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MicroRNA-21 (miR-21) IN ORAL CARCINOMA (OC): UNRAVELING DIAGNOSTIC AND THERAPEUTIC HORIZONS IN PRECISION ONCOLOGY

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ABSTRACT

Background: Oral Squamous Cell Carcinoma (OSCC) poses a significant global health challenge, necessitating a nuanced understanding of its molecular underpinnings for improved diagnostics and therapeutic interventions. MicroRNA-21 (miR-21) has emerged as a key player in OSCC, demonstrating intricate involvement in tumorigenesis and offering potential clinical applications. **Methods**: A comprehensive exploration of miR-21 in OSCC was conducted, encompassing its oncogenic nature, progressive expression patterns, diagnostic potential, therapeutic implications, and clinical significance. The analysis included studies on miR-21's functional diversity, its diagnostic utility in lesion progression, and the use of targeted interventions to inhibit tumor formation. **Results**: MiR-21 exhibits a multifaceted role in OSCC, extending beyond cell proliferation to intricate regulatory functions in inflammatory pathways. Its progressive expression patterns throughout lesion development position it as a promising diagnostic marker, detectable in non-invasive samples. Antisense oligonucleotide-based interventions demonstrate therapeutic potential, suggesting miR-21 as a viable target for precision medicine. **Conclusion**: The study underscores miR-21's central role in OSCC, presenting a dynamic landscape of diagnostic and therapeutic opportunities. As a potential biomarker, prognostic indicator, and therapeutic target, miR-21 holds promise for personalized approaches in oral cancer management. Further research, including exploration of molecular intricacies and crosstalk, is warranted for transformative breakthroughs in OSCC diagnosis and treatment.

Keywords: MicroRNA-21, Oral Squamous Cell Carcinoma, Tumorigenesis, Diagnostic Biomarkers, Therapeutic Targets, Precision Oncology

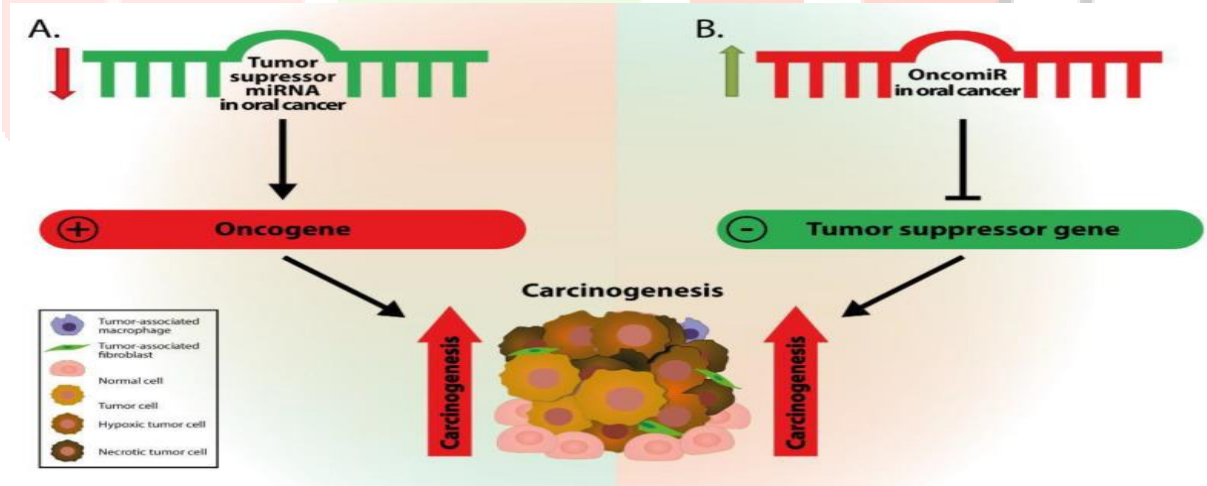
INTRODUCTION

Malignant diseases pose an ongoing challenge for the scientific community, consistently resulting in elevated mortality rates despite relentless efforts to uncover novel and more effective treatments. In the year 2020 alone, an alarming 10 million cancer-related deaths were reported globally, underscoring the intricate nature of cancer cells marked by genetic heterogeneity and plasticity. Although surgery and chemo/radiotherapy remain primary treatment modalities, the persistent threat of tumor relapse and the often debilitating side effects of therapy underscore the critical need for innovative and targeted approaches in the field of oncology.[1]

Among the myriad forms of cancer, oral cancer stands out as a particularly insidious malignancy affecting both the lip and the oral cavity. The disease manifests in diverse locations, ranging from salivary glands to lymphoid tissues. However, the most prevalent subtype originates in the squamous cells of the oral mucosa. Epidemiologically, oral cancer accounts for more than 377,713 new cases annually, representing almost 2% of all cancer diagnoses. The grim reality is further emphasized by the staggering statistic that over 177,757 individuals succumbed to this malignancy in 2020, solidifying oral cancer's position among the top 20 most lethal forms of cancer.[2]

The unique challenge posed by oral cancer lies not only in its prevalence but also in its propensity for multiple tumor emergence within five years after the initial treatment. Compounding this issue is the often insidious onset of oral cancer, masked by the intricate anatomical elements of the oral cavity. This stealthy nature underscores the critical importance of discovering reliable biomarkers capable of early detection, offering a potential advantage in the battle against this life-threatening malignancy.[3]

