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FOXM1 Upregulates CEP55 in a PI3K/Akt-Dependent Manner to Promote Oral Squamous Cell Carcinoma Metastasis

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Background: Oral squamous cell carcinoma (OSCC) is characterized by high aggressiveness and poor prognosis due to frequent metastasis. Forkhead box M1 (FOXM1) acts as a potent oncogene in various cancers; however, the downstream molecular mechanisms by which FOXM1 drives OSCC metastasis remain unclear. This study aimed to investigate the regulatory relationship between FOXM1 and Centrosomal protein 55 (CEP55), and the involvement of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway in OSCC progression.
Methods: The clinical relevance of FOXM1 and CEP55 was first validated using RNA sequencing (RNA-seq) data from the Cancer Genome Atlas Head and Neck Squamous Cell Carcinoma (TCGA-HNSC) dataset. For gene regulation analysis, *FOXM1* and *CEP55* expression in OSCC cell lines (CAL27 and SCC-9) was manipulated using small interfering RNAs (siRNAs) or overexpression plasmids, and regulatory relationships were assessed by quantitative reverse transcription PCR (qRT-PCR) and Western blotting. For functional assays, cell migration and invasion were assessed using wound healing and Transwell assays under serum-free conditions. Mechanistic studies examined the involvement of the PI3K/Akt pathway using SC79 as a specific Akt activator, and rescue experiments were performed by co-transfection of the CEP55 overexpression plasmid.
Results: Bioinformatics analysis revealed that both FOXM1 and CEP55 were significantly overexpressed in head and neck squamous cell carcinoma (HNSCC) tumor tissues compared to normal tissues ($p < 2 \times 10^{-16}$ for both), with a strong positive correlation between their expression levels (Spearman r = 0.754). We found that *FOXM1* positively regulated *CEP55* expression at both mRNA and protein levels ($p < 0.001$). Functionally, *FOXM1* knockdown significantly inhibited, whereas *FOXM1* overexpression promoted, the migration and invasion capabilities of OSCC cells ($p < 0.001$). Mechanistically, *FOXM1* depletion suppressed Akt phosphorylation ($p < 0.001$). Notably, pharmacological activation of Akt by SC79 successfully restored CEP55 protein abundance in FOXM1-silenced cells ($p < 0.001$), suggesting that the PI3K/Akt pathway is critical for maintaining CEP55 levels downstream of FOXM1. Furthermore, rescue experiments demonstrated that re-introduction of *CEP55* reversed the migration and invasion defects induced by *FOXM1* knockdown ($p < 0.001$).
Conclusion: Our findings indicate that FOXM1 promotes migration and invasion in OSCC cell lines by upregulating CEP55 through the PI3K/Akt signaling axis. This study highlights the FOXM1/PI3K/Akt/CEP55 network as a potential therapeutic target worthy of further *in vivo* and clinical investigation in OSCC.

Keywords: OSCC; FOXM1; CEP55; PI3K/Akt signaling; metastasis

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide, with oral squamous cell carcinoma (OSCC) being the most prevalent subtype [1]. Despite advancements in multimodal treatment strategies, including surgery, radiotherapy, and chemotherapy, the 5-year survival rate for OSCC patients has remained at approximately 50% over the past few decades [2,3]. The poor prognosis is largely attributed to the highly aggressive nature of OSCC, which frequently leads to local recurrence and distant metastasis [4,5]. Therefore, elucidating the molecular mechanisms underlying OSCC metastasis is of paramount importance for the identification of novel therapeutic targets and biomarkers.

Forkhead box M1 (FOXM1) is a member of the Forkhead box transcription factor family and is widely recognized as a master regulator of the cell cycle [6]. FOXM1 is predominantly expressed in proliferating cells and is essential for G1/S and G2/M transitions [7,8]. Beyond its physiological roles, aberrant overexpression of *FOXM1* has been observed in a wide array of human malignancies, functioning as a potent oncogene [9]. In the context of OSCC, elevated FOXM1 levels have been corre-

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lated with aggressive clinicopathological features, including lymph node metastasis and poor patient survival [10]. While FOXM1 is known to transcriptionally regulate genes involved in metastasis, such as matrix metalloproteinases (MMPs) [11], the complex signaling networks and downstream effectors by which FOXM1 drives the metastatic phenotype in OSCC remain to be fully characterized.

Centrosomal protein 55 (CEP55) is a coiled-coil protein that plays a crucial role in cytokinesis by facilitating the abscission of the midbody [12]. Under normal physiological conditions, *CEP55* expression is tightly regulated; however, it is frequently overexpressed in various cancers, where it contributes to genomic instability and aneuploidy [13,14]. A recent study suggested that CEP55 can also promote cell motility and invasion via the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway [15]. Notably, using immunohistochemistry, qPCR, and microarray analysis, Waseem *et al*. [16] demonstrated that CEP55 expression positively correlates with head and neck squamous cell carcinoma (HNSCC) progression from normal mucosa through dysplasia to carcinoma, and proposed CEP55 as a downstream biomarker of FOXM1. Previous studies in breast cancer have suggested a potential FOXM1-CEP55 regulatory link, as CEP55 expression decreases following FOXM1 knockdown in breast cancer cells and correlates with FOXM1 expression in basal-like breast carcinoma [17,18]. Nevertheless, direct functional evidence demonstrating that FOXM1 regulates CEP55 to drive metastasis phenotypes in OSCC, as well as the underlying signaling mechanisms, remains lacking.

The PI3K/Akt signaling pathway is one of the most frequently dysregulated pathways in HNSCC [19]. Hyperactivation of Akt is a key driver of epithelial-mesenchymal transition (EMT), migration, and invasion [20,21]. Emerging evidence suggests a bidirectional regulatory relationship between FOXM1 and the PI3K/Akt pathway, where FOXM1 can sustain Akt phosphorylation, which in turn stabilizes FOXM1 protein [22,23]. Given these connections, we hypothesized that FOXM1 might exert its pro-metastatic effects by upregulating CEP55 through a PI3K/Akt-dependent mechanism.

In the present study, we investigated the biological function of FOXM1 in OSCC cell lines (CAL27 and SCC-9). We examined the regulatory relationship between FOXM1 and CEP55 and utilized a pharmacological rescue approach to determine the involvement of the PI3K/Akt pathway. Our findings provide novel insights into the FOXM1/PI3K/Akt/CEP55 axis, highlighting its potential as a therapeutic target for metastatic OSCC.

