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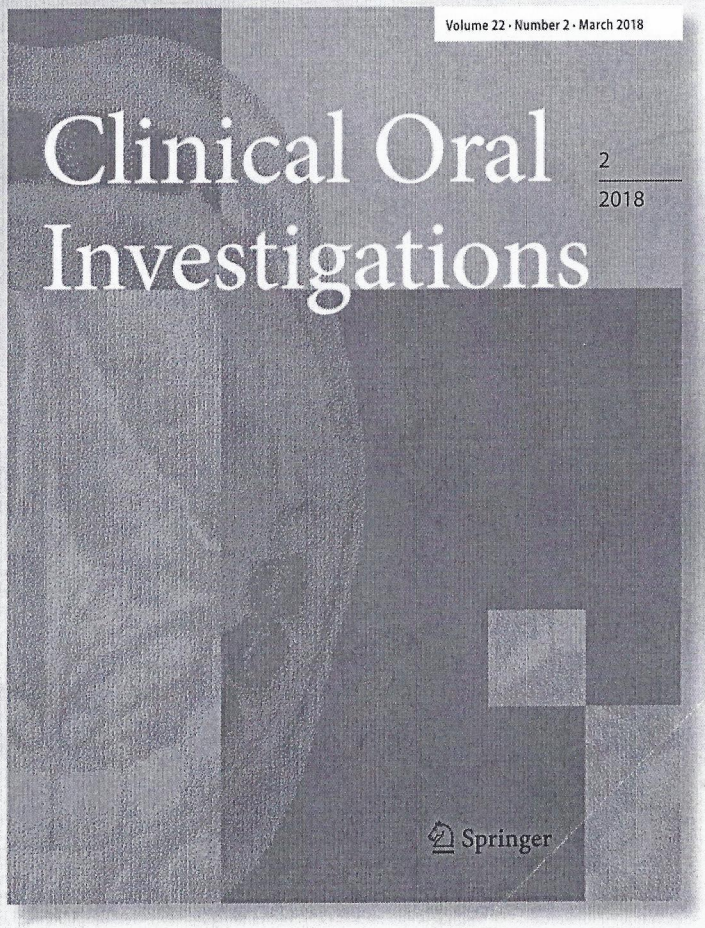

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REVIEW

MicroRNAs as effective surrogate biomarkers for early diagnosis of oral cancer

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Abstract

Background Oral squamous cell carcinomas (OC) are life-threatening diseases emerging as major international health concerns.
Objective Development of an efficient clinical strategy for early diagnosis of the disease is a key for reducing the death rate. Biomarkers are proven to be an effective approach for clinical diagnosis of cancer. Although mechanisms underlying regulation of oral malignancy are still unclear, microRNAs (miRNAs) as a group of small non-coded RNAs may be developed as the effective biomarkers used for early detection of oral cancer.
Methods A literature search was conducted using the databases of PubMed, Web of Science, and the Cochrane Library. The following search terms were used: miRNAs and oral cancer or oral carcinoma. A critical appraisal of the included studies was performed with upregulated miRNAs and downregulated miRNAs in oral cancer.
Results In this review, we summarize the research progress made in miRNAs for diagnosis of oral cancer. The involvement of miRNAs identified in signal transduction pathways in OC, including Ras/MAPK signaling, PI3K/AKT signaling, JAK/STAT signaling, Wnt/β-catenin signaling, Notch signaling, and TGF-β/SMAD signaling pathway.
Conclusions A number of studies demonstrated that miRNAs may be developed as an ideal set of biomarkers used for early diagnosis and prognosis of cancers because of the stability in human peripheral blood and body fluids and availability of non-invasive approaches being developed for clinical utility. Clinical relevance: These findings suggest that miRNAs as biomarkers may be useful for diagnosis of OC.

Keywords Oral cancer · Pathogenesis · Biomarkers · miRNA biology · Early diagnosis

Min Cao and Lijuan Zheng contributed equally to this work.

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Introduction

Oral cancer (OC) is a common malignancy worldwide. Each year, more than 300,000 new cases of the disease are diagnosed and over 140,000 deaths due to oral cancer occur [1]. The 5-year survival rate was improved from 54% in 1987–1989 to 66% in 2005–2011 [2]. The incidence of male-to-female ratio is approximately 2:1, mostly occurred in patients at 45–64 years old (about 50%), and increased by ages. OC occurred commonly in the tongue [3–5]. About 90% of OC is classified as oral squamous cell carcinomas (OSCC) [6].

