Impact of miRNAs involved in the STAT3 signaling pathway on esophageal cancer (Review)

YING XIONG[1], YI-FAN LIU[1], ZHI-HUI YANG[2,3] and CONG-GAI HUANG[2,3]

[1]School of Basic Medical Sciences, Southwest Medical University, Luzhou, Sichuan 646000, P.R. China;
[2]Department of Pathology, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan 646000, P.R. China;
[3]Precision Pathology Diagnosis for Serious Diseases Key Laboratory of Luzhou, Luzhou, Sichuan 646000, P.R. China

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Abstract. Esophageal cancer (ESCA) is a common tumor noted in the digestive tract, which is highly malignant due to unclear early symptoms and poor last-stage treatment effects; its mortality rate is relatively high. MicroRNA (miR) and signal transducer and activator of transcription 3 (STAT3) are key components of cellular signaling pathways; their interaction forms a complex and intricate information network that controls several types of biological behaviors in the cells. In the tumor cell, these signal transduction pathways are abnormally active, indicating that the STAT3 signaling pathway mediated by miRs is involved in the progression of various cancer types. The present review introduces the biological characteristics of miR and STAT3 and their relationship with ESCA. It summarizes the regulation of ESCA by the miR and STAT3 signaling pathways and analyzes the effects of these pathways on proliferation, apoptosis, invasion, metastasis and immune escape of cancer cells, as well as the impact on patient survival and prognosis. The purpose of the present review is to assess the miR/STAT3 signaling pathway in ESCA, improve the understanding of the pathogenesis of ESCA and facilitate the identification of therapeutic targets for ESCA.

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Correspondence to: Dr Cong-Gai Huang or Professor Zhi-Hui Yang, Department of Pathology, The Affiliated Hospital of Southwest Medical University, 25 Taiping Street, Jiangyang, Luzhou, Sichuan 646000, P.R. China
E-mail: huangconggai66@163.com
E-mail: yzhih73@swmu.edu.cn

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Introduction

Esophageal cancer (ESCA) is a solid tumor and frequently occurs in the digestive tract. It is highly invasive and has a high incidence rate and mortality (1); its cancer mortality ranks sixth worldwide and the overall 5-year survival rate is low (2-4); it is estimated to be ~15-25% (4,5). According to histopathological results, it can be classified into esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). Due to differences in etiology and geographical incidence rate, EAC is common in the Western population, while ESCC is prevalent in the Eastern population (5-8). The incidence of ESCA is closely associated with smoking, alcohol consumption, unhealthy dietary habits and obesity (9). In China, the incidence rate of ESCC is higher due to its early symptoms not being obvious (10); therefore, the majority of the patients have developed late-stage disease when diagnosed, with low quality of life and poor prognosis (2). At present, the conventional clinical treatment methods for ESCA are surgery, chemotherapy and radiotherapy (11); however, with the complex development of the disease, including invasion and metastasis, as well as drug resistance and normal cell toxicity, traditional treatment methods face significant challenges (12). In order to enhance treatment effectiveness and improve the low survival rate, treatment methods need to be constantly updated and strengthened, which requires an urgent proposal of new strategies.

MicroRNAs (miRNAs/miRs) are a class of non-coding conserved small-molecule RNAs with a length of ~20 nucleotides (13). Mature RNA binds to the corresponding mRNA molecule, regulates the relevant gene expression, participates in the regulation of biological behaviors, such as cell proliferation, differentiation, apoptosis and metabolism, and plays a wide range of regulatory roles (13-18). In cancer, certain miRNAs are often abnormally expressed and become tumor promoters or suppressors (13,16,19-23). Signal transduction and transcription activator 3 (STAT3) is a widely studied crucial component that connects