Cancer, as a disease entity, is intricately associated with altered gene expression levels and function, driven by a complex interplay of genetic and epigenetic modifications. The result is high genomic instability, which, over time, can lead to the development of a malignant phenotype characterized by anarchic cell proliferation and metastasis. Specifically, tumor-suppressor genes are inactivated, while proto-oncogenes are activated, setting the stage for cancer initiation and progression.[4]



The impact of miRNA dysregulation on gene expression and, further, on carcinogenesis. (**A**) Downregulation of tumor suppressor miRNAs results in increased expression of oncogenes, and further to elevated levels of tumor-promoting proteins, leading to increased carcinogenesis. (**B**) Upregulation of an oncogenic miRNA (OncomiR) leads to repression of tumor suppressor gene expression and reduced expression of tumor suppressor proteins that further promote carcinogenesis.[1]

In this complex landscape, microRNAs (miRNAs) emerge as key players. These short (22–23 nucleotides) non-coding RNAs, first described in Caenorhabditis elegans, play critical roles in regulating gene expression. Their unique ability to pair with specific messenger RNAs (mRNAs) and silence them through the formation of the RNA-Induced Silencing Complex (RISC) positions miRNAs as influential regulators in numerous processes in mammals. According to miRGate, 2680 mature miRNAs target more than 60% of protein-coding genes, highlighting the broad impact of miRNA dysregulation on cellular processes.[5]

Dysregulated miRNAs have been implicated in the development of diverse diseases, ranging from cancer and liver cirrhosis to neurodegenerative disorders such as Parkinson's and Alzheimer's. Cancer cells, characterized by the loss of homeostasis and inherently altered regulatory pathways, naturally become a focal

point for miRNA research. Altered levels of miRNA expression have been highlighted in various neoplastic diseases, including cervical, colon, lung, ovarian, and breast cancers.[6]

Recent studies have unequivocally established that oral cancers are no exception to the rule, with altered levels of miRNAs playing a pivotal role in carcinogenesis. The intricate interplay between miRNA dysregulation and the onset and development of oral cancer forms the crux of ongoing research endeavors. These studies not only shed light on the molecular intricacies of oral cancer but also provide a foundation for the identification of novel biomarkers crucial for early detection.[7]

Moving beyond the molecular landscape, the review aims to comprehensively explore the essential roles of miRNA dysregulation in oral cancer development and progression. It delves into the most relevant miRNA transcripts, elucidating their distinct functions as either tumor suppressors or oncogenes in the context of oral cancer. Additionally, the review pays specific attention to the implication of miRNAs in modulating the tumor microenvironment, recognizing the intricate role these molecules play in shaping the conditions conducive to cancer growth and progression.[8]

As researchers unravel the complexities of miRNA involvement in oral cancer, the potential for translating these findings into clinical applications becomes increasingly apparent. Beyond the fundamental understanding of molecular mechanisms, the focus extends to the practical implications for patient care.[9] Discovering and validating novel biomarkers through miRNA research holds the promise of revolutionizing early detection strategies for oral malignancies, potentially improving prognosis and treatment outcomes.[10]

The intricate relationship between miRNA dysregulation and oral cancer represents a multifaceted field of study with far-reaching implications for both basic science and clinical practice.[11] By elucidating the roles of specific miRNAs in the initiation and progression of oral cancer, researchers are paving the way for targeted interventions, personalized treatment approaches, and the development of urgently needed early detection biomarkers. As the scientific community continues to unravel the mysteries of miRNA involvement in oral cancer, the potential for transformative breakthroughs in cancer management remains an exciting prospect on the horizon.[12]

Cancer metastasis

Cancer metastasis is a critical aspect of cancer progression, where cancer cells detach from the primary tumor and establish additional tumors at distant sites. Despite advancements in early detection and treatment of primary tumors, metastasis remains a major contributor to cancer-related mortality, causing approximately 9 out of 10 cancer deaths and significant morbidity.[13]

In 1889, Stephen Paget proposed the theory that metastasis is not a random process but involves an interaction between "seeds" (cancer cells) and a "congenial soil" (organs prone to certain tumor types). This theory has gained widespread acceptance, shaping the understanding of how secondary tumor sites are determined.[14]

Traditionally, cancer research focused on early tumor detection and therapeutic agents to inhibit tumor growth. Advances in early cancer detection and treatment have led to increased curability for solid tumors when detected early.[15] However, once cancer has metastasized beyond the primary site, it becomes typically incurable and fatal, highlighting the urgency in understanding and controlling the metastatic process.[16]

The complex process of metastasis involves sequential steps and biochemical reactions. Detachment, invasion, migration, and adhesion are four crucial processes that collectively contribute to the formation of metastases.[17] Following detachment from the primary tumor, cancer cells migrate, invade blood and lymphatic vessels, travel to distant locations, adhere, proliferate, and form secondary tumors. Multiple signaling mechanisms, along with the influence of the extracellular matrix (ECM) at the destination site, play crucial roles in controlling metastatic growth.[18]

The poorly understood mechanisms underlying the metastatic process pose a significant challenge in preventing and controlling cancer metastasis. Anoikis, a form of cell death induced by ECM detachment, typically occurs when normal cells become separated from their ECM.[19] However, metastatic cancer cells develop resistance against anoikis, enabling them to survive and thrive in different environments. The

phenomenon known as epithelial-mesenchymal transition (EMT) describes the resistance of tumor cells to anoikis and involves various alterations in cell adherence, invasion, migration, and polarity.[20]

