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Prospective applications of microRNAs in oral cancer (Review)

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Abstract. MicroRNAs (miRNAs) are non-coding RNA molecules that are generally encoded by endogenous genes and exert suppressive effects on post-transcriptional regulation of their target genes by translation repression or degradation of mRNA. This subsequently mediates activation or blocking of downstream signaling pathways associated with oral malignancies. Aberrant levels of certain miRNAs have been identified in cell experiments, clinical carcinomatous specimens, saliva, serum or plasma samples of patients with oral malignancies. miRNAs are associated with multiple aspects of oral cancer, including tumor growth, cellular proliferation, apoptosis, migration, invasion, metastasis, glycometabolism, radiosensitivity and chemosensitivity. miRNAs have the potential to be used in clinical applications as minimally invasive or non-invasive tools for early diagnosis and prognosis by the detection of serum, plasma and saliva levels, and may provide a new ancillary or additional reference index of traditional pathological grading and clinical staging. Furthermore, miRNAs may be used as prognostic biomarkers or targets for novel therapies for oral cancer.

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1. Introduction

Oral cancer is a common and fatal malignancy among head and neck malignant neoplasms; the number of new cases of oral cancer globally was 354,864 in 2018 (1). At present, principal treatments of oral cancer include extensive exeresis of the primary carcinoma, with or without neck dissection, and pre- or postoperative adjuvant chemotherapy and radiotherapy (2). However, the overall 5-year survival rate of patients with oral cancer was 65%, and the overall 5-year survival rate of patients with advanced oral cancer was as low as 27% between 2007 and 2013 in the USA (3). Despite the application of reconstructive radical resection and postoperative radiotherapy or chemotherapy, the 5-year survival rate of patients with terminal oral cancer has not improved effectively over the past years (4-6). Furthermore, the dysphagia, maxillofacial malformation and dysarthria induced by the aforementioned therapies negatively affect the quality of life and psychology of patients (7). Therefore, there is a requirement to identify more effective treatment strategies to improve the survival rate and reduce complications of patients with oral cancer.

MicroRNAs (miRNAs/miRs) have attracted increasing attention over the past years as their roles in malignant tumors, where they regulate target genes and downstream signaling pathways, have been recognized (8). Non-coding RNA, composed of 18-22 nucleotides, silences corresponding target genes by binding to the 3'-untranslated regions (3'UTRs) of mRNA to mediate the biological behavior of cancer cells (9). Dysregulation of miRNA in hepatoma, lymphoma and colorectal, ovarian and pancreatic cancer has been previously reported (10-15). In oral carcinoma, miRNAs are associated with oral carcinomatous cell proliferation, apoptosis, invasion, metastasis, epithelial-mesenchymal transition (EMT), chemoresistance, radioresistance and cell cycle arrest. The abnormal expression of miRNA detected in tumor, serum and saliva samples obtained from patients with oral cancer has clinical significance in prognosis prediction and the development of effective treatments (16-19). The present review discusses recent developments with regard to miRNAs and their potential clinical applications in oral cancer.

2. Biogenesis and function of miRNA

The biogenesis of miRNA involves processes in the nucleus and cytoplasm. In the nucleus, primary miRNA (pri-miRNA), a type of miRNA that contains 300-1,000 nucleotides, is generally

issued from the miRNA gene and is transcribed by RNA polymerase II. Subsequently the long transcript, pri-miRNA, is cleaved by the drosha ribonuclease III (DROSHA)/DiGeorge syndrome chromosomal region 8 (DGCR8) complex into a ~70-nt structure termed precursor miRNA (pre-miRNA), which has lost a 7-methyl guanine nucleoside in the 5'-capped end and a 3'poly-(A) tail, but has a conserved stem-loop. Subsequently, the aforementioned stem-loop is sheared by RNA III enzyme Dicer and double-strand RNA-binding domain protein after the GTP-binding nuclear protein Ran/exportin-5 (RanGTP/XPO5) complex carries pre-miRNA to the cytoplasm, to form a double-strand miRNA molecule consisting of 22 nucleotides. Transactivation response element RNA binding protein (TRBP) recruits the mature miRNA to RNA-induced silencing complex (RISC) together with argonaute 2 (Ago2) that has endonuclease activity. A single strand of the double-strand miRNA is conserved in the RISC, and another one is degraded (20,21). Partial or complementary pairing between the RISC and the 3'-UTR of target mRNA functionally plays a role in repressing the translation of mRNA or degrading target mRNA (22,23). The mechanisms are presented in Figs. 1 and 2.

3. miRNAs in oncogenesis, diagnosis and prognosis of oral cancer

Previous studies suggested that common potentially malignant disorders and precancerous conditions, including oral leukoplakia (OL) and oral lichen planus (OLP), were correlated with aberrant miRNA, but the mechanism of malignant transformation by miRNA remains unclear (24,25). However, investigating unknown neoplastic transformations for precancerous lesions or conditions may provide novel insight into the mechanisms of tumorigenesis. In addition, the significant differential expression of miRNA between normal tissue, potential malignant disorders and oral cancerous specimens indicates that miRNA may be used as an independent prognostic marker (26,27). Ultimately, a minimally invasive or non-invasive method, such as the detection of miRNA in saliva or serum, may be applied in preoperative prediction and postoperative follow-up (28-30). Indeed, a number of recent studies demonstrated that the aberrant expression of different miRNAs, such as miR-195-5p, miR-375, miR-143, miR-26b, miR-155-5p and miR-483-5p, was associated with oral cancer (31-36). Therefore, miRNAs may have prognostic and diagnostic value in oral cancer and may serve as targets for novel therapeutic strategies.