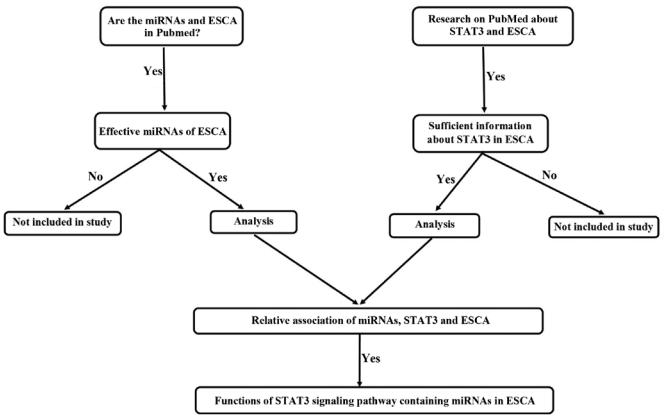

Figure 1. Literature search strategy design to search for the interaction between STAT3 and miRNAs, and the influence of miRNAs on the STAT3 signaling pathway in ESCA. STAT3, signal transduction and transcription activator 3; miRNA, microRNA; ESCA, esophageal cancer.

cellular signaling and transcription (24), controls multiple signaling pathways and acts as a hub gene (25). Abnormal expression of STAT3 can lead to cellular dysfunction, development of diseases and various malignant tumors in humans (26). In tumor tissues, constitutively activated STAT3 can promote multiple malignant behaviors of cancer cells (24,25,27-33). Numerous studies have shown that miRNAs can participate in regulating the STAT3 signaling pathway; furthermore, STAT3 can modulate the expression levels of multiple miRNAs. MiRNAs and STAT3 interact via direct or indirect mechanisms, forming signaling circuits that affect cellular balance (34-37).

With the continuous advancement in molecular biology research, an accumulating number of studies have indicated that the occurrence of cancer is related to unusual signaling routes within cells. Furthermore, targeted therapy has become a method of precision treatment for tumors (12). The STAT3 signaling pathway mediated by miRNAs has been widely explored in various cancer types; e.g. in gastric cancer (38), leukemia (39), colorectal cancer (26) and ESCA (40). A review was conducted on the miRs involved in the STAT3 signaling pathway in ESCA following a literature search in the PubMed database using the key words 'esophageal cancer', 'STAT3' and 'miRNA'. The present review unveiled the complex pathogenesis behind ESCA by analyzing the interaction between STAT3 and different miRNAs, as well as the impact of miRNAs on the STAT3 signaling pathway (Fig. 1); it also reviewed the effects of different miRNAs and the STAT3 signaling pathway on the proliferation, invasion, metastasis, apoptosis, drug resistance and immune escape of ESCA. Understanding the molecular mechanisms of the interaction between miRNAs and STAT3 can provide favorable conditions to identify potential therapeutic targets for ESCA and develop novel anticancer drugs, laying a foundation for formulating new clinical plans. This is of great significance for improving disease prognosis and provides hope for the survival of patients with ESCA.

2. STAT3 signaling pathway mediated by miRNAs inhibits ESCA proliferation, invasion and metastasis, and aids apoptosis

The majority of the miRNAs associated with the STAT3 signaling pathway exert inhibitory effects on tumors, including miR-124 (41,42), miR-125a-5p (43), miR-296-5p (44), miR-874-3p (45), miR-17-5p (46), miR-149-5p (47), miR-30b (48), miR-181c-5p (49), miR-494 (50), miR-495-3p (51) and miR-34a (52) (Table I; Figs. 2 and 3).

