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Research Progress on miR-143 and miR-145 in Esophageal Cancer

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Abstract

Esophageal cancer is one of the malignancies that with high occurrence in China. Its high morbidity and mortality have caused huge disease burden for the society. Therefore, it is getting necessary to elucidate the molecular mechanisms regarding the onset and progression of esophageal cancer. Increasing studies suggest that miR-143 and miR-145 are differentially expressed and deeply involved in the progression, chemotherapy resistance, radiotherapy resistance and other processes in esophageal cancer. The two miRNAs also associate with the prognosis of patients with esophageal cancer. Discussing the roles of miR-143 and miR-145 in esophageal cancer may further contribute to ascertain their relevant molecular mechanisms and clarify the value of the two miRNAs as potential biomarkers and molecular targets, in an attempt to provide new insights for the clinical treatment of esophageal cancer.

Keywords: miR-143, miR-145, esophageal cancer, ERK signaling pathway, p38 signaling pathway, JAK/STAT signaling pathway, PI3K/AKT signaling pathway, Wnt signaling pathway

1. Introduction

Esophageal cancer is one of the most common gastrointestinal malignancies, which has two main histological subtype: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) (1). ESCC is the prevalent subtype in China with low 5-year survival rate, while EAC take dominance in developed countries (2). The pathogenesis of esophageal cancer remains to be fully demonstrated, but a series of signaling pathway regulators and small molecules like miRNAs have been identified to participate in the onset and development of esophageal cancer, providing several potential targets for treatment. We are currently in the quantitative accumulation stage to explore the complex mechanisms of esophageal cancer before qualitative breakthrough. Therefore, elucidation of miRNAs and signaling pathways relevant to esophageal cancer progression is a problem to be deeply solved at present. miR-143 and miR-145 have been studied extensively for their cancerous roles in modulating oncogenic signaling pathways (3). The two miRNAs form a bicistronic cluster in 5q33.1, and they have been considered as tumor suppressors in epithelial cell malignancies (4-6). In this present study, we reviewed the regulation of several pivotal oncogenic signaling pathways by the miR-143/145 gene cluster in the development of esophageal cancer, which may provide insights and novel alternative molecular agents for targeted therapy.

2. Synthesis, Function and Regulation of miRNAs

miRNAs are a class of single-stranded non-coding RNAs (18~25 nucleotides), widespreading in eukaryotic cells (7). The DNA encoding miRNA is first transcribed to form the initial miRNA (pri-miRNA), which is then cleaved into stem-loop structured miRNA (pre-miRNA, that contains approximately 70 nucleotides) by Drosha, a member of the RNase III family. RanGTP/Exportin5 is employed to transport nuclear miRNA to cytoplasm, whereby miRNA then cleaves into double-stranded miRNAs of approximately 22 nucleotides via Dicer, a member of the RNase III family. Mature miRNA is ultimately processed by helicase. miRNA binds to miRNA response elements (MRE) in the 3’ non-coding region of target mRNA in a non-completely complementary method at the post-transcriptional level (7). The binding blocks subsequent translational process or even directly induces the degradation of mRNA, so as to downregulate the expression of specific genes (8). Therefore, miRNA regulation affects cellular function metabolism and plays an indispensible role in numerous activities such as

inflammation, blood glucose regulation, fat mobilization, reproductive development and particularly, the formation of cancer cells (9-12).

The molecular regulatory network of miRNAs is complex and mainly includes two aspects: regulation of miRNA biogenesis and post-transcriptional regulation of target genes by miRNA. The regulation of miRNA biogenesis is mainly affected by transcription factor-miRNA regulatory network. The post-transcriptional regulation of target genes by miRNA is summatized to be the miRNA-target gene regulatory network. Both transcriptional factor-miRNA regulation network and miRNA-target gene regulation network are characterized by one-to-many and many-to-one regulatory axis. For instance, transcriptional factor SNAI1 can regulate the expression of multiple miRNAs, and miR-143 is also regulated by multiple transcriptional factors such as FSH, SMAD and LIMK (13,14). miR-145 can affect the mRNAs of multiple target genes such as DHRS2, MYO1B and c-Myc, and ATF2 is also post-transcriptionally modulated by different miRNAs (miR-181a and miR-203) (15-17). The transcriptional factor-miRNA-target gene regulatory network renders the celluar regulation by miRNAs more precise and more comprehensive. In addition, competitive endogenous RNA (ceRNA) can also compete with target mRNA via its MRE to combine with relevant miRNAs, serving as another way of miRNA regulation (18).

