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The Inhibition of Oral Squamous Cell Carcinoma Proliferation and Metastasis by MiR-143 through Modulation of the AKT/STAT3/NF-κB Signaling Pathway

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Abstract: *Oral squamous cell carcinoma (OSCC) accounts for over 90% of all oral cancers and ranks as the sixth most common malignancy worldwide. Among OSCC subtypes, tongue squamous cell carcinoma (TSCC) is the most prevalent and aggressive. Currently, multidisciplinary sequential therapy centered on surgery remains the primary treatment strategy for OSCC. However, delayed diagnosis and high rates of postoperative recurrence and metastasis continue to limit overall treatment efficacy. Recent studies have shown that microRNAs (miRNAs) play pivotal roles in the regulation of tumor initiation and progression. Notably, miR-143 has been identified as a potential tumor suppressor. This study aimed to investigate the biological functions and molecular mechanisms of miR-143 in OSCC.CAL-27 cells were transfected with miR-143 mimics, and cell proliferation, colony formation, migration, and invasion were evaluated using Cell Counting Kit-8(CCK-8), colony formation, wound healing, and Transwell assays, respectively. Tumorigenicity in vivo was assessed using a xenograft model in nude mice. The expression of key components of the AKT/STAT3/NF-κB signaling pathway was examined by Western blotting and quantitative real-time PCR (qRT-PCR). The results demonstrated that miR-143 expression was significantly upregulated in transfected cells, resulting in reduced proliferative, migratory, and invasive capacities. In vivo experiments further confirmed the tumor-suppressive effect of miR-143, as evidenced by smaller tumor volumes in the treatment group. Mechanistically, miR-143 overexpression led to downregulation of p-AKT, p-STAT3, p-p65, and CDK2, and upregulation of E-cadherin. In conclusion, these findings indicate that miR-143 functions as a tumor suppressor in OSCC by inhibiting the AKT/STAT3/NF-κB pathway and promoting E-cadherin expression, suggesting its potential as a therapeutic target for oral cancer.*

Keywords: *miR-143; Oral Squamous Cell Carcinoma; Proliferation; Metastasis; AKT/STAT3/NF-κB*

1. Introduction

Oral cancer is one of the most common malignancies worldwide, with over 90% of cases represented by oral squamous cell carcinoma (OSCC)[1]. OSCC is a malignant tumor arising from the oral mucosal epithelium, characterized by high invasiveness and a strong tendency to metastasize. Among its subtypes, tongue squamous cell carcinoma (TSCC) is both the most prevalent and the most aggressive[2]. The pathogenesis of OSCC is considered a multifactorial and multistep process, primarily influenced by environmental risk factors such as tobacco carcinogens, alcohol consumption, and viral infections. Unhealthy lifestyle behaviors—including smoking, heavy drinking, and betel nut chewing—further elevate the risk of OSCC[2]. Clinically, OSCC often compromises key oral functions such as speech, chewing, and swallowing, leading to a significantly diminished quality of life and substantial psychological distress[3]. At present, the standard of care for OSCC is surgery-based multidisciplinary sequential therapy. Although recent advances have led to modest improvements, overall treatment efficacy and long-term prognosis remain unsatisfactory[4]. Delayed diagnosis due to nonspecific early symptoms often results in late-stage detection. Additionally, while conventional treatments may improve local tumor control, they frequently cause functional impairments and maxillofacial deformities, and are associated with high rates of recurrence and metastasis[5]. Therefore, elucidating the underlying mechanisms of OSCC, identifying sensitive and specific biomarkers, and

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developing effective molecular-targeted therapies are of great clinical importance. These efforts may facilitate earlier diagnosis, guide personalized therapeutic strategies, and ultimately improve patient outcomes.

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression at the transcriptional and post-transcriptional levels[6]. They have been shown to influence a wide range of biological processes, including cell proliferation and apoptosis[7]. Increasing evidence suggests that miRNAs play pivotal roles in tumor development and progression, including in OSCC[8]. For example, Hunt et al. reported that overexpression of miR-124 downregulates endogenous ITGB1 expression and suppresses OSCC cell invasion and metastasis[9]. Another study revealed that miR-155 contributes to tumor progression in OSCC through modulation of the BCL6/cyclin D2 axis[10]. Among tumor-suppressive miRNAs, miR-143 is well-recognized for its inhibitory effects on tumor cell growth, migration, invasion, apoptosis, and differentiation via regulation of multiple signaling pathways, including Ras-Raf-MEK-ERK, PI3K-AKT, TGF-β, and JNK[11-13]. Previous studies have demonstrated that miR-143 expression is downregulated in OSCC tissues and cell lines, and is negatively correlated with tumor size and clinical stage[14]. Furthermore, Sun et al. confirmed that miR-143 overexpression suppresses migration, glucose metabolism, and proliferation in OSCC cells[15]. These findings support the hypothesis that miR-143 may act as a negative regulator of OSCC cell function. However, the precise mechanisms underlying its tumor-suppressive role in OSCC remain poorly understood.

