directly targets STAT3 to suppress STAT3 expression, thus inhibiting migration and invasion of ESCC cells.

Similar to miR-296, miR-874 also has two subtypes, miR-874-3p and miR-874-5p (105). Recent studies have confirmed the antitumor effects of miR-874 in gastric cancer (106), osteosarcoma (107,108), glioma (109), epithelial ovarian cancer (110), and nasopharyngeal carcinoma (111). In gastric cancer, miR-874 was demonstrated to target aquaporin-3, and downregulate the levels of MMP2, MMP9, MT1-MMP, and Bcl-2, thus inducing cell apoptosis and inhibiting cell invasion (112). miR-874 directly suppresses STAT3 in several types of cancer, including colorectal cancer (113), NSCLC (114), and gastric cancer (115), thus decreasing the expression of the downstream genes and inhibiting tumor growth. In a study on the link between miR-874-3p and STAT3 in ESCC, Yuan *et al* (116) determined that miR-874-3p expression was suppressed in both ESCC tissues and cell lines. miR-874-3p overexpression decreased STAT3 expression at the mRNA and protein levels, and a functional target site in the 3'-UTR of STAT3 for miR-874-3p was shown to be present. Expression of miR-874-3p, lymph node metastasis, and clinical stage were all found to be independent predictive indicators of ESCC. Additionally, overexpression of miR-874-3p was shown to inhibit ESCC cells from proliferating, migrating, and invading.

There are also antitumor miRNAs that indirectly regulate the activity of JAK, including miR-30b and miR-613. miR-30b plays essential roles in suppressing hepatocellular carcinoma, colorectal cancer, gastric cancer, bladder cancer, and breast cancer (117). In ESCC, miR-30b acts as a JAK suppressor by downregulating chromobox 3 (CBX3) and inhibiting the migration and invasion of tumor cells (118). CBX3 is a CBX protein, which serves functions in stem cell self-renewal and cancer development (119). Therefore, miR-30b is associated with a better prognosis in ESCC (120).

Unlike other tumor suppressor miRNAs, miR-613 regulates STAT3 signaling pathways indirectly. miR-613 has been shown to exert a tumor-suppressive role in colorectal cancer (121), gastric cancer (122), lung cancer (123), hepatocellular carcinoma (124,125), and laryngeal carcinoma (126), by downregulating the expression of oncogenes and reducing the malignant potential of tumors. In ESCC, miR-613 targets glucose-6-phosphate dehydrogenase (G6PD). G6PD can promote the phosphorylation of STAT3 and STAT5, which miR-613 negatively regulates (127). Su *et al* (128) revealed that miR-613 expression was reduced in ESCC tissues, whereas G6PD expression was increased in ESCC tissues; miR-613 inhibited ESCC migration and invasion by targeting G6PD and reducing MMP2, MMP9, and p-STAT3 expression.

Tumor promoter miRNAs. Compared to tumor suppressor miRNAs in EC, there are fewer tumor promoter miRNAs associated with STAT3 (Fig. 4). miR-4286 has been identified to act as a tumor promoter of prostate cancer (129), gastric cancer (130), NSCLC (131), and glioblastomas (132). In EC, miR-4286 was demonstrated to indirectly inhibit JAK, which is closely related to inositol polyphosphate 4-phosphatase type I (INPP4A). INPP4A is a negative regulator of Akt and is confirmed to function as a tumor suppressor in breast cancer and prostate cancer (133). Zhang *et al* (134) found that miR-4286 was overexpressed in and significantly promoted the viabilities of TE-1, HCE-4, and HCE-7 cells, and it also