3. miR-143/145 Gene Cluster and Esophageal Cancer

3.1 Roles of miR-143/145 Gene Cluster in Esophageal Cancer

The encoding genes of miR-143 and miR-145 mapped at 5q33. As they are within 2000 bp and share a common promoter region, thus miR-143 and miR-145 are called gene cluster. Michael *et al*. (19) first reported the low expression of miR-143 and miR-145 in colorectal cancer tissues. It was then gradually reported that miR-143 and/or miR-145 were downregulated in a variety of malignant tumors. Wu *et al*. (20) first reported that miR-143 and miR-145 are significantly downregulated in ESCC and correlated with the depth of tumor invasion. They further found that the migration capability of ESCC cells are significantly inhibited by overexpressing miR-143 and miR-145 *in vitro*. Liu *et al*. (21) analyzed 110 fresh pathological specimens from patients with ESCC without intervention. They observed that miR-143 and miR-145 were expressed synchronously in adjacent normal tissues, cancer tissues and four ESCC cell lines. In the meanwhile, combined low expression of the two miRNAs would significantly increase the risk of lymph node metastasis. Mao *et al*. (22)

revealed that upregulation of miR-143 is able to attenuate the proliferation, invasion, migration and G1/G0 transition of ESCC cells, which can be rescued by miR-143 silencing. Chen *et al*. (23) showed that the high expression of miR-145 can sensitize ESCC cells to 5-FU chemotherapy *in votro*. Jin *et al*. (24) analyzed 126 postoperative pathological specimens from ESCC patients and found that the expression level of miR-145 is positively correlated with higher grade of tumor differentiation, lymph node status, distant metastasis, TNM stage and other clinicopathological parameters. The overall survival probability of patients with low miR-145 expression was shorter than that of patients with high miR-145 expression. Furthermore, the expression level of miR-145 could be used as an independent factor to predict the overall survival of patients with ESCC. Besides, Wang *et al*. (25) also reported that miR-145 can be used as potential serum biomarkers for clinical screening and diagnosis of ESCC, but further clinical verification and improvement are needed before the actual application.

Studies above have confirmed that miR-143 and miR-145 are deeply involved in the onset and progression of ESCC by means of modulating proliferation, migration, invasion, metastasis and chemo/radiotherapy resistance. The abberant expression of the two miRNAs may serve as potential prognostic and diagnostic biomarkers for patients with ESCC.

Feber *et al*. (26) observed that the expression levels of miR-143 and miR-145 in EAC tissues were lower than those in normal tissues. However, most subsequent studies showed that the expressions of miR-143 or miR-145 in EAC tissues were significantly upregulated compared with the normal (27,28). It is possible that the downregulation of miR-143 or miR-145 is conducive to the early occurrence of EAC, while subsequential upregulation renders EAC cells stronger malignant potential. It is worth mentioning that overexpression of miR-145 in EAC cells can upregulate ITGA5 and ITGB3, improving the adhesion of cancer cells to fibroadhesin and enhancing the invasion and apoptosis resistance of cancer cells (16). This is in contrast to the inhibition of cancer cell proliferation and enhanced anoikis caused by upregulation of miR-145 expression in ESCC cell lines (29). This suggested that the cancerous roles of the two miRNAs are not absolutely the same in most malignant tumors. They may propel tumor progression in certain cancer types. It also indicated that the molecular mechanisms regulating the onset and progression of the two histological subtypes are different, which highlighted the importance of miRNA in guiding personalized therapy.

