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MicroRNA-625-3p promotes cell migration of oral squamous cell carcinoma by regulating SCAI expression

D. XU, M. GU, H.-L. LIU

Department of Stomatology, The Third Affiliated Hospital of Soochow University, The First People's Hospital of Changzhou City, Changzhou, China

Abstract. – OBJECTIVE: The aim of this study was to investigate the role of microRNA-625-3p in the occurrence and progression of oral squamous cell carcinoma (OSCC) and its underlying mechanism.

PATIENTS AND METHODS: Expression levels of microRNA-625-3p, SCAI and E-cadherin in OSCC tissues and paracancerous tissues were detected by quantitative real time-polymerase chain reaction (qRT-PCR). MicroRNA-625-3p expression in OSCC tissues with different tumor stages and lymph node metastasis stages was analyzed. Survival analyses were conducted to access the diagnostic values of microRNA-625-3p and SCAI in OSCC. The effect of microRNA-625-3p on regulating cell migration of OSCC was detected by transwell assay. Luciferase reporter gene assay was conducted to verify the binding condition between microRNA-625-3p and SCAI. Rescue experiments were performed by co-transfection of microRNA-625-3p inhibitor and si-SCAI, followed by cell proliferation detection.

RESULTS: MicroRNA-625-3p was highly expressed in OSCC tissues than that of paracancerous tissues. OSCC patients with T3+T4 presented higher expression of microRNA-625-3p than those with T1+T2. Similarly, OSCC patients with N1+N2 presented higher expression of microRNA-625-3p than those with N0. Luciferase reporter gene assay identified that SCAI is the target gene of microRNA-625-3p. Furthermore, we found that SCAI and E-cadherin are lowly expressed in OSCC tissues than that of paracancerous tissues. ROC curve showed that microRNA-625-3p and SCAI exert certain values in diagnosing OSCC. MicroRNA-625-3p promoted migration of OSCC cells, which was reversed by SCAI knockdown.

CONCLUSIONS: MicroRNA-625-3p is highly expressed in OSCC, which promotes cell migration of OSCC by regulating SCAI expression.

Key Words:
MicroRNA-625-3p, OSCC, SCAI, Cell migration.

Introduction

Oral squamous cell carcinoma (OSCC) is a common malignancy of the head and neck, accounting for 70-90% of all oral malignancies[1]. In the past two decades, with the advanced diagnostic techniques and treatment methods, the incidence of OSCC has decreased. However, the therapeutic effect of OSCC is still poor, with the 5-year survival rate of only 50%. Local recurrence rate and distant metastasis rate[2,3] are as high as 25%. Currently, surgical resection, radiotherapy, and chemotherapy are the major treatments for OSCC. Life quality of OSCC patients undergoing radiotherapy or chemotherapy remarkably decreases, often resulting in disfigurement and disability. Therefore, it is of great significance to explore the pathogenesis of OSCC, so as to improve the early diagnosis and treatment efficacies[4,5]. MicroRNAs are non-coding RNAs with approximately 22 nucleotides in length. MicroRNA regulation was first described in the development of Caenorhabditis elegans in 1993[6,7]. So far, more than 1,400 microRNAs have been found in humans, accounting for approximately 1%-3% of the human genome[8]. It is estimated that 30%-60% of protein-coding genes are regulated by microRNAs[9,10]. Functionally, microRNAs recognize target mRNAs and degrade and/or inhibit their expressions at post-transcriptional level[11]. Studies have confirmed that microRNAs are involved in tumorigenesis and tumor development. Some certain microRNAs are closely related to tumor migration and metastasis. These results provide new ideas for the diagnosis and treatment of tumors. MiR-15a and miR-16-1 were the earliest discovered tumor-associated microRNAs located between

