MicroRNA Deregulations in Head and Neck Squamous Cell Carcinomas

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ABSTRACT

Objectives: Head and neck/oral cancer, predominantly head and neck squamous cell carcinoma (HNSCC), is the sixth most common cancer in the world. While substantial advances have been made to define the genomic alterations associated with head and neck/oral cancer, most studies are focused on protein coding genes. The aim of this article is to review the current literature on identified genomic aberrations of non-coding genes (e.g., microRNA) in head and neck/oral cancer (HNOC), and their contribution to the initiation and progression of HNOC.

Material and Methods: A comprehensive review of the available literature relevant to microRNA deregulation in HNSCC/HNOC, 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 and oral cancer, microRNA and carcinogenesis in the head and neck/oral cavity. Only full length articles in the English language were included.

Results: We recently identified a panel of microRNA deregulations that were consistently observed in HNSCC [Chen et al., Oral Oncol. 2012;48(8):686-91], including 7 consistently up-regulated microRNAs (miR-21, miR-7, miR-155, miR-130b, miR-223, miR-34b), and 4 consistently down-regulated microRNAs (miR-100, miR-99a, miR-125b, miR-375). In this review, we will first provide an overview on microRNA and HNSCC. We will then provide a comprehensive review on the roles of microRNA deregulations in HNSCC. The functional significance of the identified HNSCC-associated microRNAs and a number of other relevant microRNAs (e.g., miR-138, miR-98, miR-137, miR-193a and miR-218) will be discussed in detail.

Conclusions: Based on current literature, microRNA deregulation plays a major role in head and neck/oral cancer.

Keywords: squamous cell carcinoma of the head and neck; microRNA; carcinogenesis tests.
INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC)

Head and neck cancer, predominantly head and neck squamous cell carcinoma (HNSCC), is the sixth most common cancer, with a mortality rate of approximately 50%. In the United States, while overall new cancer cases increased about 10% during the past 5 years, the new cases for oral cancer increased about 15%. New cases for SCC of the tongue (one of the most frequent oral cancers) increased over 23% in the same period (Table 1). More strikingly, while deaths associated with all cancers increased slightly (2%), the deaths associated with oral cancer increased by over 4%. The number of deaths associated with tongue SCC has increased about 11% during the past 5 years [1-5]. Worldwide the problem is even worse, with over 263,000 new cases being diagnosed each year. In some parts of the world, such as South-Central Asia, home to one fifth of the world’s population, oral cancer is a major health problem (the 2nd most common cancer and 2nd leading cause of cancer death in males in South-Central Asia, Global Cancer Facts & Figures, 2nd Edition; ACS, 2011). As an invasive epithelial neoplasm, HNSCC most commonly arises in the tongue, floor of the mouth, gingiva, buccal mucosa and pharynx. It typically presents as a painless ulcer with raised borders, firm mass or indurated nodule, and may show early and extensive lymph node metastases. The stages (tumour, node and metastasis, TNM) of HNSCC at diagnosis have an important influence on survival and prognosis. Lymph node metastasis decreases the survival rate by about 50% [6]. Known risk factors for HNSCC include tobacco smoking, smokeless tobacco use, alcohol consumption, and/or inflammation [7]. As a primary factor in the aetiology of HNSCC, the intensity and duration of tobacco consumption is directly correlated with the risk of developing HNSCC. Results from recent molecular and epidemiologic studies suggest that human papillomavirus (HPV) is also an important aetiologic factor in a subset of HNSCC [8], particularly those that develop in the pharynx, such as oropharyngeal and tonsillar cancers. In fact, HPV is implicated in the increased incidence of HNSCC in many areas of the world over the last few decades [9-11]. In the United States, the incidence of HPV-negative HNSCC declined by about 50% from 1988 to 2004, while the incidence of HPV-positive HNSCC increased by over 200% during the same period. Most impacted by this increase were young individuals, Caucasian individuals, and men [11], which happen to be the same groups of individuals that are associated with a higher percentage of oral HPV infection in the United States [12].