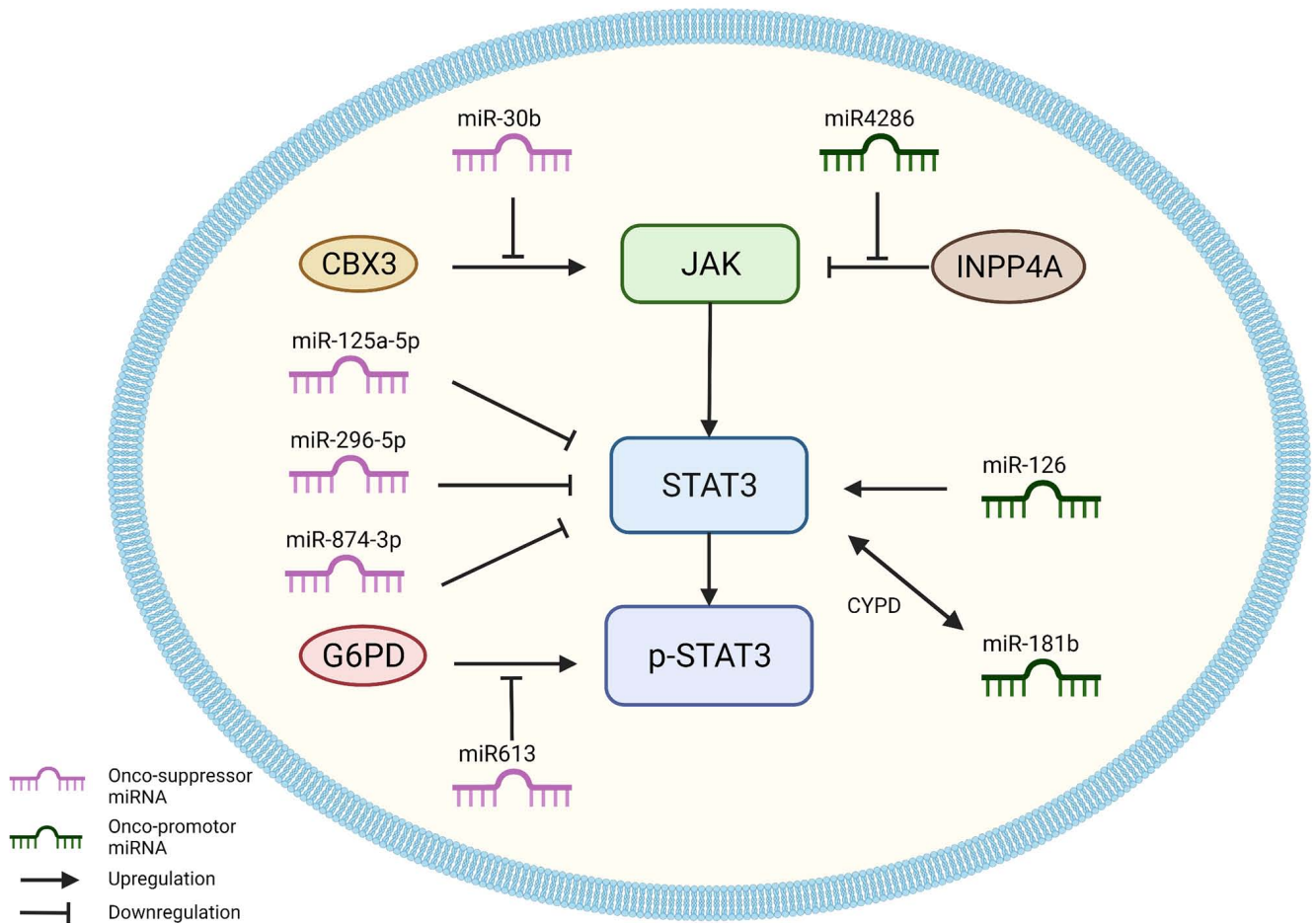


Figure 4. miRNAs play an essential role in regulating STAT3. Tumor promoter miRNAs promote the STAT3 signaling pathway, while tumor suppressor miRNAs inhibit STAT3 signaling pathways. STAT3, signal transducer and activator of transcription 3; miRNA or miR, microRNA; CBX3, chromobox 3; JAK, Janus kinase; INPP4A, inositol polyphosphate 4-phosphatase type I; G6PD, glucose-6-phosphate dehydrogenase; p-, phosphorylated.

activated the JAK2/STAT3 pathway by inhibiting the function of INPP4A.

miR-126 tumor regulation is dependent on the specific tissue type and is essential to inflammation, angiogenesis, and cell migration (135). In lung cancer, overexpression of miR-126 resulted in decreased caspase-3 mRNA expression and increased STAT3 protein expression, increasing tumor cell proliferation and migration (136). However, in osteosarcoma and cervical cancer, miR-126 played an opposite role. miR-126 inhibited proliferation, migration, and invasion of cervical cancer cells *in vitro* by reducing MMP2 and MMP9 production and inactivating the JAK2/STAT3 signaling pathway by targeting ZEB1 (137). Additionally, miR-126 suppressed osteosarcoma proliferation, migration, invasion, and EMT by targeting ZEB1 and inactivating the JNK and JAK1/STAT3 pathways (138). The role of miR-126 in ESCC was investigated in a study by Li *et al* (139), which revealed that miR-126 was upregulated in TE13 cells, Eca109 cells, and ESCC tissues, and targeted the 3'-UTR of STAT3, enhancing its transcription and translation, and thus increasing tumor cell viability. Considering its differing characteristics in other types of cancer, the specific role of miR-126 under certain conditions of EC remains to be determined.

Similarly, miR-181b has been shown to possess an interesting association with STAT3. miR-181b is a member of the miR-181 family, which affects a variety of tumor-related

biological processes including cell proliferation, apoptosis, autophagy, mitochondrial function, and the immune response (140). In a previous study, STAT3 was hypothesized to be the target of miR-181b in cutaneous melanoma cells (141). In EC stem-like cells, miR-181b increased the levels of STAT3, and overexpression of STAT3 transactivated the levels of miR-181b. The reciprocal activation of miR-181b and STAT3 was mediated by cylindromatosis (CYLD) and enhanced EC stem-like cell viability and sphere formation (142).

lncRNA-mediated regulation of STAT3. lncRNAs are a type of ncRNA that are >200 nucleotides in length and have been shown to play essential roles in the epigenetic control and regulation of transcription, translation, and RNA metabolism (143). The effects of lncRNAs on cancer progression have attracted considerable research interest for decades, and several advances have been made recently. In the research on EC, the effects of lncRNA on STAT3 pathways have been gradually recognized (Fig. 5; Table II).

In EC, tumor promoter lncRNAs directly target JAK or STAT3, including lncRNAs LINC01535, LINC00857, and miR22HG. LINC01535 is a relatively recently discovered lncRNA of which little is known regarding its characteristics. Current research has shown that LINC01535 expression is correlated with the development of osteosarcoma (144),

Table I. Regulatory roles of miRNAs on STAT3 in esophageal cancer.

miRNA	miRNA type	Cell lines	Major outcomes	Effect on STAT3	(Refs.)
miR-296-5p	Tumor suppressor	ESCC cell lines: ECA109 and TE-1.	Directly targets STAT3 to suppress STAT3 expression. Inhibits migration and invasion <i>in vitro</i> .	Downregulation	(104)
miR-874-3p	Tumor suppressor	ESCC cell lines: ECA109, KYSE410 and TE-1.	Inhibits proliferation, migration, and invasion of tumor cells. Promotes the overall survival of patients.	Downregulation	(116)
miR-30b	Tumor suppressor	ESCC cell lines: TE-1 and TE-2.	Downregulates CBX3 to inhibit the JAK2/STAT3 pathway. Inhibits proliferation and migration. Induces apoptosis. Associated with a better prognosis.	Downregulation	(118,120)
miR-613	Tumor suppressor	ESCC cell line: ECA109.	Suppresses the expression of MMP2 and MMP9 and inactivates the STAT3 signaling pathway via G6PD. Suppresses migration and invasion <i>in vitro</i> .	Inhibits phosphorylation of STAT3	(128)
miR-4286	Tumor promotor	ESCC cell lines: TE-1, HCE-4, and HCE-7. EAC cell lines: SKGT-4 and BIC-1	Activates the JAK2/STAT3 pathway by negatively regulating INPP4A. Increases viability, migration, and invasion of tumor cells.	Upregulation	(134)
miR-126	Tumor promotor	ESCC cell lines: TE13 and ECA109.	Inhibits autophagy and apoptosis. Promotes tumor growth <i>in vivo</i> .	Upregulation	(139)
miR-181b	Tumor promotor	ESCC cell lines: ECA109 and ECA9706	miR-181b and STAT3 reciprocally activate each other via the CYLD pathway. Increases sphere formation and proliferation of tumor cells. Inhibits the apoptosis of tumor cells	Upregulation	(142)

miRNA or miR, microRNA; STAT3, signal transducer and activator of transcription 3; ESCC, esophageal squamous cell carcinoma; CBX3, chromobox 3; JAK2, Janus kinase 2; MMP, matrix metalloproteinase; G6PD, glucose-6-phosphate dehydrogenase; INPP4A, inositol polyphosphate 4-phosphatase type I; CYLD, cylindromatosis.