Therefore, this study aims to investigate the biological roles of miR-143 in OSCC, particularly in relation to cell proliferation, migration, invasion, and tumorigenesis in vivo. Additionally, we seek to elucidate the molecular mechanisms through which miR-143 exerts its regulatory effects, in order to provide a theoretical foundation for future molecular-targeted therapies.

2. Materials and Methods

2.1 Cell Lines and Animal Models

The human tongue squamous cell carcinoma cell line CAL-27 was obtained from the American Type Culture Collection (ATCC, USA). Female BALB/c nude mice (4–5 weeks old, ~20 g) were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. All animals were housed under specific pathogen-free (SPF) conditions with free access to food and water.

2.2 Cell Culture, Transfection, and Grouping

CAL-27 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) in a humidified incubator at 37 °C with 5% CO_2. Cells were transfected with either miR-143 mimics or negative control (miR-NC) using Lipofectamine 2000 (Invitrogen, USA). Experimental groups included a blank control group, a miR-143 mimics group, and a miR-NC group. Transfection efficiency was confirmed by quantitative real-time PCR (qRT-PCR).

2.3 Quantitative Real-Time PCR

Total RNA was extracted using TRIzol reagent (Invitrogen), and reverse transcription was performed using the PrimeScript RT reagent kit (Takara, Japan). SYBR Green-based qPCR was conducted using Takara reagents. U6 served as the internal control, and relative expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method. The primer sequences used for gene amplification are listed in Table 1.

Table 1: The primer sequences used for gene amplification.

Gene	*Primer sequence (5'→3')*
miR- 143	*F: CCGCTCGAGTTAGGCTGGAATGCGCCAAG*
	R: TGAGATGAAGCACTGTAGCTC
STAT3	*F: AGCAGCACCTTCAGGATGTC*
	R:GCATCTTCTGCCTGGTCACT
NF-κB	*F: GCTTGGCAACAGCACAGAC*
	R: CCATCAGCATGGGCTCAGTT

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CDK2	*F: CCAGGAGTTACTTCTATGCCTGA*
	R: TTCATCCAGGGGAGGTACAAC
AKT	*F: TCCTCCTCAAGAATGATGGCA*
	R: GTGCGTTCGATGACAGTGGT
U6	*F: CTCGCTTCGGCAGCACA*
	R: AACGCTTCACGAATTTGCGT

2.4 Cell Proliferation and Colony Formation Assays

Cell proliferation was assessed using the Cell Counting Kit-8 (CCK-8, Dojindo) on days 1, 3, 5, and 7 post-transfection. For the colony formation assay, 1,000 cells per well were seeded into six-well plates and cultured for 10–14 days. Colonies were fixed with paraformaldehyde, stained with crystal violet, and those containing more than 50 cells were counted.

2.5 Cell Cycle Analysis

Forty-eight hours after transfection, cells were collected, fixed with ethanol, and stained with propidium iodide (PI) and RNase A. Cell cycle distribution (G0/G1, S, G2/M phases) was analyzed using a flow cytometer (BD Biosciences).

2.6 Wound Healing and Transwell Migration/Invasion Assays

Wound healing assays were performed when cell confluency reached 90%. Linear scratches were created, and migration was monitored at 24, 48, and 72 hours. For the Transwell assay, chambers with or without Matrigel coating (for invasion and migration, respectively) were used. After 24 hours of incubation, migrated or invaded cells were fixed, stained with crystal violet, and counted under a microscope.

2.7 Tumor Xenograft Model

CAL-27 cells stably transfected with either miR-143 or miR-NC were injected subcutaneously into the right axilla of BALB/c nude mice. Subcutaneous nodules appeared at the injection sites after approximately two weeks. On day 28, the mice were sacrificed, and tumors were harvested. Tumor volume was calculated using the formula: (length × width²)/2.