As a highly conserved miRNA, miR-124 is a mediator of the STAT3 signaling pathway, which inhibits cancer development; it has been confirmed in various studies. Overexpressed miR-124 can downregulate STAT3 and further inhibit the growth of bladder cancer (53), colorectal cancer (54) and hepatocellular carcinoma (55). In ESCA, the expression levels of miR-124 are significantly reduced, STAT3 is constitutively activated and its content is negatively associated with miR-124. Previous research studies have shown that miR-124 can directly inhibit STAT3 and further hinder cell proliferation, invasiveness and metastasis and aid the induction of apoptosis (41,42). Similarly, upregulation of miR-125a-5p levels causes binding to STAT3 and reduces STAT3 expression, leading to cell-cycle arrest and prevention of cell growth in ESCC (43); miR-296-5p inhibits the occurrence of ESCC by downregulating STAT3 levels (44). STAT3 is a direct functional target of miR-874-3p in ESCC cells; following their combination, they can form the miR-874-3p/STAT3 signaling axis to prevent the malignant behaviors of tumor cells (45). STAT3 is the direct downstream target of miR-17-5p, which binds to STAT3 to reduce the proliferative, migratory and invasive capacities of esophageal cancer cell line TE-1 (46).

In addition to the direct binding to STAT3, miRNAs can indirectly mediate the STAT3 signaling pathway. MiR-149-5p inhibits the expression of interleukin-6 (IL-6) at the transcriptional and translational level. IL-6 is a general STAT3 activator (29,56) and overexpression of miR-149-5p can suppress the abnormal proliferation, migration and invasion of ESCC cells via the miR-149-5p/IL-6/STAT3 signaling pathway (47). Chromobox 3 (CBX3) is a member of the chromobox protein family, which promotes the development of various cancer types, including gastric cancer (57), breast (58) and pancreatic cancer (59). The Janus kinase (JAK)2/STAT3 is a common signaling pathway found in various tumors (24,31,60-62). CBX3 is a downstream target of miR-30b expressed in ESCC cells. When the levels of miR-30b are reduced, the expression levels of CBX3, phosphorylated (p-)JAK2 and p-STAT3 are markedly increased and the JAK2/STAT3 signaling pathway is apparently active. Therefore, upregulation of miR-30b expression can inhibit cancer development via the miR-30b/CBX3/JAK2/STAT3 signaling axis (48). MiR-181c-5p indirectly controls ESCC by binding to LIM and the SH3 protein 1 (LASP1), which can activate STAT3. MiR-181c-5p decreases STAT3 expression and hinders cell proliferation, invasiveness and migration by interacting with LASP1 (49). MiR-494 can negatively regulate the expression of cyclin-dependent kinase (CDK)6, which promotes cell-cycle progression (63). Upregulated miR-494 binds to CDK6 to inhibit the downstream JAK2/STAT3 signaling pathway, resulting in an antitumor effect (50). By targeting Budding uninhibited by benzimidazoles 1 (BUB1), which can directly upregulate the phosphorylation levels of STAT3, miR-495-3p can also hinder the growth of ESCA via the miR-495-3p/BUB1/STAT3 signaling pathway (51). The aforementioned miRNAs are upstream molecules of STAT3 and miR-34a, an effective tumor suppressor, which can form a feedback loop with STAT3 to inhibit ESCA. Programmed cell death-ligand 1 (PD-L1) and IL-6 receptor (IL-6R) are targets in the loop and miR-34a competitively blocks the binding of IL-6

Table I. STAT3 signaling pathway mediated by miRNA in ESCA.

