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miRNAs in Oral Leukoplakia – A Review

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Abstract

Oral potentially malignant disorders (OPMD) are well known entities. Among this oral Leukoplakia is globally known to turn into malignancy according to the literatures. The molecular level studies help to under stand such lesions and to confirm precise diagnosis for better prognosis. So, miRNAs are such one of such molecules which can aid to identify this kind of OPMD lesions. There are many miRNAs which are studied across to have attempt confirmation of such lesions. In this present review we went with many miRNAs' studies and their behaviour biologically and pathologically to know the action in these lesions especially oral Leukoplakia.

Keywords: Oral potentially malignant disorders Malignant transformation, Oral Leukoplakia, miRNAs

Introduction

Oral potentially malignant disorders (OPMDs) comprise variety of lesions and conditions which have high risk for changing into malignant transformation (MT) to oral squamous cell carcinoma (OSCC). Among these Oral Leukoplakia (OL) and erythroplakia are well known.[1] In

1805 the concept of 'precancer' was noticed that gave vision that these can be potential to turn into invasive malignancy over a period of time. Victor Babes was the first to coin the term 'precancer' in 1875. Oral precancer, in particular, have a rich and fascinating literature extending as far back as 1870s, when Sir James Paget, one of the England's most renowned surgeons, proposed that 'leukokeratosis' or 'smokers' patch' of the hard palate which carried an increased risk of eventual cancer trans formation. Later, various terminologies were suggested in relation to the 'precancer' concept like 'premalignant', 'preneoplastic', 'carcinoma prone', 'intra-epithelial neo plasia' and many more. But the information concerned the evolution of these terminologies is unavailable in the international literature. WHO has periodically convened International Workshops to redefine the term 'precancer' and various precancerous lesions and finally recommended the use of the term Oral Potentially Malignant Disorders (OPMDs) in a workshop held in London 2005.

It has been given good review by researchers that virtually all oral cancers are preceded by clinical changes in the oral mucosa usually in the form of white or erythematous patch (two-step process of cancer development).

Careful observation of these oral potentially malignant disorders (OPMDs) will minimize the occurrence and diagnosis with proper treatment can have positive prognostic effect on who develop oral cancer.[2]

The most important concept to consider is epithelial dysplasia features which will guide histopathologic ally assign MT risk. but, histopathological analysis only does not render to check MT risk, so take consideration of other features like molecular parameters.[1]

For decades the research has given a hint that changes in protein coding tumor suppressor genes and/or oncogenes may be the main drivers of tumor development. But, the current discovery of a number of genes that transcribe noncoding RNAs (including miRNAs) makes it obvious that cancer biology is more complex. Molecular regulators (e.g., mRNA, miRNA, and protein) are main source in the involvement process of cancerous phenotypes. Considering this miRNA have major role in physiology and pathology.[3]

In this review, we reviewed variety of miRNAs studies as a biomarker in OL and their role in malignant transformation. We focused mainly on most relevant miRNAs which were employed with different type of methodology and sampling and their role as upregulation or downregulation at genetic level. Also, we considered the different miRNAs interaction with other mRNAs and proteins. We made an attempt to know whether early detection of these biomarkers can minimize the morbidity and improve the prognosis of patients.

Methodology

Literature search mode for this review, Mesh terms were searched in PubMed data base. The Mesh words used were micro-RNA (miRNA), miRNAs in oral potentially malignant disorders and oral Leukoplakia. We noticed about many articles based on our search criteria. After filtering, like not selecting the common articles and based on our reviewing method only few articles were selected specially focusing on miRNAs role in oral Leukoplakia.

Selection of studies

Inclusion

- studies done on miRNA in OPMD
- studies done using human body fluids

Exclusion

- studies done using miRNAs on other carcinoma except OPMD and OL

Pathophysiology of miRNAs expression

miRNAs are 18–25 nucleotides long, noncoding RNA molecules which have recently gained significant attention as potential regulators and biomarkers for human carcinogenesis. At the molecular level, miRNA binds to 3'-untranslated region (3'-UTR) of target mRNA(s) and suppresses its expression by either translational repression or mRNA cleavage. A single miRNA can regulate expression and/or function of hundreds of target mRNAs and proteins and regulates several biological processes like cell proliferation, differentiation, migration, apoptosis, and signal transduction which have definite imparting effect for cancer development.[3]