Among all risk factors, cigarette, alcohol, and nutritional deficiency are the most common risk factors [7, 8]. In addition, virus infection, such as Epstein–Barr virus (EBV) and human papillomavirus (HPV), is also one of the major factors of OSCC [9–12]. The bad habit, such as betel quid chewing in South and Southeast Asia, enhances the incident risk [13, 14].

Table 1 Summary of miRNA profile in OC sample

Assay type	Sample type	Number of samples (experimental /control)	Number of probes	Number of candidate miRNAs	Reference
Agilent's SurePrint G3 Human v16 miRNA Array	Whole blood	20/20	1349	21	[26]
GSE28100 [the Gene Expression Omnibus (GEO) accession number] were downloaded from the GEO database	Resected tissue	17/3	NR	15	[27]
miRCURY LNA microRNA power labeling	Fresh frozen tumor tissue	16/10	1719	25	[28]
Affymetrix GeneChip miRNA array	Resected tissue	51/40	847	25	[29]
Agilent's SuperPrint G3 Human miRNA microarray System (V16)	Cell	1/1	NR	53	[30]
Ncode™ Multi-Species miRNA Microarray	Resected tissue	8/7	329	22	[31]
miRCURY LNA™ microRNA Array	Resected tissue	21/8	1168	46	[32]
TaqMan® Array MicroRNA Cards (Cards A and B)	Saliva	15/7	754	25	[33]

NR not reported

Additionally, air pollution, solar radiation, and other factors also have the potential to cause OC [3].

Currently, diagnosis of OC still remains a challenge. Development of biomarkers used for early diagnosis and effective therapeutic targets of OC is unmet for reducing the death rate [15–19]. MicroRNAs (miRNAs) as a new set of biomarkers play an important role in oral carcinogenesis. miRNAs are one of the small non-coding RNAs, which can regulate a variety of biological processes by targeting messenger RNAs (mRNAs) specifically [20]. Thus, dysregulated expression of miRNAs occurred in different cancers and even in different malignant stages of the same cancer [21]. A number of studies demonstrated that miRNAs may be developed as an ideal set of biomarkers used for early diagnosis and prognosis of cancers because of the stability in human peripheral blood and body fluids and availability of non-invasive approaches being developed for clinical utility [22]. In this review, we will summarize what have been achieved in miRNAs as biomarkers for diagnosis of OC and the molecular mechanisms underlying miRNA regulation in OC, indicating potential for development of new anti-OC drugs in the future.

miRNA profiling in OC

miRNAs are about 22 nucleotides in length and one of the classes of endogenous small non-coding RNAs, which typically inhibit the translation and the stability of mRNAs, controlling genes involved in cellular processes, such as inflammation, cell cycle regulation, stress response, differentiation, apoptosis, and migration [23]. They are deregulated in cancer versus the normal tissue and actively participate in human carcinogenesis [24]. According to its chemical property of miRNAs, circulating miRNAs are practically useful in clinic because of its stability in serum and reproducibility in each clinical assay [21]. In oral cancer, oncogenic miRNAs were shown to suppress tumor suppressor genes resulting in reducing expression of the target proteins vice per se [10, 25].

Extensive studies of miRNA profiling in blood, saliva, cell, and surgical tissues of OC have been performed and showed that several hundreds to thousands of miRNAs have been identified in the past decade. In the present review, we review the findings made in those studies in OC as listed in Table 1 [26–33]. The findings in Table 1 from five microarray studies using resected tumors and from three studies using whole blood, saliva, and cell lysates, respectively, show the upregulated miRNAs, including miR-182, miR-31, and miR-155, and downregulated miRNAs, including let-7, miR-125b, and miR-34a, in cancer as compared to the adjacent tissues or health subjects. Surprisingly, there are some of the unconfirmed observation made in those studies, showing some research group reported miRNAs to be upregulated but actually reported to be downregulated in another study group, including miR-378, miR-27a, miR-181b, miR-155, miR-146a, let-7f, and let-7g, suggesting that further investigation regarding those miRNAs unconfirmed is propelled.

