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MINI REVIEW

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The regulatory relationship between transcription factor STAT3 and noncoding RNA

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Abstract

Signal transducer and activator of transcription 3 (STAT3), as a key node in numerous carcinogenic signaling pathways, is activated in various tumor tissues and plays important roles in tumor formation, metastasis, and drug resistance. STAT3 is considered a potential subtarget for tumor therapy. Noncoding RNA (ncRNA) is a special type of RNA transcript. Transforming from "junk" transcripts into key molecules involved in cell apoptosis, growth, and functional regulation, ncRNA has been proven to be closely related to various epithelial–mesenchymal transition and drug resistance processes in tumor cells over the past few decades. Research on the relationship between transcription factor STAT3 and ncRNAs has attracted increased attention. To date, existing reviews have mainly focused on the regulation by ncRNAs on the transcription factor STAT3; there has been no review of the regulation by STAT3 on ncRNAs. However, understanding the regulation of ncRNAs by STAT3 and its mechanism is important to comprehensively understand the mutual regulatory relationship between STAT3 and ncRNAs. Therefore, in this review, we summarize the regulation by transcription factor STAT3 on long noncoding RNA, microRNA, and circular RNA and its possible mechanisms. In addition, we provide an update on research progress on the regulation of STAT3 by ncRNAs. This will provide a new perspective to comprehensively understand the regulatory relationship between transcription factor STAT3 and ncRNAs, as well as targeting STAT3 or ncRNAs to treat diseases such as tumors.

Keywords: circRNA, LncRNA, microRNA, STAT3, Transcription factor

Introduction

Signal transducer and activator of transcription 3 (STAT3) is one of the seven members of the STAT family, being involved in regulating cell growth, differentiation, and survival [1, 2]. As the core regulator of the antitumor immune response, STAT3 can promote the production of immunosuppressive factors and participates in various biological processes, such as cell proliferation, differentiation, angiogenesis, and immune suppression [3, 4]. About 75% of the human genome is transcribed into RNA, but only 3% is transcribed into protein-encoding mRNA, while most will be transcribed into noncoding

RNA (ncRNA) [5, 6]. At present, the most well-studied "classical ncRNA" types mainly include long noncoding RNA (lncRNA), microRNA (miRNA), and circular RNA (circRNA). They are widely recognized as various cancer biomarkers [7–9]. miRNAs can bind to mRNA to inhibit translation, and it is estimated that a single miRNA might simultaneously regulate hundreds of mRNA sequences [10]. Ongoing research has identified lncRNAs as the main regulatory factors for transcription and translation [11, 12], and their roles and mechanisms in various cancers have also been widely studied. circRNAs are circular RNAs produced by back-splicing of introns, exons, or intergenic regions [13]. The structural stability of circRNA also plays an important role in transcriptional regulation, intercellular information transmission, and translation processes [14–16].

Previous studies have mainly focused on the regulatory effect and mechanism of ncRNAs on the transcription factor STAT3. However, in recent years, researchers have shifted their attention to the regulation by STAT3 on ncRNAs and its mechanism. With the continuous recognition of the molecular mechanisms underlying the regulation of ncRNAs by STAT3 and its impact on tumor occurrence and development, new targeted anticancer strategies based on STAT3 or ncRNAs are gradually being developed, which might also provide potential therapeutic targets for cancer [17]. Therefore, it is important to summarize the research progress on the regulation by STAT3 on ncRNA and its mechanism to comprehensively understand STAT3's function. In this review, we summarize the regulatory effects and possible mechanisms of STAT3 on lncRNAs, miRNAs, and circRNAs. At the same time, we provide an update on the progress of research into ncRNA-mediated regulation of STAT3, providing a basis for a comprehensive understanding of the mutual regulatory relationship between transcription factor STAT3 and ncRNAs, especially the mechanism by which STAT3 regulates ncRNAs.

Transcription factor STAT3 directly binds to the LncRNA promoter to upregulate lncRNA expression, thereby affecting the biological phenotype and disease progression of cells

Studies have shown that transcription factor STAT3 can upregulate the expression of lncRNAs by directly binding to their promoters. LncRNAs, in turn, upregulate the expression of target genes by sponging miRNAs, ultimately promoting the proliferation, migration, and invasion of tumor cells [17–20], or regulating the differentiation of Th17 and M2 macrophages [21, 22], promoting the occurrence and development of immune-related diseases.

STAT3 directly binds to lncRNA promoters to upregulate lncRNA expression, which sponge miRNAs to affect downstream target genes and regulate the biological phenotype of tumor cells

STAT3 is a transcription factor that is overactivated in most human cancers. The activation of signaling pathways such as JAK/STAT3 and vascular endothelial growth factor receptor 2 (VEGFR2)/STAT3/PD-L1 can promote STAT3 phosphorylation. JAKs can be activated by various receptors, including interleukin-6 (IL-6), IL-6 family cytokines, Toll-like receptors (TLRs), and G protein coupled receptors (GPCRs) [23]. Activated JAKs, such as JAK1 and JAK2, phosphorylate STAT3 at the Tyr705 site, leading to recruitment