miRNAs in tissue samples

Xiao W et al studied miRNA expression in OL and malignantly transformed OL (mtOL) tissue samples. They noticed 25 upregulated miRNAs and nine downregulated miRNAs with greater than 2-fold changes in mtOL. Fluore scence in situ hybridization infestation was incorporated to verify one of the significantly altered miRNAs, miRNA-31 later there result showed that miRNA-31 was more expressive in mtOL. miRNA-31* may have considerable distinguishable effects on physiology of in oral cells with other malignancy. Later they gave message that miRNA-31 dysregulation is involved in the OL progression through regulating FGF3 and miRNA components may have definite role in oral carcinogenesis.

Also they observed upregulation of miRNA-142-3p, miRNA-223, miRNA-31, miRNA-21, let-7b, miRNA-19a, miRNA-200a, miRNA-200b, miRNA-30e, miRNA-146a, miRNA-141, miRNA-222, miRNA-374a, miRNA-221, miRNA-24-2, and miRNA-16 as well as downregulation of miRNA-373. However, the upregulation of miRNA-31, miRNA-142-5p, miRNA-33a, miRNA-1259, miRNA-146b-5p, miRNA-886-3p, miRNA-886-5p, miRNA-519d, and miRNA-301a along with the downregulation of miRNA-572, miRNA-611, miRNA-602, miRNA-675, miRNA-585, miRNA-623, miRNA-637, and miRNA-1184 were in consideration. Interestingly, they noticed that miRNA-31 and miRNA-31, being same precursor, both are more expressive / upregulated in mtOL.

Among these altered miRNAs, the authors chose miRNA-31 for their investigation and it was found that miRNA-31 showed a significant considering change among the upregulated miRNAs. The first and foremost investigation of this study drived to know miRNA-31 expression in cancer. They conveyed that miRNA-31 is derived from the same precursor with miRNA-31 and miRNA-31 was also overexpressed in the mtOL samples studied. Finally they suggested that upregulation of miRNA-31 is negatively correlated with recurrent/newly formed OL. MiRNA-31 may exert different effects on biological function in oral cells with different malignant potential. FGF3 is the target of miRNA-31* and miRNA-31* may play an important role during OL progression through regulating FGF3.[4]

Brito et al selected samples which were stored at -80°C until processing. Normal oral mucosa samples (controls) were collected during removal of impacted third molar. Peripheral blood from 4 healthy volunteers was used as calibrators. The samples were subjected to quantitative polymerase chain reaction (qPCR). Their study involved OL and oral OSCC to know the differential expression of different miRNAs. Based on the previous literature they stated that the expression of miRNA-21, miRNA-345, and miRNA-181 gradually increases as lesions progress from OL to oral OSCC, they wanted to investigate whether associations can be made between

the expression of these 3 potentially cancer-related miRNAs and the cytological and histopathological features that are used to grade oral dysplasia. Their hypothesis was that distinct morphological aspects commonly used to grade dysplasia may not present the same molecular profile. Their comparison analysis was in OL, normal oral mucosa and OSCC samples. Expression of miRNA-21 was higher in the OSCC group than in the OL (P = 0.02) and normal oral mucosa (P = 0.01) groups. Increased expression of miRNA-21 was also observed in OL samples when compared with normal oral mucosa (P = 0.01).

No statistically significant association was found in the expression of miRNA-21 and the severity of dysplasia. OL lesions with moderate/severe dysplasia showed similar expression to OSCC. Although, overall, the OL lesions with architectural or cytological alterations exhibited higher expression of miRNA-21 than those without, statistical significance was only observed in the cases with increased number of mitotic figures (P = 0.02), abnormally superficial mitosis (P = 0.01), increased nuclear/ cyto plasmic ratio (P = 0.03), or hyperchromasia (P = 0.02)

The OSCC samples showed higher expression of miRNA-181b than OL (P = 0.02) and normal oral mucosa (P = 0.05) samples (Fig. 1B). No statistical difference regarding miRNA-181b expression was observed among the OL group according to the severity of dysplasia. When the architectural and cytological alterations were evaluated separately, higher expression of miRNA-181b was noted in OL with increased number of mitotic figures (P = 0.01), increased nuclear/cytoplasmic ratio (P = 0.02), or hyper chromasia (P = 0.02).