As with other cancers, treatment for HNSCC often utilizes a multimodality approach and usually includes surgery, often a radical en bloc resection of the tumour, lymph nodes, and involved soft tissue and bone, combined with pre- and/or post-operative chemotherapy and radiotherapy, depending on clinical judgment and histopathological results. Despite these interventions, more than 50% of patients with HNSCC will experience local relapse and distant metastasis. Recurrences and distant metastases are associated with poorer prognoses [13]. Furthermore, surgical intervention causes facial contour defects and can lead to functional impairment and psychological trauma in HNSCC patients. This is disappointing and points to the need for novel therapeutic approaches. Tumourigenesis has proven to be a multi-gene and multi-step process; as an emerging mode of treatment, gene therapy may provide aid in the battle with this disease. As an etiologically-based therapeutic modality, gene therapy-based approach continues to grow more promising in the treatment of tumours

Table 1. Changes in oral cancer incidence and death (2007 - 2011)

| Year | New Cases | Tongue cancer | Deaths |
|------|-----------|---------------|--------|
|      | All cancers | Oral cancer |                |
| 2007 | 1,444,920 | 34,360        | 7,800  |
| 2008 | 1,437,180 | 35,310        | 7,100  |
| 2009 | 1,479,350 | 35,720        | 7,530  |
| 2010 | 1,529,560 | 36,540        | 7,990  |
| 2011 | 1,596,670 | 39,400        | 8,000  |
| Total (2007 - 2011) | 7,487,680 | 181,330 | 53,520 |
| 5-year increase | 151,750 | 5,040 | 2,260 |
| % increase | 10.5% | 14.7% | 23.1% | 2.2% | 4.6% | 10.9% |

*The number of new cancer cases and deaths is based on the cancer statistics compiled by American Cancer Society from year 2007 to year 2011 [1-5]."
as the understanding of molecular pathogenicity expands.

MicroRNA biology

The microRNA field has experienced a major explosion in recent years. The microRNA gene family is continuously growing with novel members discovered in association with rapid advances in genomic technologies. It was previously predicted in 2005 that the human genome contains about 1000 microRNA genes [14]. As of today, there are 2,042 known mature microRNA species in human in miRBase (version 19). MicroRNAs are 21 to 23 nucleotide single stranded RNA molecules found in eukaryotic cells. MicroRNAs regulate the expression of over 50% of human genes at the post-transcriptional level guided by partial complementarities to specific sequences in their target messenger RNAs [15]. Each microRNA can target many mRNA transcripts and regulate hundreds of genes downstream. One microRNA can have multiple target sites in the mRNA transcript of a downstream gene. Therefore, microRNAs contribute a newly recognized level of gene expression regulation. The microRNA-mediated post-transcriptional regulation of gene expression is achieved through several mechanisms, including (1) site-specific cleavage; (2) enhanced mRNA degradation; and (3) translational inhibition [16]. MicroRNAs are involved in many essential biological activities such as cellular differentiation, proliferation, apoptosis and the cell cycle. Since the first evidence revealed the relationship between down-regulation of miR-15a, miR-16-1 and chronic lymphoid leukaemia (CLL) in 2002 [17], deregulations of microRNA have been reported in various types of cancers, and have been demonstrated to play crucial roles in the initiation and progression of tumours [18,19]. It is logical to hypothesize that microRNA alterations associated with tumours (including HNSCC) may serve as biomarkers for early diagnose, prognosis, evaluating treatment and monitoring the recurrence of cancers, and also serve as targets for novel therapeutic strategies. Here, we will summarize the current progress on microRNA studies in HNSCC and provide potential application perspectives.

![Figure 1. MicroRNA biogenesis (modified from Dai and Zhou, Open Access Bioinformatics 2010;2:29-39).](http://www.ejomr.org/JOMR/archives/2013/1/e2/v4n1e2ht.htm)
Two microRNA biogenesis pathways have been described (Figure 1). A majority of the microRNA genes are intergenic and utilize a canonical microRNA biogenesis pathway for their expression. MicroRNAs are first transcribed as primary transcripts (pri-miRNA) containing a local-hairpin structure, which also possess many characteristics of typical message RNAs (mRNA), such as a 5’ cap and a 3’ poly-A tail. Unlike the maturation of mRNA that occurs in the nucleus, the pri-miRNAs are processed into 70-nucleotide stem-loop structures (known as pre-miRNA) in the cell nucleus. In animal cells, this processing is performed by a protein complex consisting of the nuclease Drosha and the double-stranded RNA binding protein Pasha. The pre-miRNAs are then transported to the cytoplasm by Exportin-5 (Exp5; a member of the Ran transport receptor family). Once in the cytoplasm, pre-miRNAs are further cleaved by Dicer (a second RNase III endonuclease) to form a short double-stranded microRNA:miRNA* duplex. Finally, the microRNA:miRNA* duplex is unwound into mature microRNA and miRNA* by a helicase. The mature microRNAs are then incorporated into the RNA-induced silencing complex (RISC). RISC, also known as a microRNA ribonucleoprotein complex (miRNP), is responsible for the RNA-dependent gene silencing process (i.e., RNA interference) which is initiated by both microRNA and small interfering RNA (siRNA). The biogenesis pathway is different for microRNAs derived from intronic stem-loops which are processed by Dicer. No Drosha activity is needed for their maturation. For detailed discussion on microRNA biogenesis, we refer you to earlier reviews [20,21].

