

Review of MicroRNA Deregulation in Oral Cancer. Part I

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ABSTRACT

Objectives: Oral cancer is the sixth most common malignancy worldwide. Cancer development and progression requires inactivation of tumour suppressor genes and activation of proto-oncogenes. Expression of these genes is in part dependant on RNA and microRNA based mechanisms. MicroRNAs are essential regulators of diverse cellular processes including proliferation, differentiation, apoptosis, survival, motility, invasion and morphogenesis. Several microRNAs have been found to be aberrantly expressed in various cancers including oral cancer. The purpose of this article was to review the literature related to microRNA deregulation in the head and neck/oral cavity cancers.

Material and Methods: A comprehensive review of the available literature from 2000 to 2011 relevant to microRNA deregulation in oral cancer was undertaken using PubMed, Medline, Scholar Google and Scopus. Keywords for the search were: microRNA and oral cancer, microRNA and squamous cell carcinoma, microRNA deregulation. Only full length articles in the English language were included. Strengths and limitations of each study are presented in this review.

Results: Several studies were identified that investigated microRNA alternations in the head and neck/oral cavity cancers. Significant progress has been made in identification of microRNA deregulation in these cancers. It has been evident that several microRNAs were found to be deregulated specifically in oral cavity cancers. Among these, several microRNAs have been functionally validated and their potential target genes have been identified.

Conclusions: These findings on microRNA deregulation in cancer further enhance our understanding of the disease progression, response to treatment and may assist with future development of targeted therapy.

Keywords: oral cancer; oral neoplasms; head and neck cancer; head and neck neoplasms; microRNA; review.

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INTRODUCTION

Cancer of the oral cavity and oropharynx (OCC) remains among the top ten malignancies in the United States and worldwide. These cancers account for 4% of malignancies in men and 2% of malignancies in women. In the United States despite current advances in treatment one human life every hour is lost to this cancer. According to American Cancer Society while overall new head and neck/oral cavity cancer cases increased about 8% during the past 5 years, the new cases for oral cancer increased about 21% (Table 1). In the 2010 cancer statistics published by the American Cancer Society there are 36,540 estimated new cases of oral cavity/oropharynx cancers and 7,880 deaths from these cancers [1]. An alarming fact is the recent increase of these cancers worldwide among younger individuals often without risk factors or not engaged in known high risk social habits such as smoking and alcohol consumption [2,3]. Despite current advances in treatment the reported overall five year disease free survival worldwide remains largely unchanged over the past several decades for all races (range between 45 - 65%) [1,4-7]. Failure to cure OCC despite optimal treatment is a reality and these cancers remain an undertreated and poorly understood disease process that represents a major health problem. Improvement of survival and treatment outcomes require a better understanding of the disease progression so that these cancers can be diagnosed early and most importantly targeted therapy can be initiated accordingly.

The initiation and progression of OCC is a highly complex multistep process that entails progressive acquisition of genetic and epigenetic alterations and dynamic changes in the genome. Thus far, the majority of the studies on the cancer genome have focused primarily on the protein coding genes and their alterations. The impact of non coding sequences

in disease initiation and progression including cancers remain largely unknown [8-10]. Although at least 65% of the genome is transcribed, protein-coding transcripts are derived from less than 2% of the human genome [11]. The mammalian genome harbours genes that although they do not encode proteins have an important role in normal cell development and disease process and these non protein transcripts may make up at least half of all transcripts in mammals [12].

RNA interference (RNAi) in a variety of organisms is a known process of sequence specific post-transcriptional gene silencing initiated by double-stranded RNA [13,14]. RNAi was first discovered in 1998 in the nematode *Ceanorhabditis elegans*, but is conserved in variety of organisms and is considered a major regulatory mechanism in eukaryotic gene expression [15]. In mammalian cells RNAi regulation of endogenous genes occurs by the production of short double-stranded RNA molecules or microRNA. MicroRNAs mediate gene expression at the post-transcriptional level by degrading or repressing target messenger RNAs (mRNA) or by translational inhibition of target genes. Since the initial discovery of the founding members of the microRNA family, *lin-4* and *let-7* several hundreds have been identified in all species by combination of molecular cloning and bioinformatics. It is now estimated that 1,000 microRNAs exist in the human genome [16-24]. The purpose of this article was to review the literature related to microRNA deregulation in the head and neck/oral cavity cancers.