Corresponding Author: Min Gu, MD; e-mail: gumin106@163.com

the 5th and 6th exons of the LEU2 gene in the 13g14 region of human chromosome. The deletion of this region is thought to be responsible for tumor metastasis and metastasis of chronic lymphocytic leukemia[12]. MiR-21 is highly expressed in colon cancer, gastric cancer, prostate cancer and pancreatic duct cancer by analyzing the microRNA expression profiles, indicating its carcinogenesis in multiple tumors[13]. Several microRNAs regulate tumor cell functions in endometrioid tumors by targeting PTEN (phosphatase and tensin homolog deleted on chromosome ten) and activating mTOR pathway, such as miR-221, miR-222, miR-144, miR-26a, and miR-92a[14,15]. MicroRNA-625-3p has been found to affect the efficacy of oxaliplatin in colon cancer patients[16]. It is also reported that microRNA-625-3p can promote the migration and metastasis of thyroid cancer cells[17]. However, studies on biological functions of microRNA-625-3p in OSCC development have rarely been reported. This study aims to explore the role of microRNA-625-3p in the pathogenic progression of OSCC. We hope to provide new directions in the clinical treatment of OSCC.

Patients and Methods

Patients

OSCC tissues and paracancerous tissues were harvested from OSCC patients undergoing surgical resection in The Third Affiliated Hospital of Soochow University from 2015 to 2017 (Soochow, China). Patients did not receive preoperative treatments and had no family history. Enrolled patients had complete clinical data and signed the informed consent before the study. All experimental procedures were approved by The Third Affiliated Hospital of Soochow University Ethics Committee (Soochow, China).

Cell Culture and Transfection

OSCC cell lines (HIOEC, SCC25, CAL27, HB, WSU-HN4, and WSU-HN6) were obtained from American Type Culture Collection (ATCC, Manassas, VA, USA). Cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640; HyClone, South Logan, UT, USA) containing 10% fetal bovine serum (FBS) (Gibco, Rockville, MD, USA). Cell passage was performed until 80% of confluence. One day prior to cell transfection, cells were seeded in the 6-well plates and transfected with corresponding plasmids until 50% of confluence, following the instructions of Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). Culture medium was replaced 6 hours later. MicroRNA-625-3p mimics, microRNA-625-3p inhibitor, siRNA-SCAI and negative control were constructed by GenePharma (Shanghai, China).

RNA Extraction and Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

Total RNA in treated cells was extracted using the TRIzol method (Invitrogen, Carlsbad, CA, USA) for reverse transcription according to the instructions of PrimeScript RT reagent Kit (TaKaRa, Otsu, Shiga, Japan). RNA concentration was detected using a spectrometer and those samples with A260/A280 ratio of 1.8-2.0 were selected for the following qRT-PCR reaction. QRT-PCR was then performed based on the instructions of SYBR Premix Ex Taq TM (TaKaRa, Otsu, Shiga, Japan). The relative gene expression was calculated using the $2^{-\Delta Ct}$ method. Primers used in the study were as follows: SCAI forward, 5′-ACCCCTGTTCATCGTTGTG-3′, reverse, 5′-CGAGTGGCTGTCCAAACAA-3′; E-cadherin forward, 5′-TCGACACCCGATTCAAAGTGG-3′, reverse, 5′-TTCCAGAAACGGAGGCCTGAT-3′; Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) forward, 5′-ACGGGAAGCTCACTGGCATGG-3′, reverse, 5′-GGTCCACCACCCTGTTGCTGTA-3′; MicroRNA-625-3p forward, 5′-ACACTCCAGCTGGGGACTATAGAACTTTCC-3′, reverse, 5′-TGGTGTCGTGGAGTCG-3′; U6 forward, 5′-CTCGCTTCGGCAGCACATATA-3′, reverse, 5′-AAATATGGAACGCTTCACGA-3′.

Transwell Assay

OSCC cells were resuspended in serum-free medium at a dose of 1×10^5/mL. 100 μL of the suspension were added in the upper transwell chamber of the 24-well plates. 24 h later, penetrating cells in the lower chamber were fixed with 4% paraformaldehyde and stained with 0.5% violet crystal for 10-15 min. 5 randomly selected fields in each well were captured for cell counting.