Migration and invasion are essential components of the metastatic cascade, and metastatic cells can infiltrate the ECM through mesenchymal (fibroblastoid) and amoeboid cellular migration. Mesenchymal migration relies on protease-dependent enzyme activities, such as matrix metalloproteinases (MMPs), to break down the ECM structure.[21] Amoeboid migration, on the other hand, is protease-independent and involves mechanical forces to create a passageway. Metastatic cancer cells can move individually or as large clusters, and both modes of migration contribute to the spread of cancer throughout the body.[22]

Understanding the distinct characteristics of metastatic cells, such as their ability to migrate and invade, has been crucial in unraveling the complexities of cancer metastasis. The coordination of individual cells or clusters during migration is influenced by ongoing production of adhesion molecules.[23] The migration of clustered cells can be highly effective in obliterating lymphatic or blood vessels and preserving cells under flow conditions. Various types of cancer, including squamous cell carcinoma and basal cell carcinoma, undergo collective cell migration.[24]

Over the past 30 years, significant progress has been made in understanding cancer metastasis at the molecular, cellular, and signaling pathway levels.[25] This progress has identified potential targets for preventing cancer metastasis by modifying the biochemical mechanisms and signaling pathways that control cell adhesion, dissociation, invasion, migration, and interaction with the tumor microenvironment.[26]

In summary, cancer metastasis is a complex and multifaceted process that significantly impacts the prognosis of cancer patients. Despite progress in early detection and treatment, metastasis remains a major challenge in cancer management.[27] Understanding the molecular and cellular mechanisms underlying metastasis opens avenues for potential therapeutic targets. In the context of oral cancer, exploring the regulation of invasion, migration, and adhesion by various microRNAs (miRNAs) and other non-coding RNAs (ncRNAs) becomes crucial for devising targeted strategies to impede the metastatic cascade and improve patient outcomes. The intricate interplay between these regulatory molecules and the metastatic processes forms a rich area of investigation with the potential to enhance our understanding and pave the way for innovative therapeutic interventions in oral cancer metastasis.[28]

MicroRNA biogenesis

MicroRNAs (miRNAs), initially discovered by Ambros et al. in 1993, are a class of endogenous non-coding RNAs crucial in controlling the stability and translation of messenger RNAs (mRNAs).[29] Typically ranging from 19 to 25 nucleotides in length, these small RNA molecules have since emerged as key regulators in cellular processes, particularly in post-transcriptional gene regulation.[30]

Canonical miRNA processing initiates with the transcription of miRNA genes by RNA polymerase II, generating primary miRNA (pri-miRNA) molecules that exhibit a stem-loop structure.[31] The Drosha and DGCR8 microprocessor complex then cleaves the pri-miRNA, resulting in a hairpin miRNA precursor of approximately 70 nucleotides. Following this, exportin-5 facilitates the cytoplasmic entry of pre-export miRNAs, setting the stage for further processing.[32]

In the cytoplasm, the TRBP and Dicer complex, a double-stranded RNA-specific endoribonuclease, converts the pre-miRNA into a mature miRNA duplex. The complex that induces silencing via RNA, known as the RNA-induced silencing complex (RISC), appears to contain both mature miRNA duplex strands.[33] Selective destruction of one strand, possibly determined by thermodynamic stabilities, is essential for the intended mRNA to be repressed.

The mature miRNA, guided by the RISC complex, is directed to a target mRNA. The RISC complex incorporates Argonaute 2 (AGO2) as a key component after strand selection.[34] Interactions between the miRNA and the target mRNA promote destabilization of the target mRNA and translational repression. This intricate process ensures precise control over gene expression at the post-transcriptional level.[35]

The mechanisms of target mRNA repression involve either cleavage of the target mRNA or deadenylation, which entails the shortening of the 3' poly-A tail of the target mRNA. The selection of the repression mechanism may depend on various factors, including the specific characteristics of the miRNA and the target mRNA.[36]

Beyond their role in basic molecular biology, miRNAs have broad regulatory implications in gene expression, impacting various cellular processes such as development, differentiation, and response to environmental stimuli. Dysregulation of miRNAs has been implicated in numerous diseases, with cancer being a prominent example. Aberrant miRNA expression can contribute to oncogenesis and metastasis, making miRNAs potential therapeutic targets.[37]

Understanding the intricate mechanisms of miRNA-mediated gene regulation provides insights into potential therapeutic strategies. Targeting specific miRNAs or their downstream pathways holds promise for developing novel treatments for diseases characterized by dysregulated gene expression.[38]

Ongoing research in the field of miRNA biology continues to uncover new aspects, including non-canonical processing pathways and interactions with other regulatory molecules. Advancements in technologies such as CRISPR-Cas9 and high-throughput sequencing contribute to a deeper understanding of miRNA function, offering opportunities for therapeutic innovation.[39]

The miRNAs play a pivotal role in the post-transcriptional regulation of gene expression, offering a nuanced control mechanism over mRNA stability and translation. Their discovery has transformed our understanding of molecular biology, and ongoing research holds the promise of unlocking further therapeutic potentials in diverse fields, including cancer biology and beyond.[40–42]

