

MicroRNA in Oral Cancer Research: Future Prospects

MicroRNA (miRNA) and related therapeutic approaches hold great promise in the field of cancer managements. Various studies on epithelial malignancies have shown encouraging results on various fronts. Its association with invasion, tumor growth, epithelial mesenchymal transition (EMT), angiogenesis, cancer stem cells (CSCs), metastasis and reflects the diversified role of miRNA. Moreover, miRNA plays an important role in determining the prognosis of the patients. MicroRNAs interactions with each other and with external factors [human papilloma virus (HPV) (like oncoproteins)] intrigue us to explore more deep into this fascinating world.¹

Unlike other epithelial malignancies, oral squamous cell carcinoma (OSCC) has also shown great advancement in the field of miRNA research. In this regard, various aspects explored till date in OSCC are angiogenesis, EMT, metastasis, invasion and so on. Some of the miRNA studied in OSCC till date are miR-21, miR-218, miR-23b, miR-34a, miR-15a, miR-16-1, miR-125b, miR-203, miR-146b, miR-181b, miR-345, miR-518b, miR-649, miR-184, miR-196a, miR-206 and so on.² Through literature search (PubMed, Scopus, Medline), we have identified many aspects that need to be explored in OSCC with respect to the miRNA research. These unexplored aspects and associated miRNA are shown in Table 1. The listed miRNAs have been studied in different epithelial malignancies other than OSCC with promising results.

Table 1: List of unexplored miRNAs in oral cancer and their roles

S. No.	Aspects	miRNA involves
1	Human papilloma virus interaction	146a, 324-5p, 203, 34a, 218, 23b, 29, 15b, 16-1
2	Cancer stem cells	34, 200b, 302, 367, 22
3	Anticancer drug resistance	296, let-7, 326, 297, 9, 328, 200c, 214, 16, 205, 125
4	Epithelial mesenchymal transition	101, 612, 34, 490, 22
5	Angiogenesis	141, 503
6	Tumor growth apoptosis cell proliferation	122, 199, 182, 144, 452, 616, 202, 766, 744, 338-3p, 185, 485
7	Tumor cell migration and invasion	122, 199, 550a, 424, 519d, 485, 338-3p, 182, 639
8	Tumor metastasis	290, 550, 185, 450, 190, 639

The absolute untouched areas in OSCC research on miRNA are HPV oncoprotein interaction, CSCs and cancer drug resistance. There are many evidences showing reciprocal interactions between HPV oncoproteins and miRNAs in different cancer cell lines. E6 regulates the expression of miRNA 23a, miRNA-26a and miRNA-34a,² and E7 regulates the expression of miRNA-17-92, miRNA-15b/16-2 and miRNA-106b-25.³ With regards to CSCs, family members of miRNA 200 are significantly downregulated as compared with non-CSCs tumor cells.⁴ Some miRNA families, like miR-302/367 (coded on chromosome 4 and consist of 9 miRNAs), were indicated to be upregulated in CSCs and significantly repressed during differentiation. Interestingly, miRNAs, associated with EMT like miR-34, miR-200, let-7 and miR-302 families, have been indicated as prominent regulators in CSC regulation as well.⁵ In terms of multiple drug resistance, miRNAs usually act either by decreasing expression of genes associated with resistance or by preventing apoptosis and CSC development.⁶ Different miRNAs in this regard are listed in Table 1.

There is scarcity of literature on OSCC with respect to the role of miRNA in EMT and angiogenesis. MicroRNA 138 is associated with EMT and reported to be downregulated in OSCC cell lines, resulting in cell migration and invasion.⁷ With respect to angiogenesis, VEGF-A is negatively regulated by miRNA-126 and decreased expression of this miRNA has been reported in OSCC, leading to angiogenesis, lymphangiogenesis, tumor progression, nodal metastasis and poor prognosis in the OSCC cases.⁸

Oral carcinogenesis is a multistep process and OSCC is usually preceded by many potentially malignant disorders.³ MicroRNA expression profile can be used as a biomarker for predicting malignant potential of the lesions. In this regard, Yang et al⁹ reported group of miRNAs which are downregulated in leukoplakias and thus are responsible for malignant transformation. These miRNAs are miR-197, miR-let-7, miR 99a/b, miR-126 and miR-145. Albeit, scarcity of literature on the aforementioned aspect expresses need for future research.

In the view of multifactorial etiology and varied carcinogenesis mechanisms, OSCC is unique at molecular level as compared to other epithelial malignancies of the body.^{10,11} Hence, miRNA expression profile is expected to be different for various aspects of OSCC. We believe that future studies on aforementioned aspects of miRNA (Table 1)

will unveil a new pathogenesis and open an opportunity for different therapeutic targets in OSCC. Moreover, exploring aspect of miRNA in anticancer drug resistance will help us in development of new therapeutic applications.

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