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Research progress of miRNA-326 in malignant tumors

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Abstract

MicroRNAs (miRNAs) are endogenous mediators of RNA interference and have key roles in the regulation of cell and tissue gene expression under a healthy, inflamed, stimulated, carcinogenic, or pathological states. The imbalance between miRNA and genes can cause a series of diseases, including malignancies. The role of miR-326 as a tumor suppressor miRNA in much human cancer confirmed. Low expression of miRNA-326 in tumor tissue cells activates proto-oncogenes, while upregulation of miRNA-326 can inhibits the activation of proto-oncogenes, inhibiting cancer cell growth, proliferation, and metastasis. This paper reviews the research progress of miRNA-326 in lung cancer, gastric cancer, colorectal cancer, glioblastoma, prostate cancer, etc, with the aim of understanding the mutual regulation mechanism between miR-326 and related genes and signaling pathways, as well as to elaborate on the value of miR-326 as a diagnostic biomarker and potential therapeutic target for tumours.

Keywords: microRNAs; miR-326; Malignant tumour; Signal pathway; Therapeutic target.

Introduction

Malignant tumors are classified as the third leading cause of death in the world next to cardiovascular diseases and infectious diseases [1]. In recent years, many studies have explored the diagnosis, treatment, and prognosis of cancer from the perspective of genetic and epigenetic factors. Epigenetic regulation is mainly based on DNA methylation, histone modification, chromosomal remodeling, and non-coding RNAs, especially miRNAs. MiRNAs are a class of endogenous, short-chain and conservative noncoding RNAs, that can play an important role in the occurrence and development of tumors as potential oncogenes or tumor suppressors [2]. Therefore, to explore the regulatory mechanism of miRNA in the occurrence and development of various malignant tumors is of great significance for the early diagnosis and prognosis evaluation of malignant tumors. In this paper, the expression, function and regulation mechanism of miRNA-326 in malignant tumors will be elaborated.

MiRNAs

MicroRNAs (miRNAs) are short non-coding single-stranded RNA molecules about 22nt in length, mainly acting by binding to the 3'- the untranslated reign (3'-UTR) of target mRNAs and repressing protein production by destabilizing mRNA and translational silencing [3]. It has been reported that more than 2500 miRNAs have been identified.They can participate in cell proliferation, differentiation, migration and apoptosis Among them, more than 50% of the identified human miRNAs are located in fragile sites of cancer-related genomes or chromosomes that are involved in the occurrence and development of malignant

tumors as oncogenes or tumor suppressor genes [4]. MiRNAs can be divided into oncogenic miRNAs (oncomiR) and tumor suppressor miRNAs, the former are generally overexpressed in cancer and target antiproliferative, cell differentiation and pro-apoptotic genes, such as miR-21, miR-23, miR-107, miR-155, miR-210, miR-221, Clusters of miR-17-92,the latter are generally expressed in lower levels in cancers compared to normal tissue and target pro-survival, cell cycle, and pro-proliferative genes, such as miR-34 family, miR-200 family, let-7 family, miR-15/16, miR-375, miR-506.At the same time, many miRNAs can be oncogenic in certain tumors and tumor suppressive in other cancers [5]. A single miRNA can regulate expression of many genes, while many miRNAs may affect a single mRNA [6]. These aberrantly expressed miRNAs form a complex biological regulatory network through their target genes, upstream transcription factors to participate in various biological processes of tumorigenesis.

miR-326

miR-326, a 20nt miRNA on chromosome 11, was first recognized as a neural-specific miRNA in neurons [7]. It plays a key role in the regulation of host gene expression at the post-transcriptional level. In recent years, there is increasing evidence showing that miR-326 serving as a tumor suppressor and is downregulated in various cancerous tissues.It is involved in the occurrence and development of human cancer, such as non-small cell lung cancer (NSCLC), colorectal cancer, gastric cancer, breast cancer (BC), esophageal cancer, glioma, prostate cancer, cervical cancer, osteosarcoma, etc, but miR-326 is highly expressed in prostate cancer plasma samples [8]. Low expression of miR-326 is significantly associated with poor prognosis, tumor development, metastasis and progression in cancer patients. For example, down-regulation of miR-326 is positively correlated with metastasis risk of NSCLC, gastric cancer, prostate cancer, and esophageal cancer [9,10]. MiR-326 is involved in tumor cell invasion and metastasis in NSCLC, gastric cancer, colorectal cancer, glioma, breast cancer and cervical cancer [11,12].