Latent mechanism of tumorigenesis by miRNAs. Previous studies identified that the miR-31 expression level in oral potential malignant disorder (OPMD) is higher than that in normal oral mucosa, which is correlated with higher expression of vascular endothelial growth factor and lower expression of E-cadherin in OPMD. miR-31 expression was further upregulated in patients with recurrent OPMD and malignant transformation (37). Another previous study suggested that aberrant expression of miR-200c was associated with oral submucous fibrosis (OSF). The overexpression of miR-200c inhibited collagen gel contraction and migration and invasion of fibrotic buccal mucosal fibroblasts induced by arecoline via inhibition of zinc finger E-box binding homeobox 1 (ZEB1). Additionally, reverse transcription-quantitative PCR (RT-qPCR) analysis revealed that miR-200c was downregulated in 25 OSF samples compared with 25 normal mucosae (38). Brito *et al* (39) concluded that higher expression of miR-21 in OL was associated with increased mitotic figures, incremental nuclear/cytoplasmic ratio and hyperchromasia. Nylander *et al* (40) found that miR-21 was upregulated in 30 patients diagnosed with multifocal OLP compared with 10 healthy subjects, and in agreement, another study demonstrated that upregulation of miR-21 served a tumor-promoting role in oral cancer and upregulation of miR-21 was observed in 60 of 79 individuals with the disease (41). Aghbari *et al* (26) identified that miR-27b and miR-137 levels were downregulated in tissue and saliva samples of patients with OLP compared with those in normal controls. Among OLP subgroups, it was demonstrated that miR-137 exhibited the lowest expression level in the erosive type, suggesting that it serve as a biomarker for monitoring potential malignant transformation. The level of miR-375 in progressive lesions was significantly downregulated compared with that in non-progressive control lesions, and miR-375 expression was significantly downregulated in tissues following the transformation of premalignant lesions (including verrucous hyperplasia and verrucopapillary hyperkeratosis) into carcinoma, by comparison of premalignant lesions and oral carcinoma *in situ* (27). While only 2-3 and 0.4-2% of patients with OL and OLP, respectively, exhibit malignant transformation (42,43), further investigation of the roles of miR-21, miR-27b, miR-137, miR-200c and miR-375 may provide novel insights into pathways involved in the development of oral cancer.

Aberrant expression of miRNA in oral cancer tissues. Dysregulation of specific miRNAs has been previously reported in oral cancer. Wang *et al* (31) reported that miR-195-5p was significantly downregulated in 40 oral cancerous tissues compared with non-tumor tissues. Another study reported a distinct downregulation of miR-375 in 44 cancerous tissues compared with that in normal mucosae (32). Furthermore, a previous study revealed that miR-143 was downregulated in cancerous tissues compared with that in corresponding adjacent non-cancerous tissues in 81.6% (40/49) of patients (33). miR-802 was downregulated in 60.0% (12/20) of tongue squamous cell carcinoma (TSCC) cases compared with that in normal tissues (44). The expression levels of miR-137 (n=25) and miR-204-5p (n=52) were downregulated in oral cancer samples compared with those in matched normal tissues (45,46). Moreover, upregulation of specific miRNAs was observed in oral cancer tissues. Upregulation of miR-183 was identified in 68.3% (41/60) of TSCC tissues compared with adjacent non-cancerous tissues (47). The miR-373-3p expression level in oral cancerous tissues (n=63) was increased compared with that in adjacent non-cancerous tissues (48). The miR-155 expression level was upregulated in oral squamous cell carcinoma (OSCC) tissues (n=46) compared with that in normal oral mucosa, and the expression level was increased with increasing Tumor-Node-Metastasis (TNM) stage (49). miR-31, miR-182, miR-200a and miR-141 were significantly upregulated in cancerous tissues in 10 patients compared with adjacent non-cancerous tissues (50). The expression