MATERIAL AND METHODS

A comprehensive review of the available literature relevant to microRNA deregulation in HNSCC/HNOC 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 and oral cancer, microRNA and carcinogenesis in the head and neck/oral cavity. Only full length articles in the English language were included.

RESULTS

MicroRNAs deregulation in HNSCC

While the first microRNA, lin-4, was characterized in C. elegans in the early 1990s [22], it was not until 2000 that researchers knew that microRNAs existed in humans. In the early years, investigators mainly relied on 3 basic biochemical methods for the detection of microRNAs, including hybridization based methods (e.g., Northern blots), PCR-based detection, and cloning methods. However, the short length and uniqueness of each microRNA rendered many conventional methods ineffective; very small RNAs are difficult to reliably amplify or label without introducing bias. Recent advances in high-throughput genomic profiling technologies (e.g., microarray, deep sequencing) led to a number of studies that attempted to define comprehensive microRNA profiles of various cancer types, including HNSCC. However, one of the bottlenecks in microRNA profiling is that there tends to be poor agreement among these profiling studies. Numerous potential factors may affect the observed inconsistencies such as heterogeneity in tissue samples, variations in genetic and environmental backgrounds of subjects, and differences in profiling technologies [23].

Although reanalysis of profiling data as a whole remains a challenge, meta-analysis of multiple studies is a reasonable approach for identifying consistently-reported, differentially-expressed microRNAs in malignances. We recently performed a meta-analysis based on 13 independent microRNA profiling studies on HNSCC [24]. Among the 432 differentially expressed microRNAs reported in these studies, 90 were reported by at least 2 studies; of those 90 microRNAs, 67 (74.4%) demonstrated a consistent direction of change, and 23 (25.6%) with an inconsistent direction. Among the 67 microRNAs with consistent directions, 46 (68.7%) were reported to be up-regulated, and 21 (31.3%) were reported to be down-regulated. There were 11 differentially expressed microRNAs reported in at least four studies with consistent direction, including seven consistently up-regulated microRNAs (miR-21, miR-7, miR-155, miR-130b, miR-31, miR-223, miR-34b), and four consistently down-regulated microRNAs (miR-100, miR-99a, miR-125b, miR-375) in HNSCC (Table 2).

Functional relevance of the deregulated microRNAs in HNSCC

Up- or down-regulation of microRNAs observed in tumours are not necessarily indicative of a causative role in tumourigenesis. It may be a secondary event as the consequence of the loss of normal cellular identity through malignant transformation. Thus, as Castoldi [25] proposed, to define the function of a microRNA as tumour suppressor or oncogene, four types of evidence must be provided: (1) data demonstrating widespread deregulation in diverse cancers, (2) gain or loss of microRNA function in tumours owing to deletion,
amplification or mutation, (3) direct documentation of tumour-suppressing or tumour-promoting activity using animal models and (4) identification and verification of cancer-relevant targets that illuminate mechanisms through which the microRNA participates in oncogenesis. MicroRNA expression patterns are highly specific to different cell-type and cellular differentiation status. A number of microRNAs have been reported to be up-regulated in one type of cancer but down-regulated in other cancers. For some microRNAs, both up- and down-regulation have been reported in the same cancer type by different studies. As such, they can not simply be defined as “oncomiR” or “tumour suppressor” without considering their molecular functions and their specific roles in malignancies.