Relationship between miR-326 and malignant tumors and its significance

miR-326 and lung cancer

Lung cancer is the most common cause of cancer mortality in the world, accounting for over 1 million deaths annually. Non-small cell lung cancer (NSCLC) is common and accounts for about 80% of lung cancer and lung adenocarcinoma (LAC) [13]. Survival analysis showed that compared with patients with high expression of miR-326, patients with low expression of miR-326 had shorter overall survival, suggesting that low expression of miR-326 is associated with poor prognosis in NSCLC. Sun [14] et al found that miR-326 is downregulated in NSCLC tissues and cell lines. miR-326 overexpression inhibits the proliferation, migration and invasion, and induces apoptosis of NSCLC cell lines. Li [15] et al found nucleosome-binding protein 1 (NSBP1) is a new target of miR-326 in NSCLC, miR-326 bound to 3'UTR of NSBP1. Enforced expression of miR-326 decreased accumulation of NSBP1 and inhibited the proliferation and invasion ability of NSCLC cells, suggesting that miR-326-NSBP1 may be a potential therapeutic target for the treatment of NSCLC. Wang [16] et al. found that in NCSLC cells, silencing of LncRNA HOTAIR caused increased expression of miR-326, and HOTAIR was a negative regulator of miR-326. Meanwhile, luciferase assays confirmed that Phox2a is a functional target of miR-326, and exogenous expression of Phox2a compromised the inhibitory effects of miR-326 on cell proliferation. miR-326 regulates cell proliferation and migration in lung cancer by targeting Phox2a and is regulated by HOTAIR. Cai [17] et al. found that ADAM17, as a target of miR-326, promoted epithelial-to-mesenchymal transition (EMT) -induced cell invasion in Lung Adenocarcinoma (LAC). Zheng [18] et al found that interferon-alpha receptor 2(IFNAR2) was confirmed as a downstream target of miR-326 in gefitinib resistance of NSCLC, and miR-326 can inhibit the proliferation of gefitinib resistance of NSCLC cells by inhibiting IFNAR2 expression. In addition, it was proved that PCAT6, as an endogenous competing RNA(ceRNA) of miR-326, upregulated IFNAR2 and inhibited the sensitivity of NSCLC to gefitinib by absorbing miR-326, which might offer a new therapeutic strategy against gefitinib resistance of NSCLC patients.

miR-326 and gastric cancer

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer death in the world [19]. Currently, a growing number of studies have shown that miR-326 is downregulated in GC and serves as a tumor suppressor, involved in the migration of gastric cancer cell lines. Ji [20] et al. found that miR-326 significantly induced GC cell G2/M arrest, thus inhibiting cell proliferation. Dual luciferase reporter assay identified one of the proto-oncogene NOB1 as a direct target of miR-326, and NOB1 can save growth inhibition caused by miR-326.They also confirmed that the growth inhibition caused by miR-326 is associated with AKT pathway activation. Ma [21] et al. Through database analysis and clinical data, identified high expression of lncRNA FAM225A in GC, which was positively correlated with a more profound lymphatic metastasis rate, larger tumor size, and more advanced tumor stage. Functional experiments showed that FAM225A acted as a miR-326 sponge to upregulate its direct target PADI2, promoting the progression of gastric cancer. Liu [22] et al. found that the oncogene DDX11-AS1 is overexpressed in GC tissues and acted as a miR-326 sponge. In OXA-resistant GC cells, DDX11-AS1 promoted cell growth by antagonizing miR-326-mediated Insulin Receptor Substrate 1(IRS1). These results provided a comprehensive analysis of DDX11-AS1 / miR-326 /IRS1 axis and proposed a potential therapeutic strategy for the treatment of GC drug-resistant patients.

miR-326 and colorectal cancer

Colorectal Cancer (CRC) is a common malignancy and causes about one million deaths every year [23]. Increasingly reports showed that miR-326 exhibited anticancer properties in various cancer types and was regulated by lncRNA [24]. Liu [25] et al. revealed the necessary association of miR-326 /EWSAT1 to mediate CRC growth. They found that lncRNA EWSAT1 was highly expressed in CRC tissues and cell lines and associated with poor overall survival. As a target of EWSAT1, miR-326 inhibitor can reverse the effect on CRC cell progression induced by si-EWSAT1. EWSAT1 could promote CRC cell proliferation, migration, invasion by sponging miR-326, and upregulating FBXL20. Hao [26] et al. found that hsa_circRNA_000166 was upregulated in CRC tissues and cell lines, and associated with a lower 5-year sur-

vival rate. Further bioassay and luciferase reports showed that hsa_circRNA_000166 directly targeted mir-326 /LASP1 axis. Down-regulated hsa_circRNA_000166 inhibited cell growth and promoted cell apoptosis by sponging miR-326 /LASP1 axis. Wu [27] et al. found that miR-326 inhibited cell proliferation, migration and invasion, and induced cell apoptosis and cell cycle arrest of CRC cells by directly targeting NOB1.CRC patients with high expression of miR-326 or low expression of NOB1 had a better prognosis, suggesting that miR-326 or NOB1 may be independent prognostic biomarker for CRC patients. Exogenous overexpression of miR-326 is considered as a potential strategy for targeting therapy in CRC .