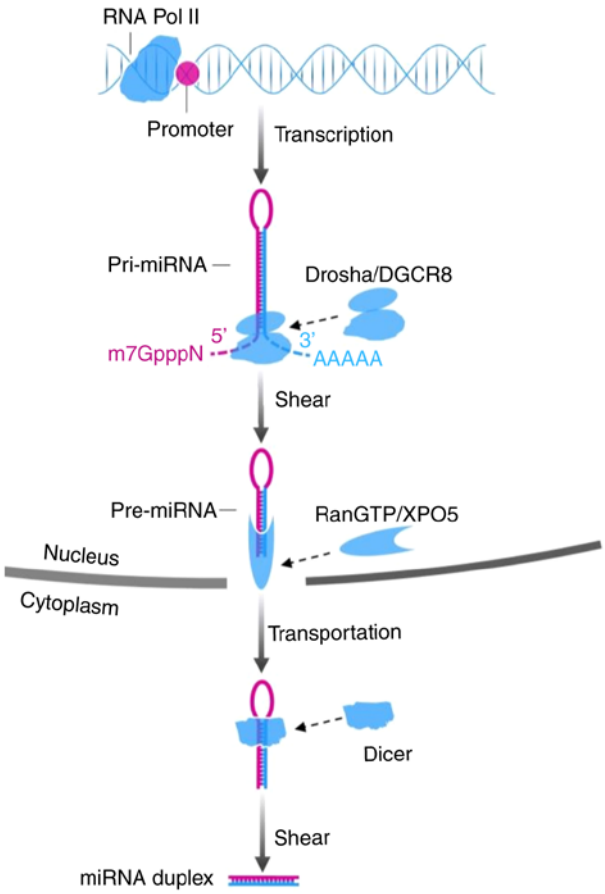

Figure 1. Biogenesis of miRNA. Pri-miRNA is transcribed by RNA Pol II. Drosha/DGCR8 shears the 7-methyl guanine nucleoside (m7GpppN) and 3'poly-(A) tail (AAAAA), which forms pre-miRNA. The RanGTP/XPO5 complex functions as a carrier for nucleocytoplasmic transport of pre-miRNA. miRNA duplex is generated after Dicer cleaves the stem-loop of pre-miRNA. miRNA, microRNA; pri-miRNA, primary miRNA; RNA Pol II, RNA polymerase II; pre-miRNA, precursor miRNA; DGCR8, Drosha/DiGeorge syndrome chromosomal region 8; RanGTP/XPO5, GTP-binding nuclear protein Ran/exportin-5.

of miR-24 was significantly increased in TSCC tissues of 84 patients compared with adjacent non-cancerous tissues (51). Liu *et al* (52) demonstrated that 67% (10/15) of patients with primary oral cancer had increased miR-1275 expression in tumor tissues compared with that in adjacent tissues.

Aberrant expression of miRNA in serum, plasma and saliva. Previous studies showed that RNA in saliva is protected from degradation by binding to macromolecules such as apoptotic bodies and RISC, a mechanism also observed in plasma and serum RNAs (53-55). Park *et al* (56) analyzed saliva by immunoblotting analysis using an antibody against Ago2, and demonstrated that Ago2 was present in saliva, where it may confer stability to miRNAs. Furthermore, Park *et al* (56) found lower levels of miR-125a and miR-200a in the saliva of patients with oral cancer (n=12) compared with those in healthy controls (n=12), suggesting that the aforementioned miRNAs may serve as stable biomarkers of the disease. Liu *et al* (28) reported that the level of miR-31 in the saliva of patients with OSCC (n=45) prior to surgery was significantly increased compared with that in healthy subjects (n=24). Moreover, the miR-31 level in saliva samples was higher compared with that in plasma samples. The upregulation of miR-31 was detected with high sensitivity even in very small tumors, and the ability to detect miR-31 levels in the saliva of patients with small tumors was not significantly different compared with patients with advanced tumors, suggesting that salivary miR-31 may be utilized to detect and diagnose oral cancer lesions in high-risk populations. Zahran *et al* (29) reported a significant upregulation in salivary miR-21 and miR-184 levels in patients with oral cancer compared with those in healthy controls. Specifically, a four-fold increase in miR-21, with 65% specificity and 65% sensitivity, and a three-fold increase in miR-184, with 75% specificity and 80% sensitivity, were observed. The expression of salivary miR-145 was significantly decreased in patients with OSCC compared with clinically healthy controls, with 70% specificity and 60% sensitivity. Ries *et al* (30) reported that miR-3651 and miR-494 levels were upregulated, while the miR-186 level was significantly downregulated in whole blood samples of patients with recurrent tumors compared with non-recurrent controls. Therefore, miRNAs may be promising candidates for the development of diagnostic tools for oral cancer.

miRNAs as feasible biomarkers of pathology, metastasis and prognosis. Certain miRNAs are known to be downregulated in tumor tissues compared with noncancerous tissues. Lower levels of miR-195-5p were associated with higher pathological differentiation grade (31). In comparison with patients without lymph node metastases (n=26), patients with lymph node metastases (n=18) had significantly downregulated miR-375. Furthermore, the overall survival of patients with oral cancer with low miR-375 expression (n=19) was lower than that of patients with high miR-375 expression (n=25) (32). Cao *et al* (34) revealed that advanced clinical stage and large tumor size of oral cancer were associated with low miR-26b expression. The 5-year survival rates of patients with low and high miR-26b levels were 26.7 and 53.3%, respectively.

On the other hand, certain miRNAs are upregulated in tumor tissues compared with adjacent non-cancerous tissues. Upregulation of miR-183 in patients with oral cancer markedly shortened the overall survival time and increased the risk of poor prognosis by 5.666 times. Upregulation of miR-21 resulted in a higher risk of short survival time (47). The expression of miR-373-3p was higher in primary tumors with metastases compared with that in tumors with no metastases (48). The upregulation of miR-24 was associated with advanced clinical stage in patients with oral cancer (51). A positive correlation between a high miR-155-5p level and cervical lymphatic metastases was observed, and the survival analysis of carcinomatous recurrence and metastasis identified an association between high miR-155-5p expression and a poor survival rate (n=73); miRNA-155-5p may be considered as a specific factor resulting in a worse prognosis (35).

