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Review Article

MicroRNAs and Oral Cancer

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Abstract

One of the most prevalent cancers and the important cause of cancer-related deaths in Asia is oral cancer. The pathophysiology of oral cancer is complex and a significant number of deaths are caused by this disease because there are insufficient reliable diagnostic techniques and effective treatment approaches. Thus, the development of new diagnostic instruments and focused treatments is desperately needed. MicroRNAs (miRs/miRNAs) have emerged as pivotal regulators in cancer biology, influencing tumorigenesis, progression and resistance to therapy. They are positioned as potential therapeutic targets or tools due to their potential to alter a variety of tumor-suppressive and oncogenic pathways. The aim of the review is to highlight an interconnection between miRs and oral cancer. [2025, 6(1): 9-14]

Keywords: MicroRNA, Oral cancer, Oncogenic pathways, Tumorigenesis.

Introduction

Despite the enormous efforts made to find new and more effective therapies, malignant diseases continue to pose fascinating challenges to the scientific community because of their consistently high fatality rates. The intricacy, genetic variability and flexibility of cancer cells can be linked to the approximately 10 million cancer deaths that were reported in 2020. Cancer that affects the lip and oral cavity is called oral cancer. Although its locations range from lymphoid tissues to salivary glands, the most common subtype is found in the squamous cells of the oral mucosa. According to epidemiology, around 377,713 new cases are diagnosed each year, making up over 2% of all sites. Furthermore, it has been noted that in 2020, at least 177,757 people suffered from this cancerous condition, placing oral cancer in the top 20 most dangerous cancer types (1).

MicroRNAs (miRs/miRNAs) are short (22–23 nucleotides), non-coding RNAs which target particular mRNAs and are involved in the control of numerous physiological processes. According to reports, miRs have a significant regulatory role in the development as well as progression of cancer. They have the ability to pair with specific messenger RNAs (mRNAs) and to silence them through an RNA-Induced Silencing Complex (RISC). An increasing number of research suggest that miRs may be an ideal set of biomarkers used in early cancer diagnosis and prognosis due to their stability in human peripheral blood and bodily fluids and disease-specific expression (1).

The current review concentrated on the precise regulatory function of miRs in oral cancer as well as their diagnostic and therapeutic utility. The review's findings could aid in the early detection and focused treatment of oral cancer.

miR Genes

Though some are positioned in the introns of genes in the sense or anti-sense orientation and controlled alongside their host genes, the majority of miR genes are located in the intergenic region more than 1 kb from the specified gene.As a result, it was determined that the majority of miR genes might be independently transcribed (2). The likelihood of a single polycistronic transcription unit is raised because almost half of the miR were discovered close to their peers. It was discovered that MiR genes had their own promoters.

Biogenesis

The biogenesis of miR is broadly divided into canonical (usually dominant pathway) and non-canonical pathways (independent of Drosha/DGCR8 and Dicer)

1. Canonical Pathway of Biogenesis

The predominant mechanism for processing miRNAs is the canonical biogenesis pathway. The microprocessor complex, which is made up of the ribonuclease III enzyme, Drosha and the RNA binding protein DiGeorge Syndrome Critical Region 8 (DGCR8), converts pri-miRNAs from their genes into pre-miRNAs in this route. Drosha cleaves the pri-miRNA duplex at the base of the distinctive hairpin structure of pri-miRNA, whereas DGCR8 identifies an N6-methyladenylated GGAC and other motifs within the pri-miRNA. As a consequence, a 2 nt 3′ overhang forms on pre-miRNA.An exportin 5 (XPO5)/RanGTP complex exports the produced pre-miRNAs to the cytoplasm, where they are subsequently broken down by the RNase III endonuclease Dicer. A mature miRNA duplex is produced by this processing, which includes the elimination of the terminal loop. The nomenclature of the mature miRNA form is determined by the directionality of the miRNA strand. The pre-miRNA hairpin's 5′ end gives rise to the 5p strand, whereas the 3′ end is where the 3p strand begins.In an ATP-dependent manner, both strands derived from the mature miRNA duplex can be loaded into the Argonaute (AGO) family of proteins (AGO1-4 in humans). The percentage of AGO-loaded 5p or 3p strand varies greatly depending on the type of cell or cellular environment, ranging from nearly equal proportions to predominantly one or the other. The selection of the 5p or 3p strand is partly based on the thermodynamic stability at the 5′ ends of the miRNA duplex or a 5′ U at nucleotide position 1.The guide strand is often the strand that preferentially loads into AGO and has reduced 5′ stability or 5′ uracil (3). Depending on the level of complementarity, the unloaded strand, also known as the passenger strand, will unwind from the guide strand using a variety of methods. AGO2 cleaves the passenger strands of miRNA that are mismatch-free, and cellular machinery breaks them down, which can result in a significant strand bias. Otherwise, non-AGO2-loaded miRNA or miRNA duplexes with central mismatches are passively unraveled and destroyed.

