

Review

The role of microRNAs in the occurrence and development of esophageal squamous cell carcinoma

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Abstract

Esophageal carcinoma (EC) is a malignancy with high metastatic potential. Although the treatment has improved over the past few decades, the survival rate is still low, and there is a pressing need for targeted therapies. A variety of microRNA (miRNA) expression profiles and candidate genes have been studied in EC, which obviously supports the key role of miRNA in the pathogenesis of EC. In order to better understand the importance of miRNA in the development of EC, this article reviews the current information about many important miRNAs as they relate to the progression of EC.

Keywords: miRNA; esophageal carcinoma cell carcinoma; prognosis; chemosensitivity

INTRODUCTION

Esophageal carcinoma (EC) is a common cancer that causes a high rate of cancer-related mortality around the world. The five-year survival rate of patients with advanced stage or metastatic EC is reported to be below 20% [1]. EC is a malignant lesion formed by abnormal hyperplasia of the squamous epithelium or glandular epithelium of the esophagus, so EC usually occurs as either esophageal adenocarcinoma (EAC) or esophageal squamous cell carcinoma (ESCC) [2]. ESCC forms in squamous cells and occurs mainly in the upper 1/3 of the esophagus. However, EAC begins in glandular cells and usually forms in the lower part of the esophagus near the stomach. Of the two histological types of EC, ESCC is the more aggressive malignant tumor [3]. The incidence of EAC is rare in Asian and African countries where ESCC remains the dominant form. In China, more than 90% of the ECs are ESCC [4]. Although multimodulated treatment for ESCC patients exists, such as surgery, chemotherapy, and radiation therapy, the prognosis is still poor. Therefore, this review aims to enhance our understanding of the molecular mechanisms associated with the development and progression of ESCC.

MicroRNAs (miRNAs) are endogenous small noncoding RNAs which exist in various plants and animals [5]. They

regulate gene expression by repressing the translation of target cellular transcripts, and they therefore take part in physiological and pathological processes that include cell proliferation, differentiation, and apoptosis. In the last century, scholars mainly paid attention on the protein-coding genes, and the existence of miRNAs was unknown. However, the small noncoding RNA lin-4, which was discovered in 1993, completely changed the opinion and perspective of scholars [6]. The biogenesis processing of these miRNAs happens in the nucleus/cytoplasm, while the final maturation occurs in the cytoplasm. Existing research has determined that miRNA genes are processed via both a regulated and a non-regulated biogenesis pathway and transcribed by RNA polymerase II. In the biological regulating processes, primary miRNAs (pri-miRNAs) are processed into a nucleus to generate approximately 70 nucleotide precursor miRNA (pre-miRNA) products by the ribonuclease III (RNase III) enzyme Drosha. While in the non-regulated biogenesis pathway, pre-miRNAs are instead generated by the mRNA splicing machinery, thereby avoiding Drosha digestion [7]. Currently, because the miRNA situation is very complicated due to the increased number of miRNA genes, it remains difficult to define their function clearly.

The changed expression of miRNA will regulate the oncogenes or the tumor suppressor expression, which will further influence cancer cell proliferation, apoptosis, migration, and invasion, among other things. This is the case with ESCC, in which there are various miRNA expression profiles that have been reported as possible useful biomarkers. Therefore, in this review, we summarized the characterization of miRNAs

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Table 1. Tumor suppressive miRNA in Esophageal Carcinoma

| miRNAs | Biological mechanisms | Target genes | Reference |
|----------|---|--------------|-----------|
| miR-107 | inhibits proliferation, migration and invasion | Cdc42 | [9] |
| miR-143 | induces G1/G0 phase arrest | FAM83F | [10] |
| miR-181d | inhibits proliferation, migration and arrests cell cycle transition in vitro and tumorigenicity in vivo | DERL1 | [11] |
| miR-195 | decreases cell growth, migration, and invasion in vitro | Cdc42 | [12] [23] |
| miR-126 | inhibits the proliferation and migration | PIK3R2 | [13] |
| miR-29b | inhibits angiogenesis | VEGFA | [14] |
| miR-27a | attenuates proliferation, invasion and tumor growth in nude mice | KRAS | [15] |
| miR-200b | induces cell cycle arrest and represses cell growth | PAF, CDK1 | [16] |
| miR-29c | induces G1/G0 phase arrest | cyclin E | [17] |
| miR-203 | Causes G1 Arrest | E2F1 | [18] |
| miR-210 | induces G2/M phase cell cycle arrest | PLK1 | [19] |
| miR-495 | suppresses cell cycle transition | AKT | [20] |
| miR-143 | inhibits tumor cell proliferation and invasion | STAT3 | [21] |
| miR-26b | regulates cancer proliferation migration and cell cycle transition | TRAF5 | [22] |

involved in ESCC, and we discussed the various miRNAs that could be biomarkers or therapeutic targets.