Serum miR-483-5p was higher in patients with oral cancer (n=101) compared with healthy controls (n=103); the survival rates of patients with high miR-483-5p serum level (n=43; >3.23-fold higher compared with healthy controls) were decreased compared with that of patients with lower miR-483-5p serum levels (n=42; <3.23-fold higher compared with healthy controls), and multivariate analyses for overall

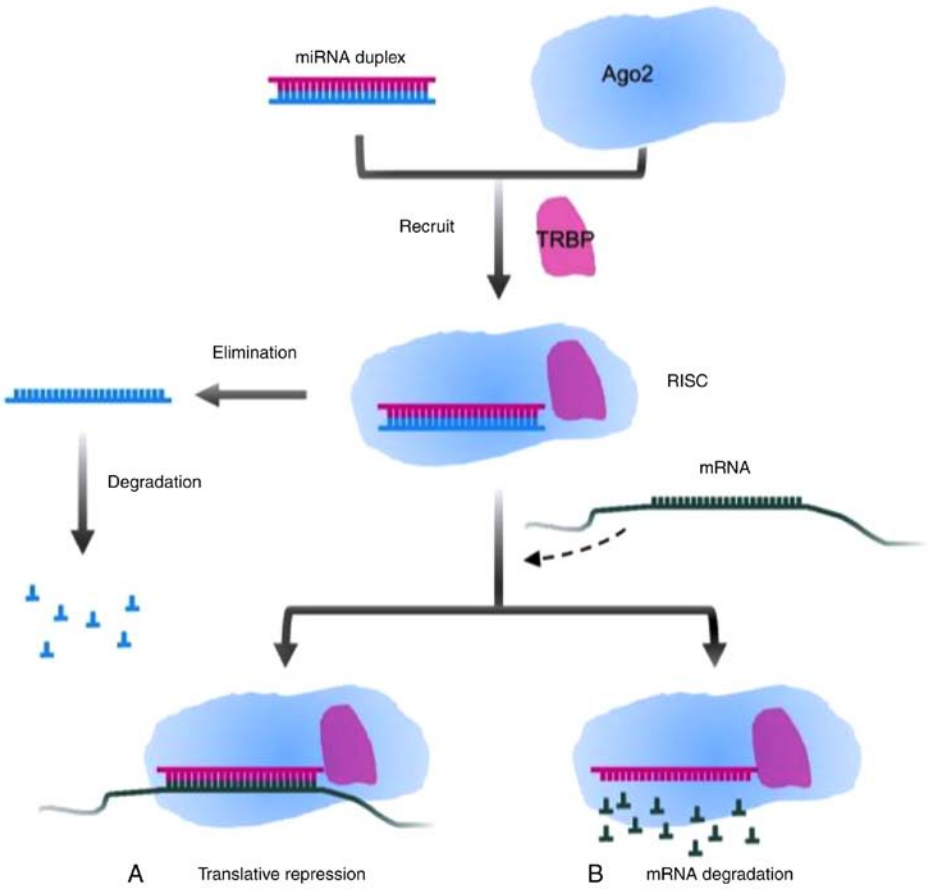

Figure 2. Modulatory mode of miRNA and target mRNA. TRBP recruits the miRNA duplex and Ago2, forming RISC. One strand of miRNA degrades and the other remains, which targets mRNA. There are two ways to silence the target genes: (A) Translative repression by incomplete pairing and (B) degradation of target mRNA by complementary pairing. miRNA, microRNA; TRBP, transactivation response element RNA binding protein; Ago2, argonaute 2; RISC, RNA-induced silencing complex.

survival suggested that a high miR-483-5p serum level was an independent prognostic indicator (36). Furthermore, patient follow-up revealed that patients with higher blood miR-372 levels had more extensive primary tumors, a greater tendency of node metastases, a more terminal stage and higher mortality rates (57). Additionally, miR-372 was downregulated in plasma and saliva among postoperative patients compared with preoperative patients (57). By measuring salivary miR-31, it was determined that 86.4% (19/22) of patients exhibited a significant decrease in miR-31 levels following tumor resection (28). miR-372 and miR-31 may therefore serve as biomarkers for the evaluation of surgical efficacy (28,57). Sun *et al* (58) suggested that serum miR-9 is an independent prognostic factor for oral cancer, as downregulated miR-9 was associated with lymph node metastases, advanced TNM stage and poor prognosis. Patients with low serum miR-9 expression had a worse disease-free survival rate compared with patients with high miR-9 expression (26.5 and 54.6%, respectively). The overall survival rate of patients with low and high miR-9 expression was 42.9 and 67.3%, respectively. By determining levels of miRNAs in the serum or saliva of patients, miRNAs may be used in minimally or non-invasive methods to predict lymph node metastasis and assess the prognosis of patients with oral cancer. Table I presents the aberrant levels of other miRNAs in the saliva, blood, serum and plasma (28-30,59-68).