and activation of STAT3 in the cytoplasm and translocation to the nucleus. Meanwhile, serine/threonine kinases mediate Ser727 phosphorylation of STAT3, enhancing its transcriptional activity [24]. It has been reported that STAT3 can promote the progression of breast cancer (BC), non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and other cancers after phosphorylation.[25–28]. Recently, studies reported a close correlation between STAT3 and abnormal upregulation of specific lncRNAs in these cancers. Some lncRNAs can serve as competitive endogenous RNAs (ceRNAs) that function as miRNA molecular sponges [29]. They inhibit binding of miRNAs to their downstream cancer-related target genes by sponging the miRNAs, thereby upregulating the expression of the target genes. An et al. suggested that STAT3 can directly bind to the P2 site in the lncRNA *LINC006688* promoter region, inducing upregulation of *LINC00668* expression. Subsequently, *LINC00668* upregulated *KLF7* (encoding KLF transcription factor 7) expression by sponging miR-193a, thereby promoting NSCLC cell proliferation, migration, and invasion, and inhibiting cell apoptosis [18]. Wang and colleagues found that, in human BC cell lines, STAT3 binds to the promoter of lncRNA *TINCR*, thereby enhancing its transcription. Subsequently, *TINCR* upregulates the expression of the miR-503-5p target gene, *EGFR* (encoding epidermal growth factor receptor), by adsorbing miR-503-5p, ultimately promoting tumor development [17]. In addition, Zheng and colleagues confirmed that lncRNA *RHPN1-AS1* is overexpressed in CRC cell lines. STAT3 promotes the transcription of *RHPN1-AS1* by binding to the upstream transcription start site (TSS) at −1915 to −1905 in the *RHPN1-AS1* promoter region. Subsequently, *RHPN1-AS1* accelerates the progression of CRC through sponging miR-7-5p-mediated *O*-GlcNAcy transfer (OGT) [19]. In summary, JAK1 or JAK2 is activated by various receptors such as IL-6, IL-11, LIF, GPCR, TLRs, etc., in most cancer cells. After activation, JAKs mediate the activation of STAT3 by promoting its phosphorylation, upregulating its expression [24]. Subsequently, STAT3 can promote transcription of lncRNAs and upregulate their expression by directly binding to their promoters. Ultimately, the lncRNAs induce tumor cell proliferation, migration, and invasion by adsorbing miRNAs to upregulate the expression of downstream target genes.

To date, research on the regulation of lncRNA expression by STAT3 has mainly focused on the upregulation of lncRNA expression by STAT3 binding to its promoter. However, further research is needed to determine whether STAT3 can enhance or inhibit the expression of LncRNAs via other regulatory mechanisms, thereby affecting the biological phenotype of tumor cells.

STAT3 directly binds to an lncRNA promoter to upregulate the expression of lncRNA, thus forming a STAT3/lncRNA/miRNA positive feedback loop, thus affecting the biological phenotype of tumor cells

LncRNAs have been revealed to play important roles in a wide range of fields, such as human tumors and cardiovascular system disorders [30], and the transcription of lncRNAs might be regulated by certain transcription factors [18], such as STAT3. Liu et al. confirmed that STAT3 and lncRNA *CASC9* are highly expressed in glioma specimens and cells, and STAT3 can directly bind to the second site (P2) of the *CASC9* promoter to promote its expression. At the same time, *CASC9* upregulates the expression of STAT3 through sponging miR-519d, forming a positive feedback loop

of STAT3/CASC9/miR-519d. Ultimately, it enhances tumor proliferation, invasion, and migration in vitro, and promotes tumor growth in vivo [31]. Yang et al. showed that STAT3 is an upstream factor for lncRNA *SNHG16* transcriptional activation in vascular smooth muscle cells (VSMCs). STAT3 promotes *SNHG16* expression by binding to the E1 site of the promoter. Meanwhile, lncRNA *SNHG16* upregulates the expression of STAT3 by inhibiting the binding of miR-106b-5p to STAT3, ultimately forming a complex deteriorating loop in abdominal aortic aneurysm (AAA) by regulating VSMCs [20]. Meanwhile, Xie et al. found that STAT3 transcriptionally activates lncRNA *LOXL1-AS1*, upregulating its expression in VSMCs and human umbilical vein endothelial cells (HUVECs) by binding to the promoter. In addition, *LOXL1-AS1* sponges miR-515-5p to inhibit its binding with STAT3, thereby increasing the expression of STAT3, forming a *LOXL1-AS1*/miR-515-5p/STAT3 positive feedback loop, and promoting cell proliferation and migration in atherosclerosis (AS) [32]. (Fig. 1). In summary, STAT3 can directly upregulate its expression by binding to the promoters of lncRNAs. Subsequently, the lncRNAs absorb miRNAs targeting STAT3, thereby increasing the expression of STAT3, and forming a STAT3/lncRNA/miRNA positive feedback loop, which promotes the occurrence and development of tumors.

These findings strongly support STAT3 as a downstream target for lncRNAs and as a transcription factor involved in the upregulation of lncRNAs, forming a feedback loop. At the same time, the proposed loop might also provide reference significance for the study of STAT3 and other gene regulatory mechanisms, and provide valuable treatment strategies for cancer. However, it is unclear whether there are other downstream miRNA target genes that are involved in the development of gliomas, AAA, and AS, which also use feedback loops to ultimately regulate the occurrence and development of tumors. These questions should be addressed in future studies.

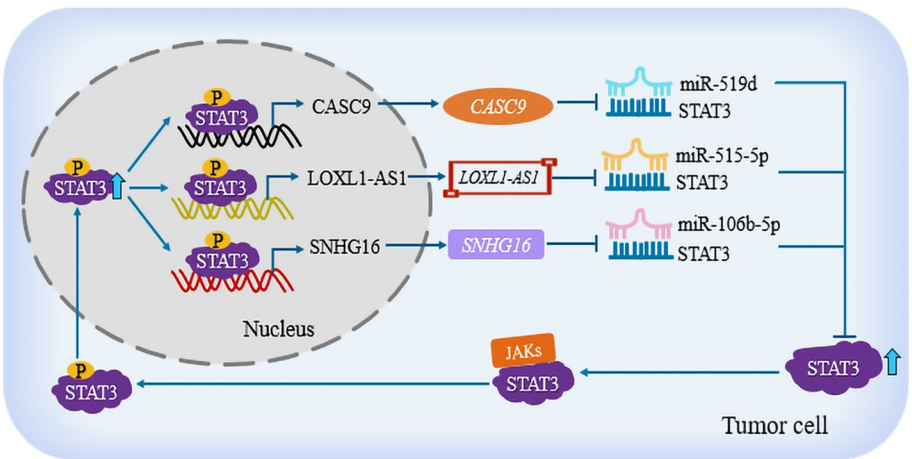

Fig. 1 STAT3 binds to lncRNA promoters to upregulate their expression, forming a STAT3/lncRNA/miRNA positive feedback loop. In tumor cells, STAT3 upregulates lncRNA expression, such as *CASC9* and *LOXL1-AS1*, and SNHG16, by binding to their promoter. Subsequently, the lncRNAs relieve the inhibition of miRNAs (such as miR-519d, miR-515-5p, and miR-106b-5p) on STAT3 by adsorbing them, thereby restoring the expression of STAT3, forming a STAT3/lncRNA/miRNA positive feedback loop, and promoting the occurrence and development of tumors