Luciferase Reporter Gene Assay

3’UTR of SCAI transcript was cloned into a pGL3 vector for constructing wild-type 3’UTR SCAI. Corresponding mutant-type 3’UTR SCAI was constructed as well by site-directed mu-

tagenesis kit. OSCC cells were co-transfected with wild-type or mutant-type 3'UTR SCAI and microRNA-625-3p mimics for 36 h. Cells were lysed for detecting luciferase activity using the luciferase assay system.

Western Blot

Cells were lysed for protein extraction. The concentration of each protein sample was determined by a BCA (bicinchoninic acid) kit (Abcam, Cambridge, MA, USA). The protein sample was separated by gel electrophoresis and transferred to PVDF (polyvinylidene difluoride) membranes. After incubation with primary and secondary antibody, immunoreactive bands were exposed by enhanced chemiluminescence method.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 13.0 (Chicago, IL, USA) was used for data analyses, followed by Mann Whitney test or Kruskal Wallis test. Survival analyses were conducted to calculate AUC, specificity, and sensitivity. The correlation coefficient (r) was calculated by Pearson correlation analyses. $p < 0.05$ considered the difference was statistically significant.

Results

MicroRNA-625-3p Was Highly Expressed in OSCC

We first detected microRNA-625-3p expression in 21 pairs of OSCC tissues and paracancerous tissues by qRT-PCR (Table I). The data showed that microRNA-625-3p is highly expressed in OSCC tissues than that of paracancerous tissues (Figure 1A). Subsequently, ROC curve indicated the diagnostic value of microRNA-625-3p in OSCC (AUC=0.9625, cut-off value = 4.014, Figure 1B). We also detected microRNA-625-3p expression in OSCC cells and normal oral epithelial squamous cells. Similarly, microRNA-625-3p was highly expressed in OSCC cells compared with that of controls, especially in SCC25 and WSU-HN6 cells (Figure 1C). Furthermore, we accessed differentially expressed microRNA-625-3p in OSCC with different tumor stages and lymph node metastasis stages. The results indicated that OSCC patients with T3+T4 or N1+N2 presented higher expression of microRNA-625-3p than those with T1+T2 or N0 (Figure 1D and 1E).

SCAI Was the Target Gene of MicroRNA-625-3p

Bioinformatics analyzed that SCI is the potential target gene of microRNA-625-3p. We