Materials and Methods

Cell Culture and Treatment

Human OSCCcell lines CAL27 (CRL-2095) and SCC-9 (CRL-1629) were obtained from the American Type Culture Collection (ATCC; Manassas, VA, USA). These cells were cultured in DMEM (D6429, Sigma-Aldrich, St. Louis, MO, USA) supplemented with 10% fetal bovine serum (FBS; C0226, Beyotime, Shanghai, China) and 1% penicillin-streptomycin (C0222, Beyotime, Shanghai, China) in a humidified incubator containing 5% CO_2 at 37 °C. The cells were authenticated using Short Tandem Repeat (STR) analysis and confirmed to be free of mycoplasma.

For the PI3K/Akt pathway activation assay, cells were treated with the Akt activator SC79 (SML0749, Sigma-Aldrich, St. Louis, MO, USA). SC79 was dissolved in DMSO (ST038, Beyotime, Shanghai, China) and added to the culture medium at a final concentration of 10 µM for 24 h prior to collection. Control cells were treated with an equivalent volume of DMSO.

Cell Transfection

Small interfering RNA (siRNA) targeting *FOXM1* (si-*FOXM1*) and a negative control siRNA (si-NC) were synthesized by GenePharma (Shanghai, China). The *FOXM1* overexpression plasmid (OE-*FOXM1*), *CEP55* overexpression plasmid (OE-*CEP55*), and their corresponding empty vectors (pcDNA3.1) were purchased from GenePharma (Shanghai, China). Cells were seeded into 6-well plates and cultured until they reached 60–70% confluence. Transfection was performed using Lipofectamine3000 (L3000001, Invitrogen, Waltham, MA, USA) according to the manufacturer's instructions. The cells were harvested 48 h after transfection for subsequent RNA or protein extraction. The sequences of the siRNAs are listed in Table 1. The knockdown efficiency of both siRNA sequences was validated by qRT-PCR. si-*FOXM1*#1, which demonstrated superior knockdown efficiency, was selected for all subsequent functional experiments and is referred to as si-*FOXM1* hereafter.

Quantitative Real-Time PCR (qRT-PCR)

Total RNA was extracted from CAL27 and SCC-9 cells using the TRIzol reagent (DP424, TIANGEN, Beijing, China) following the manufacturer's protocol. RNA concentration and purity were determined using a NanoDrop spectrophotometer (OSE-260, TIANGEN, Beijing, China). Subsequently, RNA was reverse-transcribed into cDNA using the SweScript All-in-One RT SuperMix reagent Kit (G3337, Servicebio, Wuhan, China). qRT-PCR was performed using SYBR® Premix Ex Taq™ (FP205, TIANGEN, Beijing, China) on the LightCycler96 Real-Time PCR System (Roche, Mannheim, Germany). The relative expression levels of mRNA were calculated using the $2^{-\Delta\Delta Ct}$ method, with GAPDH serving as the internal control. The primer sequences used are listed in Table 2.

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Table 1. Sequences of siRNAs used in this study.

Name	Sequence (5′ to 3′)
si-*FOXM1*#1 (Sense)	5′-GGACCACUUUCCCUACUUUdTdT-3′
si-*FOXM1*#1 (Antisense)	5′-AAAGUAGGGAAAGUGGUCCdTdT-3′
si-*FOXM1*#2 (Sense)	5′-UGAAUCUGCGUUUUCACUCUCdTdT-3′
si-*FOXM1*#2 (Antisense)	5′-GAGAGUGAAAACGCAGAUUCAdTdT-3′
si-NC (Sense)	5′-UUCUCCGAACGUGUCACGUdTdT-3′
si-NC (Antisense)	5′-ACGUGACACGUUCGGAGAAdTdT-3′

siRNAs, small interfering RNAs; si-*FOXM1*, small interfering RNA targeting Forkhead box M1; si-NC, negative control siRNA.

Table 2. Primer sequences.

Primer	Sequence (5′-3′)
hum-*FOXM1*-F	GTTTAAGCAGCAGCAGAAACGAC
hum-*FOXM1*-R	TCCTCAGCTAGCAGCACCTT
hum-*CEP55*-F	GGAGGGCAGACCATTTCAGA
hum-*CEP55*-R	GGCTTCGATCCCCACTTACT
hum-*GAPDH*-F	GTGGATATTGTTGCCATCAATGACC
hum-*GAPDH*-R	GCCCCAGCCTTCTTCATGGTGGT

FOXM1, Forkhead box M1; *CEP55*, Centrosomal protein 55; *GAPDH*, glyceraldehyde-3-phosphate dehydrogenase.

Western Blotting

Total protein was extracted using RIPA lysis buffer (P0013J, Beyotime, Shanghai, China) supplemented with protease and phosphatase inhibitors (PMSF; ST506, Beyotime, Shanghai, China). Protein concentration was measured using a BCA Protein Assay Kit (P0010S, Beyotime, Shanghai, China). Equal amounts of protein (approximately 20–30 µg) were separated by 10% SDS-PAGE and transferred onto PVDF membranes (IPVH00010, Millipore, Burlington, MA, USA). After blocking with 5% non-fat milk in TBST for 1 h at room temperature, the membranes were incubated with primary antibodies overnight at 4 °C. The primary antibodies used were: anti-FOXM1 (1:1000; HA723197, HUABIO, Woburn, MA, USA), anti-CEP55 (0.2–1 µg/mL; PA5-42846, Invitrogen, Waltham, MA, USA), anti-AKT (1:1000; 10176-2-AP, Proteintech, Rosemont, IL, USA), anti-p-AKT (Ser473) (1:1000; 80455-1-RR, Proteintech, Rosemont, IL, USA), and anti-GAPDH (1:1000; TA-08, ZS Golden Bridge, Beijing, China). Subsequently, the membranes were incubated with HRP-conjugated secondary antibodies (1:2000; ZB2301/ZB-2305, ZS golden Bridge, Beijing, China) for 1 h at room temperature. Protein bands were visualized using an Enhanced Chemiluminescence (ECL; P0018S, Beyotime, Shanghai, China) kit and analyzed using ImageJ software (version 1.54b; National Institutes of Health, Bethesda, MD, USA).