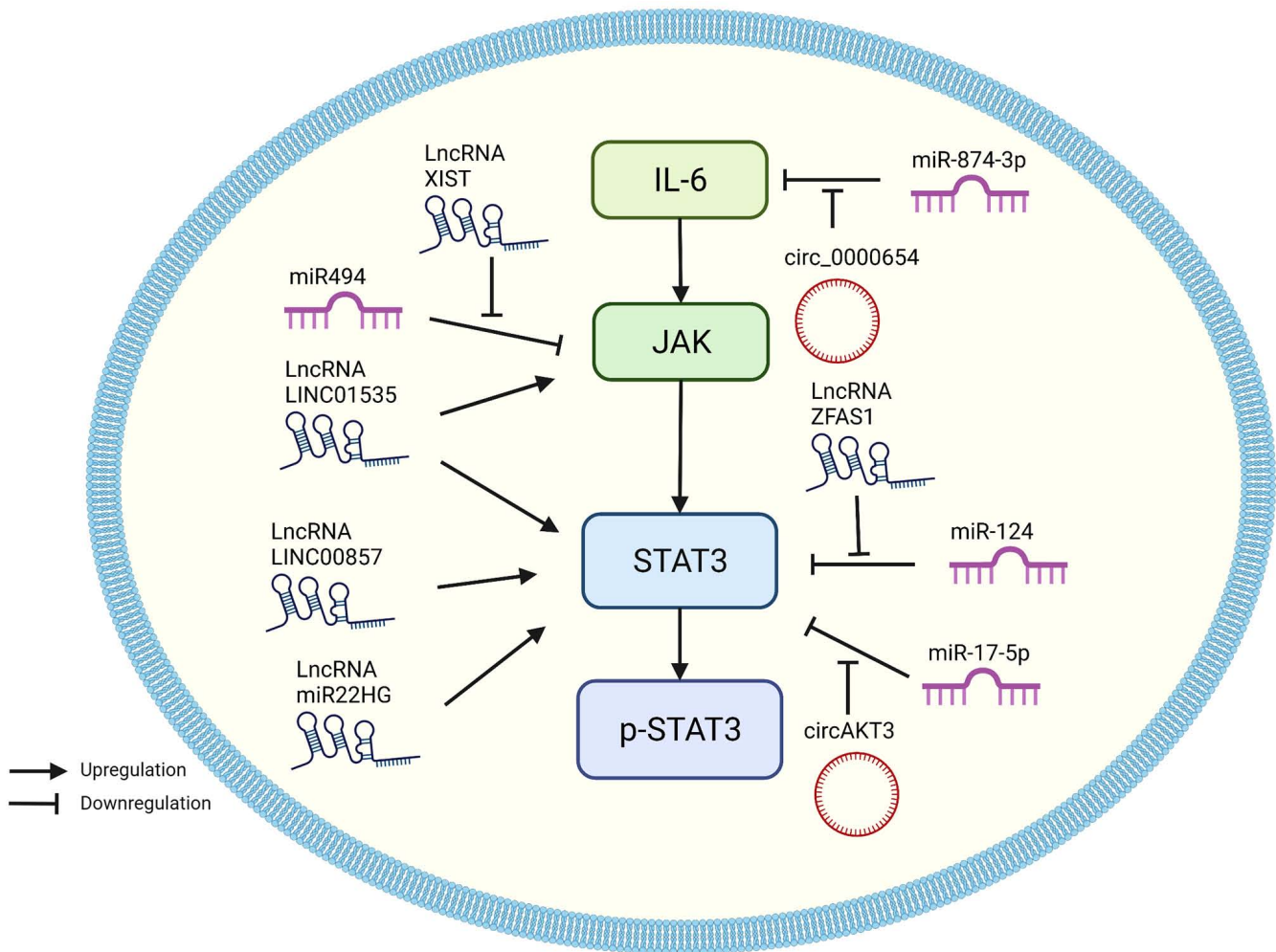


Figure 5. LncRNAs and circRNAs regulate STAT3 signaling pathways directly and indirectly. LncRNA, long non-coding RNA; circRNA, circular RNA; STAT3, signal transducer and activator of transcription 3; IL-6, interleukin-6; miR, microRNA; JAK, Janus kinase; p-, phosphorylated.

cervical cancer (145), and colorectal cancer (146). In ESCC, LINC01535 expression was upregulated, and this increased proliferation and prevented apoptosis by activating the JAK/STAT3 pathway (63). LINC00857 is another tumor promoter lncRNA that can promote tumor progression in lung adenocarcinoma (147), ovarian cancer (148), and hepatocellular carcinoma (149). In EAC, LINC00857 expression was shown to be upregulated. After knocking down LINC00857, STAT3 expression was decreased and the proliferation, migration, and invasion of cells decreased, showing that LINC00857 affected EAC tumor cell progression by upregulating the expression of oncoproteins including STAT3 (150).

The mechanism of tumor-suppressing lncRNAs differs considerably from miRNAs. The expression of the 19-kb lncRNA X inactive-specific transcript (XIST) has been reported to be dysregulated in NSCLC (151), thyroid cancer (152,153), and colorectal cancer (154). XIST expression is upregulated and sponges miR-494 in ESCC and EAC cell lines (155). miR-494 is the suppressor of the JAK/STAT3 pathways (156). Therefore, XIST can indirectly promote the proliferation, colony formation, migration, and invasion of EC cells by upregulating JAK/STAT3 activity (155). Coincidentally, lncRNA ZFAS1 was shown to exhibit a similar mechanism, which is closely related to miRNAs and exosomes.

Exosomes assist communication between cancerous cells by delivering lncRNA ZFAS1 in gastric cancer to promote tumor progression (157). In ESCC, ZFAS1 was transmitted to surrounding cells via exosomes, which facilitated ESCC cell proliferation and migration by downregulating miR-124 and increasing STAT3 expression (158). Another study confirmed in ESCC tissues, that ZFAS1 expression was increased and this was associated with a poorer prognosis (159).