STAT3 directly binds to lncRNA promoters to upregulate their expression, which promotes cell differentiation by regulating the expression of some Th17 or M2 macrophage differentiation-related genes, thereby promoting the occurrence and development of immune-related diseases

STAT3 is a key regulatory factor for human Th17 cell differentiation, and abnormalities of its signaling pathway are key factors in chronic inflammation and autoimmune diseases [33, 34]. After STAT3 binds directly to the promoter of an lncRNA and upregulates its expression, the lncRNA can promote cell differentiation by regulating the expression of genes or proteins related to Th17 and M2 macrophage differentiation, ultimately promoting the occurrence and development of immune-related diseases [21, 22]. Khan et al. found that STAT3 directly binds to −1500 to +250 from *MIAT* TSS, which induces its expression in the early stages of Th17 cell differentiation. Upregulated *MIAT* resides in the nucleus and regulates the expression level of protein kinase C α (PKC-α). PKC-α is one of the early signaling molecules activated in response to T cell activation. It regulates the expression of several key Th17 genes, including *IL17A* (encoding interleukin 17A), *IL17F* (encoding interleukin 17F), *CCR6* (encoding C–C motif chemokine receptor 6), and *CXCL13* (encoding C-X-C motif chemokine ligand 13), through SMAD regulation of TGF signal transduction [35], ultimately regulating human Th17 differentiation and mediating the occurrence of autoimmune diseases such as rheumatoid arthritis (RA) and psoriasis [21]. In addition, Chen et al. showed that *lnc-M2* is highly expressed in M2 macrophages. STAT3 promotes the transcription of *lnc-M2* and upregulates the epigenetic histone modification marker at the promoter of *lnc-M2*, which suggested that STAT3 activates *lnc-M2* and promotes the differentiation of M2 macrophages through the protein kinase A (PKA)/cAMP response element binding protein (CREB) pathway, ultimately mediating the core role of macrophages in the pathogenesis of asthma and allergy, tumorigenesis, and atherosclerosis [22] (Fig. 2). The above studies confirmed that STAT3 directly binds to the promoters of lncRNAs *MIAT* and *lnc-M2*. Upregulated expression of these lncRNAs promotes the differentiation of Th17 and M2 macrophages

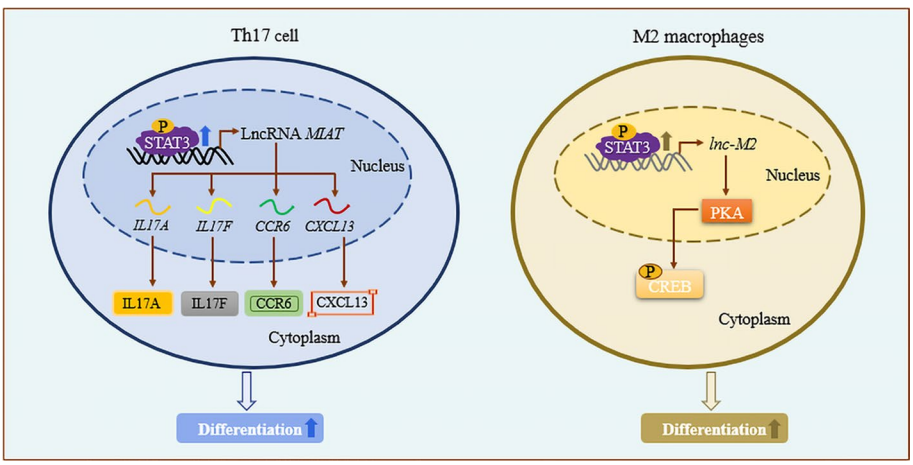

Fig. 2 STAT3 binds to lncRNA promoters to upregulate their expression, promoting Th17 or M2 macrophage differentiation. In Th17 and M2 macrophages, STAT3 directly binds to the promoters of lncRNAs *MIAT* and *lnc-M2* to upregulate their expression. The lncRNAs promote the differentiation of Th17 and M2 macrophages by upregulating the expression of differentiation-related genes

by upregulating the expression of differentiation-related genes, ultimately accelerating the development of autoimmune diseases such as RA and asthma.

Determination of the specific molecular mechanism of STAT3 in the differentiation process of Th17 and M2 macrophages could increase our understanding of the role of STAT3. Meanwhile, it also provides us with new research ideas: Can STAT3 regulate the differentiation of other tumor-related immune cells? Does it have a more profound impact on the tumor microenvironment? Currently, further work is needed to clarify how STAT3 upregulates lncRNA expression and affects the differentiation of Th17 and other immune cells, mediating the development of autoimmune diseases. This might provide potential therapeutic methods to alleviate autoimmune diseases.

STAT3 affects miRNA expression by binding to miRNA promoters, promoting the occurrence and development of diseases

Current research indicates that STAT3 not only has the ability to directly regulate lncRNAs, but also exerts a regulatory role on miRNAs. STAT3 can upregulate the expression of miRNAs by directly binding to their promoters, thereby forming a STAT3/miRNA/IL-6 loop or affecting the expression of downstream target genes, ultimately promoting tumor cell proliferation, invasion, and migration, and accelerating tumor growth [36–39]. In addition, specific miRNAs have conserved STAT3 binding sites, which prevent STAT3 from binding to them, leading to downregulation of miRNA expression and ultimately promoting tumor cell invasion and migration [40, 41].

STAT3 directly combines with miRNA promoters to upregulate miRNA expression, thus forming STAT3/miRNA/IL-6 positive feedback loops or affecting downstream target genes, thus affecting the occurrence and development of tumors and diseases

STAT3 enhances the expression of miRNAs by directly binding to their promoters. After the miRNA is upregulated, it can induce the production of IL-6 to form a STAT3/miRNA/IL-6 loop [36, 37], or can regulate the expression of downstream target genes, thereby promoting tumor cell growth and accelerating cancer progression [38, 39].

