Article

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Identification of *KIF26B* as a Tumor Marker for Oral Squamous Cell Carcinoma

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Background: Kinesin family member 26B (*KIF26B*) has been closely linked to the occurrence and progression of various tumors. However, there is limited research on its role in oral squamous cell carcinoma (OSCC). This article aims to investigate the expression levels and mechanisms of *KIF26B* in OSCC.

Methods: Real time quantity polymerase chain reaction (RT-qPCR) and Western blot analyses were conducted to assess the expression levels of *KIF26B* in 35 OSCC specimens and their corresponding non-cancerous tissues. Overexpression and silencing of *KIF26B* were achieved in HSC6 and SCC25 cells, respectively, resulting in the establishment of *KIF26B*-overexpressing and si-*KIF26B* cell lines, designated as the *KIF26B* group and si-*KIF26B* group. Proliferation assays using 5-Ethynyl-2′-deoxyuridine (EdU) labeling and clone formation were performed to evaluate the proliferative capacity of cells in these groups. The invasive and migratory abilities of cells in the *KIF26B* and si-*KIF26B* groups were assessed using Transwell assay. Additionally, the influence of *KIF26B* on the glycogen synthase kinase (GSK)-3β/β-catenin pathway was investigated through Western blot analysis.

Results: According to the results of RT-qPCR and Western blot analyses, the expression of *KIF26B* was predominantly higher in OSCC tissues compared to normal tissues ($p < 0.01$). Overexpression of *KIF26B* notably accelerated cell migration, invasion, and proliferation ($p < 0.01$), whereas knockdown of *KIF26B* significantly inhibited these processes ($p < 0.01$). Additionally, *KIF26B* overexpression led to increased levels of active β-catenin, p-GSK-3, and c-myc ($p < 0.01$), while *KIF26B* silencing decreased the levels of these proteins ($p < 0.01$).

Conclusion: Our findings suggest that *KIF26B* may play a role in the pathogenesis and progression of OSCC as an oncogene. This study establishes a foundation for the identification of potential therapeutic targets for OSCC.

Keywords: oral squamous cell carcinoma; *KIF26B*; GSK-3β/β-catenin pathway; proliferation

Introduction

Oral squamous cell carcinoma (OSCC) comprises over 90% of oral and maxillofacial malignancies and approximately 3% of systemic malignancies [1]. With more than 350 thousand new cases reported annually, OSCC stands as the leading cause of morbidity and mortality among patients with head and neck cancer [2]. While OSCC can manifest in any part of the mucous membrane, it most frequently arises on the tongue and floor of the mouth. Currently, surgical resection serves as the primary treatment for early stage of OSCC, while advanced stage OSCC typically necessitates radiotherapy, chemotherapy, and targeted therapy [3]. Nevertheless, the prognosis for OSCC remains suboptimal, with a 5-year survival rate hovering around 50% [4]. Compounded by the unique anatomical location of oral cancer, OSCC patients often experience oral dysfunction such as loose teeth and facial nerve damage, significantly diminishing quality of life of patients [5]. Therefore, the quest for novel therapeutic approaches to address OSCC has emerged as a pressing clinical concern.

The kinesin superfamily proteins (KIFs) constitute a diverse molecular motor protein superfamily present widely in eukaryotic cells. These proteins facilitate the transportation of various membranous organelles, protein complexes, and mRNA complexes to cellular locations by binding to microtubules or adenosine triphosphate (ATP) [6]. Crucial to the normal functioning of organisms, KIFs participate in numerous physiological processes including cell mitosis, signal transduction, development of mature neurons, formation of brain memory, and morphogenesis of the urinary system [7,8]. An expanding body of research underscores the close association between KIFs and the malignancy of various tumors. For instance, Li *et al.* [9] demonstrated that the downregulation of eight types of KIFs (KIF14, KIF2C, KIF10, KIF11, KIF18B, KIF23, KIF4A and KIF20A) effectively inhibited the growth of hepatocellular carcinoma cells.

Kinesin family member 26B (*KIF26B*) is located on chromosome 1 (1q44) and consists of 2108 amino acids, with a molecular weight of approximately 223.8 kDa. Recent study has highlighted the association between *KIF26B*

and various tumors [10]. Zhang *et al*. [11] demonstrated that *KIF26B* acts as novel oncogene, promoting the growth and metastasis of gastric cancer by stimulating vascular endothelial growth factor. Moreover, *KIF26B* has been implicated in driving breast cancer progression through the regulation of cyclin-dependent kinase 4, cyclin D1, and c-Myc [12]. Utilizing data from CPTAC, GEO and TCGA databases, Sun *et al*. [13] observed significantly higher gene expression levels of *KIF26B* in 23 types of tumor tissues compared to normal tissues, including head and neck squamous cell carcinoma. Nonetheless, the expression pattern of *KIF26B* in OSCC and its impact on OSCC progression remain unexplored.

