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Roles of Wnt/ β -catenin signaling pathway related microRNAs in esophageal cancer

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Abstract

MicroRNAs (miRNAs) are endogenous, noncoding, single-stranded small RNAs that regulate expression of tumor suppressor genes and oncogenes and are involved in almost all tumor-related processes. MiRNA dysregulation plays an important role in the occurrence and development of esophageal cancer through specific signal pathways, including the Wnt/ β -catenin signaling pathway, and is closely related to the malignant characteristics of esophageal cancer. The interaction between miRNAs and the Wnt/ β -catenin signaling pathway, which is specifically expressed in esophageal cancer tissues, shows potential as a new biomarker and therapeutic target. This article reviews the role of miRNAs related to the Wnt pathway in the carcinogenesis of esophageal carcinoma and its role in Wnt signal transduction. The content of this review can be used as the basis for formulating or improving the treatment strategy of esophageal cancer.

Key Words: Wnt signal pathway; MicroRNA; Esophageal cancer; Esophageal cancer tissues

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Core tip: MicroRNAs (miRNAs) related to the Wnt pathway are regulated in varying degrees in esophageal cancer. They regulate the proliferation, invasion and metastasis, radiosensitivity, autophagy, phenotype and chemotherapy resistance of esophageal cancer cells and promote stem-cell-like characteristics of esophageal cancer cells. The interaction between the Wnt signaling pathway and miRNA plays an important role in the occurrence and development of tumors. These results suggest that the miRNA-Wnt signaling pathway can be used as a potential target for tumor therapy and a diagnostic index for predicting treatment response.

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INTRODUCTION

Esophageal squamous cell carcinoma (ESCC) accounts for more than half of esophageal cancer patients in China. ESCC and esophageal adenocarcinoma (EAC) differ at the genomic level and have contrasting molecular characteristics[1]. China is one of the countries with the highest incidence of esophageal cancer. In recent years, although the incidence of esophageal cancer in China has declined, the absolute incidence of esophageal cancer is still high due to the large population[2]. At present, the 5-year survival rate of esophageal cancer is 15%-25%, but if esophageal cancer is diagnosed in the early stage, the survival rate can be as high as 80%[3]. In fact, most patients with esophageal cancer are diagnosed and treated at an advanced stage, which is the main reason for the poor prognosis[4]. Although endoscopy has proven to be an effective method for detecting early esophageal cancer and can reduce mortality[5], its high cost and invasiveness limit its use as a tool for extensive screening of early esophageal cancer [6]. Therefore, developing a noninvasive method for the early detection of esophageal cancer is undoubtedly an effective way to improve the early diagnosis and prognosis of esophageal cancer patients.

MicroRNAs (miRNAs) are a class of small, conservative, noncoding RNAs that play an important role in regulating mRNA translation. miRNAs are involved in a plethora of biological and pathological processes, including cell differentiation, apoptosis, proliferation and metabolism[7]. Since their discovery, miRNAs have been shown to play a potential role in cancer pathogenesis through their function as oncogenes or tumor suppressors. Since a large number of miRNAs are differentially expressed in esophageal cancer tissues, the potential of miRNA use for diagnosis has been extensively studied. In addition, more attention has been paid to characterization of the downstream targets and action mechanisms of miRNAs and evaluate their usefulness as prognostic markers, as well as to assess their potential use for monitoring therapeutic responses.

The Wnt signaling pathway is an important extracellular signaling pathway discovered together with proto-oncogene *Int1* (also known as *Wnt1*) in 1982[8]. This complex and conserved pathway is involved in various developmental processes, such as cell growth, differentiation, ontogeny, migration, genetic stability, apoptosis, self-renewal of stem cells, maintenance of homeostasis in adult tissue, tissue regeneration and tumorigenesis[9,10].

The Wnt signaling pathway consists of two different intracellular signaling pathways, including the typical (initiated by Wnt proteins such as Wnt1, Wnt2, Wnt3, Wnt3a, Wnt7 and Wnt8) and the atypical (activated by Wnt proteins such as Wnt4, Wnt5A, Wnt 5B and Wnt 11) pathways. Typical Wnts activate the transcription of β -catenin/Tcf/Lef target genes through β -catenin transduction signal[11,12]. Atypical Wnt pathways can be further divided into the Wnt/ Ca^{2+} pathway and the Wnt/plane cell polarity pathway. Atypical Wnts are related to the activation of the Wnt plane cell polarity pathway, Wnt/JNK signaling pathway, Wnt/Ror receptor pathway, Wnt/GSK3MT pathway, Wnt/aPKC pathway, Wnt/Ryk pathway and Wnt/mTOR pathway[13].