It is worth mentioning the unique role of lncRNA miR22HG in EC. lncRNA miR22HG primarily functions as a tumor suppressor in thyroid carcinoma, hepatocellular carcinoma, endometrial carcinoma, cholangiocarcinoma, colorectal cancer, gastric cancer, and NSCLC (160). However, Su *et al* (161) showed that silencing miR-22HG expression reduced STAT3 protein expression and induced apoptosis in the OE33, OE19, and FLO-1 EAC cell lines, which indicated that miR-22HG functioned as a tumor promotor in EAC.

circRNA-mediated regulation of STAT3. circRNAs have a closed-loop structure and play a role in gene regulation by sponging miRNAs and interacting with RNA binding proteins. Upregulated expression of circRNAs in tumor tissues and cell lines is involved in modulating the tumor cell malignant phenotypes (Fig. 5; Table II).

Table II. Regulatory roles of ncRNAs on STAT3 in esophageal cancer.

ncRNA	RNA type	Cell lines	Major outcomes	Effect on STAT3	(Refs.)
LINC01535	Tumor promoter	ESCC cell lines: KYSE30, EC9706, TE-13 and ECA109.	Promotes proliferation. Inhibits apoptosis.	Upregulation	(63)
LINC00857	Tumor promoter	EAC cell lines: OE19 OE33 and FLO-1.	Promotes proliferation, colony formation, migration, and invasion Inhibits apoptosis	Upregulation	(150)
lncRNA XIIST	Tumor promoter	ESCC cell lines: TE-1, HCE-4 and HCE-7. EAC cell lines: SKGT-4 and Bic-1.	Downregulates miR-494 to activate the JAK/STAT3 pathway. Promotes viability, colony formation, migration, and invasion. Inhibits apoptosis.	Upregulation	(155)
lncRNA ZFAS1	Tumor promoter	ESCC cell lines: EC9706, ECA109, TE-13, TE-1 and TTN.	Promotes tumor proliferation, invasion, and migration, <i>in vitro</i> and <i>in vivo</i> . Inhibits apoptosis.	Upregulation	(158,159)
lncRNA MIR22HG	Dual function	EAC cell lines: OE33, OE19 and FLO-1.	Promotes proliferation, migration, invasion. Inhibits apoptosis	Dual function	(161)
circAKT3	Tumor promoter	ESCC cell lines: KYSE-150, TE-10 and TE-1.	Downregulates miR-17-5p, thus upregulating STAT3 and RHOC. Promotes proliferation, migration, and invasion <i>in vitro</i> . Promotes tumor growth <i>in vivo</i> .	Upregulation	(165)
circ_0000654	Tumor promoter	ESCC cell lines: TE-1 and KYSE450.	Downregulates miR-145-5p to modulate the IL-6/STAT3 signaling pathway indirectly. Promotes proliferation, migration, and invasion. Inhibits apoptosis.	Upregulation	(166)

ncRNA, non-coding RNAs; STAT3, signal transducer and activator of transcription 3; ESCC, esophageal squamous cell carcinoma; miRNA or miR, microRNA; JAK, Janus kinase; RHOC, Ras homolog gene family member C; IL-6, interleukin-6.

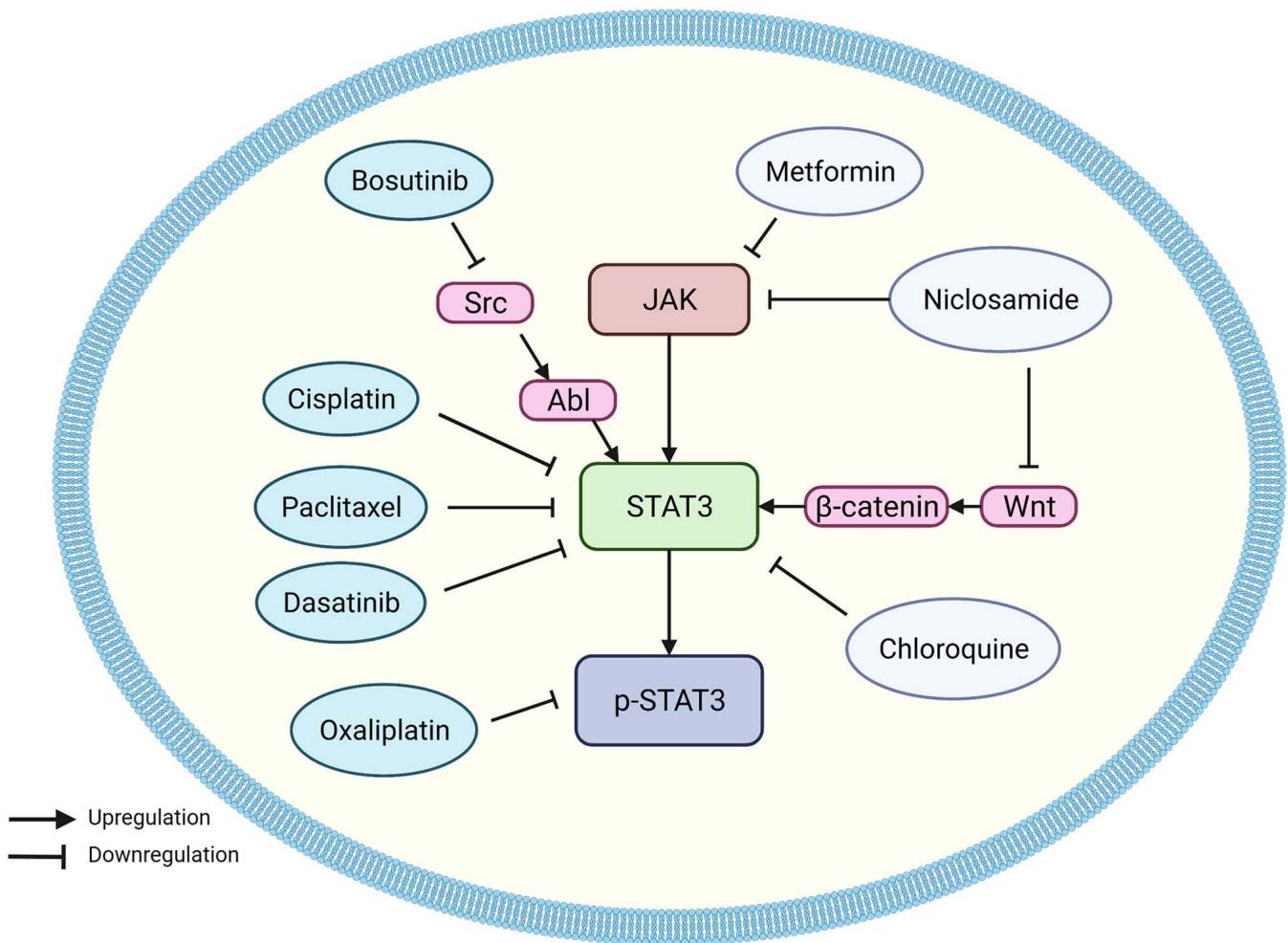


Figure 6. Drug-mediated regulation of STAT3 in EC. Several canonical and non-canonical anticancer drugs are associated with the regulation of the STAT3 signaling pathways, showing the therapeutic potential of targeting STAT3. STAT3, signal transducer and activator of transcription 3; EC, esophageal cancer; JAK, Janus kinase; p-, phosphorylated.