2.8 Western Blotting

Total protein was extracted using RIPA lysis buffer and quantified using a BCA protein assay kit. Equal amounts of protein were separated via SDS-PAGE and transferred onto PVDF membranes. Membranes were blocked and incubated with primary antibodies against CDK2, E-cadherin, p-AKT, p-STAT3, p-p65, and β-actin (all from Abcam), followed by HRP-conjugated secondary antibodies. Immunoreactive bands were visualized using enhanced chemiluminescence (ECL) and quantified using ImageJ software.

2.9 Statistical Analysis

All experiments were performed in triplicate. Data are presented as mean ± standard deviation (SD). Statistical analysis were conducted using SPSS 19.0 software. Differences between groups were evaluated using Student's t-test. A P-value of < 0.05 was considered statistically significant.

3. Results

3.1 Validation of miR-143 Overexpression Efficiency in CAL-27 Cells

Forty-eight hours after transfection with miR-143 mimics, the expression level of miR-143 in CAL-27 cells was assessed by qRT-PCR. As shown in Figure 1, miR-143 expression was significantly upregulated in the miR-143 mimics group compared to the miR-NC and blank groups ($P < 0.05$), while no significant difference was observed between the miR-NC and blank groups ($P > 0.05$).

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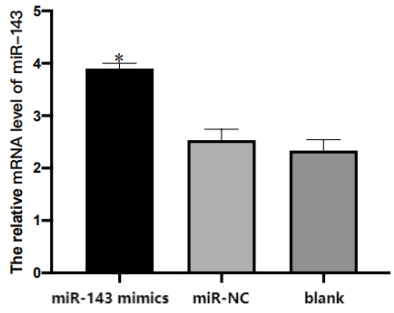

Figure 1: mRNA level of miR-143 in each group.

3.2 miR-143 Overexpression Inhibits CAL-27 Cell Proliferation

As shown in Figure 2, the proliferative capacity of cells in the miR-143 mimics group began to decline significantly from day 3 post-transfection, with statistically significant differences compared to both the miR-NC and blank control groups ($P < 0.05$).

A

Group	0day	1day	3day	5day	7day
blank	0.252±0.2515	0.463±0.0328	0.863±0.0291^{bc}	0.862±0.0299^{bc}	0.862±0.0291^{bc}
miR-NC	0.263±0.1703	0.441±0.1973	0.848±0.0227^{a}	0.848±0.0227^{ac}	0.848±0.0227^{ac}
miR-143 mimics	0.259±03023	0.416±0.1501	0.733±0.0235^{a}	0.733±0.0235^{ab}	0.733±0.0235^{ab}

a: blank; b: miR-NC; c:miR-143 mimics

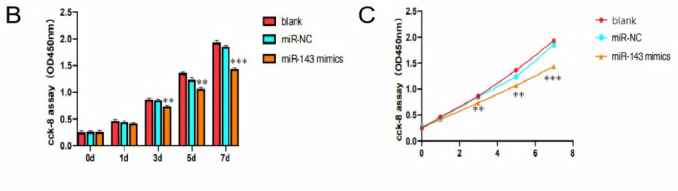

Figure 2: Effect of miR-143 mimics on proliferation of CAL-27 cells.

3.3 miR-143 Overexpression Reduces Clonogenic Potential of CAL-27 Cells

The colony formation rate reflects the survival and proliferative capacity of cells. As shown in Figure 3A, the number of colonies formed in the miR-143 mimics group was markedly reduced compared to the miR-NC and blank control groups. Quantitative analysis (Figure 3B) further confirmed that the colony count in the miR-143 mimics group was significantly lower than in the other two groups ($P < 0.001$), indicating that miR-143 suppresses the clonogenic ability of CAL-27 cells.

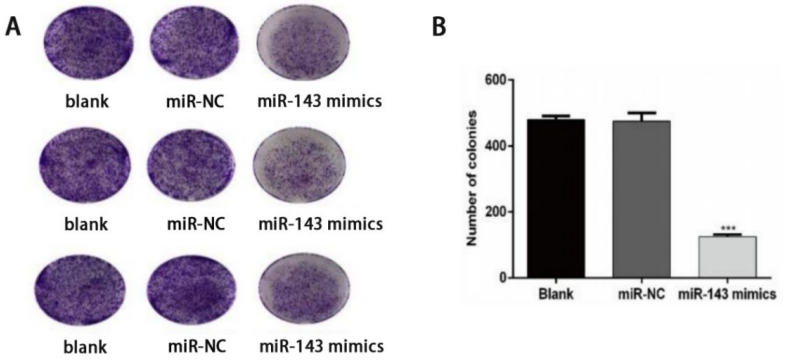

Figure 3: The effect of miR-143 mimics on the clonogenic ability of CAL-27 cells. (A) Cell colony diagram; (B) Cell colony count diagram.