The Wnt signaling pathway should be maintained at a normal level to perform normal physiological functions. However, extensive research has shown that the Wnt pathway is structurally activated in many cancers[14]. Therefore, the determination of genetic factors and biomarkers is important in predicting the efficacy of Wnt pathway modulator therapy, diagnosing and judging the prognosis of tumors, and developing new treatment methods. In order to explore the different roles of miRNAs in the progression of esophageal cancer through the Wnt pathway, we enumerated all the reported miRNAs related to the Wnt pathway.

MiRNAs REGULATE PROLIFERATION, INVASION AND METASTASIS OF ESOPHAGEAL CANCER CELLS THROUGH THE WNT SIGNALING PATHWAY

Ma *et al*[15] collected 58 cases of ESCC and adjacent normal tissue samples for comparative analysis. Expression of long noncoding RNA MEG3 is downregulated in ESCC, which is associated with tumor progression and poor prognosis. The expression level of miR-4261 in ESCC tissues is significantly higher than that in normal tissues, and negatively correlated with expression of MEG3 in ESCC tissues. In addition, *in vivo* and *in vitro* experiments have shown that miR-4261 is the target of MEG3, and MEG3 can directly regulate the expression of miR-4261, upregulate Dickkopf-related protein 2 (DKK2) and block the Wnt/ β -catenin signaling pathway to inhibit cell proliferation, migration and invasion[15].

Qiao *et al*[16] used real-time quantitative polymerase chain reaction (RT-qPCR) to detect expression of miR-106b-3p in 50 pairs of ESCC and paracancer tissues in surgical specimens. It was confirmed that the expression of miR-106b-3p was upregulated in ESCC tissues, while zinc and ring finger 3 (ZNR3) was downregulated in ESCC. ZNR3 is a negative regulator of Wnt/ β -catenin signal transduction and is considered to be a direct target of miR-106b-3p. Clinical research has shown that miR-106b-3p promotes the proliferation and invasion of ESCC cells by downregulating ZNR3 and inducing epithelial-mesenchymal transition (EMT) of ESCC cells through the Wnt/ β -catenin signal pathway[16].

Some laboratory studies have found that expression of miR-301a is upregulated in esophageal cancer cells. According to the results of luciferase reporter analysis, it has been confirmed that Wnt1 is the target gene of miR-301a, indicating that miR-301a inhibits the activity of ESCC cells by targeting Wnt1. MiR-301a blocked the Wnt/ β -catenin signal pathway and reversed EMT by targeting Wnt1, which inhibits the proliferation and migration of esophageal cancer cells and enhances radiosensitivity[17].

MiRNA let-7 is one of the most prominent miRNAs associated with human malignant tumors[18]. A study has previously shown that, compared with clinically collected paracancer tissues, the inhibition of let-7a in tumors is closely related to the invasion, metastasis and poor prognosis of ESCC. LIN28 is an RNA-binding protein that plays a key role in signal transduction and regulates the expression of genes downstream of LET-7a and Wnt signaling pathways[19,20]. Wnt/ β -catenin/LIN28 signal transduction induces EMT and promotes the invasion, metastasis and poor prognosis of ESCC by eliminating let-7a [21].

According to the analysis of public microarray data and the verification of ESCC biopsy, miR-30a-3p/5p is downregulated in ESCC tissues compared with the paired adjacent normal tissues. The published microarray analysis showed that the downregulation of miR-30a-3p/5p expression is related to the activation of the Wnt signal in ESCC. Fzd2 is one of the receptors of Wnt2 that contributes to increasing the invasiveness of ESCC cells[22]. MiR-30a-3p/5p can directly target the 3'-UTR of Wnt2 and Fzd2, inhibiting their expression and resulting in the inhibition of the Wnt signaling pathway. This might be the main mechanism by which miR-30a-3p/5p regulates the proliferation of ESCC cells[23].