The aim of this study was to explore the biological role of *KIF26B* in OSCC. Initially, we assessed the expression of *KIF26B* in OSCC tissues, followed by an investigation into its impact on cell proliferation, migration, invasion, and the proteins involved in the glycogen synthase kinase (GSK)-3β/β-catenin pathway. Our findings offer new insights into the potential for early diagnosis and targeted therapy of OSCC.

Materials and Methods

Tissue Specimen

The 35 cases of OSCC tissues and 35 cases of adjacent normal tissues utilized in this study were obtained from OSCC patients admitted to our hospital. Upon isolation, the tissues were promptly flash-frozen in liquid nitrogen and stored at –80 °C. Informed consent forms were signed by all patients or their family members. Inclusion criteria were as follows: (1) Patients meeting the relevant diagnostic criteria for OSCC; (2) Patients with no prior history of cancer-related treatment; (3) Patients aged 18 years or older. Exclusion criteria included: (1) Patients with a history of malignant tumors such as esophageal squamous cell carcinoma or gastric cancer; (2) Patients with severe hepatic or renal dysfunction and autoimmune deficiency diseases.

This study adheres to the principles outlined in the Declaration of Helsinki and received approval from the Medical Ethics Committee of the Third Affiliated Hospital of Southern Medical University (Approval No: 2021026).

Cell Lines

Normal human oral keratinocytes (HOK: YS1199C) and OSCC cells (SCC25: YS1748C; HSC6: YS1165C; Cal-27: YS498C; SCC-15: YS1754C) were obtained from YaJi Biological (Shanghai, China) and cultured routinely in a 5% CO_2 incubator at 37 °C. The cells were maintained in DMEM medium (11995065, Invitrogen, Carlsbad, CA, USA) supplemented with 10% FBS (10099-141, Invitrogen, Carlsbad, CA, USA). Prior to experimentation, all cell lines were subjected to mycoplasma contamination testing and short tandem repeat (STR) analysis.

Small interfering RNA specific to *KIF26B* (si-*KIF26B*: 5′-CCACCUCUUUGAGAAGGATT-3′), interfering siRNA control (*si-NC*: 5′-UUCUCCGAACGUG UCACGUTTTT-3′), pcDNA3.1-*KIF26B* (*KIF26B* vector), and plasmid control (vector-NC) were synthesized by GenePharm (Shanghai, China). Routine transfection was performed with Lipofectamine 3000 (L3000075, Invitrogen, Carlsbad, CA, USA). After 48 h, the efficacy of transfection was detected by Western blot assay.

RNA Extraction and Real Time Quantity Polymerase Chain Reaction (RT-qPCR) Detection

Cell disruption was performed using Trizol (15596-018, Thermo Fisher Scientific, Waltham, MA, USA). Subsequently, chloroform and isopropyl alcohol were added, and the supernatant was discarded after centrifugation at 4 °C. The concentration of RNA was determined using Nanodrop, ensuring that the OD260/280 value of qualified RNA fell within the range of 1.8–2.0. Next, RNA was reverse-transcribed into cDNA using the Transcript First Strand cDNA Synthesis Kit (04896866001, Roche, Basel, Switzerland). PCR was then conducted on a 7500 Fast Real-Time System using SYBR Green reagent (HY-K0521, MedChemExpress, Princeton, NJ, USA). The primer sequences used were as follows: *KIF26B* forward: 5′-GCGTCGGTGGAACCTTTAGA-3′, reverse: 5′-GCAGACTTCATTCACCCCGT-3′; glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) forward: 5′-GGAGCGAGATCCCTCCAAAAT-3′, reverse: 5′-GGCTGTTGTCATACTTCTCATGG-3′. The relative quantification of *KIF26B* expression was normalized using the $2^{-\Delta\Delta CT}$ method.

