MicroRNA-145 in Oral Cancer: A Short Review

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ABSTRACT

Oral squamous cell carcinoma (OSCCs) is increasing very fast rate in the developed and developing countries. Nowadays in OSCCs, many miRNAs (miRs) are playing important roles as diagnostic as well as prognostic and therapeutic biomarkers, in which miRNA-145 is one of them. MiR-145 behaves as a tumor suppressor miRNA in OSCCs, and it’s over expression promotes various cellular processes such as cell proliferation inhibition, G1 cell cycle arrest and apoptosis. miR-145 participates in different types of cancers like pancreas, liver, prostate and breast cancer including oral cancer. This novel biomarker may be used as diagnostic as well as prognostic biomarker in different types of cancers including oral cancer also. Few more validated results are required to prove miR-145 as a diagnostic, prognostic and therapeutic biomarker in cancers. This review aims to recap about the role of miR-145 in oral cancer and its use as a diagnostic as well as prognostic biomarker.

Keywords: MicroRNA, Micro RNA-145, Oral Squamous Cell Carcinoma, Tumor Suppressor


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INTRODUCTION

Oral cancer is a sixth most common cancer in the world, may arise from other than oral cavity, such as nasal cavity, larynx, pharynx and nasal cavity (1). According to Altekruse et al., more than 12,000 lung cancer patients died from oral cancer every year in United States (2). In India, oral cancer accounts for 40% of all cancers (3). Approximately 650,000 new more cases of OSCC estimated with 350,000 mortality of patients yearly in the world (4). About 90% of oral cancer is squamous cell carcinoma, display from mucosal layer of the different parts of the mouth (5). Near about 30% to 50 % oral cancer (OC) caused by Human Papillomavirus (HPV), while 80% to 90% oral cancer is associated with alcohol and tobacco chewing patients history. OSCC does not have any symptoms in early stage, so the survival of OSCC patients are very poor, because of its late stage diagnosis, accounts for 5 year survival in 30% to 50% with smoking history of OSCC patients (6). There is need to cultivate innovative molecular techniques for early diagnosis and advanced targeted drugs for survival improvement of OSCC patients. Nowadays several molecular studies are going on in cancer biology, in which microRNAs are one of them. miRNAs are playing major role in several diseases including carcinomas. Several miRNAs are participating in oral cancer in deregulated manner, may be unregulated or downregulated, these are non-coding RNA with 18 to 25 nucleotides (nt) long (7). miRNAs attract the scientific bodies as a potential biomarkers and regulators of carcinogenesis. Recent scientific studies have found deregulated miRNAs expression in OSCC cases with tumor promoters or as tumor suppressor in OSCC (8).

MicroRs function as diagnostic and prognostic biomarker in OSCC tumorogenesis including miR-145, Figure 1, with the help of alteration in expression profiles and the correlation with their clinical and pathological variables (9,10). It was reported that Among the all miRs, the miR-145 plays a vital role in OC, as a tumor suppressor (11). Shao Y et al., worked in detail on miR-145 expression in OSCC cohort, compared with normal tissue and normal mucosa tissue using RT-qPCR. He saw decreased expression of miR-145 in OSCCs in comparison to normal tissues. After this result, it has been
proved that, it is a tumor suppressor miR. Cancers cells have a unique property of uncontrolled division, which can be controlled by apoptosis and cell cycle arrest. miR-145 promote programed cell death and cell cycle arrest (in G1 phase) in case of OSCCs. Shao et al, concluded that, miR-145 targets Cdk6 and c-Myc for the inhibition of OSCCs cell growth (11).