MiR-455-3p is upregulated in ESCC and many different types of cancer, and miR-455-3p can promote or inhibit tumors according to different tumor types[24]. Liu *et al*[25] used the PDX model to prove that miR-455-3p is significantly upregulated in ESCC and correlated with the overall survival time and short disease survival time of ESCC patients. At the same time, it has been confirmed that silencing of miR-455-3p decreases luciferase reporter activity and expression of genes downstream of β -catenin and transforming growth factor (TGF)- β /Smad signaling pathways. This suggests that miR-455-3p contributes to the activation of Wnt/ β -catenin and β -Smad pathways in ESCC and promotes the metastasis and invasion of esophageal cancer cells.

Previous basic studies have shown that miR-200b is an invasive inhibitor of ESCC[26]. Zhang *et al*[27] have verified that miR-200b mainly induces G2 phase arrest, apoptosis, inhibition of cell growth and clone formation potential of ESCC lines, thereby mediating its tumor inhibition in ESCC. Cyclin-dependent kinase 2 and platelet-activating factor (an effective oncoprotein) have been identified as miR-200b targets and inhibit cell growth by reducing Wnt/ β -catenin signal transduction. These studies have suggested that miR-200b is a promising therapeutic target in ESCC.

Xu *et al*[28] established 30 ESCC samples and adjacent normal tissue models, which showed that the level of β -catenin in ESCC specimens was significantly increased, while the level of miR-214 was significantly decreased. There was a negative correlation between the levels of β -catenin and miR-214 in ESCC specimens. The binding of miR-214 to the 3'-UTR of β -catenin mRNA inhibits the protein translation of β -catenin mRNA and directly promotes tumor growth and metastasis. It has been shown that the downregulation of miR-214 promotes the growth and invasion of ESCC cells by activating the Wnt/ β -catenin pathway, highlighting that miR-214 is an effective inhibitor of ESCC.

Several clinical studies have shown that human papilloma virus-16 (HPV-16) infection may be an important risk factor for ESCC[29]. Zang *et al*[30] found that HPV-16 E6 activated the Wnt/ β -catenin pathway at different levels by directly downregulating several regulatory factors, including transducer-like enhancer of split 1 (TLE1), glycogen synthase kinase-3 β (GSK-3 β) and secreted frizzled-related proteins (SFRPs). The overexpression of miR-125b restored the expression level of these proteins. The expression of miR-125b was low in HPV-16 E6 positive esophageal carcinoma, and it was negatively correlated with the level of HPV-16 E6 mRNA. These clinical results indicate that HPV-16 E6 promotes the tumorigenesis of esophageal cancer by downregulating miR-125b, and this potential mechanism is involved in the activation of the Wnt/ β -catenin signal pathway.

MiRNAs REGULATE RADIOSENSITIVITY OF ESOPHAGEAL CANCER THROUGH THE WNT PATHWAY

Radiotherapy is one of the main treatments for advanced esophageal cancer. A randomized study showed that radical radiotherapy and chemotherapy for locally advanced esophageal cancer have greater survival advantages than radiotherapy alone, but the local recurrence rate and distant metastasis rate are still high[31]. Radiotherapy resistance has long been considered to be the most important cause of local tumor recurrence or metastasis. Studies have shown that miR-301a is a candidate for abnormal distribution of radiosensitive miRNAs and is related to the radiosensitivity of ESCC. MiRNA hsa-miR-301a is downregulated in esophageal cancer cell lines, while its target gene Wnt is upregulated, suggesting that the Wnt/ β -catenin signal pathway plays an important role in the radiation resistance of esophageal cancer cells[32]. Su *et al*[17] and others have shown that the proliferation rate of radioresistant ESCC cell line KYSE-150R transfected with miR-301a is decreased, while radiosensitivity and mobility are increased. Dual-luciferase report analysis has shown that Wnt1 is the target gene of miR-301a, suggesting that miR-301a may be a new type of radiosensitivity-related miRNA and could be a potential target for radioresistant ESCC therapy.