Western Blot Assay

The transfected OSCC cells were centrifuged with RIPA lysis buffer (20101ES60, Yi Sheng Biotechnology, Shanghai, China) to extract total protein. Following SDS-PAGE gel electrophoresis, the proteins were transferred to a PVDF membrane using the semi-dry transfer method. The membrane was then blocked with 5% skim milk powder for 2 hours, followed by overnight incubation with primary antibodies (anti-*KIF26B*: 17422, 1:1000, Proteintech, Rosemont, IL, USA; anti-p-GSK-3β: sc-373800, Santa Cruz, CA, USA; anti-GSK-3β: sc-7291, 1:200, Santa Cruz, CA, USA; anti-β-catenin: 9561, Cell Signaling; anti-c-myc: 10828, 1:2000, Proteintech, Rosemont, IL, USA; anti-GAPDH: 10494, 1:5000, Proteintech, Rosemont, IL, USA). Subsequently, the membrane was incubated with the corresponding secondary antibody for 1 hour, followed by detection using ECL reagent (D003, R&S Biotechnology, Shanghai, China) for chemiluminescence. The gray values were analyzed using ImageJ 5.0 software (National Institutes of Health, New York, NY, USA).

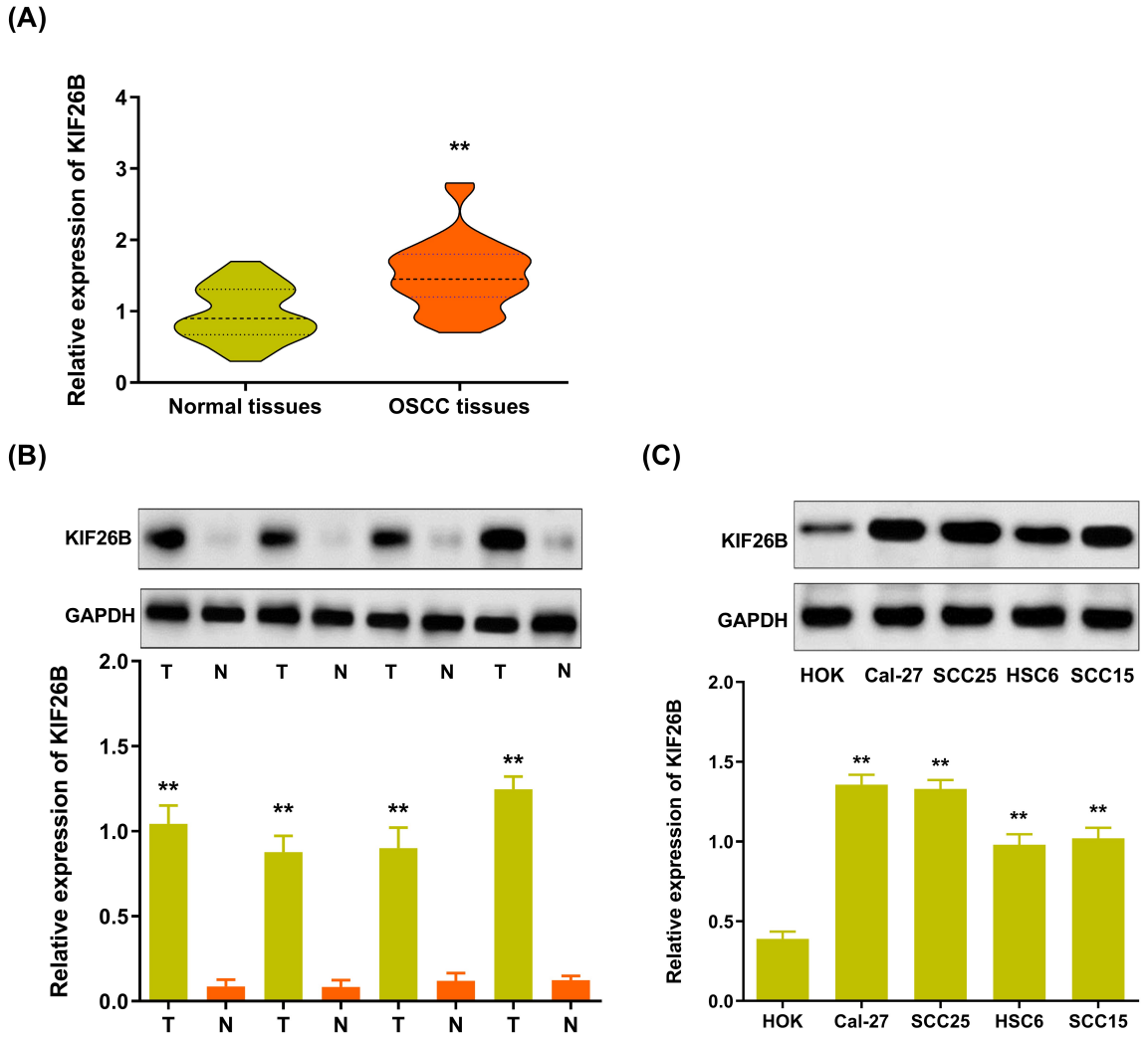

Fig. 1. *KIF26B* expression level in OSCC. (A) RT-qPCR showed the expression of *KIF26B* in OSCC tissues (n = 35). (B) The protein expression of *KIF26B* in OSCC tissues by Western blot analysis (n = 4) (N: normal tissues, T: OSCC tissues). (C) The protein expression of *KIF26B* in HOK, SCC15, SCC25, Cal27 and HSC6 cells (n = 3). $^{**}p < 0.01$. *KIF26B*, kinesin family member 26B; OSCC, oral squamous cell carcinoma; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; RT-qPCR, real time quantity polymerase chain reaction.