3.2 Target Genes Regulated by miR-143/145 in Esophageal Cancer

3.2.1 Target Genes in MAPK Signaling Pathway Regulated by miR-143/145

Overexpression of miR-143 could significantly inhibit invasion and migration of ESCC cells, and the expression level of ERK5 (MAPK7) showed a significant dose-dependent decrease after overexpressing miR-143 (30). However, the expression levels of RAS and BCL2, the two target genes of miR-143 that have been widely reported in other cancer species, were relatively stable, suggesting that the anti-cancer function of miR-143 in ESCC is at least partially achieved by inhibiting the ERK5 signaling pathway. Xue *et al*. (31) transfected ESCC cells with miR-143-3p simulators (mimic group) and repressors (repressor group) respectively. It was found that miR-143-3p could significantly inhibit the proliferation and invasion of ESCC cells, and the weight of tumor formation in nude mice in the mimic group was the lowest. In addition, the expression of MAPK7 protein in tumor tissue of nude mice in the mimic group was also the lowest, suggesting that miR-143-3p may inhibit the proliferation and invasion of ESCC cells by targeting MAPK7.

3.2.2 Target Genes in PI3K/AKT Signaling Pathway Regulated by miR-143/145

Zheng *et al*. (32) observed that miR-145 is downregulated and AKT3 is upregulated in ESCC tissues and cell lines. They then utilized dual luciferase reporting analysis to confirm that miR-145 can directly target AKT3 mRNA. In the meanwhile, transfection of miR-145 mimics or knockdown of AKT3 expression can promote cell cycle arrest and apoptosis induced by cisplatin chemotherapy *in vitro*, which can be rescued by upregulation of AKT3 expression. This suggested that miR-145 can sensitization ESCC to cisplatin chemotherapy by directly targeting AKT3 and inhibiting PI3K/AKT signaling pathway.

3.2.3 Target Genes in Wnt/β-catenin Signaling Pathway Regulated by miR-143/145

CD44 is one of the recognized downstream targets of the classical Wnt/β-catenin signaling pathway, which is mainly involved in the heterogeneous adhesion of cancer cells (33-35). Yan *et al*. (36) found that the expression levels of Wnt, β-catenin and CD44 in highly invasive ESCC cell lines were higher than those of other types of ESCC cell lines and normal esophageal epithelial cell lines, while the expression level of miR-143 was the lowest and negatively correlated with the expression levels of Wnt, β-catenin and CD44. They further

performed bioinformatic prediction and dual luciferase reporting assays and confirmed that miR-143 can directly target CD44 mRNA, suggesting that miR-143 can inhibit the invasion of ESCC cells by targeting CD44 in the Wnt/β-catenin signaling pathway. Myc gene can be activated as the downstream of Wnt/β-catenin signaling pathway in some cancer types, exerting a series of cancer-promoting potential (37-39). Li *et al*. (40) constructed a nanoparticle platelet-loaded drug delivery system for miR-145 and observed its influence on Myc protein expression and inhibitory ability on ESCC cells through co-culture *in vitro*. The results showed that nano-platelet-loaded miR-145 can significantly inhibit the expression of Myc protein in ESCC cells and promote the apoptosis of ESCC cells compared with platelet-loaded miR-145 and miR-145 alone.