STAT3 directly binds to the promoters miR-223 and miR-29a-5p to upregulate their expression, thus forming STAT3/miR-223/IL-6 or STAT3/miR-29a-5p positive feedback loops, and regulating the biological phenotype of tumor cells

STAT3/miRNA/IL-6 feedback loops promote tumor cell proliferation and epithelial–mesenchymal transition (EMT), and accelerate the development of various diseases, such as cervical squamous cell carcinoma (CSCC) [36]. Zhang and colleagues found that the expression of STAT3 was significantly increased in CSCC. STAT3 binds to the *MIR233* promoter to upregulate miR-223 expression. Subsequently, miR-223 targets the 3′-untranslated regions (UTRs) of *TGFBR3* (encoding transforming growth factor beta receptor 3) and *HMGCS1* (encoding 3-hydroxy-3-methylglutaryl-CoA synthase 1), significantly downregulating their expression, and ultimately promoting CSCC tumor growth in vitro and in vivo. In addition, exosomal miR-223 from CSCC cells induces monocytes and macrophages to secrete IL-6 in a co-culture system in vitro, which in turn mediated enhance STAT3 activity in CSCC cells, thus forming a positive feedback loop to accelerate CSCC deterioration [36]. Wang et al. also confirmed that, in colorectal

cancer (CAC) cell lines, activation of STAT3 by the inflammatory factor IL-6 might lead to upregulation of miR-29a-5p in epithelial and immune cells, as well as inhibition of the expression of the miR-29a-5p target gene *TET3* (encoding Tet methylcytosine dioxygenase 3), thereby inducing a decrease in 5-hydroxymethylcytosine (5hmC) in epithelial cells. In addition, overexpression of miR-29a-5p can also increase the expression of STAT3, forming a positive feedback loop of STAT3/miR-29a-5p, leading to a reduction of TET3 and 5hmC levels, and promoting the development of CAC [37] (Fig. 3). The above research has clarified the role of STAT3/miR-223/IL-6 and STAT3/miR-29a-5-p feedback loops in the occurrence and development of CSCC and CAC, and marking them as potential therapeutic targets in CSCC and CAC. In addition, clarification of the feedback loop also provides a new perspective on the regulatory relationship between STAT3 and miRNAs.

However, these studies also have limitations. Current research has confirmed that there is a positive feedback loop between STAT3 and miR-29a-5-p; however, the specific regulatory mechanism between them has not been determined, thus requiring further exploration. Meanwhile, the above studies were conducted in vitro, and it is necessary to supplement relevant in vivo animal model experiments.

STAT3 directly binds to miRNA promoters to upregulate their expression, thereby affecting downstream target genes and promoting the occurrence and development of diseases

Research has shown that STAT3 inhibits the expression of downstream genes by upregulating miRNA expression, which contributes to the occurrence and development of diseases, such as hepatocellular carcinoma (HCC) and ischemic retina [38, 39]. Wang et al. found that, in mouse liver tumors and primary human HCC, IL-6 activates STAT3 and upregulates its expression. Subsequently, STAT3 directly binds to the promoter region of *MIR23A* and enhances miR-23a expression. miR-23a then directly targets and reduces

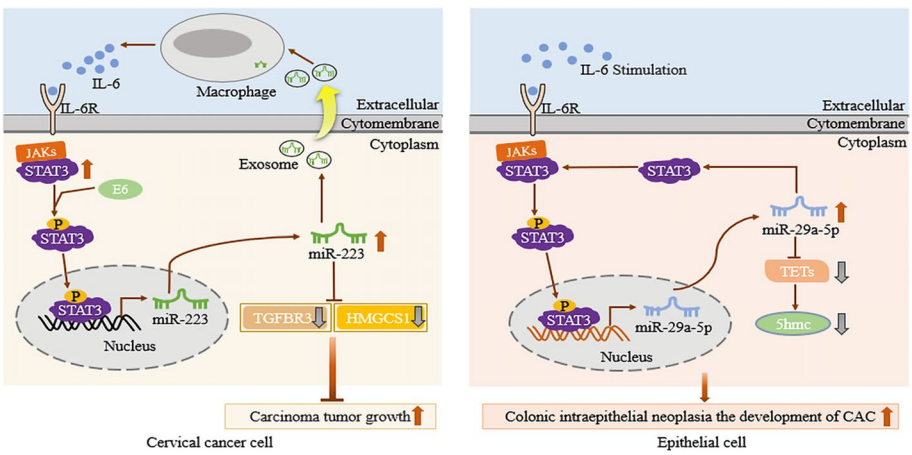

Fig. 3 STAT3 directly binds to miRNA promoters to upregulate their expression, forming STAT3/miR-223/IL-6 or STAT3/miR-29a-5p loops. In CSSC and CAC, STAT3 upregulates miRNA expression by binding to the miR-223 and miR-29a-5p promoters. Subsequently, exosomal miR-223 induces monocytes/macrophages to secrete IL-6, which in turn mediates the upregulation of STAT3 expression in CSSC cells. Meanwhile, overexpression of miR-29a-5p also increases the expression of STAT3. Finally, a positive feedback loop is formed to promote the growth of CSCC and CAC tumors

the expression of *PGC1A* (encoding PPARG coactivator 1 alpha) and *G6PC* (encoding glucose-6-phosphatase), leading to a decrease in glucose production, which might ultimately contribute to the survival of tumor cells under hypoxic conditions [38]. A study by Gutsaeva et al. confirmed that the expression of miR-21 in human retinal endothelial cells (HRECs) exposed to hypoxia is dependent on STAT3. STAT3 can upregulate *MIR21* expression by directly binding to its transcription start, thus promoting the activation of the STAT3/miR-21 signaling pathway. Upregulated miR-21 then inhibits *TIMP3* (encoding tissue inhibitor of matrix metalloproteinase-3) expression, thereby promoting the occurrence of retinal neovascularization, and possibly causing ischemic retinopathy [39]. In summary, STAT3 can directly bind to the promoter regions of *MIR23A* and *MIR21* to upregulate their expression. miR-23a and miR-21 in turn inhibit the expression of *PGC1A*, *G6PC*, and *TIMP3*, thereby promoting tumor growth or accelerating the development of ischemic retinopathy.