2. Non-Canonical Pathways of Biogenesis

The non-canonical pathways can be broadly categorized as either Dicer-independent or Drosha/DGCR8-independent. Pre-miRs from the Drosha/DGCR8-independent pathway resemble Dicer substrates in appearance. An illustration would be miRs produced after mRNA splicing from introns, which do not form the microprocessor complex known as Mirtrons.Mirtrons, which were previously thought to only exist in fruit flies and C. elegans, have also been found in mammals. 7-methyl guanosine (m7G) capping of pre-miR provides an additional illustration. Without being cleaved by Drosha, such capped miRs are immediately exported into the cytoplasm via exportin 1 (4). Drosha uses transcripts of short hairpin RNA, or shRNA, to process MiRs that are not dependent on Dicer. Because these pre-miRs are too short to be Dicer substrates, they require Ago2 in order to mature in the cytoplasm. The 5p strand is trimmed in the 3′ 5′ direction to complete their maturation.

Expression profile of miRNAs in oral cancer

The short, single-stranded, small non-coding RNAs known as miRNAs have between 20 and 22 nucleotides (5). MiRNA expression levels and profiles vary between cancer patients and healthy people, and they are linked to the development of human cancer. Circulating miRNAs are persistent in serum, plasma, and other bodily fluids based on their chemical and structural characteristics, and they could be regarded as prospective clinical diagnostic and prognostic biomarkers.

miRNAs as novel diagnostic biomarkers in oral cancer

Oral cancer is a complex disease that is associated with both genetic and epigenetic instability. As next-generation sequencing has become more widely used, more research has shown that oral cancer has variable expression of certain miRNAs. Furthermore, the findings of area under the curve (AUC) and receiver operating characteristic (ROC) curve analysis have suggested that the differentially expressed miRNAs may aid in differentiating oral cancer patients from healthy individual. 35 miRNAs having a ROC (AUC) >0.500 that had been reported in the previous five years were screened.

For instance, Momen-Heravi et al. found that saliva-derived increased miR-27b and downregulated miR-136 may distinguish between individuals with oral cancer and healthy individuals. MiR-99a from the serum and miR-21 extracted from oral cytology had respective ROCs (AUCs) of up to 0.910 and 0.911. According to Gombos et al., tissue-derived miR-155 may differentiate between oral cancer patients and healthy people [ROC (AUC)=0.925] (6). These findings showed that miRNAs from various samples could be used as biomarkers to diagnose oral cancer.

miRNAs as novel prognostic biomarkers in oral cancer

According to Lai et al., dysregulated miR-31-5p expression accelerated the evolution of oral cancer and improved OSCC cell migration and invasion. According to recent reports, there is a high correlation between miRNAs and oral cancer patients' survival. According to Chen et al., patients with higher levels of miR-99a expression had longer overall life and a better prognosis. Patients with miR-183 overexpression had a significantly lower overall survival and a higher chance of a poor outcome, according to Supic et al. According to Zheng et al., patients with oral cancer had overexpression of miR-503-5p, miR-450b-5p, miR-27a-3p, miR-181a-5p, and miR-183-5p, all of which were strongly linked to the growth of cancer cells, an advanced clinical stage, and a bad prognosis (7).