MATERIAL AND METHODS

A comprehensive review of the available literature from 2000 to 2011 relevant to microRNA deregulation in oral cancer was undertaken using PubMed, Medline, Scholar Google and Scopus. Keywords for the search were: microRNA and oral cancer, microRNA and squamous cell carcinoma, microRNA deregulation. Only full length articles in the English language were included. Strengths and limitations of each study are presented in this review.

MicroRNA formation

MicroRNAs are encoded by genes located either in non coding regions or in introns of protein coding genes and require a complex set of proteins for their formation [25,26]. Thus primary microRNA transcription may be by an independent promoter or by a promoter of the proximal coding gene. Most microRNAs are transcribed by the RNA

Table 1. The changes of head and neck/oral cavity cancer (HNOCC) incidence and death for the past 5 years

Year	New cases		Deaths	
	All cancers	HNOCC	All cancers	HNOCC
2005	1.372.91	29.37	570.28	7.32
2006	1.399.79	30.99	564.83	7.43
2007	1.444.92	34.36	559.65	7.55
2008	1.437.18	35.31	565.65	7.59
2009	1.479.35	35.72	562.34	7.6
Total (2005 - 2009)	7.134.15	165.75	2.822.75	37.49
5 year increase	106.44	6.35	-7.94	280
% increase	7.8%	21.6%	-1.4%	3.8%

polymerase II to primary microRNAs that are longer nucleotide sequences (hundreds to even thousands of nucleotides). Approximately 20% are transcribed by the RNA polymerase III into primary microRNAs. These are then spliced and capped with a 5' 7-methylguanosine cap (^{m7}G) and poly-adenylated at the 3' end. This is a process similar to protein-coding messenger RNA process. The primary microRNAs form specific hairpin-shaped stem loop secondary structures prior to be processed by a microprocessor complex (500 - 650 kDa) into pre-microRNAs. The complex, consistent of Drosha (RNase III endonuclease) and the essential cofactor DGCR8/Pasha, processes the primary microRNAs into 60- to 70- nucleotide long pre-microRNA with a 5' phosphate and a 3' nucleotide overhang. Exportin 5, a member of the Ran transport receptor family, transports the pre-microRNA to the cytoplasm. In the cytoplasm further processing to short double strand microRNA/microRNA* occurs by Dicer, a second RNase III endonuclease, prior to unwind of the duplex by a helicase to reveal the final mature microRNA and microRNA*, which is quickly degraded [27]. The average ratio of microRNA to microRNA* is approximately 100 to 1 but can be much lower in cases of both strands are functional and incorporated into RISC that is shown to occur [27-29]. The mature microRNA product is noncoding, regulatory RNA molecules 22 nucleotides long that can be asymmetrically incorporated into RNA-induced silencing complexes (RISC) that are then guided to the target mRNA [9,30-32].

MicroRNA physiologic functions

It is well established that microRNAs are involved in diverse physiologic processes [33-36]. Studies with mouse embryos and zebra fish Dicer-null phenotype revealed that microRNA pathway is not generally required for cellular viability but plays a prominent role in various tissue specific cell types and morphogenesis of embryonic structures. Such examples are impact of microRNAs on T-cell development/differentiation as well as morphogenesis of lung, limb and skin as well as maintenance of hair follicles [37-42]. The ability of microRNAs to dramatically influence tissue(s) specific generation and behaviour is another important function of these molecules. This is demonstrated in studies on *microRNA-181*, the first mammalian microRNA to be carefully studied as well as *microRNA-1* the most highly conserved microRNA. *MicroRNA-181*'s ectopic expression in hematopoietic progenitor cells skews their differentiation towards the B-cell lineage while the same microRNA is up-regulated during differentiation and regeneration of muscle cells [43,44]. *MicroRNA-1* conversely demonstrates skeletal and

