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Review Article

Human Salivary microRNA as Biomarkers in Oral Potentially Malignant Disorder-A Narrative Review

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ABSTRACT

Oral potentially malignant disorders (OPMDs) denote mucosal disorders of oral cavity with higher possibility for malignant transformation. The relatively stable salivary single stranded non-coding RNAs (microRNA) can be utilized as biomarker in different malignancies for diagnosing and management purposes. This paper aims to assess the clinical application of salivary miRNAs in OPMD patients from the available literature for early discovery of oral cancer. A systematic electronic search was made and 13 articles were collected and included to fulfill the study objective. Evidence from numerous reports suggested that majority of the salivary miRNAs have significantly overexpressed in different OPMD patients. These include miR21,miR31,miRNA-184,miR-30e-3p, let-7a-5p,miR-335-5P,miR-144,miR-25-3p,miR19a-3p,miR-25-3p,miR19a-3p,miR-660-5p,miR-140-5p,miR-590-5p,miR-9. The downregulated markers are miR-27a/b,microRNA 320a,miR 200a,miRNA-145,miR-10b-5p,miR-99a-5p,miR-99b-5p,miR-145-5p,miR-100-5p,miR-125b-5p,miR-181b,miR-181c, miR-331-3p, miR-15a-5p, miR-708, miR-150-5p. Among the above mentioned markers, the miR-31,miR-21,miR-184,miR-27b have shown promising clinical utilization in OPMDs since the AUC results suggested acceptable to excellent discrimination between OPMDs from other study groups. Besides, the miR-31and miR-21 is frequently studied among others. Micro RNAs have distinctive expression patterns in OPMDs and furnish them a specific tool in diagnostic/prognostic applications in these patients. In addition, the miRNAs could also be used as therapeutic tool for specific gene target thereby improved management of OPMD patients is possible.

Key words: Saliva, Biomarker, Oral potentially malignant disorders, microRNA, Oral cancer.

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INTRODUCTION

Squamous cell carcinoma (OSCC) of the mouth is the eleventh most frequent cancer in the world. It is responsible for the majority of oral cancers. Almost 80% of the OSSC proceeds by Oral Potentially Malignant Disorders (OPMD). In India, the prevalence rate ranges from 2.5 to 8.4% with a 17% malignant transformation(MT) rate. The degree of epithelial dysplasia is the primary factor which contributes the malignant progression of OPMD.[1-6] There are several types of OPMD among which leukoplakia, lichen planus and submucous fibrosis are frequently reported clinical cases. The chief risk factors are tobacco, alcohol habits and oncogenic viruses. The poor survival rate is associated with diagnosis in later stage of the disease. Further, the screening of OPMDs would be beneficial as a secondary prevention of cancer in multistep carcinogenesis process of oral cancer.

The genetic, epigenetic and transcriptional biomarkers help to diagnose the early stage OSCC. MicroRNA (miRNA) is the emerging biomarker which serves as prognostic and/or diagnostic purpose in OPMD and OSCC. The deregulation of miRNA in OSCC has been proven in numerous OSCC samples. MicroRNAs are tiny endogenous (18-22 nucleotides), noncoding RNA molecules which are accountable for variety of cellular and metabolic pathways comprising cell proliferation, differentiation and survival both in normal and disease states. They also contribute to a vital role in protein expression by attaching to their messenger RNA. They are one among the most popular types of gene-control molecules in the transcriptional and post translational levels.[2] Saliva being non-invasive sample has got its own advantage for biomarker study. With the advent of advanced detection methods, several salivary miRNA studies had given promising results for the OPMD prognosis and OSCC diagnosis with reliable sensitivity, specificity and AUC values. This paper reviews the various types and expression profiles of salivary miRNA and their clinical applications in OPMD patients. The goal of this study is to determine the expression levels of salivary miRNA in OPMD patients and to determine the most sensitive and specific salivary miRNA as diagnostic/ cancer predictive marker in OPMD patients.

MATERIALS AND METHODS

A meticulous review of literature has been carried out to gather data regarding the application of salivary miRNAs expression as diagnostic/ prognostic marker in OPMD patients.

Search Strategy

Both manual and electronic search were carried out from 2010-2020 in PubMed, Science Direct, SCOPUS and Google Scholar using the MeSH words in English language such as miRNA and saliva, salivary miRNA and oral cancer, Mirna and OSCC, miRNA and oral potentially malignant disorder, miRNA and leukoplakia, miRNA and lichen planus, miRNA and OSMF. Supplementary data was collected from reference list of articles and other relevant articles. By using filters, articles were sourced from years 2010-2020. Clinical trials, case-control Studies on expression of human salivary miRNA in OPMD as general and studies on expression of salivary miRNA in individual OPMDs such as leukoplakia, lichen planus and OSMF were included. Reviews, studies on tissues, cell lines, blood and studies other than the above mentioned OPMD lesions were omitted for this review.