The above research confirmed that STAT3 regulates gluconeogenesis and retinal neovascularization in HCC and retinal diseases, respectively, by upregulating specific miRNAs, providing strong support for the diversity of STAT3 functions. Studies have also found that STAT3 mediates changes in the expression level of specific miRNAs in different tumor cells, leading to different results. For example, miR-21 has a dual role in angiogenesis, not only promoting the occurrence of retinal neovascularization, but also inhibiting the generation of choroidal neovascularization [42]. The reason for this difference might be the different properties of retinal and choroidal endothelial cells [39]; however, the specific molecular mechanism that leads to the difference requires further research.

STAT3 can downregulate miRNA expression, forming a STAT3/miRNA/IL-6R positive feedback circuit, and regulating the biological phenotype of tumor cells

There is ample evidence that STAT3 directly upregulates expression of miRNAs by binding to their promoters; however, a few studies have found that STAT3 can downregulate miRNA expression. A study by Rokavec et al. showed that exposure of human CRC cells to cytokine IL-6 activated STAT3, but the expression of miR-34a was inhibited. Examination of the *MIR34A* genome region showed a phylogenetically conserved STAT3 binding site in the first intron near the first exon, which prevented STAT3 from binding to the *MIR34A* promoter, resulting in direct inhibition of miR-34a expression. In addition, downregulation of miR-34a leads to less binding of miR-34a to its downstream target, *IL6R* (encoding IL-6 receptor), thereby upregulating IL-6R levels, which ultimately promoted IL-6-induced STAT3 expression, forming a STAT3/miR-34a/IL-6R feedback loop, and promoting tumor cell invasion and migration [40]. In addition, Zhu et al. found that exposure of epithelial ovarian cancer (EOC) cells to IL-6 activated STAT3 and upregulated its expression. Subsequently, STAT3 directly inhibited the expression of miR-204 through the conserved STAT3 binding site near the *TRPM3* (encoding transient receptor potential cation channel subfamily M member 3) promoter region upstream of miR-204. Inhibition of miR-204 enhanced the activity of IL-6R, as the direct target of miR-204, which prompted IL-6 to upregulate the expression of STAT3, forming a

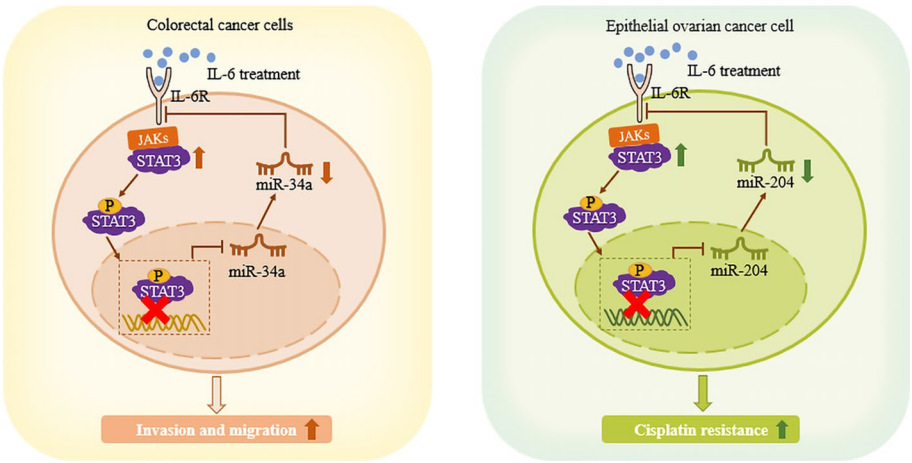

Fig. 4 STAT3 can downregulate miRNA expression, forming a STAT3/miRNA/IL-6R positive feedback loop. STAT3 cannot bind to the miR-34a and miR-204 promoters, resulting in inhibition of miRNA expression. At the same time, after IL-6 stimulates CAC cells and EOC cells, the activity of IL-6R, as the direct target of miR-34a and miR-204, is enhanced, and then mediates IL-6 to upregulate the expression of STAT3, forming a positive feedback loop, and promoting the invasion and migration of colorectal cancer cells and the cisplatin resistance of EOC cells

STAT3/miR-204/IL-6R positive feedback loop, ultimately promoting enhanced cisplatin resistance of EOC cells, inducing treatment failure and EOC recurrence [41] (Fig. 4).

Cisplatin is a commonly used chemotherapy drug for treating various types of cancer [43]. However, intrinsic or acquired resistance to cisplatin remains a major obstacle in the cancer treatment process [44]. A large number of studies currently indicate that STAT3 plays an important role in mediating drug resistance in cancer treatment [45]. Therefore, considering that the miR-34a/IL-6R/STAT3 pathway regulates cisplatin resistance in EOC cells proposed by the above study, we can also reflect on whether there are other miRNAs in EOC cells that can regulate STAT3 expression and thereby affect cisplatin resistance in EOC cells. This may be very beneficial for the treatment of EOC.

In summary, the presence of conserved STAT3 binding sites near the *MIR34A* and *MIR204* promoter regions means that their transcription is inhibited by STAT3, thereby enhancing the expression of IL-6R. IL-6R ultimately promotes the expression of STAT3, forming a STAT3/miRNA/IL-6R feedback loop, promoting tumor cell invasion and migration. The above research proves that the transcription factor STAT3 can not only promote miRNA expression but also inhibit miRNA expression. In addition, current research on the STAT3/miR-34a/IL-6R loop has not only clearly confirmed that it is necessary to maintain the mesenchymal phenotype of CRC cell lines but also detected its activation in BC and prostate cancer cell lines with mesenchymal characteristics [40]. This suggests that this loop might represent a new mechanism of carcinogenesis in cancer cells exhibiting a mesenchymal phenotype and might become a useful prognostic marker for cancer progression. However, it is unclear whether the STAT3/miR-34a/IL-6R loop plays the same role in different tumor cells, which requires further research.