**Biogenesis of MicroRNA**

MiRs are short nucleotides (18-25 nt) double stranded RNA and highly conserved. These miRs regulate several target genes expression at post transcriptional level such as apoptosis, proliferation and differentiation of the cells in normal biological mechanisms. Near about 1,872 miRs have been discovered in Homo sapiens and its number is rising day by day (12). These miRs engage in cell differentiation, embryonic development, inflection in immunity and in several diseases including cancers by inhibition of tumor suppressor gene or the activation of oncogene and also in cell cycle regulation (13). Biogenesis of miRs starts in nucleus in intricate manner (14). RNA polymerase II plays a major role in the synthesis of Primary miRNA (pri-miRNA), this pri-miRNA may be monocistronic or polycistronic (15). In next step, pri-mRNA get spliced, polyadenylate at 3’ end and capped with 7-methylguanosine cap at 5’end (16). MiRNA get form a secondary structure (hairpin stem loop) and After all these processes it is processed by RNase III enzyme Drosha and DGCR8 generating near about 70 nt long pre-miRNA (precursor-miRNA) secondary structure (17). After all these above processes, pre-miRNA transported to the cytoplasm with the help of exportin-5 (Ran transport receptor family) and cleaved by Dicer (RNase III family endonuclease) with the help of dsRBD protein, TRBP protein of 22 nt long double stranded miRNA duplex (18). Pooja et al., and other researchers reviewed that miRNA duplex get unwound and loaded into RISC (RNA-induced silencing complex). miRNA-RISC complex regulate gene expression by binding to the 3’ untranslated regions (3’UTRs) of mRNA. miRNA-RISC complex degrade target mRNA transcript and/or inhibit target mRNA translation into protein, Figure 2 (19).
MicroRNA-145 and Oral Cancer

There are several miRs playing important role in cancer biology, it may show downregulation (tumor suppressor) or up-regulation (oncogenic) in the diseases, in which miR-145 is one of them, it participates in the differentiation of smooth muscle cells and miR-145 encouraging programmed cell death (20, 21). This miR-145 present in downregulated manner in several cancers, including oral cancer, gallbladder cancer, gastric cancer, colon cancer, prostate cancer, bladder cancer, Non-small cell lung carcinoma (22-28). MiR-145 present on fragile position of the chromosome 5 (5q32-33) and it is co-transcribed with miR-143 (29, 30).

Shi-Yun Cui et al., has reviewed that miR-145 acts as tumor suppressor and also participate in several cellular events like cell proliferation, cell cycle, invasion and programmed cell death, by targeting several oncogenes, Figure 3 (30). MiR-145 shows poor prognosis in case of cancers, which is associated with its reduced expression and may be used as a good cancer biomarker and also may be used as cancer therapy target (31). Its low expression level was firstly observed in colon cancer by Michael et al. in 2003 (32). P53 is a well-known tumor suppressor and it controls several cellular pathways. Current researches found some indications about p53, it regulates miRs such as including miR-145, miR-192/215 and miR-34 (33, 34).

MiR expression increased by the binding of p53 to p53 response elements-2 (p53RE-2) in the promoter of miR-145, it may be the mechanism of p53- mediated repression of c-Myc (35). P53 activation plays important function in the role of miRNA-145, as tumor suppressive effect (36). The pri-miR-145 processing mediated by Drosha, which is facilitated by p53 with the help of DEAD-box RNA helicase p68 (DDX5), is a main component of Drosha complex, representing post transcriptional regulation (36). In 2009, Xu N et al. found strong correlation between miR-145 and reprogramming factors (37). Other researchers defined the negative regulation of miR-145 and OCT4 and SOX2, miR-145 suppresses the proliferation of cancer stem cells (CSCs) and promote
suppression of tumor growth, induces differentiation, migration and EMT, Epithelial-mesenchymal transition (38-40).

**CONCLUSION**

Recent evidences suggest that miR-145 involves in several cancer causing mechanisms like cell cycle, apoptosis, invasion and cell proliferation, and it function as oncosuppressor. It has been proved that miR-145 present in down-regulated manner in case of OSCCs. It inhibits OSCC cell growth by targeting Cdk6 and e-Myc. miR-145 may be used as diagnostic, prognostic as well as therapeutic biomarker in cancers, including OSCCs.

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**Conflicts of Interest**

The author declares no conflict of interest.

**Authors’ Contributions**

All authors have made an equal contribution to the manuscript design, writing, and editing of the final submitted paper.
REFERENCES


Figure 1: miR-145 may be used as diagnostic as well as prognostic biomarker in different types of cancers including oral cancer
Figure 2: Showing miR biogenesis and its function. miR transcribed by RNA polymerase III, form primary miRNA (pri-miRNA), further converted into precursor miRNA (pre-miRNA) by Drosha then goes to cytoplasm with the help of Exportin 5. Dicer processes this pre-miRNA into double stranded miRNA-miRNA duplex form. RISC binds to one strand of the miR duplex. This RISC complex binds to its target site of mRNAs and promotes to mRNA degradation or translational repression.
Figure 3: Targets of miRNA-145 and its role in different cellular mechanisms