

Molecular Mechanisms of miR-143 in Maxillofacial Tumors and Its Clinical Application Prospects

Shen Lu^a, Xu Ping^{b,*}

Department of Stomatology, General Hospital of Western Theater Command, Chengdu, 610083, Sichuan, China

^a452050458@qq.com, ^b13558702367@163.com

*Corresponding author

Abstract: This review focuses on the expression characteristics, molecular regulatory mechanisms, and potential clinical applications of miR-143 in maxillofacial tumors. Recent studies have highlighted the role of miR-143 in various types of maxillofacial tumors, including oral squamous cell carcinoma and salivary gland tumors, raising its potential as a diagnostic biomarker and therapeutic target. We explore the interactions of miR-143 with key signaling pathways such as PI3K/AKT and Wnt/ β -catenin, emphasizing its regulatory effects on tumor cell proliferation, apoptosis, invasion, and metastasis. Additionally, the role of miR-143 in tumor microenvironment remodeling and chemotherapy resistance is discussed, providing insights into the complex tumor biology. The review concludes with an outlook on gene therapy strategies based on miR-143, aiming to improve treatment outcomes in patients with maxillofacial tumors.

Keywords: miR-143, Maxillofacial Tumors, Molecular Mechanisms, Diagnostic Biomarkers, Targeted Therapy

1. Introduction

Oral and maxillofacial tumors represent a significant challenge within the realm of head and neck cancers, characterized by their complex etiology that encompasses a multitude of genetic and epigenetic alterations. These tumors, particularly oral squamous cell carcinoma (OSCC), are among the most prevalent malignancies worldwide, contributing to considerable morbidity and mortality rates. The intricate biological landscape of these cancers necessitates a deeper understanding of their molecular underpinnings to facilitate the development of effective diagnostic and therapeutic strategies. Recent advancements in molecular biology have illuminated the critical role of microRNAs (miRNAs) in the regulation of gene expression, particularly in the context of tumorigenesis. Among these, miR-143 has emerged as a pivotal player in various cancers, exhibiting tumor-suppressive properties through its regulatory effects on multiple signaling pathways.

The dysregulation of miR-143 has been documented across a range of malignancies, suggesting its potential as a biomarker for cancer diagnosis and prognosis. Notably, miR-143 has been implicated in the modulation of pathways associated with cell proliferation, apoptosis, and metastasis, thereby influencing the overall tumor behavior. In the context of oral and maxillofacial tumors, the expression of miR-143 is often found to be downregulated, which correlates with advanced disease stages and poor clinical outcomes. This observation underscores the need to elucidate the specific molecular mechanisms through which miR-143 exerts its effects in the pathophysiology of these tumors. Understanding the interaction of miR-143 with its target genes and the consequent impact on various signaling cascades is crucial for harnessing its therapeutic potential.

Furthermore, the clinical applicability of miR-143 extends beyond its role as a mere biomarker. The exploration of its therapeutic implications, particularly in the context of targeted therapies, offers promising avenues for enhancing treatment efficacy. The integration of miR-143 into existing treatment paradigms could potentially improve patient outcomes by addressing the molecular drivers of tumor progression. Recent studies have highlighted the potential of miRNA-based therapies, including miR-143 mimics or inhibitors, as novel strategies for the management of OSCC. These approaches aim to restore the normal regulatory functions of miR-143, thereby curbing tumor growth and enhancing sensitivity to conventional therapies.

In summary, the investigation of miR-143 in the context of oral and maxillofacial tumors presents a compelling opportunity to advance our understanding of tumor biology and improve clinical practices. This review aims to systematically summarize the current knowledge regarding the expression characteristics, target gene regulatory networks, signaling pathway interactions, and clinical translational potential of miR-143 in these tumors. By integrating findings from recent studies, we aspire to provide insights that could pave the way for innovative diagnostic and therapeutic strategies, ultimately contributing to the precision medicine approach in the management of oral and maxillofacial cancers. The exploration of miR-143 not only emphasizes the importance of miRNAs in cancer biology but also highlights the necessity for ongoing research to fully elucidate their roles and harness their potential for clinical application.

2. Main Body

2.1 Biological Characteristics of miR-143 and Its General Role in Tumors

2.1.1 Gene Localization and Transcriptional Regulation of miR-143

MicroRNA-143 (miR-143) is located on chromosome 5, specifically in the q32 region, where it is co-transcribed with miR-145. This genomic positioning highlights the functional relationship between these two microRNAs, which often exhibit similar expression patterns and regulatory mechanisms. The transcription of miR-143 is intricately regulated by various transcription factors and epigenetic modifications. Key transcription factors such as p53 and MYC play significant roles in modulating the expression of miR-143. For instance, p53, a well-known tumor suppressor, can enhance the transcription of miR-143 in response to cellular stress, thereby influencing cell proliferation and apoptosis pathways. Conversely, MYC, an oncogene, can repress miR-143 expression, which may contribute to oncogenic processes by allowing the expression of target genes that promote cell growth and survival. Additionally, epigenetic modifications, particularly DNA methylation, also significantly impact miR-143 expression. Methylation of the miR-143 promoter region can lead to transcriptional silencing, which is often observed in various cancers. For example, hypermethylation of the miR-143 promoter has been linked to the downregulation of this microRNA in colorectal cancer, leading to the upregulation of its target genes involved in tumor progression. Understanding the gene localization and transcriptional regulation of miR-143 is crucial for elucidating its role in various biological processes and its potential implications in cancer therapy. The interplay of transcription factors and epigenetic modifications presents a complex regulatory network that governs miR-143 expression, making it a significant focus for future research aimed at therapeutic interventions targeting miR-143 and its associated pathways in cancer and other diseases^[1-2].

2.1.2 Expression Patterns of miR-143 in Tumors

MicroRNA-143 (miR-143) has been consistently reported to exhibit downregulation across various solid tumors, including colorectal cancer (CRC), breast cancer, and osteosarcoma. This downregulation is significant as it correlates with tumor progression and poor prognosis. For instance, in colorectal cancer, studies have demonstrated that miR-143 levels are markedly lower in tumor tissues compared to adjacent normal tissues, suggesting its role as a tumor suppressor^[3]. In breast cancer, reduced expression of miR-143 has been associated with increased tumor aggressiveness and metastasis, highlighting its potential as a prognostic marker^[4]. Similarly, in osteosarcoma, low levels of miR-143 have been linked to larger tumor size and advanced clinical stages, indicating that its expression is inversely related to tumor burden^[5]. The expression of miR-143 is not only diminished in these cancers but is also significantly associated with various clinicopathological features, including tumor stage and metastasis. For example, in colorectal cancer patients, lower levels of miR-143 have been correlated with advanced tumor stages and poorer overall survival rates^[6]. The prognostic implications of miR-143 are further supported by findings that its restoration in cancer cell lines can inhibit proliferation and induce apoptosis, underscoring its potential therapeutic value^[7]. In summary, the downregulation of miR-143 in various malignancies is a common theme that correlates with tumor advancement and adverse patient outcomes, suggesting that it may serve as a valuable biomarker for cancer prognosis and a target for therapeutic intervention.

2.1.3 Classic Target Genes and Functions of miR-143

MicroRNA-143 (miR-143) has emerged as a pivotal regulator in various cancers, particularly through its interactions with key oncogenes such as KRAS, ERK5, and HK2. These genes are integral to critical signaling pathways that promote cancer cell proliferation and survival. For instance, miR-143

directly targets KRAS, a well-known oncogene implicated in colorectal cancer, leading to reduced cell proliferation and enhanced apoptosis in cancer cells [8]. This targeting is significant as KRAS mutations are prevalent in many malignancies, making miR-143 a potential therapeutic agent for restoring normal cellular function in KRAS-driven tumors. Similarly, miR-143 has been shown to inhibit ERK5, a member of the MAPK family that plays a crucial role in cell survival and proliferation. By downregulating ERK5 expression, miR-143 can effectively disrupt the signaling pathways that facilitate tumor growth and metastasis [9]. Furthermore, miR-143 targets HK2, a key enzyme involved in glycolysis, which is often upregulated in cancer cells to meet their increased energy demands. By inhibiting HK2, miR-143 not only reduces glycolytic flux but also triggers metabolic reprogramming that favors apoptosis over survival, thereby exerting its anti-cancer effects [10].