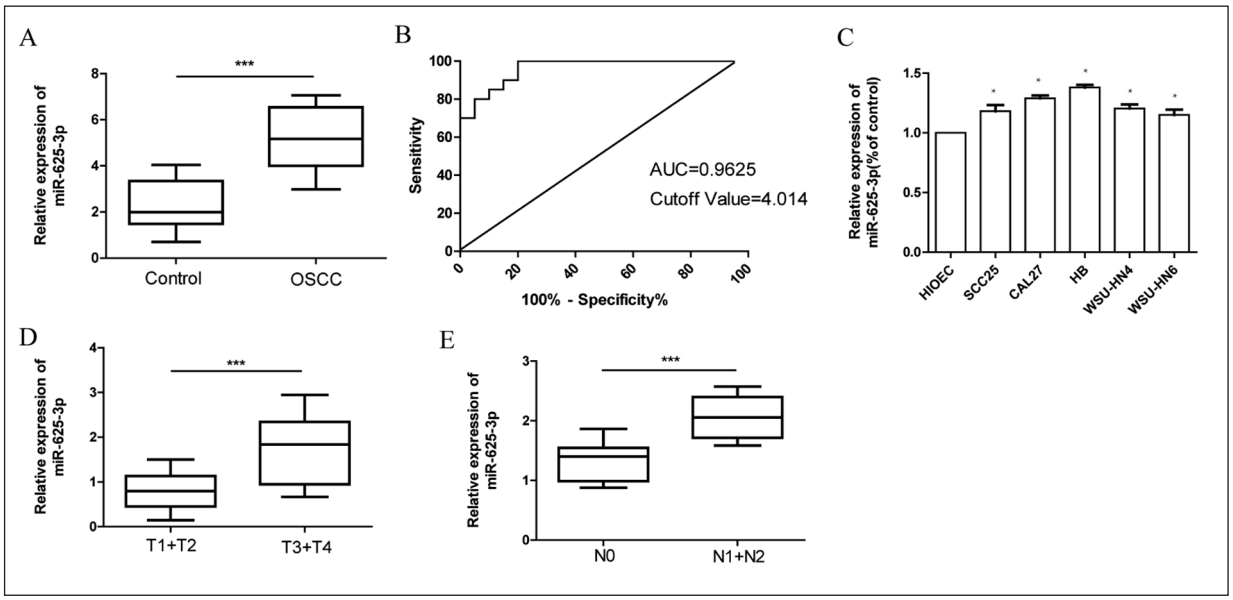

Figure 1. MicroRNA-625-3p was highly expressed in OSCC. ***A,*** MicroRNA-625-3p was highly expressed in OSCC tissues than that of paracancerous tissues. ***B,*** ROC curve indicated the diagnostic value of microRNA-625-3p in OSCC (AUC=0.9625, cut-off value=4.014). ***C,*** MicroRNA-625-3p was highly expressed in OSCC cells, especially in SCC25 and WSU-HN6 cells. ***D, E,*** OSCC patients with T3+T4 or N1+N2 presented higher expression of microRNA-625-3p than those with T1+T2 or N0.

detected SCAI expression in OSCC tissues and paracancerous tissues by qRT-PCR and Western blot to further verify their relationship. QRT-PCR data showed that SCAI is lowly expressed in OSCC tissues than that of paracancerous tissues (Figure 2A). The protein level of SCAI was also lower in OSCC tissues than that of paracancerous tissues (Figure 2B). Next, we detected SCAI expression in OSCC cells and normal oral epithelial squamous cells. Similarly, SCAI was lowly expressed in OSCC cells as well (Figure 2C). ROC curve indicated the diagnostic value of SCAI in OSCC (AUC = 0.8275, cut-off value = 3.818, Figure 2D). Luciferase reporter gene assay verified that SCAI could bind to microRNA-625-3p (Figure 2E). Previous studies have indicated that SCAI exerts its biological function through regulating E-cadherin expression. Hence, we speculated that E-cadherin is lowly expressed in OSCC as well. Both mRNA and protein levels of E-cadherin were lower in OSCC tissues and cells than those of controls (Figure 2F).

MicroRNA-625-3p Was Negatively Correlated to SCAI/E-Cadherin

Since SCAI was the target gene of microRNA-625-3p and E-cadherin was the target gene of SCAI, we speculated that microRNA-625-3p is negatively correlated to SCAI/E-cadherin. Pearson correlation analyses verified the correlation between microRNA-625-3p and SCAI (r^2 = 0.2668, p = 0.0025). MicroRNA-625-3p was also correlated to E-cadherin (r^2 = 0.2924, p =0.0014, Figure 3A). Moreover, we transfected microRNA-625-3p inhibitor in SCC25 and WSU-HN6 cells. Both mRNA and protein levels of SCAI and E-cadherin were upregulated by microRNA-625-3p knockdown (Figure 3B and 3C).

MicroRNA-625-3p Promoted Cell Migration by Regulating SCAI

To further discuss the role of microRNA-625-3p in the occurrence and progression of OSCC, we first transfected microRNA-625-3p mimics in SCC25 and WSU-HN6 cells. Compared with those of controls, microRNA-625-3p overexpression remarkably promoted the migratory capacity of OSCC cells (Figure 4A). Transfection of microRNA-625-3p inhibitor, on the contrary, inhibited migration of OSCC cells. However, the inhibited migration was partially reversed in OSCC cells co-transfected with microRNA-625-3p inhibitor and siRNA-SCAI (Figure 4B). It is concluded that microRNA-625-3p promotes migration of OSCC cells by regulating SCAI/E-cadherin. Moreover, we detected the role of microRNA-625-3p/SCAI in regulating the proliferative ability of OSCC cells and no significant change was found (data not shown).

