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# Clinical Significance of microRNA Polymorphisms and Expression Profiles in Oral Cancer Development

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## Abstract

MicroRNAs (miRNA) are potent regulators, controlling multiple biological processes, including cell growth, differentiation, cell death, development and immune responses. With emerging data supporting that miRNAs play a central role in gene dysregulation in human malignancies, unraveling the miRNA genetic variations in cancer is essential and critical if we want to develop better diagnostic and prognostic system for our patients. Oral cancer may have a unique miRNA profiles in different cancer sub-types, which in turn may play a critical role in cancer development, progression, and can therefore be useful for cancer diagnosis and prognosis. Based on our findings and reviewing current literature, this article presents some of the miRNA expression profiles of different cancer tumors to understand its functional relevance and its genetic polymorphism with the oral risk of cancer.

**Keywords:** miRNAs; Cancer; Polymorphism; Genetic Variations; Clinical Significance.

## Introduction

Head and neck cancers are the sixth most prevalent and, many a times, most preventable type of cancer in the world and one of the leading causes of death in developing countries [1,2]. Among them, oral cancer is most common worldwide with a predicted 275,000 new cases each year [3]. Global statistics indicate that people in the South Asian region, including India, are particularly affected with oral cancer, ranking either first or second, among the different types of cancer prevalence in these countries [4,5]. This could be due to their smoking or/and drinking habits plus their economic status. Perhaps, the two greatest health concerns worldwide at present are cancer and smoking, both of which are continuously rising in incidence and are associated with high morbidity and mortality. Understanding the aetiology and mechanisms of these diseases is critical for developing clear and effective strategies for improving global health [6]. Many studies have also shown that cancer is not only related to environmental factors, but also to individuals' genetic susceptibility (predisposition) [7-10]. Further, Ambrose *et al*. proposed a new mechanism of microRNA(miRNA)-mediated transcriptional regulation that could promote cancer development [11]. miRNA has been another hotspot in cancer research in recent years [12,13]. Most miRNAs reside within intergenic or intronic regions of other genes. They are non-coding, single stranded RNAs of ~22 nucleotides and negatively regulate their target mRNAs at the post transcriptional level [14-16].

### MicroRNA Biogenesis

miRNAs are single strands of 18-22 nucleotides in size and serve as very important regulators of gene expression at the post-transcriptional level. The biogenesis or the processing of miRNA is a two-step procedure and takes place in both nucleus and cytoplasm [17] (Figure 1).

In the nucleus, a large precursor RNA known as a pri-miRNA is transcribed by the RNA polymerase II enzyme. The pri-miRNA is processed by the RNase III enzyme, Drosha, into a ~70-nucleotide pre-miRNA. The pre-miRNA is exported from the nucleus to the cytoplasm by the RAN GTP-dependent transporter exportin 5 (XPO5). In cytoplasm, the pre-miRNA is further processed into a double-stranded RNA of ~22 nucleotides-miRNA: miRNA* duplex by another RNase III enzyme, Dicer. Finally, one strand of the duplex is incorporated into the RNA induced silencing complex (RISC) that is composed of the Argonaute proteins, Gemin3 and Gemin4 and others; and the target mRNA will be degraded or repressed for the translation depending on the degree of the complementarity of the miRNA to its target sequences. So far, miRNAs have been identified to regulate one third of human mRNA expression, and impact various genetic pathways including carcinogenesis-

related pathways; thus, it is possible that the disrupted function of miRNAs may contribute to diverse diseases, including cancer [18-21]. Also, miRNAs themselves can be oncogenic or tumor suppressing [22,23].