STAT3 directly binds to circRNA promoters to upregulate their expression, thereby forming a STAT3/circRNA positive feedback loop or adsorbing miRNA to affect downstream target genes and regulate the biological phenotype of tumor cells

STAT3 plays a significant regulatory role in the expression of various lncRNAs and miRNAs. However, there are far fewer cases of STAT3 regulating circRNA expression. Sun et al. showed that circ-LRIG3 is significantly upregulated in HCC. STAT3 can directly bind to the *circ-LRIG3* promoter, thereby increasing *circ-LRIG3* transcription activity. In turn, circ-LRIG3 forms a ternary complex with EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) and STAT3. After phosphorylation by AKT at serine residue 21 (pS21-EZH2), EZH2 can promote the methylation and phosphorylation of STAT3, thereby enhancing STAT3 activity, activating STAT3 signal transduction [46], and forming a positive feedback loop of STAT3/circ-LRIG3, which ultimately promotes the proliferation, migration, and invasion of HCC cells, and reduces cell apoptosis [47]. In addition, Wang and colleagues found that circCCDC66 is highly expressed in NSCLC cells [48]. STAT3 has been shown to bind to the *CCDC66* promoter site 1, activating *CCDC66* transcription into CCDC66 mRNA. And then CCDC66 mRNA is translated into CCDC66 protein, thus increasing the expression of CCDC66 protein and circCCDC66 in NSCLC cells [48]. Subsequently, circCCDC66, as a molecular sponge for miR-33a-5p, downregulates miR-33a-5p expression and inhibits its binding to the target gene *KPNA4* (encoding karyopherin subunit alpha 4). This upregulates *KPNA4* levels, ultimately promoting the proliferation, migration, and invasion of NSCLC cells, and inhibiting cell apoptosis [48]. STAT3 is considered an oncogenic gene or RNA transcription activator in various human cancers, such as cervical cancer, BC, and oral squamous cell carcinoma [49–51]. These studies confirmed the carcinogenic effect of STAT3 in NSCLC via circCCDC66 regulation. They also identified the molecular mechanism by which STAT3 binds to the *CCDC66* promoter at site #1, thereby promoting its expression in NSCLC cells. Subsequently, CCDC66 upregulated the expression of *KPNA4* by adsorbing miR-33a-5p, which might provide new ideas for molecular targeted therapy of NSCLC.

CircRNA, as an important noncoding RNA, also plays an important role in the development of cancer. However, there are currently few studies on the regulation of STAT3 expression by circRNA, and more research is needed to explore the regulatory role of STAT3 on circRNAs. In addition, the above research did not mention how STAT3 upregulates the expression of target genes via circRNAs, and how the target genes promote cancer development, which requires further research and exploration.

LncRNAs regulate STAT3 expression directly or indirectly, affecting the biological phenotype of tumor cells or the occurrence and development of diseases

In HCC, BC, ovarian cancer (OV), and HCC, lncRNAs mainly alter the expression of STAT3 by directly binding to STAT3 [52–59], inhibiting the binding of miRNAs to downstream target genes [60–67], regulating the expression of IL-6, IL-11, and IL-23

[68–80], or regulating the protein level of STAT3 [81, 82], ultimately affecting the biological phenotype of tumor cells or the occurrence and development of diseases.

Firstly, LncRNAs can regulate STAT3 expression by directly binding to it. On the one hand, lncRNAs such as *FAL1*, *FEZF1-AS1*, *PVT1*, and *RP11-334E6.12* can upregulate STAT3 expression by binding to the STAT3 promoter and inducing STAT3 phosphorylation, thereby directly inducing tumor cell proliferation and inhibiting apoptosis [52–58, 83]. On the other hand, studies have confirmed that *lncRNA-p21* binding to STAT3 inhibits the phosphorylation of STAT3, thereby decreasing its stability, ultimately significantly inhibiting tumor cell proliferation and promoting apoptosis [59]. The above research determined that *lncRNA-p21* can downregulate the expression of STAT3 by binding to it, thereby inhibiting the proliferation ability of HNSCC cells. However, whether *lncRNA-p21* can act as a cancer promoting factor, like most lncRNAs, in the occurrence and development of HNSCC or other cancers, has not yet been determined, which requires further exploration.

Secondly, lncRNAs can regulate STAT3 expression by adsorbing miRNAs. Studies have shown that lncRNAs, such as *H19*, *HOST2*, *SNHG16*, *MIAT*, *NEAT1*, *GACAT3*, and *SNHG1*, serve as molecular sponges for miRNA, which can downregulate miRNA levels and inhibit their binding to STAT3 to enhance STAT3 expression, thereby accelerating the progression of cancers such as BC [60, 61], HCC [62–64], gastric cancer (GC) [65], renal cell carcinoma (RCC) [66], and CRC [67, 84], by inducing tumor cell proliferation, migration, and invasion. Meanwhile, studies have also found that lncRNAs such as *SNHG14*, *CASC2*, *LINC00982*, and *BCAR4* serve as molecular sponges for miRNAs, thereby inhibit the binding of miRNAs to downstream target genes, thus upregulating their expression, and indirectly regulating the expression of STAT3, ultimately affecting tumor cell proliferation and apoptosis [85–96]. However, most of these studies did not mention how the lncRNA/miRNA/STAT3 axis affects downstream signals and promotes tumor occurrence and development. And further exploration is still needed to provide relevant evidence in animal model experiments to verify the above conclusions.

Thirdly, lncRNAs can regulate STAT3 expression by regulating the lncRNA/ILs/STAT3 positive feedback loops or ILs/STAT3 signaling pathways. LncRNAs *TCF7* and *DANCR* can induce IL-6 expression, while *HEGBC* can upregulate IL-11 expression. LncRNAs activate STAT3 expression by inducing IL autocrine signaling. At the same time, STAT3 upregulates the expression of lncRNAs by binding to their promoters, forming lncRNA/IL-6/STAT3 or lncRNA/IL-11/STAT3 loops, which enhance the drug resistance of tumor cells [68, 97], or promoting tumor growth and metastasis in vivo and inhibiting tumor cell apoptosis [69, 70]. LncRNAs such as *LNRRIL6*, *TSLNC8*, *IL6ST-AS*, and *BHLHE40-AS1* can mediate changes in IL-6 expression. And *ATB* and *LINC01152* upregulate IL-11 and IL-23 expression, respectively, by binding to their promoters in HCC cells. Altered expression of these ILs regulates the expression of STAT3, ultimately affecting the proliferation, migration, and invasion of tumor cells [69, 71–80]. In summary, these research findings emphasize the important role of the lncRNA/IL/STAT3 axis in tumor development. Nevertheless, the above experiments were conducted in vitro on cancer cell lines. Future research might consider using lncRNAs in animal models for in vivo experiments to evaluate their safety and efficacy, and for further in-depth investigation.