Discussion

To date, more than 2,000 microRNAs have been discovered that regulate over 30% of genes in humans. Differentially expressed microRNAs may contribute to diagnosis, treatment, and prognosis of tumors[18]. Based on the different regulations on target genes, tumor-associated microRNAs are classified into oncogenes and tumor-suppressor genes[19]. These microRNAs closely participate in the pathogenesis, metastasis, migration and drug resistance in OSCC[20]. For example, miRNA-1246 is highly expressed in OSCC, which is correlated to lymph node metastasis, TNM stage, tumor stage and overall survival of affected patients[21]. MiRNA-363 is significantly upregulated in OSCC tissues and involved in tumorigenesis by inhibiting PDPN expression[22]. The miRNA-181 expression is upregulated in OSCC originated from leukoplakia, dysplasia, and invasive carcinoma, and its expression level is correlated to lymph node metastasis and vascular invasion[23]. Although some differentially expressed microRNAs have been found in OSCC, their specific roles have not been fully elucidated. In this study, we found that microRNA-625-3p is highly expressed in OSCC tissues and cells. MicroRNA-625-3p expression was closely related to tumor stage and lymph node metastasis, showing certain value for the early diagnosis of OSCC. We then predicted through the online website that SCAI is a potential target gene for microRNA-625-3p. SCAI is located at position 9q33.3 and capable of encoding cell metastasis regulators. A large number of studies[24-26] demonstrated that SCAI is lowly expressed in tumors and can inhibit cell migration. For example, the low expression of SCAI in gliomas can promote glioma cell migration by activating Wnt/β-catenin pathway[27]. In the present study, we first detected SCAI expression in