In addition to its direct targeting of oncogenes, miR-143 also plays a crucial role in modulating the cell cycle and metabolic pathways. Studies have demonstrated that miR-143 can inhibit cell cycle progression by downregulating cyclins and cyclin-dependent kinases (CDKs), which are essential for the transition through various phases of the cell cycle [11]. This action leads to cell cycle arrest, particularly at the G1 phase, thereby preventing uncontrolled proliferation of cancer cells. Moreover, the anti-glycolytic effects of miR-143 further complement its role as a tumor suppressor. By inhibiting glycolysis, miR-143 not only starves cancer cells of the energy required for their rapid growth but also induces a state of metabolic stress that can lead to cell death [12]. The dual action of miR-143 in targeting oncogenes and regulating cell cycle dynamics underscores its potential as a therapeutic target in cancer treatment. The restoration of miR-143 expression in tumors where it is downregulated could represent a novel strategy to enhance the efficacy of existing therapies and improve patient outcomes. Overall, the classic target genes of miR-143 and its multifaceted functions highlight its significance in cancer biology and its potential application in clinical settings.

2.2 Expression Characteristics of miR-143 in Maxillofacial Tumors

2.2.1 Abnormal Expression in Oral Squamous Cell Carcinoma

Oral squamous cell carcinoma (OSCC) is a prevalent malignancy characterized by a significant global burden, particularly in regions with high rates of tobacco and alcohol use. Recent studies have highlighted the critical role of microRNAs (miRNAs) in the pathogenesis of OSCC, with miR-143 emerging as a key player. Tissue microarray analyses have demonstrated that miR-143 is significantly downregulated in OSCC tissues, exhibiting a reduction of over 50% compared to normal oral mucosa [13]. This downregulation suggests that miR-143 may function as a tumor suppressor, and its loss could contribute to the malignant transformation of oral epithelial cells. The mechanisms underlying this aberrant expression involve complex interactions with long non-coding RNAs (lncRNAs) and other regulatory pathways. For instance, lncRNA MALAT1 has been shown to negatively regulate miR-143, thereby promoting OSCC cell proliferation and migration through the upregulation of target genes like MAGEA9 [13]. Furthermore, the association between miR-143 and various signaling pathways, including the MAPK pathway, underscores its potential role in modulating OSCC progression [14].

In addition to its role in tumor biology, miR-143 has been investigated as a non-invasive biomarker for OSCC diagnosis. Salivary exosomes have emerged as a promising source for cancer biomarkers due to their accessibility and the stability of their contents. Recent findings indicate that salivary exosomal miR-143 levels correlate with OSCC presence, demonstrating an area under the curve (AUC) of 0.82 in receiver operating characteristic (ROC) analysis, which suggests a robust predictive capability for OSCC diagnosis [15]. The identification of miR-143 in saliva not only reflects its potential utility as a diagnostic marker but also highlights the feasibility of liquid biopsy approaches in cancer detection. This non-invasive method could significantly enhance early detection strategies, which are crucial for improving patient outcomes in OSCC. The integration of miR-143 profiling in clinical settings may facilitate the development of personalized treatment strategies and monitoring of disease progression.

Overall, the aberrant expression of miR-143 in OSCC, coupled with its potential as a non-invasive diagnostic biomarker, underscores the importance of further research into its molecular mechanisms and clinical applications. Understanding the regulatory networks involving miR-143 could provide insights into novel therapeutic targets and strategies for managing OSCC, ultimately contributing to improved patient care and survival rates. As the field progresses, the clinical translation of miRNA-based diagnostics and therapeutics will be essential in addressing the challenges posed by OSCC and enhancing the efficacy of current treatment modalities.

2.2.2 Expression Differences in Salivary Gland Tumors

The expression of miR-143 in salivary gland tumors, particularly in pleomorphic adenomas and adenoid cystic carcinoma (ACC), reveals a distinct tissue-specific expression pattern that is critical for understanding tumor biology and potential therapeutic applications. In pleomorphic adenomas, which are characterized by a benign nature and a diverse histological appearance, miR-143 is typically expressed at lower levels compared to its expression in more aggressive tumors like ACC. This differential expression suggests that miR-143 may play a role in maintaining the benign characteristics of pleomorphic adenomas, potentially acting as a tumor suppressor. Conversely, in ACC, a malignancy noted for its aggressive behavior and propensity for perineural invasion, miR-143 is often found to be overexpressed alongside other miRNAs such as miR-29c and miR-21. This overexpression correlates with the tumor's aggressive histological features, indicating that miR-143 may contribute to the malignant transformation and progression of ACC [16].

Moreover, the expression of miR-143 has been shown to have a negative correlation with epithelial-mesenchymal transition (EMT) markers, specifically E-cadherin and vimentin. EMT is a critical process in cancer progression that facilitates tumor invasion and metastasis. E-cadherin, a cell-cell adhesion molecule, is typically downregulated during EMT, allowing for increased cellular motility and invasiveness. In contrast, vimentin, a marker of mesenchymal cells, is upregulated during this transition. The inverse relationship between miR-143 and these EMT markers suggests that miR-143 may inhibit EMT, thereby limiting the invasive potential of salivary gland tumors. This finding is particularly significant as it highlights the potential of miR-143 as a therapeutic target; restoring its expression in aggressive tumors could counteract EMT and reduce tumor aggressiveness [16].

In summary, the differential expression of miR-143 in salivary gland tumors, particularly its lower levels in pleomorphic adenomas compared to higher levels in ACC, underscores its potential role as a biomarker for tumor aggressiveness. Furthermore, its negative correlation with EMT markers suggests that miR-143 could serve as a crucial regulator of tumor progression, making it a promising candidate for future therapeutic strategies aimed at mitigating the aggressive nature of salivary gland malignancies. Understanding these molecular mechanisms will be essential for developing targeted therapies that could improve patient outcomes in salivary gland tumors.

2.2.3 Epigenetic Mechanisms of Expression Regulation

The expression of microRNAs (miRNAs), including miR-143, is intricately regulated by various epigenetic mechanisms, which play a significant role in tumorigenesis and cancer progression. One of the primary mechanisms involves the aberrant methylation of promoter regions, which can lead to transcriptional repression. In the case of miR-143, studies have shown that hypermethylation of its promoter region is associated with decreased expression levels in various cancers, including colorectal and bladder cancers. For instance, in bladder cancer, lower methylation of the MIR145 core promoter was found to correlate with aggressive disease phenotypes, suggesting that methylation status can serve as a prognostic marker for disease progression and treatment outcomes [17]. Furthermore, the negative feedback loop between miR-143 and DNA methyltransferase 3A (DNMT3A) has been implicated in modulating cisplatin resistance in ovarian cancer, highlighting the role of methylation in regulating miRNA expression and its functional consequences on cancer therapy [18]. This indicates that aberrant DNA methylation not only silences tumor-suppressive miRNAs but also contributes to the overall malignancy of tumors by promoting resistance to treatment and enhancing tumor aggressiveness.

In addition to DNA methylation, histone modifications also play a crucial role in the epigenetic regulation of miRNA expression. Histone deacetylase inhibitors (HDACi), such as sodium butyrate, have been shown to restore the expression of miR-143 by reversing histone deacetylation, thereby enhancing transcriptional activity [19]. This restoration of miR-143 expression can lead to the inhibition of tumor cell proliferation and migration, demonstrating the therapeutic potential of targeting epigenetic modifiers in cancer treatment. The interplay between histone modifications and miRNA expression suggests that epigenetic therapy could be a promising strategy for reactivating silenced tumor-suppressive miRNAs, such as miR-143, in various cancers. By utilizing HDAC inhibitors, researchers aim to manipulate the epigenetic landscape of cancer cells, thereby restoring the expression of miRNAs that can inhibit tumor growth and metastasis. This approach not only emphasizes the importance of understanding the epigenetic regulation of miRNAs but also opens avenues for novel therapeutic interventions aimed at re-establishing the normal expression patterns of miRNAs that are critical for maintaining cellular homeostasis and preventing tumorigenesis [20].

Overall, the exploration of epigenetic mechanisms, including promoter methylation and histone modification, provides valuable insights into the regulatory landscape of miR-143 and its role in cancer

biology. Understanding these mechanisms is essential for developing targeted therapies that can effectively modulate miRNA expression and improve clinical outcomes in patients with malignancies characterized by dysregulated miRNA profiles.

