

A Review of MicroRNA Associated with Oral Cancer

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Abstract

Cancer of oral cavity is the sixth most common malignancy worldwide with over 500,000 new cases diagnosed annually and its incidence is rising in many countries. It is associated with a poor prognosis with less than 50% of 5-year survival rate. Oral cancer incidence in Malaysia varies between the different ethnic communities due to different sociocultural risk factors such as the betel chewing habit which it is a traditional stimulant mixture of areca nut and tobacco with the betel leaf. Moreover, despite recent advances in various treatment modalities, the survival rates of cancer patients had shown not markedly improved.

MicroRNAs or miRNAs are a group of small non-coding RNAs that post-transcriptionally regulate gene expression. Recent findings have strongly supported its role in cell regulations of essential processes including cell proliferation, apoptosis, development, differentiation and metabolism. However, dysregulation of miRNAs expressions have been implicated in malignancy which affects its functions as tumor suppressors and oncogenes in various cancers. Thus, this review of microRNA expression would provide information on microRNAs with potential role as the biomarkers in oral cancer treatment in the future.

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Introduction

Cancer is listed as the major public health issues with considerable individual and socioeconomic impacts worldwide until today. It is also considered as a complex genetic disease that involves long-term accumulation of various mutations in coding as well as non-coding genes¹. Cancer is appointed as one of the disease accounting topmost mortality rate, globally. In 2012, an estimated 14.1 million new cases of cancer were diagnosed worldwide with 8.2 million of death reported².

The most frequently diagnosed cancers by sex vary considerably across country³. The most commonly diagnosed cancer among men is lung cancer in most parts of Eastern Europe and Asia⁴. Among women, the most frequently diagnosed cancer is breast cancer in most parts of the world, including Australia, Western Asia, North Africa, North America, and parts of South America². In many parts of the globe, oral cancer currently serves as one of the increasingly serious problems. An estimation of more than 500,000 new cases diagnosed every year pointed out that oral cancer is one of the most frequent cancers worldwide⁵. It is heterogeneous in nature and shows dismal survival rate of approximately 50% that has not changed for decades⁶.

The reported 5-year disease-specific survival rate in stage II of oral cancer patients was 39-85%⁷. While specific survival rate for stage III and IV of oral cancer patients were 27-

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70% and 12-50 %, respectively ⁷. Oral cancer includes cancers of the lip, tongue and rest of the oral cavity ⁸. Oral cancer which occurs among middle age male gives terrific impact towards their family and society ⁵.

Recently, miRNAs expression has been linked to cancer ⁹. Cancer is the product of alterations in oncogenes, tumour suppressor genes and most recently microRNA genes not as a single event or single change, but rather as a multistep process ¹⁰. MicroRNA (miRNA) mediates gene expression at the post-translational level by degrading or repressing target messenger RNAs (mRNA) or by translational inhibition of target genes ¹¹. Several miRNAs have been identified associated with cancer, for examples, miR-143 and miR-145 have been found down-regulated in colorectal cancer ¹² and let-7a in lung cancer ¹³.

There are many classes of small endogenous RNA molecules, such as small transfer RNA (tRNA), ribosomal RNA (rRNA), small nucleolar RNA (snoRNA), small interfering RNA (siRNA) and microRNA (miRNAs) ¹⁴. These molecules are distinguished based on their respective origins ¹⁴. miRNAs are short non-coding RNAs of 20-24 nucleotides that post-transcriptionally regulate gene expression ¹. miRNAs can be located in introns, exons of coding genes, non-coding genes and intergenic regions ⁶. miRNAs precursors are usually found in clusters through various different regions of the genome, most frequently within intergenic regions and introns of protein coding genes ¹⁴.

The biogenesis and function of miRNAs (Figure 1) starts with the pri-miRNA transcripts which is generated by RNA polymerase II, either as separate transcriptional units or embedded within the introns of protein ¹⁵. After the pri-miRNA is synthesized, it is cleaved and a small hairpin structure that is termed pre-miRNA is released ¹⁵. In the nucleus, the microprocessor complex containing the RNase III enzyme Drosha and the DiGeorge syndrome critical region gene 8 (DGCR8), trims the primary transcript to release pre-miRNA hairpin ¹⁶. Pre-miRNA hairpin are exported out of the nucleus to the cytoplasm by exportin 5 (XPO5), a RAN-GTP dependent nucleocytoplasmic cargo transporter ¹⁷.