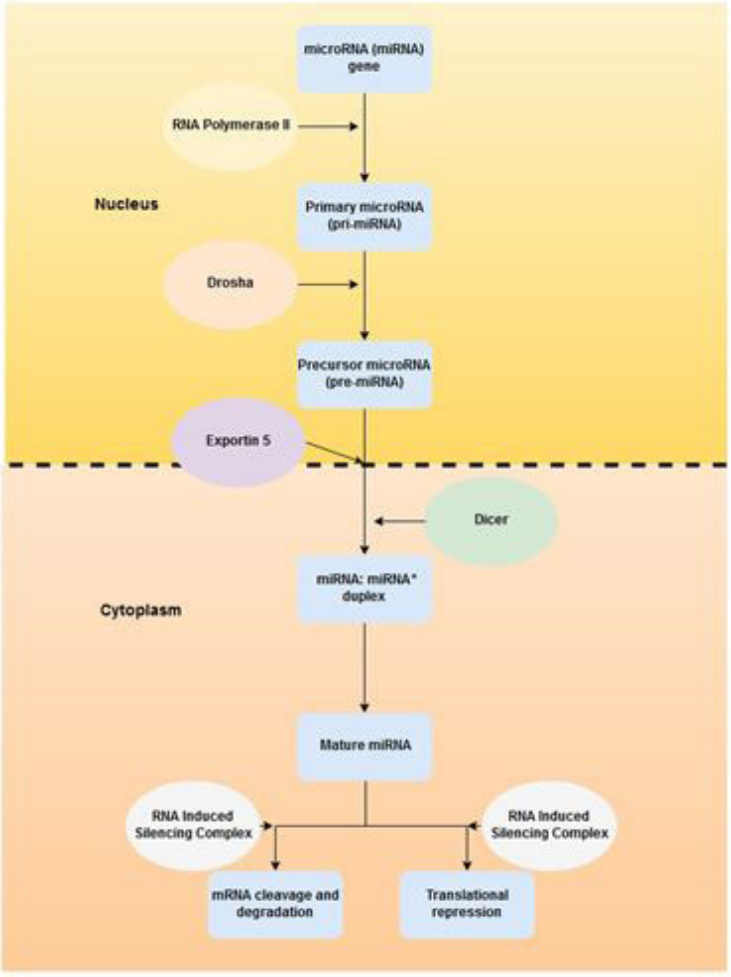


**Figure 1:** Overview of miRNA biogenesis

## Genetic Variations in miRNAs

The binding of miRNA to mRNA is critical for regulating the mRNA level and protein expression. However, this binding can be affected by single-nucleotide polymorphisms that can reside in the miRNA target site, which can either abolish existing binding sites or create illegitimate binding sites. Therefore, polymorphisms in miRNA can have a differing effect on gene and protein expression and represent another type of genetic variability that can influence the risk of certain human diseases. The increase or decrease in miRNA binding caused by the variations would probably lead to a corresponding decrease or increase in protein translation.

To date, more than 2500 miRNA molecules have been identified in the human genome and they play important roles in a broad range of physiological and pathological processes and miRNAs are proposed to influence gene expression of 30% of protein-coding genes [24]. Recent studies have also implicated miRNAs in the genesis, progression and prognosis of multiple human malignancies [22,23,25-29]. Up and down regulation in the level of expression of distinct miRNAs have been observed to be associated in the development and progression of cancer. It is therefore possible that variations in miRNA expression may promote carcinogenesis by modulating the expression patterns of essential genes involved in tumor growth and progression and suppressing the functions of tumor suppressor genes.

Aberrant miRNA expression in malignant cells may occur due to alterations in variations in copy numbers and amplification, deletion or translocation of genes, or loss of heterozygosity of tumor suppressor genes. Deregulation of transcription factors (eg., p53, c-Myc) that control expression of miRNAs may result in increased cell cycling, for instance via promoting progression from G1 to S phase, thus aiding proliferation of cancer cells. Epigenetic alterations such as DNA methylation and histone acetylation of miRNAs that function in tumor suppression may lead to their inactivation, thus promoting carcinogenesis [20,21,30].

There are several mechanisms through which miRNAs function in carcinogenesis. miRNAs function in several crucial cell

growth pathways, and their dysregulation contributes to hindering growth suppressors and increased cancer cell proliferation. miRNA may also aid in circumvention of apopotic signaling, leading to increased cancer cell growth. miRNAs may also function in epithelial-mesenchymal transition and cancer metastasis, through loss of cell adhesion and activation of genes that promote tumor cell motility and invasion. miRNAs that target angiogenesis signaling pathways may aid hypoxia in the tumor microenvironment, contributing to the maintenance of cancer cells [20,21].

Since most of the miRNA genes are found to be located in cancer-related chromosomal regions functioning either as oncogenes or tumor suppressor genes; single nucleotide polymorphisms (SNPs) in these genes could therefore be the most common form of variations present in the human genome.

It is widely accepted that SNPs are associated with cancer risk. SNPs occurring in miRNA sequences can affect processing and binding ability of mature miRNA associated with susceptibility to different cancers [27-29]. As miRNAs have a widespread effect on mRNA transcripts, a description of human natural variation associated with the miRNA system is warranted for understanding its functional and evolutionary significance. Technologies and new methodologies have helped us to identify miRNAs and their binding sites (i.e., targets) [31-33]. Table 1 presents an overview of some of the experimental and computational methods used for identification of miRNAs and their targets. The availability of comprehensive genomic databases of SNPs provides an unprecedented opportunity to explore human evolution at miRNAs levels and their targets. Recent knowledge on miRNA target genes indicates their involvement in cell proliferation, differentiation and apoptosis [19,53].

| S.No. | Method | Experimental/ Computational | Reference |
|---|---|---|---|
| 1. | Expression Profiling using by microarray, high-throughput sequencing, or proteomics | Experimental | [34] |
| 2. | Polysome Profiling by high-throughput sequencing | Experimental | [35] |
| 3. | Pull-Down Assays (eg., Labeled microRNA pull-down assay, Immunoprecipitation), followed by microarray or high-throughput sequencing | Experimental | [36-41] |
| 4. | MiRscan http://genes.mit.edu/mirscan/ | Computational | [42,43] |
| 5. | TargetScan http://www.targetscan.org/ | Computational | [44] |
| 6. | TargetScanS http://genes.mit.edu/tscan/targetscanS2005.html | Computational | [45] |
| 7. | RNA22 http://cm.jefferson.edu/rna22v1.0/ | Computational | [46] |
| 8. | PITA http://genie.weizmann.ac.il/pubs/mir07/ | Computational | [47] |
| 9. | RNAhybird http://bibiserv.techfak.uni-bielefeld.de/rnahybrid/submission.html | Computational | [48] |
| 10. | DIANA-microT http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=microT_CDS/index | Computational | [49,50] |
| 11. | ToppMiR https://toppmir.cchmc.org/ | Computational | [51] |
| 12. | MiRNet http://www.mirnet.ca | Computational | [52] |