Expression of miRNA-345 was higher in the OSCC group than in the OL (P = 0.0002) and normal oral mucosa (P = 0.005) groups. No statistical difference was observed in the expression of this miRNA between OL cases and the normal oral mucosa, as well as among the OL samples with different grades of dysplasia. Higher expression of miRNA-345 was observed in OL samples with increased nuclear/cytoplasmic ratio (P = 0.005) or increased number and size of nucleoli (P = 0.04) than in those without these alterations. No statistical difference was found in any of the miRNAs measured between OL located in high-risk sites and OL located in low-risk sites.

They found higher expression of the miRNAs miRNA-21, miRNA-181b, and miRNA-345 in OL that showed hyperchromasia, increased number of mitotic figures, increased nuclear/cytoplasmic ratio, abnormally superficial mitosis, or increased number and size of nucleoli. Because every OL lesion presented with more than one morphological alteration, some overlap of the molecular data is expected. Even so, they found that not all histological parameters are associated with significant molecular alterations. They concluded that that some cytological and histopathological parameters used to grade dysplasia are associated with altered miRNA expression.[5]

Nikitakis NG et al, noted that molecular markers are vital to know the disease progress specially emphasizing on OPMD. The study involved many molecular markers in that miRNAs also were shown as they have significant and precise role. miRNA-31, miRNA-21, miRNA-146 a, miRNA-211, miRNA-204, miRNA-24, and miRNA-155 were most frequently upregulated in 80% of oral cancer samples. At the same time, several miRNAs, including miRNA-125 b, miRNA-145, miRNA-126, miRNA-203, miRNA-218, miRNA-585, miRNA-99 a, and miRNA-137, were frequently downregulated in oral cancers. Moreover, these authors

emphasized that miRNA-31, miRNA-21, miRNA-146 a, miRNA-211, miRNA-204, miRNA-24, miRNA-155, miRNA-125 b, miRNA-145, miRNA-126, miRNA-203, miRNA-218, and miRNA-99 act as regulators of invasion and metastasis in oral cancer.

So, based on their study the authors assumed that future studies should use well-annotated biospecimens that allow for thorough correlation with histologic and molecular biomarkers to yield greater disease outcome prediction. This can lead to improved prognosis and life expectancy of patients with cancer. Accordingly, a more thorough understanding of the critical molecular events heralding and driving OMPD progression to OSCC will lead to the identification of more accurate markers for determining the risk of MT, thus facilitating clinical decision making. In addition, effective therapeutic strategies for preventing oral cancer will target the specific genetic and epigenetic aberrations driving cancer development.[6]

Chattopadhyay E et al studied miRNA204, miRNA31, miRNA31*, miRNA133a, miRNA7, miRNA206 and miRNA1293 in oral potentially malignant disorders and cancer. Their results showed except hsa-miRNA-204, expression of remaining 6 miRNAs, were found to be significantly up regulated in Leukoplakia. Expression of hsa-miRNA-7, hsa-miRNA-31, hsa-miRNA-31* and hsa-miRNA-1293 was significantly up-regulated in cancer, Leukoplakia and other OMPD. hsa-miRNA-204 was significantly down-regulated in cancer and hsa-miRNA-31 is the only miRNA which was significantly up-regulated in cancer and all precancer tissues.[7]

Philip one E et al, conducted a retrospective search of our pathology database to identify 100 adult patients ≥21 years old, with a clinical leukoplakia diagnosed as ‘epithelial hyperplasia’, ‘epithelial hyperplasia with hyperkeratosis’, ‘epithelial atypia limited to the basal cell region’ or ‘mild epithelial dysplasia’ prior to 2008 and which also had a minimum of 5-year follow-up information available. Only the patients who had an incisional biopsy of the leukoplakia were selected. As an excisional biopsy could account for the reason why the leukoplakia did not progress to cancer, the patients who had excisional biopsy were excluded from the study. Identified patients were stratified into the following two groups; Group 1 ‘Progressive Group’ (patients with leukoplakia that progressed to OSCC within 5 years) and Group 2 ‘Non-Progressive Group’ (patients with leukoplakia that did not progress to OSCC within 5 years). The age and gender of the patient, histologic diagnosis, and the location of lesion were recorded. Archived formalin-fixed paraffin-embedded (FFPE) tissue blocks were retrieved for all subjects.