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3.4 miR-143 Alters Cell Cycle Progression in CAL-27 Cells

Flow cytometry analysis (Figure 4) revealed that miR-143 overexpression significantly increased the proportion of cells in the G0/G1 phase and decreased the proportions of cells in the S and G2/M phases. These changes were statistically significant compared with those in the miR-NC and blank control groups ($P < 0.001$).

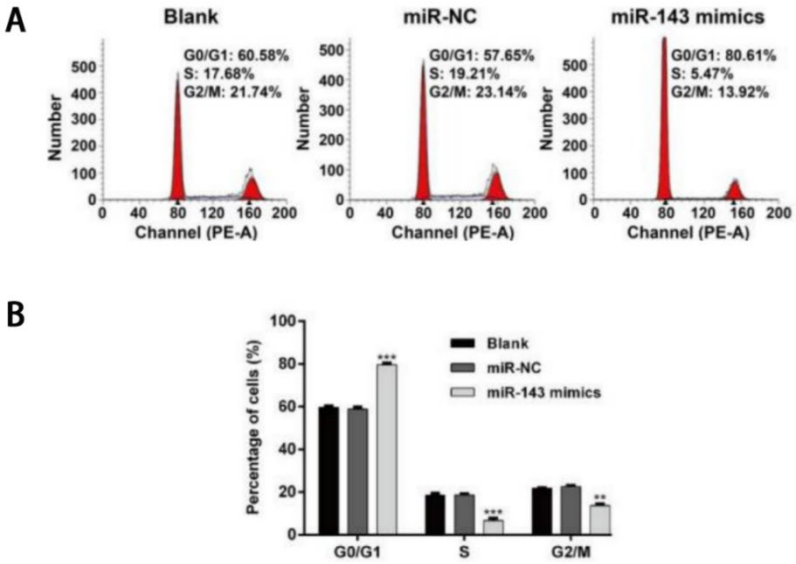

Figure 4: Effect of miR-143 mimics on CAL-27 cell cycle progression.

3.5 miR-143 Inhibits the Migration and Invasion of CAL-27 Cells

The wound healing assay (Figure 5A) demonstrated a significant delay in scratch closure in the miR-143 mimics group, indicating impaired migratory capacity. Consistently, the Transwell assay (Figure 5B) revealed a marked reduction in the number of invading cells in the same group, suggesting that miR-143 overexpression strongly inhibits the invasive potential of CAL-27 cells.

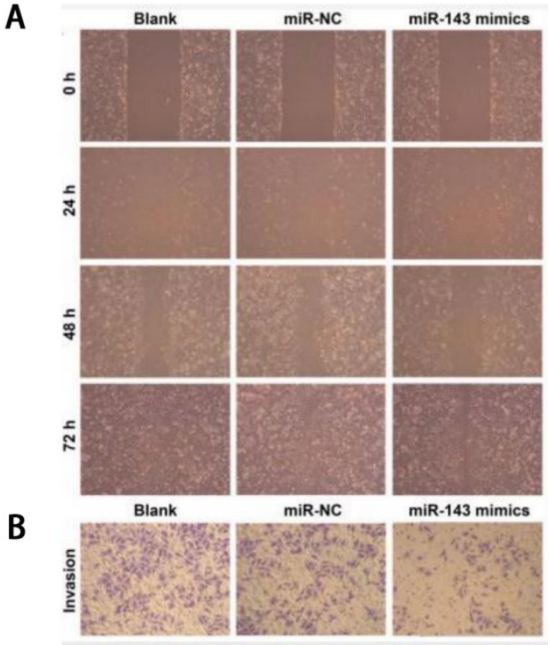

Figure 5: Effect of miR-143 mimics on invasion and migration of CAL-27 cells. (A) Scratch assay; (B) Transwell assay.