DATA EXTRACTION AND RESULTS

The articles were chosen with a set of suitability principles and for the valuation of articles that fit the criteria. After eliminating the repetition of articles, the evaluation was completed with all cited publications' abstracts, as well as the complete text of the one that is available. Totally 13 studies were selected for this review. Each study's data was retrieved which includes type of OPMD, miRNA profiling, cohort size, expression of miRNA and the study inference. In descending order all the data are presented consecutively from the most recent to the oldest articles starting from year 2010 until 2020 with summaries in Table 1.[3-15]

Significance of miRNA in OPMD patients

The patient's prognosis would be considerably improved if OSCC was detected early in the high-risk group of OPMD. Treatment decisions can also be determined promptly based on the diagnosis and the risk for MT. A biomarker that is reliable, accurate, cost-efficient, and non-invasive can also be a beneficial tool for cancer screening and prevention programs.

The miRNA had participated in many pathological and physiological processes. These regulatory target repressions will lead to decreased mRNA levels and lowered translational efficiency.[16] Several studies have reported the diverse expression patterns of these miRNA in OPMDs when compared to normal patients, OSCC ,different grades of OPMDs and before after therapeutic interventions. According to research, miRNAs are variably expressed in certain cancer cells compared to normal ones. Moreover, miRNAs appear to cluster distinct types of solid tumors more precisely than mRNA and the fold change in miRNAs between cancer cells and normal cells is greater than miRNA expression.[17] A follow-up study of 820 days on Taiwan cohort have also proved that the OPMDs with recurrence and/or cancer transformation demonstrated an increased expression of miRNA-31 over the epithelium and they concluded that increased miR-31 and epithelial dysplasia are both risk factors for the advancement of OPMD.[9]

DISCUSSION

Source of miRNA

The lin-4 and let-7 miRNAs, which are key regulators of animal development, were initially identified in Caenorhabditis elegans.[18] The miRNA mode of action and mechanism of production are extensively studied and well characterized. Each miRNA can influence the expression of numerous target genes, and each target gene's expression can likewise be controlled by multiple miRNAs. The RNA-induced silencing complex is formed when mature RNAs are integrated and this miRNA-mRNA communication regulates the production of target mRNA by merging to their 3'-untranslated region (3' UTR) in a number of physiological and pathological processes.[2] In the process of carcinogenesis, miRNAs can control the expression of oncogene or tumor suppressor gene and might directly serve as oncogene or tumor suppressor gene. Hence, OSCC is expected to be a result of dysregulated miRNA expression.[19]

Circulating miRNA[20]

The circulating miRNAs are usually found in a variety of body fluids such as saliva. They exist either exosomal or non-exosomal forms. The sources include a product of cell damage, apoptosis, chronic inflammation, and necrosis or from passive leaking that occur in cells with a short half-life, such as platelets. They can also occur by means of active secretion such as cell derived membrane vesicles such as Micro particles (MP), shedding vesicles, exosomes and apoptotic bodies. They can be found in association with high- density lipoprotein (HDL) and argonaute protein (Ago2) through active secretion by protein-miRNA complex.

Advantages of salivary miRNA application in OPMD[20,21]

The miRNA in saliva are relatively stable and they are resistant towards the action of ribonucleases and long living in body fluids. They are packaged in the form of a vesicle, such as exosomes or apoptotic bodies. They are present in Ago-containing ribonucleic acid (RNP) complexes with nucleophosmin or with high density lipoproteins (HDL). The fold change and expression level is greater with miRNA than mRNA. They are easily accessible and collection procedures are non-invasive. The miRNAs are resilient towards the extremely stressing conditions of sample processing methods. Studies have shown that salivary miRNA profiling can discriminate between oral normal, OPMDs, cancerous, between subgroups and response to therapy.

Detection methods[22]

The preserved whole or supernatant saliva is used for detection methods. After the RNA extraction, the pre-amplification or without amplification, the miRNA can be discovered with reverse transcriptase quantitative PCR and miRNA stability assays. Quantitative RT-PCR with endogenous controls can be used to analyze circulating fluid miRNA levels. Real time PCR methods, digital droplet PCR, microarray hybridization and next generation sequencing techniques are also used to detect miRNAs.