circRNA AKT3 (circAKT3) originates from the AKT3 gene and promotes cell proliferation, survival, and drug resistance (162,163). In EC, circAKT3 expression was shown to be upregulated and it sponged miR-17-5p. miR-17-5p directly targets STAT3 and Ras homolog gene family member C (RHOC). Similar to STAT3, RHOC plays a key role in tumor invasion and metastasis (164). circAKT3 increases EC cell proliferation, migration, and invasion by decreasing miR-17-5p activity and indirectly facilitating STAT3 and RHOC activity. circAKT3 knockdown decreased EC tumor growth *in vivo*, suggesting that it could be a target of further study to improve our understanding of the underlying processes in the development and progression of EC (165).

Another circRNA, circ_0000654 acts as a tumor promoter and was shown to be highly expressed in ESCC tissues and cells. In EC cells, circ_0000654 was demonstrated as an inhibitor of miR-145-5p, and miR-145-5p targeted IL-6 to reduce STAT3 expression. Therefore, by downregulating miR-145-5p activity, circ_0000654 could indirectly affect the IL-6/STAT3 signaling pathway and enhance cell proliferation, migration, and invasion (166). The roles of various circRNAs have been confirmed in several types of cancers; however, the current body of literature regarding circRNAs in EC is still

in its infancy compared to the other types of ncRNAs. The application of circRNAs in treating EC may have considerable potential and should thus be further explored.

Drug-mediated regulation of STAT3 in EC. Studies have focused on regulating and targeting STAT3 as a potential therapeutic approach, as STAT3 has been linked to EC cell proliferation and malignancy, and considerable progress has been made in this field (Fig. 6; Table III).

Canonical anticancer drugs. Several canonical anticancer drugs have been shown to be closely related to STAT3 regulation. Platinum-based chemotherapeutic drugs have been widely used for their broad spectrum of antitumor activity (167). There are three generations of platinum-based drugs, the first generation: Cisplatin, is effective against a variety of solid tumors, including lung, ovarian, and testicular cancer (168). Cisplatin is most commonly combined with 5-FU for the treatment of EC. However, the therapeutic effects are not satisfactory (169). In a study by Zhao *et al* (88), cisplatin was shown to inhibit proliferation, migration, invasion, and EMT, whilst inducing apoptosis in ESCC cells by downregulating STAT3, p-STAT3, and VEGF levels, promoting E-cadherin expression, and suppressing N-cadherin and vimentin expression.

Table III. Drug-mediated regulation of STAT3 in esophageal cancer.

Drug	Model	Major outcomes	(Refs.)
Cisplatin	ESCC cell lines: Eca109, EC9706, EC1, TE1, KYSE450, and KYSE70.	Downregulates the levels of STAT3, p-STAT3, and VEGF. Inhibits proliferation, migration, invasion, and EMT. Induces apoptosis.	(88)
Oxaliplatin	ESCC cell lines: TE-4 and TE-7.	Decreases the expression of p-STAT3 and survivin. Induces apoptosis.	(170)
Paclitaxel	ESCC cell lines: EC-1 and ECA-109.	Decreases the levels of STAT3 and p-STAT3. Inhibits proliferation and mitochondrial respiration. Induces apoptosis.	(175)
Dasatinib	ESCC cell lines: KYSE140, KYSE150, KYSE30, KYSE410, KYSE450 and KYSE510.	Suppresses PI3K/AKT and STAT3 pathways. Induces c-Myc and MMP9 expression. Enhances apoptosis induction, and the anti-invasive and anti-angiogenic ability of cisplatin in ESCC cells.	(180)
Bosutinib	ESCC cell lines: ECA109 and KYSE450.	Inhibits Src/Abl signaling and its downstream signaling pathways, PI3K/AKT/mTOR and JAK/STAT3. Inhibits proliferation, colony formation, apoptosis. Promotes the cytotoxic effect of doxorubicin.	(183)
Metformin	ESCC cell lines: ECA109, KYSE450 and KYSE70. Patient-derived xenograft model. model.	Downregulates the levels of JAK/STAT3 and the downstream protein: Bcl-2, c-Myc. Inhibits the proliferation, migration, invasion, angiogenesis, DiI-Ac-LDL uptake, and tube formation in ESCC cells. Induces apoptosis.	(78,186)
Niclosamide	ESCC cell line: ECA-109, ECA cell lines: ESO26, FLO-1, KYAE-1, OE33, SK-GT-4 and OE19.	Overcomes drug resistance to paclitaxel, 5-FU, and cisplatin. Inhibits the JAK/STAT3, Wnt/ β -catenin, and mTORC1 pathways. Decreases the levels of cyclin D1, E, A, and B1. Inhibits proliferation and colony formation. Induces apoptosis.	(89,189)
Chloroquine	ESCC cell line: EC109. Xenograft nude mouse model.	Decreases the levels of STAT3 and CXCR4 in ESCC cells. Induces apoptosis of tumor cells. Inhibits tumor growth <i>in vivo</i> .	(85)

STAT3, signal transducer and activator of transcription 3; ESCC, esophageal squamous cell carcinoma; p-, phosphorylated; VEGF, vascular endothelial growth factor; EMT, epithelial-mesenchymal transformation; JAK, Janus kinase; 5-FU, 5-fluorouracil; CXCR4, CXC chemokine receptor 4.

miR-125a-5p increased the cytotoxic effects of cisplatin, while IL-6 attenuated it. Chemoresistance is the most common cause of chemotherapy failure, and this study provides a novel viewpoint for explaining and solving the problems of drug resistance in EC.