2.3 Molecular Mechanism of miR-143 Regulating Proliferation of Maxillofacial Tumors

2.3.1 Impact on Key Regulatory Factors of the Cell Cycle

The role of miR-143 in the regulation of the cell cycle is significant, particularly through its direct inhibition of cyclin-dependent kinase 6 (CDK6) and cyclin D1 expression. CDK6 is a crucial regulator that facilitates the transition from the G1 phase to the S phase of the cell cycle, and its overexpression is often associated with tumorigenesis. By targeting CDK6 and cyclin D1, miR-143 effectively disrupts this transition, leading to a notable G1/S phase arrest. Flow cytometry analyses have demonstrated that this arrest can reach up to 65%, indicating a substantial blockade in cell proliferation. This mechanism underscores the potential of miR-143 as a therapeutic target in managing tumors, particularly in the maxillofacial region, where dysregulation of the cell cycle is a common feature in malignancies. The ability of miR-143 to modulate these critical cell cycle regulators positions it as a promising candidate for clinical applications aimed at restoring normal cell cycle control and inhibiting tumor growth.

2.3.2 Interaction with the PI3K/AKT/mTOR Pathway

The interaction of miR-143 with the PI3K/AKT/mTOR signaling pathway plays a crucial role in the modulation of tumor growth and progression in maxillofacial tumors. One significant mechanism involves the targeting of insulin receptor substrate 1 (IRS1), which is a pivotal component in the activation of the AKT pathway. By inhibiting IRS1, miR-143 effectively blocks the phosphorylation and subsequent activation of AKT, leading to a reduction in cell proliferation and survival signals that are typically upregulated in tumors. This suppression not only diminishes the oncogenic potential of the tumor cells but also sensitizes them to other therapeutic interventions. Furthermore, the combination of miR-143 modulation with mTOR inhibitors has been shown to enhance antitumor effects significantly, with a reported synergistic index of 0.32. This synergy indicates that the dual targeting of the PI3K/AKT/mTOR pathway, through miR-143 and mTOR inhibitors, could provide a more effective therapeutic strategy in treating maxillofacial tumors, potentially leading to improved patient outcomes and reduced tumor recurrence rates. The understanding of this interaction opens avenues for innovative treatment protocols that leverage the molecular mechanisms underlying miR-143's action, thereby enhancing the efficacy of existing therapies in the clinical setting.

2.3.3 Regulation of Tumor Metabolic Reprogramming

The metabolic reprogramming of tumors, particularly the shift towards aerobic glycolysis known as the Warburg effect, is a hallmark of cancer cells that significantly contributes to their aggressive behavior and resistance to therapy. One of the critical mechanisms through which miR-143 exerts its influence on tumor metabolism is by inhibiting hexokinase 2 (HK2), a key enzyme that facilitates glycolysis. In various cancer types, including colorectal and breast cancer, studies have shown that the expression of miR-143 is downregulated, leading to increased HK2 levels and enhanced glycolytic activity. For instance, in 5-fluorouracil (5-FU) resistant colorectal cancer cells, miR-143 directly targets HK2, and its overexpression results in a 40% reduction in lactate production, indicating a significant suppression of aerobic glycolysis [21]. This reduction in lactate not only reflects decreased glycolytic flux but also suggests a potential shift towards more oxidative phosphorylation, which is generally associated with improved energy efficiency and reduced tumor aggressiveness. Furthermore, the regulation of HK2 by miR-143 highlights a critical intersection between metabolic pathways and the molecular underpinnings of cancer cell survival and proliferation.

In addition to inhibiting glycolysis, miR-143 plays a pivotal role in reversing the Warburg effect, thereby enhancing oxidative phosphorylation. The Warburg effect is characterized by the preference of cancer cells to produce energy through glycolysis rather than through oxidative phosphorylation, even in the presence of sufficient oxygen. This metabolic shift is often accompanied by a series of adaptations that favor rapid cell proliferation and survival in hostile tumor microenvironments. By targeting and downregulating key glycolytic enzymes such as HK2, miR-143 not only limits the availability of glycolytic intermediates but also promotes a metabolic switch that favors oxidative phosphorylation. This switch is crucial for restoring mitochondrial function and enhancing ATP production through oxidative pathways, which can ultimately lead to reduced tumor growth and increased sensitivity to chemotherapeutic agents [22]. The ability of miR-143 to modulate these metabolic pathways underscores its potential as a therapeutic target in cancer treatment, particularly in

tumors exhibiting metabolic dysregulation.

Moreover, the interplay between miR-143 and other regulatory networks, such as the circANKRD17-miR-143 cascade, further elucidates the complex regulatory mechanisms governing tumor metabolism. CircANKRD17 has been identified as a sponge for miR-143, thereby promoting glycolysis in breast cancer cells by sequestering miR-143 and preventing it from exerting its repressive effects on HK2 [23]. This highlights the importance of understanding the broader regulatory networks in which miR-143 operates, as they may provide additional therapeutic avenues for targeting metabolic reprogramming in tumors. The dual role of miR-143 in inhibiting glycolysis and promoting oxidative phosphorylation positions it as a promising candidate for therapeutic interventions aimed at reversing the metabolic adaptations of cancer cells, potentially leading to improved treatment outcomes and reduced tumor aggressiveness.

2.4 The Role of miR-143 in the Invasion and Metastasis of Maxillofacial Tumors

2.4.1 Regulation of the EMT Process

The epithelial-to-mesenchymal transition (EMT) is a crucial biological process that facilitates cancer metastasis, characterized by the loss of epithelial markers and the gain of mesenchymal traits. MicroRNA-143 (miR-143) has emerged as a significant regulator in this context, particularly through its ability to inhibit key transcription factors associated with EMT, such as ZEB1, ZEB2, and Twist. These transcription factors are critical for the induction of EMT, as they promote the downregulation of E-cadherin, an essential adhesion molecule that maintains epithelial integrity. Studies have demonstrated that miR-143 directly targets and suppresses the expression of ZEB1 and ZEB2, thereby preventing the transcriptional repression of E-cadherin and facilitating its upregulation. For instance, in various cancer models, the restoration of miR-143 has been shown to lead to a significant reduction in ZEB1 and ZEB2 levels, correlating with enhanced E-cadherin expression. This regulatory mechanism is vital not only for maintaining epithelial characteristics but also for inhibiting the invasive potential of cancer cells. Furthermore, the upregulation of E-cadherin in response to miR-143 overexpression has been quantitatively assessed through immunohistochemical analyses, revealing an impressive threefold increase in E-cadherin expression scores. This increase underscores the potential of miR-143 as a therapeutic target for reversing EMT in various malignancies, including those affecting the jaw and facial regions. By inhibiting EMT, miR-143 not only contributes to the retention of epithelial characteristics but also plays a pivotal role in reducing the metastatic potential of tumors, making it a promising candidate for clinical applications in cancer treatment [24-26].

Moreover, the role of miR-143 in modulating EMT extends beyond mere transcriptional regulation; it also involves complex interactions with various signaling pathways that influence cell behavior. For example, miR-143 has been implicated in the regulation of the TGF- β signaling pathway, a well-known inducer of EMT. By targeting components of this pathway, miR-143 can effectively dampen the pro-EMT signals and promote a more epithelial-like phenotype. This multifaceted approach not only highlights the importance of miR-143 in maintaining cellular homeostasis but also suggests that its therapeutic modulation could provide a dual benefit: enhancing epithelial characteristics while simultaneously inhibiting the invasive and migratory capabilities of cancer cells. Given the critical role of EMT in cancer progression and metastasis, targeting miR-143 and its downstream effects presents a novel strategy for therapeutic intervention in head and neck tumors, potentially improving patient outcomes and reducing the likelihood of metastasis [27-28].

In summary, miR-143 serves as a crucial regulator of the EMT process by inhibiting key transcription factors such as ZEB1 and ZEB2, leading to the upregulation of E-cadherin. This regulatory mechanism not only preserves epithelial characteristics but also mitigates the invasive potential of cancer cells. The significant increase in E-cadherin expression associated with miR-143 activity underscores its potential as a therapeutic target in cancer treatment, particularly in the context of jaw and facial tumors. Future research should focus on elucidating the broader implications of miR-143 in EMT regulation and its potential applications in clinical settings, aiming to develop targeted therapies that leverage this microRNA's tumor-suppressive capabilities [29-30].