In the cytoplasm, a protein complex including DICER and Transactivating response

RNA-Binding Protein (TRBP) further trims the pre-miRNA to produce an imperfect duplex containing both the mature miRNAs strand and its complementary strand (miRNA:miRNA*) ¹⁴. Argonaute 2 (Ago2) will then select the appropriate strand based on thermodynamic rules, leading to RNA-induced silencing Complex (RISC) formation and regulation of specific messenger RNA (mRNAs) ¹⁸. The mature miRNA then induces post-transcriptional gene silencing by tethering RISC to partly complementary sequence motifs in target mRNAs mostly found within the 3' untranslated regions (UTRs) ^{19,20}. miRNAs guide miRISC to specifically recognize mRNA and downregulate gene expression by one of the two posttranscriptional mechanisms: (i) translational repression and (ii) mRNA cleavage ²¹.

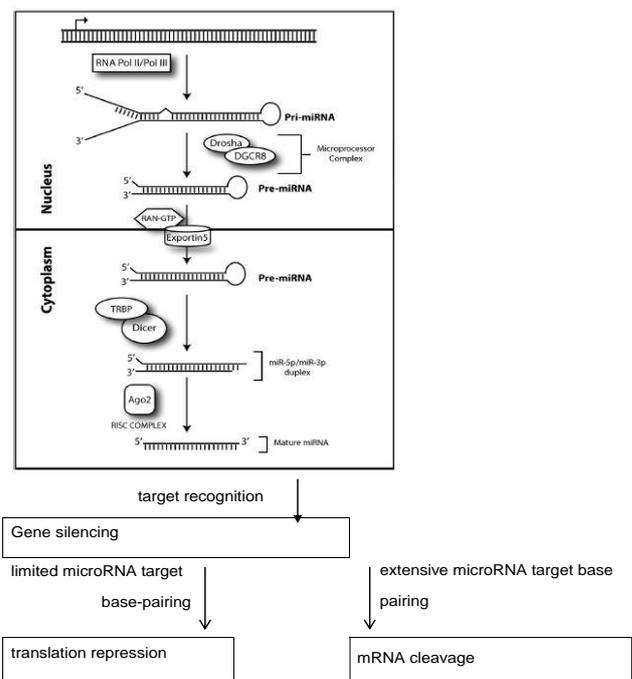


Figure 1. MicroRNA maturation and function ^{14,18}.

miRNAs provide a vital and powerful tool in gene regulation and thus a potential novel class of therapeutic targets ²¹. miRNAs play an evolutionarily conserved developmental role and diverse physiological functions in mammal ²¹. They play important function as regulatory molecules in post-transcriptional gene silencing for the regulation of cellular bio-functions. In mammals, miRNAs are predicted to control the activity of approximately 50% of all protein-coding genes ²². Functional studies indicate that

miRNAs participate in the regulation of almost every cellular process investigated so far and that changes in their expression are associated with many human pathologies²³. Findings over the five years have strongly supported a role for miRNAs in the regulations of essential processes including cell proliferation, apoptosis, development, differentiation and metabolism².

miRNA Expression in Oral Cancer Study

miRNA has been proposed to have an association with oral cancer. According to several recent studies, approximately 30-50 miRNAs have been suggested to be linked with oral cancer using either independent *in vitro* or *in vivo* experiments and human study²⁴. However, there are only a few miRNA that have been proven to be involved in oral cancer²⁵. Table 1 summarizes miRNA expressions that have been reported recently.

Most miRNA expression profiling has been performed with the microarray analysis method and quantitative real-time Polymerase Chain Reaction (qPCR)²⁶. Using these methods, some miRNAs show consistently altered expressions in different studies. For example, expression of miR-125b, miR-155, miR-124a, and miR-124b has been reported by at least two independent studies (Table 1). In the study by Faraoni et al.(2009) miR-155 has been found to be overexpressed in many cancer types including hematopoietic cancers, breast, lung and colon cancer²⁷.

