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Current Research Status of MicroRNAs in Squamous Cell Carcinoma of the Tongue

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Abstract

Tongue squamous cell carcinoma (TSCC) is the most invasive type of oral malignant tumor, posing a serious threat to human life and health. Its pathogenesis is complex and has a high degree of malignancy. Recurrence and metastasis often lead to poor prognosis. MicroRNAs are a type of single stranded small molecule RNA with only 18 - 25 nucleotides, which can regulate the expression of various genes and participate in the occurrence and development of tumors. Studies have found that microRNA expression profiling can serve as a reliable and stable biological indicator for early diagnosis and prognosis of tumors. This article provides a review of the research status of MicroRNAs in squamous cell carcinoma of the tongue.

Keywords

MicroRNAs, Tongue Squamous Cell Carcinoma Cells, Tumor, Pathogenesis

1. Introduction

Oral cancer is one of the common malignant tumors in the head and neck. In China, tongue cancer accounts for 50% - 60% of oral cancer, ranking first in oral cancer [1]. The common pathological type of tongue cancer is squamous cell carcinoma of the tongue, abbreviated as tongue squamous cell carcinoma. MicroRNAs are endogenous non protein coding RNAs that are formed by RNA enzymes (RNase) III Drosha and Dicer through multi-step cleavage, resulting in mature single stranded small molecules containing 18 - 25 nucleotides. The function of MicroRNAs is to bind to target gene mRNA, causing mRNA degradation on one hand and inhibiting protein translation on the other, thereby regulating the expression of target genes. Research has confirmed the presence of

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various abnormally expressed MicroRNAs in tongue squamous cell carcinoma tissue, which plays important regulatory roles in its proliferation, differentiation, growth, apoptosis, invasion, and metastasis [2]. This article provides a review of the research status of MicroRNAs in squamous cell carcinoma of the tongue.

2. MircoRNAs Participate in Regulating the Activity of Tongue Squamous Cell Carcinoma Cells

Rapid growth is one of the biological characteristics of malignant tumors, characterized by uncontrolled cell cycle regulation, leading to a lack of cell differentiation and abnormal cell growth, resulting in unlimited cell proliferation. MircoRNAs promote the proliferation of tongue squamous cell carcinoma cells and inhibit their apoptosis.

Research has shown that miR-21 is currently the only MicroRNAs expressed in solid tumors. By using PCR technology to detect miR-21 in tongue squamous cell carcinoma tissue, researchers have found that the expression of miR-21 in tumor tissue is significantly higher than that in normal tissue. After transfection with miR-21, it was found that the stability of the transfected cell lines increased, indicating that miR-21 promotes cancer cell proliferation and inhibits apoptosis [3]. In the early days, scholars believed that miR-184 may be a potential oncogene in tongue squamous cell carcinoma cells. They found overexpression of miR-184 in 20 cases of tongue squamous cell carcinoma and normal tissues. After inhibiting miR-184 expression, the proliferation of tongue squamous cell carcinoma cells also decreased [4]. In recent years, Yan [5] found that overexpression of miR-183 can be detected in SCC25, and miR-183 inhibitors can reduce the growth and colony formation of SCC25, while significantly increasing its apoptosis. Cyclin dependent kinase (CDK) is the core of the cell cycle regulatory network, responsible for the initiation, progression, and termination of the cycle. The cell cycle regulatory protein (cyclin) has a positive regulatory effect on CDK, while the cell cycle dependent kinase inhibitor (CKI) has a negative regulatory effect. Liu [6] found that high expression of miR-24 can promote proliferation and inhibit apoptosis of tongue squamous cell carcinoma cells. The mechanism is that miR-24 targets the RNA binding protein DND1 and inhibits the expression of CDKN1B.

MircoRNAs also inhibit the proliferation of tongue squamous cell carcinoma cells and promote their apoptosis. In the MircoRNAs family, some members can inhibit the proliferation of tongue squamous cell carcinoma while promoting its apoptosis. Early in vitro studies have found that overexpression of miR-133a and miR-133b in Tca8113 leads to a significant decrease in cell proliferation [7]. Jia [8] found through in vitro and in vivo experiments that miR-195, miR-34a, miR-26a, miR-29b, and miR-375 were significantly downregulated in tongue squamous cell carcinoma tissues. Overexpression of the aforementioned MircoRNAs in tongue squamous cell carcinoma cells slowed down cell proliferation and increased apoptosis. Research has confirmed that the mechanism by which

MircoRNAs inhibit the proliferation of tongue squamous cell carcinoma cells is that they can target and regulate the expression of cell cycle related molecules. For example, miR-375 can inhibit the expression of transcription factor Sp1, and downregulation of Sp1 expression can lead to downregulation of cyclinD1, thereby inhibiting cell division; MiR-25-3p can regulate the upregulation of cell cycle related proteins p21cip1 and p27kip1 expression, downregulation of cyclinD1, AKT, and FOXO1 expression, and inactivation of AKT and FOXO1 phosphorylation, resulting in significantly reduced cell proliferation after transfection; MiR-509 regulates the expression of EGFR and can inhibit the proliferation of tongue squamous cell carcinoma cells in vitro; MiR-7 targets IGF1R, and overexpression of miR-7 significantly reduces IGF1R at both mRNA and protein levels, leading to cell cycle arrest and increased apoptosis [9] [10] [11] [12].