Xie *et al*[33] have demonstrated that miR-1275 inhibition increases the radioresistance of KYSE-150 cells by promoting EMT, while the enhanced expression of miR-1275 increases the radiosensitivity of KYSE-150R cells by inhibiting EMT. It has been shown that the direct targeting of miR-1275 to Wnt1 inactivates the Wnt/ β -catenin signaling pathway in esophageal cancer cells. In addition, Wnt1 deletion counteracts the effect of miR-1275 inhibition on radiation resistance of KYSE-150 cells by inhibiting EMT, while overexpression of Wnt1 rescues miR-1275 upregulation-mediated damage of EMT, reducing the radiation sensitivity of KYSE-150R cells. These results suggest that miR-1275 inhibits the radiosensitivity of esophageal cancer cells by targeting the Wnt/ β -catenin signaling pathway activated by Wnt1, which provides a new therapeutic approach for overcoming radioresistance in patients with esophageal cancer.

MiRNAs REGULATE AUTOPHAGY AND PHENOTYPE OF ESOPHAGEAL CANCER CELLS THROUGH THE WNT PATHWAY

Autophagy is an evolutionarily conservative process from yeast to mammals, mainly through the degradation of nonessential proteins and damaged organelles to maintain intracellular metabolic homeostasis[34,35]. Limited energy in the form of ATP can activate AMP kinase and drive autophagy. Similarly, autophagy can occur by inhibiting mammalian target of rapamycin, using rapamycin or the deprivation of growth factors and amino acids. Autophagy can be induced by some anticancer treatments, such as chemotherapy, radiotherapy and targeted therapy, and can promote the survival of cancer cells from stress-induced damage. Increasing evidence has shown the important role of autophagy in cancer due to its function in inducing the survival or death of cancer cells[36]. In addition, anticancer therapy can also induce autophagy to cause the death of cancer cells. Therefore, the contribution of autophagy to cancer development is still controversial.

MiR-638 is a potential oncogene that promotes tumorigenicity, including cell proliferation, migration and invasion, and overexpression of miR-638 promotes hunger and rapamycin-induced autophagy[37]. Disheveled-associated antagonist of β -catenin 3 (DACT3), a member of the DACT gene family, is a negative regulator of Wnt/ β -catenin signal transduction and is transcriptionally suppressed in a variety of malignant tumors[38]. Ren *et al*[39] have shown that miR-638 regulates transport of DACT3 and is involved in autophagy. Downregulation of DACT3 leads to strong induction of Disheveled (Dvl) expression and Dvl-mediated Wnt/ β -catenin signaling pathway. This clinical research has shown that the expression of miR-638 is increased while DACT3 expression is decreased in human clinical ESCC specimens. The autophagy-related miR-638/DACT3 axis may be an attractive target for cancer therapy intervention.

MiRNAs REGULATE CHEMOTHERAPY RESISTANCE OF ESOPHAGEAL CANCER THROUGH THE WNT PATHWAY

In the past 20 years, more evidence has shown that a minority cell group in tumors, called tumor stem cells or tumor-initiation cells, are related to cancer recurrence, metastasis and drug resistance to conventional treatment, and they are the key determinants of human cancer prognosis[40,41]. Liu *et al*[25] successfully enriched chemotherapy-resistant ESCC cells by using a xenograft model derived from chemotherapy-resistant human ESCC patients. MiRNA analysis was carried out in chemotherapy-resistant and normal esophageal cancer cells. Expression of miR-455-3p in chemotherapy-resistant esophageal cancer cells was significantly higher than that in normal esophageal cancer cells. Inhibition