Oxaliplatin belongs to the third generation of platinum-based antitumor agents. Ngan *et al* (170) found that oxaliplatin could decrease the levels of p-STAT3 and reduce the viability of ESCC cells, whilst also inducing apoptosis of tumor cells. Survivin belongs to the inhibitor of apoptosis family of proteins; it plays a significant role in cell division and inhibits apoptosis (169), and its expression is upregulated in EC (171). At the transcriptional level, survivin is one of the downstream targets of STAT3 in breast cancer cells (172). Oxaliplatin can reduce survivin levels in EAC cells by altering the STAT3 signaling pathway, causing EAC cell apoptosis.

Paclitaxel is a cytotoxic drug for treating a variety of malignancies such as breast cancer, NSCLC, and ovarian cancer (173). A recent study revealed that neoadjuvant concurrent chemoradiotherapy with paclitaxel and carboplatin is associated with improved survival rates, higher surgical resection rates, and better safety profiles than the combination of cisplatin and 5-FU for treating locally advanced EC (174). Paclitaxel reduced mitochondrial respiration in ESCC cells by downregulating STAT3 and p-STAT3 expression, resulting in depolarization of the mitochondrial membrane potential and significantly increasing the reactive oxygen species (ROS) levels (175).

Using targeted therapies, tyrosine kinase inhibitors have seen widespread adoption. Dasatinib, a short-acting tyrosine kinase inhibitor, has become the first-line treatment for chronic myeloid leukemia in Philadelphia chromosome-positive patients (176). Several studies have indicated that the antitumor effects of dasatinib in renal cell carcinoma (177), pancreatic cancer (178), and NSCLC (179) are closely related to STAT3. Chen *et al* (180) found that dasatinib could improve ESCC cisplatin sensitivity by inhibiting the PI3K/AKT and STAT3 pathways. Bosutinib (SKI-606) is a second-generation tyrosine kinase inhibitor approved for the treatment of chronic myeloid leukemia and it selectively inhibits the kinase activity of Src (181). STAT3 was shown as a downstream target of Src (46,182), thus it can be speculated that bosutinib may also have an antitumor effect in EC. Ha *et al* (183) showed that bosutinib induced apoptosis of ESCC by inhibiting Src/Abl and its downstream JAK/STAT3 signaling pathway, and this increased the cytotoxic effects of doxorubicin on ESCC cells.

Non-canonical anticancer drugs. Recently, several non-chemotherapeutic drugs have been found to possess anticancer activity, including metformin, niclosamide, and chloroquine (CQ). Metformin is one of the most commonly used drugs for treating type 2 diabetes (184). Recent studies have shown the chemopreventative and antineoplastic effects of metformin in various types of malignancies, including bone cancer, breast cancer, melanoma, endometrial cancer, and colorectal cancer (185). The mechanism underlying the anticancer effects of metformin is also closely related to STAT3. Metformin was demonstrated to suppress the COX2/PGE2/STAT3 axis and inhibit EMT in prostate cancer (56). Similar effects were confirmed in ESCC; Feng *et al* (186) showed that metformin promoted autophagy and

apoptosis in ESCC, and downregulated STAT3 signaling and its downstream protein Bcl-2. In a further study, Yang *et al* (78) emphasized the anti-angiogenic effects of metformin in ESCC. Metformin reduced ESCC tumor angiogenesis *in vitro* and *in vivo* by suppressing the JAK/STAT3/c-Myc pathway. Since the pharmacological effects of metformin and the adverse reactions have been defined previously, metformin may be a promising therapeutic option for the management of EC.

Niclosamide is a well-tolerated anthelmintic drug used to treat cestodes. Several studies have consistently identified niclosamide as a possible antitumor drug (187,188). Liu *et al* (73) found that nimesulide decreased COX2 by suppressing JAK2 and STAT3 phosphorylation in ECA-109 cells, thus mediating tumor cell apoptosis and growth inhibition *in vitro* and *in vivo*. In EC cells, Wei *et al* (189) discovered that niclosamide inhibited the Wnt/ β -catenin, STAT3, and mTORC1 pathways and that it was more efficient in suppressing EC cell activity than normal cells.

CQ is the most widely used anti-malarial agent and is an autophagy inhibitor (190). In EC cells, CQ can target CXCR4-positive ESCC cells via modulation of the STAT3 signaling pathway, resulting in downregulation of CXCR4 expression and thus inducing cell apoptosis (85).

Natural compounds that mediate regulation of STAT3 in EC. Numerous natural compounds extracted from herbal medicines exhibit anticancer activity, and rapid progress concerning the mechanisms of natural compounds has been made in recent years. The natural compounds that regulate the STAT3 signaling pathway can be divided into two types: JAK inhibitors and STAT3 inhibitors (Fig. 7; Table IV).

Natural JAK inhibitors. All the natural JAK inhibitors in EC play anticancer roles by suppressing the activation of JAK. Curcumin (diferuloylmethane), a naturally occurring substance found in *Curcuma longa*, has been shown to reduce tumor proliferation and suppress a variety of signaling pathways, including prostate cancer, head and neck squamous cell carcinoma, lung cancer, breast cancer, and brain tumors (191). In EC, curcumin downregulated p-JAK, p-STAT3, and total STAT3 expression, and improved cell-cell and cell-matrix adhesion in ECA-109 cells (192). According to another study, curcumin was demonstrated to enhance cell cycle arrest and induce cell death in ESCC *in vitro* and *in vivo* (193). Additionally, one of the curcumin analogs, 2-pyridyl cyclohexanone, also exhibits similar functions. Through the JAK2/STAT3 pathway, 2-pyridyl cyclohexanone suppressed the development of EC cells by triggering apoptosis in a dose-dependent manner (194).

Licochalcone B, a root extract of *Glycyrrhiza inflata*, contains the same caffeic acid scaffold as curcumin and has been used to treat Alzheimer's disease (195). It was shown that licochalcone B is a direct JAK2 inhibitor in ESCC, decreasing the activity of JAK2, and thus decreasing the expression of STAT3, p-STAT3, and Mcl-1, arresting the cell cycle at the G2/M phase and inducing cell apoptosis (196).