cardiac muscle specific expression and is shown to be critical in development of normal muscle [21,45,46]. Over-expression or inhibition of *microRNA-1* promotes or inhibits respectively mammalian muscle cell differentiation *in vitro* [45,47]. In addition *microRNA-1* has been shown to also play an important role in muscle physiology [45,48-50]. The involvement of *microRNA-138*, that is also frequently deregulated in OSCC as will be discussed later, in differentiation of human adipose tissue derived mesenchymal stem cells is another recent discovery. During adipose differentiation *microRNA-138* was found to be significantly down-regulated, while it's over expression effectively reduced lipid droplets accumulation and inhibit expression of key adipogenic transcription factors. These findings could provide insights into the pathogenesis of a number of diseases such as obesity and diabetes and potentially broaden the spectrum of stem cell based therapy for these conditions [51]. These findings stress the fact that a single microRNA can participate and impact on distinct pathways in various tissues and have the ability to influence the generation and behaviour of tissue-specific cell types.

It is now accepted that microRNAs are important in establishing and/or maintaining gene expression patterns that are characteristic of specific tissues [52]. It has been shown that many microRNAs and their predicted target are reciprocally expressed [53,54]. Lastly, several cell-autonomous functions, not related to development or differentiation, have been shown to be controlled by microRNAs. Such examples include insulin regulation and specific expression of *microRNA-375* in pancreatic islet beta cells and cholesterol homeostasis by liver specific *microRNA-122*. The brain and nervous system is perhaps the most extensively studied in reference to microRNA and regulation of function in vertebras. For example neuronal differentiation and synaptic function have been found to be controlled by *microRNA-9* and *microRNA-124* while neuronal outgrowth and dendritic morphogenesis by *microRNA-134*, *microRNA-132*. Another interesting implication of microRNAs in function has originated from identification of *microRNA-138* involvement in dendritic spine size morphogenesis, via synaptic protein synthesis, that is associated with formation of long lasting memories [55-61]. In addition to key roles in the nervous system development and function *microRNA-138* has been implicated in cardiac patterning-compartmentalization during embryonic development [62]. It is evident from the current and growing literature that microRNAs have global participation and impact on normal physiologic processes. A logical extension to this conclusion is that any alteration or abnormalities in

their function would influence disease phenotypes in all organisms [44,63,64]. Additional information on microRNA functions and microRNAs in physiology and disease process can be found in the excellent reviews on the subject by Bushati et al. and Chang et al. [63,64].

MicroRNA and cancer of the oral cavity and oropharynx (OCC)

Since their initial discovery the microRNA gene family is continuously growing with novel members discovered in association with several disease processing. Once sufficient information on microRNA was made available several commercially available microRNA array platforms were developed and subsequently employed successfully in identification of microRNA deregulation in head and neck/oral cancers. The currently available technology has necessitated and facilitated the establishment of several online databases for tracking and to accommodate this constantly growing list. Identification of potentially "cancerous" microRNAs has been based mainly in their differential expression in cancers compared with controls. Interestingly enough studies have suggested that microRNA signatures could be used to classify malignancy based on their tissue of origin [65,66].

Jiang et al. in 2005 employed real time quantitative PCR - based methods to successfully identify microRNA deregulations in thirty two cancer cell lines including five from the head and neck/oral cavity [67]. Clustering analysis based on the expression values of these microRNA precursors enabled most of the cancer cell lines to be clustered based on the tissue of origin [67]. This is suggestive of the presence of microRNA expression signatures/profiles of cancers based on the specific tissue of origin. This is in line with the previously discussed identification of organ/tissue specific microRNAs and their link to physiologic function and disease process [43,45,48,51,55,58, 60,64]. Tran et al. in 2007 using microarray profiled for 261 microRNAs using 9 cell lines (from hypopharynx, base of tongue, oral tongue, tonsil and larynx) identified 33 up-regulated and 22 down-regulated microRNAs, several of which are known to be involved in carcinogenesis [68]. This study remains the first to provide such a large genome-wide survey of mature microRNA in head and neck cancer.