Possible roles of miRNAs identified in OC

The possible functions of some miRNAs identified in OC were further characterized in several groups as listed in Tables 2 and 3 and Fig. 1 and summarized in the following sections.

Table 2 miRNAs upregulated in OC

miRNAs	Biopsies	Targets	Effect characteristic	Reference
miR-182	Tissue and cell	RASA1 and SPRED1	Promotes cell proliferation, cell cycle progression, colony formation, and invasion capacity	[34]
miR-31	Tissue and cell	AKT and C/EBPβ	Enhances among malignant phenotypes and OSCC tumorigenesis	[35]
miR-21	Tissue and cell	PTEN	miR21 upregulation was significantly correlated with PTEN depletion	[36]
	Tissue and cell	STAT3	miR-21 overexpression was dependent on STAT3 activation and induces tumor growth	[37]
	Tissue	Bcl-2	Indicates poor survival and therapeutic outcomes	[38]
miR-424-5p	Tissue and cell	STAT5	Promotes OSCC cell invasion and migration through direct inhibition of SOCS2 expression	[39]
miR-155-5p	Tissue and cell	SOCS1	Induces epithelial-mesenchymal transition (EMT) by upregulating STAT3 via SOCS1	[40]
miR-155	Tissue and cell	AGTR1 and MEIS1	Silences MEIS1 and AGTR1 via p53 and upregulates miR-155 in HNSCC	[41]
miR-20a	Tissue	Casp-2/-7/-8, Bcl-2 and DIALO	Evades apoptosis	[38]
miR-17-5p	Tissue	Casp-2/-7/-8, Bcl-2 and DIALO	Inhibits hypoxia-induced apoptosis	[38]
miR-15a	Blood and tissue	Not reported	Reduced expression of mir15a is associated with OSCC staging	[42]
miR-92b	Tissue and cell	NLK	Activates NF-κB signaling via regulation of NLK and induces cell proliferation	[43]
miR-223	Plasma, tissue and cell	STMN1 and IGF1R	Inhibits cell proliferation and induces apoptosis	[44]
miR-455-5p	Tissue and cell	UBE2B	Binds SMAD3-specific promoter regions, leads to UBE2B downregulation, and contributes to oral cancer tumorigenesis	[45]
miR-221	Tissue, cell, and mouse model	TCF12	Induces cell proliferation	[46]

Ras/MAPK pathway

Mutations often occurred in the Ras-Raf-MEK-ERK-MAPK (Ras-MAPK) axis in OC, which is playing an important role in the regulation of proliferation, differentiation, and survival [77–79]. Recent studies showed that miR-182 was significantly upregulated in tissues and cell lines of OC. Further study using luciferase-binding assays suggested that miR-182 suppressed RASA1 and SPRED1 by directly binding to the 3′ UTRs of those genes, leading to activation of the Ras–MEK–ERK pathway. An ectopic study of miR-182 in an OC cell line enhanced cell proliferation, cell cycle progression, colony formation, and invasion capacity [34]. Another study showed that miR-126b induced apoptosis of human tongue carcinoma cell Tca8113-P60 by activation of p38 MAPK (mitogen-activated protein kinase) signaling pathway [54]. In addition, a recent study showed that miR-596 activated the ERK1/2 signaling pathway by targeting LGALS3BP. Either downregulated expression of miR-596 or upregulated expression of LGALS3BP inhibits proliferation significantly resulting in apoptosis [52].

Recent study showed that miR-181a suppressed K-ras expression in OSCC cell lines, thus, upregulation of miR-181a inhibits proliferation and anchorage independent growth ability of OSCC by suppressing K-ras activity [47]. Further, downregulation of let-7 family increases K-ras expression [49]. Additionally, studies showed that miR-125b-1 and miR-99a inhibited activation of the MAPK pathway by directly targeting TACSTD2 and insulin-like growth factor 1 receptor (IGF1R), respectively [48, 50]. A study showed that miR-126 suppressed cell proliferation, cell cycle progression, cell invasion, and colony formation leading to cell apoptosis by targeting EGFL7 [53]. These studies showed that those miRNAs downregulated in OSCC may be developed as therapeutic agents for OC.