Table 1 MicroRNA associated with Wnt pathway in esophageal carcinoma

MicroRNAs	Target genes	Molecular functions	Expression pattern	Interaction with Wnt signaling	Cancer phenotype	Ref.
MiR-1275	Wnt1	Receptor targeting Wnt protein	Up	Repress	Inhibition of radiosensitivity of ESCC cells	[32]
MiR-4261	DKK2	The proliferation, migration and invasion of esophageal cancer cells can be inhibited	Up	Repress	Involvement in tumor progression and poor prognosis of ESCC	[15]
MiR-106b-3p	ZNRF3	Promote epithelial-mesenchymal transition	Up	Activate	Promote cell proliferation and invasion	[16]
MiR-301a	Wnt1	Increased resistance to autophagy and radiation	Up	Repress	Inhibition of proliferation and migration of ESCC cells and enhancement of radiosensitivity	[17]
MiR-let-7a	LIN28	Transformation, matrix decomposition and angiogenesis	Down	Activate	Promoting invasion, metastasis and poor prognosis of ESCC	[21]
MiR-30a-3p/5p	Wnt2 and Fzd2	Gene transcription	Down	Activate	Promote the proliferation of ESCC cells	[22]
MiR-455-3p	DKK3/GSK3 β /TCF7L1	Stem cell development	Up	Activate	Promoting chemotherapy resistance and invasiveness of ESCC	[24]
MiRNA-638	DACT3	Autophagy	Up	Activate	Promote autophagy and malignant phenotype of cancer cells	[38]
MiR-221	DKK2	Imbalance of signal transduction and chemoresistance target genes	Up	Activate	Mediating chemotherapy resistance of esophageal adenocarcinoma	[41]
MiR-200b	CDK2 and PAF	Apoptosis and cell cycle progression	Down	Repress	Induction of cell cycle arrest and inhibition of cell growth in ESCC	[26]
MiR-214	β -catenin mRNA3'-UTR	Inhibit protein translation	Down	Repress	Inhibit cell growth and invasion	[27]
MiR-125b	SFRP4	The cause is unknown	Down	Activate	Promote the growth of ESCC cells	[29]
MiR-942	SFRP4/GSK3 β /TLE1	Promote stem-cell-like characteristics	Up	Activate	Promoting tumor stem cell-like characteristics of ESCC	[43]

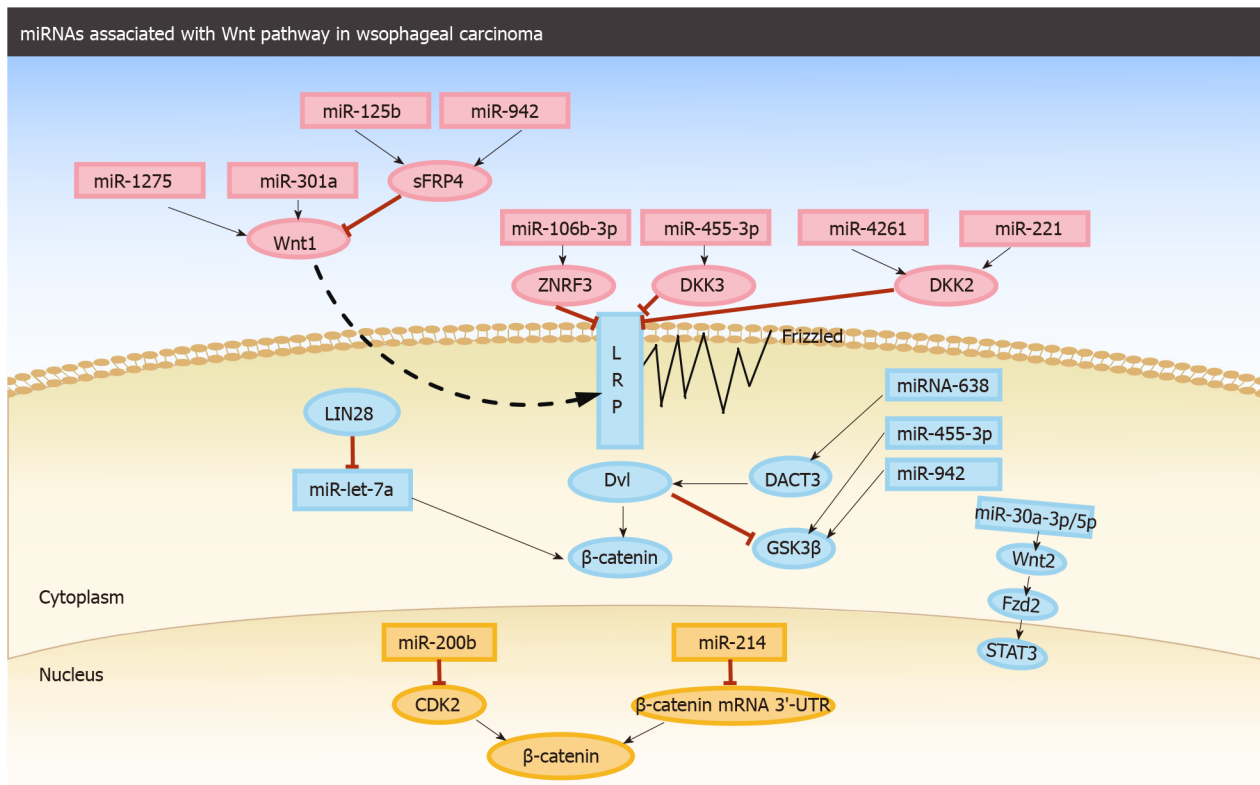
ESCC: Esophageal squamous cell carcinoma; DKK2: Dickkopf-related protein 2; ZNRF3: Zinc and ring finger 3; PAF: Platelet-activating factor; CDK2: Cyclin-dependent kinase 2; TLE1: Transducer-like enhancer of split 1; GSK3 β : Glycogen synthase kinase-3 β ; SFRP: Secreted frizzled-related protein; DACT3: Dishevelled-associated antagonist of β -catenin 3.