Hebert et al. in 2007 studied microRNA expression patterns in squamous cell cancer cells from the head and neck that were cultured under hypoxia conditions [69]. Cells from 3 cell lines were grown under normoxic conditions or hypoxia (5% and 1% oxygen) and profiling was carried using Human_V7.1C_051017 microRNA array (LC Sciences). Interestingly twenty microRNAs

were up-regulated including *microRNA-572*, *microRNA-214*, *microRNA-563*, *microRNA-15a*, *microRNA-200a*, *microRNA-7*, *let-7a*, *let-7g*, *let-7i*. Among the 16 down-regulated microRNAs under these conditions were *microRNA-122a*, *microRNA-565*, *microRNA-195*, *microRNA-30e-5p*, *microRNA-374*, *microRNA-19a*, *microRNA-22*. Hypoxia is important in progression and treatment as it has been implicated in development of chemoresistance in head and neck/oral cancers. The results reflected profiling differences in the cancer cell lines and no nonmalignant controls were used, but the study associates hypoxia conditions with microRNA deregulation and potential development of resistance to chemotherapy. Identification of microRNA alterations in these conditions could facilitate our understanding of this adaptation by the cancer cell and guide targeted therapy [69].

An array containing 646 mature and pre-microRNA, GenoExplorer™ from Genosensor Corporation (Tempe, AZ, USA) was used to screen for altered microRNA expression by Chang et al. in 2008 [10]. The study, that included head and neck squamous cell carcinoma cell lines, primary tissue samples and normal tissue controls, identified eight microRNAs to be up-regulated and one down-regulated in the cancer samples compared to controls. *MicroRNA-21*, *microRNA-18*, *microRNA-19*, *microRNA-29c*, *microRNA-142*, *microRNA-3p*, *microRNA-155*, *microRNA-146b* and *let-7* that known to be involved in tumorigenesis were in the unregulated group [10].

Profiling of squamous cell carcinoma of the tongue was carried in two studies by Wong et al. in 2008 [70,71]. Laser dissected cells from four tongue cancers and paired normal tissue were used to examine expression levels of 156 human mature microRNAs using qRT-PCR (Tan Man microRNA Assays; Human Panel). Twenty four microRNAs, including *microRNA-184* and *microRNA-21*, were up-regulated and 13 were down-regulated, including *microRNA-100*, *microRNA-125*, *microRNA-133a* and *microRNA-133b*. A 3-fold expression difference was the cut-off level used [70,71]. In their attempt to identify a microRNA signature specific to oral cavity squamous cell carcinoma, Kozaki et al. in 2008 examined the expression profile of 148 microRNAs in 18 cancer cell lines and immortalized oral keratinocyte line RT7 that served as control [72]. The cancer cell lines originated from ten stage 2 (T2) and one stage 4 (T4) frozen primary samples. The expression levels of the microRNA genes were examined using the Tan Man microRNA assay (Applied Biosystems). Eleven micro-RNAs were up-regulated by at least 1.5-fold expression or higher and 54 were down-regulated by less than 0.5-fold expression in the cancer

cell lines compared to RT7. The latter group included *microRNA-137*, *microRNA-139a*, *microRNA-133b* and *microRNA-138* [72].

The mirVana miRNA bioarray system from Ambion (Austin, TX, USA) was used in two studies aiming to provide a microRNA expression profile for head and neck cancers including oral cavity tumours. This microarray platform was used by Avissar et al. in 2009 to determine microRNA expression of 662 microRNAs in 16 fresh-frozen HNSCC tumours, 5 nondiseased head and neck epithelial tissues, and 2 individual HNSCC

cell lines in one study [73]. Eleven microRNAs, including *microRNA-21*, were up-regulated and one was down-regulated, (*microRNA-375*). This study demonstrated a significant variation of microRNA expression between tissue samples and cell lines putting emphasis on the possibility that cultured cell lines maybe not appropriate for microRNA profiling of cancer. In the second study Ramdas et al. in 2009 employing the same microRNA microarray platform five tumour samples from four subsites, that included the tongue (2 out of 5) and floor of the mouth

Table 2. Studies demonstrating microRNA deregulation in head and neck/oral cavity cancer (HNOCC)