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3.6 miR-143 Suppresses Xenograft Tumor Growth

In the BALB/c nude mouse xenograft model, tumor morphology and volume measurements (Figure 6) showed that tumors formed in the miR-143 mimics group were significantly smaller than those in the miR-NC and blank control groups ($P < 0.001$), indicating that miR-143 overexpression effectively inhibits the in vivo growth of OSCC cells.

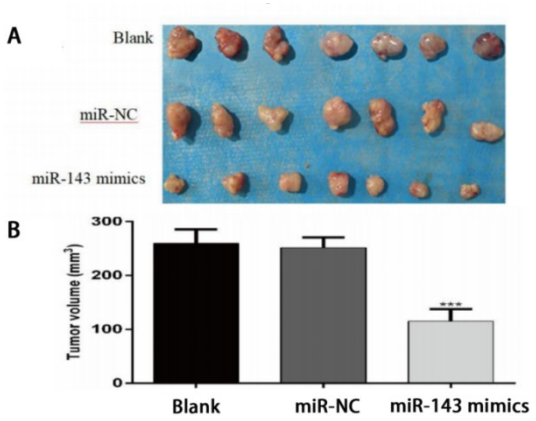

Figure 6: The volume of tumor grafts in nude mice of all groups. (A) Subcutaneous neoplasms of nude mice in each group were photographed; (B) Statistical analysis of subcutaneous tumor volume of various nude mice.

3.7 miR-143 Regulates the Expression of Proteins Related to Proliferation and Metastasis in CAL-27 Cells

Western blot analysis (Figure 7) revealed that the expression levels of CDK2, p-AKT, p-STAT3, and p-p65 were markedly reduced, whereas E-cadherin expression was significantly increased in the miR-143 mimics group. These changes were consistent with cell cycle arrest and reduced migratory capacity.

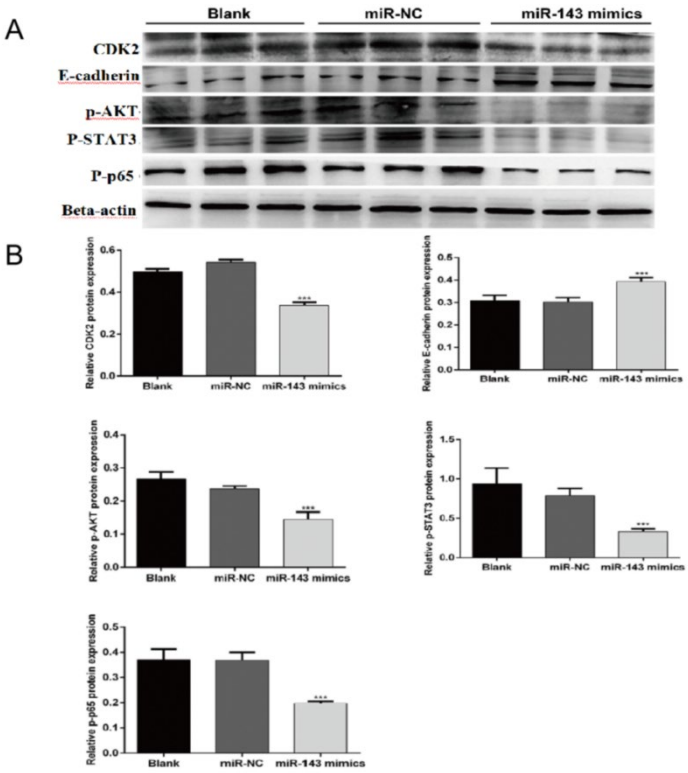

Figure 7: Effects of miR-143 on the expression of CDK2, E-cadherin, p-AKT, p-STAT3, and p-p65.

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3.8 miR-143 Modulates mRNA Expression of Related Signaling Pathways

qRT-PCR analysis (Figure 8) further confirmed that mRNA levels of CDK2, STAT3, and NF-κB were significantly decreased, whereas E-cadherin mRNA expression was upregulated in the miR-143 mimics group. These findings support the notion that miR-143 inhibits OSCC cell proliferation and migration by modulating the AKT/STAT3/NF-κB signaling pathway.