3.2.4 Target Genes in NF-κB Signaling Pathway Regulated by miR-143/145

Mei *et al*. (41) confirmed the downregulation of miR-145-5p in ESCC tissues and cohort from GEO database. The researchers then transfected miR-145-5p mimics into ESCC cell lines and observed that the overexpression of miR-145-5p significantly inhibits the proliferation, migration, and invasion of ESCC cells. In addition, the overexpression of miR-145-5p also caused a significant increase of epithelial marker E-cadherin and a significant decrease of mesenchymal cell marker N-cadherin, as well as a significant decrease of EMT-related transcriptor Slug protein. All these results suggested that miR-145-5p may inhibit the EMT process of ESCC cells. More importantly, they found that Sp1 is a target gene of miR-145-5p and knocking down its expression can further reduce mRNA and protein expression levels of NF-κB (p65). In addition, knockdown of NF-κB can also inhibit ESCC cell proliferation, migration, invasion and EMT in the same way as miR-145-5p did. This demonstrated that miR-145-5p may exert its anti-cancer effects by targeting the Sp1/NF-κB signaling pathway. Li *et al*. (42) detected significant downregulation of miR-145 in ESCC tissues and four ESCC cell lines, accompanied by abnormal upregulation of the expression level of PLCE1. The expression level of miR-145 and PLCE1 were significantly negatively correlated with each other, and low expression of miR-145 was correlated with the depth of tumor invasion and TNM stage. Bioinformatic prediction and dual luciferase reporting assays confirmed that PLCE1 can be directly targeted as the downstream of miR-145. This revealed that miR-145 may regulate the invasion and proliferation of ESCC cells by targeting PLCE1. Additionally, another study showed that the abnormally high expression of PLCE1 in ESCC tissues is caused by hypomethylation of its promoter region whereby activating the NF-κB signaling

pathway through the PI-PLCε signaling pathway, thereby propelling ESCC cell proliferation and angiogenesis in the tumor microenvironment. This may potentially be one of the important ways utilized by ESCC for progression (43).

3.2.5 Other Target Genes Regulated by miR-143/145

We found that there are certain target genes regulated by miR-143/145 that can not be simply placed under one specific signaling pathway. Therfore, we summarized and displayed them in **Table 1**.

Table 1. The regulatory effect of miR-143/145 to other target genes in esophageal cancer.

Number	Researcher	miRNA	Target Gene	Regulatory Effect
1	Liu *et al*. (44)	miR-143	LASP1	miR-143 inhibited the proliferation, invasion and migration of ESCC cells via targeting LASP1
2	Hu *et al*. (45)	miR-143	PLK1 BUBR1	miR-143 attenuated the proliferation of ESCC cells and ameliotared cisplatin resistance via targeting PLK1 and BUBR1
3	Zhang *et al*. (46)	miR-145	SMAD5	miR-145 promoted the proliferation, migration, invasion and metastasis of ESCC cells via targeting SMAD5
4	Chen *et al*. (23)	miR-145	REV3L	miR-145 enhanced the apoptosis of ESCC cells to 5-FU chemotherapy
5	Shang *et al*. (47)	miR-145	FSCN1	Downregulation of miR-145 propelled the invasion and migration of ESCC cells via targeting FSCN1
6	Zhang *et al*. (48)	miR-143-3p	EPS8	miR-143-3p suppreesed the growth and metastasis and induced apoptosis of ESCC cells via targeting EPS8
7	Fan *et al*. (49)	miR-145-5p	ABRACL	miR-145-5p inhibited the proliferation, invasion and migration of esophageal cancer cells via targeting ABRACL
8	Tang *et al*. (50)	miR-145	PLCE1	miR-145 attenuated the proliferation and migration of ESCC cells via targeting PLCE1

4. Outlook for Application of miR143/145 in Esopageal Cancer

The regulatory network between miR-143/145 and several target genes in esophageal cancer was primarily integrated and depicted (**Figure 1**). In the signaling network with miRNA as the center molecule, the abnormal expression of miRNA will inevitably affect the complex

expression of many downstream target genes thereby endowing esophageal cancer cells with certain malignant potential, such as increased invasiveness, lymph node metastasis, lower differentiation degree and resistance to chemo/radiotherapy. As emerging star molecules in recent years, miR-143 and miR-145 regulate cell signaling pathways through numerous downstream target genes and participate in the process of proliferation, invasion, migration, metastasis and chemoradiotherapy resistance of esophageal cancer. Therefore, targeted intervention of miR-143 and miR-145 expression in patients may effectively inhibit the evolution of esophageal cancer and guide the personalized therapy. Secondly, traditional surgical combined radiotherapy and chemotherapy remain to be the main clinical treatments for esophageal cancer, while the resistance to radiotherapy and chemotherapy is a bottleneck at present. miR-143 and miR-145 may provide new ideas for the sensitization of radiotherapy and chemotherapy for esophageal cancer. Finally, due to the possibility of missed diagnosis and misdiagnosis in morphological observation under esophageal endoscopy. miR-143 and miR-145 is differentially expressed in esophageal cancer, and their expression levels relate to the natural history of esophageal cancer. Therefore, employing miR-143 and miR-145 as biomarkers to aid clinical screening, diagnosis and prognosis prediction of esophageal cancer is conducive to improving the early detection rate. It is worth mentioning that it is still unclear whether miR-143 and miR-145 act as gene clusters or play regulatory roles independently when regulating target genes. Feng *et al*. (51) speculated that the consistent downregulation of miR-143 and miR-145 expression is highly likely to play a synergistic role as a gene cluster, but this needs to be confirmed by more comprehensive experimental data in the future.