Wound Healing Assay

Cell migration was assessed using a wound healing assay. Transfected cells were seeded into 6-well plates and cultured until they reached approximately 95–100% confluence. A straight scratch was created across the cell monolayer using a sterile 200 µL pipette tip. The cells were washed twice with phosphate-buffered saline (PBS) to remove cell debris and then cultured in serum-free medium. Images of the wounds were captured at 0 h and 24 h using an inverted microscope (CKX53, OLYMPUS, Tokyo, Japan). The wound closure rate was calculated as: (Width at 0 h – Width at 24 h) / Width at 0 h × 100%. For presentation purposes, all captured images were uniformly processed using a standardized, minimal pipeline. A single linear contrast adjustment (factor 1.2) was applied globally to the entire field of view. No brightness shifting, histogram stretching, sharpening, denoising, or region-specific modifications were performed. Red dashed lines indicating the original wound boundaries at 0 h were added to all panels in a consistent manner. All quantifications were performed on the unprocessed raw images.

Transwell Invasion Assay

Cell invasion capacity was evaluated using Transwell chambers (8-µm pore size; 3422, Corning, NY, USA) pre-coated with Matrigel (BD Biosciences, Franklin Lakes, NJ, USA), which was diluted 1:8 with serum-free medium. Transfected cells (5×10^4 cells) suspended in 200 µL of serum-free medium were added to the upper chamber. The lower chamber was filled with 600 µL of medium containing 10% FBS as a chemoattractant. After incubation for 24 h at 37 °C, non-invading cells on the upper surface were removed with a cotton swab. Cells that had invaded the lower surface were fixed with 4% paraformaldehyde (P0099, Beyotime, Shanghai, China) and stained with 0.1% crystal violet (G1064, Solarbio, Beijing, China). The invaded cells were photographed and counted under a microscope in five randomly selected fields.

Bioinformatics Analysis

To validate the clinical relevance of *FOXM1* and *CEP55* in a HNSCC, we analyzed RNA-seq data from The Cancer Genome Atlas (TCGA) HNSC dataset. Gene expression quantification data (TPM values generated by the STAR-Counts workflow) were downloaded using the TCGAbiolinks R package (version 1.30.0). Samples were clas-

sified as tumor or normal based on TCGA barcode annotations. Expression values were log2-transformed ($\log_2$[TPM + 1]) for visualization and statistical analysis. Differential expression between tumor and normal tissues was assessed using the Wilcoxon rank-sum test. The correlation between *FOXM1* and *CEP55* expression in tumor samples was evaluated using Spearman's rank correlation coefficient. All bioinformatics analyses were performed in R (version 4.5.2; R Foundation for Statistical Computing, Vienna, Austria).

Statistical Analysis

All statistical analyses were performed using GraphPad Prism (Version number 8.0; GraphPad Software, Boston, MA, USA) software. All experiments were repeated at least three times independently, and data are presented as mean $\pm$ standard deviation (SD). Prior to group comparisons, the normality of data distribution was assessed using the Shapiro-Wilk test, and the homogeneity of variance was evaluated using the F-test (for two-group comparisons) or the Brown-Forsythe test (for multi-group comparisons). For data that satisfied both normality and homogeneity of variance assumptions, differences between two groups were analyzed using the unpaired two-tailed Student's *t*-test. Differences among multiple groups were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. For data that did not conform to a normal distribution, such as the TCGA-HNSC gene expression data shown in **Supplementary Fig. 1**, non-parametric methods were employed. Specifically, differences between two independent groups (tumor vs. normal) were assessed using the Wilcoxon rank-sum test (Mann-Whitney U test), and the correlation between FOXM1 and CEP55 expression was evaluated using Spearman's rank correlation coefficient. Where appropriate, the Kruskal-Wallis test followed by Dunn's post hoc test was applied for multi-group comparisons of non-normally distributed data. A *p*-value of $<$0.05 was considered statistically significant.

Results

FOXM1 and CEP55 are Significantly Upregulated in HNSCC Tissues

To establish the clinical relevance of FOXM1 and CEP55 in HNSCC, we first analyzed their expression profiles using publicly available data from The Cancer Genome Atlas (TCGA). Analysis of the TCGA-HNSC dataset revealed that both *FOXM1* and *CEP55* mRNA levels were significantly elevated in tumor tissues compared to adjacent normal tissues ($p < 2 \times 10^{-16}$ for both, Wilcoxon rank-sum test; **Supplementary Fig. 1A,B**). Furthermore, Spearman correlation analysis demonstrated a strong positive correlation between *FOXM1* and *CEP55* expression in tumor samples (r = 0.754, $p < 2.2 \times 10^{-16}$; **Supplementary Fig. 1C**). These bioinformatics findings support the hypothesis that *FOXM1* and *CEP55* are co-upregulated in HNSCC and provide a rationale for investigating their functional relationship in OSCC cell lines.

FOXM1 Positively Regulates CEP55 Expression and Activates PI3K/Akt Pathway in OSCC Cells

We first validated the knockdown efficiency of two independent siRNA sequences targeting *FOXM1* in CAL27 and SCC-9 cells. Both si-*FOXM1*#1 and si-*FOXM1*#2 significantly reduced *FOXM1* mRNA expression compared to si-NC (**Supplementary Fig. 2**; $p < 0.001$). si-*FOXM1*#1 exhibited a higher knockdown efficiency and was therefore used for all subsequent experiments. To investigate the potential regulatory role of *FOXM1* in OSCC, we manipulated *FOXM1* expression in CAL27 and SCC-9 cell lines using specific siRNAs (si-*FOXM1*) and overexpression plasmids (OE-*FOXM1*). The qRT-PCR results showed that *FOXM*1 knockdown significantly decreased the mRNA levels of *CEP55*, whereas *FOXM1* overexpression markedly upregulated *CEP55* mRNA expression (Fig. 1A,B; $p < 0.001$). Consistent with the mRNA data, Western blot analysis revealed that silencing FOXM1 led to a significant reduction in CEP55 protein levels ($p < 0.001$). Furthermore, we examined the activity of the PI3K/Akt signaling pathway. The results demonstrated that FOXM1 knockdown suppressed the phosphorylation of AKT (p-Akt, Ser473; $p < 0.001$) without affecting total AKT levels. Conversely, overexpression of FOXM1 resulted in elevated levels of both CEP55 protein and p-AKT (Fig. 1C,D; $p < 0.001$). These findings suggest that FOXM1 positively regulates CEP55 and activates PI3K/Akt signaling in OSCC cells.

