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Role of MiRNAs in Oral Cancer

Tingting Jia[1], Li Wang[2], Rui Zhao[1], Liang Zhu[1], Lejun Xing[1] and Bin Guo[1]*

[1]*Department of stomatology, Medical College of People's Liberation Army & Chinese People's Liberation Army General Hospital, China*

[2]*Department of Stomatology, Hangzhou Dental Hospital, China*

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***Corresponding author:** Bin Guo, Department of stomatology, Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China, Tel: 86-10-66937964; Fax: 86-10-68223575; Email: 479002797@qq.com

Abstract

Oral cancer, one of the most common cancers worldwide, exhibits high mortality and morbidity rates. The incidence rate of oral cancer is high in developing countries, especially in Asian countries. MiRNAs are non-coding RNAs with significant regulatory functions, such as mRNA degradation or translation inhibition. Understanding of the tumorigenesis of oral cancer has significantly progressed at multiple levels. MiRNAs play an important role in oral tumors and have been associated with specific oral cancer phenotypes, such as tumorigenesis, progression, recurrence, or postoperative survival. MiRNAs exist stably in common body fluids and are thus ideal biomarkers for oral cancer. The miRNA profiles hallmark a potential diagnostic value for detection of oral cancer and potentially malignant disorders. In this review, we will summarize our current knowledge regarding the most active miRNAs involved in oral cancer, focusing our discussion on their role in tumor diagnosis, development, and progression.

Keywords: MiRNAs; Oral cancer; Tumorigenesis; Biomarker; Diagnosis; Prognosis

Introduction

Oral cancer, also known as "oral cavity cancer," is the sixth most common cancer worldwide and has high mortality and morbidity rates. Oral squamous cell carcinoma is the most common type, accounting for approximately 90% of oral cancers [1]. The 5-year survival rate of oral cancer is approximately 50%, and more than 11,000 deaths are recorded annually [2]. Approximately 500,000 individuals are diagnosed annually worldwide, and the incidence rate continuously increases [3]. Oral cancer is prevalent in developing countries, especially in South Asia [2]. Oral cancer is significantly caused by environmental carcinogens, particularly smoking, alcohol, and betel quid chewing [4]. Patients with oral cancer experience poor quality of life because of the side effects of clinical treatments and cosmetic problems. Oral cancer is a multi-step disease, but its precise mechanism remains unknown [5]. Therefore, the pathogenesis of oral cancer and its earlier biomarkers must be further explored.

MiRNAs are non-coding RNAs with approximately 17 to 25 nucleotides in length [6]. The biogenesis of miRNAs begins with transcription of pri-miRNAs by RNA polymerase II. Pri-miRNAs are then cleaved by Drosha in the nucleus, producing pre-miRNAs [6,7]. Pre-miRNAs are subsequently exported into the cytoplasm and processed by Dicer to form mature ~21bp miRNAs, which are incorporated into RNA-induced silencing complex [6,8]. Mature miRNAs bind to complementary sequences of conserved 3′untranslated regions (UTRs), repressing translation and promoting degradation of target genes (Figure 1) [6,9-11].

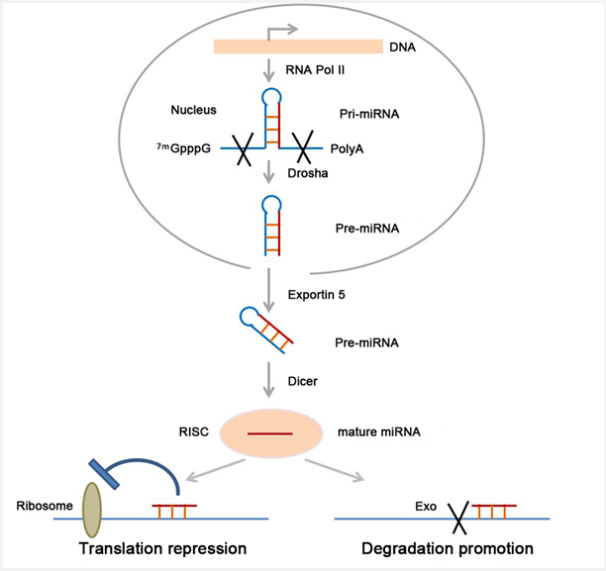

Figure 1: The biogenesis process of miRNA.

In recent decades, miRNAs have been regarded as important factors for tumorigenesis [5,12]. Evidence suggests that miRNAs function as either tumor suppressors or oncogenes [13,14].