THE ROLE OF MIRNAS IN THE OCCURRENCE OF EC

A number of dysregulated miRNAs have been identified in ESCC, including the upregulation of miR-10b, miR-151, miR-93, miR-21, miR-192, miR-194, and miR-106-25 polycistron, and the downregulation of let-7c, miR-125b, miR-27b, miR-145, miR-203, miR-100, miR-205, and miR-375. The majority of these are also abnormally expressed in other forms of cancer, and their target genes are widely studied in different cancers [8]. These abnormal miRNAs strongly suggest their important roles in ESCC development.

MiRNAs as tumor suppressors of EC

The tumor suppressive miRNA in EC is shown in Table 1. It has been determined that miR-107 functions as a tumor suppressor and inhibits the proliferation, migration, and invasion of ESCC cells [9]. MiR-143 plays the role of inhibiting tumors through inducing G1/G0 phase arrest of ESCC cells by negatively regulating FAM83F expression [10]. MiR-181d is aberrantly downregulated in ESCC cell lines and performs a tumor suppressive function by inversely regulating

its downstream target gene of DERL1 [11]. MiR-195 can target Cdc42 and serve as a tumor suppressor in ESCC [12]. MiR-126 is significantly downregulated in ESCC tissues compared to adjacent normal tissues, and the PI3K/AKT pathway has been found to be activated in ESCC tissues. Nie et al. [13] demonstrated that the PIK3R2 is a direct target of miR-126, which reveals that targeting miR-126 may be an effective strategy for ESCC diagnosis and treatment. VEGFA is upstream of the MAPK/ERK and PI3K/Akt signaling pathways, and miR-29b has been found to negatively modulate the MAPK/ERK and PI3K/Akt signaling pathways to inhibit angiogenesis in EC by targeting VEGFA [14]. MiR-27a functions as a tumor suppressor by targeting KRAS, which further inhibits the KRAS-related ERK pathways [15]. MiR-200b has been reported to modulate Wnt/ β -Catenin signaling by targeting PAF (PCNA-associated factor) in ESCC [16]. MiR-29c suppresses tumor growth by modulating cyclin E expression to induce cell cycle G(1)/G(0) arrest [17]. Zhang et al. [18] find that miR-203 is a target of E2F1 and regulated cell cycle arrest by taking part in a feedback loop with E2F1. MiR-210 has been reported to inhibit ESCC cell proliferation by targeting PLK1 to induce G2/M phase cell cycle arrest [19]. MiR-495 suppresses cell cycle transition through targeting Akt1 in ESCC cells [20]. MiR-143 represses the cell cycle transition by targeting STAT3 in ESCC cells [21]. MiR-26b regulates cancer cell cycle transition by suppressing

Table 2. Oncogenic miRNA in Esophageal Carcinoma

| miRNAs | Biological mechanisms | Target genes | Reference |
|------------|---|---------------------|-----------|
| miR-483-3p | promotes cell proliferation | EI24 | [24] |
| miR-208 | promotes cell proliferation | SOX6 | [27] |
| miR-16 | inhibits cell apoptosis | RECK, SOX6 | [26] |
| miR-27a-3p | as a tumor promoter | FBXW7 | [25] |
| miR-18a | increases cell cycle | PTEN | [29] |
| miR-130b | increases proliferation, enhances their ability to migrate and invade | PTEN | [28] |
| miR-508 | suppresses multiple phosphatases, promotes the aggressive phenotype of ESCC | PTEN | [29] |
| miR-21 | promotes the proliferation and inhibits apoptosis | ERK1/2/MAPK pathway | [32] |
| miR-183 | accelerates G1/S transitions | PDCD4 | [28] |

TRAF5 in ESCC cells [22].