Effect	miRNA	Relevant signaling pathway
Inhibition of ESCA		
	miR-124	miR-124/STAT3
	miR-125a-5p	miR-125a-5p/STAT3
	miR-296-5p	miR-296-5p/STAT3
	miR-874-3p	miR-874-3p/STAT3
	miR-17-5p	miR-17-5p/STAT3
	miR-149-5p	miR-149-5p/IL-6/STAT3
	miR-30b	miR-30b/CBX3/JAK2/STAT3
	miR-181c-5p	miR-181c-5p/LASP1/STAT3
	miR-494	miR-494/CDK6/JAK2/STAT3
	miR-495-3p	miR-495-3p/BUB1/STAT3
	miR-34a	miR-34a/STAT3/IL-6R
Promotion of ESCA	miR-126	miR-126/STAT3
	miR-4286	miR-4286/INPP4A/JAK/STAT3
	miR-106b-5p	miR-106b-5p/CPBE3/STAT3
	miR-181b	miR-181b/STAT3
	miR-19b-3p	miR-19b-3p/MAP2K3/STAT3
Drug resistance	Let-7	Let-7/IL-6/STAT3
	miR-125a-5p	miR-125a-5p/STAT3
	miR-21	miR-21/STAT3
Immune escape	miR-34a	miR-34a/STAT3/IL-6R
Survival and prognosis	miR-106b-5p	miR-106b-5p/CPBE3/STAT3
	miR-19b-3p	miR-19b-3p/MAP2K3/STAT3
	miR-21	miR-21/STAT3
	miR-125a-5p	miR-125a-5p/STAT3
	miR-874-3p	miR-874-3p/STAT3
	Let-7	Let-7/IL-6/STAT3

ESCA, esophageal cancer; STAT3, signal transduction and transcription activator 3; miRNA/miR, microRNA; IL-6, interleukin-6; CBX3, chromobox3; JAK, Janus kinase; CDK6, cyclin-dependent kinase 6; LASP1, LIM and SH3 protein 1; BUB1, budding uninhibited by benzimidazoles 1; IL-6R, IL-6 receptor; INPP4A, inositol polyphosphate-4-phophatase type IA; CPBE3, cytoplasmic polyadenylation element binding protein 3; MAP2K3, mitogen-activated protein kinase kinase 3.

to its receptor to inhibit STAT3 activation. However, overactivated STAT3 can induce IL-6. Ultimately, they can form the miR-34a/STAT3/IL-6R feedback loop and increase miR-34a expression, which can hinder the progression of ESCC (52). In addition, miR-34a targets the E2F transcription factor 5, which can affect epithelial mesenchymal transition (EMT) and inhibit migration of ESCC (64). By inhibiting the PI3K/AKT/mTOR signaling pathway, miR-34a can reverse radiation resistance of ESCC and improve radiotherapy efficacy (65). Overexpressed miR-34a levels can also control the expression of matrix metalloproteinase (MMP)-2 and MMP-9 or bind to Yinyang-1 to inhibit ESCC metastasis and invasion (66,67).

3. MiRNA-mediated STAT3 signaling pathway promotes ESCA proliferation and invasion and restrains apoptosis

Compared to inhibitory miRNAs, promoters are fewer, namely miR-126 (68), miR-4286 (69), miR-106b-5p (70), miR-181b (71) and miR-19b-3p (72) (Table I; Figs. 2 and 3).

As an important coordinating factor, miR-126 binding to different targets exerts a certain influence on ESCA. A previous study indicated that overexpressed miR-126 can downregulate the content of microtubule-associated protein 1 light chain 3β and sequestosome 1 (p62) related to autophagy. STAT3 is a direct target of miR-126 and its silencing leads to a decrease in autophagy; therefore, miR-126 can bind to STAT3 and may activate it, which further inhibits apoptosis and autophagy of the esophageal squamous cell and promotes the development of ESCC (68). However, miR-126 has an inhibitory effect on ESCC via integrating with vascular endothelial growth factor-A (VEGF-A) (73) or insulin receptor substrate-1 (IRS-1) and Golgi phosphoprotein 3 (GOLPH3) (74) and it can also mediate the PI3K/AKT (75) or the ADAM metallopeptidase domain 9 (ADAM-9)/EGFR/AKT (76) signaling pathway to suppress the progression of ESCC. In addition, miR-126-5p can influence the proliferation and invasion of ESCC by negatively regulating CDK (77). The different signaling pathways involved in miR-126 have the opposite effect; therefore, the