4. Partial subtypes of oral cancer and miRNAs

Mucoepidermoid carcinoma. As a salivary gland-derived malignancy, mucoepidermoid carcinoma may occur in the oral cavity. Shin *et al* (69) reported that the overexpression of miR-127-3p led to an increase in the number of cells in the G_1 phase, indicating that miR-127-3p resulted in G_1/S cell cycle arrest *in vitro*. miR-127-3p-induced cell cycle arrest in mucoepidermoid carcinoma MC-3 cells was associated with the increase of cyclin-dependent kinase inhibitor 1A and interferon α inducible protein 27 expression via the regulation of Sp1 transcription factor (69). Binmadi *et al* (70) found that miR-302a was significantly increased in mucoepidermoid carcinoma tissues compared with normal tissues. Furthermore, upregulated miR-302a induced invasion of mucoepidermoid carcinoma cells *in vitro*.

Adenoid cystic carcinoma. Adenoid cystic carcinoma (ACC) generally occurs in the minor salivary glands and has a poor long-term prognosis due to perineural invasion and lung metastasis (71). Wang *et al* (72) analyzed the expression of miR-130a in 21 patients with ACC and corresponding normal salivary gland tissues. Compared with that in normal salivary gland tissues, the expression of miR-130a in ACC tissues increased by 1.58-29.1 times. In addition, the level of miR-130a was negatively correlated with N-myc downstream-regulated gene 2

Table I. Dysregulation of miRNAs associated with oral cancer detected in saliva, blood, serum and plasma.

Author, year	miRNA	Dysregulation	Sample	(Refs.)
Liu *et al*, 2012	miR-31	Upregulation	Saliva	(28)
Zahran *et al*, 2015	miR-21	Upregulation	Saliva	(29)
	miR-184	Upregulation	Saliva	
Ries *et al*, 2017	miR-186	Downregulation	Blood	(30)
	miR-3651	Upregulation	Blood	
	miR-494	Upregulation	Blood	
Yang *et al*, 2011	miR-181	Upregulation	Plasma	(59)
Wong *et al*, 2018	miR-184	Upregulation	Plasma	(60)
Lu *et al*, 2012	miR-10b	Upregulation	Plasma	(61)
	miR-196a	Downregulation	Plasma	
	miR-196b	Downregulation	Plasma	
	miR-582-5p	Downregulation	Plasma	
	miR-15b	Downregulation	Plasma	
	miR-301	Downregulation	Plasma	
	miR-148b	Downregulation	Plasma	
	miR-128a	Downregulation	Plasma	
	miR-503	Downregulation	Plasma	
	miR-31	Downregulation	Plasma	
Kao *et al*, 2015	miR-21	Upregulation	Plasma	(62)
	miR-31	Upregulation	Plasma	
	miR-146	Upregulation	Plasma and saliva	
	miR-184	Upregulation	Plasma	
	miR-372	Upregulation	Plasma	
Liu *et al*, 2013	miR-196a	Upregulation	Plasma	(63)
Lin *et al*, 2010	miR-24	Upregulation	Plasma	(64)
Lu *et al*, 2015	miR-196a	Upregulation	Plasma	(65)
	miR-196b	Upregulation	Plasma	
Liu *et al*, 2017	miR-187*	Upregulation	Plasma	(66)
Lo *et al*, 2012	miR-27b	Downregulation	Plasma	(67)
Ries *et al*, 2014	miR-494	Upregulation	Blood	(68)
	miR-3162	Upregulation	Blood	
	miR-3651	Upregulation	Blood	
	miR-186	Downregulation	Blood	
	let-7	Downregulation	Blood	

miRNAs associated with oral cancer detected in saliva, blood, serum and plasma may serve as tumor biomarkers. The upregulation of miR-31, miR-494, miR-3651 and miR-196a, and the downregulation of miR-186 are associated with tumor recurrence. High expression levels of miR-181 and miR-196a indicate a poor prognosis. miRNA/miR, microRNA.

in ACC tissues. Chen *et al* (73) analyzed miRNAs during the metastasis of ACC cells and found that the expression levels of miR-4487, miR-4430 and miR-486-3p were upregulated, and the expression levels of miR-5191, miR-3131 and miR-211-3p were downregulated. Andreasen *et al* (74) found that high expression levels of miR-21, miR-181a-2 and miR-152 in patients with ACC was associated with a decreased overall survival rate, and high expression of miR-374c was associated with an improved relapse-free survival rate. Wang *et al* (75) found that an miR-21 inhibitor significantly reduced the resistance of lung metastatic salivary adenoid cystic carcinoma cells (SACC-LM) to simvastatin. Furthermore, the combination of simvastatin and miR-21 inhibitor decreased the proliferation of SACC-LM cells (75).

5. Conceivable therapeutic value of miRNAs

Tumor suppressor miRNAs. Yang *et al* (76) found that when a recombinant lentivirus carrying the miR-381-3p gene was transduced into SCC-9 and Tca-8113 cell lines, miR-381-3p-overexpressing cells demonstrated downregulation of fibroblast growth factor receptor 2. Furthermore, the percentage of cells at the G_1/G_0 phase was increased and the number of cells at the S phase was decreased. In addition, the apoptotic rate was significantly increased and the number of colonies was decreased in SCC-9 and Tca-8113 cells overexpressing miR-381-3p compared with those in the negative control group. EMT, an important mechanism of invasion or

Table II. Tumor suppressor miRNAs, and their respective target genes or signaling pathways in oral cancer.