Invasion and metastasis are another major biological feature of malignant tumors, often determining tumor staging and patient prognosis, and are difficult and key points for control and treatment. MicroRNAs promote invasion and metastasis of tongue squamous cell carcinoma cells. Research confirms that abnormal activation of the Wnt/β-catenin signaling pathway is related to the tumors. After activation, it can cause epithelial mesenchymal transition (EMT). Through EMT, epithelial cells lose cell polarity, lose connection with the basement membrane, and other epithelial phenotypes, resulting in higher migration and invasion, anti-apoptosis, and degradation of the extracellular matrix. In vitro experiments have found that high expression of miR-21, miR-373-3p, and miR-362-5p can be detected in tongue squamous cell carcinoma cell lines, and Wnt/β-catenin signal is overactivated, causing EMT and thereby enhancing the invasive ability of tongue squamous cell carcinoma [13] [14] [15].

On the other hand microRNAs inhibit the invasion and metastasis of tongue squamous cell carcinoma cells. Identifying molecular targets that inhibit the invasion and metastasis of tongue squamous cell carcinoma can serve as an important means of treating tumors. Research has found that miR-138 can regulate the expression of Rho GTPase and ROCK2 in the Rho GTPase pathway, thereby inhibiting the degradation of extracellular matrix [16]. MiR-802 can inhibit the expression of MAP2K4, thereby inhibiting tumor formation and metastasis [17]. MiR-299-3p can downregulate TRIM27 expression [18]. Overexpression of miR-34a can target the coding region and the 3 untranslated region, inhibiting the expression of MMP9 and MMP14 [19]. MiR-143-3p inhibits tumor growth and in vitro metastasis by targeting HMGA2 [20]. MicroRNAs can also affect the invasion and metastasis of tongue squamous cell carcinoma by regulating EMT. Overexpression of miR-488 can significantly inhibit EMT and invasion of tongue squamous cell carcinoma cells, while knocking out miR-488 promotes these two processes [21]. MiR-296-3p regulates EMT by targeting negative regulation of NUPR1 expression [22]. MiR-200c regulates EMT by targeting ZEB1 [23]. Low expression of miR-639 affects TGF-β. The mechanism of inducing EMT in tongue squamous cell carcinoma by targeting FOXC1 and inhibiting the inva-

sion and metastasis of tongue squamous cell carcinoma [24].

3. MicroRNAs Affect the Sensitivity of Tongue Squamous Cell Carcinoma to Radiotherapy and Chemotherapy

MicroRNAs affect radiotherapy sensitivity. Trachostatin A (TSA) is a histone deacetylase inhibitor used as an anticancer and radiosensitizer in various cancers. Jia [25] found that TSA has a promoting effect on the expression of miR-375. After overexpression of miR-375 in tongue squamous cell carcinoma cells, TSA increases the histone acetylation state of the miR-375 promoter region, causing upregulation of miR-375, leading to a decrease in 3-phosphoinositol dependent protein kinase 1 (PDK1) and phosphorylated protein kinase B (AKT).

MicroRNAs weaken chemotherapy resistance in tongue squamous cell carcinoma cells. Drug tolerance is the biggest obstacle to chemotherapy in cancer patients, often the main cause of clinical treatment failure, resulting in tumor patients becoming less sensitive to drug treatment and leading to recurrence. Research has found that miR-200c derived from exosomes can weaken the chemical resistance of docetaxel in tongue squamous cell carcinoma [26]. MicroRNAs weaken cisplatin resistance through different mechanisms of action, such as miR-5787 inhibiting the translation of mitochondrial cytochrome C oxidase III (MT-CO3), thereby inhibiting mitochondrial activity [27]. MiR-22 enhances the apoptotic response of tongue squamous cell carcinoma cells to cisplatin [28]. MiR-590 inhibits the expression of FasL in SCC-3, blocks immune escape of tumor cells, and reduces cisplatin resistance in SCC-3 [29]. MiR-181a can inhibit cisplatin induced EMT in tongue squamous cell carcinoma cell lines, thereby weakening their drug resistance [30].