MiR-455-5p may be a viable prognostic marker for forecasting the prognosis of patients with oral cancer, since Cheng et al. found that the expression level of miR-455-5p was connected with the patients' nodal status, stage, and overall survival. According to all of the previously described evidence, miRNAs may be useful prognostic markers for oral cancer.

miRNAs' therapeutic impact on oral cancer

By interacting with the coding or 3' untranslated region (3'UTR) of mRNAs and controlling the expression level of their target genes, miRNAs play a crucial role in controlling the translation or degradation of mRNAs. Cancer's cellular activities, including inflammation, proliferation, stress response, growth, apoptosis, survival, and migration, are influenced by miRNAs. As a result, modifying miRNA expression in cancer has gained more and more interest as a cutting-edge therapeutic approach.

MiR-24-3p, miR-155-5p, and miRNA-10a have been shown to significantly promote the growth of oral cancer cells. These results showed that inhibiting the expression of particular miRNAs could stop oral cancer from spreading.On the other hand, it has been discovered that several miRNAs have anticancer properties. MiR-6887-5p, miR-34a-5p, and miR-142-3p significantly inhibited oral cancer cell growth. Additionally, some miRNAs, such miR-204-5p and miR-34a-5p, work against cancer by preventing oral cancer cells from becoming aggressive and spreading (8).

miRNAs' regulatory mechanism in oral cancer

By interacting with their target mRNAs, miRNAs, a family of non-coding RNAs, play important roles in either promoting or suppressing cancer. Numerous investigations have shown that miRNAs

play a role in the development, progression, and metastasis of oral cancer.

miRNAs and oral cancer : occurrence and progression

It is well established that the mammalian target of rapamycin (mTOR) and protein kinase B (AKT) pathways influence the development of oral cancer. More than 40 miRNAs that are differently expressed in OSCC may activate the AKT pathway, according to Manikandan et al. By specifically targeting Rictor, miR-218 can prevent the mTOR/AKT pathway from being activated, hence suppressing oral carcinogenesis. By directly interacting with mTOR mRNA, miR-99 has been shown to reduce the expression level of mTOR in oral cancer, which promotes the proliferation of cancer cells and enlarges tumors.
It has been discovered that the TGF-β-dependent pathway controls the expression level of miR-455-5p, which in turn downregulates ubiquitin-conjugating enzyme E2B (UBE2B) to promote oral carcinogenesis. According to Chen et al., CD36 aided in the invasion and growth of OSCC, and by partially downregulating CD36 expression, miR-1254 may prevent OSCC from progressing. Furthermore, by suppressing the expression of SRY-box transcription factor 12 (SOX12), miR-423-5p may be able to reverse the carcinogenic effect of lncRNA CASC9 (9). These findings demonstrated that miRNAs regulate their target genes, hence contributing to the development and progression of oral cancer.

miRNAs and oral cancer : cell proliferation and apoptosis

Rastogi et al. found that by controlling HDAC9 and its pro-apoptotic target, NR4A1/Nur77, in vitro restoration of miR-377 inhibited OSCC cell proliferation and promoted apoptosis. By targeting fibroblast growth factor 2 (FGF1), miR-23a-3p may inhibit OSCC cell proliferation and encourage apoptosis. However, via down-regulating Foxo3a expression, miR-155 was found to promote oral cancer cell proliferation, prevent cell apoptosis, and lessen the sensitivity of oral cancer cells to DDP (10).

miRNAs and oral cancer : cell migration, invasion and metastasis

Oral cancer cell migration, invasion, and metastasis are closely linked to the treatment approach. In oral cancer cells, miRNAs play a role in controlling these mechanisms.

According to Fang et al., miR-204-5p inhibited the production of Huntingtin-interacting protein 1 (HIP1), which in turn reduced the aggressiveness, viability and migration of oral cancer cells. The overexpression of miR-143 and miR-145 in OSCC cells significantly reduced the production of activinA, inhibited oral cancer cell motility and invasion, stopped lymph node metastasis, enhanced tumor differentiation, and extended patient life.

