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Is Oral Cancer predictable with miRNA: A Review

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Abstract

Oral cancer 6th most common cancer worldwide. Main contributing factor for oral cancer is tobacco chewing, smoking and alcohol consumption. The 5-year survival rate for oral cancer is approximately 50%. This due to late detection of oral cancer. miRNA (micro Ribo Nucleic Acid) is small noncoding RNA. Its functions are in RNA silencing and post-transcriptional regulation of gene expression miRNA can be used as early diagnostic tool. This review aims to present the fundamental aspects of microRNA in oral squamous cell carcinoma (OSCC), oral premalignant lesions and progression of premalignant lesion to oral cancer. With help of miRNA, we can not only predict oral cancer, but also prediction of transformation of oral premalignant lesion to oral squamous carcinoma. Specific miRNAs are dysregulated in Oral cancer, oral Premalignant lesion and in progression of premalignant lesion to OSCC. Specific miRNAs are dysregulated in oral cancer, oral premalignant lesion and in progression of premalignant lesion to OSCC. In oral cancer miRNA-223, miRNA-211, miRNA-182-5p, miRNA-450a are upregulated in comparison to healthy controls. miRNA-1290, miR-1246, miR-1258, miRNA-199a-5p, miRNA-495 are downregulated in oral cancer. In premalignant oral lesion miRNA-146a and miRNA-155 are upregulated. We can predict transformation of premalignant lesion to oral cancer because miR-21, miR-181b are upregulated and miR-345 downregulated.

Keywords: microRNA In Oral Cancer, Oral Cancer Prediction, Mir in Premalignant Lesions.

INTRODUCTION

Oral cancer is 6th most common cancer all over the globe [1]. Main contributing factor for oral cancer is tobacco chewing, smoking and alcohol consumption [2]. Due to the complex anatomy of the head and neck region and unpredictable tumor invasion. Therefore, this results in difficulties in treating patients and which leads to high mortality in head and neck cancer patient. Oral squamous carcinoma is the most frequent type of oral cancer (approximately 90%) [3]. Worldwide incidence estimated to be >500,000 annually [4]. Despite all advances in treatment therapy but the 5-year survival rate is 50% in the past year [5]. The low 5-year survival rate is due to late diagnosis of oral cancer. This can be improved by early diagnosis [6].

In the current scenario, a biopsy is a gold standard for the diagnosis of oral cancer[i] which is an invasive procedure. Generally, patients deny biopsy because of its invasive nature. Also, biopsy unable to predict the transformation of premalignant to the malignant lesion.

So, there is a need for a diagnostic tool which is invasive and also accurate. Diagnosis with saliva is a burning topic in the world. The main benefit of saliva is it is an invasive procedure. Through saliva, we can find proteomic analysis, transcriptome analysis, microRNA, genomic analysis. They can be used as biomarkers in the prediction of oral cancer.

In this review, we summarize the present understanding of miRNA deregulation. We outline how the miRNA alterations correlate with cancer hallmarks as well as how miRNAs can predict conversion of oral premalignant lesion to oral cancer. The potential role of miRNAs as diagnostic tools and predictive biomarkers of oral cancer is also discussed.

microRNA (miRNA) as Biomarker

miRNAs are an evolutionarily conserved group of endogenous, small, noncoding single-stranded RNAs.

It consists of 18 to 24 nucleotides within diverse cell types that negatively regulate gene expression at post-transcriptional level [8]. In 1993 Ambrose and colleagues first identified miRNA in *Caenorhabditis elegans*, a nematode and showed it to be involved in regulating the timing of larval development [9]. miRNAs are encoded in the genome in various forms like expression from intronic or intergenic transcripts, which may encode a single miRNA hairpin precursor, or clusters of multiple precursors. Biogenesis of miRNAs occurs by a well-characterized conserved processing mechanism (Figure 1) wherein, Initially, miRNAs are transcribed from miRNA coding sequences (residing principally in intergenic regions or within introns of genes) as a form of long primary transcript (pri-miRNAs) by the RNA polymerase II (Pol II) or Pol (III) enzyme [10,11]. Function of miRNA are RNA silencing and post-transcriptional regulation of gene expression [12].

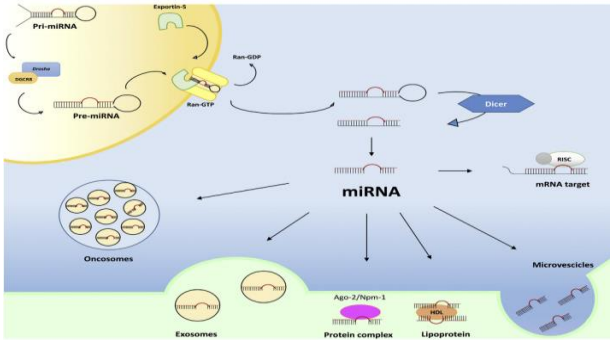

Figure 1: Synthesis of miRNA

miRNA expression is altered in oral cancer showing either upregulation or downregulation. Numerous studies in literature have reported aberrant miRNA expression in patients with oral cancer. miRNA act as a diagnostic and prognostic marker for premalignant lesions and oral cancers and can also help in deciding the therapeutic gene therapy.