PI3K/AKT pathway

The PI3K/AKT pathway resides the downstream of the Ras pathway and directly regulates protein synthesis, cell cycle progression, and metabolism [80]. PTEN is a tumor suppressor gene in PI3K-AKT-mTOR pathway and involved in many cellular processes, which is targeted by miR-9 and miR-21 [36, 55]. Downregulation of miR-9 is associated with methylation in OC cells; thus, activation of PTEN may demethylate miR-9 resulting in inhibition of cell proliferation and viability significantly. Nevertheless, miR-21 upregulation is significantly correlated with PTEN depletion, which may influence OC tumorigenesis. Moreover, miR-139 transfected into OC cells inhibited cell proliferation leading to cell apoptosis [57, 58]. Interestingly, a study showed that miR-218 suppressed the TOR-AKT signaling by targeting the mTOR component

Table 3 miRNAs downregulated in OC

miRNAs	Biopsies	Targets	Effect characteristic	Reference
miR-181a	Cell	K-ras	Suppresses proliferation and anchorage-independent growth ability	[47]
miR-125b-1	Cell and tissue	TACSTD2	Inhibits activation of the MAPK pathway through modulation of TACSTD2 expression	[48]
miR-125b	Tissue and cell	BAK1	Boosts the level of BAK1 that is controlling the apoptotic pathway	[41]
Let-7	Whole blood or buccal cells	K-ras	Significantly associates with poor prognosis	[49]
miR-99a	Tissue and cell	IGF1R	Reduces migration and invasion	[50]
	Tissue	Akt/mTOR	Regulates the Akt/mTOR signaling	[51]
miR-596	Cell and primary tumor samples	LGALS3BP	Activates the ERK1/2 signaling pathway	[52]
miR-126	Tissue and cell	EGFL7	Suppresses cell proliferation, cell cycle progression, cell invasion, and colony formation while inducing cell apoptosis	[53]
miR-126b	Tca8113-P60 cell	p38 signaling pathway	Induces apoptosis of human tongue carcinoma Tca8113-P60 cells	[54]
miR-9	Tissue and cell	PTEN	Inhibits cell proliferation and elevation of the tumor suppressor PTEN	[55]
		IL6	Activates IL6-STAT3 axis	[36]
		CXCR4	miR-9 underexpression led to constitutive activation of β-catenin through activation of CXCR4 expression	[56]
miR-139	Cell	AKT	Inhibits oral cancer cell proliferation and induces cell apoptosis	[57]
	Saliva	Not report	miR-139-5p may serve as a potential biomarker for early TSCC detection	[58]
miR-34a	Tissue and cell	Nanog and p53	Suppresses CD44 expression and directly targets Nanog	[36]
	Tissue	MDM4 and SIRT1	Relieves MDM4 and SIRT1and sequesters p53	[51]
	Tissue	Casp-2, BBL3 and Bcl-2	Induces cell cycle arrest and apoptosis, whereas its downregulation attenuates p53-dependent apoptosis	[38]
miR-34b/c	Tissue and cell	p53	Tp53 upregulates miR-34b/c in normal condition	[41]
miR-542-3p	Tissue and cell	p53	Protects genome and inhibits cell growth and tumor formation in vivo	[36]
miR-218	Tissue and cell	Rictor	Targets the mTOR component Rictor and inhibits AKT phosphorylation	[59]
miR-203	KB cell	Yes-1	Induces the apoptosis of KB cells by directly targeting Yes-1	[60]
miR-329 miR-410	Tissue and cell	Wnt-7b	Attenuates Wnt–β-catenin pathway and inhibits cancer cell proliferation and invasion capabilities	[61]
miR-205	KB cell	Axin-2	Downregulates Axin-2 in KB human oral cancer cell	[62]
		caspase-3/-7 and IL-24	As a tumor suppressor increases the KB cell cytotoxicity and induces apoptosis	[63]
miR-494	Tissue and cell	Bmi1 and ADAM10	Silibinin (SB) upregulates miR-494 that inhibits Bmi1 and ADAM10 expression	[64]
miR-494-3p	Tissue and cell	Bmi1, p16 and RB1	Increases the radiosensitivity of OSCC cells through the induction of cellular senescence caused by the downregulation of Bmi1	[65]
miR-140-5p	Cell	ADAM10	Inhibits the invasion and migration of TSCC cells	[66]
miR-215	Tissue and cell	DTL and TYMS	Contributes to cell cycle arrest and cell detachment	[41]
miR-107	Tissue and cell	p53	p53 upregulates miR-107 in normal condition	[41]
miR-143	Cell and mouse model	PKCε, CDK6 and HIF1-β Nanog, Oct3/4, and Sox2	Inhibits clonogenic survival, cell invasion, and cell migration of HNSCC cells	[67]
	Tissue	MDM2	Relieves MDM2 and regulates p53 indirectly	[51]
miR-380-5p	Tissue	p53	Directly targets the 3′UTR of TP53	[51]
miR-504	Tissue	p53	Directly targets the 3′UTR of TP53	[51]
	Tissue and cell	CDK6	Suppresses HSCC cell proliferation	[68]
	Cell and animal model	FOXP1	Inhibits migration and invasion in SAS/CTGF-M3 cell	[69]
miR-137	Tissue and cell	CDK6	Arrests cell cycle at the G1-S checkpoint	[70]
miR-193a	Tissue and cell	E2F6	Arrests cell cycle at apoptotic change	[70]
miR-375	Tissue and cell	Sp1 and cyclin D1	Inhibits cell growth and its expression is correlated with prognosis of TSCC	[71]
miR-99b-3p	Tissue and cell	GSK3β	Inhibits OSCC cell proliferation and suppression of p65 (RelA) and G1 regulators (cyclin D1, CDK4, and CDK6) in vitro via GSK3β downregulation	[72]
miR-125a	Tissue and cell	ESRRA	Reduces the level of ESRRA, decreases cell proliferation, and increases apoptosis	[73]
miR-15a	Tissue	Bcl-2	As an antiapoptotic and proapoptotic BCL2 family gene which promotes the survival of oral cancer cells	[38]