Upregulated markers

When compared to healthy patients, mi RNA -21 is elevated in oral sub mucous fibrosis. Significant upregulation of miR-21 and miR-31 were found in severe dysplastic OPMDs compared to normal. Significantly higher levels of miR-21 were seen in patients with oral lichen planus (OLP), dysplastic OLP, and OSCC and in dysplastic OLP and OSCC; miR-31 levels were considerably higher. Micro RNA-21 and miRNA-184 levels were significantly higher in the OPMD vs normal and OSCC vs normal groups. Significantly increased miRNA-184 was reported in OPMD when compared to healthy control groups. 12 miRNAs were up regulated in progressive low grade dysplasia in comparison with non-progressive dysplasia which includes miR-30e-3p,miR21,let-7a-5p,miR-335-5P,miR-144,miR-25-3p,miR19a-3p,miR-25-3p,miR19a-3p,miR-660-5p,miR-140-5p,miR-590-5p,miR-9.

Downregulated markers

MicroRNA-27a/b was downregulated in OLP patients in comparison with healthy individuals. The microRNA- 320a was significantly decreased in OSCC and dysplastic OLP not in OLP patients without dysplasia. In compared to OLP patients, microRNA-27 b was considerably over expressed in OSCC patients. When compared to healthy controls, OLP, dysplastic OLP, and patients with OSCC had significantly lower levels of miR-200a.Thirteen miRNAs were down regulated in progressive low grade dysplasia when compared to non-progressive dysplasia which includes miR-10b-5p,miR-99a-5p, miR-99b-5p, miR-145-5p,miR-100-5p,miR-125b-5p,miR-181b,miR-181c,miR-331-3p,miR-15a-5p,miR-708,miR-150-5p. MicroRNA-145 was considerably lower in OPMD vs healthy control and in OSCC vs healthy control.

Treatment related markers

MicroRNA- 155 is upregulated before treatment and reduction after four weeks of topical steroid treatment. OPMD had significantly higher levels of salivary miRNA-21 and miRNA-31 expression than controls. In addition, higher levels of miRNA-31 expression have been seen in recurrent and cancer progressive lesions.

Among the above-mentioned markers, the miR-31, miR-21, miR-184, miR-27b have shown promising clinical utility in OPMDs. The

Table 1: Summary of the salivary MicroRNAs in OPMDs.

Author year	Lesion	Demography	Study population	MiRNA	Expression profile	Significance
Ge X *et al.*,[3]	OLP	China	Buccal mucosal biopsies, blood and saliva samples from OLP patients.	miR-27a/b	Down regulation	Vitamin D/VDR (Vitamin D receptor) signaling can induce miR a/b expression in OLP. Vitamin D/VDR signaling plays protects oral keratinocytes from OLP by decreasing cytokine production and death.
Amr E *et al.*,[4]	OLP	Egypt	15 healthy patients and 15 OLP patients before and after four weeks of topical steroid therapy	miR- 155	Overexpression of miRNA before treatment and reduction after four weeks of treatment. Highly significant direct correlation between miR-155 and VAS score.	miR -155 acts as a negative regulator of tumor suppressor p53 pathway which regulates differentiation and cell growth in malignancies.
Prasad *et al.*,[5]	OSMF	India	61 patients with chewing habits had OSMF, 61 patients with chewing habits did not have OSMF and 63 healthy patients.	miR21	Upregulation. There was statistically significant expression between OSMF and normal and habits vs normal group.	miRNA 21 is oncogenic and could be an indicator of malignant transformation
Uma Maheswari *et al.*,[6]	OPMD	India	36 healthy participants and 36 patients	miR-21,miR- 31	Significant upregulation of miR-21 and miR-31 in severe dysplasia compared to normal.	miR- 21 can be used as a potential diagnostic marker to evaluate very early malignant changes.
Mehdipour *et al.*,[7]	Lichen planus	Iran	30 patients from OLP, 15 OSCC and 15 healthy controls.	miRNA-21,miRNA-125a,miRNA-31 and miRNA-200a	Significantly increased levels of miR-21 and significantly decreased levels of miR-200a in OLP, dysplastic OLP and OSCC patients when compared to healthy control. miR-31 was significantly increased in dysplastic OLP and OSCC.	Increased miR-21 levels conjunction with miR-125a levels in saliva of OLP patients may be indicative of poor prognosis.
Shahidi *et al.*,[8]	Oral lichen planus	Iran	Oral lichen planus 32,(22 dysplastic),15 OSCC,15 age and gender matched controls	microRNA- 320a, CRP and IL-6	A significant decrease in salivary microRNA-320a OLP and OSCC not in OLP without dysplasia was found which is confirmed by VEGFR-2 expression in tissues.	Salivary microRNA -320A, hs-CRP may offer a useful noninvasive predictive tool for dysplastic OLP.
Hung *et al.*,[9]	OPMD with mean follow-up of 820 days	Taiwan	20 saliva samples, 24 healthy, 46 tissue samples	MicroRNA-21, MicroRNA-31	Significantly increased expression of salivary miRNA 21, miRNA-31 was observed in OPMD than in controls. Further increased levels of miRNA-31 expression are observed in recurrent and lesions with malignant transformation.	Salivary miR-21 and Mir-31 are valuable screening tools for OPMD and miR-31 is an ancillary method to screen OPMD with high risk of malignant transformation.
Zahran *et al.*,[10]	OPMD	Saudi Arabia	40 OPMD, 20 OSCC, 20 RAS and 20 healthy controls.	miRNA-21 miRNA-184 miRNA-145	Significantly increased miRNA-21, miRNA-184 OPMD vs normal, OSCC vs normal. OPMD vs OSCC significantly decreased in non-dysplastic opmd. miRNA-145 is significantly decreased in OPMD vs normal and in OSCC vs normal	miR-184 might furnish a quick, non-invasive ancillary aid for disclosing malignant transformation in oral mucosal lesions.
Lundegard *et al.*,[11]	Oral lichen planus	Sweden	7 OLP and 14 healthy individual.	miR-203	Not able to detect miRNA.	More efficient and pre amplification for analysis of miRNA.
Byun *et al.*,[12]	lichen planus	South Korea	14 lichen planus/6 healthy control	Salivary exosomal miRNA-4484 miRNA-1246 miRNA-1290	Significantly increased miRNA- 4484 in OPMD vs control.	miRNA -4484 can be used as a potential biomarker to identify OLP patients.
Momen-Heravi *et al.*,[13]	Lichen planus	USA	9 OSCC,8 OSCC-Remission,8 lichen planus and 9 healthy control	miRNA-27	miRNA-27 b was significantly overexpressed in OSCC patients compared to OLP patients.	To distinguish OSCC from other study group miRNA-27b can be used as a relevant biomarker.
Yang *et al.*,[14]	Leukoplakia	China	8 progressive leukoplakia patients, 7 non-progressive leukoplakia and 7 healthy controls.	25 miRNAs were differentially expressed.	13 miRNAs were down regulated and 12 miRNAs were up regulated in progressive low grade dysplasia when compared to non-progressive dysplasia.	Salivary miRNA signature is a promising non-invasive assay for monitoring of cancer precursor lesions and early detection of disease progression.
Liu *et al.*,[15]	Oral verrucous Leukoplakia	Taiwan	45 Oral carcinoma,10 oral verrucous leukoplakia, 24 healthy individuals.	miR-31	No increase of salivary miR-31 in patients with oral verrucous leukoplakia relative to controls. Significantly increased expression in OSCC and remarkably reduced after excision of oral cancer.	Salivary miR-31 can be utilized as a biomarker of early detection and post-operative follow-up of OSCC.