MiRNAs as oncogenes of EC

The oncogenic miRNA in EC is shown in Table 2. MiR-483-3p is upregulated in ESCC cell lines, and it promotes ESCC cell proliferation by directly targeting EI24, which suggests a potential strategy for miRNA-based ESCC therapy [24]. Wu et al. [25] discovered that miR-27a-3p, a tumor promoter which targets FBXW7, has a significantly inhibitory effect on the proliferation of Eca109 cells, indicating a potential therapeutic strategy for ESCC therapy. MiR-16 can inhibit ESCC cell apoptosis while promoting growth by the two genes, RECK and SOX6, which also play important roles in the etiopathogenesis of ESCC [26]. In ESCC cell lines and tissues, there is increased miR-208, which could promote ESCC cell proliferation. Further investigation found that miR-208 participates in ESCC carcinogenesis by targeting SOX6 [27]. MiR-183 accelerates G1/S transitions through inhibiting PDCD4 expression [28]. Phosphatase and tensin homolog (PTEN) is a tumor suppressor gene. Loss of its function is the most frequent genetic alteration in EC. The PI3K-Akt-mTOR pathway regulates cellular growth, and PTEN is a negative regulator of this pathway. Zhang et al. [29] reported that miR-18a-increased cyclin D1 expression is associated with decreased PTEN, which has been demonstrated to be a direct target of miR-18a, indicating that upregulation of miR-18a promotes cell proliferation via regulating the PI3K-AKT-mTOR signaling axis by targeting PTEN. MiR-130b and miR-508 were also found to regulate p-Akt expression by targeting PTEN, thereby activating PI3K-Akt signaling [30, 31]. In addition, miR-21 can

activate the ERK1/2/MAPK pathway to promote Eca109 cell proliferation [32].

MicroRNAs and metastasis of EC

Epithelial-mesenchymal transition (EMT) is a signal pathway, which includes successive cell detaching, migrating, invading, dispersing, and residing, and has been classified as a hallmark of tumor metastasis. EMT is a crucial component of the invasive and metastatic properties of malignant tumor cells during tumor progression. One of the important mediators of EMT is the Snail1 protein (encoded by SNAI1), which facilitates the transition to the mesenchymal state by transcriptionally repressing the epithelial cell marker E-cadherin (Figure 1). It was reported that miR-153 can inhibit tumor progression in ESCC cells by targeting SNAI1 [33]. MiR-9 induces EMT in ESCC metastasis by targeting E-cadherin [34]. Slug is another EMT transcription factor, and miR-630 inhibits EMT by targeting Slug in ESCC [35]. Zeb2 (Sip1/Zfhx1b) is a member of the zinc-finger E-box-binding (ZEB) family of transcriptional repressors previously demonstrated to regulate EMT processes during embryogenesis and tumor progression. MiR-205 is an ESCC-specific miR that exerts tumor-suppressive activities with EMT inhibition by targeting ZEB2 [36]. MiR-655 is an EMT-suppressive miRNA targeting ZEB1 and TGFBR2 [37]. SOX4 knockdown delays TGF- β -induced EMT, and MiR-133a suppresses the migration and invasion of EC cells by targeting the EMT regulator SOX4 [38].

Numerous signaling pathways are involved in the process of EMT in cancer, such as the SMAD7 pathway, STAT3 signaling pathway, PTEN/PI3K pathway, etc., which have a certain relationship with EMT. MiR-424-5p mediates EMT in ESCC via the SMAD7

the miR-17-92 cluster have been reported to be highly expressed in several cancers. MiR-18a, miR-19a, and miR-17 are members of the miR-17-92 cluster, and the univariate and multivariate analysis demonstrated that they may be prognostic indicators for progression-free survival and overall survival, which indicates that miR-17, miR-18a, and miR-19a can serve as potential unfavorable prognostic biomarkers in ESCCs which are associated with some clinicopathologic factors [52]. In addition, the miR-18a that is located in the miR-17-92 cluster was further reported as being highly expressed in tissues of ESCC [53]. The miR-181b, miR-21, and miR-146b expression in tumor tissue are associated with overall survival of patients, indicating that they may be used as prognostic classifiers for ESCC [54]. Measuring the levels of miRNAs in 64 EC patients who underwent neoadjuvant chemotherapy, Tanaka et al. concluded that the miR-200c expression in serum can predict the response to chemotherapy and the prognosis of EC patients who receive neoadjuvant chemotherapy [55]. Combining the expressions of miR-133a and miR-133b were found to be an effective prognostic marker of ESCC [56].