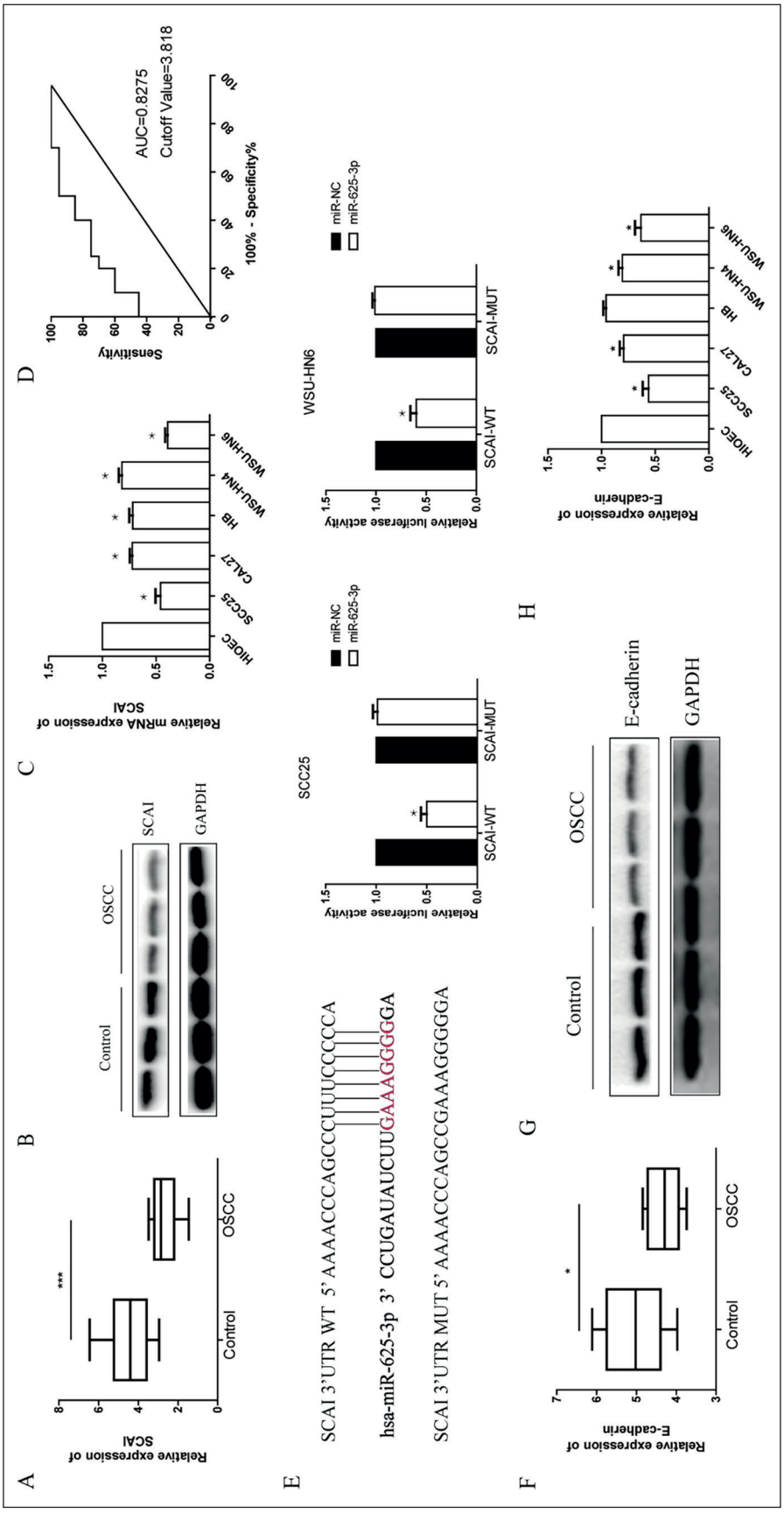

Figure 2. SCAI was the target gene of microRNA-625-3p. ***A***, QRT-PCR data showed that SCAI is lowly expressed in OSCC tissues than that of paracancerous tissues. ***B***, Protein level of SCAI was lower in OSCC tissues than that of paracancerous tissue. ***C***, SCAI was lowly expressed in OSCC cells. ***D***, ROC curve indicated the diagnostic value of SCAI in OSCC (AUC=0.8275, cut-off value=3.818). ***E***, Luciferase reporter gene assay verified that SCAI could bind to microRNA-625-3p. ***F***, Both mRNA and protein levels of E-cadherin were lower in OSCC tissues and cells than those of controls.

