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Research Progress of Mir143 in Tumors and Its Guiding Significance in Lung Cancer Research

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Abstract: MicroRNA-143 (miR-143) is a non-coding RNA molecule that plays a critical regulatory role in various biological processes, including cell proliferation, differentiation, and apoptosis. This review summarizes the structural characteristics of miR-143 and its expression patterns in different tumor types, with a particular focus on cervical cancer, colon cancer, and lung cancer. In most malignancies, miR-143 is downregulated and functions as a tumor suppressor by targeting oncogenes and modulating key signaling pathways. However, emerging evidence suggests that miR-143 may exhibit dual roles depending on the tumor context, as seen in certain lung cancer studies where its elevated expression correlates with poor prognosis. The interaction between miR-143 and long non-coding RNAs (lncRNAs) further expands its regulatory network and highlights its potential as a diagnostic biomarker and therapeutic target. A deeper understanding of miR-143's multifaceted functions may offer new insights into tumor biology and treatment strategies.

Keywords: miR-143; microRNA; Tumor suppressor

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1. Introduction

miRNAs are a group of non-coding single-stranded RNA molecules, 20–24 nucleotides in length, encoded by endogenous genes. They do not encode proteins, lack open reading frames, and exhibit high conservation. These molecules bind to specific mRNA molecules, degrade the corresponding target mRNA, thereby inhibiting its normal translation process. They regulate gene expression during the post-transcriptional stage and are widely involved in vital biological processes such as growth, development, differentiation, metabolism, and defense. Recent studies have revealed that multiple miRNAs exhibit distinct expression patterns in normal cells versus tumor cells. These differentially expressed miRNAs function similarly to proto-oncogenes or tumor suppressor genes by regulating various target genes, playing critical roles in tumor initiation, apoptosis, invasion, and drug resistance [1–3].

2. Structure and characteristics of miR-143

miR143 is located in the precursor of the stem-loop structure of the 5th human chromosome (5q32). Depending on the different cleavage sites, it can be processed into miR-143-3p (21nt) and miR-143-5p (22nt). Currently, the more well-studied variant is miR-143-3p. Mir-143 regulates target gene expression at the post-transcriptional level, modulates related signaling pathways, and influences cell proliferation, differentiation, and apoptosis. Consequently, it regulates organismal growth, development, and disease onset. Studies have shown its close association with the occurrence of obesity, inflammation, and tumors [4,5].

miR-143 is lowly expressed in various tumors such as colorectal cancer, cervical cancer, ovarian cancer, and gastric cancer. It acts on multiple target genes, inhibiting tumor cell proliferation, invasion, and metastasis while promoting tumor cell apoptosis, thereby exerting a tumor suppressor-like effect [6–8]. Recent studies have revealed that lncRNAs may function as endogenous sponges to modulate the expression and function of miRNAs, while miRNAs bind to lncRNAs to regulate their stability. The mechanisms underlying lncRNA/miRNA interactions have gradually become a focal point of research.

3. miR143 and cervical cancer

Recent studies have demonstrated that miR-143 is closely associated with the occurrence and progression of cervical cancer. Chen Cuiyun et al. employed multivariate analysis to show that miR-143 is an independent prognostic factor in cervical cancer patients. ROC curve analysis revealed that the combined parameter of miR-143 and MRI exhibited the highest area under the curve, with a sensitivity of 84.8% and specificity of 96.2% [9]. The study found that overexpression of miR-143 significantly inhibited the proliferation of cervical cancer Hela cells and promoted their apoptosis. Compared with normal tissues, the expression of Bcl-2 was markedly upregulated in cervical cancer tissues with downregulated miR-143 expression, confirming that the regulation of Bcl-2 expression by miR-143 may be one of the important mechanisms in the pathogenesis of cervical cancer [10]. In normal cervical tissue, intraepithelial neoplastic tissue, and cervical cancer tissue samples, the expression of miR-143 was significantly reduced in cervical cancer tissue compared to normal tissue, with a statistically significant difference. Furthermore, overexpression of miR-143 in the Hela cell line was found to markedly promote apoptosis [11]. Furthermore, overexpression of miR-143-3p suppresses the tumorigenicity of cervical cancer cells by targeting CDK1, thereby inhibiting the occurrence and progression of cervical cancer.

With the gradual deepening of research on the mechanisms of ncRNA/miRNA interactions, researchers have found that compared to normal tissues adjacent to the tumor, cervical cancer tissues exhibit reduced expression of miR-143-3p and increased expression of lncRNA MAFG-AS1 mRNA. MAFG-AS1 can target and regulate the expression of miR-143-3p, and inhibiting miR-143-3p expression can reverse the downregulation of MAFG-AS1 expression, which suppresses cell proliferation and promotes apoptosis in Hela cells. By investigating the relationship among lncRNA ACTA2-AS1, miR-143-3p, and SMAD3, researchers discovered that lncRNA ACTA2-AS1 is highly expressed in cervical cancer while miR-143-3p is lowly expressed, with a negative correlation between their expression levels. SMAD3 is a target gene of miR-143-3p, and ACTA2-AS1 may upregulate SMAD3 expression by competitively binding to the endogenous RNA of miR-143-3p. The interplay among these three factors plays a critical role in the proliferation, migration, and apoptosis of cervical cancer cells [12].

