

Diagnostic and therapeutic role of microRNAs in oral cancer (Review)

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Abstract. Oral cancer is one of the leading types of cancer and remains the most common cause of cancer-related mortality in Asia. The pathogenesis of oral cancer is complicated and, due to lack of accurate diagnostic methods and efficient treatment strategies, oral cancer is responsible for a large number of deaths. Therefore, there is an urgent need for developing novel diagnostic tools and targeted therapies. MicroRNAs (miRNAs) represent a class of small non-coding RNAs that are key elements and play critical regulatory roles in the pathological processes of various diseases. miRNAs are widely distributed in body fluids and are specifically expressed in different cancers, and they may represent effective biomarkers that may be used for early detection of oral cancer. In addition, miRNAs are involved in oral cancer development, progression and prognosis by targeting a broad range of mRNAs that may

be of therapeutic value for oral cancer. The aim of the present review was to summarize the role of miRNAs as new diagnostic tools and potential therapeutic targets in oral cancer, and investigate the underlying molecular mechanisms.

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1. Introduction

Oral cancer is a type of head and neck cancer and its main subtype is oral squamous cell carcinoma (OSCC) (1). OSCC occurs in the oral cavity, which includes the tongue, floor of the mouth, buccal mucosa and alveolar rim (2). OSCC presents a major global health concern, with an estimated >300,000 cases per annum (3) and ~1.8 million deaths (4). Currently, the diagnosis and treatment of OSCC represent a clinical challenge.

miRNAs are a class of small non-coding RNAs that are involved in the regulation of a variety of physiological processes by targeting specific mRNAs (5). miRNAs have been reported to play an important regulatory role in cancer occurrence and progression (6), and they may be of value as targets in oral cancer treatment (7). Due to their stability in human peripheral blood and body fluids and disease-specific expression, an increasing number of studies indicate that miRNAs may represent an ideal set of biomarkers applied in early diagnosis and prognosis of cancers (8).

The focus of the present review was the detailed regulatory role of miRNAs in oral cancer and their value in diagnosis and treatment. The conclusions of this review may contribute to the early diagnosis and targeted therapy of oral cancer.

2. Expression profile of miRNAs in oral cancer

miRNAs are a family of short, single-stranded, small non-coding RNAs, containing ~20-22 nucleotides (9). The miRNA expression profiles and levels differ between patients with cancer and healthy individuals, and they are implicated

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Abbreviations: OSCC, oral squamous cell carcinoma; ROC, receiver operating characteristics; AUC, area under the curve; mTOR, mammalian target of rapamycin; AKT, protein kinase B; UBE2B, ubiquitin-conjugating enzyme E2B; SOX12, SRY-box transcription factor 12; FGF1, fibroblast growth factor 2; NR4A1/Nur77, nuclear receptor subfamily 4 group A member 1; Foxo3a/p27^{Kip1}, forkhead box O3A/cyclin-dependent kinase inhibitor 1B; HIP1, Huntingtin-interacting protein 1; GIT1, GPCR kinase 2 interacting protein 1; LATS2, large tumor suppressor kinase 2; PER1, period 1 gene; ACOX1, acyl-CoA oxidase 1; HBp17, heparin-binding protein 17; ARID2, AT-rich interaction domain 2; GLUT1, glucose transporter 1; TMEM182, transmembrane protein 182; CDH1, E-cadherin gene 1; RGMA, repulsive guidance molecule A; RIG-I, retinoic acid-inducible gene-I; TNF- α , tumor necrosis factor- α ; ROR α , retinoic acid receptor-related orphan receptor α ; BIN1, bridging integrator 1; AXL, receptor tyrosine kinase; PDCD7, programmed cell death 7; Bmi-1, B-cell-specific Moloney murine leukemia virus integration site 1; BIRC3, baculoviral IAP repeat-containing 3; FAP, fibroblast activation protein; DENND2D, differentially expressed in normal cells and neoplasia domain containing 2D; TGFBR1, TGF- β receptor 1