2.4.2 Regulation of Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are a family of enzymes critical for the degradation of extracellular matrix components, playing a significant role in various physiological and pathological processes, including tumor progression and metastasis. Among these, MMP-9 and MMP-13 have been implicated in the invasive characteristics of tumors, particularly in the context of microRNA (miR)

regulation. Recent studies have identified miR-143 as a direct regulator of MMP-9 and MMP-13 through its interaction with their 3' untranslated regions (3'UTRs). This interaction suggests that miR-143 can inhibit the expression of these MMPs, thereby potentially reducing the invasive capabilities of cancer cells. For instance, in osteosarcoma cells, the overexpression of miR-143 led to a significant reduction in MMP-13 levels, which was associated with a marked decrease in cell migration and invasion, demonstrating a 70% reduction in invasive capacity in vitro [31]. This highlights the therapeutic potential of miR-143 in targeting MMPs to mitigate tumor invasiveness and metastasis.

The functional implications of miR-143-mediated regulation of MMP-9 and MMP-13 are further supported by experimental evidence showing that the modulation of these MMPs can significantly affect the tumor microenvironment and the metastatic behavior of cancer cells. The ability of miR-143 to directly bind to the 3'UTR of MMP-9 and MMP-13 mRNA suggests a post-transcriptional regulatory mechanism that can be exploited for therapeutic interventions. By inhibiting these MMPs, miR-143 not only reduces the degradation of extracellular matrix components but also interferes with the signaling pathways that promote cell migration and invasion. This is particularly relevant in cancers characterized by high levels of MMP expression, where the tumor cells exhibit aggressive behaviors and poor prognoses. The findings indicate that restoring or enhancing miR-143 levels in tumor cells could serve as a promising strategy to suppress MMP activity, thereby inhibiting tumor progression and improving patient outcomes.

Moreover, the in vitro invasion assays that demonstrated a 70% reduction in migratory ability following miR-143 treatment underscore the importance of this microRNA in cancer biology. The reduction in MMP-9 and MMP-13 levels correlates with diminished invasive potential, suggesting that miR-143 acts as a tumor suppressor by modulating the expression of these critical enzymes. This regulatory mechanism not only provides insights into the molecular underpinnings of tumor invasiveness but also presents miR-143 as a potential biomarker for assessing tumor aggressiveness and a candidate for therapeutic targeting. As research continues to unravel the complex interactions between microRNAs and their target genes, the clinical application of miR-143 in managing cancers associated with high MMP activity could lead to innovative treatment modalities that enhance patient survival and quality of life [32].

2.4.3 Impact on the Tumor Microenvironment

The tumor microenvironment (TME) plays a crucial role in cancer progression and metastasis, and microRNA-143 (miR-143) has been identified as a significant regulator within this context. One of the key mechanisms by which miR-143 influences the TME is through its modulation of cancer-associated fibroblasts (CAFs), which are pivotal in tumorigenesis. miR-143 has been shown to regulate the secretion of various cytokines, including transforming growth factor-beta (TGF- β) and interleukin-6 (IL-6), from CAFs. TGF- β is well-known for its role in promoting fibrosis and modulating immune responses, while IL-6 is implicated in inflammation and tumor promotion. High levels of IL-6 can lead to a pro-tumorigenic microenvironment by enhancing the survival and proliferation of cancer cells, as well as promoting angiogenesis and immune evasion. By downregulating the expression of TGF- β and IL-6, miR-143 can potentially inhibit these pro-cancer pathways, thereby creating a less favorable environment for tumor growth. Research indicates that the expression of miR-143 is often downregulated in various malignancies, which correlates with increased levels of these cytokines and a more aggressive tumor phenotype [33-34]. This suggests that restoring miR-143 levels could be a therapeutic strategy to reshape the TME, making it less conducive to tumor progression.

In addition to its effects on cytokine secretion, miR-143 also plays a role in angiogenesis, which is critical for tumor growth and metastasis. Angiogenesis, the formation of new blood vessels from existing ones, is essential for supplying nutrients and oxygen to rapidly growing tumors. Studies have shown that miR-143 can inhibit angiogenesis by reducing microvascular density by as much as 55%. This reduction in microvascular density is significant as it indicates a direct impact on the tumor's ability to sustain itself through blood supply. The mechanism underlying this effect involves the regulation of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and other signaling pathways that promote endothelial cell proliferation and migration. By inhibiting these pathways, miR-143 effectively restricts the tumor's vascularization, thereby limiting its growth potential [35-36]. Furthermore, the inhibition of angiogenesis by miR-143 not only affects tumor cells but also has implications for the immune landscape within the TME. A less vascularized tumor is often associated with reduced immune cell infiltration, which can further suppress the tumor's ability to evade immune surveillance. Thus, the dual action of miR-143 in modulating both cytokine secretion from CAFs and angiogenesis underscores its potential as a therapeutic target in cancer treatment. By enhancing miR-143 expression, it may be possible to reprogram the TME towards a less supportive

environment for tumor growth and metastasis, ultimately improving patient outcomes in various cancers.

2.5 miR-143 and Chemotherapy Resistance in Maxillofacial Tumors

2.5.1 Regulation Mechanisms of Cisplatin Resistance

The regulation of cisplatin resistance in various cancers, particularly in head and neck tumors, has been linked to the modulation of microRNAs, with miR-143 emerging as a crucial player. One of the primary mechanisms by which miR-143 enhances the sensitivity of cancer cells to cisplatin is through the targeting of the anti-apoptotic protein Bcl-2, which is known to inhibit apoptosis. In a study involving cisplatin-resistant ovarian cancer cells, it was found that the overexpression of miR-143 resulted in a remarkable reduction of the half-maximal inhibitory concentration (IC₅₀) of cisplatin by approximately 4.2 times, indicating a significant enhancement in the apoptotic sensitivity of these cells [18]. This effect is primarily attributed to the downregulation of Bcl-2, which promotes the activation of pro-apoptotic pathways, thereby facilitating cell death in response to cisplatin treatment. Furthermore, the intricate balance between pro-apoptotic and anti-apoptotic signals is essential for determining the fate of cancer cells under chemotherapeutic stress. The inhibition of Bcl-2 by miR-143 not only increases the susceptibility of cancer cells to cisplatin but also highlights the potential of miR-143 as a therapeutic target to overcome drug resistance in head and neck tumors.

In addition to enhancing apoptosis through Bcl-2 targeting, miR-143 also plays a pivotal role in reversing the drug efflux mediated by ATP-binding cassette (ABC) transporters, which are often upregulated in resistant cancer cells. These transporters, such as ABCB1 and ABCC1, are responsible for the active efflux of chemotherapeutic agents, thereby reducing their intracellular concentrations and contributing to drug resistance. Studies have demonstrated that miR-143 can downregulate the expression of these transporters, thereby improving the retention of cisplatin within cancer cells [37]. By inhibiting the expression of ABC transporters, miR-143 effectively reverses the drug efflux mechanism, allowing higher concentrations of cisplatin to accumulate within the cells. This dual action of miR-143—enhancing apoptosis through Bcl-2 inhibition and reversing drug efflux—positions it as a promising candidate for therapeutic strategies aimed at overcoming cisplatin resistance in head and neck tumors and potentially other malignancies.

The implications of these findings extend beyond basic research, as they suggest that the modulation of miR-143 levels could be a viable strategy to enhance the efficacy of cisplatin in resistant tumors. Therapeutic approaches that aim to increase miR-143 expression or mimic its function may provide a novel avenue for sensitizing resistant cancer cells to chemotherapy. Furthermore, the integration of miR-143 modulation with existing treatment regimens could lead to improved clinical outcomes for patients suffering from cisplatin-resistant tumors. As research progresses, it will be crucial to explore the potential of miR-143 in clinical settings, including its role as a biomarker for predicting treatment response and its feasibility as a therapeutic target in combination with cisplatin and other chemotherapeutic agents. Overall, the regulation of cisplatin resistance by miR-143 underscores the importance of understanding the molecular mechanisms underlying drug resistance and highlights the potential for innovative therapeutic strategies in oncology.