FOXM1 Promotes Migration and Invasion of OSCC Cells

To evaluate the biological function of FOXM1 in OSCC, we performed wound healing and Transwell invasion assays. The procedures were performed in serum-free medium, which minimizes cell division during the 24-hour observation period to exclude the potential interference of cell proliferation on migration assessment. In the wound healing assay, cells transfected with si-*FOXM1* exhibited a significantly slower wound closure rate compared to the si-NC group after 24 hours ($p < 0.001$). In contrast, *FOXM1* overexpression accelerated wound closure (Fig. 2A,C; $p < 0.001$). Similarly, the Transwell invasion assay showed that *FOXM1* knockdown significantly reduced the number of invaded cells, while *FOXM1* overexpression promoted cell invasion (Fig. 2B,D; $p < 0.001$). Collectively, these data indicate that FOXM1 acts as an oncogene by enhancing the migratory and invasive capabilities of CAL27 and SCC-9 cells.

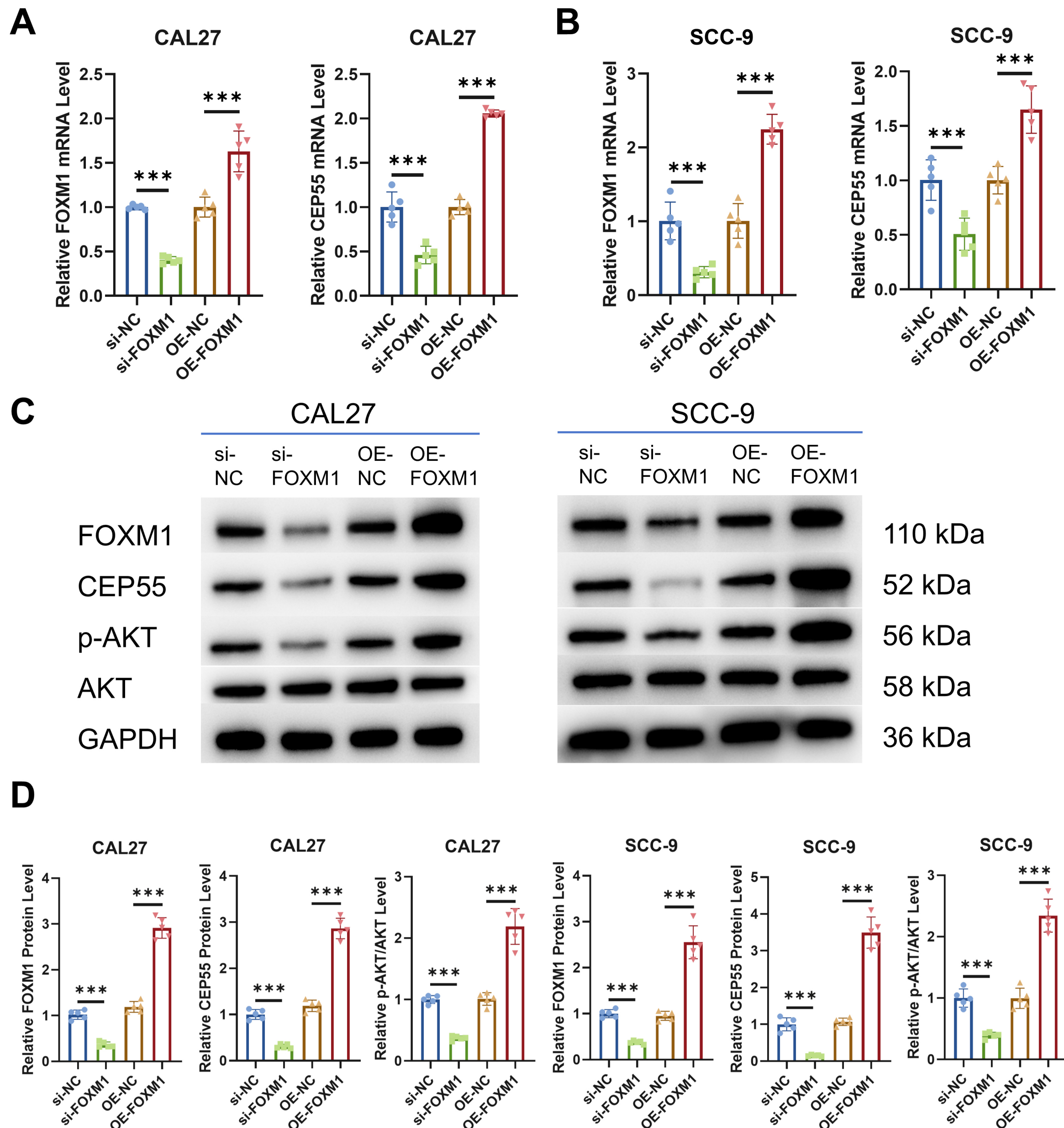

Fig. 1. FOXM1 positively regulates CEP55 expression and PI3K/Akt signaling in OSCC cells. (A,B) The mRNA expression levels of *FOXM1* and *CEP55* in CAL27 (A) and SCC-9 (B) cells transfected with si-NC, si-*FOXM1*, OE-NC, or OE-*FOXM1* were measured by qRT-PCR. (C) Western blot analysis of FOXM1, CEP55, p-AKT, and total AKT protein levels in the indicated groups. GAPDH was used as a loading control. (D) Quantitative analysis of the relative protein expression of FOXM1, CEP55, and the p-AKT/AKT ratio based on gray scale values. Data are presented as mean ± SD with individual data points (n = 5). ****p* < 0.001. FOXM1, Forkhead box M1; CEP55, Centrosomal protein 55; PI3K, phosphatidylinositol 3-kinase; OSCC, oral squamous cell carcinoma; si-NC, negative control small interfering RNA; si-*FOXM1*, small interfering RNA targeting *FOXM1*; OE-NC, negative control overexpression plasmid; OE-*FOXM1*, *FOXM1* overexpression plasmid; p-AKT, phosphorylation of AKT; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; SD, standard deviation.