Functional MiRNAs in Oral Cancer

Many studies have highlighted the association of microRNAs (miRNAs) with specific oral cancer phenotypes, including tumorigenesis, progression, recurrence, and postoperative survival. In this comprehensive review, we delve into the commonly known miRNAs related to oral cancer, shedding light on their biological functions and cellular mechanisms.[1,2,43–50]

1. **Let-7b:**
    - Biological Function: Let-7b, initially discovered in 1993, is a pivotal regulator of cell proliferation and differentiation. In oral cancer, its down-regulation contributes to disease progression.
    - Canonical Processing: Generated from a stem-loop-structured primary miRNA (pri-miRNA) through the Drosha and DGCR8 microprocessor complex.
    - Target Genes: Down-regulates Dicer and IGF1R, influencing the Akt pathway and inhibiting cell proliferation.
2. **miR-7/miR-21:**
    - Keratinization-Associated: miR-7 and miR-21 are up-regulated in keratinized tumors, impacting RECK expression crucial for tumor progression.
    - Clinical Implications: Upregulation of miR-21 is associated with poor prognosis in oral cancer patients.
    - Functional Insights: Their roles in silencing RECK contribute to the aggressiveness of tumors.

3. **miR-99a:**
    - Tumor Suppressor: miR-99a, down-regulated in oral cancer cell lines, suppresses tumor migration/invasion and lung colonization.
    - Target Gene: IGF1R, a transmembrane tyrosine kinase receptor, is negatively correlated with miR-99a expression.
    - Therapeutic Potential: miR-99a holds promise as a target for cancer therapy due to its regulation of IGF1R.
4. **miR-100:**
    - Down-regulation in Oral Cancer: miR-100 is down-regulated in oral cancer cells, impacting cell proliferation.
    - Target Genes: Overexpression downregulates key genes involved in cell metastasis, myelin development, cell adhesion, and cell growth.
    - Functional Impact: miR-100 inhibits cell proliferation by targeting critical genes, playing a crucial role in oral cancer development.
5. **miR-125:**
    - Down-regulation in Oral Cancer: miR-125b, located in chromosome 11q, is down-regulated in oral cancer cell lines.
    - Target Genes: Regulates key factors (KLF13, CXCL11, FOXA1) involved in tumorigenesis, inflammation, angiogenesis, and metastasis.
    - Clinical Relevance: miR-125b down-regulation correlates with increased cell proliferation rate and decreased radio-sensitivity in oral cancer.
6. **miR-145:**
    - Tumor Suppressor: miR-145, down-regulated in oral cancer tissues, induces G1 phase arrest and apoptosis, suppressing cell proliferation.
    - Target Genes: Directly targets oncogenes c-Myc and Cdk6, contributing to the inhibition of oral cancer cell growth.
    - Therapeutic Potential: miR-145 restoration offers potential diagnostic and therapeutic applications in oral cancer.
7. **miR-146a:**
    - Up-regulation in Oral Cancer: miR-146a, usually suppressed in malignancies, is up-regulated in oral cancer.
    - Targets: Directly targets IRAK1, TRAF6, and NUMB, enhancing cell proliferation, invasion, and metastasis.
    - Biomarker Potential: Elevated plasma miR-146a levels suggest its use as a diagnostic biomarker for oral cancer.

8. **miR-155:**
    - Oncogenic Role: miR-155, overexpressed in various cancers, targets CDC73, a negative regulator of β-catenin, cyclin D1, and c-MYC.
    - Therapeutic Implications: Inhibiting miR-155 presents a potential avenue for reversing its pro-oncogenic properties in cancer therapeutics.
9. **miR-196:**
    - Diverse Roles: miR-196 exhibits varied expression patterns, being both up- and down-regulated in different cancers.
    - Oral Cancer Impact: Highly up-regulated in oral cancer cells, promoting invasive and migratory phenotypes by targeting NME4 and regulating the JNK-TIMP1-MMP signaling pathway.
10. **miR-205:**
    - Tumor Suppressor: miR-205 functions as a tumor suppressor in human oral cancer, significantly down-regulated compared to normal cells.
    - Functional Impact: Overexpressing miR-205 reduces cell viability, induces apoptosis, and upregulates IL-24, suggesting its therapeutic potential in oral cancer treatment.
11. **miR-483-3p:**
    - Wound Healing Connection: miR-483-3p, involved in skin wound healing, is down-regulated in oral cancer cells.
    - Tumor Suppression: Overexpression hinders tumor growth by targeting API5, RAN, and BIRC5, inducing apoptosis and inhibiting cell proliferation.
12. **miR-518c-5p:**
    - Metastasis Involvement: miR-518c-5p, enriched in neuronal and hematopoietic cells, is induced and exhibits metastatic potential in oral cancer.
    - Functional Impact: Inhibition reduces cell growth and migration, making it a potential target for therapies against metastasis in oral cancer.