The human gene for miR-21 is located on the plus strand of chromosome 17q23.2, within a coding gene transmembrane protein 49 (TMEM49). Despite being located in the intronic region of a coding gene in the direction of transcription, it has its own gene promoter which independently regulates the transcription of miR-21 gene. The up-regulation of miR-21 is the most frequently observed microRNA deregulation in HNSCC (reported in 11 out of 13 studies we surveyed [26-36]), and in other cancer types including breast [37], ovary [38], cervix [39], colon [40], liver [41], brain [42] and esophagus [43]. MiR-21 is one of the most well-established oncogenic microRNAs. Significant association between miR-21 over-expression and poor prognosis of HNSCC patients has been reported recently [26,44]. Over-expression of miR-21 has also been observed in oral premalignancy lesions (leukoplakia), and the miR-21 expression was associated with increases in lesion severity during disease progression [36].

Results from a study by Hsu et al. [45] demonstrated that the miR-21 level in plasma was significantly higher in HNSCC patients as compared to normal control subjects. Furthermore, the plasma miR-21 level was also significantly reduced in the post-operative samples from the HNSCC patients as compared to the pre-operative samples. As such, miR-21 may serve as a novel biomarker for both diagnosis and prognosis of HNSCC.

A large number of target genes for miR-21 have been identified and experimentally confirmed, and most of them are established tumour suppressors (e.g., PTEN [41], PDCD4 [40], Tropomyosin [46], Sprouty 1 and 2 [47,48], Bcl2 [49], RECK [50], JAG1 [51], HNRPK [52], TGFBR2 [53], P12/CDK2AP1 [54], MEF2C [55], Rhob [55] and hMSH2 [56]), which supports the role of miR-21 as an oncomiR. A recent report by Zhang et al. [57] also suggested that miR-21 could affect formation of reactive oxygen species (ROS) by directly attenuating superoxide dismutase (SOD) family member 3, SOD3, and also by an indirect mechanism that limited TNF-a production, thereby reducing SOD2 levels to promote tumourigenesis.

MiR-155 has been suggested as an oncogene [58], and has been implicated in the regulation of cell survival, growth, and chemosensitivity [59-61]. Over-expression of the miR-155 gene has also been observed in several tumours, such as leukaemia and lymphoma [62,63], thyroid carcinoma [64], breast cancer [37], cervical cancer [65], pancreatic cancer [66,67], lung cancer [68], and HNSCC [27,29,31,33,35,36] and is associated with poor prognosis in patients with breast and lung cancers [69,70]. The expression of miR-155 is regulated by the TGF-beta/SMAD signaling pathway [39], which is frequently activated in HNSCC [71].

Table 2. Differentially expressed microRNAs that were consistently reported in HNSCC (by at least 4 independent studies) (adopted from Chen et al., Oral Oncol. 2012;48(8):686-91)

| MicroRNA | Chromosomal location | Mature miR sequence | Up-/down-regulation | References | No. of reports | Sample size (SCC/ctrl) |
|----------|----------------------|---------------------|---------------------|------------|---------------|------------------------|
| miR-21   | 17q23.1              | uagcuaauacagacuagau  | Up                  | [25-35]    | 11            | 192/112                |
| miR-155  | 21q21.3              | uuuagcuaauacagacuaggg | Up                  | [26-28,30-32,34-35] | 6            | 133/68                 |
| miR-130b | 22                   | cagugcaagaggauggcag   | Up                  | [28,30,33,34] | 4             | 129/58                 |
| miR-223  | Xq12                 | uagcuaauacagacuagauacca | Up                  | [28,30,33,34] | 4             | 125/60                 |
| miR-31   | 9p21.3               | aggcaagacuagacuagauac | Down               |            |               |                        |
| miR-7    | 9q21.32 or 15q26.1 or 19p13.3 | uaggaagacuagacuagauaggu | Up                  | [29,35,102,103] | 4            | 48/30                  |
| miR-34b  | 11q23.1              | caauccauacacucugcacc | Up                  | [26,28,35,103] | 4            | 31/26                  |
| miR-100  | 11q24.1              | aacccgauacacucugcaccu | Down                | [26,28,30,34] | 5             | 127/67                 |
| miR-99a  | 21q21.1              | aacccgauacacucugcaccu | Down                | [26,28,30,34] | 5             | 127/67                 |
| miR-375  | 2q35                 | uuagcuaauacacuccuacug | Down                | [29,30,33,34] | 4             | 129/58                 |
| miR-125b | 11q24.1 or 21q21.1   | uccagacucacuacuacug   | Down                | [26,29,30,34] | 4             | 117/57                 |