Activation of PI3K/Akt Signaling Rescues FOXM1-Depletion Induced Downregulation of CEP55 Protein

To determine whether the regulation of CEP55 by FOXM1 is dependent on the PI3K/Akt pathway, we utilized SC79, a specific activator of Akt. CAL27 cells were transfected with si-*FOXM1* and subsequently treated with SC79. Western blot analysis (Fig. 3) confirmed that SC79 treatment effectively increased p-Akt levels ($p < 0.001$). Notably, while *FOXM1* knockdown suppressed CEP55 expression ($p < 0.001$), the addition of SC79 significantly restored the protein abundance of CEP55 even in the pres-

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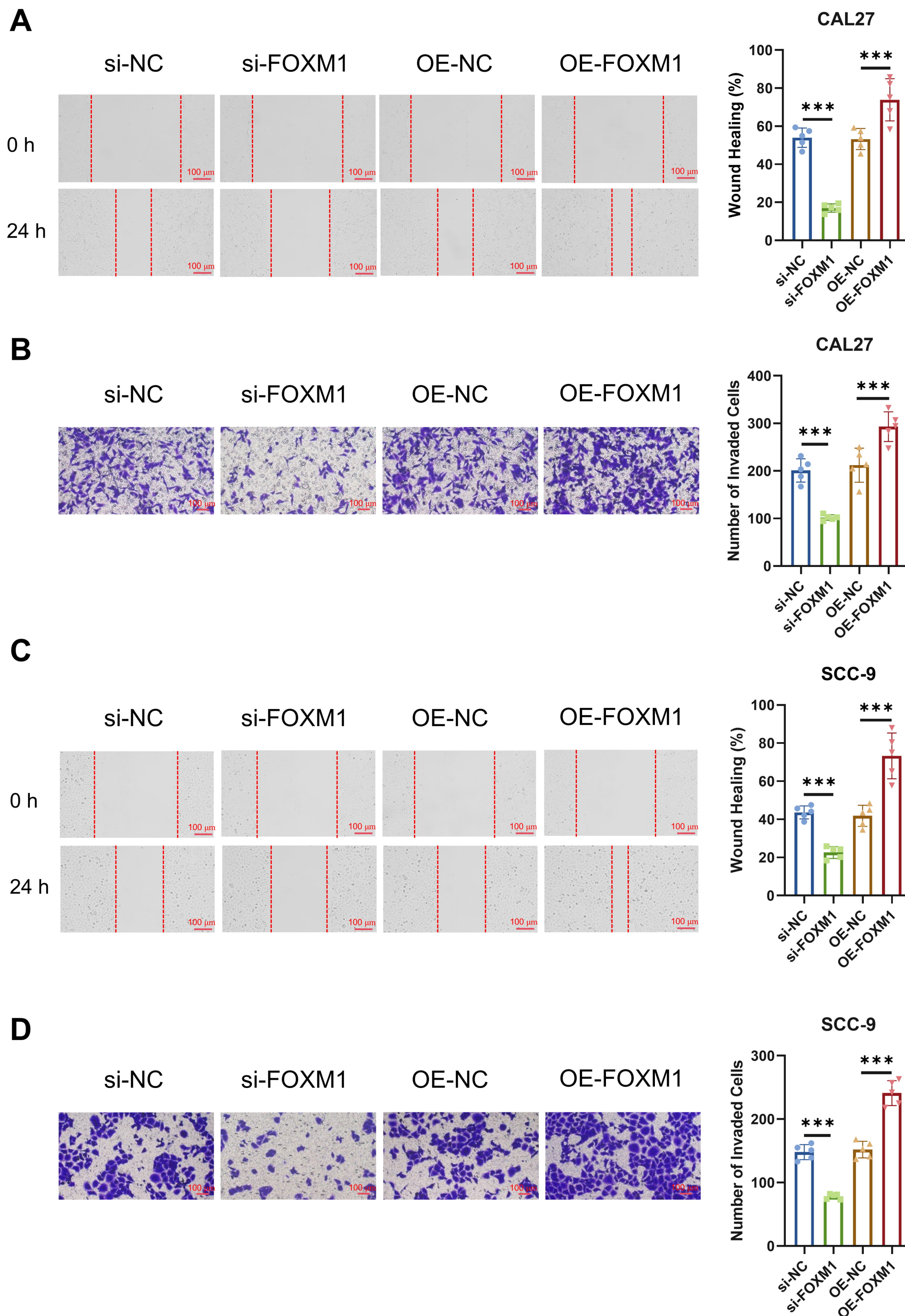

Fig. 2. FOXM1 promotes the migration and invasion abilities of CAL27 and SCC-9 cells. (A) Representative images and statistical analysis of the wound healing assay performed on CAL27 cells at 0 h and 24 h post-transfection (Scale bar = 100 μm). (B) Representative images and quantitative analysis of the Transwell invasion assay performed on CAL27 cells (Scale bar = 100 μm). (C) Representative images and statistical analysis of the wound healing assay performed on SCC-9 cells at 0 h and 24 h post-transfection (Scale bar = 100 μm). (D) Representative images and quantitative analysis of the Transwell invasion assay performed on SCC-9 cells (Scale bar = 100 μm). Data are presented as mean ± SD with individual data points (n = 5). ***$p < 0.001$. Red dashed lines indicate the original wound boundaries at 0 h and are uniformly applied to all panels. Images were uniformly adjusted for contrast (1.2× linear contrast enhancement) across the entire field of view. No selective modifications, sharpening, or histogram stretching were applied.

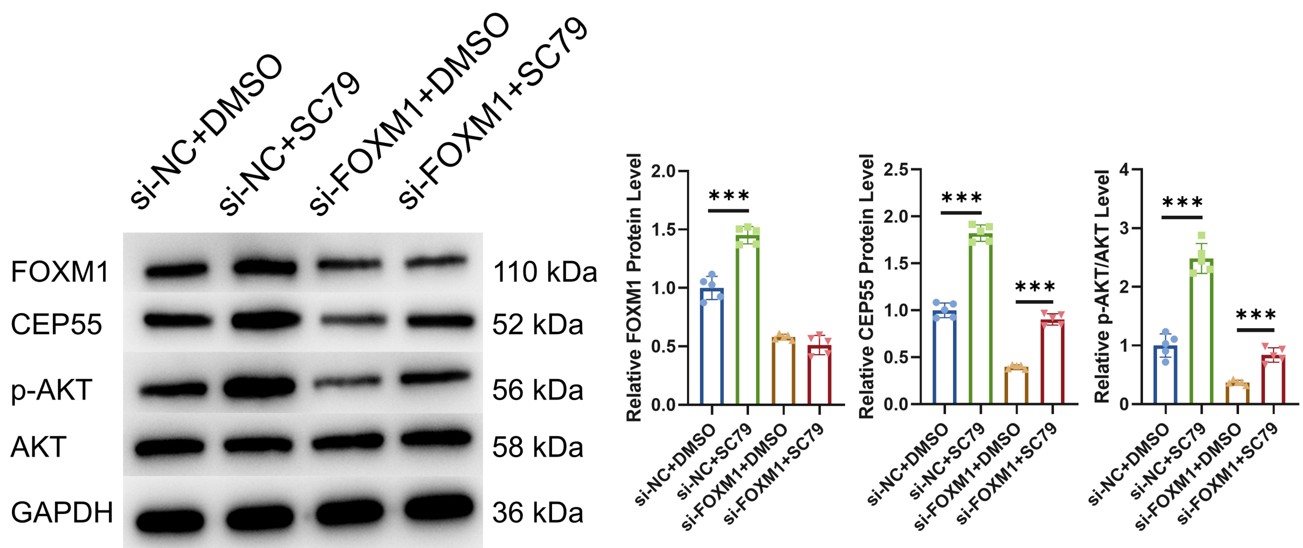

Fig. 3. Activation of Akt restores CEP55 expression in FOXM1-silenced cells. Western blot analysis of p-AKT, AKT, FOXM1, and CEP55 protein levels. CAL27 cells were transfected with si-NC or si-FOXM1 and treated with DMSO or SC79 (Akt activator). Data are presented as mean ± SD with individual data points (n = 5). ***$p < 0.001$. DMSO, dimethyl sulfoxide.