MicroRNA-21 (miR-21) in Oral Squamous Cell Carcinoma (OSCC)

MicroRNA-21 (miR-21), a pivotal player in cancer biology, has become a focal point in the study of Oral Squamous Cell Carcinoma (OSCC). Numerous investigations have consistently demonstrated the deregulation of miR-21 in OSCC, making it an intriguing subject for in-depth exploration.[3]

In a comprehensive review by Kolokythas in 2011, encompassing nine studies, miR-21 emerged as consistently upregulated in OSCC. Its prominence was further highlighted by being the most highly expressed microRNA among the 255 identified in OSCC tissues. Delving deeper, a recent study analyzing the expression of miR-21 alongside miR-375 in 25 cases of OSCC brought forth compelling findings. Although these results are yet to be published, a significant 17.39-fold upregulation of miR-21 was observed in OSCC compared to its paired normal oral tissues.[40]

The spatial intricacies of miR-21 expression within OSCC tissues add a layer of complexity to its role. Notably, the center of the lesion exhibited higher miR-21 expression than the tumor margins, and its intensity within the cytoplasm surpassed that in the nucleus of tumor cells.[51] Beyond the conventional focus on squamous dysplastic epithelial cells, miR-21's expression has been detected in myofibroblasts, endothelial cells, and salivary acinar cells within the tumor stroma, as revealed by Nora et al.'s groundbreaking work.

The exploration of miR-21 extends beyond traditional tissue analysis. Its presence has been quantified in oral cytological samples, offering a non-invasive avenue for understanding its implications in OSCC. Moreover, miR-21 has been identified in serum and saliva of oral cancer patients, indicating its stability in bodily fluids and its potential as a diagnostic biomarker.[52,53]

Functionally, miR-21 has been associated with the regulation of cell proliferation and differentiation. It exerts its influence by targeting key genes such as Dicer and IGF1R. Overexpression of miR-21 leads to a reduction in Dicer expression, crucial for miRNA maturation, and targets IGF1R, influencing cell proliferation through the Akt pathway.[54–56]

The clinical significance of miR-21 in OSCC is underscored by its potential as a diagnostic biomarker and therapeutic target. Its consistent upregulation and detectability in various sample types position it as a promising biomarker for OSCC.[57,58] In addition, the understanding of miR-21's role in influencing critical pathways opens avenues for targeted therapeutic interventions, suggesting that inhibiting miR-21 may impede cancer progression.[59]

Looking forward, ongoing research aims to identify additional target genes of miR-21 and elucidate their roles in OSCC. Bridging the gap between laboratory findings and clinical applications remains a challenge, and further validation of miR-21's diagnostic potential in larger cohorts and diverse populations is essential for its translation into routine clinical practice.[60–62]

The miR-21 stands out as a central figure in the OSCC narrative, showcasing its intricate expression patterns, spatial dynamics within tissues, and promising avenues for non-invasive diagnostics. The functional insights into its role in cellular processes and its clinical significance underscore the potential for miR-21 to be not just a biomarker but a therapeutic target in the complex landscape of oral cancer. As research unfolds, miR-21 continues to unravel its secrets, holding the key to transformative advancements in OSCC diagnosis and management.[63]

MicroRNA-21 (miR-21) : Complex Role in Tumorigenesis

MicroRNA-21 (miR-21) has emerged as a central player in the intricate web of molecular events governing tumorigenesis, particularly in the context of Oral Squamous Cell Carcinoma (OSCC). Its multifaceted roles encompass not only the initiation and progression of tumors but also its potential as a therapeutic target. This comprehensive exploration delves into the intricate details of miR-21's involvement in OSCC, shedding light on its oncogenic nature, its progressive expression patterns in oral lesions, and its association with inflammatory pathways.[64,65]

1. Oncogenic Nature of miR-21:

MicroRNAs, small non-coding RNAs, have been increasingly recognized for their regulatory roles in gene expression. MiR-21, among the myriad of microRNAs, stands out as an oncogene, influencing tumorigenesis across various cancers. In the realm of OSCC, miR-21's significance becomes apparent through its ability to modulate crucial pathways involved in tumor development.

2. Progressive Expression in Oral Lesions:

The journey from normal mucosa to precancerous lesions and eventually to OSCC is marked by a progressive increase in miR-21 expression. Cervigne et al's meticulous study not only highlights this stepwise elevation but also associates the degree of miR-21 expression with the severity of the lesion. This suggests a potential role for miR-21 not just as a bystander but as an active participant in the initiation of oral tumors.

3. Association with Tumor Initiation:

Comparative studies on miR-21 levels in the serum of OSCC cases and patients with oral submucous fibrosis underscore its potential association with tumor initiation. Elevated miR-21 levels in OSCC cases hint at its involvement in the early stages of tumor development, making it a promising candidate for further exploration as a diagnostic marker.

4. Inhibition of Tumor Formation:

The functional relevance of miR-21 in OSCC is accentuated by experiments employing specific antisense oligonucleotides to antagonize its effects. The inhibitory outcomes on tumor formation in nude mice demonstrate not only the significance of miR-21 in driving tumor development but also hint at its potential as a therapeutic target. This opens avenues for investigating miR-21-targeted therapies for OSCC.

5. Involvement in Inflammatory Pathways:

Inflammation, a well-established player in tumorigenesis, intertwines with miR-21 in OSCC. The cyclooxygenase/prostaglandin E2 (PGE2) pathway, implicated in the progression of squamous cell carcinoma, becomes a focal point. Qianting He et al's elucidation of miR-21's role in regulating this pathway by targeting Hydroxyprostaglandin Dehydrogenase adds a layer of complexity. This regulatory mechanism appears to play a critical role in the initiation of tongue squamous cell carcinoma (TSCC), further emphasizing miR-21's intricate involvement in OSCC pathogenesis.