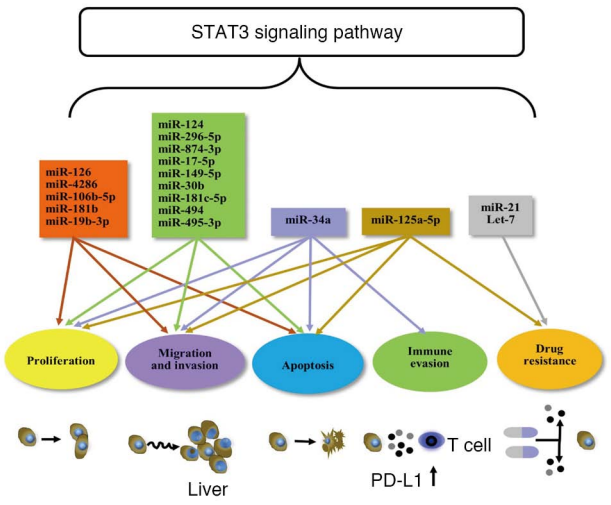

Figure 2. Functions of the STAT3 signaling pathway mediated by miRNAs in esophageal cancer, including proliferation, migration, invasion, apoptosis, immune evasion and drug resistance. STAT3, signal transduction and transcription activator 3; miRNA/miR, microRNA; PD-L1, programmed cell death ligand 1.

definite role of miR-126 requires further exploration under specific conditions in ESCA. Unlike miR-126, miR-4286 and miR-106b-5p bind to downstream molecules to indirectly induce STAT3 activation. MiR-4286 targets inositol polyphosphate-4-phophatase type IA and negatively regulates it to evoke the JAK/STAT3 pathway; in this way, it indirectly facilitates ESCA (69). Furthermore, miR-4286 can be a member of the miR spectrum that distinguishes ECA from Barrett's esophagus (78). Overexpression of cytoplasmic polyadenylation element binding protein 3 (CPBE3) can hinder tumor migration, invasion, angiogenesis and STAT3 activity and suppress EMT in ESCA. MiR-106b-5p can negatively regulate CPBE3, thereby enhancing the activation of STAT3 and facilitating EMT; this results in the formation of the miR-106b-5p/CPBE3/STAT3 signaling axis, which aids tumor growth (70).

MiR-181b and miR-19b-3p promote the development of ESCA via feedback loops. In ESCA stem cells, the combination of STAT3 and miR-181b promoter induces miR-181b expression; furthermore, upregulated miR-181b can increase p-STAT3 levels, resulting in the formation of a feedback loop that leads to anti-apoptotic effects and the formation of cell colonies (71). In addition, the interaction of miR-181b-1, cylindromatosis and STAT3 can establish a link between inflammation and tumor formation (79). By analogy, miR-19b-3p can inhibit mitogen-activated protein kinase kinase 3 (MAP2K3) that can bind to STAT3 and facilitate its degradation. STAT3 is a transcription driver of miR-19b-3p and the three components form a positive circuit to induce ESCC progression (72). Furthermore, miR-19b-3p targeting phosphatase and tensin homolog can induce the occurrence of ESCA (80), which is of great significance for miR biomarker studies performed in ECA (81).

4. Drug resistance caused by the STAT3 signaling pathway involves the interaction with miRNAs in ESCA

Cisplatin is a conventional first-line chemotherapeutic drug used for the treatment of ESCA and resistance to this drug limits its clinical application (82). Tumor cells treated with cisplatin can release IL-6 and induce the phosphorylation of STAT3 in ESCA. The release of IL-6 can evoke the survival of the IL-6/STAT3 signaling pathway, finally protecting cancer cells from cisplatin. Low expression of Let-7 is associated with low chemotherapy sensitivity. In contrast to these observations, upregulation of Let-7 can decrease p-STAT3 levels to counteract the activation of the IL-6/STAT3 pathway by cisplatin and reduce the resistance to this drug (83). The cisplatin resistance mechanism of miR-125a-5p is similar to that of Let-7, which is in parallel to the deactivation of the STAT3 signaling pathway. The ability of miR-125a-5p to regulate EMT is also relevant to the chemical sensitivity of cisplatin. By contrast, STAT3 activated by miR-21 can increase the production of monocytic myeloid-derived suppressor cells, which can protect tumor cells against the effects of cisplatin. MiR-21 can increase cisplatin resistance via the STAT3 signaling pathway in ESCC (84) (Table I, Fig. 2).