MiRNAs are differentially expressed in distinct tumors and involved in important tumor-related cellular programs, such as cell proliferation, cell survival, cell differentiation, anti-angiogenesis, invasion, or metastasis [15].

Functional MiRNAs in Oral Cancer

Many studies reported that miRNAs are associated with specific oral cancer phenotypes, such as tumorigenesis, progression, recurrence, or postoperative survival [5,16]. In this review, we summarize commonly known miRNAs related to oral cancer and discuss their biological functions or cellular mechanisms [5] (Table 1). In addition, the stable existence of miRNAs in common body fluids makes them ideal biomarkers for diagnosis or prognosis of oral cancer.

Table 1: miRNAs involved in oral cancer.

Expression in Oral Cancer	miRNA	Target Genes	Cellular Function
Up-regulated	miR-7	RECK	metastasis
	miR-21	RECK, PDCD4	chemoresistance
	miR-146a	IRAK1, TRAF6, NUMB	metastasis
	miR-155	CDC73	apoptosis
	miR-196	NME4	proliferation
	miR-518c-5p	unknown	apoptosis
	Let-7b	Dicer, IGF1R	proliferation
	miR-99a	IGF1R	apoptosis
	miR-100	ID1, EGR2, MMP13, FGFR3	proliferation
Down-regulated	miR-125b	KLF13, CXCL11, FOXA1, ICAM2	proliferation
	miR-145	c-Myc, Cdk6	proliferation
	miR-205	IL-24	apoptosis
	miR-483-3p	API5, RAN, BIRC5	apoptosis

Let-7b

Let-7b miRNA, one of the first discovered miRNAs, is a key regulator for cell proliferation and differentiation [17,18]. Let-7b miRNA is found in many cancers, including colon, pancreatic endocrine, acinar tumors, and pancreatic adenocarcinoma [19]. Andrew et al. [20] found that let-7b, but not let-7a, was significantly reduced in oral cancer cell lines compared with control cells. Over-expression of let-7b significantly reduced the expression of its target gene Dicer, which is an RNase III endonuclease required for miRNA maturation and aberrantly expressed in different types of cancer [20]. Another study found that let-7b also targets insulin-like growth factor 1 receptor (IGF1R), which is activated by IGF1 or IGF2 through autocrine and paracrine signaling. Let-7b inhibits cell proliferation and colony formation and triggers S/G2 cell cycle arrest by targeting IGF1R and IRS-2 through the Akt pathway [1]. Hence, let-7b down-regulation contributes to oral cancer progression. Over-expressing let-7b could be a potential therapy target for inhibition of cancer cell proliferation.

miR-7/miR-21

MiR-7 and miR-21 are two keratinization-associated miRNAs that are up-regulated in keratinized tumors compared with normal or non-keratinized tumors [21]. Jung et al. [22] found that miR-7 and miR-21 are up-regulated; in silico analysis results indicated that RECK is the optimal candidate target gene for miR-7 and miR-21. RECK plays crucial roles for tumor progression by degrading the extracellular matrix barriers, encompassing the tumor and permitting invasion into surrounding connective tissues. In oral cancer cells, miR-7 and miR-21 are inversely correlated with the expression of RECK [22]. Patricia et al. [23] also found that miR-21 is up-regulated in oral cancer; this study revealed that miR-21 directly binds to the 3'UTR of PDCD4, which is associated with disease progression and metastasis [23]. Further study showed that the expression of miR-21 is the major factor related to the poor prognosis of patients with oral cancer [24]. Overall, miR-7/miR-21-induced deregulation of RECK may contribute to the aggressiveness of tumors.

miR-99a

MiR-99a is characterized as tumor suppressor in several human cancers, including childhood adrenocortical tumors, prostate cancer, liver cancer, head and neck cancer, and oral cancer [25-27]. MiR-99a is one of the most down-regulated miRNAs in oral cancer cell lines compared with normal oral keratinocytes. Transwell and tail vein injection assays indicated that miR-99a functions in tumor migration/invasion and lung colonization. Moreover, target prediction and real-time PCR assay validated that IGF1R is the target gene of miR-99a, which is a transmembrane tyrosine kinase receptor [28]. The expression of miR-99a is negatively correlated with the expression of IGF1R in oral cancer cells. Activation of IGF1R leads to activation of the Ras, Raf, and mitogen-activated protein kinase pathway and thus enhances the proliferation and stimulation of the phosphatidylinositol 3-kinase pathway, resulting in apoptosis inhibition [29]. Collectively, miR-99a mutually regulates its own target, IGF1R, suggesting the possibility of miR-99a for targeting IGF1R in cancer therapy.