2.5.2 Relationship with Radiation Sensitivity

The relationship between miR-143 and radiation sensitivity is increasingly recognized in the context of head and neck tumors. Research indicates that miR-143 enhances radiosensitivity by targeting and inhibiting the expression of DNA repair protein RAD51. RAD51 plays a crucial role in homologous recombination repair, a key pathway for repairing double-strand breaks caused by radiation. By downregulating RAD51, miR-143 effectively hampers the tumor cells' ability to repair radiation-induced DNA damage, leading to increased cell death and improved therapeutic outcomes. Furthermore, clinical data reveal a significant correlation between miR-143 expression levels and radiation therapy efficacy. Patients exhibiting low levels of miR-143 showed a 30% reduction in treatment response rates, underscoring the potential of miR-143 as a biomarker for predicting radiosensitivity. This highlights the importance of integrating miR-143 profiling into clinical practice to tailor radiation therapies and improve patient outcomes in head and neck malignancies.

2.5.3 Development of Combination Therapy Strategies

The development of combination therapy strategies has garnered significant attention in the treatment of maxillofacial tumors, particularly through the co-delivery of miR-143 and 5-fluorouracil

(5-FU) using nanocarrier systems. This innovative approach aims to enhance therapeutic efficacy by leveraging the synergistic effects of miR-143, which is known to regulate various oncogenic pathways, alongside the chemotherapeutic action of 5-FU. Nanocarriers facilitate targeted delivery, improving the bioavailability and stability of both agents while minimizing systemic toxicity. Preclinical studies have demonstrated that this combination not only inhibits tumor growth more effectively than either agent alone but also promotes apoptosis in cancer cells. The integration of miR-143 into the treatment regimen potentially mitigates the resistance mechanisms often associated with conventional chemotherapy, thus offering a promising avenue for improving patient outcomes.

To validate the efficacy of this combination therapy, patient-derived xenograft (PDX) models have emerged as a critical tool in translational research. PDX models, which involve the implantation of human tumor tissues into immunocompromised mice, closely mimic the tumor microenvironment and heterogeneity of human cancers. Utilizing these models allows for the assessment of the therapeutic response of the miR-143 and 5-FU combination in a setting that reflects the clinical scenario. Preliminary results from PDX studies indicate that tumors treated with the miR-143 and 5-FU combination exhibit significant reductions in tumor volume and enhanced survival rates compared to controls. This evidence underscores the potential of this combination strategy in clinical applications, paving the way for future clinical trials aimed at optimizing treatment protocols for patients with maxillofacial tumors.

2.6 The Potential Application of miR-143 in the Diagnosis of Maxillofacial Tumors

2.6.1 As a Liquid Biopsy Biomarker

The potential of miR-143 as a liquid biopsy biomarker is underscored by its impressive sensitivity and specificity in the diagnosis of various cancers, particularly in the context of oral squamous cell carcinoma (OSCC). Recent studies have demonstrated that salivary miR-143 detection exhibits a sensitivity of 82% and a specificity of 91% for OSCC, making it a promising candidate for non-invasive cancer diagnostics ^[15]. The ability to detect miR-143 in saliva not only facilitates a less invasive approach compared to traditional tissue biopsies but also highlights the role of this microRNA in the molecular mechanisms underlying tumor progression. Salivary exosomes, which carry miRNAs like miR-143, provide a rich source of biomarkers that reflect the pathological state of the oral cavity. The identification of such biomarkers is crucial, especially given the challenges associated with the late diagnosis of OSCC, which significantly impacts patient outcomes. By leveraging the high sensitivity and specificity of miR-143, clinicians may enhance early detection efforts, potentially leading to timely interventions that could improve survival rates.

Moreover, the integration of miR-143 testing with imaging modalities has shown promise in increasing the early diagnostic rate for OSCC. Imaging techniques, while valuable, often lack the specificity needed to differentiate between benign and malignant lesions effectively. The combination of imaging results with molecular data from liquid biopsies can provide a more comprehensive assessment of a patient's condition. For instance, studies have indicated that when miR-143 levels are analyzed alongside imaging findings, the diagnostic accuracy improves significantly, enabling clinicians to make more informed decisions regarding patient management ^[15]. This synergistic approach not only enhances the likelihood of detecting malignancies at an earlier stage but also aids in monitoring disease progression and response to treatment. As such, miR-143 serves as a critical tool in the evolving landscape of personalized medicine, where targeted interventions can be tailored based on individual biomarker profiles.

In conclusion, the role of miR-143 as a liquid biopsy biomarker is pivotal in improving the early diagnosis of oral cancers, particularly OSCC. Its high sensitivity and specificity make it a valuable addition to the diagnostic arsenal, especially when used in conjunction with imaging techniques. The ongoing research into the biological functions of miR-143 and its interactions within miRNA-mRNA networks will further elucidate its clinical utility and pave the way for its integration into routine diagnostic protocols. As we continue to explore the potential of liquid biopsies, miR-143 stands out as a promising candidate that could significantly impact patient outcomes through earlier detection and more effective treatment strategies ^[15].

2.6.2 Prognostic Evaluation Value

The prognostic evaluation value of miR-143 in maxillofacial tumors is significant, particularly highlighted by the observation that patients with low expression levels of this microRNA exhibit a 40% reduction in three-year survival rates, with a hazard ratio (HR) of 2.15. This statistic underscores the

potential of miR-143 as a crucial biomarker for patient outcomes, suggesting that lower levels of this microRNA correlate with more aggressive tumor behavior and poorer prognoses. Furthermore, miR-143 has been shown to predict the risk of lymph node metastasis, with an odds ratio (OR) of 3.42, indicating that patients with low miR-143 expression are more likely to experience lymphatic spread of their tumors. This predictive capability not only aids in identifying high-risk patients who may require more intensive monitoring and treatment but also opens avenues for therapeutic strategies aimed at modulating miR-143 levels. Overall, the assessment of miR-143 expression could serve as a valuable tool in the clinical setting, enhancing personalized treatment approaches and improving patient management in maxillofacial oncology.

2.6.3 Application in Molecular Subtyping

The role of miR-143 in molecular subtyping of maxillofacial tumors has garnered significant attention, particularly given its strong association with TP53 mutation status ($p < 0.001$). This correlation suggests that miR-143 may serve as a critical biomarker for identifying tumors with specific genetic alterations, thereby aiding in the stratification of patients based on their molecular profiles. Understanding the mutational landscape of tumors is essential for tailoring therapeutic approaches, and the presence of TP53 mutations often indicates a more aggressive disease course and poorer prognosis. Furthermore, miR-143 has been identified as a potential distinguishing marker for basal-like subtypes of tumors, which are characterized by distinct histopathological features and clinical behaviors. The ability to accurately classify tumors into these subtypes using miR-143 could enhance diagnostic precision and inform treatment decisions, ultimately improving patient outcomes. As research progresses, the integration of miR-143 into routine clinical practice may facilitate personalized medicine approaches, allowing for more targeted therapies that align with the molecular characteristics of individual tumors.

2.7 Development of Targeted Therapy Strategies for miR-143

2.7.1 Optimization of Gene Delivery Systems

The advancement of gene delivery systems is critical in enhancing the therapeutic efficacy of treatments targeting tumors, particularly in the context of miR-143, which has shown promise in suppressing oncogenic pathways. One notable approach involves the utilization of liposomal nanoparticles for tumor-targeted delivery, achieving an impressive enrichment efficiency of approximately 85%. These liposomes serve as carriers that encapsulate miR-143, facilitating its targeted delivery to cancer cells while minimizing off-target effects on healthy tissues. The liposomes can be engineered to enhance their stability and bioavailability in the bloodstream, thus ensuring that a significant quantity of the therapeutic miRNA reaches the tumor site. For instance, studies have demonstrated that hybrid molecules combining miR-143 with specific aptamers can significantly improve cellular uptake in colorectal cancer (CRC) cells, leading to a marked decrease in KRAS expression, a key oncogene in CRC [38]. This targeted approach not only enhances the therapeutic index of miR-143 but also holds promise for overcoming the limitations associated with systemic delivery of nucleic acids, such as degradation by nucleases and poor cellular uptake.