http://www.ejomr.org/JOMR/archives/2013/1/e2/v4n1e2ht.htm J Oral Maxillofac Res 2013 (Jan-Mar) | vol. 4 | No 1 | e2 | p.5 (page number not for citation purposes)
Functional studies revealed that miR-155 directly targets tumour protein 53-induced nuclear protein 1 (TP53INP1) and suppresses apoptosis in tumour cells [72,73]. Other experimentally confirmed target genes of miR-155 include: ARID2 (AT rich interactive domain 2), BACH1 (BTB and CNC homology 1), HIF (Hypoxia-inducible factor 1); receptors such as AT1R (Angiotensin II receptor, type 1) and CSF1R (Colony stimulating factor 1 receptor); kinases such as IKK2 (Inhibitor of kappa light polypeptide gene enhancer in B cells) and MAP3K7IP2 (Mitogen-activated protein kinase 7 interacting protein 2); and nuclear binding proteins such as AID (Activation-induced cytidine deaminase), JARID2 (Jumonji, AT rich interactive domain 2), PICALM (Phosphatidylinositol binding clathrin assembly protein), RHOD (Ras homolog gene family, member A) and SLA (Scr-like-adaptor) [74]. MiR-155 has also been shown to be involved in mammalian innate and adaptive immunity and viral infection [75,76].

MiR-130b is consistently up-regulated in HNSCC [29,31,34,35]. In addition to HNSCC, miR-130b has also been shown to facilitate the growth and self-renewal of liver cancer-initiating cells [77], and to suppress the expression of tumour suppressor gene RUNX3 in gastric cancer [78]. The miR-130b signature may also serve as a potential prognostic marker for renal cell carcinoma patients [79]. Recent studies demonstrated that miR-130b also plays a role in regulating the senescence of keratinocytes and mammary epithelial cells [80,81]. Up-regulation of miR-130b has been suggested to contribute to human T-cell lymphotrophic virus 1 (HTLV-1)-mediated cellular transformation by targeting TP53INP1 and promoting cell proliferation and survival [82]. MiR-130a, another member of miR-130 family, was significantly down-regulated in Docolaxel induced multidrug cross-resistant HNSCC cell lines, and may contribute to multidrug resistance (MDR) [83].

MiR-223 was previously described as a haematopoietic specific microRNA, and it plays crucial role in myeloid lineage development [84,85]. The role of miR-223 in tumourigenesis appears to be cancer type specific. Reduced level of miR-223 is often observed in chronic lymphocytic leukaemia [86], acute lymphoblastic leukaemia [87], and acute myeloid leukaemia [88,89]. Enhanced expression of miR-223 is observed in several types of solid tumours, including esophageal cancer [90] and HNSCC [29,31,35,36]. MiR-223 functions as an oncogene in gastric cancer, and promotes gastric cancer invasion and metastasis by targeting tumour suppressor genes F-box and WD40 domain protein 7 (FBXW7) and erythrocyte membrane protein band 4.1-like 3 (EPB41L3) [91,92]. Increases of miR-223 in serum may serve as a biomarker for hepatocellular cancer [93].

As shown in Table 2, up-regulation of miR-31 is frequently observed in HNSCC. Increases of miR-31 in plasma and saliva have also been suggested as a potential biomarker for early detection of OSCC [94]. However, the expression pattern of miR-31 appears to be cancer type specific. While up-regulation of miR-31 has also been observed in colorectal cancer [95,96] and hepatocellular carcinoma [97], reduced level of miR-31 has been observed in breast cancer [98], and frequent homozygous deletion of miR-31 gene has been reported in urothelial carcinomas [99]. The role of miR-31 in tumourigenesis also appears to be cancer type (or cell type) specific. While miR-31 inhibits metastasis in breast cancer [100], up-regulation of miR-31 is essential to the TGF-beta-induced invasion and metastasis of colon cancer cells [101]. For pancreatic cancer, both inhibition and enhanced expression of miR-31 lead to reduced migration and invasion in different pancreatic cancer cell lines [102]. More studies will be needed to define the role of miR-31 in tumourigenesis.