Fourthly, lncRNAs can regulate the expression of STAT3 by regulating the expression of other downstream genes or proteins. Studies have shown that lncRNAs, such as *LOC645166* and *TRPM2-AS*, can upregulate the expression of STAT3 by regulating downstream genes or proteins other than miRNAs and ILs, such as GATA binding protein 3 (GATA3) and p38 mitogen-activated protein kinase, ultimately promoting tumor cell proliferation, migration, and invasion, or enhancing tumor tissue chemotherapy resistance [98–102]. In addition, other studies have confirmed that lncRNAs *UCA1*, *PRECSIT*, etc. can also regulate the expression of glutamate/aspartate transporter 1 (GLAST) or matrix metalloproteinase (MMP)-1, MMP-3, MMP-10, and MMP-13, which then downregulates the expression of STAT3, thereby inhibiting disease progression [103, 104]. However, in the process of finding new targets for cancer treatment, analyzing the relationship between lncRNA expression and cancer recurrence is also very important. Therefore, it would be meaningful to further explore the impact of lncRNAs regulating STAT3 expression on cancer recurrence in the future.

Finally, lncRNA alters STAT3 levels by stabilizing or downregulating STAT3 protein levels. Numerous studies have shown that specific lncRNAs, such as *UICC* and *NEAT1*, can protect STAT3 from degradation, thereby stabilizing STAT3 protein levels [81, 105]. *Lnc-UICC* can directly interact with phosphorylated STAT3 and improve the stability of STAT3 protein by protecting it from proteasome-dependent degradation [81]. In addition, STAT3 is a downstream molecule of lncRNA *NEAT1*, which can positively regulate STAT3 cell levels by reducing ubiquitination levels [105], ultimately promoting the growth and metastasis of cervical cancer tumors or accelerating RA progression. However, studies have also found that lncRNA *GAS5* can accelerate the degradation of STAT3 by promoting TNF receptor-associated factor 6 (TRAF6)-mediated ubiquitination. TRAF6 is a well-known ubiquitin ligase that has been reported to bind to STAT3 and mediate its ubiquitination [106]. The decrease in protein levels of STAT3 ultimately inhibits Th17 cell differentiation and inhibits the development of immune thrombocytopenia (ITP) in vivo [82]. The above research reflects the regulatory function of specific lncRNAs on inflammation, which suggests that further research on lncRNAs might reveal more potential functions. Meanwhile, most current research on lncRNA regulation of STAT3 expression has focused on lncRNAs altering the transcription or activation of STAT3, while there are relatively few studies on lncRNA regulation of STAT3 protein levels by promoting or inhibiting STAT3 degradation.

MicroRNAs directly target STAT3 signaling pathway components, regulate STAT3 expression, and affect the biological phenotype of tumor cells

First, many studies have found that miRNAs can directly target STAT3, downregulate its expression, and inhibit the occurrence and development of tumors [107–110]. Therefore, the expression levels of some tumor suppressor miRNAs are typically significantly downregulated in tumor tissue samples. The significant downregulation of miR-361 and miR-4500 expression in extracapsular nodal spread (ECS) and acute lymphoblastic

leukemia (ALL) cell lines leads to inhibition of their binding to the target gene STAT3, thereby enhancing STAT3 expression and ultimately accelerating the occurrence and development of ECS and ALL [107–109]. Second, miRNAs can target components of the STAT3 signaling pathway to alter STAT3 expression, ultimately regulating the biological phenotype of tumor cells [111–118]. miRNAs (e.g., miR-19a and miR-18a) can downregulate components of the STAT3 signaling pathway, such as suppressor of cytokine signaling 3 (SOCS3), SOCS5, and protein inhibitor of activated STAT3 (PIAS3), in tumor cells, thereby activating STAT3, and ultimately promoting tumor cell migration, invasion, and EMT [111–113]. However, when miR-9 and miR-218 downregulated the expression of IL-6 and Janus kinase 2 (JAK2), they inhibited the activation of STAT3, leading to the downregulation of STAT3 expression and thus inhibiting the growth of tumor cells [111, 114, 115].

As is well known, STAT3 is an important regulatory factor for cell proliferation and survival. However, in recent years, a large number of studies have shown that STAT3 also plays an important role in maintaining stem cells and their differentiation, thereby participating in the occurrence of diseases and various types of cellular carcinogenesis [119]. Cai et al. found that, in bone marrow-derived mesenchymal stem cells (BMSCs) co-cultured with cardiomyocytes, miR-124 inhibits the expression of STAT3 protein by targeting STAT3 mRNA. The downregulation of STAT3 levels will affect the expression of cardiac-specific markers such as atrial natriuretic peptide (ANP), troponin T (TNT), α-myosin heavy chain (α-MHC), and GATA-binding factor 4 (GATA-4), ultimately regulating the differentiation of BMSCs into cardiomyocytes. These findings will greatly improve the effectiveness of BMSC-based therapy for damaged myocardial repair and regeneration [120]. Zhang and colleagues confirmed that miR-7 was downregulated in breast cancer stem cells (BCSC) isolated from human breast cancer cell lines. miR-7 downregulates the expression of STAT3 by inhibiting the binding of SETDB1 to the STAT3 promoter, thereby inhibiting the expression of c-myc, twist, and miR-9. This leads to a decrease in the BCSC population, partial reversal of EMT in BC cells, and inhibition of invasion and metastasis of BC cells [121]. In addition, Jiang et al. also found that the expression of miR-1181 was significantly downregulated in cancer pancreatic tissue and cells. miR-1181 can reduce the transcriptional activity of STAT3 and SOX2 by targeting the 3′-UTR of them in cancer pancreatic cells, and inhibit STAT3 trans activators. This leads to downregulation of SOX2 and inhibition of the STAT3 pathway, ultimately inhibiting the CSC-like phenotypes in vitro and tumorigenicity in vivo [122].