Cryptotanshinone is a fat-soluble diterpenoid anthraquinone compound that primarily exists in the plants of the genus *Salvia* (197). In ESCC, cryptotanshinone decreased phosphorylation of JAK2 and STAT3, inhibited proliferation and migration *in vitro*, and inhibited tumor growth *in vivo* (198).

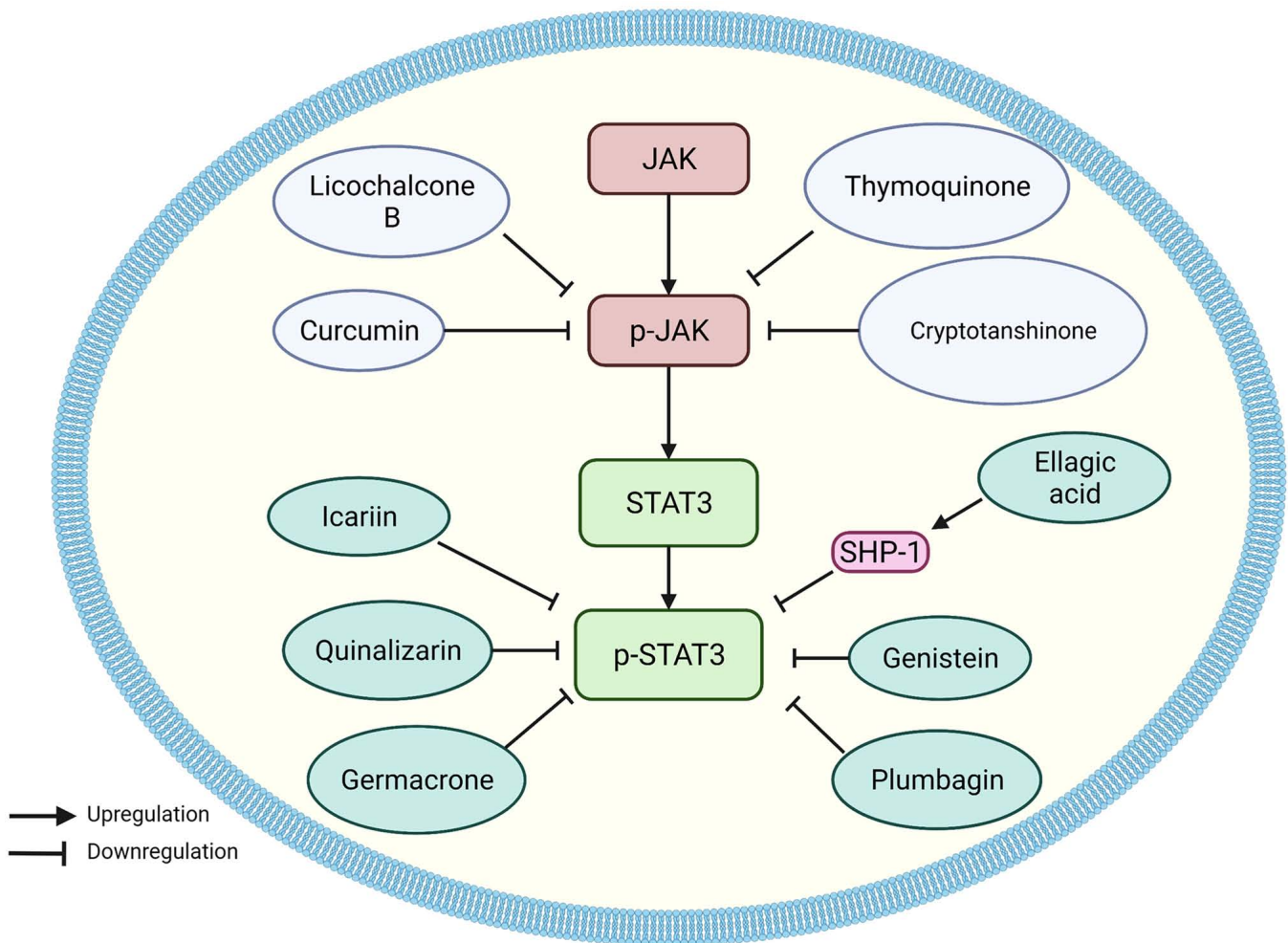


Figure 7. Natural compounds can target JAK or STAT3 to downregulate STAT3 signaling in EC. JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; EC, esophageal cancer; p-, phosphorylated.

Thymoquinone is isolated from the black seed of *Nigella sativa* (199) and is another JAK2 inhibitor in ESCC (200). *In vitro*, thymoquinone blocks the activation of JAK2, and decreases the levels of p-JAK2 and p-STAT3, thereby augmenting cisplatin-induced apoptosis.

Natural STAT3 inhibitors. Some natural compounds can directly target STAT3. Quinalizarin, also known as 1,2,5,8-tetrahydroquinone, is a dual anthraquinone compound derived from the roots of the *Rubiaceae* herb (201). Quinalizarin is a compound found in several herbal remedies that have anti-tumor properties. Zang *et al* (202) determined that quinalizarin induced apoptosis and G0/G1 cell cycle arrest of HCE-4 cells via inhibition of the NF- κ B, MAPK, and STAT3 signaling pathways, whilst also decreasing the levels of cyclin D1/E and CDK2/4, and increasing the intracellular ROS levels.

Plumbagin, a natural naphthoquinone ingredient derived from the roots of the medicinal plant *Plumbago zeylanica L.*, has been shown to possess anticancer effects in a range of cancer cell lines, including leukemia, breast cancer, melanoma, and liver cancer (203). In ESCC cells, Cao *et al* (66,67) confirmed that plumbagin downregulated STAT3 levels and arrested cells in the G0/G1 phase.

Genistein is a simple isoflavone derived from soybeans and is associated with a reduced risk of prostate, breast, and lung

cancer (204). It can significantly decrease EGFR expression and STAT3 phosphorylation in ESCC cells, thus inhibiting STAT3 nuclear translocation, thereby suppressing the activity of the STAT3 signaling pathway (62). As a result, genistein was demonstrated to inhibit tumor proliferation *in vitro* and *in vivo*, halt the cell cycle in the G0/G1 phase, and downregulate the expression of cell cycle-related genes: Cyclin D1, Bcl-2, Bcl-x1, CDK4, and CDK6, induce apoptosis and upregulate the expression of apoptosis-associated genes including Bax, Bid, PARP, caspase-3, and p53.