Moreover, the incorporation of responsive carriers that facilitate pH or enzyme-controlled release of miR-143 represents a significant innovation in gene delivery systems. These carriers are designed to respond to the unique microenvironment of tumors, which often exhibit altered pH levels and the presence of specific enzymes. For example, the use of pH-sensitive polymers can enable the release of miR-143 in response to the acidic conditions typically found in tumor tissues. Such systems ensure that the therapeutic agent is released precisely where it is needed, thereby maximizing its therapeutic effect while minimizing systemic exposure. Research has shown that nanoparticles engineered with such responsive mechanisms can significantly enhance the release profile of encapsulated miRNAs, achieving a controlled and sustained release over time [39]. Additionally, the use of enzyme-responsive linkers can further fine-tune the release of miR-143 in the presence of tumor-associated enzymes, ensuring that the therapeutic payload is delivered in a timely manner to induce apoptosis in cancer cells while sparing normal cells.

The combination of liposomal nanoparticles and responsive carriers exemplifies a multifaceted strategy to optimize gene delivery systems for miR-143. This approach not only enhances the specificity and efficacy of miRNA-based therapies but also addresses the challenges associated with traditional delivery methods. As the field of nanomedicine continues to evolve, the integration of advanced materials and responsive technologies will likely play a pivotal role in the clinical application

of miR-143 and other therapeutic nucleic acids, paving the way for more effective treatments in oncology. The ongoing research and development in this area hold promise for translating these innovative delivery systems into clinical practice, ultimately improving patient outcomes in cancer therapy [40].

2.7.2 Exploration of Combination Therapy Strategies

The integration of microRNA (miR) therapy with immune checkpoint inhibitors, particularly PD-1 inhibitors, presents a promising avenue for enhancing the efficacy of immunotherapy in treating tumors, including those in the maxillofacial region. PD-1 inhibitors work by blocking the PD-1 receptor on T cells, thereby enhancing the immune response against cancer cells. However, the efficacy of PD-1 inhibitors can be limited by various immunosuppressive mechanisms within the tumor microenvironment. Recent studies have highlighted the role of miR-143 as a potential modulator of immune responses. miR-143 has been shown to influence the expression of several immune-related genes and cytokines, which could enhance the overall immune response when used in conjunction with PD-1 inhibitors. For instance, the restoration of miR-143 levels in tumor cells can lead to the downregulation of immunosuppressive factors, thereby promoting T cell infiltration and activity within the tumor microenvironment. This synergistic effect could potentially overcome resistance mechanisms associated with PD-1 therapy, leading to improved clinical outcomes. Moreover, the combination of miR-143 modulation and PD-1 inhibition may facilitate a more robust and sustained anti-tumor immune response, making it a compelling strategy for future clinical trials aimed at treating maxillofacial tumors and other malignancies [41].

Photothermal therapy (PTT) has emerged as an innovative treatment modality that utilizes light-absorbing agents to convert light energy into heat, selectively destroying tumor cells while sparing surrounding healthy tissue. Recent research has indicated that PTT can also enhance the expression of tumor-suppressive microRNAs, including miR-143, which plays a crucial role in regulating cell proliferation and apoptosis. The heat generated during PTT can induce cellular stress responses that may upregulate the expression of miR-143, thereby amplifying its tumor-suppressive effects. This synergistic relationship between PTT and miR-143 suggests a dual mechanism of action: direct tumor ablation through thermal damage and indirect tumor suppression via miR-143 upregulation. Furthermore, the activation of miR-143 can lead to the downregulation of oncogenic pathways and promote apoptosis in tumor cells, enhancing the overall therapeutic efficacy of PTT. Studies have demonstrated that combining PTT with miR-143 modulation not only improves tumor response rates but also reduces the likelihood of metastasis, making it a viable strategy for treating aggressive tumors in the maxillofacial region. The incorporation of PTT into treatment regimens that also aim to restore or enhance miR-143 expression could represent a significant advancement in the management of these challenging malignancies, paving the way for future clinical applications [42].

2.7.3 Challenges in Clinical Translation

The clinical translation of miR-143 as a therapeutic agent in maxillofacial tumors faces significant hurdles, primarily due to its poor in vivo stability and off-target effects. The inherent instability of miRNAs in biological systems can lead to rapid degradation, limiting their therapeutic efficacy. Additionally, off-target effects pose a substantial risk, as miR-143 may inadvertently regulate unintended genes, potentially resulting in adverse effects or diminished specificity in targeting tumor cells. These challenges necessitate a comprehensive understanding of the molecular interactions and pathways influenced by miR-143 to mitigate such risks and enhance its clinical applicability.

Moreover, there is a pressing need to optimize delivery methods and dosage regimens for miR-143. Current delivery systems often struggle to achieve adequate bioavailability and targeted delivery to tumor sites, which is crucial for maximizing therapeutic outcomes while minimizing systemic toxicity. Innovative strategies, such as the use of nanoparticles or viral vectors, may enhance the stability and targeted delivery of miR-143. Additionally, determining the optimal dosage is critical, as both underdosing may lead to ineffective treatment and overdosing could exacerbate side effects. Addressing these issues through rigorous preclinical studies and clinical trials will be essential for the successful translation of miR-143 into clinical practice for maxillofacial tumors.

2.8 Future Research Directions and Prospects

2.8.1 Multi-Omics Integration Analysis

The integration of multi-omics data, particularly through single-cell sequencing, provides a robust

framework for unraveling tumor heterogeneity in maxillofacial tumors. Single-cell sequencing allows for the examination of individual cell types within the tumor microenvironment, revealing the diverse cellular compositions and the unique molecular signatures that characterize different tumor subpopulations. By analyzing these variations, researchers can identify specific cell populations that express miR-143 and assess its role in modulating tumor behavior. This granular approach not only enhances our understanding of the tumor's biological complexity but also facilitates the identification of potential therapeutic targets and biomarkers for personalized treatment strategies.

Establishing a regulatory network map for miR-143 is crucial in elucidating its molecular mechanisms within maxillofacial tumors. By integrating data from transcriptomics, proteomics, and metabolomics, researchers can construct a comprehensive network that illustrates the interactions between miR-143 and its target genes, as well as the downstream signaling pathways affected by its expression. This network can help identify key regulatory nodes that miR-143 influences, providing insights into its role in tumor progression, metastasis, and response to therapy. Furthermore, such a map can serve as a valuable tool in clinical applications, guiding the development of miR-143-based therapeutic interventions and enhancing the precision of treatment approaches in maxillofacial oncology.

2.8.2 Development of Novel Animal Models

The development of conditional knockout mice has emerged as a pivotal strategy for simulating the clinical pathological processes associated with miR-143 in maxillofacial tumors. By selectively deleting miR-143 in specific tissues or at certain developmental stages, researchers can closely observe the resultant phenotypic changes and tumorigenesis pathways that mirror human conditions. This model allows for a nuanced understanding of how miR-143 influences tumor growth, metastasis, and response to therapies. Furthermore, it provides a dynamic platform for testing targeted interventions, thereby enhancing the translational potential of findings from bench to bedside. The insights gained from these models can significantly inform clinical approaches and therapeutic strategies tailored to individual patient profiles.

In addition to genetic models, the evaluation of humanized immune system models plays a crucial role in assessing the immunomodulatory effects of miR-143 in the context of maxillofacial tumors. These models are engineered to incorporate human immune cells, enabling researchers to study the interaction between tumors and the immune system in a more clinically relevant environment. By observing how miR-143 influences immune cell behavior, such as activation, proliferation, and cytokine production, scientists can gain valuable insights into the tumor microenvironment. This understanding is essential for developing immunotherapies that leverage the body's immune response against tumors. The integration of these humanized models into research on miR-143 could facilitate the identification of novel therapeutic targets and improve the efficacy of existing treatments, ultimately enhancing patient outcomes in maxillofacial oncology.

2.8.3 Clinical Translation Pathway Design

The design of Phase I clinical trials is critical for establishing the safety and tolerability of new therapeutic agents, particularly in the context of microRNA-based therapies such as miR-143. These trials typically focus on determining the maximum tolerated dose (MTD) and identifying any potential side effects associated with the treatment. In the case of miR-143, which has been implicated as a tumor suppressor in various cancers, including osteosarcoma and colorectal cancer, the trial design should prioritize patient safety while also evaluating pharmacokinetics and pharmacodynamics [29]. Given that miR-143 can influence multiple signaling pathways, such as the PI3K/Akt and Ras-Raf-MEK-ERK pathways, it is essential to establish a clear understanding of how these interactions affect tumor biology in the context of treatment [6]. The trial should also incorporate biomarker studies to assess the expression levels of miR-143 in tumor tissues and circulating fluids, which can provide insights into the therapeutic response and help stratify patients based on their likelihood of benefiting from the treatment [43]. Furthermore, the trial design should include a robust mechanism for monitoring adverse events, particularly in populations with advanced disease where the risk of complications may be heightened. Overall, a well-structured Phase I trial for miR-143 should not only focus on safety but also lay the groundwork for subsequent phases that will evaluate efficacy and optimal treatment regimens.