of miR-455-3p increased the sensitivity of ESCC cells. MiR-455-3p, as a negative regulatory factor, simultaneously activates the Wnt/regulatory factors and TGF-regulatory factors signaling pathways involved in chemotherapy resistance of esophageal cancer.

Wang *et al*[42] established a series of EAC cell lines resistant to 5-fluorouracil (5-FU) and analyzed their miRNAs differential expression by RT-qPCR. In a group of 5-FU-resistant esophageal cancer cells (OE19, OE33, PT1590 and LN1590), miR-221 was overexpressed in all drug-resistant variants. Increased expression of miR-221 led to a decrease in the expression of DKK2, resulting in the release of Wnt/ β -catenin signaling pathway blockage mediated by DKK2, indicating that miR-221-induced chemical resistance was mediated by the Wnt/ β -catenin signaling pathway.

MiRNAs PROMOTE TUMOR STEM-CELL-LIKE CHARACTERISTICS THROUGH THE WNT PATHWAY

The Wnt/ β -catenin signaling pathway is a key molecular pathway that can control stem cell function and promote tumor progression and has been demonstrated to play an important role in tumor stem cells[43]. Ge *et al*[44] analyzed the microarray data set of the cancer genome map composed of 177 cases of primary esophageal cancer and 13 cases of normal esophageal tissue. Compared with normal tissues, miR-942 was significantly upregulated in tumor tissues. It was also shown that the overexpression of miR-942 upregulated Wnt/ β -catenin signal transduction activity and promoted stem-cell-like characteristics and tumorigenesis in ESCC by directly inhibiting SFRP4, GSK3 β and TLE1, which are negative



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Figure 1 MicroRNAs associated with Wnt pathway in esophageal carcinoma. miRNAs: MicroRNAs; Dvl: Dishevelled; DKK2: Dickkopf-related protein 2; ZNRF3: Zinc and ring finger 3; CDK2: Cyclin-dependent kinase 2; GSK3 β : Glycogen synthase kinase-3 β ; SFRP: Secreted frizzled-related protein; DACT3: Dishevelled-associated antagonist of β -catenin 3.

regulators of the Wnt/ β -catenin signal pathway. This revealed a new molecular mechanism revealing how the constitutive activation of the Wnt/ β -catenin pathway is maintained in cancer and suggests that miR-942 is a potential therapeutic target for esophageal cancer.

CONCLUSION

Recent clinical data indicate that the incidence of esophageal cancer and the rate of recurrence and metastasis are still high, and the overall therapeutic effect is not promising. miRNAs regulate gene expression through different mechanisms. Importantly, miRNAs can activate or inhibit Wnt signaling by interacting with other cellular macromolecules, thereby providing signals for the malignant transformation of esophageal cancer. Besides, miRNAs related to the Wnt pathway are regulated to varying degrees in esophageal cancer, regulating the proliferation, invasion and metastasis, radio-sensitivity, autophagy, phenotype and chemotherapy resistance of esophageal cancer cells, as well as promoting stem-cell-like characteristics of esophageal cancer cells (Table 1). The interaction between the Wnt signaling pathway and miRNA plays an important role in the occurrence and development of tumors (Figure 1). These results suggest that the miRNA/Wnt signaling pathway can be used as a potential target for tumor therapy and a diagnostic index for predicting treatment response. Although considerable effort has been made to develop new treatments, there is still some controversy about the molecular mechanism of the Wnt pathway targeting in esophageal cancer. Further studies are warranted to improve the efficacy and develop new potent combination therapies.

FOOTNOTES

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