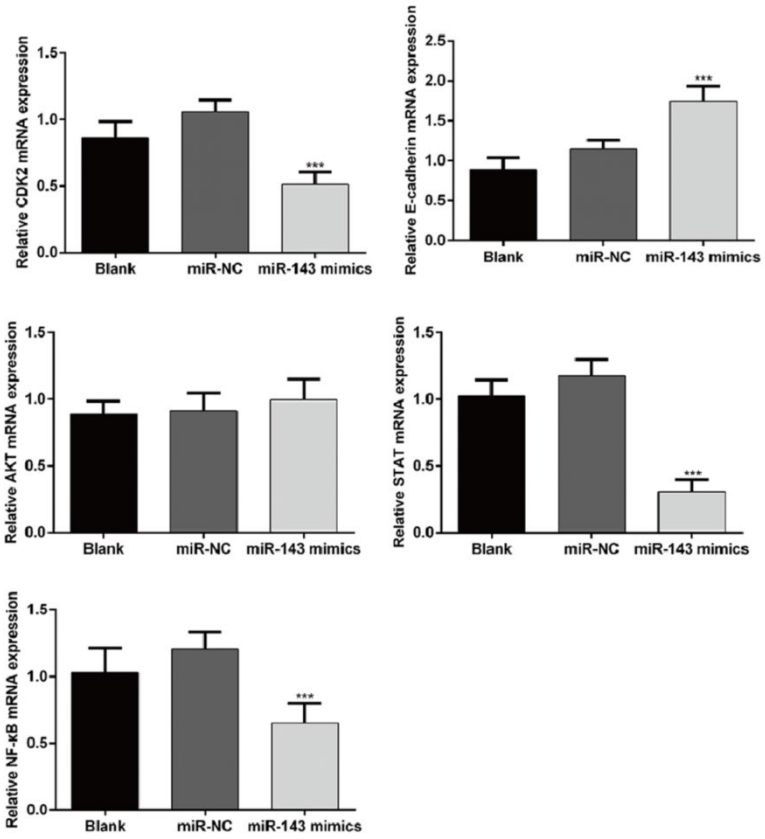

Figure 8: Effects of miR-143 on mRNA expression of CDK2, STAT3, NF-κB, and E-cadherin.

4. Discussion

This study systematically investigated the biological functions of miR-143 in OSCC and explored its potential molecular mechanisms. In vitro experiments demonstrated that miR-143 overexpression significantly suppressed OSCC cell proliferation, migration, invasion, and colony formation, and also induced cell cycle arrest. These antitumor effects were further validated in vivo using a xenograft mouse model, where miR-143 overexpression markedly inhibited tumor growth. At the molecular level, miR-143 upregulated E-cadherin, a key inhibitor of epithelial-mesenchymal transition(EMT), and downregulated CDK2, a critical cell cycle regulator. Moreover, it reduced the phosphorylation levels of AKT, STAT3, and NF-κB, thereby attenuating the activation of these oncogenic pathways. Collectively, these findings suggest that miR-143 functions as a tumor suppressor in OSCC through coordinated regulation of EMT, cell cycle, and multiple signaling pathways.

OSCC is the most common type of oral cancer worldwide, characterized by high incidence, frequent metastasis, high recurrence rates, and a generally poor prognosis[1]. Although diagnostic and therapeutic techniques have advanced in recent years, late-stage detection and tumor metastasis remain the primary causes of mortality[16]. Therefore, investigating the molecular mechanisms underlying OSCC is critical for discovering potential biomarkers and therapeutic targets.

MiRNAs, which are highly conserved across species, regulate various biological processes, including tumorigenesis, metastasis, and apoptosis[17]. Numerous studies have confirmed that many cancers display distinct and differential miRNA expression profiles, providing valuable insights for cancer diagnosis and prognosis[18]. Among these, miR-143 has been identified as a tumor-suppressive

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miRNA, frequently downregulated in malignancies such as lung, colon, and nasopharyngeal cancers[19-21]. It has been implicated in the regulation of cellular processes such as proliferation, migration, invasion, and apoptosis. The role of miR-143 in OSCC has also drawn increasing attention. Bufalino et al. reported that miR-143 downregulation is associated with activin overexpression, which enhances OSCC cell proliferation and invasiveness[22]. Similarly, Sun et al. showed that overexpression of miR-143 in oral cancer cell lines promotes apoptosis and induces significant G1-phase cell cycle arrest[15]. Consistent with these findings, our study demonstrated that miR-143 is downregulated in CAL-27 OSCC cells. Overexpression of miR-143 significantly inhibited cell proliferation, colony formation, migration, and invasion, and caused G0/G1 cell cycle arrest. Moreover, xenograft experiments in nude mice further confirmed that miR-143 suppresses in vivo tumor growth, highlighting its potential as a therapeutic target in OSCC.