They subjected the samples for deep sequencing analysis, bioanalyzer and fluorometer. They undertook miRNAs for the analysis were namely miRNAs-208b-3p, 204-5p, 129-2-3p and 3065-5p. miRNAs (miRs-129-2-3p, 204-5p, 208b-3p and 3065-5p) were identified to be differentially expressed in the progressive group (Group 1) compared to non-progressive group (Group 2) with at least 1.25 log2 fold change with unadjusted $p<0.05$ and to be expressed in close to (at least 80%) if not all samples. One of the miRNAs (miR-208b-3p) was overexpressed in the progressive group and 3 were under expressed (miRs-129-2-3p, 204-5p and 3065-5p) in the progressive group.

To confirm overexpression of miR-208b-3p and under expression of miRs-204-5p, 129-2-3p and 3065-5p, these four miRNAs were quantified using qRT-PCR additional 40 patients that progressed to OSCC (Group 1) and 40 patients that did not progress to OSCC (Group 2). Only two of the four selected microRNAs showed changes in expression level consistent with that of the deep

sequencing; miR-208b-3p was overexpressed and miR-3065-5p was under expressed in the progressive group. This finding is consistent with the putative role of these miRNAs; miR-208b-3p with on-cogenic function, and miR-3065-5p with tumor suppress sor role. Although statistically insignificant, the other two miRNAs, miR-129-2-3p and miR-204-5p, showed overexpression in the progressive group (significant under expression of these two microRNAs were demonstrated in the deep sequencing analysis), despite their presumptive role as tumor suppressors.

For clinical practicality, they conducted an exploratory study to assess the feasibility of developing a parsimonious risk score formula from their final model. The main purpose of risk score formula is to translate miRNA expression levels assessed by qRT-PCR at the time of initial biopsy into a score that reflects the patient's risk of cancer progression. Using the risk score formula, 31 of the 39 progressive cases (80%) were accurately identified as high risk for cancer progression. Conversely, 24 of the 38 non-progressive cases (63%) were properly identified as minimal risk of cancer progression. Those cases identified as high risk would have been treated aggressively initially which would potentially have prevented carcinoma development. The 63% of the low cancer progression risk group could have potentially been spared from unnecessary surgical excision. They planned future investigations to determine if their model can be utilized as a predictive modality for progression in early oral leukoplakia.[8]

Sun L collected serum from 104 OSCC patients, 30 OLK patients who did not receive any kind of therapy before and 40 healthy volunteers. They drew 4-ml blood samples from subjects and then the specimens were centrifuge at 3500g at room temperature for 5 min. Serum was transferred into RNA-free EP tubes and stored at –80°C until use. After isolating RNA with standard protocol Real-Time PCR System was used for the further study. RNU6B was used as internal control for normalization of data, and the expression level of serum miR-9 was calculated and determined using the 2–DDCT method.

and his research team studied the role of serum miRNA-9 in OL & OSCC. Their results showed that the expression level of serum miRNA-9 was significantly down-regulated in patients with OSCC or OL, indicating that miRNA-9 might be involved in regulating the initiation and progression of OSCC. Detecting serum miRNA-9 expression level in patients with oral pre-cancer might help to screen and identify the high risk population that has the potential to develop into OSCC. In addition, low serum miRNA-9 expression level was associated with advanced stage and poor prognosis of OSCC, and serum miRNA-9 was an independent risk factor for OSCC. Based on their results, miRNA-9 probably acts as a tumor suppressor in OSCC and this finding is consistent with previous reports.

Previous literature showed that miRNA-9 was under-expressed in OSCC tissues and oral cancer cell lines. In addition, overexpression of miRNA-9 could suppress the proliferative capacity of oral cancer cells both in vitro and in vivo. miRNA-9 might have a tumor-suppressive role by downregulating the expression of CXC chemokine receptor 4 via the Wnt/b catenin signaling pathway. Curcumin, a phytochemical derived from the rhizome of Curcuma longa, has demonstrated antitumor activity in many types of tumors. It was recently reported that curcumin inhibited proliferation of oral cancer cells by upregulating miRNA-9 expression and inhibiting Wnt/b-catenin signaling, indicating that the regulatory role of miRNA-9 in OSCC closely interacts with Wnt/b-catenin signaling.