6. Changes in miR-21 Expression Post-Surgery:

Dynamics in miR-21 expression post-surgery in OSCC patients reveal a gradual reduction in plasma levels compared to pre-surgery. This intriguing finding hints at the reversibility of miR-21-associated processes and further establishes its link to the pathogenesis of oral cancer. Monitoring these post-surgical changes in miR-21 expression could potentially serve as a prognostic indicator, contributing to our understanding of its role in tumor microenvironments.

7. Clinical Implications and Future Prospects:

As we unravel the complexities of miR-21 in OSCC, its clinical implications become increasingly evident. Diagnostic applications, prognostic indicators, and targeted therapeutic interventions all beckon exploration. The potential of miR-21 as a biomarker for early detection and its role in guiding treatment decisions offer new avenues for personalized medicine in OSCC.

The miR-21's involvement in OSCC transcends mere association, positioning it as a key orchestrator in the intricate symphony of tumorigenesis. From its progressive expression patterns in oral lesions to its regulatory roles in inflammatory pathways, miR-21 emerges as a central figure with far-reaching implications. The inhibitory effects on tumor formation and the post-surgical dynamics in its expression underscore the complexity of its involvement. As research advances, delving deeper into the molecular intricacies of miR-21 holds promise for unlocking novel therapeutic strategies and refining our approach to managing OSCC.[66–71]

Tumor Growth, Invasion and Metastasis

Tumor Growth Inhibition by Antagonizing miR-21:

Tumor growth is a multifaceted process driven by a delicate balance of various molecular regulators. In the intricate world of Oral Squamous Cell Carcinoma (OSCC), miR-21 emerges as a key player. Sustained growth signals and angiogenesis are crucial components of tumor progression, and studies have shown that antagonizing miR-21 in TSCC cell lines leads to a promising inhibition of miR-21 expression. This inhibition results in a significant suppression of tumor growth, a reduction in atypia, and a decrease in angiogenesis. The potential of miR-21 as a therapeutic target becomes evident in its ability to disrupt the complex process of tumor growth in OSCC.[1,2,66–71]

Cell Cycle Regulation and PTEN-Mediated Arrest:

The intricate orchestration of the cell cycle is a critical aspect of tumorigenesis, and miR-21's involvement in cell cycle regulation in OSCC sheds light on its multifaceted role. Inhibition of miR-21 in OSCC demonstrates a PTEN-mediated S-G2/M cell cycle arrest. PTEN, a tumor suppressor gene intricately linked to cell cycle control, becomes a key player in the regulatory dance orchestrated by miR-21. These findings provide deeper insights into the molecular mechanisms through which miR-21 contributes to cell cycle dysregulation in oral cancer.[3–5]

Modulation of Clusterin (CLU) Gene and Tumor Growth:

Recent studies delve into the intricate molecular network that fuels tumor growth in OSCC, with a specific focus on miR-21's modulation of the Clusterin (CLU) gene. Clusterin, involved in various cellular processes, including apoptosis and cell adhesion, becomes a key target of miR-21. This newfound understanding opens avenues for targeted therapeutic strategies aimed at disrupting the miR-21-CLU axis, providing a potential avenue for precision medicine in the context of OSCC.[6,7]

Invasion, Metastasis, and the Role of Epithelial-Mesenchymal Transition (EMT):

Invasion and metastasis, the hallmarks of aggressive cancers, are intricately regulated in OSCC, and miR-21 emerges as a central figure in this narrative. Epithelial-Mesenchymal Transition (EMT) is a pivotal event in oral carcinogenesis, equipping squamous cells with invasive and metastatic properties. Studies demonstrate that inhibiting miR-21 maturation with Sophocarpine leads to p38MAPK signal pathway-mediated inhibition of proliferation, invasion, and migration of HNSCC cells. The prospect of reversing EMT through miR-21 modulation introduces a novel dimension to our understanding of OSCC progression.[8,10]

Targeting DKK Gene and the Wnt/β-Catenin Pathway:

The invasive nature of TSCC finds its roots in the interplay between miR-21 and the Wnt/β-catenin pathway, with a specific focus on the DKK gene. Understanding the intricate molecular pathways that drive invasion in OSCC provides critical insights for targeted interventions. This knowledge forms the basis for developing strategies aimed at disrupting the cascade of events leading to invasion in oral cancer.[9,11]

Role of miR-21 in Lymph Node Metastasis and Anchorage-Independent Growth:

Metastasis in OSCC often involves the cervical lymph nodes, marking a critical aspect of disease progression. miR-21's contribution to metastasis is underscored by its targeting of slug transcription factors and its correlation with lymph node metastasis in TSCC. Moreover, miR-21's role in imparting anchorage-independent growth to oral cancer cells highlights its significance in facilitating metastasis. These findings unravel the multifaceted role of miR-21 in promoting metastasis, providing valuable insights for developing targeted therapies against specific metastatic traits in OSCC.[12,13]

Contrasting Findings and Tumor Suppressive Gene Tagging:

The heterogeneity within oral cancer is evident in studies presenting a downregulation of miR-21, such as Chih-Yu's study, which offers a contrasting perspective. Despite the majority of studies pointing towards miR-21's oncogenic role, this study highlights the complexity within oral cancer. Interestingly, miR-21 is tagged as a tumor-suppressive gene in this context, with its suppression enhancing tumorigenicity and metastasis in OSCC. This paradoxical finding underscores the need for further exploration into the diverse roles of miR-21 in different OSCC subtypes, emphasizing the intricate nature of its regulatory functions.[14–16]