The above research reveals the mechanism by which miRNAs regulate STAT3 expression and the subsequent impact of STAT3 on the differentiation characteristics of stem cells/tumor stem cells. In the future, these molecular targets may be used to treat diseases related to JAK-STAT3 signaling disorders or stem cells/CSCs differentiation. However, compared with the research on the mutual regulatory loop between lncRNAs and STAT3, there is currently sparse evidence to confirm the existence of feedback loops between specific miRNAs and STAT3. To further understand the close connection between miRNAs and STAT3 for the treatment of other diseases, further in-depth research is required.

circRNAs, as miRNA sponges, can inhibit miRNA function, thereby promoting the expression of STAT3 and affecting the occurrence and development of diseases

Research has found that a large amount of circRNA can act as a miRNA sponge or RNA binding proteins (RBPs), thereby inhibiting miRNA function [123]. For example, circRNAs such as AKT3, RHOT1, SPARC, and UBE2Q2, as molecular sponges, can reduce the levels of miR-516b-5p, miR-106a-5p, etc., thereby hindering their binding to STAT3. The expression of STAT3 is ultimately upregulated, which plays a crucial role in promoting the occurrence and development of various cancers, as well as the proliferation, invasion, and migration of cancer cells [124–129]. These studies confirmed that certain specific circRNAs might be key tumor promoters and potential therapeutic targets for diseases [130]. Currently, most studies on the regulation of STAT3 by circRNAs have focused on upregulating the expression of STAT3 by adsorbing miRNAs. Recent studies have also found that, in squamous cell carcinoma (SCC), circFAT1 can prevent Src homology 2 domain-containing protein tyrosine phosphatase 1 (SHP-1) from dephosphorylating STAT3 and promotes STAT3 activation by binding to STAT3 in the cytoplasm [131]. However, compared with the mechanism by which lncRNAs regulate STAT3, there is relatively little research on the mechanism of circRNA regulation of STAT3. Is there any other molecular mechanism for circRNA to alter the expression of STAT3? If so, what are the specific mechanisms? These aspects require further exploration.

Conclusions

STAT3 serves as a key signaling node for tumor cells, especially tumor infiltrating immune cells. At the same time, ncRNAs participate in various cell behaviors, and control cell apoptosis, cell growth, and cell function through the expression of regulator genes at the transcriptional, posttranscriptional, and epigenetic levels [5], which are related to tumorigenesis, drug resistance, and EMT of various types of cancer [88]. Therefore, understanding the regulatory relationship between STAT3 and ncRNAs and targeting STAT3 or ncRNAs is expected to provide valuable new strategies for cancer disease treatment and drug development. However, most studies have focused on ncRNA regulation of STAT3, and there is relatively little research on the molecular mechanism of STAT3 regulation of ncRNAs, especially circRNA expression. A deeper understanding of circRNA and the mechanisms regulating ncRNA expression may improve this situation. At the same time, the existing mechanistic research is more focused on in vitro experiments in relevant tumor cell lines. Therefore, it is necessary to use animal models in vivo to verify the results. Further in-depth research and analysis might provide potential directions and perspectives for cancer, disease diagnosis, and treatment (see Outstanding questions).

Outstanding questions

1. Can the transcription factor STAT3 downregulate the expression of lncRNAs and thereby affect the biological phenotype of tumor cells? What is the specific molecular mechanism?
2. In addition to regulating the differentiation of Th17 and M2 macrophages, can STAT3 affect the differentiation of other tumor-related immune cells and have a more profound impact on the tumor microenvironment?
3. What is the specific role of the STAT3/miR-34a/IL-6R loop when activated in cancer cell lines with multiple mesenchymal phenotypes? Does this loop represent a new mechanism of carcinogenesis in these cancer cells?
4. In addition to circ-LRIG3 and circCCDC66, which other specific circRNAs are regulated by STAT3? Are there any other regulatory mechanisms?
5. In addition to the direct inhibition of miR-204 by STAT3 to mediate cisplatin resistance in EOC cells, can STAT3 affect the chemotherapy resistance of EOC cells by regulating other miRNAs?

Abbreviations

STAT3	Signal transducer and activator of transcription 3
NcRNA	Noncoding RNA
LncRNA	Long noncoding RNA
miRNA	MicroRNA
circRNA	Circular RNA
NSCLC	Non-small cell lung cancer
CRC	Colorectal cancer
ceRNA	Competitive endogenous RNA
KLF7	Encoding KLF transcription factor 7
BC	Breast cancer
EGFR	Encoding epidermal growth factor receptor
TSS	Transcription start site
OGT	*O*-GlcNAcy transfer
VSMCs	Vascular smooth muscle cells
AAA	Abdominal aortic aneurysm
HUVECs	Human umbilical vein endothelial cells
AS	Atherosclerosis
PKC-α	Protein kinase C α
IL17A	Encoding interleukin 17A
IL17F	Encoding interleukin 17F
CCR6	Encoding C–C motif chemokine receptor 6
CXCL13	Encoding C-X-C motif chemokine ligand 13
RA	Rheumatoid arthritis
PKA	Protein kinase A
CREB	CAMP response element binding protein
EMT	Epithelial–mesenchymal transition
CSCC	Cervical squamous cell carcinoma
UTRs	Untranslated regions
TGFBR3	Encoding transforming growth factor beta receptor 3
HMGCS1	Encoding 3-hydroxy-3-methylglutaryl-CoA synthase 1
CAC	Colorectal cancer
TET3	Encoding Tet methylcytosine dioxygenase 3
5hmC	5-Hydroxymethylcytosine
HCC	Hepatocellular carcinoma
PGC1A	Encoding PPARG coactivator 1 alpha
G6PC	Encoding glucose-6-phosphatase
HRECs	Human retinal endothelial cells
TIMP3	Encoding tissue inhibitor of matrix metalloproteinase-3
IL6R	Encoding IL-6 receptor
EOC	Epithelial ovarian cancer

EZH2	Enhancer of zeste 2 polycomb repressive complex 2 subunit
OV	Ovarian cancer
GC	Gastric cancer
RCC	Renal cell carcinoma
GATA3	GATA binding protein 3
GLAST	Glutamate/aspartate transporter 1
ITP	Immune thrombocytopenia
ECS	Extracapsular nodal spread
ALL	Acute lymphoblastic leukemia
SOCS3	Suppressor of cytokine signaling 3
PIAS3	Protein inhibitor of activated STAT3
JAK2	Janus kinase 2
RBPs	RNA binding proteins
SCC	Squamous cell carcinoma
SHP-1	Src homology 2 domain-containing protein tyrosine phosphatase 1

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