ence of *FOXM1* siRNA ($p < 0.001$). Interestingly, SC79 treatment also resulted in a modest increase in FOXM1 protein levels ($p < 0.001$), suggesting potential positive feedback from Akt to FOXM1. Nevertheless, the primary direction of signal flow in our model remains from FOXM1 to Akt to CEP55, as FOXM1 knockdown robustly suppressed both Akt phosphorylation and CEP55 expression ($p < 0.001$), whereas Akt activation alone could not fully restore FOXM1 levels to baseline. These results suggest that FOXM1 upregulates CEP55 expression, at least in part, through activation of the PI3K/Akt signaling pathway, and that a positive feedback loop between FOXM1 and Akt may amplify this signaling axis.

Overexpression of CEP55 Rescues the Migration and Invasion Defects Induced by FOXM1 Knockdown

To further verify whether CEP55 is a functional downstream effector of FOXM1, we performed rescue experiments in CAL27 cells. Cells were co-transfected with si-*FOXM1* and a *CEP55* overexpression vector (or empty vector). Western blot analysis confirmed that the reduced CEP55 protein levels caused by si-*FOXM1* were successfully restored by the co-transfection of the *CEP55* plasmid (Fig. 4A; $p < 0.001$). Subsequent functional assays demonstrated that the restoration of CEP55 expression significantly reversed the inhibition of cell migration (Fig. 4B) and invasion (Fig. 4C) induced by *FOXM1* knockdown ($p < 0.001$). These findings imply that the FOXM1-mediated promotion of OSCC metastasis is largely dependent on CEP55.

Discussion

OSCC represents the most common malignancy of the head and neck region, characterized by a high propensity for local invasion and lymph node metastasis [24]. Despite advances in multimodal therapies, the 5-year survival rate for patients with metastatic OSCC remains unsatisfactory [25]. Therefore, elucidating the molecular mechanisms driving OSCC metastasis is urgently needed to identify novel therapeutic targets. In the present study, we provided evidence that the transcription factor FOXM1 acts as a critical oncogene in OSCC. We demonstrated that FOXM1 promotes cell migration and invasion by upregulating the centrosomal protein CEP55. Furthermore, using a pharmacological rescue strategy, we found that this regulatory axis is dependent on the activation of the PI3K/Akt signaling pathway.

FOXM1 is a proliferation-associated transcription factor that is widely overexpressed in various human cancers, including breast, lung, and colorectal cancers [26]. It is well-documented that FOXM1 plays a pivotal role in cell cycle progression by regulating the expression of G2/M phase genes [7]. However, recent studies have highlighted its non-canonical role in promoting epithelial-mesenchymal transition (EMT) and metastasis [17,27]. Consistent with these findings, our bioinformatics analysis of the TCGA-HNSC dataset confirmed that both *FOXM1* and *CEP55* are significantly overexpressed in tumor tissues compared to normal tissues (**Supplementary Fig. 1**), and functional experiments demonstrated that FOXM1 depletion significantly impaired cell migration and invasion capabilities. Conversely, FOXM1 overexpression markedly enhanced these malignant phenotypes. Since FOXM1 is a well-known regulator of the cell cycle, it is crucial to differentiate

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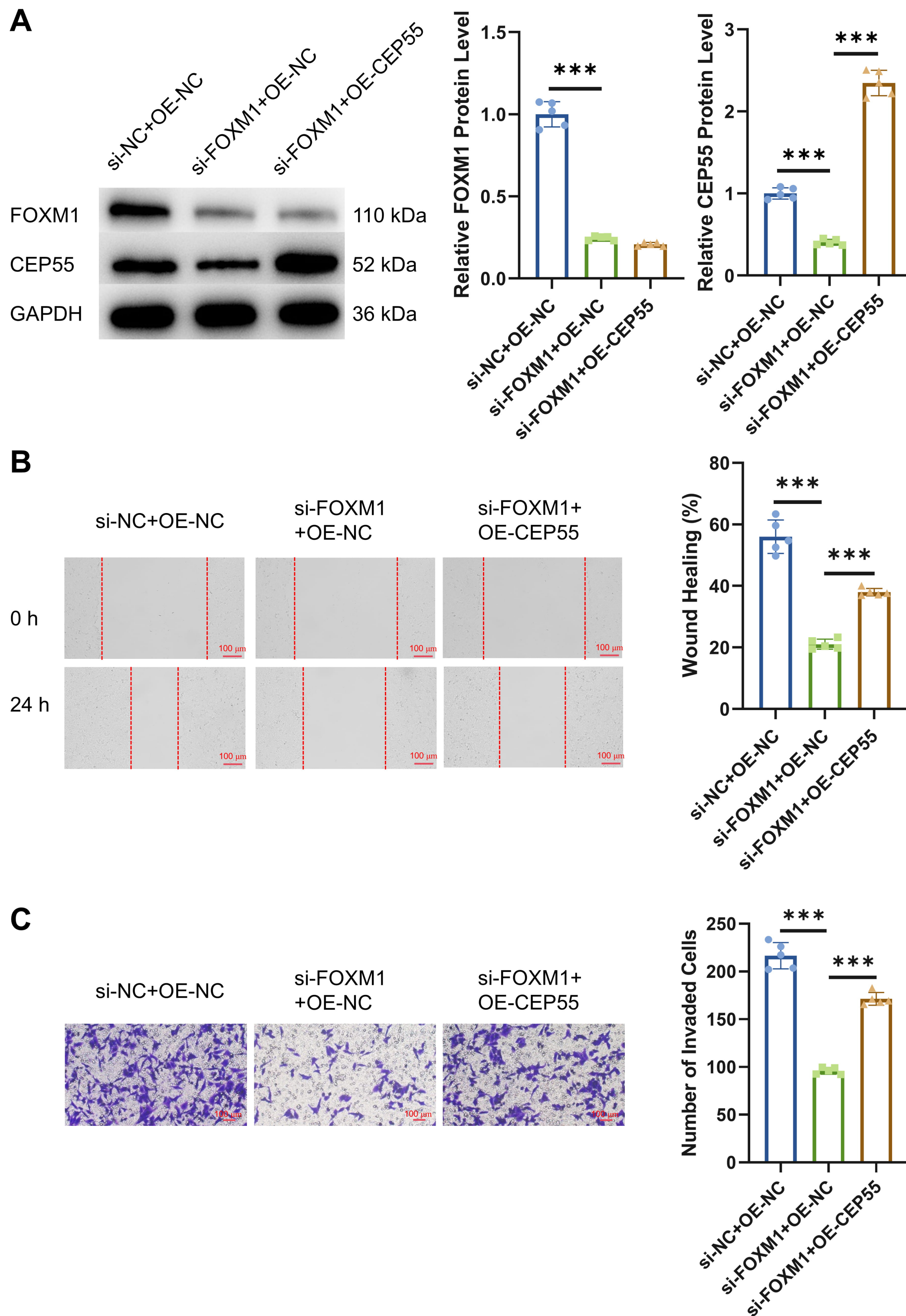