Key words: microRNAs, oral cancer, biomarker, target therapy

in human carcinogenesis (10,11). According to their chemical and structural properties, circulating miRNAs are stable in the serum, plasma and other body fluids (8), and they may be considered as potential clinical diagnostic and prognostic biomarkers.

miRNAs may be novel diagnostic biomarkers in oral cancer. The occurrence of oral cancer is multifactorial, and is accompanied by genetic and epigenetic instability (12). With the widespread application of next-generation sequencing, a growing number of studies have demonstrated that certain miRNAs are differentially expressed in oral cancer. In addition, the results of receiver operating characteristic (ROC) curve and area under the curve (AUC) analysis have indicated that the differentially expressed miRNAs may help distinguish patients with oral cancer from healthy subjects (13,14). As revealed in Table I (13-31), 35 miRNAs were screened, which were reported in the last 5 years with a ROC (AUC) >0.500. For example, Momen-Heravi *et al* reported that upregulated miR-27b and downregulated miR-136 derived from the saliva were able to differentiate between patients with oral cancer and healthy subjects (15). The ROC (AUC) of miR-21 extracted from oral cytology and miR-99a from the serum were up to 0.910 (16) and 0.911 (17), respectively. Gombos *et al* reported that miR-155 derived from tissues was able to distinguish between patients with oral cancer and healthy individuals [ROC (AUC)=0.925] (13). These data revealed that miRNAs originating from different samples may be considered as biomarkers for oral cancer diagnosis.

miRNAs as novel prognostic biomarkers in oral cancer. The expression profiles of certain miRNAs have demonstrated a positive correlation with clinical stage, metastasis and patient survival, indicating that these miRNAs may be considered as prognostic indices in oral cancer. Lai *et al* revealed that dysregulated miR-31-5p expression enhanced OSCC cell migration and invasion and accelerated oral cancer progression (32). In recent years, miRNAs have been reported to be strongly correlated with the survival of oral cancer patients. Chen *et al* indicated that patients with high expression level of miR-99a displayed a better prognosis and longer overall survival (17). Supic *et al* revealed that patients with miR-183 overexpression had markedly shorter overall survival and higher risk of poor outcome (23). Zheng *et al* reported that miR-503-5p, miR-450b-5p, miR-27a-3p, miR-181a-5p and miR-183-5p were overexpressed in patients with oral cancer, and they were all highly associated with cancer cell proliferation, advanced clinical stage and poor prognosis (33). Cheng *et al* revealed that the expression level of miR-455-5p was associated with the nodal status, stage and overall survival of the patients, suggesting that miR-455-5p may be a promising prognostic marker for predicting the outcome of patients with oral cancer (34). We herein also summarized other miRNAs that may be of prognostic value in oral cancer (Table II). All the aforementioned data indicated that miRNAs may be valuable prognostic indicators in oral cancer.

3. Therapeutic effects of miRNAs in oral cancer

miRNAs play a key role in regulating the translation or degradation of mRNAs by interacting with the 3' untranslated

region (3'UTR) or coding region of mRNAs and regulating the expression level of their target genes (35). miRNAs are involved in the cellular processes of cancer, such as inflammation, proliferation, stress response, growth, apoptosis, survival and migration (10). Therefore, manipulating miRNA expression in cancer has been attracting increasing attention as a novel therapeutic strategy. It was reported that miR-24-3p, miR-155-5p and miRNA-10a may significantly promote the proliferation of oral cancer cells (18,36,37). These findings suggested that silencing the expression of specific miRNAs may prevent the progression of oral cancer. Conversely, numerous miRNAs have been revealed to have an anticancer function. miR-6887-5p, miR-34a-5p and miR-142-3p markedly suppressed the proliferation of oral cancer cells (38-40). In addition, certain miRNAs, such as miR-204-5p and miR-34a-5p, exert their anticancer effects by inhibiting the aggressiveness and metastasis of oral cancer cells (39,41). The targets and functional roles of miRNAs are listed in Table II (17-19,23,32,33,36-54).