Author	Year	Materials	Comments
Jiang et al.	2005	32 cell lines various cancers	Cancer cells were clustered based on tissue of origin
Tran et al.	2007	9 cell lines HNOCC	No controls. First study to provide a genome-wide survey of mature microRNA in head and neck 23 microRNAs up-regulated, among them <i>let-7</i> , <i>microRNA-16</i> , <i>microRNA-21</i> and <i>microRNA-205</i> (some known carcinogens) 22 microRNAs down-regulated
Chang et al.	2008	4 HNOCC cell lines, 4 tumour tissue samples and 4 normal tissue control	8 microRNAs up-regulated in cancer tissue versus control among them <i>microRNA-21</i> , <i>microRNA-18</i> , <i>microRNA-19</i> , <i>microRNA-29c</i> , <i>microRNA-142</i> , <i>microRNA-3p</i> , <i>microRNA-155</i> , <i>microRNA-146b</i> and <i>let-7</i> (some known to be involved in carcinogenesis) 1 microRNA down-regulated, <i>microRNA-494</i>
Wong et al.	2008	4 tumour tissue samples from OT cancer and 4 paired normal controls	24 microRNAs up-regulated among them <i>microRNA-184</i> and <i>microRNA-21</i> (known to be involved in carcinogenesis) 13 microRNAs down-regulated among them <i>microRNA-100</i> , <i>microRNA-125</i> , <i>microRNA-133a</i> and <i>microRNA-133b</i>
Kozaki et al.	2008	18 OSCC cancer cell lines, 11 primary frozen OSCC samples and immortalized keratinocyte line RT17 as control	11 microRNAs up-regulated among them <i>microRNA-374</i> , <i>microRNA-340</i> , <i>microRNA-224</i> , <i>microRNA-31</i> , <i>microRNA-9</i> (some known to be involved in carcinogenesis) 54 microRNAs down-regulated among them <i>microRNA-137</i> , <i>microRNA-139a</i> , <i>microRNA-133b</i> and <i>microRNA-138</i>
Avissar et al.	2009	16 fresh-frozen HNOCC tumours, 5 non diseased epithelial tissues and 2 HNOCC cell lines	11 microRNAs up-regulated among them <i>microRNA-21</i> (known to be involved in carcinogenesis) 1 microRNA down-regulated, <i>microRNA-375</i>
Ramdas et al.	2009	5 tumour samples including OT and FOM and adjacent normal tissue as controls	16 microRNAs up-regulated including <i>microRNA-21</i> , <i>microRNA-7</i> , <i>microRNA-34b</i> , <i>microRNA-155</i> , <i>microRNA-182</i> , <i>microRNA-15b</i> , <i>microRNA-185</i> , <i>let-7</i> (some known to be involved in carcinogenesis) 4 microRNAs down-regulated among them <i>microRNA-23b</i> , <i>microRNA-125a</i> , <i>microRNA-125b</i> The study demonstrated potential for stratification of tumour versus adjacent normal tissue based on the differential expression of microRNA and their targeted genes
Scapoli et al.	2010	15 OSCC tumour samples (8 without known metastasis and 7 with nodal involvement)	13 microRNAs up-regulated among them <i>microRNA-21</i> (known to be involved in carcinogenesis) 4 microRNAs down-regulated among them <i>let-7i</i> , <i>microRNA-155</i> and <i>microRNA-146a</i> that were found to characterize disease progression – nodal metastasis
Lajer et al.	2011	51 OSCC and pharyngeal cancer samples and 40 controls	114 microRNAs deregulated between OSCC and normal control among them up-regulation of <i>microRNA-31</i> and down-regulation of <i>microRNA-375</i> were the most significant 38 microRNAs deregulated between pharyngeal cancers and normal 21 microRNAs deregulation were associated with HPV infection among them <i>microRNA-127-3p</i> and <i>microRNA-363</i>

(1 out of 5) were compared to normal tissue harvested from adjacent to the tumour [74]. In addition to identifying 16 up-regulated microRNAs (including *microRNA-21*) and 4 down-regulated microRNAs the study demonstrated potential for stratification of tumour versus adjacent normal tissue based on the differential expression of microRNA and their targeted genes.

A comprehensive list of the studies demonstrating microRNA deregulation in head and neck/oral cancer is provided in Table 2.

Most recently, Clague et al. in 2009 examined the potential role of microRNA polymorphism in identifying patients with oral premalignant lesions (OPL) that maybe at high risk for progression into cancer [75]. They concluded that individual and combined genotypes of microRNA-related variants could potentially be used to predict risk for progression. The potential role of microRNAs in tumour progression was investigated by Scapoli et al. using microarray analysis the group examined 15 oral cancers (8 without evidence of metastasis and 7 with nodal involvement) and among the 19 deregulated microRNAs they identified three (*let-7i*, *microRNA-155* and *microRNA-146a*) to be associated with disease progression, signified by nodal involvement [76]. Lajer et al. in 2011 identified differences in microRNA expression patterns of normal epithelia and squamous cell carcinoma of the oral cavity and developed a molecular classifier that included 61 microRNAs and provided 93% accuracy [77]. In addition the group concluded that HPV (human papilloma virus) infected tumours may have a distinct clinical behaviour potentially due to influence of HPV on microRNA.