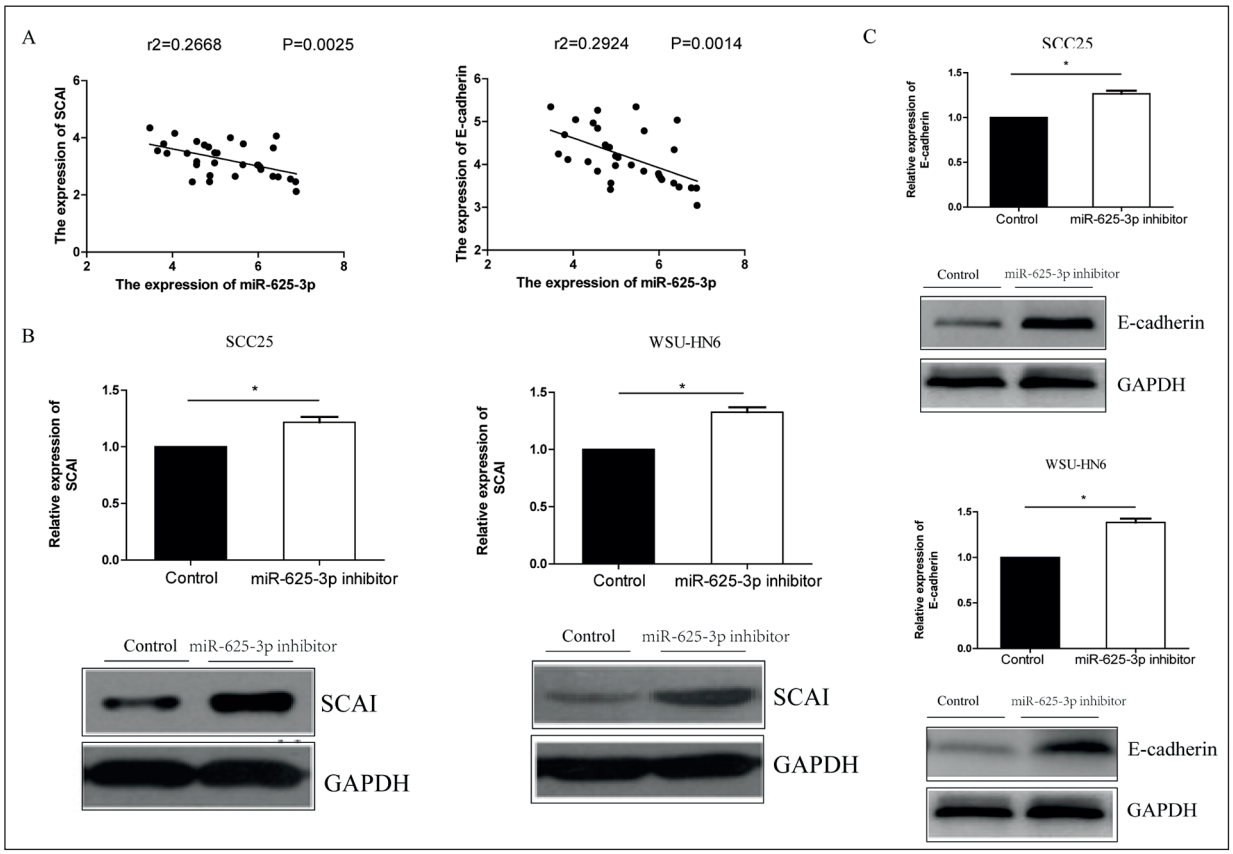

Figure 3. MicroRNA-625-3p was negatively correlated to SCAI/E-cadherin. ***A,*** Pearson correlation analyses verified the correlation between microRNA-625-3p and SCAI (r^2=0.2668, p=0.0025). MicroRNA-625-3p was also correlated to E-cadherin (r^2=0.2924, p=0.0014). ***B, C,*** Both mRNA and protein levels of SCAI and E-cadherin were upregulated after transfection of microRNA-625-3p inhibitor in SCC25 and WSU-HN6 cells.

OSCC tissues and cell lines by qRT-PCR and Western blot. SCAI was lowly expressed in OSCC, showing some certain diagnostic value in OSCC patients. Subsequently, luciferase reporter gene assay verified that SCAI could bind to microRNA-625-3p. We transfected microRNA-625-3p inhibitor in SCC25 and WSU-HN6 cells. Both mRNA and protein levels of SCAI and E-cadherin were upregulated after the microRNA-625-3p knockdown. Transwell assay indicated that microRNA-625-3p overexpression remarkably promotes the migratory ability of OSCC cells. To explore the specific mechanism of microRNA-625-3p in regulating migration of OSCC cells, cells were co-transfected with microRNA-625-3p inhibitor and si-SCAI. The data showed that SCAI knockdown partially reserves the regulatory effect of microRNA-625-3p on promoting migration of OSCC cells. Our results demonstrated that microRNA-625-3p promotes migration of OSCC cells by regulating the SCAI/E-cadherin pathway.

Conclusions

We observed that microRNA-625-3p is highly expressed in OSCC, which promotes cell migration of OSCC by regulating SCAI expression. MicroRNA-625-3p may serve as a new therapeutic target for early treatment of OSCC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