Huang et al. found that GPCR kinase 2 interacting protein 1 (GIT1) expression was considerably downregulated when miR-491-5p expression was increased,therefore preventing lung metastases in vivo and OSCC cell migration in vitro. On the other hand, in patients with OSCC, overexpression of miR-21 was linked to perineural invasion and a poorer prognosis. Tu et al. found that by controlling the expression of large tumor suppressor kinase 2 (LATS2) in OSCC cells, overexpression of miR-372 and miR-373 was linked to lymphatic vascular invasion, nodal metastasis, and poor survival (11).

Tumor Suppressor miRNAs in Oral Cancer

Cancer-associated protein levels can be affected by tumor suppressor miRNAs, which are miRs that are downregulated in oral cancer and can target oncogenes.

Because of its tumor suppressor properties, miR-203 has attracted special attention under physiological settings. MiR-203 targets and inhibits the expression of YES Proto-Oncogene 1 (Src Family Tyrosine Kinase, YES1) simultaneously.In an OSCC cell line, overexpression of miR-203 has an antiproliferative effect. This is explained by miR-203's capacity to attach to the 3-UTR region of the Phosphatidylinositol4,5-Bisphosphate 3-Kinase Catalytic Subunit gene (PI3KCA), thereby restoring the AKT Serine/Threonine Kinase's activity and, in turn, the signaling pathway as a whole.

Apart from its antiproliferative properties, miR-203 can also make tumor cells more susceptible to the death caused by cisplatin.

Both miR-133a and miR-133b are upregulated in normal tongue squamous cells as opposed to malignant cells, according to miRNA profiling of normal tongue squamous and malignant TSCC and malignant tissues. Therefore, it is hypothesized that miR-133a and miR-133b regulate both proliferation and apoptosis.

The gene encoding for the G Protein Subunitalfa I2, GNAI2, serves as a target for miR-138.It has been reported that miR-138 influences levels of the Ras homolog family member Concogene (Rhoc), a factor that contributes to cancer stem cell formation in the HNSCC.

Oral cancer has been thought to have downregulated miR-375 (12).

miRNAs as novel therapeutic tools in oral cancer

Oral cancer occurrence and proliferation, cancer cell migration and invasion, cancer progression, and patient prognosis are all significantly influenced by miRNAs.

According to this data, miRNAs might be regarded as cutting-edge treatment options for oral cancer. MiR-375 may be a possible therapeutic target for OSCC patients, as evidenced by reports indicating overexpression of the gene significantly reduced cell proliferation, caused cell cycle arrest in the G0/G1 phase, encouraged apoptosis, and enhanced radiosensitivity in OSCC cells.
By encouraging cellular senescence, miR-494-3p was able to increase the radiosensitivity of OSCC cells (13).

By specifically targeting WNT10B, Min et al. demonstrated that overexpression of miR-148a in cancer-associated fibroblasts dramatically reduced the migratory and invasion capacities of oral cancer cells, indicating that miR-148a may be a novel and potential target for OSCC treatment.

Conclusion

Even though oral cancer diagnosis has advanced significantly, early diagnosis and prognostic techniques still need to be improved. Patients with oral cancer may live longer and receive more effective therapy if they receive an early diagnosis. Thus, it is imperative to create new biomarkers that are easier to use for clinical detection and have improved accuracy, sensitivity, and specificity.

As sequencing technology has advanced, more and more miRNAs have been identified as being expressed uniquely in a range of oral cancer samples. Additionally, these miRNAs are essential for controlling cellularbehaviors and processes. miRNAs might be the best biomarkers and novel treatment approaches for oral cancer.

miRNAs' origin, synthesis, and regulatory networks are highly intricate, and their expression levels vary depending on the stage of oral cancer. In order to aid in early diagnosis, targeted therapy, and prognostic assessment of patients with oral cancer, it is imperative to clarify the mechanism of miRNA production.

Notably, more study is needed to determine appropriate and efficient in vivo delivery mechanisms for the therapeutic miRNAs that might be utilized to create novel targeted medicines. Our next research priority will include determining important targets and developing a specific delivery mechanism (like a nano-miRNA system).

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