Recently, upregulated expression of miRNA-21 in cell lines of oral cancer has been reported by Scapolli et al (2010)²⁸. Another study by Garzon et al (2008)²⁹ and Calin et al (2006)³⁰ showed that miR-21 is also upregulated in acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL)²⁹. There are also study discovered upregulated of miR-21 in oral cancer and other cancer include breast, colon, pancreas, lung, prostate, liver, stomach, and glioblastoma⁹. These facts strongly suggest that miR-21 may be one of the most important miRNAs in various types of cancers including oral cancer.

In study by Scapoli *et al.* (2010) showed that upregulated expression of miR-129 has been detected in oral cancer cell lines²⁸. Recently, there have been no reports suggesting

downregulated of miR-129 towards oral cancer cell lines⁵. However, its downregulated expression has been reported in bladder cancer³¹ and gastric cancer³². Another study by Lu *et al.* (2013) showed that miR-129-2 was frequently hypermethylated in hepatocellular carcinoma cells (HCC) and clinical samples³³. Another study identified the down-regulated expression of miR-129-2 in HCC tissues in a manner reversely correlated with the level of miR-129-2 methylation³⁴. It was also reported that miR-129 levels was low in cancer cell line than in neural and colorectal tissues^{35,36}. The function of miR-129 in tumorigenesis remains unclear however it might have diverse biological activities depending on the type of cancer³⁴.

In contrast, some miRNAs such as miR-34b, miR-100, miR-125b, miR-137 and miR-203 have been found to be significantly downregulated in OSCC samples. In terms of the functional analysis, transfection of miR-125b and miR-100 to OSCC-derived cells significantly reduced cell proliferation in some studies^{37,38}. A study done by Shiiba and friends (2010) found that the expression level of 133a and 133b in oral cancer were low³⁹. Downregulation of miR-133a has also been observed in bladder cancer and colorectal cancer progression⁴⁰. Besides that, decreased expression of miR-133b has also been demonstrated in bladder cancer⁴¹ and colorectal cancer⁴². This could be due to direct genetic loss, alterations in their biogenesis pathway, epigenetic changes, altered transcription factor expression or changes to their target site where these mechanisms are still unclear⁴³.

Study by Peng et al. (2014) showed that miR-218 have been found to be downregulated, and suggested that miR-218 may function as a tumor suppressor gene in oral cancer⁴⁴. Moreover, recent studies have shown that miR-218 and let-7g can inhibit cell invasion and metastasis in gastric cancer⁴⁵ and breast cancer⁴⁶. Examples of upregulation and downregulation of miRNA in cancer studies have been summarized and tabulated in Table 1 as shown below:

References	Samples/ Materials	Methods	miRNA Deregulation	
			Upregulated	Downregulated
(Kozaki et al., 2008) ⁴⁰	Oral cancer cell line	Quantitative reverse transcription-PCR (qRT-PCR)	miR-374, miR-340, miR-224, miR-10a, miR-140, miR-181a, miR-146a, miR-126, miR-31, miR-9, miR-9*	miR-27a, miR-34b, miR-34c, miR-203, miR-302c, miR-23a, miR-27b, miR-34a, miR-215, miR-299, miR-330, miR-337, miR-107, miR-133b, miR-138, miR-139, miR-223, miR-204, miR-370, let-7d, miR-95, miR-302a, miR-367, let-7g, miR-23b, miR-128a, miR-148a, miR-155, miR-200c, miR-302b, miR-368, miR-122a, miR-371, let-7a, miR-26b, miR-30e-5p, miR-96
(Wong et al., 2008) ⁴⁷	Tissues of tongue SCC	Quantitative reverse transcription-PCR (qRT-PCR)	miR-184, miR-34c, miR-137, miR-372, miR-124a, miR-21, miR-124b, miR-31, miR-128a, miR-34b, miR-154, miR-197, miR-132, miR-147, miR-325, miR-181c, miR-198, miR-155, miR-30a-3p, miR-338, miR-17-5p, miR-104, miR-134, and miR-213	miR-133a, miR-99a, miR-194, miR-133b, miR-219, miR-100, miR-125b, miR-26b, miR-138, miR-149, miR-195, miR-107, and miR-139.
(Avissar et al., 2009) ⁴⁸	Oral cancer cell line	Microarray	miR-21, miR-181d, miR-181b, miR-491, miR-455, miR-18a, miR-130b, miR-221, miR-193b, miR-181a, miR-18b	miR-375
(Liu et al., 2009) ⁴⁹	Oral cancer cell line	Quantitative reverse transcription-PCR (qRT-PCR)	miR-31, miR-21, miR-96, miR-224, miR-182, miR-135b, miR-183, miR-301, miR-147, miR-373, miR-155, miR-223, miR-372, miR-130b, miR-187, miR-371, miR-34b, miR-34c, miR-216, miR-10a, miR-128b, miR-104	miR-100, miR-328, miR-99a, miR-124b, miR-149, miR-139, miR-124a, miR-204, miR-211
(Scapoli et al., 2010) ²⁸	oral cancer cell line	Microarray	hsa-miR-489, hsa-miR-129, hsa-miR-23a, hsa-miR-214, hsa-miR-23b, hsa-miR-92, hsa-miR-25, hsa-miR-210, hsa-miR-212, hsa-miR-146b, hsa-miR-21, hsa-miR-338	hsa-miR-520h, hsa-miR-197, hsa-miR-378, hsa-miR-135b, hsa-miR-224, hsa-miR-34a
(Rentoft et al., 2011) ⁵⁰	Oral cancer cell line	Microarray	miR-659, miR-146b-3p, miR-1301, miR-665, miR-142-5p, miR-7, miR-142-3p, miR-21, miR-936, miR-206	miR-617, miR-29b-2, miR-132, miR-548b-5p, miR-509-5p, miR-22
(Lu et al., 2012) ⁵¹	Oral cancer cell line	Quantitative reverse transcription-PCR (qRT-PCR)	miR-10b, miR-196a, miR-196b, miR-582-5p, miR-15b, miR-301, miR-148b, and miR-128a	miR-503 and miR-31
(Soga et al., 2013) ⁵²	Oral cancer cell line	Quantitative reverse transcription-PCR (qRT-PCR)	hsa-miR-31*, hsa-miR-31, hsa-miR-135b, hsa-miR-193a-5p, hsa-miR-103, hsa-miR-224, hsa-miR-93, hsa-miR-200c, hsa-miR-183, hsa-miR-203, hsa-miR-21, hsa-miR-223	hsa-miR-133a, hsa-miR-376c, hsa-miR-411, hsa-miR-30a-3p, hsa-miR-489, hsa-miR-139-5p, hsa-miR-483-5p, hsa-miR-30e-3p, hsa-miR-409-3p, hsa-let-7c, hsa-miR-486-5p
(Fukumoto et al., 2015) ⁵³	Oral cancer cell line	Quantitative reverse transcription-PCR (qRT-PCR)	-	miR-126-5p, miR-145-5p, miR-145-3p, miR-26b-5p, miR-26a-5p, miR-204, miR-29c, miR-195, miR-30c, miR-10b, miR-656, miR-30e-3p, miR-140-5p, miR-23b, miR-10b, miR-126-3p, miR-143, miR-30d, miR-139-5p, miR-19b-1-5p, miR-598, miR-885-5p, miR-376c, miR-487b, miR-101, miR-886-5p, miR-140-3p, miR-30e, miR-125b, miR-378a-5p, miR-320, miR-136-3p, miR-26a-1-3p, miR-127-3p, miR-411, miR-30a-3p, miR-29c-5p, miR-376a, miR-26b-3p, miR-770-5p, miR-433, miR-375

Table 1. miRNA expression in recent oral cancer studies.

Conclusions

Despite advances in treatment modalities, mortality rates of oral cancer patients have not markedly improved over the past three decades⁵⁴. Thus, better understanding of this disease needs to be discovered immediately. Many studies strongly suggest that miRNA plays crucial

roles in many human cancers including oral cancer⁶. This is because they have an important function in cellular processes including proliferation, differentiation, apoptosis, survival, motility, and morphogenesis². Recent advances in miRNA expression profiling have led to a better understanding of the oral cancer pathogenesis. This will lead to the discovery of

specific miRNA expression patterns that may become successful biomarkers for diagnosis and prognosis of oral cancer in the future.

Declaration of Interest

The authors report no conflict of interest.

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