MicroRNAs enhance chemotherapy resistance of tongue squamous cell carcinoma cells. Research has found that miR-17 enhances chemotherapy resistance in tongue squamous cell carcinoma cells through two pathways. One is that miR-17 positively regulates the STAT3 signaling pathway, inhibiting cell apoptosis and autophagy. The other is that miR-17 can weaken the expression of pro apoptotic proteins Bax and Mcl-1 in oral cancer cells induced by oxaliplatin, enhance the expression of anti apoptotic protein Bcl-2, and thus inhibit apoptosis in tongue squamous cell carcinoma cells [31]. MiR-21 is highly expressed in tongue squamous cell carcinoma tissue, promoting the proliferation and migration of tongue squamous cell carcinoma cells. Similarly, high expression of miR-21 can enhance the chemotherapy resistance of tongue squamous cell carcinoma cells. The mechanism is that miR-21 directly targets CADM1 expression, enhancing the adhesion between cancer cells [32]. Peng [33] found that miR-23a induces Twist expression through a JNK dependent mechanism, promotes cancer cell metastasis, and produces chemical resistance. The latest research has found that changes in mitochondrial dynamic related protein function are closely related to cisplatin resistance. For example, miR-593-5p can inhibit the translation of MFF, weaken mitochondrial division, and sensitivity to cisplatin

[34]. MiR-483-5p inhibits mitochondrial fission and cisplatin sensitivity by targeting mitochondrial fission protein 1 (FIS1) [35]. In addition, Lin [36] screened differentially expressed mitochondrial microRNAs (mitomiRs) in cisplatin resistant and sensitive tongue squamous cell carcinoma cells. High expression mitomiRs may play an important role in chemotherapy resistance in tongue squamous cell carcinoma.

4. MicroRNAs Affect Clinical Staging and Prognosis of Tongue Squamous Cell Carcinoma

The clinical staging of tongue squamous cell carcinoma is a significant factor affecting its prognosis and is currently the main basis for selecting treatment options in clinical practice. Research has found that the expression levels of miR-125b and miR-183 are not correlated with age, gender, pathological grade, and lymph node metastasis, but are significantly correlated with TNM staging. Patients with high expression of miR-125b and miR-183 have significantly shortened overall survival and increased risk of poor prognosis [37] [38]. Jia [8] found that low expression of miR-195, combined with low expression of miR-26a and MEG3, is an independent prognostic factor for poor clinical prognosis in tongue squamous cell carcinoma patients. Cai [39] found that the median survival time of patients with high expression of miRNA-31 was 37 months, while the median survival time of patients with low expression was 65 months, which was negatively correlated with survival time. Zhang Wei [40] found that the five-year survival rate of patients with low expression of miR-15b was only 21.4%, and the median survival period was only 18 months. The five-year survival rate of patients with high expression of miR-15b was 43.3%, with a median survival of only 36 months.

5. MicroRNAs Can Serve as Early Diagnostic Markers and Potential Therapeutic Targets for Tongue Squamous Cell Carcinoma

When tumors are in different stages and stages, MicroRNAs have certain characteristic expression profiles, making them recognized diagnostic and prognostic markers as well as potential therapeutic targets. The abnormally high expression of miR-21 has been confirmed to have a carcinogenic effect in tongue tissue [38]. Scholars such as Wong *et al.* [4] discovered early that plasma miR-184 levels were associated with the presence of primary tumors in tongue squamous cell carcinoma through plasma testing. To determine the expression characteristics of saliva microRNAs in tongue squamous cell carcinoma patients, Duz [41] found significant differences in miR-139-5p expression among tongue cancer patients before and after surgery, as well as normal individuals, through microarray analysis. The above research suggests that miR-21, miR-184, and miR-139-5p can serve as early screening indicators in high-risk populations for tongue squamous cell carcinoma, such as smoking, drinking alcohol, and chewing betel nuts.

6. Outlook

Tongue squamous cell carcinoma, as the most common malignant tumor in the head and neck, has a very complex pathogenesis. With the unremitting efforts of scientists and the continuous updates of experimental conditions and technical methods, scholars have found that microRNAs play a crucial role in the occurrence, development, diagnosis, treatment, and prognosis of tongue squamous cell carcinoma and other cancers. In theory, any key microRNAs molecule can become a potential target, but there are still some issues that require continuous research and summary by industry scholars. How to use microRNAs to reduce chemotherapy resistance in tongue squamous cell carcinoma? What technological means are microRNAs used for targeted therapy? We look forward to more and better research to help clinical doctors diagnose and treat tongue squamous cell carcinoma better, and improve the quality of life of patients.

Conflicts of Interest

No other author has reported a potential conflict of interest relevant to this article.

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