5-Ethynyl-2′-deoxyuridine (EdU) Test

A total of 2×10^4 cells were seeded in each well of a 24-well plate. Following transfection for 48 hours, 50 µmol/L 5-Ethynyl-2'-deoxyuridine (EdU) (C0081L, Beyotime, Shanghai, China) was added and the cells were cultured for an additional 2 hours. Subsequently, the cells were fixed with 4% formaldehyde for 30 minutes, followed by glycine (300 µL) treatment for decolorization. After incubation with 5% Triton X-100 (E-IR-R122, Elabscience, Wuhan, China) for 20 minutes, Hoechst 33342 (CC1141, G-Clone, Beijing, China) was added. The percentage of EdU-positive cells was quantified using fluorescence microscopy (Olympus, CKX41, Tokyo, Japan).

Transwell Assay

For the invasion assay, Matrigel was applied to coat the Transwell basement membrane. Following digestion and re-suspension, 500 µL of 10% FBS medium was added to the lower chamber. OSCC cells (4×10^5 cells/mL) were then added to the upper chamber. Subsequently, 4% paraformaldehyde (PN4204, G-Clone, Beijing, China) was used for fixation, and crystal violet (CS5417, G-Clone, Beijing, China) was applied for staining. After cleaning and drying, the cells that had penetrated the membrane were observed under 200× magnification.

For the cell migration assay, the procedure was similar to the invasion assay with the exception of Matrigel being absent in the upper chamber and the number of inoculated cells being halved.