Table 2: Sensitivity, Specificity and AUC values of MiRNAs in OPMDs.

Author and Year	MiRNA identified	Result	Comparison groups	Sensitivity	Specificity	AUC
Uma Maheswari *et al.*,[6]	miRNA-21 ,miRNA-31	Increased expression	Severe dysplasia vs control	66%, 36%	69%, 40%	0.82 and 0.5
Hung KF *et al.*,[9]	MirRNA-21,mirRNA-31	Increased expression	OPMD vs normal	100%	Not mentioned	0.74 and 0.76
Zahran *et al.*,[10]	miRNA-184	Increased expression	OPMD with dysplasia vs OSCC	80%	75%	0.86
Momen-Heravi *et al.*,[13]	miRNA-27b	Increased expression	OSCC vs OLP patients	85.71%	100%	0.98

area under curve (AUC) results suggested acceptable to excellent discrimination between OPMD from other study groups. Table 2 summarizes the specificity, sensitivity and area under curve values of the reviewed miRNAs.

Limitations

The major discrepancies in miRNA expression pattern are the poor consensus between different studies on the similar disease and these are concerned to the study and control population, type of sample, localization and origin of cancer, platforms used, choice of internal and exogenous control and the type of lesion studied. The relative size of the sample and the external factors like ethnicity, age, gender, influence of habits are also considered as limiting factors for the reliability of study results. The factors like financial and infrastructure facility issues to perform large scale studies for arriving a conclusive results and the difficulty in finding the particular pinpoint origin of miRNA need further justification.[23]

CONCLUSION

Biomarkers, as byproduct of cancerous cells, may potentially aid as a target for treatment intervention to prevent disease development. Micro RNAs have distinctive expression patterns in OPMDs furnish them a specific tool in diagnostic/prognostic applications in OPMD patients. Clinical biomarkers in OPMDs that are scientifically established, dependable, and cost-effective would help patients receive evidence-based treatment. Salivary biomarkers serve as a non-invasive adjuvant aid in anticipating malignant progression of OPMD. In addition, the miRNAs could also be utilized as therapeutic tool for specific gene target thereby improved management of OPMD patients is possible. To confirm the utility of miRNA as diagnostic/prognostic indicators in OPMDs, more longitudinal studies with enhanced research design are warranted.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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