The miR-21's involvement in OSCC extends beyond simple oncogenicity, encompassing intricate roles in tumor growth, invasion, and metastasis. From its influence on the cell cycle to modulation of specific genes and pathways, miR-21 emerges as a central orchestrator in the complex landscape of oral cancer progression. Targeting miR-21 holds promise for future therapeutic interventions, demanding continued research to unravel its multifaceted contributions to OSCC pathogenesis.[17–19]

Regulation of Apoptosis by miR-21 in Oral Cancer Cells:

1. **Direct Targets of miR-21 in Apoptosis Regulation:** MicroRNA-21, a key player in the intricate landscape of oral cancer, intricately regulates apoptosis by targeting pivotal genes. Apoptotic genes such as Programmed Cell Death 4 (PDCD4), Phosphatase and Tensin Homolog (PTEN), and B cell lymphoma-2 (Bcl-2) are direct targets of miR-21. The delicate balance orchestrated by miR-21 in controlling these genes reflects its pivotal role in determining the fate of oral cancer cells.[72,73]

2. PTEN and TPM1 as Tumor Suppressor Genes: PTEN and Tropomyosin-1 (TPM1), both tumor suppressor genes, find themselves entwined in the regulatory web of miR-21. With frequent mutations in various human cancers, PTEN witnesses a significant reduction in gene expression in oral cancer. Simultaneously, TPM1, known for inducing apoptosis in cancer cells, emerges as a critical player in the miR-21 regulatory axis. The inverse correlation between miR-21 levels and the expression of TPM1 and PTEN in OSCC signifies the intricate dance of molecular interactions governing apoptosis.

3. Apoptosis Induction by miR-21 Suppression: Suppression of miR-21 using Antisense Oligonucleotides (ASO) becomes a potential avenue for apoptosis induction in TSCC cell lines. The regulatory influence of miR-21 on TPM1 and PTEN takes center stage, paving the way for targeted interventions aimed at reinstating apoptotic pathways in oral cancer. These findings unveil the therapeutic potential of modulating miR-21 to tip the balance in favor of apoptosis.[74–76]

4. Bcl-2 Regulation by miR-21: While miR-21 is known to upregulate Bcl-2 and prevent apoptosis in various cancers, its specific impact on Bcl-2 in oral cancer was previously unexplored. The intricate connections between miR-21 and Bcl-2 in the context of oral cancer remain an intriguing area for further investigation. Unraveling these connections will shed light on the nuanced regulatory mechanisms governing apoptosis evasion in OSCC.

5. Caspase-Dependent Pathway and Mitochondrial Regulation: Studies unveil that miR-21 controls apoptosis in cancer cells through the caspase-dependent pathway. By blocking the release of cytochrome-c enzyme from mitochondria into the cytosol, miR-21 orchestrates a series of molecular events that contribute to the evasion of apoptosis. Understanding the intricacies of the caspase-dependent pathway provides valuable insights into the molecular arsenal employed by miR-21 to enhance cell survival in OSCC.[77–79]

6. Implications for Cell Survival in OSCC: The cumulative data points towards a compelling narrative where increased expression of miR-21 leads to the evasion of apoptosis, thereby promoting cell survival in OSCC. The intricate interplay between miR-21 and its target genes, PTEN, TPM1, and Bcl-2, positions miR-21 as a master regulator determining the fate of oral cancer cells. This regulatory axis becomes a focal point for therapeutic interventions aimed at reinstating apoptosis and curtailing the survival advantage conferred by miR-21 in OSCC.[80–82]

The role of miR-21 in apoptosis regulation adds another layer of complexity to its multifaceted contributions in oral cancer. By directly targeting key apoptotic genes and orchestrating intricate molecular pathways, miR-21 emerges as a central player in determining the survival or demise of oral cancer cells. Unraveling the specifics of its interactions with PTEN, TPM1, and Bcl-2 opens avenues for targeted therapeutic strategies aimed at restoring apoptosis in the context of OSCC.

MicroRNA-21 and its Prognostic Implications in OSCC:

1. Correlation with Clinical Parameters: MicroRNA-21 emerges as a powerful prognostic indicator in Oral Squamous Cell Carcinoma (OSCC), showcasing a negative correlation with crucial clinical parameters. Its expression levels escalate with advancing clinical stages, higher histopathological grades, and the occurrence of metastasis. This strong association positions miR-21 as a potential biomarker for gauging the severity and prognosis of oral cancer.[83,84]

2. Impact on Survival: Overexpression of miR-21 presents a grim outlook for patients with Tongue Squamous Cell Carcinoma (TSCC), indicating poor survival tendencies. Meta-analytical evidence further solidifies miR-21's predictive capacity for a dismal prognosis in oral cancer. The intricate interplay between miR-21 and the clinical trajectory of OSCC patients underscores its pivotal role in shaping disease outcomes.

3. Association with Neural Invasion: Neural invasion, a recognized poor prognostic indicator in OSCC, establishes an intriguing link with miR-21 expression. Studies demonstrate a direct association between miR-21 and perineural invasion in OSCC, suggesting a potential role for miR-21 in promoting the invasion of tumor cells into nerve bundles. Despite this association, the molecular pathways facilitating such invasion remain an enigma, warranting further exploration.