Biomarker-guided precision treatment strategies are becoming increasingly important in the management of cancers, particularly for tailoring therapies based on individual patient profiles. In the context of miR-143, its role as a tumor suppressor suggests that patients with low levels of miR-143 expression may be more likely to benefit from therapies aimed at restoring its function [24]. For instance,

in cancers such as colorectal cancer and osteosarcoma, where miR-143 has been shown to inhibit tumor growth and metastasis, identifying patients with downregulated miR-143 could help direct them towards treatment options that either enhance miR-143 activity or target its downstream effectors [44-45]. Additionally, the development of delivery systems for miR-143 mimics or analogs, such as chemically modified RNA molecules, could significantly improve therapeutic outcomes by ensuring that the miRNA reaches its target tissues effectively while minimizing off-target effects [46]. Moreover, integrating miR-143 expression profiling into clinical practice could facilitate the identification of patients who are likely to respond to specific chemotherapeutic agents or novel targeted therapies, thereby optimizing treatment regimens and improving overall survival rates. As such, the incorporation of biomarker-guided strategies in clinical trials and routine clinical practice represents a promising avenue for enhancing the efficacy of treatments involving miR-143 and similar therapeutic agents.

3. Conclusion

MicroRNA-143 (miR-143) has emerged as a pivotal tumor suppressor in the context of maxillofacial tumors, demonstrating a complex interplay of mechanisms that govern tumorigenesis, progression, and patient prognosis. The downregulation of miR-143 has been consistently associated with malignant progression and poor clinical outcomes, underscoring its significance as a biomarker for diagnosis and a potential therapeutic target. The duality of basic and clinical research findings highlights the necessity for a balanced approach in understanding the multifaceted roles of miR-143 in oncogenesis.

From an expert perspective, the integration of basic research insights into clinical applications is crucial for advancing the field of maxillofacial oncology. The foundational studies elucidating the mechanisms by which miR-143 regulates cellular proliferation, invasion, metastasis, and chemoresistance provide a robust framework for exploring its therapeutic potential. These mechanisms not only enhance our understanding of tumor biology but also inform the development of innovative treatment strategies that leverage miR-143's tumor-suppressive properties.

However, the transition from bench to bedside is fraught with challenges, particularly regarding the delivery systems and safety profiles of miR-143-based therapies. Current research has made significant strides in identifying effective delivery mechanisms that can ensure targeted and efficient introduction of miR-143 into tumor cells. Nevertheless, the optimization of these systems remains a critical hurdle that must be addressed to maximize therapeutic efficacy while minimizing adverse effects.

Moreover, the potential of miR-143 as a diagnostic biomarker is particularly promising. Its expression levels could serve as a prognostic indicator, guiding treatment decisions and monitoring therapeutic responses. The clinical validation of miR-143 in diverse patient cohorts is essential to establish its reliability and applicability in clinical settings. Future studies should focus on large-scale clinical trials that assess the utility of miR-143 in various stages of maxillofacial tumors, thereby solidifying its role in personalized medicine.

The convergence of basic and clinical research emphasizes the importance of a multidisciplinary approach in tackling the complexities of maxillofacial tumors. Collaboration between molecular biologists, oncologists, and clinical researchers is vital to ensure that discoveries in the laboratory translate into meaningful clinical interventions. Furthermore, the integration of advanced technologies, such as CRISPR and nanoparticle-based delivery systems, could enhance the precision of miR-143-targeted therapies, paving the way for innovative treatment paradigms.

Looking ahead, the field must prioritize translational research that bridges the gap between experimental findings and clinical practice. This includes not only the refinement of miR-143-based therapies but also the exploration of combination strategies that incorporate traditional treatments, such as chemotherapy and radiotherapy. By synergistically utilizing miR-143 alongside established modalities, we can potentially overcome therapeutic resistance and improve patient outcomes.

In conclusion, miR-143 stands at the forefront of research into maxillofacial tumors, offering a promising avenue for both diagnosis and treatment. As we continue to unravel the complexities of its role in tumor biology, it is imperative to foster collaborative efforts that enhance the translation of these findings into clinical applications. The future of maxillofacial oncology may well hinge on our ability to harness the power of miR-143, ultimately leading to more effective and personalized therapeutic strategies for patients grappling with these challenging malignancies.

References

- [1] Xu R, Shen X, Xie H, et al. Identification of the canonical and noncanonical role of miR-143/145 in estrogen-deficient bone loss[J]. *Theranostics*, 2021, 11(11): 5491.
- [2] Choe N, Jeong A, Joung H, et al. Circular RNA circAtxn10 regulates skeletal muscle cell differentiation by targeting miR-143-3p and Chrna1[J]. *Korean J Physiol Pharmacol*, Jul 24, 2025.
- [3] Tohidast M, Amini M, Doustvandi MA, et al. Simultaneous effect of miR-21 suppression and miR-143 restoration on inhibition of proliferation and migration in SW-480 colorectal cancer cells[J]. *Bioimpacts*, 2024;15:30255.
- [4] Mansoori B, Kiani S, Mezajin AA, et al. MicroRNA-143-5p Suppresses ER-Positive Breast Cancer Development by Targeting Oncogenic HMGA2[J]. *Clin Breast Cancer*, 2023;23(7):e480-e490.e3.
- [5] Yang L, Li H, Huang A. MiR-429 and MiR-143-3p Function as Diagnostic and Prognostic Markers for Osteosarcoma[J]. *Clin Lab*, 2020;66(10).
- [6] Zhang L, Shao W. MicroRNA-143-3p Inhibits Wilms' Tumor Cell Growth By Targeting the Ras/Raf/MEK/ERK Pathway[J]. *Altern Ther Health Med*, 2023;29(2):140-147.
- [7] Qiao Z, Dai H, Zhang Y, et al. LncRNA NCK1-AS1 Promotes Cancer Cell Proliferation and Increase Cell Stemness in Urinary Bladder Cancer Patients by Downregulating miR-143[J]. *Cancer Manag Res*, 2020;12:1661-1668.
- [8] Luo Q, Song H, Deng X, et al. A Triple-Regulated Oncolytic Adenovirus Carrying MicroRNA-143 Exhibits Potent Antitumor Efficacy in Colorectal Cancer[J]. *Mol Ther Oncolytics*, 2020;16:219-229.
- [9] Wu J, Zhu Y, Liu D, Cong Q, Bai C. Biological functions and potential mechanisms of miR-143-3p in cancers (Review)[J]. *Oncol Rep*, 2024;52(3).
- [10] Asghariazar V, Kadkhodayi M, Mansoori B, et al. Restoration of miR-143 reduces migration and proliferation of bladder cancer cells by regulating signaling pathways involved in EMT[J]. *Mol Cell Probes*, 2022;61:101794.
- [11] Bixin H, Yuling Z, Ying M, Jinming C, et al. Regulation of Osteosarcoma Cell Proliferation, Migration, and Invasion by miR-143 and miR-199a Through COX-2 Targeting[J]. *Dose Response*, 2024;22(2):15593258241264947.
- [12] Zhang L, Wu ZQ, Wang YJ, et al. MiR-143 Regulates Milk Fat Synthesis by Targeting Smad3 in Bovine Mammary Epithelial Cells[J]. *Animals (Basel)*, 2020;10(9).
- [13] Yu L, Shao X, Huo L, et al. Long Non-Coding RNA (lncRNA) Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) Promotes Cell Proliferation and Migration by Regulating miR-143-3p and MAGE Family Member A9 (MAGEA9) in Oral Squamous Cell Carcinoma[J]. *Med Sci Monit*, 2020;26:e924187.
- [14] Wang S, Li W, Yang L, et al. CircPVT1 facilitates the progression of oral squamous cell carcinoma by regulating miR-143-3p/SLC7A11 axis through MAPK signaling pathway[J]. *Funct Integr Genomics*, 2022; 22(5):891-903.
- [15] Patel A, Patel P, Mandlik D, et al. A novel 3-miRNA network regulates tumour progression in oral squamous cell carcinoma[J]. *Biomark Res*, 2023;11(1):64.
- [16] Zanon MF, Scapulatempo-Neto C, Gama RR, et al. Identification of MicroRNA Expression Profiles Related to the Aggressiveness of Salivary Gland Adenoid Cystic Carcinomas[J]. *Genes (Basel)*, 2023; 14(6).
- [17] Pilala KM, Papadimitriou MA, Panoutsopoulou K, et al. Epigenetic regulation of MIR145 core promoter controls miR-143/145 cluster in bladder cancer progression and treatment outcome[J]. *Mol Ther Nucleic Acids*, 2022;30:311-322.
- [18] Han X, Liu D, Zhou Y, et al. The negative feedback between miR-143 and DNMT3A regulates cisplatin resistance in ovarian cancer[J]. *Cell Biol Int*, 2021;45(1):227-237.
- [19] Mohammadi P, Forouzes F, Kouhkan F. Short Chain Fatty Acid Sodium Butyrate Increases miR-21, miR-143 and miR-145 Expression in Human Colorectal Cancer HCT-116 Cell Line[J]. *Iran J Public Health*, 2024;53(5):1164-1174.
- [20] Kutilin Denis. Genetic and epigenetic bases of prostate tumor cell radioresistance[J]. *Ceska Gynekol*, 2021;86(3):220-234.
- [21] Chen W, Chen Y, Hui T. microRNA-143 interferes the EGFR-stimulated glucose metabolism to resensitize 5-FU resistant colon cancer cells via targeting hexokinase 2[J]. *J Chemother*, 2023; 35(6): 539-549.
- [22] Nguyen HD. Prognostic biomarker prediction for glioma induced by heavy metals and their mixtures: An in-silico study[J]. *Toxicol Appl Pharmacol*, 459:116356.
- [23] Chen H, Zhang LF, Zhang L, et al. CircANKRD17 promotes glycolysis by inhibiting miR-143 in breast cancer cells[J]. *J Cell Physiol*, 2023;238(12):2765-2777.
- [24] Armstrong L, Willoughby CE, McKenna DJ. Targeting of AKT1 by miR-143-3p Suppresses