3. miR143 and colon cancer

Michael MZ (2003) demonstrated a significant reduction in the expression level of miR-143 in colon cancer tissues [13]. Animal experiments confirmed that expression of miR-143 could inhibit the growth of colon cancer tumors, increase Caspase-3 activity, PARP cleavage capacity, and the number of apoptotic cells, while reducing NF-κB activity, cell proliferation index, and the expression levels of Bcl-2 and extracellular signal-regulated protein kinase 5 (ERK5) [14]. Transfection of miR-143 precursor into human colon cancer cells DLD-1 and SW480 resulted in significant inhibition of cell growth after 48 hours. In DLD-1 cells treated with growth inhibitors (arsenic trioxide or α-terpenoid), miR-143 expression was significantly upregulated, indicating a negative correlation between its expression level and the proliferation of DLD-1 cells [15]. In 2014, Su et al. detected that overexpression of miR-143 significantly inhibited the expression of IGF1R protein by transfecting human colorectal cancer cell lines Caco2, HT29, and SW480 with miR-143 precursor [16]. IGF1R, or insulin-like growth factor 1 receptor, is a transmembrane glycoprotein that promotes tumor growth and metastasis by mediating multiple signaling pathways in tumor cells [17]. Slaby et al. applied fluorescence quantification to detect the expression levels of miR-143 and miR-145 in 29 clinical primary colorectal cancer specimens and 6 non-neoplastic adjacent tissues. They found that miR-143 ($p = 0.011$) and miR-145 ($p = 0.003$) were downregulated in tumor tissues, and the expression levels of these two miRNAs were correlated with tumor size. Specifically, miR-143 and miR-145 exhibited lower expression levels in tumors with a diameter greater than 50 mm [18]. The expression of miR-143 can reduce the viability of colorectal cancer HCT116 cells by approximately 60%. When combined with the antineoplastic agent 5-fluorouracil, it enhances the activity of Caspase-3, Caspase-8, and Caspase-9, as well as nuclear fragmentation, leading to cell death. This process is regulated by the ERK5/NF-κB signaling pathway [19]. Additionally, studies using human colon cancer cell lines HCT116 and RKO to investigate cell proliferation and cell cycle have revealed that the proliferation of cells in the miR-143-upregulated group showed no significant changes compared to the negative control group [20]. Patients with TNM III-IV stage tumors exhibited higher miR-143-3p expression levels in tumor tissues compared to those with stage I-II. High-grade differentiated tumors showed elevated miR-143-3p expression levels than low-grade undifferentiated tumors. Tumors with serosal layer invasion demonstrated higher miR-143-3p expression levels than those without serosal invasion. Additionally, lymph node metastasis patients exhibited significantly higher miR-143-3p expression levels than those without metastasis (all $P < 0.05$). These findings suggest that miR-143-3p is predominantly underexpressed in colorectal cancer tissues, and its expression changes are associated with tumor progression. Expression and significance of miR-143-3p and MDR1 mRNA in colorectal cancer patients. A Japanese study employed quantitative PCR to detect miR-143 expression in formalin-fixed paraffin-embedded colon cancer specimens, showing no difference compared to that in control mucosa [21]. The conflicting conclusions from different laboratories may be attributed to variations in experimental methods and insufficient sample sizes employed by researchers, or could also result from genetic differences among populations.

4. miR-143 and lung cancer

Research reports have been published both domestically and internationally [22]. miR-143 plays a tumor suppressor gene role in lung cancer. Research on the function of miR-143 in lung cancer has attracted significant attention. miR-143 is downregulated in non-small cell lung cancer (NSCLC) tissues and cell lines, and its expression level is negatively correlated with epidermal growth factor receptor (EGFR). miR-143 inhibits the proliferation, invasion,

and metastasis of lung cancer cells by regulating the expression of its target gene, EGFR. However, a follow-up study of 110 patients undergoing lobectomy for lung cancer reported that serum levels of miR-143, CEA, CYFRA21-1, and NSE were all higher than those in healthy individuals [23]. Patients with high miR-143 expression exhibited significantly lower 5-year disease-free survival (DFS) and overall survival (OS) rates compared to those with low miR-143 expression. The expression level of miR-143 showed a significant negative correlation with postoperative 5-year DFS and OS rates. Higher miR-143 expression was associated with poorer clinical outcomes and prognosis in lung cancer patients. Yu Jianrong [24] in a lung cancer transplanted tumor model mice, researchers observed a significant increase in serum miR-143 expression levels in peripheral blood. Inhibition of miR-143 resulted in reduced lung cancer growth rates and decreased numbers of pulmonary metastatic nodules. Therefore, miR-143 may play a bidirectional regulatory role in the pathogenesis and progression of lung cancer, though the specific mechanisms remain unknown. As research on miR-143 target genes advances, a more comprehensive understanding of its network regulation will emerge, potentially providing novel therapeutic targets for lung cancer treatment.

5. Conclusion

In summary, miR-143 exhibits low expression in various tumors, and its overexpression can inhibit tumor growth, exerting a tumor suppressor-like effect. The mechanism of action may involve the interaction between miR-143 and its target genes in multiple tumors, regulating tumor cell proliferation, invasion, and metastasis. Additionally, studies on the correlation between miR-143 and cervical cancer have revealed that, in addition to suppressing tumor cell proliferation and promoting apoptosis through its interaction with target genes, miR-143 can also act as a target gene for lncRNAs, exerting inhibitory effects on tumor cell proliferation, migration, and apoptosis via various signaling pathways. However, some researchers have also found that miR-143 may have pro-tumor effects in certain tumors, such as lung cancer. It can be inferred that miR-143 acts on different target genes within the same tumor or shares common target genes across different tumors, playing a significant role in tumor proliferation, invasion, and metastasis, and is associated with tumor prognosis. Furthermore, its expression level is negatively correlated with tumor grade and stage. Therefore, further in-depth research on miR-143 may provide new therapeutic targets and strategies for tumor treatment.

Disclosure statement

The authors declare no conflict of interest.

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