MicroRNA deregulation in oral cancer and prognosis

In addition to exploring microRNA deregulation some studies have attempted to demonstrate an association between microRNA expression in head and neck including oral cavity cancer and survival. MicroRNA expression profiles from 64 squamous cell carcinomas, that included 31 oral cavity tumours, carried in fresh specimens and adjacent normal tissue identified microRNAs *let-7* and *microRNA-205* as poor prognosticators in survival. Using a custom microRNA microarray representing a total of 236 human microRNA genes deregulation was identified in 49. An average of 2-fold lower expression was demonstrated for 43, while at least a 2-fold higher expression in tumours versus controls was found for 6 microRNAs. Five microRNA genes (*microRNA-21*, *microRNA-1*, *microRNA-133*, *microRNA-205*, and *let-7d*) were selected for quantification based on existing evidence of their deregulation in head and neckcancers

from previous studies. Findings were consistent with previous studies: higher expression levels of *microRNA-21* in tumours versus controls and lower expression levels of *microRNA-205* and *let-7d* in tumours versus controls. When investigating microRNA expression and clinical outcomes the reduced expression of *let-7d* and *microRNA-205* combined were significant predictors of cancer progression independent of site [78]. Another interesting population-based case-control study that included 513 cancers (283 oral cancer, 132 pharyngeal and 98 laryngeal cancers) and 597 controls (matched to cases by gender, age and town of residency) examined the *let-7* microRNA-binding site polymorphism in the KRAS 3' UTR that arises in the *let-7* complementary site. This leads to a KRAS-LCS6 variant allele that alters the expression of KRAS and levels of *let-7*. The interest in this phenomenon was driven by observations that when this variant allele was identified in lung cancers it was associated with poor outcome [79]. The *let-7* microRNA family regulates KRAS functioning as tumour suppressor gene. Lung, pancreas and colon adenocarcinomas activation of KRAs proto-oncogene via mutation is a well documented phenomenon [80]. Although KRAS mutations are rare in cancers of the head and neck, amplifications of KRAS have been reported in squamous cell carcinomas originating from this site [81,82]. In this study two important observations were made: KRAS-LCS6 variant allele was significantly associated with poor prognosis and the prognosis was worse in cancers originating in the oral cavity [79]. Metastasis is the major distinctive event in malignancy progression and severely impacts on prognosis. Using three pairs of cancer cell lines from the head and neck with differences in migration and invasion Liu et al. in 2009 identified several microRNAs to be deregulated many of them previously implicated in tumorigenesis and metastasis [83]. These included *let-7* family members, *microRNA-7*, *microRNA-16*, *microRNA-21*, *microRNA-27* family, *microRNA-98*, *microRNA-99b*, *microRNA-101*, *microRNA-106b*, *microRNA-125*, *microRNA-138*, *microRNA-193*, *microRNA-200a*, *microRNA-203*, and *microRNA-224* [69,84-102]. Among the identified microRNA deregulations, reduced expression of *microRNA-138* was consistently observed in the highly invasive cell lines [103]. Down-regulation of *microRNA-138* has been previously observed in SCC of the tongue, thyroid carcinoma, lung cancer in never smokers and has been implicated in multidrug resistance of leukaemia cells [71, 99,103,104].

DISCUSSION

The majority of these studies especially early on utilized

cell lines originating from different sub-sites of the head and neck such as hypopharynx, oral and base of tongue or larynx. The substantial differences in behaviour, response to treatment and pathogenesis among these tumours is well known and may have contributed to some contradicting findings. Furthermore, cancer cells lines were not compared to controls or tissue from tumours in some of the studies. This may as well have contributed to some extent to the confusing reports regarding some microRNAs. Additional limitation of the studies using cancer lines that prevents definitive conclusions is that

the cultured cells may not demonstrate the same profiles as the cancers of origin. It has been suggested actually that the *in vitro* conditions, inclusion of synthetic medium and addition of fetal bovine serum may affect the expression profiles of microRNAs [105].