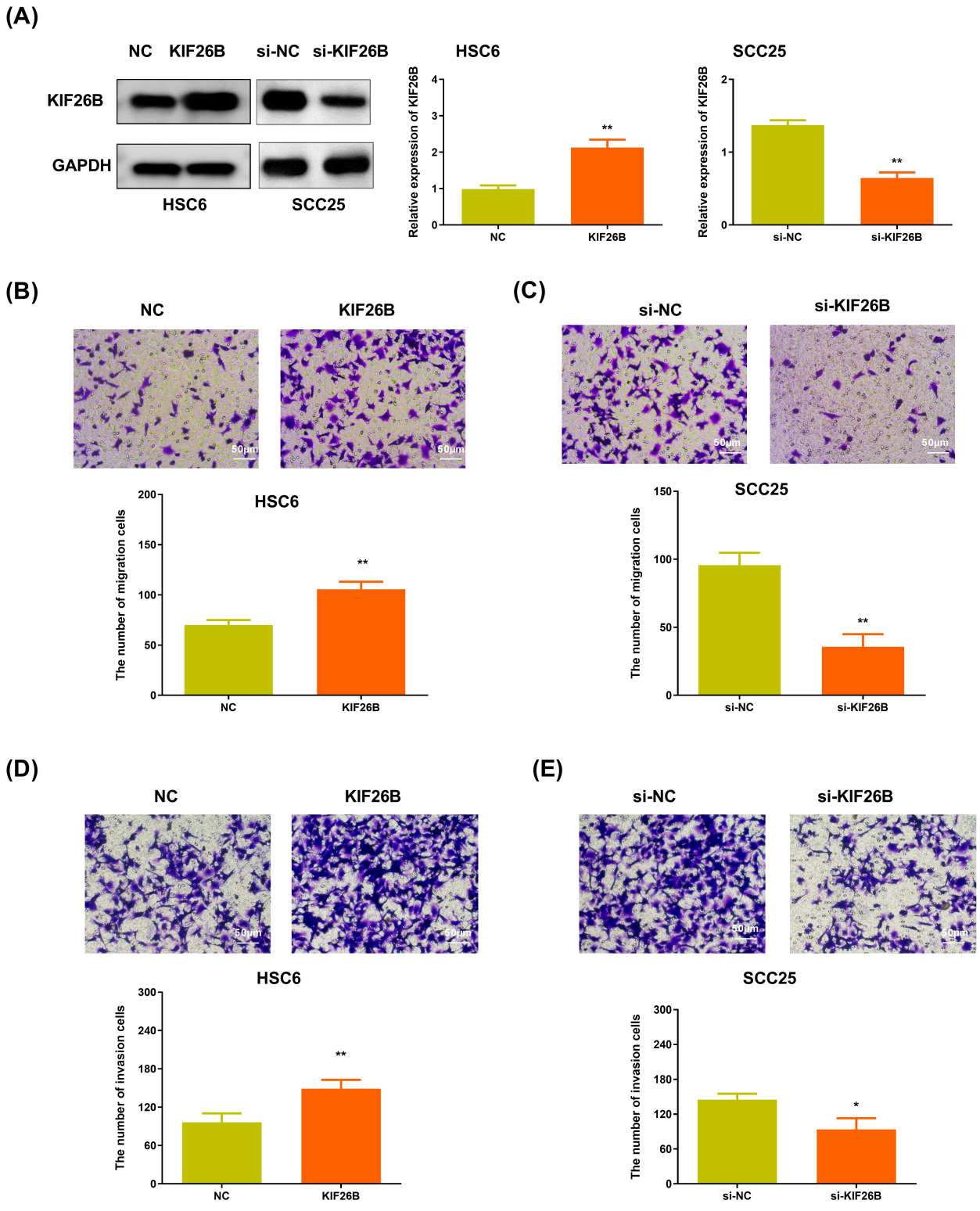

Fig. 2. Impact of *KIF26B* on invasive and migrated ability in OSCC. (A) *KIF26B* was overexpressed in HSC6 cells, and knocked down in SCC25 cells (n = 3). (B) *KIF26B* overexpression enhanced the migration ability (n = 3). (C) *KIF26B* silencing suppressed the migration ability (n = 3). (D) *KIF26B* overexpression enhanced the invasion ability (n = 3). (E) *KIF26B* silencing suppressed the invasion ability (n = 3). *$p < 0.05$, **$p < 0.01$.

Colony Formation Detection

OSCC cells (1×10^3) from each group were seeded in petri dishes. Following 2 weeks of cell culture, the culture medium was discarded. The cells were then fixed in 10% methanol for 30 minutes and stained with 1% crystal violet for 10 minutes. The number of cloned cells was observed and counted under a microscope (DM750, Leica, Heidelberg, Germany).

Statistical Analysis

Statistical analysis was conducted using SPSS 26.0 (IBM, Armonk, NY, USA) and GraphPad Prism 9 software (GraphPad Software Inc., La Jolla, CA, USA). All data are presented as mean ± SD. Differences between two groups were assessed using the *t*-test, while comparisons among multiple groups were made using one-way analysis of variance (ANOVA) followed by Tukey's test for post-hoc analysis. Statistical significance was defined as a *p*-value less than 0.05.

Results

Expression Level of KIF26B in OSCC

Real time quantity polymerase chain reaction (RT-qPCR) analysis demonstrated a significant increase in the expression of *KIF26B* in OSCC tissues compared to normal adjacent tissues ($p < 0.01$, Fig. 1A). Western blot analysis further confirmed elevated protein levels of *KIF26B* in OSCC tissues relative to normal tissues ($p < 0.01$, Fig. 1B). Additionally, compared to HOK cells, SCC15, SCC25, Cal27, and HSC6 cells exhibited higher expression levels of *KIF26B* ($p < 0.01$, Fig. 1C). These findings suggest that *KIF26B* may indeed contribute to the progression of OSCC.

Impact of KIF26B on Invasive and Migrated Ability in OSCC

To further elucidate the role of *KIF26B* in OSCC, we modulated its expression by overexpressing *KIF26*B in HSC6 cells and knocking down its expression in SCC25 cells. The efficacy of transfection was confirmed by Western blot analysis ($p < 0.01$, Fig. 2A). Subsequently, we evaluated the impact of *KIF26B* on the invasive and migratory capabilities of OSCC cells using Transwell assay. Compared to control cells, overexpression of *KIF26B* significantly accelerated the migration rate ($p < 0.01$, Fig. 2B), whereas reduced expression of *KIF26B* markedly inhibited migration ($p < 0.01$, Fig. 2C). Additionally, overexpression of *KIF26B* enhanced invasion ability ($p < 0.01$, Fig. 2D), while knockdown of *KIF26B* attenuated invasion capability ($p < 0.05$, Fig. 2E). These results underscore the contributory role of *KIF26B* in promoting the invasive and migratory potential of OSCC cells.