The expression of miR-7 in cancer cells seems to vary depending on specific cell type or tissue type. While up-regulation of miR-7 was reported in HNSCC by several studies [30,36,103,104], down-regulation of miR-7 has been reported in other cancer types [105-107], and also reported in tongue SCC cell lines [108,109]. It is worth noting that there are 3 miR-7 genes in the human genome (located at 9q21.32, 15q26.1, and 19p13.3). The tissue specific- (or cell type specific-) differential expression of these 3 miR-7 genes may contribute to the observed variation in miR-7 level in different cancer types or tissue type. Additional that studies focus on individual miR-7 genes will be needed to address these apparent contradictions. MiR-7 has been suggested as a tumour suppressor based on its target genes, including several proto-oncogenes such as insulin receptor substrate 1 (IRS1), insulin receptor substrate 2 (IRS2), epidermoid growth factor receptor (EGFR), v-raf-1 murine leukaemia viral oncogene homolog 1 (RAF1) and p21/CDC42/RAC1-activated kinase 1 (PAK1) [105-107]. A study by Jiang et al. [110] in 2010 demonstrated that insulin-like growth factor1 receptor (IGF1R) is a novel target of miR-7 in tongue SCC cell lines. They further demonstrated that miR-7-mediated down-regulation of IGF1R attenuated the insulin growth factor 1 (IGF1)-induced activation of protein kinase B, and lead to reduced cell proliferation, cell cycle arrest and an increase in apoptosis [110]. The potential oncogenic role of miR-7 appears to be linked to differentiation, as miR-7 has been suggested as one of the keratinization-associated microRNAs in oral cancer [111]. A study by Jung et al. showed that miR-7 targets
tumour suppressor gene reversion-inducing-cysteine-rich protein with kazal motifs (RECK) is a key regulator of extracellular matrix integrity [111]. As such, miR-7 regulates multiple signalling pathways in a tissue specific (and/or differentiation status specific) manner, but its precise roles in tumourigenesis are still elusive.

The role of miR-34b appears to be tumour type specific. While miR-34b has been suggested as a tumour suppressor in colorectal [112], prostate [113], gastric [114] and breast cancer [115], up-regulation of miR-34b has been consistently reported in HNSCC [27,29,36,104]. Up-regulation of other members of the miR-34 family (e.g., miR-34c) has also been reported in tongue SCC [27]. MiR-34b is involved in a number of tumourigenesis-related molecular mechanisms, including epithelial-mesenchymal-transition (EMT) [116]. The gene for MiR-34b is located in a CpG island-rich region, and aberrant DNA methylation status of its promoter has been linked to decreased levels of MiR-34b. Several studies reported that miR-34b gene was silenced by DNA methylation in various cancers, including oral cancer [117], esophageal squamous cell carcinoma (ESCC) [118], and non-small cell lung cancer (NSCLC) [119]. The expression of miR-34b appears to be further controlled by p53 at the transcriptional level (e.g., regulating the gene promoter activity) [120-122], and appears to be a critical component of the p53-regulatory network. MiR-34b has been showed to down-regulate Met, which subsequently controls its downstream signalling molecules (e.g., p53 and Mdm2). On the other hand, the p53-mediated up-regulation of miR-34b provides a feedback loop in the p53-regulatory network [123].

MiR-99a and miR-100 are members of the miR-99 family (miR-99b is the 3rd member of the miR-99 family). The miR-99 family is one of the evolutionarily most ancient microRNA families whose origin dates back before the bilaterian ancestor [124,125]. Deregression of the miR-99 family members has been consistently reported in HNSCC and other cancer types [27,29,31,35,126-131]. Forced expression of miR-99 family members in HNSCC cell lines led to a reduction in cell proliferation and cell migration, and an increase in apoptosis [24]. A number of functional studies suggested that members of the miR-99 family regulate AKT/mTOR signalling pathways by targeting insulin-like growth factor 1 receptor (IGF1R), mechanistic target of rapamycin (mTOR) and regulatory associated protein of mTOR (Raptor) [133-136]. A recent study by Mueller et al. [137] also suggested that miR-99 family members regulate the DNA damage response through their target gene SWI/SNF chromatin remodelling factor (SMARCA5).

Reduction in miR-375 expression has been correlated with poor outcome and metastasis in oral squamous cell carcinoma (OSCC) [138]. MiR-375 may function as a tumour suppressor by suppressing the tumour’s invasive properties in OSCC [138]. Frequent down-regulation of miR-375 has also been reported to be consistently repressed compared to adjacent matched normal tissues and healthy tissues in gastric, liver, and breast cancers and has been shown to inhibit cell proliferation and regulate cell survival [139-142]. Functional analysis revealed that miR-375 targets a panel of oncogenes including AEG-1/MTDH [143], lactate dehydrogenase B (LDHB) [132] and 3’-phosphoinositide-dependent protein kinase 1 (PDK1) [144].