Fig. 4. CEP55 overexpression rescues the inhibitory effects of FOXM1 knockdown on cell migration and invasion. CAL27 cells were co-transfected with si-FOXM1 and either an empty vector or a CEP55 overexpression plasmid. (A) Western blot analysis validating the transfection efficiency and protein levels of FOXM1 and CEP55. (B) Representative images and statistical analysis of the wound healing assay. (C) Representative images and statistical analysis of the Transwell invasion assay. Data are presented as mean ± SD with individual data points (n = 5). ***$p < 0.001$. Red dashed lines indicate the original wound boundaries at 0 h and are uniformly applied to all panels. Images were uniformly adjusted for contrast (1.2× linear contrast enhancement) across the entire field of view. No selective modifications, sharpening, or histogram stretching were applied.

its effects on motility from its pro-proliferative functions. In our functional assays, we utilized serum starvation to suppress cell proliferation. The significant reduction in migration and invasion observed in *FOXM1*-silenced cells under serum-free conditions indicates that FOXM1 promotes OSCC metastasis through direct regulation of the cytoskeletal machinery (e.g., CEP55), rather than solely by increasing cell number. These results are consistent with previous studies by Qiu *et al*. [10], which demonstrated that high FOXM1 expression is associated with lymph node metastasis and poor prognosis in OSCC patients [28], further supporting the notion that FOXM1 is not merely a proliferation marker but a driver of metastatic progression.

Recent studies have begun to elucidate the upstream mechanisms responsible for FOXM1 dysregulation in OSCC. Qiu *et al*. [10] demonstrated that DEPDC1 positively regulates FOXM1 expression to facilitate OSCC development and metastasis. Additionally, in head and neck cancers, MYC, USP5, and FOXM1 have each been implicated in tumor progression, while studies in other systems have shown that FOXM1 can be transcriptionally activated by MYC and stabilized through USP5-mediated deubiquitination [29,30]. FOXM1 overexpression is an early event in oral or head and neck squamous carcinogenesis and is accompanied by epigenetic remodeling, whereas dysregulated microRNA networks, including reduced miR-204 and miR-34a expression, are also common features of OSCC/HNSCC [31,32]. Regarding CEP55, its dysregulation in OSCC is less well characterized, although pan-cancer analyses have identified CEP55 as a cancer-testis antigen that is broadly upregulated across malignancies and correlates with immune infiltration and poor prognosis [14]. In terms of signaling pathways, FOXM1 dysregulation in OSCC and related head and neck squamous carcinomas has been linked to the Wnt/β-catenin, MAPK/ERK, and PI3K/Akt pathways [10,33,34]. Our study further expands this growing body of knowledge by specifically demonstrating that the PI3K/Akt pathway serves as a critical signaling intermediate linking FOXM1 to CEP55 in OSCC cell lines.

One of the key findings of this study is the identification of CEP55 as a functional downstream effector of FOXM1. CEP55 is primarily known for its function in abscission during cytokinesis [35]. However, aberrant upregulation of CEP55 has been reported to contribute to genomic instability and tumorigenesis [13,36]. Waseem *et al*. [16] reported that CEP55 expression progressively increases from normal oral mucosa through dysplasia to HNSCC, and correlates with FOXM1 as a potential biomarker set for cancer progression. While this pioneering study established the clinical expression pattern, it was designed as a biomarker profiling study and did not include functional manipulation of FOXM1 or CEP55, nor did it investigate the signaling pathways mediating this regulatory relationship. Although FOXM1 has previously been reported to transcriptionally regulate CEP55 in breast cancer, the functional relevance of this axis in OSCC metastasis remains largely unexplored [37]. Our results demonstrated a strong positive correlation between *FOXM1* and *CEP55* expression at both mRNA and protein levels. More importantly, our rescue experiments (Fig. 4) provided direct functional evidence: the reintroduction of *CEP55* significantly restored the migration and invasion potential in *FOXM1*-silenced cells. This suggests that CEP55 serves as a critical mediator of FOXM1-induced oncogenic activities in OSCC, possibly by modulating cytoskeletal reorganization or interacting with PI3K/Akt signaling components, as suggested in other cancer models [13,38]. It is worth noting that the regulatory relationship between FOXM1 and CEP55 appears to be a conserved mechanism across multiple malignancies, yet with context-dependent nuances. Similar to our findings in OSCC, previous studies in breast cancer and ovarian cancer have identified CEP55 as a direct transcriptional target of FOXM1, mediating chemoresistance and tumorigenesis [39,40]. However, in hepatocellular carcinoma and glioma, the upregulation of CEP55 is often attributed to other upstream drivers or genomic amplification [41,42]. Our study adds a crucial layer to this landscape by demonstrating that in OSCC, this axis is strongly reliant on the PI3K/Akt signaling pathway. This suggests that while the FOXM1-CEP55 link is a common theme in cancer biology, the specific signaling dependencies, such as the requirement for Akt activation observed in our data, may offer specific therapeutic vulnerabilities unique to oral cancer subtypes.