Several recent studies demonstrated that miRNAs are stably detectable in plasma/serum. Detection of circulating miRNAs might provide new complementary tumor markers for ESCC. Circulating miR-155 in plasma may serve as a reliable, novel, and noninvasive biomarker for the early diagnosis and detection of EC [57]. The miR-18a that is highly expressed in tissues of ESCC could serve as a plasma biomarker in patients with ESCC [53]. Komatsu et al. [58] selected three oncogenic miRNAs (miR-21, miR-184, and miR-221) and one tumor suppressive miRNA (miR-375), which are frequently reported in ESCC, as candidate targets for a plasma miRNA assay. The results showed that patients with a high plasma level of miR-21 tend to have greater vascular invasion and that this indicates a high correlation with recurrence. Moreover, Komatsu and his colleagues [59] once again examined the association between plasma miRNA concentrations and prognosis retrospectively in 50 preoperative plasma samples that were collected from consecutive patients with ESCC who underwent curative esophagectomy. Their research concluded that circulating miR-21 and miR-375 could be reliable prognostic markers for ESCC. These plasma markers might facilitate clinical decision-making in the selection of prospective candidates who need meticulous follow-up for early detection of recurrences and additional treatments, such as neoadjuvant chemotherapy and postoperative chemotherapy in cases of ESCC. MiR-16, miR-21, miR-185, and miR-375 were found to be significantly higher in ESCC patients than in controls, suggesting that the four plasma

miRNAs could potentially serve as novel diagnostic biomarkers for ESCC [60]. Moreover, the upregulated miR-16 and miR-21 in the plasma were correlated significantly to shortened progression-free survival and overall survival in ESCC patients, indicating that miR-16 and miR-21 can predict poor survival in ESCC. The miR-20a and let-7a levels in plasma obviously change in ESCC patients, which could be used as a biomarker for the diagnosis of ESCC [61]. The serum expression of miR-218 is downregulated in EC patients and correlates with tumor differentiation, stage, and lymph node metastasis, so serum miR-218 may be a potential biomarker for early detection and clinical evaluation in patients with EC [62]. Compared with healthy controls, the miRNA-216a/b expression in plasma from ESCC patients is markedly decreased, and the miRNA-216a/b expression in plasma is inversely correlated with the TNM stage and lymph node metastasis [63]. The reduced miR-718 expression in plasma of ESCC patients may act as a potential diagnostic marker for ESCC [64]. The patients who have high miR-506 expression have a notably shorter survival time than those with low miR-506 expression; thus, miRNA-506 can serve as a marker for the diagnosis and prognostic prediction of ESC [65].

MiRNAs and chemosensitivity of EC

Only a small number of studies have identified the significance of circulating miRNAs in blood as a predictive biomarker for chemoresistance in ESCC. Komatsu et al. [58, 59] have demonstrated that a high plasma level of miR-21 indicates a high correlation with recurrence in ESCC patients. Also, He and his colleagues [66] further verified that the overexpression of miR-21 contributes to chemoresistance, and that circulating miR-21 could be a useful biomarker for predicting chemoresistance in ESCC patients. Sugimura et al. [67] found that let-7 expression in EC can predict the response to cisplatin-based chemotherapy and the modulated chemosensitivity role of let-7 to cisplatin by regulating the IL-6/STAT3 pathway. Convincing evidence has been offered by Chen et al. [56] that miR-133a and miR-133b may predict chemosensitivity, which indicates their importance in being applied in the clinical treatment of ESCC. In order to provide new insights for ESCC treatment, Tian et al. [68] detected miR-218 in ESCC tissues and explored its effects on the biological features and chemosensitivity to cisplatin in the Eca109 cell. They found that, compared to the matched non-tumor tissues, miR-218 in the ESCC tissues was significantly increased. This supports the opinion that enforced expression of miR-218 significantly increases the sensitivity to CDDP in Eca109 cells.

CONCLUSION

The incidence rate of EC is showing rapid growth in the world. The treatment of EC is still routine surgery, radiotherapy, and chemotherapy, so the prognosis is poor. The 5-year survival rate of surgical patients is only 25%. It is encouraging to note that miRNAs have recently been shown to be involved in the whole the process of carcinogenesis, progression, and treatment of EC. Further exploration of the miRNA regulatory network will not only help us identify the pathogenesis of EC, but may also assist us in finding new therapies. However, further study is needed before miRNAs can be introduced into clinical application.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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