The down-regulation of miR-125b appears to play an essential role in the initiation and progression of HNSCC [129,145], and may contribute to resistance to cellular ionizing radiation [129]. There are 2 miR-125b genes in the human genome (located at 11q24.1 or 21q21.1). One of the genes for miR-125b is closely localized with the gene for miR-100 (11q24.1; one of the most frequently deleted genomic region in OSCC), and concurrent down-regulation of miR-125b and miR-100 is often observed in OSCC [129]. Forced expression of miR-125b down-regulated a number of differentiation- and cell cycle-related genes (including KLF13, CXCL11 and FOXA1), and consequently reduced cell proliferation [129]. MiR-125b has also been suggested to play a role in other solid tumours. Studies by Shang et al. [146] showed that miR-125b was down-regulated in endometrioid endometrial cancers (EEC), and forced expression of miR-125b in an EEC cell line suppressed cancer cell invasion. Functional studies suggested that the observed inhibitory effect of miR-125b on EEC cell invasion was mediated in part by miR-125b-mediated down-regulation of proto-oncogene ERBB2 [146]. MiR-125b has also been showed to suppress proliferation, colony formation, migratory, and invasive capacity of cutaneous squamous cell carcinoma cells [147]. Functional analysis by Xu et al. [147] showed that the observed tumour suppressive effects of miR-125b were achieved in part by inhibiting the expression of matrix metallopeptidase 13 (MMP13) expression.

Other functionally relevant microRNAs in HNSCC

While high-throughput profiling studies based on comparing tumour and normal tissue samples led to the identification of some critical microRNA players in HNSCC, these cross-sectional studies inevitably missed a number of differentially expressed microRNAs, including microRNA alterations that are associated with disease progression (and/or specific stages). Down-regulation of miR-138 is an example of one such
microRNA alteration. To identify microRNAs associated with HNSCC metastasis, Liu et al. [108] examined the differential expression of microRNAs in a panel of HNSCC cell lines with different metastatic potential. Their result showed that miR-138 is consistently down-regulated in highly metastatic cell lines. Restoring miR-138 led to suppression of cell invasion, cell cycle arrest and induced apoptosis. In contrast, knockdown of miR-138 enhanced cell invasion and suppressed apoptosis. The fact that highly metastatic cells often showed reduced expression of miR-138 suggests the potential role of miR-138 as a metastatic suppressor, and may serve as a potential therapeutic target for HNSCC patients at risk of metastasis. The same group of investigators later validated the down-regulation of miR-138 in tongue SCC tissue samples [148], and down-regulation of miR-138 was also reported in HNSCC by different labs [27, 148, 149]. Recent functional analysis demonstrated that miR-138 regulates cell migration and invasion by concurrently targeting RhoC and ROCK2, leading to the down-regulation of the Rho GTPase signalling pathway that is essential for actin cytoskeleton remodelling [150]. Tumour cells can dedifferentiate through activation of specific biological pathways associated with epithelial-mesenchymal-transition (EMT), thereby gaining the ability to migrate and invade. EMT is characterized by the loss of epithelial-cell markers (e.g., E-cadherin) and the gain of mesenchymal-cell markers (e.g., Vimentin). Previous studies suggested that members of the miR-200 family regulate EMT by targeting the Zinc finger E-box-binding homeobox (ZEB) family of transcription repressors (ZEB1 and ZEB2) which control E-cadherin expression [151]. Furthermore, down-regulation of miR-101 leads to the overexpression of polycomb group protein EZH2 [152, 153], which also acts as a transcription suppressor to inhibit the expression of E-cadherin and induce EMT [154]. Both bioinformatics analysis and in vitro experimental results indicated that miR-138 targets ZEB and EZH repressors, and other molecular regulators that control E-cadherin expression, such as FOSL1. Interestingly, miR-138 also controls Vim expression by interacting with its targeting sequences located in both the 3'-UTR and coding region of the Vim gene. As such, these studies suggested that miR-138 is an essential EMT regulator that controls EMT through multiple pathways. Taken together, these observations suggest that miR-138 is a multi-functional molecular regulator, and the down-regulation of miR-138 in HNSCC plays essential roles in the neoplastic progression of HNSCC in terms of enhancing the metastatic potential of the HNSCC cells by promoting EMT and enhancing cell migration and invasion. The ability for the cancer cells to survive under hypoxic conditions or in the presence of chemotherapeutic drugs by developing resistance contributes significantly to treatment failures, and yet the molecular mechanism is still poorly understood. Recent evidence suggested that microRNA deregulation plays a role in these adaptations in cancer cells. The High Mobility Group A2 (HMGA2) protein has been shown to be regulated in part by miR-98 in HNSCC cell lines under hypoxic conditions [155]. HMGA2 expression occurs predominantly during embryogenesis, however, proteins from the HMGA family are implicated in differentiation, neoplastic transformation, and integration and expression of viral genomes. HMGA2 has been implicated in acquisition of mesenchymal characteristics by OSCC cells. It is worth noting that MiR-98 is a member of the let-7 family, one of the first microRNAs to be identified. Let-7 has been shown to act as a master regulator for cell cycle exit [156].