Effect of KIF26B on Proliferative Ability in OSCC

The number of colonies formed by *KIF26B*-overexpressing cells was significantly increased ($p < 0.01$, Fig. 3A), whereas *KIF26B* knockdown exerted an inhibitory effect ($p < 0.01$, Fig. 3B). Furthermore, the results of the EdU experiment revealed a marked increase in the proportion of EdU-positive cells upon *KIF26B* overexpression ($p < 0.01$, Fig. 3C), while this proportion significantly decreased following *KIF26B* knockdown ($p < 0.01$, Fig. 3D). These findings confirm that *KIF26B* enhances the proliferative ability of OSCC cells.

KIF26B Enforced the Progression of OSCC Cells via the Regulation of GSK-3β/β-Catenin Pathway

Subsequently, we investigated the effect of *KIF26B* on the GSK-3β/β-catenin pathway in OSCC cells using Western blot analysis. *KIF26B* overexpression led to an increase in the expression of active β-catenin, p-GSK-3β, and c-myc ($p < 0.01$, Fig. 4A), while *KIF26B* silencing resulted in a decrease in the expression of these proteins ($p < 0.01$, Fig. 4B). These results suggest that *KIF26B* may promote OSCC progression through the activation of the GSK-3β/β-catenin pathway.

Discussion

Dysfunction of KIFs often affects tumor progression, and is closely associated with tumor prognosis. In recent years, 45 KIFs have been identified in human and mouse genomes, with many showing significant relevance to cancer processes. For example, KIF4 serves as an oncogene in gastric cancer [14], colorectal cancer [15], and prostate cancer [16]. Similarly, KIF20B is notably overexpressed in tongue cancer, and its knockdown impedes cancer cell proliferation [17]. Among these, *KIF26B*, a member of Kinesin11 family, has been linked to the malignant progression of various tumors [13]. In lung cancer, *KIF26B* is upregulated and exerts a tumor promoting effect in lung cancer [18]. In colon cancer, elevated *KIF26B* expression correlates with increased tumor immune invasion and poorer prognosis [19]. Additionally, in laryngeal adenocarcinoma, the *KIF26B* gene is positively correlated with tumor progression and stage [20]. Given this context, we sought to investigate the potential role of *KIF26B* in oral cancer.

Through Western blot and RT-qPCR analyses, we observed significantly higher expression of *KIF26B* in OSCC tissues compared to adjacent normal tissues. These findings suggest that aberrant expression of *KIF26B* may indeed influence the progression of OSCC.

In our study, we further elucidated the specific mechanism underlying the impact of *KIF26B* on OSCC cell progression. Through the construction of *KIF26B*-overexpressing and -silencing cell lines in HSC6 and SCC25 cells, respectively, we observed that overexpression of *KIF26B* cells enhanced the migratory, invasive, and