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miR-100

MiR-100 is down-regulated in many cancers, including ovarian cancer and hepatocellular carcinomas [30,31]. Genetic aberrations are common in oral cancer, and chromosome 11q is among the most common alterations [32,33]. Brian et al. [34] examined the expression of miRNAs mapped to 11q in oral cancer cell lines compared with normal human oral keratinocytes (NHOK); results indicated that mir-100 is down-regulated in oral cancer cells. Cell proliferation is significantly reduced when exogenous miR-100 is over-expressed. Microarray analysis data revealed that over-expression of exogenous miR-100 down-regulated a number of target genes including ID1, EGR2, MMP13, and FGFR3; these genes are involved in cell metastasis, myelin development, cell adhesion, and cell growth, respectively. In conclusion, miR-100 inhibits cell proliferation by targeting several key genes involved in cancer and plays an important role in the development and progression of oral cancer [34].

miR-125

MiR-125b is also located in chromosome 11q and involved in important cellular processes, especially in neuronal development and differentiation [33]. The alteration of miR-125b occurs in many cancers, including ovarian cancer, breast cancer, and prostate cancer [35,36]. Consistent with miR-100, miR-125b is also down-regulated in oral cancer cell lines. Over-expression of exogenous miR-125b significantly reduces cell proliferation. In oral cancer, miR-125b regulates the expression of key factors involved in tumorigenesis; these factors include KLF13, CXCL11, and FOXA1. All these target genes have important chemokines and transcription factors, which have crucial biological functions in cell growth, cell proliferation and differentiation, inflammation, angiogenesis, and metastasis [31,34]. Shiiba et al. [16] also found that miR-125b is down-regulated in oral cancer cell lines, resulting in increased cell proliferation rate and decreased radio-sensitivity to X-ray irradiation; this study reported a new target of miR-125b, namely, ICAM2, which is involved in cell proliferation [16]. All these lines of evidence suggest that miR-125b contributes to the development and progression of oral cancer by regulating important target genes. Thus, understanding of miR-125b increases our knowledge of the molecular mechanisms underlying oral cancer. Furthermore, miR-125b may be a potential therapeutic target for oral cancer.

miR-145

MiR-145 acts a tumor suppressor in numerous human cancers, including prostate cancer, bladder cancer, and colon cancer [37-39]. A study found that miR-145 is down-regulated in oral cancer tissues compared with normal mucosa tissues. Exogenous over-expression of miR-145 induced G1 phase arrest and cell apoptosis, which then suppressed cell proliferation and colony formation. The two direct targets of miR-145 are c-Myc and Cdk6, which are important oncogenes. In oral cancer cells, miR-145 also targets c-Myc and Cdk6, leading to inhibition of oral cancer cell growth [40]. Thus, miR-145 rescue may be a rationale for diagnostic and therapeutic applications in oral cancer.

miR-146a

MiR-146a is suppressed in many malignancies [41] but has been recently identified to be up-regulated in oral cancer [42]. Hung et al. [43] found that miR-146a exhibits higher expression in oral cancer than matched adjacent mucosal cells. Inhibition of miR-146a significantly blocks the growth of xenograft tumors. miR-146a directly targets IRAK1, TRAF6, and NUMB, thereby enhancing cell proliferation, invasion, and metastasis. The plasma miR-146a levels of patients with oral cancer are significantly higher than those of control subjects; hence, miR-146a could be a potential biomarker for diagnosis of oral cancer [43].

miR-155

MiR-155 is overexpressed in many human cancers, including lymphoma and solid tumors of diverse origin (e.g., breast, lung, stomach, prostrate, colon, thyroid, and pancreatic) [14,44,45]. MiR-155 is also up-regulated in oral cancer [46]. In oral cancer, miR-155 targets CDC73, which negatively regulates β-catenin, cyclin D1, and c-MYC. Ectopic expression of miR-155 dramatically reduced CDC73 levels, increased cell viability, and decreased apoptosis in nude mice. Conversely, inhibiting miR-155 resulted in increased CDC73 levels, decreased cell viability, and increased apoptosis. Hence, the tumor suppressor CDC73 is a target of oncogenic miR-155 [47]. Furthermore, the reversal of pro-oncogenic properties of miR-155 due to its inhibitor is a promising method for cancer therapeutics [47].

