MicroRNAs as biomarkers in Oral Cancer: *Literature Review*

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INTRODUCTION

Oral cancer (OC) is a form of head and neck cancer and **it's the sixth most common type of cancer worldwide.** OC may be preceded by **oral lesions that have higher risk of malignant transformation** (OPML). Oral squamous cell carcinoma (OSCC) is the most common cancer type arising in the oral cavity.
Early diagnosis of OC is extremely important for treatment and patients' survival. Hence, **research directed towards the identification of biomarkers** for early diagnosis of OSCC and indicators of good or bad prognosis is undeniably essential.
MicroRNAs (miRs/miRNAs) are endogenous small (18-25 ribonucleotides) noncoding RNAs that **negatively regulate gene expression** at posttranscriptional level. Many recent studies have shown **deregulated expression of miRs** in OSCC, indicating **their potential role in oral cancer development** (Fig.1) and their use as **diagnosis and prognosis biomarkers** for this disease.

AIM

The aim of this research was to **investigate the role of miRs in oral cancer**, showing some of the **most deregulated**, as well their **potential as biomarkers** for early diagnosis and prognosis in this malignancy.

MATERIALS AND METHODS

The research strategy was performed using the ***PubMed/Medline*** electronic database, using the keywords ***"microRNA"***, ***"biomarkers"*** and ***"oral cancer"*** and the Boolean operator "**AND**". **Inclusion criteria** included **studies with human samples**, published in the last 10 years (**2009-2019**) and in **English**. The **exclusion criteria** consisted in studies using cell lines or other animals, in other language besides English and without available abstract. **255 studies** were found and after reading the title and the abstract, 190 were excluded. **65 studies** were selected for full-text analysis, and **12 met the inclusion and exclusion criteria.**

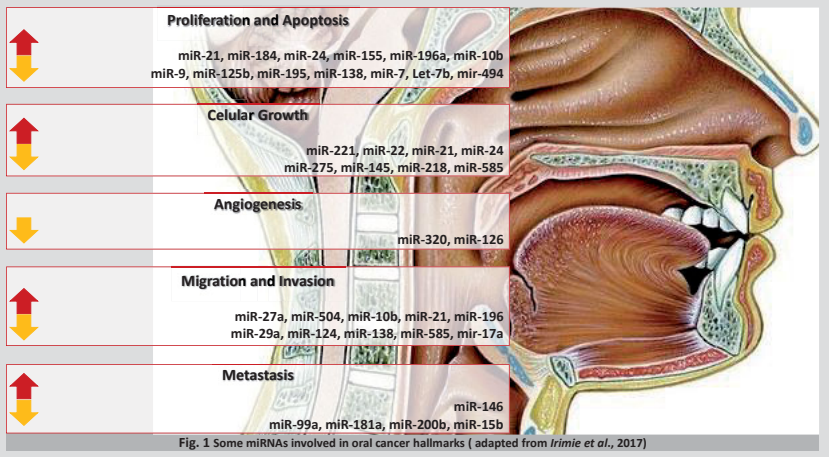

Fig. 1 Some miRNAs involved in oral cancer hallmarks (adapted from *Irimie et al.*, 2017)

RESULTS

Study	OPML studied	Number of samples (Controls/OPML/OC)	Type of sample	miR investigated	Sensitivity/ Specificity/ AUC (OPML)		Results
Zahran *et al.* (2015)	OPML not defined But divided in with dysplasia (OPML-D) and without dysplasia (OPML-ND)	80 (20/20+20/20)	Saliva	miR-184	80%/ 75%/ 0,86		**miR-21 and miR-184 overexpressed** in OC and OPML-D. **miR-145 underexpressed** in OC and OPML-ND.
				miR-145	60%/ 70%/ 0,68		
				miR-21	65%/ 65%/ 0,73		
Brito *et al.* (2013)	Oral leukoplakia (OL) with different grades of dysplasia	45 (6/22/17)	Tissue	miR-21	ND		**miR-21 and miR-345 overexpressed** in OC and OL. **miR-181b overexpressed** in OC and in OL with moderate/severe dysplasia.
				miR-345			
				miR-181b			
Lu *et al.* (2014)	Hyperkeratosis (HK), parakeratosis (PK), squamous hyperplasia (SH), verrucous hyperplasia (VH)	159 (53/16/90)	Plasma	miR-196a	56%/ 94%/ 0,76	Combined: 69%/ 85%/ 0,85	**miR-196a and miR-196b overexpressed** in OC and OPML.
				miR-196b	100%/ 59%/ 0,84		
Arão *et al.* (2012)	Oral Lichen Planus (OLP)	37 (6/31/0)	Tissue	miR-146a	ND		**miR-146a and miR-155 overexpressed** in OC and OLP.
				miR-155			
Roy *et al.* (2016)	Oral leukoplakia (OL), Oral Lichen Planus (OLP)	80 (20/20+20/20)	Tissue	miR-26a	ND		All miRs were overexpressed in OLP tissues. **miR-29a and miR-26a underexpressed** in OC and in OL.
				miR-29a			
				miR-34b			
				miR-423			
Hung *et al.* (2016)	OPML not defined	44 (24/20/0)	Saliva	miR-31	AUC= 0,81		**miR-21 and miR-31 overexpressed** in saliva of patients with OLPM.
				miR-21	AUC =0,56		

Study	Number of samples (Controls/OC)	Type of sample	miR investigated	miR expression in OC	Sensitivity/ Specificity/ AUC (OC)		Role of miR deregulation in oral carcinogenesis
Liu *et al.* (2010)	64 (21/43)	Plasma and saliva	miR-31	Overexpression	AUC = 0,82		Induces tumor initiation and progression
Sun *et al.* (2016)	144 (40/104)	Serum	miR-9	Underexpression	ND		Increases tumor growth and metastasis
Ren *et al.* (2014)	90 (32/58)	Blood	miR-21	Overexpression	62%/ 91%/ 0,79		Promotes tumor migration and invasion
Sasahira *et al.* (2012)	128 (10/118)	Tissue	miR-126	Underexpression	ND		Induces angiogenesis
Yang *et al.* (2011)	51 (12/39)	Plasma and tissue	miR-181a	Overexpression	AUC= 0,84	Combined AUC =0,89	Increases metastasis and vascular invasion
			miR-181b		AUC= 0,74		
Xu, *et al.* (2016)	204 (103/101)	Serum	miR-483-5p	Overexpression	85%/ 75%/ 0,85		Increases metastasis and tumor differentiation

CONCLUSION

Although a large number of studies are based on tissue samples, **for early diagnosis, non-invasive collection techniques and easily accessed samples are essential**. Since they have **direct contact with oral lesions, are easy to collect and their use is well accepted** by patients, **saliva and oral exfoliative cytology** represent effective samples for miRs' detection. miRs have characteristics that classify them as **ideal tumor markers**, such as their **stability at high temperatures and extreme pH values, the ease in their detection and their association with clinical-pathological parameters**.
miR-21, miR-31 and miR-181 seem to be closely related with OC and with the malignant transformation of oral lesions.
However, there are still some limitations, such as the **lack of standardization of sample processing and intra-tumor heterogeneity**, which condition their progress as clinical tool.
Therefore, **more studies and research are needed before their generalized use in the clinical field**.

CLINICAL IMPLICATIONS

Dentists have **a key role in early detection of oral malignant lesions** and monitoring conditions with high risk of malignant transformation. Studies regarding miRs show **positive perspectives for their use in clinical practice**, for diagnosis and prognosis of OC and OPML. Therefore, **clinicians should have knowledge about miRs** and be aware of new tools based on these molecules.

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