There is also altered expression of this miRNA in other cancer types. Several reasons might explain the contradictory role of miRNA-9 in different types of cancers. Firstly, the concrete function of miRNA-9 may be cancer-dependent. Because a single miRNA can target a number of downstream genes, the concrete microenvironment context might influence which targeted genes will be activated or suppressed. It is common to observe the phenomenon that a specific miRNA function as an oncogene in a certain type of cancer while it acts as a tumor suppressor in another type of cancer. Secondly, the concrete function of miRNA-9 might be cell-dependent. At the end they conluded that the expression levels of serum miRNA-9 was downregulated in patients with OL and OSCC. Low serum miRNA-9 was associated with advanced stage and poor prognosis of OSCC. Collectively, our data demonstrate that miRNA-9 is a tumor suppressor in OSCC and can serve as a potential therapeutic target to treat this malignant disease.[9]

Yang Y et al assigned 45 eligible patients between the periods 2006 to 2012 in their study. The patients had been diagnosed with LGD leucoplakias (WHO) and were given 13-cis-retinoic acid (13cRA) treatment and close follow-ups before any event (defined as the diagnosis of HGD or CIS or OSCC). A total of 45 frozen samples were collected at baseline after enrolment. Among these 45 LGD leucoplakias patients, 10 patients progressed to carcinoma in situ or OSCC after an average time of 30.1 months. 2 were excluded because of poor RNA quality. Among the 35 patients who did not develop OSCC, 5 were excluded because of poor RNA quality, and another 12 were excluded because of new lesion occurrence. Saliva samples were collected from these patients whenever tissue biopsies were collected. But only samples collected at first visit were used for analysis in order to investigate miRNA expression differences in these premalignant lesions at LGD stage. Immediately after mouthwash, about 2 ml saliva was collected and the samples were mixed with 5 ml RNA Protector, kept at room temperature for 24 hours, and then stored at −20°C until RNA or protein isolation and subsequent real time PCR study.

Used 8 salivary miRNAs miRNAs (miRNA-10b, miRNA-145, miRNA-99b, miRNA-708, miRNA-181c, miRNA-30e, miRNA-660 and miRNA-197) to distinguish OMPD patients with different malignant transform potential. They observed miRNA-10b, miRNA-660, miRNA-708 and miRNA-30e demonstrated significant over-expression in progressive low-grade dysplasia (LGD) OL; miRNA-145, miRNA-99b, miRNA-181c and miRNA-197 were under-expressed in this group of OL. Expressions of miRNA-10b, miRNA-145, miRNA-99b, miRNA-708 and miRNA-181c were significantly different in saliva of progressive LGD Leukoplakia patients, compared to that of non-progressive LGD Leukoplakia patients.

Expression of miRNA-660 was under-expressed in non progress Ing LGD leucoplakias ($p = 0.038$) but overexpression of this miRNA in progressing leucoplakias did not reach statistical significance. Also there was contradictory results with respect to miRNA 181 family compared to previous literature. They also noticed that a group of miRNAs are overexpressed in non-progressing LGD leucoplakias compared with progressing LGD OL (miRNA-197, miRNA-let-7, miRNA-99a/b, miRNA-126 and miRNA-145).

These over-expressed miRNAs are known for their tumor suppressive roles in cancers. The marked up-regulation of these miRNAs in this group of patients implies that these stable LGD lesions may possess some

mechanisms of protection from malignant transformation.

Thus, they concluded that the differential expression of miRNAs in low grade dysplasias can be made from the non-invasive methods like using saliva sample. And also they compared the miRNA expression profiles of these LGD leucoplakias with different clinical outcomes, they demonstrate a clear segregation between them and the similar expressions were detected in saliva samples of these patients.[10]

miRNA in Saliva samples:

Maheshwari T N U reviewed systematically and threw light on the sensitivity and specificity of miRNA using saliva samples. They reviewed that miRNA 27b, miRNA 145, miRNA 181, and miRNA 21 had statistically significant sensitivity and specificity to detect early malignancy. One of them reviewed study compared saliva samples with tissue samples and concluded that saliva samples were significantly better for predicting malignancy than tissue samples and miRNA 31 is a significantly better marker for predicting malignancy than miRNA 21 in saliva samples of OPMD. Almost all studies collected unstimulated whole saliva was collected before which participants refrained from drinking, eating, and oral hygiene measures. RT-qPCR was used to quantify salivary miRNA in all studies. They also showed that a total of 11 miRNAs that were deregulated in OSCC were also found to be deregulated in OPMD compared with healthy controls. [11]

miRNAs in other body fluids:

Roy R et al collected biological samples from gingivo-buccal site of patients who were diagnosed as lichen planus (N = 20), Leukoplakia (N = 20), oral cancer (N = 20) and normal individuals who had no familial history of cancer. Samples were stored in RNA Later solution at −20 °C until isolation of RNA. Tissue RNA was extracted using Qiagen All Prep DNA/RNA Mini Kit.

They attempted to see the expression of miRNA-26a, miRNA-29a, miRNA-34b and miRNA-423 and their target genes on OL and cancer tissues. The authors results showed that miRNA-29a and miRNA-26a were significantly down regulated in OL and cancer tissues. When it was compared with the target genes it was observed that mean fold change (i.e. 2−mean ΔΔCt) in expression of ATPB1, CPEB3 and PIK3R1 was significantly downregulated in Leukoplakia and cancer tissues. Also there was CDK6 had reduced expression in Leukoplakia tissues while DNMT3a had reduced expression in Leukoplakia and cancer tissues. Expression of CTDSP2, host genes of miRNA- 26a, and COL4A2 was significantly down-regulated in Leukoplakia. This shows that expression of DNMT3a was negatively correlated with that of miRNA-26a in Leukoplakia tissues.

Also they have been studied miRNA profiles in saliva of patients with progressive and nonprogressive Leukoplakia and found that miRNA-26a was down regulated in progressive Leukoplakia with respect to non-progressive samples. expression of miRNA- 26a was significantly upregulated in lichen planus but downregulated in Leukoplakia and cancer tissues suggesting role of this miRNA as tumor suppressor in both Leukoplakia and cancer. Recent report has shown that miRNA423 can target genes related to cell death and it also promotes autophagy. Hence, miRNA-423 may act as a tumor suppressor, in cancerous tissue. So they gave the idea of non-invasive technique to study micro molecules like miRNA and the target genes.[12]

El-Sakka H and others showed by their systematic review that miRNAs can not only regulate the expression levels of oncogenes and tumour suppressor

genes to influence the progression of cancer, but also might directly function as oncogenes or tumour suppressor genes in carcinogenesis. Hence, reduced miRNA expression has been shown to contribute to OSCC. They may be differentially expressed among OPMD lesions with distinct histopathological features such as oral epithelial dysplasia. miRNAs are remark ably stable both in saliva and tissue samples, which offers a great advantage over other biomarker types. Micro RNA profiling can differentiate between oral normal and cancerous tissues, discriminate between different subgroups of tumours, and predict outcome or response to therapy. These findings suggested that miRNAs can be used as potential clinical biomarkers for OSCC and OPMD prognosis, and may one day become superior objective clinical method over the current standard of oral epithelial dysplasia grading.

They also noticed that the conflicting results recorded in the literature may be due to either poor study design, or indicative of unsuitable/unreliable miRNAs biomarkers for OPMD risk stratification, or both.

Thus, their review examined the studies where the expression of miRNAs from human specimens (blood serum/plasma, saliva, tissue) as diagnostic and prognostic biomarkers in patients with OPMDs, some of which have utilised these miRNAs as risk stratification biomarkers for malignant transformation and have shown promising findings.[13]

In summary the miRNA-31 was significantly unregulated in Leukoplakia which has more potential to get transferred into malignancy. The same is with the miRNA-21 which is found to be consistently increased in Leukoplakia which progresses to oral squamous cell carcinoma. Also Maheshwari has stated that miRNA 31 is a better marker miRNA-21 especially in saliva.

Conclusion

Thus, based on our review we conclude that studying biologic micro molecules yield satisfactory results at genetic level which have remarkable results. The studies we incorporated in our review showed that number of microRNAs were upregulated or downregulated in various OL and also in OSCC. Their expression shows the way of mRNA and other protein regulation. The studies also threw light on the target genes of miRNAs. So studying the expression of miRNAs and their target genes can give scientific knowledge to know the disease course and can be implicated in early detection of oral cancer and its therapy. In future such studies results may help in gene therapy by using miRNAs as therapeutics.

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