Author, year	miRNA	Target gene/pathway	Possible role	(Refs.)
Shi *et al*, 2015	miR-375	KLF5	Proliferation, apoptosis	(80)
Wu *et al*, 2017	miR-375	SLC7A11	Proliferation, invasion	(81)
Ji *et al*, 2017	miR-138	AKT1	Invasion	(82)
Xu *et al*, 2015	miR-138	YAP-1	Proliferation	(83)
Kim *et al*, 2018	miR-203	Bmi1	Apoptosis	(84)
Lim *et al*, 2017	miR-203	SEMA6A	Apoptosis	(85)
Lin *et al*, 2016	miR-203	PIK3CA	Proliferation, chemosensitivity	(86)
Xie *et al*, 2018	miR-200c	ZEB1	EMT	(87)
Zhao *et al*, 2015	miR-222	ABCG2	Invasion, chemosensitivity	(88)
Wang *et al*, 2017	miR-15b	TRIM14	Chemoresistance, EMT	(89)
Li *et al*, 2017	miR-124	CCL-2, IL-8	Proliferation	(90)
Lin *et al*, 2017	miR-485-5p	PAK1	EMT, chemosensitivity	(91)
Lin *et al*, 2014	miR-639	FOXC1	EMT	(92)
Liu *et al*, 2017	miR-27b	FZD7	Proliferation	(93)
Min *et al*, 2014	miR-148a	Wnt10b	Migration, invasion	(94)
Nagai *et al*, 2018	miR-205-5p	TIMP2	Invasion	(95)
Qiao *et al*, 2017	miR-524-5p	ILK, TGF-β/Smad (-)	Proliferation, invasion	(96)
Qiu *et al*, 2016	miR-22	CD147	Proliferation, metastasis	(97)
Rastogi *et al*, 2017	miR-377	HDAC9, NR4A1, Nur77	Growth, migration, apoptosis	(98)
Ruan *et al*, 2018	miR-30a-5p	FAP	Proliferation, invasion	(99)
Sakha *et al*, 2014	miR-1246	DENND2D	Motility, invasion	(100)
Shang *et al*, 2017	miR-9	CDK4/6	Apoptosis, cell arrest	(101)
Shi *et al*, 2015	miR-146a	SOX-2	Invasion	(102)
Wang *et al*, 2016	miR-188	SIX1	Proliferation, invasion	(103)
Wang *et al*, 2017	miR-139-5p	HOXA9	Proliferation, invasion	(104)
Wang *et al*, 2017	miR-376c-3p	HOXB7	Proliferation	(105)
Wang *et al*, 2018	miR-655	MTDH, PTEN/AKT (-)	Proliferation, invasion	(106)
Wang *et al*, 2018	miR-1294	c-Myc (-)	Growth, migration	(107)
Weng *et al*, 2016	miR-494-3p	Bmi1	Radiosensitivity	(108)
Xu *et al*, 2016	miR-340	Glut	Glucose metabolism	(109)
Zeng *et al*, 2016	miR-27a-3p	YAP-1	EMT	(110)
Li *et al*, 2018	miR-218-5p	CD44	Invasion	(111)

Tumor suppressor miRNAs inhibit their respective target genes, which inhibit cellular proliferation, growth, motility, migration, invasion, metastasis, glucose metabolism, EMT, promote cell arrest and apoptosis and increase chemosensitivity and radiosensitivity. The (-) symbol indicates inhibition of downstream signaling pathways. miRNA/miR, microRNA; EMT, epithelial-mesenchymal transition; KLF5, kruppel like factor 5; SLC7A11, solute carrier family 7 member 11; AKT1, AKT serine/threonine kinase 1; YAP-1, yes associated protein 1; SEMA6A, semaphorin 6A; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α; ABCG2, ATP-binding cassette subfamily G member 2; TRIM14, tripartite motif containing 14; CCL-2, C-C motif chemokine ligand 2; IL-8, interleukin-8; PAK1, p21 (RAC1) activated kinase 1; FOXC1, forkhead box C1; FZD7, frizzled class receptor 7; Wnt10b, wingless-type MMTV integration site family, member 10b; TIMP2, TIMP metallopeptidase inhibitor 2; ILK, integrin-linked kinase; BSG, basigin; HDAC9, histone deacetylase 9; NR4A1, nuclear receptor subfamily 4 group A member 1; FAP, fibroblast activation protein α; DENND2D, DENN domain containing 2D; CDK4/6, cyclin-dependent kinase 4/6; SOX-2, sex determining region Y box 2; SIX1, sine oculis-related homeobox 1; HOXA , homeobox A9; HOXB7, homeobox B7; MTDH, metadherin; Glut1, glucose transporter-1. Bmi1, B lymphoma Mo-MLV insertion region 1 homolog.

metastasis of cancer, which involves the downregulation of E-cadherin and increases metastasis and invasion as a consequence of loss of intercellular adhesion, may be regulated by miRNAs (77). ZEB was reported as an EMT-related transcription factor, which was shown to directly combine with the E-cadherin promoter and inhibit its transcription (77,78). Hashiguchi *et al* (79) identified an association between miR-205 and the EMT phenotype in SQUU-B cells and demonstrated that overexpression of miR-205 downregulated ZEB1, ZEB2 and N-cadherin, and upregulated E-cadherin. Another study reported that overexpression of miR-375 significantly upregulated SCC-4 cell radiation-induced apoptosis by directly regulating the insulin-like growth factor 1 receptor (IGF1R) (32). Tumor suppressor miRNAs, and their respective target genes and downstream signaling pathways, are presented in Table II (80-111).