Regulatory mechanism of miRNAs in oral cancer. miRNAs belong to a family of non-coding RNAs that play key roles in suppressing or promoting cancer by interacting with their target mRNAs. Several studies have demonstrated that miRNAs are involved in the occurrence, progression and metastasis of oral cancer (Fig. 1) (53,55).

miRNAs and oral cancer occurrence and progression. Accumulating evidence indicates that miRNAs play a key role in the occurrence and progression of oral cancer. The protein kinase B (AKT) and mammalian target of rapamycin (mTOR) pathways are known to participate in the regulation of oral cancer occurrence (56). Manikandan *et al* revealed that >40 differentially expressed miRNAs in OSCC may activate the AKT pathway (57). miR-218 can inhibit the activation of mTOR/AKT pathway by targeting Rictor, and then suppress oral carcinogenesis (58). In oral cancer, miR-99 has been revealed to decreased the expression level of mTOR by directly binding with mTOR mRNA, thereby promoting cancer cell growth and increasing tumor size (59,60). The expression level of miR-455-5p has been revealed to be regulated by the TGF- β -dependent pathway, which subsequently promotes oral tumorigenesis by downregulating ubiquitin-conjugating enzyme E2B (UBE2B) (34). Chen *et al* revealed that CD36 contributed to the proliferation and invasion of OSCC, and miR-1254 may inhibit the progression of OSCC by partially downregulating the expression level of CD36 (61). In addition, inhibiting the expression of miR-423-5p may rescue the carcinogenic effect of lncRNA CASC9 by silencing the expression of SRY-box transcription factor 12 (SOX12) (62). These data revealed that miRNAs participate in oral carcinogenesis and progression by regulating their target genes.

miRNAs and oral cancer cell proliferation and apoptosis. The proliferation and apoptosis of oral cancer cells are regulated by multiple factors, with an increasing number of studies demonstrating that miRNAs are involved in the regulation of these cellular process. Rastogi *et al* reported that *in vitro* restoration of miR-377 suppressed OSCC cell growth and induced apoptosis by regulating HDAC9 and its pro-apoptotic target, NR4A1/Nur77 (63). miR-23a-3p may suppress proliferation

Table I. Sample source, expression level and ROC (AUC) of miRNAs in oral cancer.

No.	miRNAs	Sample type	Expression level in oral cancer vs. normal sample	ROC (AUC)	(Refs.)
1	miR-21	Oral cytology	Upregulated	0.910	(16)
2	miR-24-3p	Saliva	Upregulated	0.738	(18)
3	miR-31-5p	Serum	Upregulated	0.661	(19)
4	miR-512-3p	Saliva	Upregulated	0.847	(20)
5	miR-412-3p	Saliva	Upregulated	0.871	(20)
6	miR-222-3p	Plasma	Upregulated	0.702	(21)
7	miR-150-5p	Plasma	Upregulated	0.520	(21)
8	miR-423-5p	Plasma	Upregulated	0.677	(21)
9	miR-548b	Tissue	Upregulated	0.651	(22)
10	miR-18a	Tissue	Upregulated	0.682	(22)
11	miR-183	Tissue	Upregulated	0.700	(23)
12	miR-483-5p	Serum	Upregulated	0.850	(24)
13	miR-125b	Plasma	Upregulated	0.966	(25)
14	miRNA-184	Saliva	Upregulated	0.860	(26)
15	miR-196a	Plasma	Upregulated	0.864	(27)
16	miR-196b	Plasma	Upregulated	0.960	(27)
17	miR-494	Whole blood	Upregulated	0.720	(28)
18	miR-3651	Whole blood	Upregulated	0.800	(28)
19	miR-27b	Saliva	Upregulated	0.964	(15)
20	miR-155	Tissues	Upregulated	0.925	(13)
21	miR-221	Tissues	Upregulated	0.901	(13)
22	miR-16	Serum	Upregulated	0.840	(14)
23	let-7b	Serum	Upregulated	0.820	(14)
24	miR-3651	Tissue	Downregulated	0.779	(29)
25	miR-99a	Serum	Downregulated	0.911	(17)
26	miR-542-3p	Plasma	Downregulated	0.820	(30)
27	miR-375	Oral cytology	Downregulated	0.910	(16)
28	miR-139-5p	Saliva	Downregulated	0.805	(31)
29	miRNA-145	Saliva	Downregulated	0.680	(26)
30	miR-186	Whole blood	Downregulated	0.690	(28)
31	miR-136	Saliva	Downregulated	0.968	(15)
32	miR-191	Tissues	Downregulated	0.887	(13)
33	miR-333-3p	Serum	Downregulated	0.820	(14)
34	miR-29a	Serum	Downregulated	0.820	(14)
35	miR-223	Serum	Downregulated	0.810	(14)