miR-196

MiR-196 is an active molecule and is altered in several cancers. Studies stated that miR-196 is down-regulated in melanoma and acute lymphoblastic leukemia [48]. However, other scholars reported that miR-196 is up-regulated in several malignant diseases, including esophageal cancer, pancreatic cancer, colorectal cancer, and glioblastoma [49]. Lu et al. [50] examined the expression of miR-196 in oral cancer cell lines and normal keratinocyte cell lines; results indicated that miR-196 is highly up-regulated in oral cancer cells. In vitro experiments showed that miR-196 is responsible for cell growth, migration, invasion, and radio/chemosensitivity. Target prediction and subsequent validation experiments identified that miR-196 targets NME4, a member of the NM23 family. NME4 then regulates the downstream JNK-TIMP1-MMP signaling pathway, which plays an important role in cell mobility [50]. In conclusion, miR-196 promotes invasive and migratory phenotypes in oral cancer by targeting NME4, leading to the regulation of the downstream JNK-TIMP1-MMP signaling pathway [51].

miR-205

Various studies examined the biological functions of microRNA-205 (miR-205) as a tumor suppressor in carcinogenesis [52]. Kim et al. [53] found that miR-205 is

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significantly down-regulated in human oral cancer compared with NHOKs. Reduced miR-205 expression in oral cancer cells might be important for oral cancer progression. Over-expressing exogenous miR-205 reduced cell viability in oral cancer cells and induced cell apoptosis by activating caspase-3/-7. In addition to caspase-3/-7, over-expressed miR-205 significantly promotes the expression of IL-24, a well-known cytokine that functions in cell apoptosis. IL-24 promoter scanning analysis revealed a potential binding sequence located at position-151 in the IL-24 promoter. miR-205 interacts directly with the promoter target sequence of IL-24 [53]. Some studies stated that miRNA can up-regulate the expression of their own target genes through an interaction with the regulatory region [54,55]. These findings indicate that miR-205 functions as a tumor suppressor in up-regulating IL-24 by targeting specific sites in its promoter. Thus, miR-205 exhibits a significant therapeutic potential as molecular medicine for treatment of oral cancer.

miR-483-3p

MiR-483-3p is involved in the final stage of skin wound healing and arrest of keratinocyte proliferation [56]. MiR-483-3p is down-regulated in oral cancer cells. Over-expressing miR-483-3p significantly hinders tumor growth. Target prediction analysis and validation experiments revealed that miR-483-3p targets API5, RAN, and BIRC5, which play a main role in cell apoptosis. MiR-483-3p exhibits its pro-apoptotic activity by binding to these target genes, leading to inhibition of cell proliferation and increase in cell apoptosis [57]. Hence, miR-483-3p may be used as an adjuvant in many cancers characterized by down-regulation of miR-483-3p.

miR-518c-5p

MiR-518c-5p belongs to the miR-515 family and is located in chromosome 19. MiR-518c-5p is originally identified in 26 different organ systems of humans and rodents and is enriched in neuronal as well as normal and malignant hematopoietic cells and tissues [58]. However, the function of miR-518c-5p in cancers remains unclear. Makoto et al. [59] found that SDF-1/CXCR4 system is involved in the establishment of metastasis in oral cancer. Subsequent examination showed that miR-518c-5p is induced and exhibits distant metastatic potential. When inhibiting the function of miR-518c-5p by using LNA-modified inhibitors, the cell growth and migration of oral cells are reduced significantly. Consistently, over-expression of miR-518c-5p enhances the migration of oral cancers. An in vivo experiment indicated that exogenous miR-518c-5p significantly increased the tumor volume, lymph node metastasis, and lung metastasis in mice. The miR-518c-5p inhibitor may serve as an ideal target for development of therapies against metastasis [59]. However, the target genes of miR-518c-5p remain unknown. Future studies must critically examine the target genes of miR-518c-5p in oral cancer.

Biomarker MiRNAs for Oral Cancer

Early detection of potentially malignant oral cancer is important for improving the probability of complete recovery because the stage of malignancy at the time of diagnosis influences morbidity and mortality [60]. However, more than 60% of patients present with stage III and IV oral cancer. As such, scholars must explore the most potential biomarkers for early detection of oral cancer (Table 2) [60].

Table 2: Biomarker miRNAs for oral cancer.

Sample Type	miRNA	Clinical Use
Tissue	a group of 61 miRNAs	diagnosis
	let-7g, miR-21, miR-126, miR-218, miR-125b	prognosis
Plasma	miR-10b, miR-31, miR-184	diagnosis
Saliva	miR-125a, miR-200a, miR-10b, miR-145, miR-99b, miR-708, miR-181c, miR-375	diagnosis

Lajer et al. [61] compared 51 patients with oral cancer with 40 control patients by using microarray analysis and found 114 differentially expressed miRNAs. A molecular classifier including 61 miRNAs was generated for diagnosis of oral cancer; this classifier exhibits 93% accuracy, 100% sensitivity, and 86% specificity [61].

