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ANXA1 affects cell proliferation, invasion and epithelial-mesenchymal transition of oral squamous cell carcinoma

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Abstract. Annexin A1 (ANXA1) acts either as a tumor suppressor or an oncogene in different tumor types. Several clinical studies revealed that the expression of ANXA1 is associated with the pathologic differentiation grade in oral squamous cell carcinoma (OSCC) patients. However, the direct function of ANXA1 in OSCC progression has remained to be fully clarified. The present study was designed to investigate the role of ANXA1 in OSCC cell proliferation and invasion *in vitro*. Furthermore, whether ANXA1 was involved in transforming growth factor β1 (TGFβ1)/epidermal growth factor (EGF)-induced epithelial-mesenchymal transition (EMT) in OSCC was explored. Tca-8113 and SCC-9 cells were transfected with ANXA1-pcDNA3.1 plasmid to overexpress ANXA1. Subsequently, cell proliferation and invasion were examined using MTT and Transwell-Matrigel invasion assays. TGFβ1 and EGF were used to induce EMT in Tca-8113 and SCC-9 cells, and the expression of epithelial (E)-cadherin, neural (N)-cadherin and vimentin was determined by western blot analysis. The results demonstrated that ANXA1 overexpression induced a significant decrease of cell growth and invasiveness in Tca-8113 and SCC-9 cells. The expression of E-cadherin was significantly increased, while the expression of vimentin and N-cadherin was significantly decreased in ANXA1-overexpressing Tca-8113 and SCC-9 cells. ANXA1 expression was significantly decreased in TGFβ1/EGF-treated cells. Furthermore TGFβ1/EGF-induced EMT in OSCC cell lines was attenuated by ANXA1 overexpression. In conclusion, to the best of our knowledge, the present study was the first to evidence that ANXA1 inhibits OSCC cell proliferation and invasion *in vitro*. TGFβ1/EGF-induced EMT was reversed by ANXA1 in OSCC. ANXA1 was suggested to be a potential marker for OSCC as well as a novel treatment.

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Introduction

Oral squamous cell carcinoma (OSCC) is an aggressive tumor type that occurs at several sites of the oral mucosa. It accounts for 3% of all cancer cases (1,2), and is the most common type of head and neck cancer worldwide (3). Despite advances in its treatment, the 5-year survival rate of OSCC is only ~50%, which is due to its late diagnosis (3,4). Understanding the molecular basis for the carcinogenesis of OSCC is important and has clinical implications for the therapy of OSCC.

Annexin A1 (ANXA1) belongs to the annexin family and takes part in numerous pathophysiological processes, including cell proliferation, differentiation, motility and inflammatory responses (5-8). A increasing number of studies suggested that the expression and the function of ANXA1 in tumors are tissue- and tumor-specific (9,10). Upregulation of ANXA1 was observed in human breast cancer (11), hepatocellular carcinoma (12) and melanoma (13,14), whereas downregulation of ANXA1 was observed in gastric cancer (15), prostate cancer (16,17) and oral cancer (18,19). The function of ANXA1 in tumors appears to be paradoxical. In colon and gastric cancers, ANXA1 interacts with formyl peptide receptors to promote cell migration and invasion (20,21). In non-small cell lung cancer, ANXA1 knockdown suppressed cell proliferation and metastasis (22). However, ANXA1 acts as a tumor suppressor by reducing cell proliferation and attenuating the metastatic potential in breast cancer (23). Certain clinical studies revealed that ANXA1 is downregulated in OSCC patients, and its expression is associated with the pathologic differentiation grade in OSCC patients (18,24-26). However, the direct function of ANXA1 in OSCC progression has remained to be fully elucidated.

The aim of the present study was to investigate the role of ANXA1 in OSCC cell proliferation and invasion *in vitro*. Furthermore, whether ANXA1 is involved in transforming growth factor β1 (TGFβ1)/epidermal growth factor (EGF)-induced epithelial-mesenchymal transition (EMT) in OSCC was explored.

Materials and methods

Cell culture and transfection. The Tca-8113 cell line was purchased from Boster Biological Technology (Wuhan, China), and SCC-9 cells were obtained from the American

Type Culture Collection (Manassas, VA, USA). The cells were grown in RPMI1640 medium (Gibco; Thermo Fisher Scientific, Inc., Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS; Hyclone; GE Healthcare, Little Chalfont, UK), and they were maintained at 37˚C in a humidified atmosphere with 5% CO_2. Human EGF was from Sigma-Aldrich (Merck KGaA, Darmstadt, Germany), and human TGFβ1 was purchased from PeproTech (Rocky Hill, NJ, USA). The cells were treated with 100 ng/ml EGF in combination with 5 ng/ml TGFβ1 for 6 h. ANXA1-pcDNA3.1 plasmid and empty vector pcDNA3.1 (Shenzhen Zhonghong Boyuan Biological Technology Co., Ltd., Shenzhen, China) were transfected into the Tca-8113 and SCC-9 cells using Lipofectamine 2000 (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions.