Methodology: a comprehensive review of recent literature prevalent to miRNA deregulation in oral cancer, oral premalignant lesions using PubMed, Medline, google Scholar.

Keywords: microRNA, micro-RNA in oral cancer, microRNA in the premalignant lesion, microRNA in oral squamous cell carcinoma.

RESULTS

Table 1: List of miRNAs in oral cancer

Upregulated miRNA	Downregulated miRNA	Author	year
miR-223 [13]		Jiang L *et al*	2019
	miR-125b [14]	Chen Y F *et al*	2019
	miRNA-199a-5p [15]	Wei D *et al*	2019
miR-211 [16]		Zheng J *et al*	2019
miR-182-5p [17]		Li N *et al*	2018
MiR-450a [18]		En-Wei Hsing *et al*	2019
	miR-1290,miR-1246 [19]	Nakashima *et al*	2019
	miR-1258 [20]	Zhang *et al*	2019
	MiR-495 [21]	Wang *et al*	2018
	miR-342-3p [22]	Song *et al*	2019
	miR-16 [23]	Zhao *et al*	2019
miR-18a [24]		Hou *et al*	2018
	miR-23a-3p [25]	Chen *et al*	2018
	microRNA-218 [26]	Xu *et al*	2018
	miR-545 [27]	Yuan *et al*	2018
miRNA-21 and miRNA-184 [28]	miRNA-145[32]	Zahran *et al*	2015
	miR-188 [29]	Wang *et al*	2016

Table 2: List of microRNAs deregulated in oral premalignant lesion

Upregulated	Downregulated	Disease	Author	Year
	miRNA-137 [30]	Oral lichen planus	Aghbari SMH *et al*	2018
miRNA-146a [31] and miRNA-155		Oral lichen planus	Ma H *et al*	2016
	miRNA-26b [32]	Oral lichen planus	Danielsson K *et al*	2013
miRNA-31[37]	miRNA-204 [33]	Oral Submucous Fibrosis	Eshita Chattopadhyay *et al*	2016, 2005

Table 3: List of microRNAs deregulated in the transformation of premalignant to malignant lesion

Upregulated	Downregulated	Author	Year
	MiR-375 [34]	Harrandah AM *et al*	2016
miR-21, miR-181b and miR-345,miR-146b,miR 196a,miR-206 [35]		Cervigne NK *et al*	2009

DISCUSSION

The main aim of study to review current finding on miRNA in oral cancer either in blood, serum or saliva. The search was conducted using four databases, i.e., PubMed, Medline, Scopus and Google Scholar with focus on studies presenting statistically dysregulated expression of miRNA in either blood, serum or saliva in patients having oral premalignant lesion or oral carcinoma. Studies from whole head and neck were excluded due non homogeneity of tumors.

Particular miRNA is specific for a particular tumor, which differentiates it from normal tissue and another type of tumors. Most of cancer can be differentiated into prognostic groups on the basis of these signatures [36]. Jiang *et al* [37]. use real-time quantitative polymerase chain reaction (PCR) to a favorable result for identifying miRNA deregulation in 32 cell lines among them 5 were from the head and neck/ oral cavity. Clustering analysis on the basis of miRNA precursor expression value validated most of cancer cell lines to be clustered on the basis of tissue origin. this gives an idea that each cancer exhibits a unique miRNA expression profile or signature on the basis of specific tissue origin. According to Barker *et al* [3]. miRNA profiles were specific and distinct for head and neck SCC in tonsil, tongue base, postnasal space. Also, miRNA expression profiles among primary cancer and its metastatic disease were accordant to miRNA profile may be used as a diagnostic tool for determination of whether the nodal metastasis is from the oral cavity [39].

Since, distinct miRNA profile present for OSCC, premalignant lesion and normal tissue. therefore, miRNA offers a golden opportunity for early diagnosis of oral cancer and also, the conversion of premalignant lesion to malignant lesion. Correspondingly, a number of individual miRNAs have been advocated as distinct marker for OSCC diagnosis such as over expressed miRNA21 and miRNA 184 [22]. stated by Zahran-F *et al*. According to Jiang L *et al.* stated that up-regulation of miRNA-223 [17]. in the oral cancer patient. In consonance with Zheng *et al* up-regulation of miRNA-211 [20]. in oral patients in comparison with healthy patients. miRNA 182-5p [21]. is upregulated in a cancer patient versus healthy persons, stated by Li N *et al*. En We H sing *et al* states that miRNA-450 [22]. have high concentration value in comparison to a healthy individual. according to Hove *et al.* miRNA-18a is upregulated in oral cancer patients as compared healthy control cases.