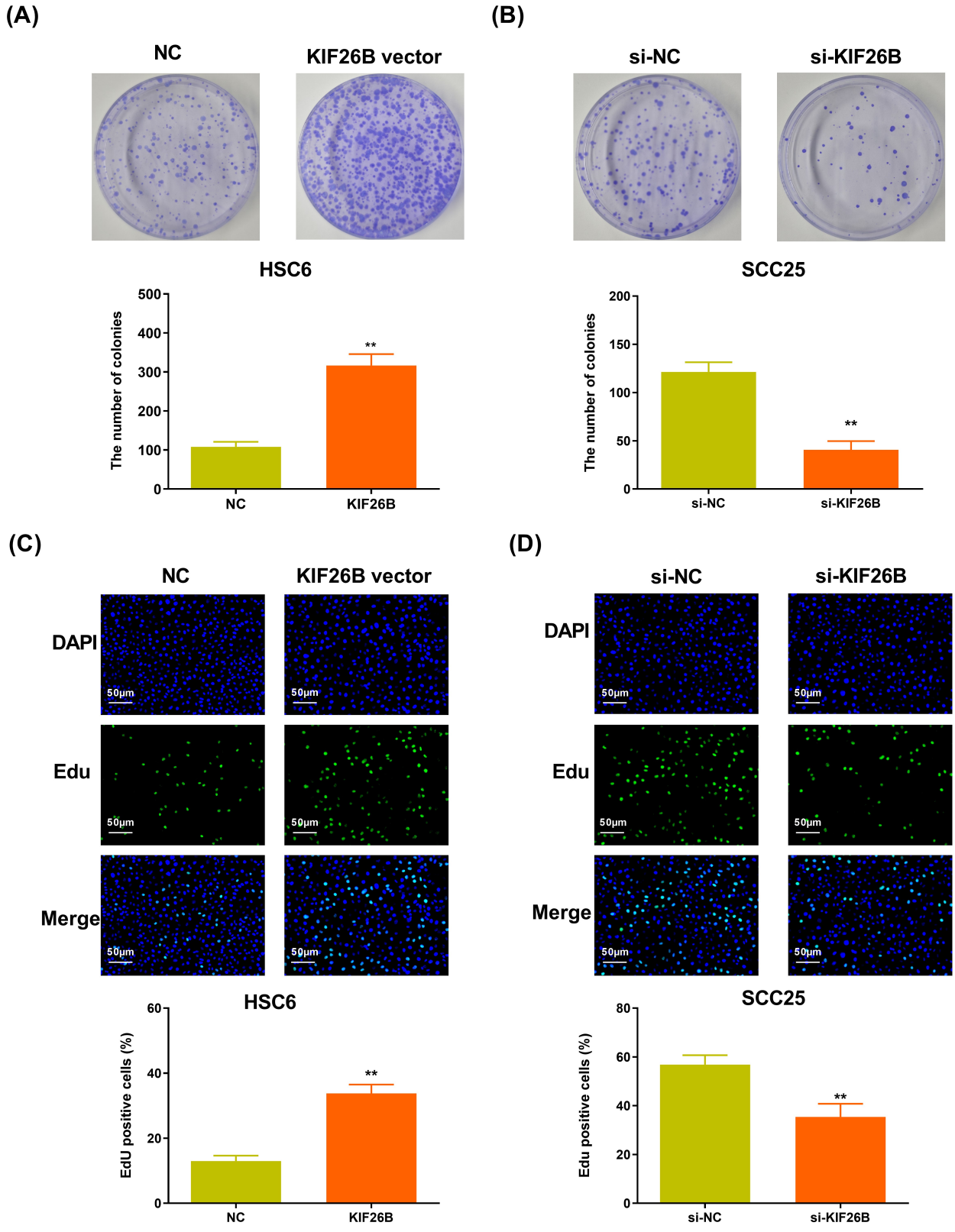

Fig. 3. Effect of *KIF26B* on proliferative ability in OSCC. (A) *KIF26B* overexpression increased the number of colonies (n = 3). (B) *KIF26B* silencing decreased the number of colonies (n = 3). (C) The proportion of EdU-positive cells was increased after overexpressing *KIF26B* (n = 3). (D) The proportion of EdU-positive cells was reduced after knocking down *KIF26B* (n = 3). $^{**}p < 0.01$. EdU, 5-Ethynyl-2′-deoxyuridine; DAPI, 4,6-diamino-2-phenyl indole.