5. Immune escape of the STAT3 signaling pathway involves the contribution of miRNAs in ESCA

MiR-34a mediates the miR-34a/STAT3/IL-6R feedback loop. PD-L1 and IL-6R are downstream targets of miR-34a present in ESCA cells. MiR-34a can inhibit them via binding to PD-L1 and IL-6R, while IL-6R can promote STAT3 expression, which can inhibit miR-34a. Based on the aforementioned mechanism, PD-L1 can participate in the miR-34a/IL-6R/STAT3 feedback loop. Furthermore, low levels of PD-L1 expression can boost the immune system. When miR-34a levels are reduced, loss of PD-L1 expression causes an upstream gene constraint, further promoting immune escape. As miR-34a levels are upregulated, PD-L1 expression is restricted by upstream molecular pathways to reverse tumor immune escape and strengthen T-cell immune response (52,85) (Table I; Fig. 2).

6. ESCA disease survival and prognosis is affected by STAT3 signaling pathway-involved miRNAs

It has been shown that downregulation of the expression levels of CPBE3 and MAP2K3 is linked to low clinical survival and poor prognosis in ESCA, whereas miR-106b-5p and miR-19b-3p respectively inhibit their expression levels (70,72). It has been suggested that certain miRNAs are associated via STAT3 signaling with low survival in patients. MiR-21, which can promote cisplatin resistance, originates from cancer-associated fibroblasts (CAFs). The highly infiltrated CAFs are associated with a low survival rate and can increase miR-21; therefore, overexpressed miR-21 levels affect patient survival in ESCC (84). A reduction in the expression levels of miR-125a-5p and miR-874-3p is often associated with a lower rate of survival and their expression levels can also aid the determination of the clinical stage of ESCC (43,45). Upregulation of Let-7 expression frequently suggests improved prognosis for patients with this disease (83) (Table I).

7. Summary

ESCA is a familiar malignant tumor with a low early diagnostic rate and late cure rate. It is necessary to positively explore the pathogenic mechanism for formulating novel treatment strategies.