Hypermethylation of DNA at CpG-islands is one of the most frequent epigenetic events that contributes to the silencing of many tumour-suppressor genes. MiR-137, miR-193a and miR-218 have been shown to be silenced by DNA hypermethylation in HNSCC [117, 157]. DNA hypermethylation-based silencing of miR-137 has also been reported in glioblastoma [158]. The forced expression of miR-137 or miR-193a in an OSCC cell line led to significant down-regulation of cyclin-dependent kinase 6 or E2F transcription factor 6, respectively, as well as reduced cell growth [117]. These observations are consistent with previous findings in which tumour suppressing roles have been suggested for miR-137 in glioblastoma [158] and melanoma [159], and for miR-193a in hepatocarcinoma, lung epithelial carcinoma and cervical adenocarcinoma cell lines [72]. The putative tumour suppression function of miR-218 in OSCC is linked to its effect on the expression of rapamycin-insensitive companion of mTOR (Rictor) and the phosphorylation of AKT [157].

CONCLUSIONS

MicroRNAs are pivotal regulators of diverse cellular processes including proliferation, differentiation, apoptosis, survival, motility and morphogenesis. While extensive literature exists on microRNAs and their involvement in tumourigenesis, the understanding of microRNA deregulation and its role in HNSCC is lagging behind. Recent advances in microRNA expression profiling have led to a better understanding of HNSCC pathogenesis. This information will lead to the identification of specific microRNA expression patterns that may become powerful biomarkers for the diagnosis and prognosis of HNSCC. In addition, the expanding knowledge of specific
roles of certain microRNAs will further contribute to our understanding of the complexity of tumour progression and behaviour. Among the deregulated microRNAs, several (e.g., miR-21) have been functionally validated and their potential target genes have been identified. Several other microRNAs known to be involved in tumourigenesis have been reported with conflicting findings; additional studies will be needed to fully explore their roles in HNSCC. Nevertheless, consideration of this information and incorporation into treatment modalities through targeted therapy could potentially enhance our abilities to improve outcomes especially when other established therapies have failed.

It is important to note that HNSCC is a group of diverse cancers that develop from many different anatomical sites and are associated with different risk factors [160], genetic characteristics [161], and different clinical outcomes [162,163]. Currently, most of the existing microRNA profiling studies on HNSCC include cases from multiple anatomical sites. Ideally, site specific microRNA signatures for various HNSCC subtypes should be identified, which will lead to substantial translational outcomes that will advance the management of these HNSCC subtypes. This has been realized to some extent already, and a few studies have been devoted to the identification of site specific microRNA signature for HNSCC, including a study by Lajer et al., [35], to identify microRNAs alterations associated specifically with HNSCCs of the oral cavity, and the HNSCCs of the oro- or hypopharynx. This apparent site specific microRNA pattern of HNSCC may also reflect the differences in etiologic factors of HNSCC (e.g., the classic tobacco/alcohol associate HNSCC vs. the HPV associated subset of HNSCC). Such advances in the understanding of HNSCC could help to devise more clinically appropriate and cost-effective therapeutic management strategies in a variety of health care settings. Enhancements to the characterization and treatment of HNSCC would add beneficial elements to a personalized medicine model that could prove helpful in maximizing disease-specific treatment options, minimizing collateral tissue damage, and allowing for improved outcomes for a greater number of patients.

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