Table 3 (continued)

miRNAs	Biopsies	Targets	Effect characteristic	Reference
miR-29a	Tissue	DIABLO, Casp-7, BBL3 and BAK1	As a positive regulator of p53	[38]
miR-200b miR-15b	Tissue and cell	BMI1	Are effective inhibitors of chemotherapy-induced EMT and tumor metastasis	[74]
miR-101	Tissue and cell	ZEB1	Inhibits OSCC cell proliferation, apoptosis resistance, migration, and invasion	[75]
miR-639	Tissue and cell	FOXC1	Underexpression of miR-639 is associated with metastasis in TSCC and poor patient survival	[76]

Rictor resulting in inhibition of AKT phosphorylation [59]. A study showed that miR-203 induces apoptosis of KB cells by directly targeting Yes-1 (Src family kinases), which activates downstream signaling, including MAPK/ERK and PI3K pathways [60]. On the other hand, upregulation of miR-31 by EGF is associated with activation of AKT and the C/EBPβ regulatory factors in OC. Curcumin attenuates both expression of the endogenous miR-31 and EGF [35]. IGF-1R signaling plays a pivotal role in normal proliferation and development of oral cells by activating PI3K/AKT and mTOR signaling [81], while miR-223 inhibits cell proliferation and induces apoptosis by targeting IGF-1R [44].