ROC, receiver operating characteristic; AUC, area under the curve.

and promote apoptosis of OSCC cells by targeting fibroblast growth factor 2 (FGF1) (64). By contrast, it was reported that miR-155 contributed to oral cancer cell proliferation, inhibited cell apoptosis and reduced the sensitivity of oral cancer cells to DDP by downregulating Foxo3a expression (65). Furthermore, miR-155 promoted cell cycle progression and cell proliferation and suppressed apoptosis by inhibiting p27^{Kip1} expression (66).

miRNAs and oral cancer cell migration, invasion and metastasis. The migration, invasion and metastasis of oral cancer cells are highly associated with the therapeutic strategy. miRNAs are

involved in the regulation of these processes in oral cancer cells. Fang *et al* reported that miR-204-5p suppressed oral cancer cell aggressiveness, viability and migration by targeting and inhibiting: Huntingtin-interacting protein 1 (HIP1) expression (41). Overexpression of miR-143 and miR-145 in OSCC cells markedly suppressed the expression of activin A, and suppressed the migration and invasion of oral cancer cells, prevented lymph node metastasis, increased tumor differentiation and prolonged the survival of the patients (67). Huang *et al* revealed that enhancing the expression of miR-491-5p significantly downregulated the expression of GPCR kinase 2 interacting protein 1 (GIT1),

Table II. Targets and functional roles of miRNAs in oral cancer.

No.	miRNAs	Targets	Pathoclinical appearances				(Refs.)
			Metastatic potential	Growth potential	Invasive status	Prognosis of patients	
1	miR-24-3p	PER1	/	↑	/	/	(18)
2	miR-31-5p	ACOX1	↑	↑	↑	/	(19,32)
3	miR-99a	/	/	/	/	↑	(17)
4	miR-183	/	/	/	/	↓	(23)
5	miR-204-5p	HIP1	↓	↓	↓	/	(41)
6	miR-6887-5p	HBp17	/	↓	/	/	(38)
7	miR-155-5p	ARID2	↑	↑	↑	/	(36)
8	hsa-mir-99b-3p	/	/	/	/	↑	(42)
9	hsa-mir-100-5p	/	/	/	/	↓	(42)
10	miRNA-10a	GLUT1	/	↑	/	/	(37)
11	hsa-miR-let.7i-3p	/	/	/	/	↑	(43)
12	miR-450a	TMEM182	/	/	↑	/	(44)
13	miR-29b-1-5p	CDH1	/	/	/	↓	(45)
14	miR-210-3p	RGMA	/	↑	/	/	(46)
15	miR-545	RIG-I	↓	↓	/	/	(47)
16	miR-21	TNF- α	/	↑	/	/	(48)
17	miR-503-5p, miR-450b-5p, miR-27a-3p, miR-181a-5p and miR-183-5p	ROR α	/	↑	/	↓	(33)
18	miR-211	BIN1	↑	↑	↑	/	(49)
19	miR-34a-5p	AXL	↓	↓	/	/	(39)
20	miR-134	PDCD7	↑	/	/	/	(50)
21	miR-203	Bmi-1	/	↓	/	/	(51)
22	miR-196a-5p	BIRC3	/	↓	/	/	(52)
23	miR-30a-5p	FAP	↓	↓	↓	/	(53)
24	miR-1246	DENND2D	↑	/	↑	/	(54)
25	miR-142-3p	TGFBR1	↓	↓	↓	/	(40)