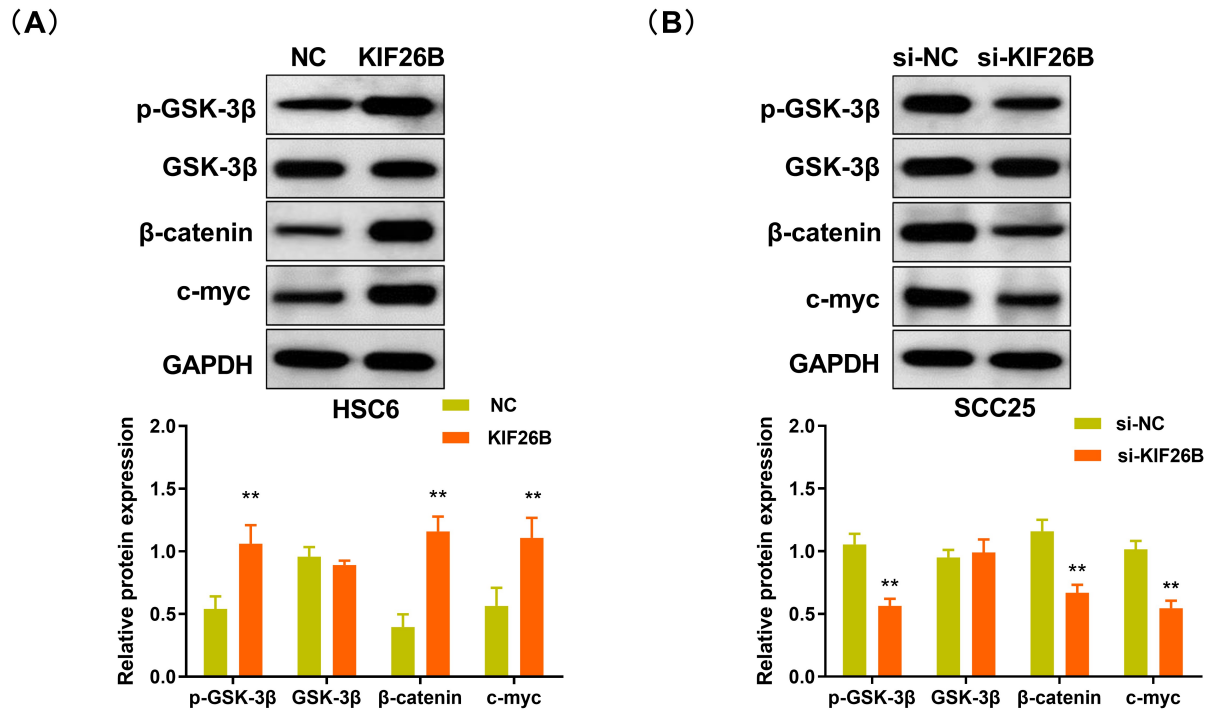

Fig. 4. *KIF26B* enforced the progression of OSCC cells via the regulation of glycogen synthase kinase (GSK)-3β/β-catenin pathway. (A) *KIF26B* overexpression increased the expression of c-myc, active β-catenin, and p-GSK-3β (n = 3). (B) *KIF26B* silencing restrained the expression of active β-catenin, p-GSK-3β, and c-myc (n = 3). $^{**}p < 0.01$.

proliferative capabilities of OSCC cells, while silencing of *KIF26B* cells led to a decrease in these abilities. Our findings align with previous studies investigating the role of *KIF26B* in other cancer types. For instance, Gu *et al*. [21], reported that *KIF26B* silencing impairs breast cancer cell proliferation, invasion and migration.

Similarly, in ovarian cancer, up-regulated expression of *KIF26B* promotes cell migration and proliferation, and higher levels of *KIF26B* expression are associated with a poorer prognosis [22]. Additionally, *KIF26B* silencing has been shown to significantly suppress the growth and migratory ability of medulloblastoma cells by affecting the phosphatidylinositol 3 kinase/protein kinase B (PI3K/AKT) pathway [23]. Combining our study with previous studies, *KIF26B* also has a cancer-promoting effect in OSCC.

The occurrence and progression of OSCC involve dysregulation of multiple signaling pathways. Among these, glycogen synthase kinase 3 (GSK-3) serves as a hub for various signaling cascades, including the nuclear factor kappa B (NF-κB) pathway, Wingless and INT-1 (Wnt)/β-catenin pathway [24,25]. As a pivotal component in the Wnt/β-catenin signaling pathway, GSK-3β can directly regulate the stability of β-catenin protein [26].

In our study, we sought to elucidate the impact of *KIF26B* on GSK-3β/β-catenin pathway. Our Western blot results revealed that overexpression of *KIF26B* led to increased levels of active β-catenin, p-GSK-3 and c-myc, whereas *KIF26B* silencing exerted the opposite effect. These findings are consistent with previous research demonstrating that inhibition of *KIF26B* suppresses the progression of non-small cell lung cancer through modulation of the AKT/GSK-3β/β-catenin pathway [18].

Herein, we conclude that *KIF26B* may influence OSCC progression through GSK-3β/β-catenin pathway. However, this study only conducted a preliminary investigation on *KIF26B*, and there was a lack of immunohistochemistry (IHC) or immunofluorescence (IF) staining of oral cancer tissue sections to demonstrate the expression of *KIF26B*. Furthermore, research on the impact of *KIF26B* on tumor growth *in vivo* is lacking. Additionally, the relationship between *KIF26B* and genes associated with oral cancer cell progression requires further investigation.

Conclusion

In this study, we presented evidence indicating that *KIF26B* is overexpressed in OSCC. Moreover, we demonstrated *in vitro* that *KIF26B* plays a significant role in OSCC metastasis and proliferation by activating the GSK-3β/β-catenin pathway. Therefore, we hypothesize that *KIF26B* serves as a novel oncogene in OSCC and could potentially serve as a valuable prognostic biomarker and therapeutic target for the disease.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

QL and XZ contributed to the conception of the study. QL and XZ contributed significantly to the data analysis and study preparation. XZ performed the data analyses and wrote the study. YT helped perform the analysis with constructive discussions. All authors have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved the final version of the manuscript.

Ethics Approval and Consent to Participate

All patients or family members have signed informed consent forms. This study adheres to the principles outlined in the Declaration of Helsinki and received approval from the Medical Ethics Committee of the Third Affiliated Hospital of Southern Medical University (2021026).

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Conflict of Interest

The authors declare no conflict of interest.

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