Germacrone is a natural compound isolated from Zingiberaceae that has been shown to possess anticancer activity in breast, brain, liver, skin, prostate, and gastric cancer (205). In ESCC, germacrone was revealed to inhibit the phosphorylation of STAT3 and increase the Bax/Bcl-2 ratio, thus triggering apoptosis and preventing cell migration (65).

Icariin is a component extracted from the traditional Chinese medicine *Epimedium grandiflorum*, which exerts several pharmacological roles in neurodegenerative diseases, cardiovascular diseases, and malignant tumors (206). Icariin induced ESCC cell apoptosis through alterations in the mitochondrial membrane potential and reducing the activation of the PI3K/AKT and STAT3 pathways (207).

Table IV. Effects of natural compounds on the regulation of STAT3 in esophageal cancer.

Natural compounds	Model	Major outcomes	(Refs.)
Curcumin	ESCC cell lines: ECA109, EC1, EC9706, KYSE450 and TE13. Patient-derived xenograft model.	Decreases intracellular ROS levels but increases SOD activity and total GSH content. Suppresses phosphorylation of JAK2 and decreases the levels of STAT3 and p-STAT3. Inhibits proliferation and colony formation <i>in vitro</i> and inhibits tumor growth <i>in vivo</i> . Induces apoptosis and promotes cell-cell adhesion and cell-matrix adhesion. Arrests the cell cycle at the S phase.	(192,193)
2-Pyridyl cyclohexanone	ESCC cell lines: ECA109 and EC9706.	Activates the MAPK pathway. Decreases the phosphorylation of STAT3 and JAK2. Inhibits the proliferation and induces apoptosis.	(194)
Licochalcone B	ESCC cell lines: KYSE450 and KYSE510.	Decreases the activity of JAK2, and the levels of p-STAT3 and Mcl-1. Arrests the cell cycle at the G2/M phase. Induces apoptosis.	(196)
Cryptotanshinone	ESCC cell lines: EC109 and CAES17. Xenograft mouse model	Decreases the phosphorylation of JAK2 and STAT3. Inhibits proliferation and migration. Inhibits tumor growth <i>in vivo</i> . Induces apoptosis.	(198)
Thymoquinone	ESCC cell line: ECA109. Xenograft mouse model.	Blocks the activation of the JAK2/STAT3 pathway, decreases the levels of p-JAK2, p-STAT3. Augments cisplatin-induced apoptosis. Inhibits tumor growth <i>in vivo</i> .	(200)
Quinalizarin	ESCC cell lines: HCE-4 and TE-2.	Inhibits the MAPK, STAT3, and NF-κB pathways. Inhibits proliferation and arrests cells in the G0/G1 cycle by decreasing the levels of CDK2/4, and cyclin D1/E.	(202)
Plumbagin	ESCC cell lines: KYSE150 and KYSE450. Xenograft mouse model	Increases the intracellular ROS levels and induces apoptosis.	(66,67)
Genistein	ESCC cell line: ECA109 Xenograft mouse model.	Inhibits proliferation and colony formation of cells. Induces apoptosis and cell cycle arrest at the G0/G1 cycle. Inhibits tumor growth <i>in vivo</i> .	(64)
Germacrone	ESCC cell lines: ECA109 and EC9706.	Decreases EGFR expression and the phosphorylation of STAT3, MDM2, Akt, and JAK1/2. Decreases the levels of ROS and the mitochondrial membrane potential.	(65)
Icariin	ESCC cell line: KYSE70. Xenograft mouse model	Inhibits tumor proliferation <i>in vitro</i> and <i>in vivo</i> . Arrests the cell cycle in the G0/G1 phase and downregulates the expression of cell cycle-related genes: Bcl-2, Bcl-x1, cyclin D1, CDK4, CDK6. Induces apoptosis and upregulates the expression of apoptosis-associated genes: Bax, Bid, PARP, caspase-3, and p53.	(207)
Ellagic acid	ESCC cell lines: EC9706 and KYSE450.	Decreases the levels of p-STAT3. Increase the Bax/Bcl-2 ratio. Induces apoptosis and inhibits migration.	(69)
		Decreases the level of p-AKT and p-STAT3. Arrests the cell cycle at the G2/M phase. Inhibits proliferation, migration, invasion, and induce apoptosis of tumor cells. Inhibits tumor growth <i>in vivo</i> .	
		Induces apoptosis. Upregulates the levels of SHP-1 and increase the cleavage PARP. Downregulates the levels of p-STAT3, RNF6, Bcl-2, and Mcl-1.	

STAT3, signal transducer and activator of transcription 3; ESCC, esophageal squamous cell carcinoma; ROS, reactive oxygen species; JAK2, Janus kinase 2; p-, phosphorylated; CDK, cyclin-dependent protein kinase.

Ellagic acid is a natural phenol with antioxidant and antiproliferative effects (208), which is an indirect STAT3 regulator in EC cells. In an *in vitro* study, Xu *et al.* (69) found that ellagic acid suppressed the activation of STAT3 in ESCC cell lines via upregulation of the levels of SHP-1. SHP-1 is a negative regulator of STAT3. Therefore, ellagic acid could induce apoptosis in EC cells.

5. Conclusions and future perspectives

In the present review, pertinent research on the STAT3 signaling pathway in EC was summarized. The STAT3 signaling pathway, which is functionally expressed in several types of cancer including EC, is a well-known oncogene. STAT3 can be activated by cytokines or growth factors via several routes, regulating the transcription of downstream genes. Continuous activation of STAT3 plays a particularly important role in the proliferation, infiltration, metastasis, angiogenesis, immune evasion, chemoresistance, and radioresistance of EC, and is associated with a poor prognosis in patients, and may thus be considered a diagnostic and prognostic factor in EC. A wide range of ncRNAs, including miRNAs, lncRNAs, and circRNAs, can modulate STAT3 in EC; some play a promoting role, while others are the inhibitors of STAT3. Finally, the effects of antitumor drugs and natural compounds for blocking the STAT3 signaling pathway in EC were examined, which are worthy of further research in EC therapy.

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Authors' contributions

ZGS and NZ designed the review. RJM wrote the manuscript. MMZ and CM prepared the figures and tables. KH revised the manuscript. Data authentication is not applicable. All the authors contributed to manuscript revision, as well as read and approved the submitted version.

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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