↑: Indicates a promoting effect; ↓: Indicates an inhibitory effect; /: Indicates an unknown effect. PER1, period 1 gene; ACOX1, acyl-CoA oxidase 1; HIP1, Huntingtin-interacting protein 1; HBp17, heparin-binding protein 17; ARID2, AT-rich interaction domain 2; GLUT1, glucose transporter 1; TMEM182, transmembrane protein 182; CDH1, E-cadherin gene 1; RGMA, repulsive guidance molecule A; RIG-I, retinoic acid-inducible gene-I; TNF- α , tumor necrosis factor α ; ROR α , retinoic acid receptor-related orphan receptor α ; BIN1, bridging integrator 1; AXL, receptor tyrosine kinase; PDCD7, programmed cell death 7; Bmi-1, B-cell-specific Moloney murine leukemia virus integration site 1; BIRC3, baculoviral IAP repeat-containing 3; FAP, fibroblast activation protein; DENND2D, differentially expressed in normal cells and neoplasia domain containing 2D; TGFBR1, TGF- β receptor 1.

thereby suppressing OSCC cell migration *in vitro* and lung metastasis *in vivo* (68). Conversely, overexpression of miR-21 was associated with perineural invasion and worse prognosis in OSCC patients (69). Tu *et al* reported that overexpression of miR-372 and miR-373 were associated with nodal metastasis, lymph vascular invasion and poor survival by regulating the expression of large tumor suppressor kinase 2 (LATS2) in OSCC cells (70).

miRNAs as novel therapeutic tools in oral cancer. A large volume of evidence has demonstrated that miRNAs play key roles in oral cancer occurrence and growth, cancer cell migration and invasion, cancer progression and patient prognosis. This evidence suggests that miRNAs may be considered as novel therapeutic tools for oral cancer.

It was reported that upregulation of miR-375 markedly inhibited cell proliferation, induced cell cycle arrest in the G0/G1 phase, promoted apoptosis and increased radio-sensitivity in OSCC cells, suggesting that miR-375 may be a potential therapeutic target for OSCC patients (71). miR-494-3p was able to enhance the radiosensitivity of OSCC cells by promoting cellular senescence (72). Min *et al* revealed that overexpression of miR-148a in cancer-associated fibroblasts significantly decreased the migration and invasion abilities of oral cancer cells by directly targeting WNT10B, suggesting that miR-148a may be a novel promising target for the treatment of OSCC (73). Chen *et al* reported that miR-1254 may inhibit the progression of OSCC, and restoring miR-1254 expression may represent an effective treatment strategy for