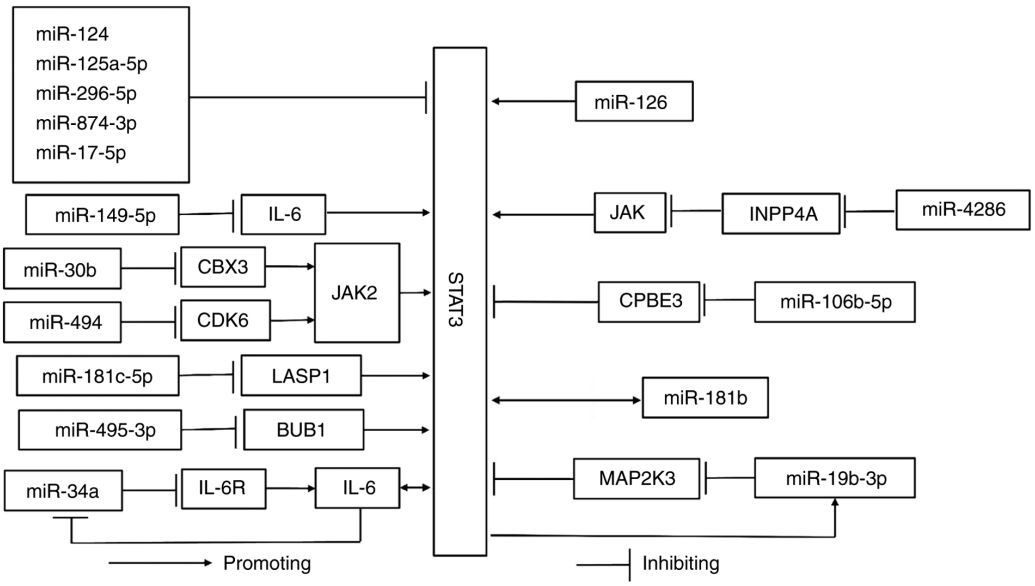

Figure 3. Regulatory network of STAT3 by promoting and inhibiting miRNAs. MiRNA plays a crucial role in modulating STAT3 by either targeting STAT3 directly or miRNA binding to a downstream target spot to regulate STAT3; miRNA and STAT3 may also form an interaction feedback loop. IL-6, interleukin-6; CBX3, chromobox3; JAK, Janus kinase; CDK6, cyclin-dependent kinase 6; LASP1, LIM and SH3 protein 1; BUB1, budding uninhibited by benzimidazoles 1; IL-6R, IL-6 receptor; INPP4A, inositol polyphosphate-4-phophatase type IA; CPBE3, cytoplasmic polyadenylation element binding protein 3; MAP2K3, mitogen-activated protein kinase kinase 3; STAT3, signal transduction and transcription activator 3; miRNA/miR, microRNA.

It has been found that the STAT3 signaling pathway involving miRNAs can play a crucial role in the occurrence and development of ESCA. Upregulation of miR-124, miR-125a-5p, miR-296-5p, miR-874-3p, miR-17-5p, miR-149-5p, miR-30b, miR-181c-5p, miR-494, miR-495-3p and miR-34a can form signaling regulatory axes with STAT3 to inhibit proliferation, invasiveness and metastasis and promote apoptosis in ESCA. However, miR-126, miR-4286, miR-106b-5p, miR-181b and miR-19b-3p positively regulate ESCA growth and foster malignant behaviors by interacting with STAT3. These roles of the miRNA/STAT3 signaling axis may provide novel opportunities for the use of miRNAs as molecular targets for treating ESCA. Perhaps targeted promotion or inhibition of the aforementioned miRNAs via various means can be used as a method to treat ESCA. The STAT3 signaling pathways mediated by Let-7 and miR-21 can influence ESCA resistance to cisplatin and further affect drug efficacy. Increasing Let-7 levels or downregulating miR-21 levels can promote the potential of drug therapy for ESCA. It is worth noting that certain signaling pathways can regulate multiple functions. MiR-125a-5p inhibits the progression of tumors and lowers resistance to cisplatin; miR-34a not only hinders cancer development but also increases immunity, weakening the escape of cancer cells. The higher survival rate and improved prognosis of patients are associated with increased expression levels of miR-125a-5p, miR-874-3p and Let-7, while overexpression of miR-19b-3p, miR-106b-5p and miR-21 are related to poor prognosis and a lower survival rate. Of note, when miR-126 targets VEGF-A, IRS-1, GOLPH3 or CDK6 and mediates the PI3K/AKT or ADAM-9/EGFR/AKT signaling axis, it has an inhibitory effect on ESCA. As it combines with STAT3, its effect is inverse. The same signaling molecules have completely opposite effects on different signaling pathways. Therefore, it is important to accurately determine the role of each signaling pathway.

In conclusion, the complex signaling network formed by miRNAs and STAT3 affects multiple pathophysiological processes in ESCA. Therefore, further research is required to assess the detailed mechanisms by which miRNAs and STAT3 signaling pathways control ESCA. These results can provide new insights into the clinical treatment required for various diseases and improve patient quality of life.

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Authors' contributions

XY made major contributions to the data analysis and manuscript writing. LYF collected data and figures. YZH and HCG participated in writing and revising the manuscript. All authors discussed, carefully read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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