4. Stromal Expression and EMT: MiR-21 doesn't confine its impact solely to cancer cells but extends its influence to the tumor microenvironment. Its expression in stromal cells and its role in Epithelial-Mesenchymal Transition (EMT) emerge as two independent factors contributing to an unfavorable prognosis in OSCC. This dual impact underscores the complexity of miR-21's role in shaping the tumor microenvironment and influencing disease progression.[85–87]

5. Implications in Chemo-Resistance: Resistance to chemotherapy and radiotherapy poses a significant challenge in cancer therapy, exacerbating prognosis concerns. High expression of miR-21 emerges as a predictive factor for poor response to chemo-radiation, particularly with cisplatin. The dysregulation of miR-21 directly targets key genes, PTEN and PDCD4, contributing to chemo-resistance in OSCC. In light of these findings, strategies aimed at inhibiting miR-21 present a promising avenue to enhance the therapeutic efficacy of OSCC treatment.

6. Therapeutic Implications: The association between miR-21 dysregulation and chemo-resistance positions miR-21 as a potential therapeutic target in OSCC. Strategies aimed at inhibiting miR-21 could potentially improve the therapeutic effects of OSCC treatment, offering a ray of hope for patients facing the challenges of chemo-resistance. The development of miR-21 inhibiting therapies stands as a promising direction for future OSCC treatment modalities.[84–86]

The miR-21's intricate involvement in OSCC prognosis extends beyond a mere biomarker. It actively participates in shaping the clinical trajectory of the disease by influencing neural invasion, impacting the tumor microenvironment, and contributing to chemo-resistance. The recognition of miR-21 as a dynamic player in OSCC prognosis opens avenues for targeted therapeutic interventions and underscores its significance in the broader landscape of oral cancer research and treatment.[87–90]

DISCUSSION

MicroRNA-21 (miR-21) is recognized as a pivotal oncogene in Oral Squamous Cell Carcinoma (OSCC), showcasing its multifaceted roles in tumorigenesis. Its influence extends beyond mere cell proliferation, emphasizing its involvement in crucial pathways related to differentiation. Of particular interest is its regulatory role in inflammatory pathways, notably the cyclooxygenase/prostaglandin E2 (PGE2) pathway. This intricate connection highlights the functional diversity of miR-21 and its active participation in shaping the tumor microenvironment, opening potential avenues for therapeutic interventions targeting these pathways.

The progressive elevation of miR-21 expression throughout the continuum from normal mucosa to precancerous lesions and eventually OSCC establishes it as a potential diagnostic marker. Its correlation with lesion severity not only implicates it in tumor initiation but also positions it as a promising tool for early detection. Moreover, its detectability in non-invasive samples such as serum, saliva, and oral cytological samples underscores its practicality in revolutionizing screening processes, enabling timely identification of individuals at risk.

The use of antisense oligonucleotides to target miR-21 and inhibit tumor formation in experimental models unveils a promising therapeutic avenue. This approach suggests that miR-21 could serve as a viable target for precise and effective treatment modalities in OSCC. The observed reversibility of miR-21-associated processes, indicated by the gradual reduction in plasma levels post-surgery, adds a dynamic element to potential treatment strategies, warranting further investigation.

MiR-21's clinical implications extend beyond its role as a diagnostic marker to prognostic indicators and personalized treatment approaches. Its potential use as a biomarker for monitoring treatment response and predicting outcomes highlights its significance in tailoring therapeutic strategies to individual patients. As research progresses, the identification of additional target genes of miR-21 and the elucidation of their roles in OSCC will contribute to a more comprehensive understanding.

The dynamic landscape of miR-21 in OSCC calls for continued research to unveil additional facets of its involvement. Exploring the molecular intricacies, such as non-canonical processing pathways and interactions with other regulatory molecules, will contribute to a more nuanced understanding of its

functions. Large-scale validation studies in diverse populations are crucial for establishing the robustness of miR-21 as a diagnostic and prognostic marker. Investigating the crosstalk between miR-21 and other molecular players in OSCC will provide a more holistic view of its role in tumorigenesis.

Detailed discussion underscores miR-21's central role in OSCC, emphasizing its multifaceted functions, diagnostic potential, and therapeutic implications. As we delve deeper into the molecular intricacies, miR-21 holds the promise of not only being a biomarker but a dynamic target for innovative and personalized approaches in the complex landscape of oral cancer. The ongoing exploration of miR-21's roles sets the stage for transformative breakthroughs, offering hope for more effective strategies in the diagnosis and treatment of this challenging malignancy.

CONCLUSION

The miR-21 emerges as a central player in the intricate landscape of OSCC, influencing tumorigenesis through its oncogenic properties, progressive expression patterns, and involvement in inflammatory pathways. The potential diagnostic, prognostic, and therapeutic applications of miR-21 underscore its significance in the clinical management of OSCC. As the scientific community continues to unravel the molecular intricacies of miR-21, there is a growing potential for transformative breakthroughs in cancer management. From early detection strategies to targeted therapeutic interventions, miR-21 represents a dynamic and promising avenue for advancing our understanding and improving outcomes in the complex realm of oral cancer. The ongoing exploration of miR-21's roles and interactions within OSCC sets the stage for future research directions and clinical applications, offering hope for more effective strategies in the diagnosis and treatment of this challenging malignancy.

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