Western blot analysis. The cells were harvested and proteins were extracted from the cells using a Total Protein Extraction kit (Applygen Technologies, Inc., Beijing, China). The protein concentration was quantified using a bicinchoninic acid protein assay kit (cat. no. C503021; Sangon Biotech Co., Ltd., Shanghai, China). A total of 40 μg protein was separated by 10% SDS-PAGE, and the separated proteins were transferred onto a nitrocellulose membrane (EMD Millipore, Billerica, MA, USA). The membranes were blocked with 5% non-fat milk at 4˚C overnight. Subsequently, the membranes were probed with primary antibodies specific for ANXA1 (cat. no. ab33061; rabbit polyclonal; 1:800 dilution; Abcam, Cambridge, MA, USA), epithelial (E)-cadherin (cat. no. BA0475; rabbit polyclonal; 1:400 dilution; Boster Biological Technology), neural (N)-cadherin (cat. no. BA0673; rabbit polyclonal; 1:400 dilution; Boster Biological Technology) or vimentin (cat. no. ab45939; rabbit polyclonal; 1:800 dilution; Abcam). GAPDH antibody (cat. no. ab9485; rabbit polyclonal; 1:2,000 dilution; Abcam) was used as an internal control. The membranes were incubated with the primary antibodies at 4˚C overnight, followed by incubation with horseradish peroxidase-conjugated goat anti-rabbit immunoglobulin G (cat. no. BA1054; 1:1,000 dilution; Boster Biological Technology) at 37˚C for 2 h. Blots were visualized using enhanced chemiluminescence (cat. no. 21050; Western Blot Signal Enhancer kit; Pierce; Thermo Fisher Scientific, Inc.). Band densities were measured using ImageJ software 1.48 (National Institutes of Health, Bethesda, MD, USA).

Cell proliferation assay. An MTT assay was used to assess the proliferation of Tca-8113 and SCC-9 cells *in vitro*. In brief, $2.5x10^4$ cells/well were cultured in 96-well plates in RPMI1640 medium supplemented with 10% FBS. Following 1, 2, 3 or 4 days of incubation, MTT solution (Sigma-Aldrich; Merck KGaA) was added to each well, and the cells were incubated at 37˚C for 4 h. The formazan crystals were dissolved in dimethyl sulfoxide (Invitrogen; Thermo Fisher Scientific, Inc.). Finally, the optical density at 570 nm was measured using a microplate reader (iMark Microplate Absorbance Reader; Bio-Rad Laboratories, Inc., Hercules, CA, USA).

Cell invasion assay. Matrigel (BD Biosciences, San Jose, CA, USA) was used to coat the Transwell inserts (Corning Costar, Lowell, MA, USA) prior to the experiments. $2.5x10^4$ cells in serum-free medium were placed on the upper chambers for the cell invasion assay. Complete medium (1 ml) was added into the lower chambers. Following incubation at 37˚C for 24 h, the non-invaded cells were removed with cotton swabs. Cells in the lower chamber were fixed in 95% ethanol for 30 min and subsequently stained with hematoxylin (Beyotime Institute of Biotechnology, Haimen, China) for 10 min. Invaded cells were counted in 10 randomly selected fields of each insert under a light microscope (BX51; Olympus, Tokyo, Japan).

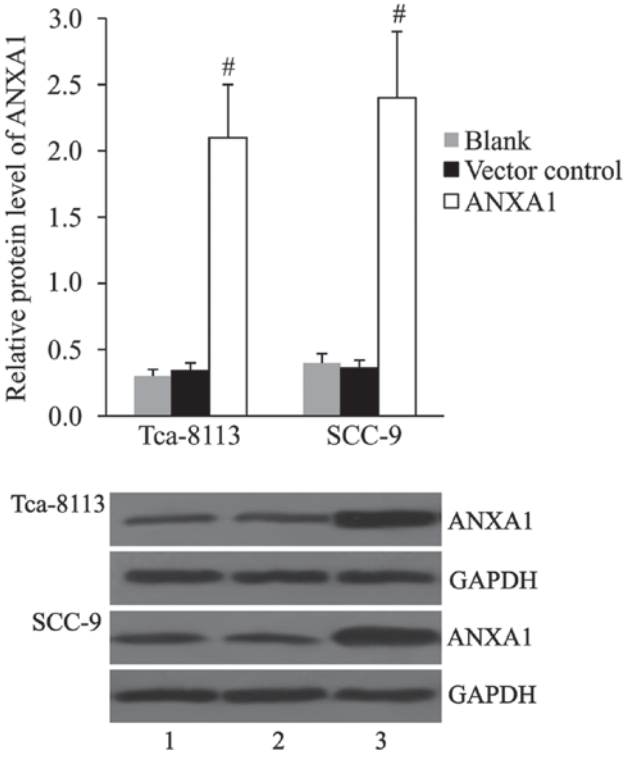

Figure 1. Relative protein levels of ANXA1 in Tca-8113 and SCC-9 cells transfected with the ANXA1-pcDNA3.1 plasmid. Lanes: 1, blank; 2, vector control; 3, ANXA1. #P<0.01 compared with the vector control group. ANXA1, Annexin A1.