Mechanistically, our study sheds light on the interplay between FOXM1, the PI3K/Akt pathway, and CEP55. The PI3K/Akt pathway is one of the most frequently hyperactivated signaling cascades in HNSCC [43]. It has been reported that FOXM1 can activate the PI3K/Akt pathway, potentially by regulating the transcription of PIK3CA or by suppressing PTEN expression [44,45]. Consistently, we observed that *FOXM1* knockdown reduced CEP55 at both mRNA and protein levels, suggesting a transcriptional regulatory mechanism. To dissect the hierarchy of this signaling axis, we utilized SC79, a specific small-molecule activator of Akt [46]. The unique mechanism of SC79 enables Akt activation in the cytosol independent of upstream growth factor stimulation [47]. Our results showed that pharmacological activation of Akt by SC79 successfully restored CEP55 protein levels in *FOXM1*-silenced cells. This finding highlights a potentially complex regulatory network: *FOXM1* regulates *CEP55* at the mRNA level, possibly through transcriptional mechanisms that remain to be fully characterized, and additionally maintains CEP55 protein abundance via the PI3K/Akt pathway.

The observation that Akt activation restores CEP55 protein abundance in *FOXM1*-depleted cells prompts a deeper examination of the post-transcriptional role of the PI3K/Akt pathway. While FOXM1 dictates the transcrip-

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tional availability of *CEP55* mRNA, the PI3K/Akt axis serves as a master regulator of protein homeostasis [41]. Canonically, activated Akt phosphorylates TSC2 to relieve the inhibition on mTORC1, thereby promoting the phosphorylation of p70S6K and 4E-BP1, which are essential for initiating cap-dependent translation [48,49]. Furthermore, Akt can inhibit the activity of GSK3β, a kinase known to target various oncogenic proteins for ubiquitin-mediated proteasomal degradation [50]. Based on these considerations, we speculate that FOXM1 may contribute to CEP55 upregulation through two complementary mechanisms, one at the mRNA level, possibly through transcriptional regulation, and another at the protein level, by activating Akt signaling to promote translation and/or protein stabilization. However, whether these two mechanisms constitute a coordinated feed-forward loop requires further experimental validation. If confirmed, such a dual mechanism could help explain why restoring Akt activity partially compensates for the loss of FOXM1-induced CEP55 expression in our experimental model.

An important observation from our SC79 rescue experiment (Fig. 3) is that pharmacological activation of Akt also led to a modest increase in FOXM1 protein abundance, even in the si-*FOXM1* group. This finding is consistent with the bidirectional regulatory relationship between FOXM1 and the PI3K/Akt pathway described in the Introduction. Previous studies have demonstrated that activated Akt can directly phosphorylate FOXM1 at Ser329, preventing its nuclear exclusion and subsequent proteasomal degradation, thereby stabilizing FOXM1 protein [22,23]. In the context of our study, this suggests the existence of a positive feedback loop that FOXM1 activates Akt (potentially through transcriptional regulation of PI3K subunits or suppression of PTEN [44,45]), and activated Akt in turn stabilizes FOXM1, creating a self-reinforcing oncogenic circuit. This feed-forward amplification loop has profound biological implications. In OSCC cells with aberrantly high FOXM1 expression, the FOXM1-Akt positive feedback would ensure sustained Akt phosphorylation, which not only maintains CEP55 protein levels through translational and post-translational mechanisms but also reinforces FOXM1 itself, making the system resistant to perturbation. This may partly explain the aggressive metastatic behavior observed in FOXM1-overexpressing tumors. However, it is important to note that in our experiments, *FOXM1* knockdown robustly suppressed Akt phosphorylation (Fig. 1), whereas Akt activation alone produced only a moderate rescue of FOXM1 levels (Fig. 3), indicating that FOXM1 is the dominant initiator of this signaling cascade. Future studies incorporating phospho-mutant FOXM1 constructs (e.g., S329A) would be valuable in precisely delineating the contribution of Akt-mediated phosphorylation to FOXM1 stability in OSCC.

Despite the promising findings, there are several limitations in the current study that should be acknowledged. Our experiments were conducted exclusively *in vitro* using OSCC cell lines. While cell culture models are valuable for mechanistic dissection, *in vivo* studies using xenograft mouse models are necessary to further validate the effect of the FOXM1/Akt/CEP55 axis on tumor metastasis. Although we demonstrated that Akt activation restores CEP55 levels, the precise molecular mechanism, whether Akt directly phosphorylates CEP55 or regulates it via intermediate transcription factors, remains to be fully elucidated. Future studies using chromatin immunoprecipitation (ChIP) and co-immunoprecipitation (Co-IP) assays are warranted to map the direct interactions within this complex. Additionally, while the rescue experiments were performed exclusively in CAL27 cells due to its superior co-transfection efficiency, the upstream regulatory relationship between FOXM1 and CEP55 was validated in both CAL27 and SCC-9 cell lines. Future studies should confirm the rescue phenotype in additional OSCC cell lines to further strengthen the generalizability of these findings.

From a clinical perspective, our findings highlight the therapeutic potential of targeting the FOXM1/Akt/CEP55 axis in metastatic OSCC. Although FOXM1 is considered a "master regulator", it remains a challenging therapeutic target due to its undruggable nature, lacking well-defined hydrophobic pockets for small-molecule binding [51]. Consequently, targeting the upstream or downstream nodes of FOXM1 signaling represents a viable alternative strategy. Our results suggest that PI3K/Akt inhibitors (e.g., Alpelisib or MK-2206), which are currently under clinical evaluation for head and neck cancers, might effectively disrupt this oncogenic axis. By blocking Akt, one could theoretically dismantle the protein stability support system for CEP55, even in tumors with high FOXM1 expression. Moreover, given that CEP55 overexpression is linked to genomic instability [36], targeting this pathway could potentially sensitize OSCC cells to DNA-damaging agents, such as cisplatin or radiotherapy. Future studies utilizing patient-derived xenograft (PDX) models are warranted to validate the efficacy of combining PI3K/Akt inhibitors with standard-of-care regimens in suppressing FOXM1-driven metastasis.

Conclusion

In summary, our study demonstrates that FOXM1 promotes migration and invasion in OSCC cell lines by upregulating CEP55 in a PI3K/Akt-dependent manner. The restoration of CEP55 by Akt activation highlights the crucial role of kinase signaling in maintaining this oncogenic axis. These findings provide preliminary *in vitro* evidence that the FOXM1/PI3K/Akt/CEP55 signaling network may represent a potential therapeutic target in OSCC, although further validation in clinical samples and *in vivo* models is required before translational conclusions can be drawn.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

SM designed the research study. SM, BL and WWH performed the research. ZLL, XZ and AWX analyzed the data. SM and WWH drafted the article. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202638209.134.

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