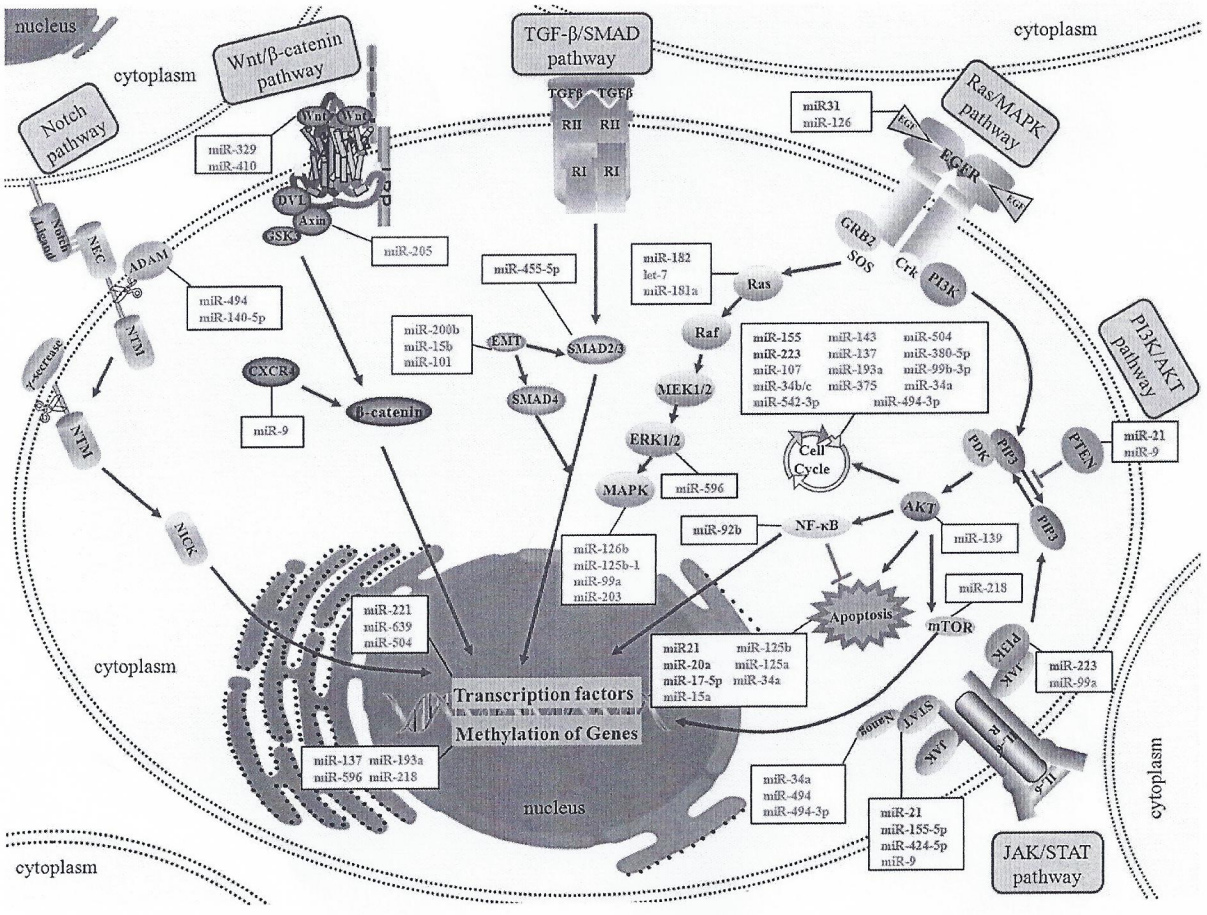

Fig. 1 This is the expression profile of miRNAs in oral cancer (OC). This cartoon describes the involvement of miRNAs identified in signal transduction pathways in OC, including Ras/MAPK signaling, PI3K/AKT signaling, JAK/STAT signaling, Wnt/β-catenin signaling, Notch signaling, and TGF-β/SMAD signaling pathway. Red or green text indicates miRNAs upregulated or downregulated, respectively

JAK/STAT pathway

The Janus kinases (JAKs) and signal transducer and activator of transcription (STAT) pathway is well known for its role in tumor cell proliferation, survival, invasion, and immunosuppression of OC [82, 83]. miR-21, miR-155-5p, and miR-424-5p are upregulated in OC [37, 39, 40]. STAT is a key regulator in JAK/STAT pathway. Enhanced expression of STAT3 by IL-6 induced miR-21 overexpression and influenced cancer cell migration and invasion ability. miR-155-5p induces epithelial-mesenchymal transition (EMT) by upregulating STAT3 via SOCS1. STAT5-dependent expression of miR-424-5p exhibits oncogenic activity by negatively regulating SOCS2 expression and plays an important role for IL-8-induced cellular invasiveness. In contrast, both miR-9 and miR-34a are downregulated in OC [36]. miR-9 modulates Nanog/STAT3 axis via IL6, and miR-34a suppresses CD44 expression and directly targets Nanog expression leading to cancer cell apoptosis and proliferation.