miR-326 and glioblastoma

Glioblastoma (GBM) is the most common aggressive malignant primary adult brain tumor, characterized by rapid tumor growth and infiltration of tumor cells throughout the brain. In recent years, miR-326 has been reported to control the development of cerebellar neuronal progenitor cells and tumor cells as a tumor suppressor. Zhou [28] et al. studied the relationship between miR -326 and NOB1, confirming that NOB1 is highly expressed in glioma tissues, and acted as a new target of miR -326. Higher levels of NOB1 mRNA are associated with a relatively shorter survival. miR-326 directly targets and inhibits the expression of NOB1, thus inhibiting the proliferation of glioma cells. In addition, the phosphorylation of three members of the MAPK pathway, P38, ERK1/2, and JNK, increased significantly after NOB1 suppression. These results suggest that the antiglioma effect of NOB1 might be mediated by MAPK activation. Overexpression of miR -326 decreased the tumorigenesis of glioma cells by targeting NOB1 and activating MAPK pathway. Lu [29] et al. found that the levels of circ_0001730 were elevated in GBM cell lines and tissues, directly targeting miR -326 and reducing its activity. circ_0001730 functions as a ceRNA for miR-326 to regulate the Wnt7B/β-catenin pathway. Therefore, circ_0001730 promoted growth and invasion in GBM cells via the miR -326 / Wnt7B axis, providing a new mechanism and target for GBM diagnosis and treatment.

miR-326 and breast cancer

Breast cancer (PCa) is the second most common cancer in humans and the leading cause of cancer-related deaths among women all around the world [30]. Jiang [31] et al found that circ_0000518 served as a sponge for miR-326, which targeted Fibroblast Growth Factor Receptor 1(FGFR1) in BCa cells. circ0000518 accelerated BCa progression via elevating FRGR1 expression by sponging miR -326. circ_0000518 silencing impeded tumor growth and induced apoptosis, cell cycle arrest, and reduced FGFR1 expression, suggesting that circ_0000518 facilitated BCa development by regulating miR -326 /FGFR1 axis. Zahra [32] et al. found that miR-326 was remarkably downregulated in BCa tissues and correlated with poor survival outcome. Further functional experiments confirmed that miR -326 regulates ErbB/PI3K signaling by targeting a network of genes (EGFR, ErbB2, ErbB3, AKT1, AKT2, and AKT3. It is suggested that miR -326 plays a tumor-suppressive role in BCa through inhibiting ErbB/PI3K pathway and miR-326 may serve as a potential therapeutic target for the treatment of BCa patients.

miR-326 and prostate cancer

Prostate cancer (PCa) is the most prevalent cancer in the urinary system, is the second most common male cancer in the world, and has a high mortality [33]. Liu [34] et al found that LncRNA PCAT6 is highly expressed in Enzalutamide-induced neuroendocrine PCa (NEPC) tissues. PCAT6 overexpression promoted Neuroendocrine Differentiation (NED) of PCa cells, PCAT6 knockdown in PCa cell repressed NED. Further functional experiments confirmed that PCAT6, functioned as competing endogenous RNA(ceRNA) via absorbing miR-326, could lead to a desuppression of hnRNPA2B1 target gene, thus promoting the proliferation and invasion of NEPC cells. The PCAT6/ miR -326 /hnRNPA2B1 signaling might be a new therapeutic target for NEPC. Combinational detection of circSLC19A1 and prostate-specific antigen (PSA) could enhance the sensitivity and specificity of the area under the curve (AUC), thus contributing to the diagnosis of PCa [35]. Huang et al. found that CircSLC19A1 expression was up-regulated in PCa tissues and cell cytoplasm. Silencing CircSLC19A1 inhibited PCa cell viability,proliferation, migration and invasion. CircSLC19A1silencing significantly inhibited PCa progression by mediating miR -326 /MAPK1 axis. CircSLC19A1functioned as ceRNA via absorbing miR -326, which could lead to a desuppression of MAPK1 target gene, thus promoting proliferation and reducing apoptosis of PCa cells. Therefore, CircSLC19A1 / miR -326 /MAPK1 axis can be used as a new potential prediction target for PCa detection.