Table III. Tumor-promoting miRNAs and their respective target genes or signaling pathways in oral cancer.

Author, year	miRNA	Target gene/pathway	Possible role	(Refs.)
Zhuang *et al*, 2017	miR-218	PPP2R5A,Wnt (+)	Cisplatin resistance	(112)
Jiang *et al*, 2014	miR-222	PUMA	Cisplatin resistance	(113)
Du *et al*, 2017	miR-221	TIMP3	Chemosensitivity	(114)
Zhou *et al*, 2016	miR-221/222	PTEN	Proliferation, invasion, apoptosis	(115)
Zheng *et al*, 2015	miR-24	PTEN, Akt (+)	Cisplatin resistance	(116)
Cheng *et al*, 2016	miR-455-5p	UBE2B	Proliferation	(117)
Guo *et al*, 2015	miR-96	MTSS1	Proliferation, metastasis	(118)
Hu *et al*, 2016	miR-497	SMAD7	Metastasis	(119)
Kawakubo-Yasukochi *et al*, 2018	miR-200c-3p	CHD9, WRN	Invasion	(120)
Li *et al*, 2018	miR-182-5p	CAMK2N1	Proliferation	(121)
Lin *et al*, 2016	miR-187	BARX2	Metastasis	(122)
Liu *et al*, 2015	miR-92b	NLK, NF-κB (+)	Proliferation, apoptosis	(123)
Lu *et al*, 2018	miR-654-5p	GRAP, Ras-ERK (+)	Metastasis	(124)
Peng *et al*, 2018	miR-134	PDCD7	Proliferation, migration	(125)
Qiao *et al*, 2017	miR-27a-3p	SFRP1, Wnt/β-catenin (+)	EMT	(126)
Zhao *et al*, 2017	miR-24	PTEN	Unknown	(127)
Zheng *et al*, 2016	miR-21	CADM1	Chemosensitivity	(128)
Chen *et al*, 2016	miR-211	TCF-12	Antioxidant activity	(129)

Oncogenic miRNAs silence their respective target genes, which facilitates cellular proliferation, growth, migration, invasion, metastasis, antioxidant activity and EMT, inhibit apoptosis of cancer cells and reduce chemosensitivity. The (+) symbol indicates activation of downstream signaling pathways. Unknown refers to target genes or possible roles of miRNAs that are not reported in previous studies. miRNA, microRNA; EMT, epithelial-mesenchymal transition; PPP2R5A, protein phosphatase 2 regulatory subunit Bα; TIMP3, tissue inhibitor of metalloproteinase 3; PTEN, phosphatase and tensin homolog; UBE2B, ubiquitin conjugating enzyme E2B; MTSS1, metastasis suppressor 1; SMAD7, SMAD family member 7; CHD9, chromodomain helicase DNA binding protein 9; WRN, Werner syndrome RecQ like helicase; CAMK2N1, calcium/calmodulin-dependent protein kinase II inhibitor 1; BARX2, BarH-like homeobox 2; NLK, nemo-like kinase; GRAP, GRB2-related adaptor protein; PDCD7, programmed cell death 7; SFRP1, secreted frizzled-related protein 1; CADM1, cell adhesion molecule 1; TCF-12, transcription factor 12.

Tumor-promoting miRNAs. Fu *et al* (49) demonstrated that miR-155 targeted the cyclin-dependent kinase inhibitor 1B (CDKN1B) 3'-UTR by a luciferase reporter assay. Furthermore, downregulation of miR-155 led to an increase in CDKN1B and inhibited cell proliferation and cell cycle progression in oral cancer Tca8113 cells (49). A previous study demonstrated that the mRNA and protein levels of vimentin and N-cadherin were upregulated in SCC-9 and UM1 cells transfected with miR-373-3p, respectively, while E-cadherin and CK18 were downregulated, suggesting that miR-373-3p may stimulate the EMT phenotype (48). The repression of the negative regulator of the Wnt signaling pathway, Dickkopf-related protein 1, and the nuclear accumulation of β-catenin promoted the Wnt signaling pathway, which facilitated proliferation of SCC-9 and UM1 cells (48). Dysregulation of the Wnt signaling pathway in tumors may result in chemoresistance. Protein phosphatase 2 regulatory subunit Bα (PPP2R5A) is a repressor of Wnt signaling, and in oral cancer cells, miR-218 increased cisplatin resistance via the Wnt signaling pathway by repressing PPP2R5A expression (112). Zhuang *et al* (112) demonstrated that when UM1 and Cal27 cells were transfected with miR-218 mimics, the miR-218 overexpression resulted in increased levels of β-catenin, indicating activation of Wnt signaling, and enhanced cell viability. Furthermore, blocking the effect of miR-218 reversed chemoresistance in resistant cells. Jiang *et al* (113) revealed that low expression of miR-222 increased the chemosensitivity of oral cancer cells to cis-diaminedichloroplatinum (CDDP) and that the combination of antisense-miR-222 and CDDP may be an effective curative strategy by upregulating the expression of p53, a modulator of apoptosis. Table III presents tumor-promoting miRNAs with their respective target genes and downstream signaling pathways (112-129).