Peng et al. [62] examined the profile of miRNA from 58 oral cancer samples and paired normal tissues through microarray assay. A total of 232 of the 760 miRNAs assessed were differentially expressed between paired tumor and normal tissue samples. Among the 232 miRNAs, the reduced expression of miR-218, miR-125b, and let-7g is associated with high risk of poor outcomes [62]. MiR-21 is a common biomarker for many cancers. A previous study on 86 patients with oral cancer revealed that miR-21 was primarily expressed in the tumor stroma but was not expressed in the adjacent normal epithelia. Multivariate Cox-regression analysis of disease-free survival revealed that miR-21 expression level was significantly associated with poor prognosis [63]. Sasahira et al. [64] found that decreased miR-126 expression was strongly correlated with disease-free survival in 118 cases with oral cancer. Another multivariate analysis of patients with oral cancer indicated that a poor prognosis was associated with low miR-126 expression compared with high miR-126 expression (P=0.0013) [64].

Circulating Biomarker MiRNAs for Oral Cancer

Some biological molecules are present in body fluids, such as plasma and saliva, and are ideal noninvasive biomarkers for oral cancer [65]. Previous studies used protein, mRNA, and DNA extracted from body fluids to detect oral cancer. Analysis using transcriptomic and proteomic technology discovered and

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validated mRNA and protein salivary biomarkers, respectively, to be highly discriminatory for oral cancer detection. Plasmic and salivary miRNAs are protected from ribonucleases present in the plasma/saliva by macromolecules called exosomes, which are known to package and transport miRNAs [65-67]. The presence of miRNAs in human body fluids, especially in saliva, is an emerging field for monitoring oral diseases.

Liu et al. [68] identified that miR-31 in plasma was significantly elevated in patients with oral cancer (n = 43) compared with control individuals (n = 21). Plasma miR-31 yielded a receiver operating characteristic curve area of 0.82 and an accuracy of 0.72 defined by leave-one-out cross-validation [68].

Wong et al. [69] profiled the expression of 156 miRNAs on four oral cancer and paired normal tissues, revealing 37 differentially expressed miRNAs (three-fold). Among the 37 miRNAs, miR-184 was further examined in the plasma from 20 patients with oral cancer and normal individuals. Plasma miR-184 level was significantly higher in patients with oral cancer and s, and significantly decreased after surgical removal of the primary tumors [69]. Lu et al. [70] found that miR-10b was considerably elevated in the plasma of patients with oral cancer [$P < 0.0001$, area under curve (AUC) = 0.932] and pre-cancer lesions ($P < 0.0001$, AUC = 0.967); hence, miR-10b could be a potential early diagnostic biomarker for oral cancer [70].

Park et al. [66] examined and compared the expression of approximately 50 miRNAs in whole saliva and saliva supernatant between patients with oral cancer and healthy controls. Two saliva miRNAs, namely, miR-125a and miR-200a, were present in significantly lower levels ($P<0.05$) in the patients than that in the controls [66]. Yang et al. [71] first examined the profile of saliva miRNAs in 10 patients who developed carcinoma and 35 patients who did not develop oral cancer; results indicated that miR-10b, miR-145, miR-99b, miR-708 and miR-181c were significantly differentially expressed [71]. Wiklund et al. [72] used TaqMan RT-PCR arrays to profile miRNA expression in saliva from 15 patients with oral cancer and 7 healthy controls; the results showed that miR-375 was down-regulated in the patients and thus could be used to diagnose oral cancer [72].

Conclusion

Oral cancer is the sixth most common cancer worldwide and has high mortality and morbidity rates. Understanding the tumorigenesis and development of oral cancer has significantly progressed. The expression of many miRNAs is altered in oral cancer, thereby regulating cell growth, cell proliferation and apoptosis, invasion, and metastasis. Accumulating evidence highlights that circulating miRNAs are significantly associated with oral cancer and thus could be used as potential biomarkers for diagnosis and prognosis of oral cancer [73-75]. However, the highly stability makes miRNA ideal biomarkers for non-invasion detection. Further work is required to elucidate the complete regulatory mechanisms of miRNAs. The clinical use of miRNA as biomarkers needs more tests and more patients to validate the most potential markers.

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