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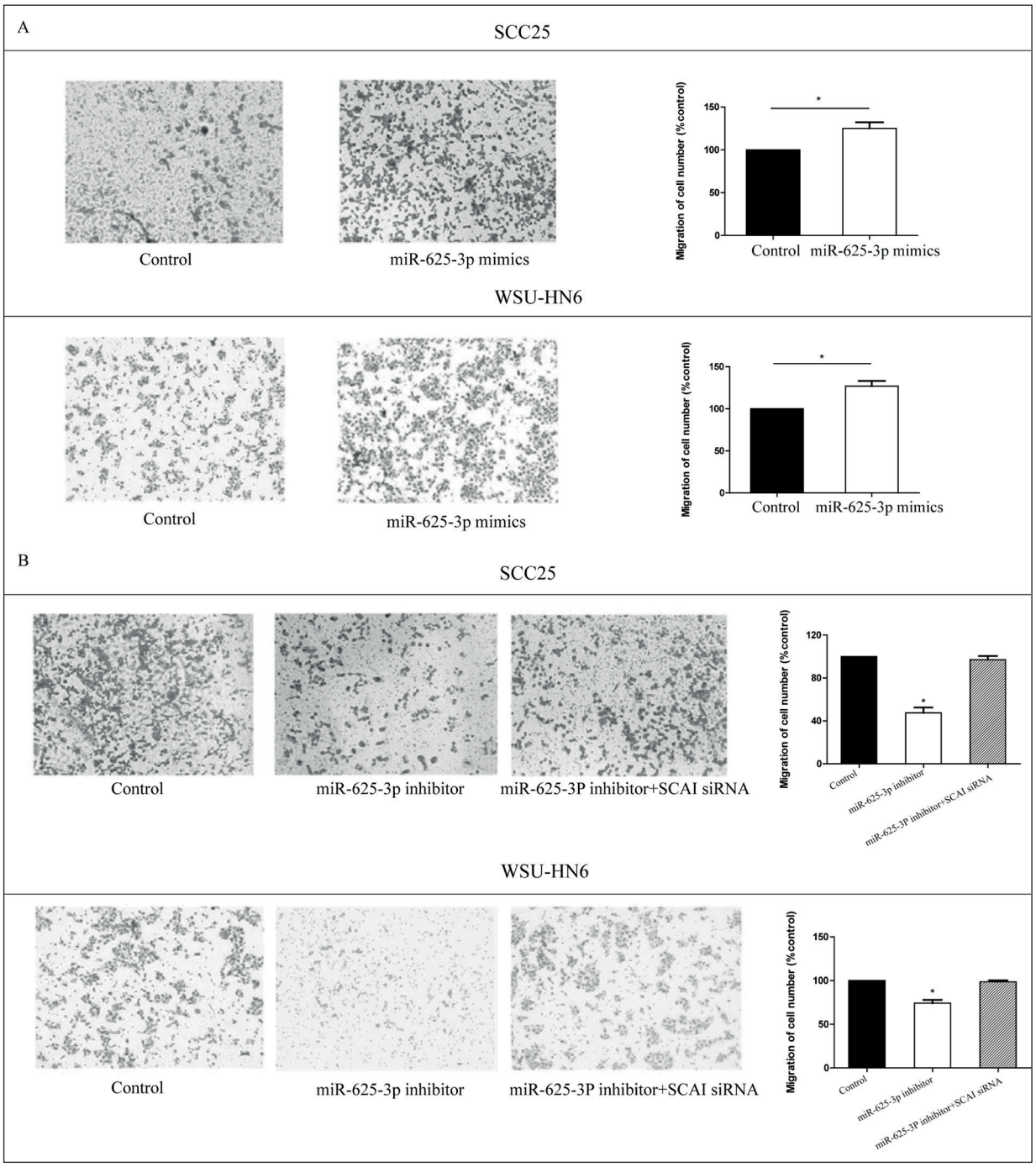

Figure 4. MicroRNA-625-3p promoted cell migration by regulating SCAI. ***A,*** Compared with those of controls, microRNA-625-3p overexpression remarkably promoted the migratory capacity of OSCC cells. Transfection of microRNA-625-3p inhibitor inhibited migration of OSCC cells. ***B,*** The inhibited migration was partially reversed in OSCC cells co-transfected with microRNA-625-3p inhibitor and siRNA-SCAI.

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