CONCLUSIONS

Significant progress has been made in identification of specific microRNAs that are consistently deregulated in

Table 3. Commonly deregulated microRNAs in head and neck/oral cavity cancer (HNOCC) and their proposed target genes

MicroRNAs deregulated in HNOCC	Proposed Target gene(s) additional mechanisms and findings	Author / Year / Journal
<i>microRNA-184</i>	c-Myc	Wong et al. / 2008 / Clin. Cancer Research.
<i>microRNA-133a</i> and <i>microRNA-133b</i>	PKM2 (pyruvate kinase type 2)	Wong et al. / 2008 / Int. J. Cancer.
<i>microRNA-137</i> and <i>microRNA-193a</i>	CDK6 (cyclin dependant kinase 6) E2F transcription factor 6 Additionally it was demonstrated that these two microRNAs are tumour suppressors epigenetically silenced during oral carcinogenesis through DNA hypermethylation	Kozaki et al. / 2008 / Cancer Research.
<i>microRNA-15a</i>	Cyclin E PKCa (protien kinase c alpha) down regulates <i>microRNA-15a</i> that directly inhibits cyclin E	Cohen et al /2009 / Cancer Research
<i>microRNA-21</i>	TPM1 and PTEN (tropomyosin 1 and phosphatase tensin) Most likely actual role of <i>microRNA-21</i> in tumorigenesis is accomplished by complex interactions with tumour / metastasis and suppressor genes	Zhu et al. / 2007 / Biol. Chem. Li et al. / 2008 / Clin. Cancer Research. Chang et al. / 2008 / J. Dent. Res.
<i>microRNA-103</i> and <i>microRNA-107</i>	PDCD4 (programmed cell death protein 4) TGFBR3 (tumour growth factor receptor beta 3)	Ramdas et al. / 2008 / Head and Neck.
<i>microRNA-205</i> and <i>let-7</i>	DHFR (dihydrofolate reductase) <i>let-7</i> has been associated in oral cancers with decreased survival in cases with the KRAS-LCS6 genotype variant	Nakashima et al. / 2008 / Acta Otolar. Christensen et al. / 2009 / Carcinogenesis.
<i>microRNA-125b</i> and <i>microRNA-100</i>	KLF13, CXCL11 and FOXA1 and EGFR3 (epidermoid growth factor receptor 3)	Henson et al. / 2009 / Genes Chromosomes Cancer.
<i>microRNA-222</i>	MMP1 (matrix metalloproteinase 1) SOD2 (manganese superoxide dismutase 2)	Liu et al / 2009/ Cancer Genom. Proteom.
<i>microRNA-24</i>	DND1 (dead end 1, an RNA binding protein which in turn regulates a group of downstream genes at post-transcriptional levels)	Liu et al. / 2009/ FEBS letters.
<i>microRNA-7</i>	IGF1R (insulin-like growth factor1 receptor)	Jiang et al. / 2010/ Biochemical Journal.
<i>microRNA-138</i>	GNAI2 (G protein alpha inhibiting activity polypeptide 2)	Jiang et al. / 2010/ International J. of Cancer.

oral cavity cancers. From the available studies, it can be concluded that *microRNA-21* and *let-7* are among the microRNAs found to be always up-regulated in cancers of the oral cavity and oropharynx versus controls while *microRNA-133a* and *microRNA-133b* are consistently down-regulated. Among the deregulated microRNAs, several have been functionally validated and their potential target genes have been identified (Table 3). Several other microRNAs known to be involved in carcinogenesis are reported with some conflicting findings potentially due to the study limitations mentioned earlier. Additional evidence exists on specific roles of these molecules and their involvement in pathways, known to be altered in cancer of the oral cavity and oropharynx as shown in table 3.

The expanding knowledge of specific roles of certain microRNAs is further contributing to our understanding of the complexity of tumour progression and behaviour. Consideration of this information and incorporation into treatment modalities through targeted therapy could potentially enhance our abilities to improve outcome especially when other established therapies have failed.

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The authors have no conflict of interest to declare.

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