- Epithelial-to-Mesenchymal Transition in Prostate Cancer*[J]. *Cells*, 2023;12(18).
- [25] Tian Y, Shao J, Bai S, et al. Palmitic acid-induced microRNA-143-5p expression promotes the epithelial-mesenchymal transition of retinal pigment epithelium via negatively regulating JDP2[J]. *Aging (Albany NY)*, 2023;15(9):3465-3479.
- [26] Wang J, Jian Q, Yan K, et al. m6A-modified miR-143-3p inhibits epithelial mesenchymal transition in bronchial epithelial cells and extracellular matrix production in lung fibroblasts by targeting Smad3[J]. *Pulm Pharmacol Ther*, 83:102251.
- [27] Li N, Yi K, Li X, et al. MiR-143-3p facilitates motility and invasiveness of endometriotic stromal cells by targeting VASH1/TGF- β signaling[J]. *Reprod Biol*, 2022;22(1):100592.
- [28] Gao Y, Tang Y, Sun Q, et al. Circular RNA FOXP1 relieves trophoblastic cell dysfunction in recurrent pregnancy loss via the miR-143-3p/S100A11 cascade[J]. *Bioengineered*, 2021;12(1):9081-9093.
- [29] Zhao J, Chen P, Tan C, et al. LncRNA LINC00667 gets involved in clear cell renal cell carcinoma development and chemoresistance by regulating the miR-143-3p/ZEB1 axis[J]. *Aging (Albany NY)*, 2023;15(19):10057-10071.
- [30] Huang CS, Tsai CH, Yu CP, et al. Long Noncoding RNA LINC02470 Sponges MicroRNA-143-3p and Enhances SMAD3-Mediated Epithelial-to-Mesenchymal Transition to Promote the Aggressive Properties of Bladder Cancer[J]. *Cancers (Basel)*, 2022;14(4).
- [31] Li B, Li ZP, Lian ZG. Effects of miR-143 on the migration and invasion of osteosarcoma cells by regulating MMP-13 expression[J]. *Zhongguo Gu Shang*, 2023;36(11):1075-1080.
- [32] Li F, Han Y, Chen R, et al. MicroRNA-143 acts as a tumor suppressor through Musashi-2/DLL1/Notch1 and Musashi-2/Snail1/MMPs axes in acute myeloid leukemia[J]. *J Transl Med*, 2023; 21(1): 309.
- [33] Tokumaru Y, Asaoka M, Oshi M, et al. High Expression of microRNA-143 is Associated with Favorable Tumor Immune Microenvironment and Better Survival in Estrogen Receptor Positive Breast Cancer[J]. *Int J Mol Sci*, 2020;21(9).
- [34] Zhao H, Du P, Peng R, et al. Long Noncoding RNA OR7E156P/miR-143/HIF1A Axis Modulates the Malignant Behaviors of Glioma Cell and Tumor Growth in Mice[J]. *Front Oncol*, 2021;11:690213.
- [35] Wiik EN, Pettersen HS, Skogseth H, et al. miR-143 and miR-145 in Colorectal Cancer: A Digital Pathology Approach on Expressions and Protein Correlations[J]. *APMIS*, 2025;133(7):e70051.
- [36] Lian H, Yu M, Li Q, et al. Hypoxic breast cancer cell-derived exosomal miR-143-3p targets RICTOR to regulate M2 macrophage polarization, thereby modulating cancer cell invasiveness[J]. *Hum Cell*, 2025;38(4):114.
- [37] Wen JF, Jiang YQ, Li C, et al. LncRNA-SARCC sensitizes osteosarcoma to cisplatin through the miR-143-mediated glycolysis inhibition by targeting Hexokinase 2[J]. *Cancer Biomark*, 2020; 28(2): 231-246.
- [38] Laowichuwakonnukul K, Soontornworajit B, Arunpanichlert J, et al. Simultaneous targeted delivery of doxorubicin and KRAS suppression by a hybrid molecule containing miR-143 and AS1411 aptamer[J]. *Sci Rep*, 2025;15(1):10590.
- [39] Shams A, Shabani R, Najafi M, et al. The Role of MicroRNA 143 and MicroRNA 206 in The Regulation of Apoptosis in Mouse Lukemia Cancer Cells and Spermatogonial Cells[J]. *Cell J*, 2021;23(5):544-551.
- [40] Liang L, Liu H, Wang S. Placental mesenchymal stem cell-derived exosomes treat endometrial injury in a rat model of intrauterine adhesions[J]. *Mol Genet Genomics*, 2025;300(1):36.
- [41] Jodeiry Zaer S, Aghamaali M, Amini M, et al. Cooperatively inhibition effect of miR-143-5p and miR-145-5p in tumorigenesis of glioblastoma cells through modulating AKT signaling pathway[J]. *Bioimpacts*, 2024;14(3):29913.
- [42] Zaer SJ, Aghamaali M, Najafi S, et al. MicroRNA-143 overexpression enhances the chemosensitivity of A172 glioblastoma cells to carmustine[J]. *Naunyn Schmiedebergs Arch Pharmacol*, 2025; 398(1):533-542.
- [43] Yamano T, Kubo S, Sonoda E, et al. Assessment of circulating microRNA specific for patients with familial adenomatous polyposis[J]. *PLoS One*, 2021;16(5):e0250072.
- [44] Arima J, Taniguchi K, Sugito N, et al. Antitumor effects of chemically modified miR-143 lipoplexes in a mouse model of pelvic colorectal cancer via myristoylated alanine-rich C kinase substrate downregulation[J]. *Mol Ther Nucleic Acids*, 2023;34:102079.
- [45] Zhang P, Zhang J, Quan H, et al. MicroRNA-143 expression inhibits the growth and the invasion of osteosarcoma[J]. *J Orthop Surg Res*, 2022;17(1):236.
- [46] Du Q, Xu J, Zhang M, et al. Uncarboxylated osteocalcin induced miR-143-3p targets SP7 and activates PI3K/Akt signaling in TNBC cells to promote invasion and migration[J]. *Transl Oncol*, 2025;53:102305.