Recent conventional experimental methods. Bioinformatics analysis may be used to predict the pairing sequences of miRNAs and target genes, which may be verified by luciferase reporter assays. Western blotting and RT-qPCR may subsequently be used to detect protein and miRNA expression, respectively. Frequently used oral cancer cell lines include SCC-9, SCC-4, Tca-8113 and Cal27 (45,48,49,51). Cell experiments demonstrated that specific miRNAs served an anticancer role such as miR-138, miR-200c, miR-15b, miR-485-5p and miR-340 (83,87,89,91,109); whereas other miRNAs stimulated oral cancer by regulating cellular proliferation, apoptosis, invasion, EMT, metastasis, radiosensitivity, chemosensitivity and glucose metabolism, such as miR-221, miR-455-5p, miR-27a-3p, miR-21 and miR-10a (114,117,126,128,130). The results obtained from *in vitro* cell experiments may provide novel therapeutic targets for potential clinical application.

Experimental conclusion in oral carcinoma. miRNAs are promising therapeutic targets, as they serve important roles

in cancer. Theoretically, by silencing tumor-promoting miRNAs and inducing the expression of tumor-suppressing miRNAs synchronously, it is possible to treat oral carcinoma. Specific miRNAs have multiple target genes, for example, miR-375 targets IGF1R (32), platelet-derived growth factor subunit A (131), Kruppel-like factor 5 (80) and solute carrier family 7 member 11 (81); miR-138 targets AKT serine/threonine kinase 1 (82) and yes-associated protein 1 (83); miR-203 targets B lymphoma Mo-MLV insertion region 1 homolog (84), semaphorin 6A (85) and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (86); and miR-221 targets tissue inhibitor of metalloproteinase 3 (114) and phosphatase and tensin homolog (PTEN) (115). A possible treatment strategy may involve anticancer drugs that selectively regulate the expression of such miRNAs. Certain genes or signaling pathways are regulated by two or more miRNAs, for instance, tripartite motif containing 14 is targeted by miR-195-5p (31) and miR-15b (89); IGF1R is targeted by miR-98 (132) and miR-375 (32); ZEB1 is targeted by miR-205 (79) and miR-200c (87); and PTEN is targeted by miR-221/222 (115) and miR-24 (116). Therefore, the combination of more specific inhibitors or activators of cancer-associated genes or signaling pathways may be a suitable therapeutic strategy. With regard to controversial miRNAs, including miR-222, which served an ambivalent role in disparate experiments, more research is required to verify their roles in oral cancer (88,113,115).

6. Conclusions

On the basis of current research, the aberrant expression of miRNAs has been demonstrated to be significantly associated with oral cancer. As either a tumor marker or a therapeutic target, miRNA has potential to diagnose or treat oral cancer and improve survival. miRNA serves important roles in the occurrence, development, therapy and prognosis of oral cancer, and is a promising target for clinical application. In terms of the mechanism of malignant transformation or oncogenicity, prognostic and diagnostic value, and potential as a therapeutic target, miR-31 seems to be a promising candidate for clinical application. miR-31 is differentially expressed in normal mucosa, OPMD and oral cancer, and may be detected with high sensitivity in tissue, saliva and plasma. Furthermore, miR-31 may be used to evaluate surgical efficacy. However, miR-375 and miR-203 may be superior therapeutic targets, as they target multiple genes that regulate additional factors and malignant biological properties in oral cancer.

There are a number of challenges in the experimental research and clinical application of miRNA. The transcriptional activation of miRNA and the regulation of indispensable components (containing Drosha/DGCR8, Dicer, XPO5 and TRBP) in the maturation process of oncogenic or antineoplastic miRNA through signaling pathways, and the interference of signaling pathways by mature miRNA, form a series of feedback loops, which may either contribute to tumorigenesis or be used for effective treatments. Further clinical trials that explore specific or highly sensitive miRNA closely associated with oral cancer are required to identify biomarkers with prognostic value. Combining multiple miRNAs for diagnosis and therapy is also a promising strategy that requires further examination, and investigating the association between oral cancer subtypes and miRNA may facilitate the development of targeted medicine in oral cancer. Identifying the detection threshold of different miRNAs in serum, specimen and saliva may aid in predicting the risk of malignant transformations and in evaluating the risk of tumor metastasis or relapse. In addition to further elucidating the mechanisms and anticancer strategies targeted at miRNA, the potential resistance and complications of new antitumor drugs are novel challenges to overcome in order to identify more effective treatments for oral cancer.

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Authors' contributions

YL designed the review and revised the manuscript. CF wrote the manuscript. Both authors reviewed the final version and approved it for publication.

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Competing interests

The authors declare that they have no competing interests.

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