**Table 1:** Experimental and computational methods used for identification of miRNAs and their targets

Over the past few years, several reports have shown that genetic variations in the precursor of miRNAs (pre-miRNAs) affect maturation/expression of respective mature miRNA and have been studied in several cancers including carcinoma of the breast, urinary bladder, cervical, head and neck, gastric, and lung. Jeon *et al.* reported that pre-miR-146a may contribute to genetic susceptibility in lung cancer, and that miR-146a might be involved in the progress of lung cancer development [26]. Shen *et al.* reported that CC genotype of miR-196a2 rs11614913 was associated with an increased esophageal squamous cell carcinoma risk while Wei *et al.* reported that the functional polymorphism in miR-196a2 rs11614913 T>C might contribute to decreased esophageal squamous cell carcinoma risk among women patients [27,28]. A meta-analysis study by Xu *et al.* has clarified that three common polymorphisms in microRNAs, miR-146aG>C, miR-196a2C>T, miR-499A>G, have different effects on cancer risk in the Asian population [29]. Previous studies showed that polymorphism in miRNA can change the expression of mature miRNAs or the binding activities to target mRNA, and thus influence cancer risk through various mechanisms and may also lead to chemoresistance [54-56]. Several authors have reported that genetic variations in miRNA are susceptible to breast cancer [57-60]. Umar, *et al.* reported that pre-miRNA polymorphisms cumulatively affected the susceptibility and survival of

esophageal cancer patients in north Indian population [61].

These reports support the exploration of miR-196a2 as a therapeutic target in cancers, especially in oral cancers. We have conducted genetic studies of miRNA SNPs in oral cancers and have demonstrated the key role of a few miRNAs (miR-196a2C>T and miR-149C>T) and their associated risk of oral cancers [23,62]. We found that the CC genotype of both the miRNAs were associated strongly with risk of development of oral cancers. Our epidemiological studies have demonstrated the association of SNPs in miRNAs with cancer susceptibility. A study by Hoffman *et al.* has shown that polymorphism in miR-499 influences the expression levels of miR-499a-5p during the tumorigenesis of oral squamous cell carcinoma [63]. Increased expression of miR-21 may aid in invasion, while upregulation of miR-31 may aid in increased proliferation, migration, and epithelial-mesenchymal transition in oral squamous cell carcinoma [64,65]. Overexpression and rs2910164 polymorphism in miR-146a have been implicated in progression of oral squamous cell carcinoma, though further studies have been suggested to confirm their role [66-68]. Increased expression of miR-155 and miR-27a were suggested to play a role in the progression of tumorigenesis of oral squamous cell carcinoma miR-27a may downregulate *MCPH1*, a tumor suppressor gene and thus promote carcinogenesis [69-70]. Few studies have reported that downregulation of tumor suppressor miRNAs may aid in oncogenesis of oral squamous cell carcinoma; for instance, downregulation of miR-1 has recently been suggested to promote increases metastasis and invasion in oral squamous cell carcinoma [71]. In another instance decreased expression of miR-99a was found to be associated with increased proliferation and survival of oral squamous cell carcinoma cells and could serve as a potential therapeutic target or as a biomarker [72]. A study by Uesugi *et al.* suggests that epigenetic silencing of miR-218 through hypermethylation may promote carcinogenesis in oral squamous cell carcinoma through activation of the mTOR-Akt signaling pathway [73]. In addition, miR-17/20a, miR-125b, miR-155, miR-181 and miR-491-5p are associated with poor patient survival in oral squamous cell carcinoma [74-78]. These findings suggest that miRNAs may be explored as prognostic and diagnostic markers in oral squamous cell carcinoma.

MiRNAs play critical roles in key cellular processes such as cell growth and differentiation,. Hence, their aberrant functioning due to alterations in their expression and/or polymorphisms in their target sites leads to altered cell cycle, loss of genome integrity and stress response, inhibition of apoptosis and promotion of metastasis in various cancers, supporting their exploration as clinical markers [23-29, 55-79]. Previous studies in other cancers from Indian population reported that polymorphisms in miRNA-related genes might alter the expression levels of mature miRNAs, with consequences on the regulation of target genes that affect cancer risk or prognosis [23,61,62]. On the other hand, gaining better insight into the regulatory mechanisms of microRNA would allow us to design new therapeutic regime, which may target the disease with better outcome for suffering patients. RNAi has also been suggested as novel therapeutic platform technology for oncological solutions [80]. However, several of the mechanisms proposed for the biogenesis or processing of miRNAs and their expressions are mostly based on animal model studies or in vitro studies, except a few recent studies which relate to human disease state; hence this topic remains a subject for future investigations.

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