Wnt/β-catenin pathway

The Wnt/β-catenin signal transduction cascade regulates myriad biological phenomena, including cancer cell proliferation, differentiation, invasion, and migration. Upon activation of Wnt pathway, β-catenin accumulates in the cytoplasm and then translocates to the nucleus, where it engages in DNA-bound TCF transcription factors. Dysregulation of the Wnt pathway is closely linked with oral carcinogenesis [84, 85]. Downregulation of miR-9 leads to activation of the CXC chemokine receptor 4 (CXCR4) gene and activates the downstream regulator, β-catenin [56]. However, overexpression of miR-205 downregulates axis inhibitor protein 2 (Axin2) in KB oral cancer cells. Axin2 is a key regulator in the Wnt/β-catenin signaling pathway [62]. miR-329 and miR-410 are low-expressed in oral tumor tissues and cells, which inhibit Wnt-7b to attenuate the Wnt–β-catenin pathway and inhibit cancer cell proliferation and invasion capabilities [61].

Notch pathway

Notch signaling plays an essential role in cell proliferation, differentiation, and development and maintaining cellular homeostasis. It is related to multiple oncogenic signaling pathways, such as NF-κB, AKT, and Ras [86]. Dysregulation of the Notch pathway may cause progression of OC [87]. Upon ligand binding, Notch receptors undertake two cleavage processes mediated by a member of a disintegrin and metalloprotease (ADAM) family and γ-secretase and led to the release of the Notch intracellular domain (NICD). As a result, it activates the transcriptional complex [88]. Among the two cleavage processes, ADAM10 was targeted by both miR-494 and miR-140-5p directly to regulate the Notch pathway [64, 66]. When silibinin (SB) is used for treatment of head and neck cancer, it was reported that tumor growth was reduced, and the survival time of the tumor-bearing mice was prolonged by overexpression of miR-494 inhibiting Bmi1/ADAM10 expression. Moreover, miR-140-5p directly targeted ADAM10 leading to inhibition of invasion and migration of TSCC cells.

TGF-β/SMAD pathway

The TGF-β/SMAD pathway plays critical roles in cellular physiology. In OC, transforming growth factor-β1 (TGF-β1) is an important regulator in cell proliferation and carcinogenesis and has been regarded as a key initiator of EMT [89, 90]. miR-455-5p binds specific promoter regions of SMAD3, leads to UBE2B downregulation, and contributes to oral tumorigenesis [45]. miR-200b and miR-15b are effective inhibitors of chemotherapy-induced EMT and tumor metastasis by directly targeting BMI1 [74]. ZEB1 is a crucial activator of the EMT in cancer and miR-101 directly targets ZEB1 and leads to induction of the EMT, and downregulation of miR-101 promotes OSCC growth and metastasis [75]. Furthermore, activated IL-6 (interleukin-6) signaling may be the mechanism underlying the effects of TGF-β1 on OC [91].

Cell cycle-associated signaling

Cell cycle is a series of cellular events being regulated synergistically by numbers of genes in normal physiological conditions for cell growth and differentiation. In normal cell physiological state, cell cycle negative regulators (e.g., p21 and p16) and its positive regulators (e.g., Rb and E2F) are tightly regulated. In abnormal conditions (e.g., UV radiation, toxins), it causes DNA damage leading to activation of p53 and p21, resulting in cell cycle arrest by inhibition of cyclins (A, B, D1, and E) and CDKs (2, 4, and 6) [92, 93].

p53 mutation anomalously alters the expressions of miR-107, miR-215, miR-34b/c, miR-125b, and miR-155. Then, miR-155 upregulation silenced MEIS1 and AGTR1 expression, which influence blood pressure and megakaryocytic lineage, respectively. miR-215 targets DTL and TYMS to regulate cell cycle; dysregulated expression of miR-125b enhances the level of BAK1 in the apoptotic pathway [41]. In addition, p53 was activated by miR-542-3p and miR-34a, leading to cell cycle arrest, in which these were downregulated in OC [36]. The regulatory effects of miRNAs on cell cycle may be initiated by targeting the cell cycle regulators in both direct and indirect ways. miR-380-5p and miR-504 directly target the 3′UTR of p53, and miR-143 and miR-34a relieve MDM2 and MDM4, respectively, to regulate p53 indirectly [51]. miR-137, miR-504, and miR-107 can

regulate CDK6 [67, 68, 70]; miR-193a targets E2F6 [70] in cell cycle. Furthermore, downregulation of miR-375 up-regulates Sp1 expression and activates Cyclin D1 [71]. miR-494-3p controls Bmi1, p16, and RB1, which increases the radiosensitivity of the OSCC cells [65]. miR-99b-3p represses p65 (Rel A) and G1 regulators (cyclin D1, CDK4, and CDK6) in vitro by downregulating GSK3β [72]. Moreover, Stathmin1 (STMN1) is a key microtubule regulatory protein that controls cellular proliferation and S phase of the cell cycle [94]; miR-223 inhibits cell proliferation and induces apoptosis by directly targeting STMN1 [44].