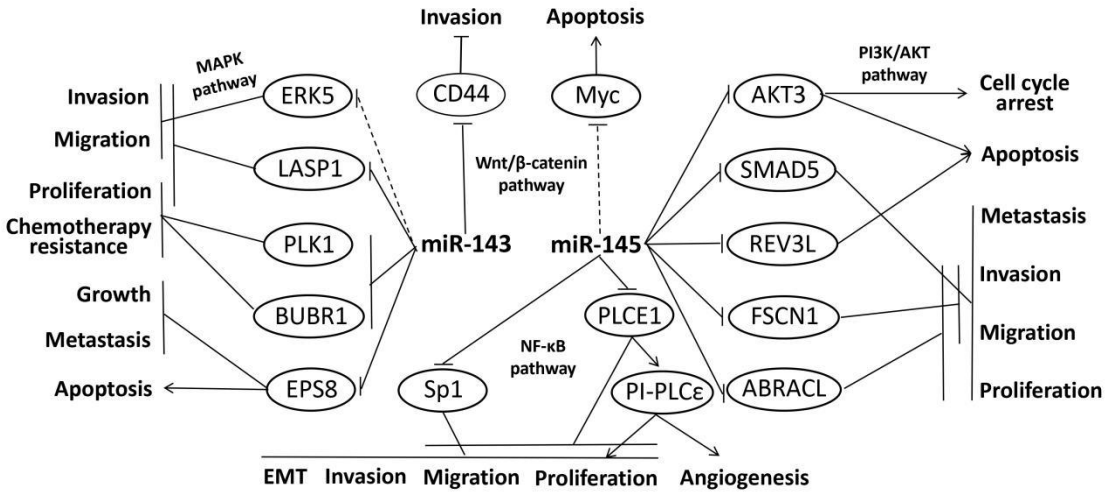

Figure 1. The progression of esophageal cancer involving mechanisms regulated by miR-143 and miR-145. Arrows indicate promotion and small vertical/horizontal bars indicate ihibition. Full lines indicate experimental verification and dashed lines indicate lack of experimental verification.

5. Conclusion

Esophageal cancer is one of the most common gastrointestinal malignancies, with a low 5-year survival rate and poor prognosis. miRNA is deeply involved in regulating the natural history of esophageal cancer. miR-143 and miR-145, as star molecules, are significantly reduced in the esophageal cancer tissues, which are closely related to the onset and progression of esophageal cancer. However, the regulatory mechanisms by miR-143 and miR-145 in the two pathological subtypes (ESCC and EAC) may be opposite. By combing the regulatory relationship between the two miRNAs and target genes of several signaling pathway, we can consider the downregulation expression of the two miRNAs in esophageal cancer as a general trend to activate the cancer-promoting signaling pathways and attenuate the anti-cancer signaling pathways to promote proliferation, differentiation, invasion and metastasis of esophageal cancer cells. Currently, in other cancer types, such as breast cancer, neuroblastoma, cervical cancer and thyroid cancer, miR-143 and miR-145 have been found to regulate corresponding target genes (52-55). More studies are required to explore the target genes related to miR-143 and miR-145 in esophageal cancer. With the in-depth study of the regulatory network of the two miRNA-centered signaling pathways in esophageal cancer cells, miR-143 and miR-145 are promising molecules to become new targets for clinical treatment of esophageal cancer.

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