miR-326 and cervical cancer

Cervical cancer is the fourth most common cancer in humans and the second leading cause of cancer death in females worldwide [36]. Tang [37] et al. found that the expression of circ_0000515 was negatively correlated with miR-326 in cervical cancer .Compared with normal adjacent tissues, circ_0000515 expression was significantly over-expressed and miR -326 was down-regulated in cervical cancer tissues and cells. It was confirmed that ETS transcription factor ELK1 was the direct target of miR -326. miR-326 directly targets and inhibits the expression of ELK1, thus inhibiting the proliferation, migration, and invasion of cervical cancer cells. circ0000515 functions as a ceRNA via absorbing miR-326,which could lead to a desuppression of ELK1,thus promoting the progression of cervical cancer. In addition, ELK1 is an integration point associated with different mitogen-activated protein kinase (MAPK) signaling pathways [38]. JIANG [39] et al. found that MAPK1 is a direct target of miR -326 in cervical cancer. lncRNA TDRG1 acts as a ceRNA to upregulate MAPK1 by sponging miR -326, thus promoting the proliferation, migration, and invasion of cervical cancer cells. CAI [40] et al. found that, the expression of circRNA_0001400 was significantly increased in cervical cancer compared with normal adjacent tissues. circRNA_0001400 silencing significantly promoted the apoptosis of cervical cancer and arrested the cell cycle and migration. circRNA_0001400_siRNA can inhibit the protein expression of Akt and the inhibition of miR-326 could rescue the inhibition of Akt in cervical cancer cells. Studies have confirmed that circRNA_0001400 could promotes cervical cancer cell proliferation, migration and invasion by sponging miR-326 and upregulating Akt. This study provides evidence that the circrNA_0001400/miR -326 /Akt network promotes cervical cancer progression.

miR-326 and hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common malignant heterogeneous disease in primary liver tumors, ranking fourth among cancer-related causes of Death [41]. He [42] et al. found that the expression level of Hsa_circ_0000517 was significantly upregulated in HCC tissues and cell lines, which was associated with poor prognosis of HCC patients. Silencing Hsa_circ_0000517 inhibited cell proliferation, migra-

tion, and invasion, and induced cell cycle arrest in HCC cells. Hsa_circ_0000517 can serve as a ceRNA to sponge miR-326 and modulate SMAD6 levels in HCC pathogenesis. In addition, HE [43] et al. found that IGF1R is also the target of miR -326. The knockdown of circ_0000517 and IGF1R inhibited the proliferation, migration and invasion of HCC cells, while knockout of miR-326 exerted the opposite effect. These results suggest that circ_0000517 / miR -326 may promote tumor progression through SMAD6 and inhibit the function of HCC cells by targeting IGF1R, which may provide a promising therapeutic target for HCC therapy. JIA [44] et al. found that circPTN is a sponge of miR-326 in HCC and plays a carcinogenic role by antagonizing the mir-326-mediated ErbB/PI3K pathway in HCC. circPTN attenuated miR -326 and upregulated the expression levels of ErbB and PI3K. Overexpression of circPTN can rescue the decreased proliferation regulated by miR-326. Therefore, circPTN acts as a carcinogenic factor via miR -326 /ErbB/PI3K pathway in HCC.

Conclusion

With the development of bioinformatics technology, the differential expression and different regulatory mechanisms of miR-326 in malignant tumors have been discovered. miR-326 plays a potential oncogenic role through influencing the expression of specific genes associated with the occurrence of malignant tumor development such as NOB1, phox2, Wnt7B, FGFR1, ELK1, MAPK1, Akt, SMAD6, LASP1. At the same time, also shows that the expression of miRNA-326 plays an important regulatory role in the aspects of cell proliferation, apoptosis, growth inhibition, metastasis, invasion, and chemotherapy sensitivity of multiple tumors. miRNA mainly regulates gene expression by degrading mRNA or inhibiting the translation process after transcription. A single miRNA may regulate several genes expression and several miRNAs may affect a single mRNA. However, most current miRNA studies only explore the correlation between a single miRNA and its target genes and tumor invasiveness. Clearly, the results obtained may not be comprehensive enough. Therefore, we need to further explore the mechanism of miRNA to clarify its questionable role in cancer and provide theoretical support for clinical gene therapy strategies.

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