EMT is a pivotal biological process in tumor progression, characterized by the loss of epithelial cell polarity and intercellular adhesion, leading to the transformation into migratory and invasive mesenchymal-like cells that facilitate metastasis[23]. During EMT, the breakdown of cell-cell junctions and degradation of the basement membrane endow cancer cells with the capacity to penetrate blood and lymphatic vessels, thereby promoting distant metastasis and increasing resistance to therapy[24]. E-cadherin, a hallmark EMT marker, is typically downregulated in this process, weakening intercellular adhesion and enhancing tumor cell migration and invasion[25]. In our study, overexpression of miR-143 significantly increased E-cadherin levels in CAL-27 cells, which coincided with suppressed cell migration and invasion, suggesting that miR-143 may inhibit OSCC progression by modulating EMT.

In addition, dysregulated cell cycle control is a fundamental mechanism underlying unchecked tumor cell proliferation[26]. CDK2, a key regulator of the G1/S transition and S-phase progression, is frequently aberrantly activated in various cancers, and its overexpression is closely linked to lymph node metastasis, aggressive tumor behavior, and poor prognosis[26,27]. Our findings demonstrated that miR-143 overexpression induced G0/G1 phase arrest in OSCC cells and concurrently downregulated CDK2 expression, reinforcing its inhibitory effect on cell cycle progression.

Moreover, the PI3K/AKT/mTOR signaling pathway has been extensively documented as a central driver of tumor cell proliferation, metastasis, and survival[28-30]. Within this cascade, AKT serves as a core kinase, whose phosphorylation-dependent activation contributes to tumor progression, drug resistance, and invasiveness[31,32]. Several miRNAs, such as miR-122[33] and miR-133a[34], have been shown to suppress tumor growth by directly or indirectly targeting AKT signaling. Consistent with these findings, our study revealed that miR-143 overexpression significantly suppressed AKT phosphorylation, indicating that miR-143 may exert antitumor effects in OSCC through inhibition of the PI3K/AKT pathway.

STAT3, a key transcription factor in the JAK/STAT signaling pathway, is constitutively activated in various tumor types and plays a central role in promoting oncogenic processes[35]. It induces the expression of multiple cancer-related genes and is involved in cell proliferation, metastasis, resistance to apoptosis, angiogenesis, and EMT[36]. Previous studies have shown that certain miRNAs, such as miR-148a[37] and miR-125a[38], exert antitumor effects by directly downregulating STAT3 expression. Consistent with these findings, our study demonstrated that miR-143 significantly inhibited STAT3 phosphorylation, supporting its role in suppressing OSCC progression via interference with this pathway.

NF-κB is another crucial transcription factor that regulates cell survival and inflammatory responses, and is also known to be aberrantly activated in many tumor types[39]. Its persistent activation contributes to tumor cell survival, metastasis, immune evasion, and chemoresistance[40,41]. Through transcriptional control of various downstream genes, NF-κB signaling promotes both inflammation and tumor progression[42]. In our study, miR-143 overexpression markedly reduced p65 phosphorylation levels, indicating that miR-143 may negatively regulate NF-κB signaling in OSCC.

In conclusion, this study provides compelling evidence that miR-143 functions as a tumor-suppressive microRNA in oral squamous cell carcinoma (OSCC). Overexpression of miR-143 in CAL-27 cells significantly inhibited proliferation, migration, invasion, and in vivo tumor growth. Mechanistically, miR-143 induced G0/G1 cell cycle arrest, upregulated the epithelial marker E-cadherin, and downregulated CDK2, while also suppressing the phosphorylation of AKT, STAT3, and NF-κB (p65). These findings indicate that miR-143 exerts its antitumor effects through coordinated modulation of the EMT process, cell cycle progression, and multiple oncogenic signaling pathways. Taken together, our results highlight the potential of miR-143 as a diagnostic biomarker and a promising molecular target for OSCC therapy. Future research should focus on the identification of its

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direct downstream targets and the development of miR-143-based delivery systems, such as lipid nanoparticles, to enable its clinical application as a novel, precise therapeutic strategy for OSCC.

5. Conclusion

Mechanistically, miR-143 may suppress OSCC progression by targeting AKT/STAT3/NF-κB pathways and promoting E-cadherin expression.

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