Distinct miRNA downregulated in oral cancer stated by various literature. miRNA-199a-5p [19]. is in low amount compared to healthy individuals, stated by weirdest al. According to Chen *et al* miRNA125b [18]. is in low quantity in comparison to a healthy person. Nakashima *et al.* stats that miRNA 1290 and miRNA1246 [23]. are decreased number versus healthy controls. In accordance with Zhang *et al* miRNA 1258 is in a reduced amount. According to Wang *et al* miRNA 495 [25]. is downregulated as compared to healthy persons. In compliance with Song *et al* micro-RNA 342-3p [26]. is reduced amount in comparison to healthy persons. According to Zhao *et al* micro-RNA 16 [27]. is in a reduced amount in oral cancer patients. micro-RNA 23a-3p [29]. is decreased the amount in OSCC patients compared to healthy individuals. Xu *et al* claimed that micro-RNA 218 [30]. is in a reduced amount in comparison to healthy control patients. In the opinion of Yuan *et al* micro-RNA 545 [31]. decreased amount in oral cancer patients. According to Zahran *et al* micro-RNA 145 [32]. is downregulated oral cancer patient in comparison healthy patients. In compliance with Wang *et al* micro-RNA 188 [33]. is in a decreased amount in oral cancer patients.

Cervine *et al.* states that miRNA changes associated with the progression of leukoplakia to oral submucous carcinoma (Figure 2). According to him over expression of miRNA 146b, miR-181bmiR-21miR, miR-345, miR-518b, miR-520g, miR-649, miR-184. He also stated that some microRNA is under expressed such as miR-196a, miR-206 [39]. These miRNAs can be considered as early detectable events in oral cancer progression. He also states that overexpression of particular miRNA in OSCC such as miR-21, miR-181b and miR-345, miR-146b, miR-196a, miR-206, miR-649, miR-518b [39]. Harada *et al* states that down expression miR-375 [38]. when lesion transforms from premalignant lesion to the malignant lesion. According to Chattopadhyay *et al* expression of 6 miRNAs were found to be significantly deregulated in cancer samples, 3 of them were up-regulated (miR-7, miR-31, miR-1293) while expression of remaining 3 miRNAs were down-regulated (miR-133a, miR-204, miR-206) [38].

Certain miRNA dysregulated in oral premalignant lesions. In Oral lichen planus, miR-137 [34]. is in low expression stated by Aghbari *et al* and miR-26b [36]. are downregulated stated by Danielsson *et al* in comparison to healthy controls. According to MaH *et al* miRNA-146a and miRNA-155 [35]. are in high amount in patients with oral lichen planus. Expression of miR-31 and miR-204 [37]. were significantly up and down regulated, respectively in Oral submucous fibrosis patients. In most of the studies expression of miR-31 was upregulated in cancer and all precancer tissues.

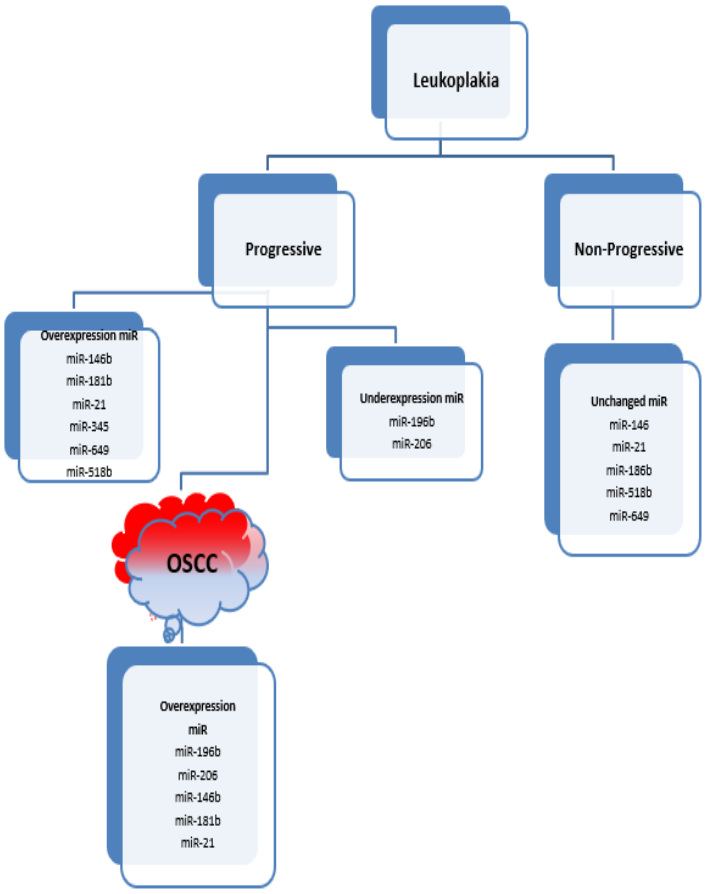

Figure 2: Expression of miRNAs

CONCLUSION

The oral cancer is now a prevailing disease in the society, predicting oral cancer with the help of microRNA is in budding state of research, so it requires more research in this field. The future research must revolve around clinical aspect, as how microRNA can eliminate diagnosis with biopsy.

Conflict of Interest

None declared.

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