Apoptosis

Cell apoptosis is mainly governed by two fundamental pathways: intrinsic pathway and extrinsic pathway [95, 96]. Defects of key regulators in these programs cause unlimited growth of OC. Caspase-3/-7/-8/-9 and Bcl-2 are the key regulators of apoptosis, which were regulated directly by miRNAs. Downregulated miR-125a activates estrogen-related receptor α (ESRRA) leading to OSCC proliferation [73]. Tumor suppressor miR-205 increases the KB cell cytotoxicity and induces apoptosis through activating Casp-3/-7 and IL-24 [63]. Besides, miR-21, miR-20a, and miR-17-5p evade apoptosis by targeting key regulators, such as Bcl-2 and Casp-2/-7/-8, while miR-34a, miR-15a, and miR-29a may induce cell apoptosis in this pathway [38]. Interestingly, there is an unconfirmed observation for miR-15a from two study groups, Brito's and Coutinho-Camil's [38, 42], indicating that the regulatory role of miR-15a is required to be further investigated in OSCC.

The transcription factor nuclear factor-kappa B (NF-κB) regulated by the tumor necrosis factor (TNF) in a TNF receptor-associated death domain (TRADD) plays an important role in oxidative stress-mediated cell apoptosis [97]. Mutation occurred in Casp-8 protein (G325A)-activated NF-κB signaling resulting in suppression of cellular apoptosis, suggesting the important role of Casp-8 and NF-κB in the cellular apoptotic pathway [98]. miR-92b activates the NF-κB signaling via regulation of NLK and induces cell proliferation [43]. miRNAs, such as miR-380-5p, miR-504, miR-542-3p, and miR-34a, regulate cell cycle activity causing cell cycle arrest and apoptosis by targeting p53.

Transcription factors and DNA methylation

Forkhead box (FOX) proteins are a subgroup of the Forkhead family of transcription factors, and FOXO1 transcription factors regulate various cellular functions, such as cell proliferation, apoptosis, and differentiation. Reduced expression of miR-639 underscores the mechanism of TGFβ-induced EMT in TSCC by targeting FOXC1 [76]. miR-504 acts on FOXP1 that takes part in the miR-504-induced cellular invasion [69]. Furthermore, miR-211 directly suppresses transcription factor 12 (TCF12) and increases antioxidant activity to induce carcinogenesis [46].

miRNA expression are closely related with DNA methylation and hypermethylation in OC. Downregulation of miR-137, miR-193a, miR-596, and miR-218 expression through tumor-specific DNA hypermethylation was observed in OC [52, 59, 70]. These miRNAs are frequently silenced by DNA methylation and loss of tumor suppressor function, which is the mode of their role as described above.

Perspectives

Although great progression has been made in diagnosis of OC, the molecular mechanism underlying drug resistance due to genetic mutations and cancer stem cells (CSC) is still a major challenge to effective therapy of OC [99]. Early diagnosis of the disease may enhance significantly the survival rate of OC. Thus, it is unmet to develop biomarkers with ideal accuracy, sensitivity, and specificity used for detection of early lesions in OC. Obviously, miRNAs may be right candidates in this regard as mentioned above [100]. Certainly, miRNAs mentioned above require to be further investigated in a number of ways including biology study and clinical validation, especially for those have not confirmed. Gene mutations may be closely associated with miRNA regulation. Moreover, it has been reported that individual as well as combined genotypes of miRNA-related variants not only used to detect cancer lesions, but also can predict the risk of oral premalignant lesions (OPL) [101].

More importantly, understanding the regulatory roles of miRNAs in metabolic reprogramming causing heterogeneity in oral tumor microenvironment is crucial for the development of effective biomarkers used for early diagnosis and targets for development of novel drug agents.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, a formal consent is not required.

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