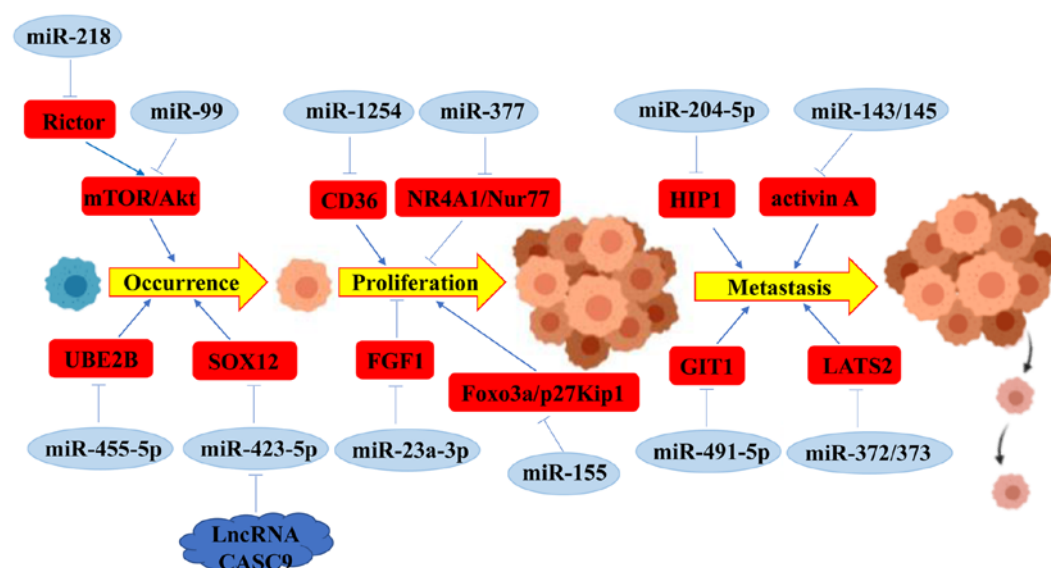


Figure 1. miRNAs involved in oral cancer progression. Summarized representation of miRNAs and their regulatory networks in oral cancer occurrence, proliferation and metastasis. mTOR, mammalian target of rapamycin; Akt, protein kinase B; UBE2B, ubiquitin-conjugating enzyme E2B; SOX12, SRY-box transcription factor 12; FGF1, fibroblast growth factor 2; NR4A1/Nur77, nuclear receptor subfamily 4 group A member 1; Foxo3a/p27^{Kip1}, forkhead box O3A/cyclin-dependent kinase inhibitor 1B; HIP1, Huntingtin-interacting protein 1; GIT1, GPCR kinase 2 interacting protein 1; LATS2, large tumor suppressor kinase 2. ↑: Promoting effect; T: Inhibiting effect. (This figure was created using BioRender.com).

OSCC (61). Similarly, miR-377 and miR-23a-3p suppressed cell proliferation and promoted apoptosis in OSCC, suggesting that both miR-377 and miR-23a-3p may prove to be of value as therapeutic targets for OSCC in the future (63,64). In summary, all the aforementioned data suggest that miRNAs may be considered as effective anticancer targets, and they may be used to develop novel treatment strategies for oral cancer.

4. Discussion and outlook

Although great progress has been made in the diagnosis of oral cancer, the methods for early diagnosis and prognosis require further improvements. Early diagnosis may markedly increase the effectiveness of treatment and prolong the survival of patients with oral cancer. Therefore, it is urgent to develop novel biomarkers with higher accuracy, sensitivity and specificity, that are more convenient for clinical detection.

With the development of sequencing technology, an increasing number of miRNAs have been revealed to be specifically expressed in a variety of samples from oral cancer (15,16). These miRNAs also play a key role in regulating cellular processes and behaviors (66,68). miRNAs may represent optimal biomarkers and new therapeutic tools for oral cancer. However, although the miRNAs aforementioned appear to be promising candidates as biomarkers, they require further investigation, including biological study and clinical verification. Furthermore, the source, formation and regulatory networks of miRNAs are quite complex, and the expression level of miRNAs in different stages of oral cancer is also different. Hence, it is necessary to elucidate the mechanism of miRNA formation, which may contribute to early diagnosis, targeted therapy and prognosis evaluation of oral cancer patients. Notably, the therapeutic miRNAs that may be used to develop novel targeted drugs require further research in terms of suitable and effective *in vivo* delivery methods. Identifying

key targets and building a targeted delivery system (such as a nano-miRNA system) will be our future research priorities.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

JW, RY, JY designed the review and edited the manuscript. JW, NL, XL wrote the manuscript. JW, RY and ZC collected and analyzed data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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