Statistical analysis. Values are expressed as the mean ± standard deviation of at least three independent experiments. The results were analyzed by one-way analysis of variance followed by least significant difference test using SPSS 19.0 software (International Business Machines Corp., Armonk, NY, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Overexpression of ANXA1 with ANXA1-pcDNA3.1 plasmid in OSCC cell lines. The pcDNA3.1 vector control and ANXA1-pcDNA3.1 plasmid were transfected into Tca-8113 and SCC-9 cells, and the expression of ANXA1 protein was detected by western blot at 48 h post-transfection. The results indicated no significant difference in ANXA1 expression between the vector control and blank groups. Compared with those in the cells transfected with vector control, the relative protein levels of ANXA1 were significantly increased in the cells transfected with ANXA1-pcDNA3.1 (Fig. 1).

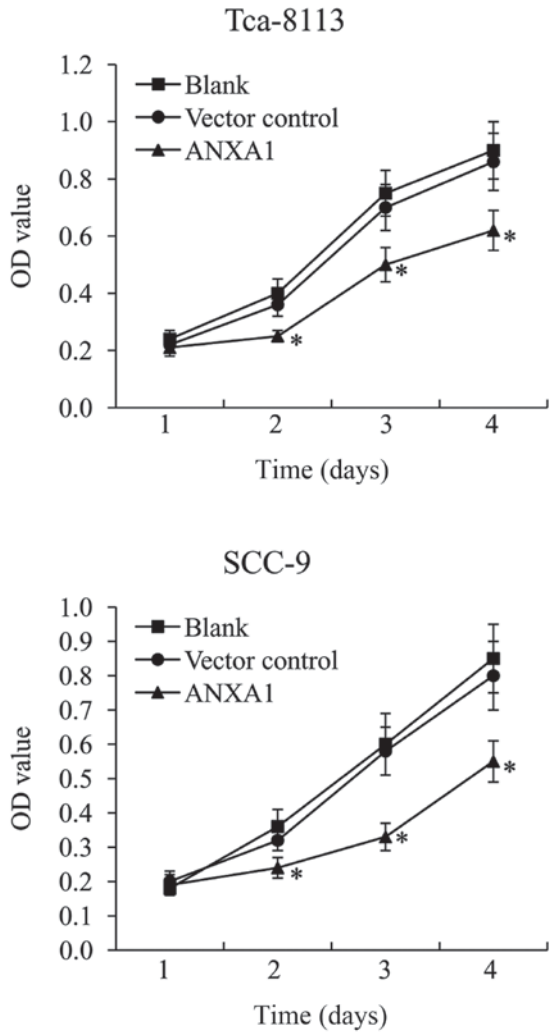

Figure 2. Effect of ANXA1 overexpression on Tca-8113 and SCC-9 cell proliferation. *P<0.05 compared with the vector control group. ANXA1, Annexin A1; OD, optical density.

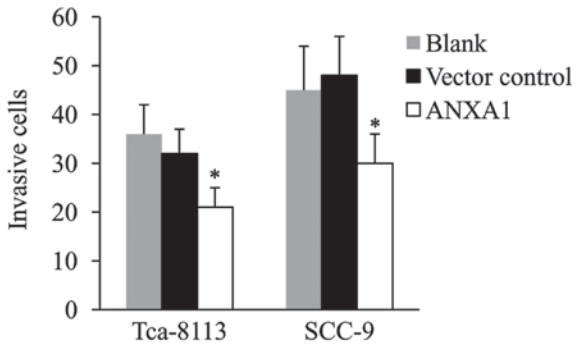

Figure 3. Effect of ANXA1 overexpression on Tca-8113 and SCC-9 cell invasion. *P<0.05 compared with the vector control group. ANXA1, Annexin A1.

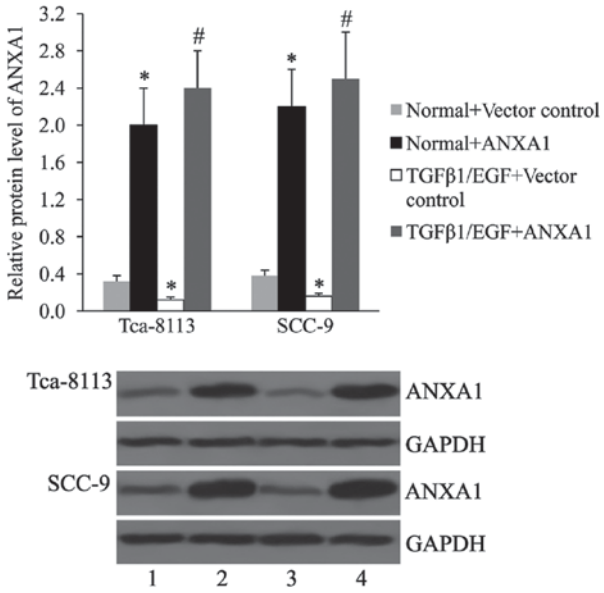

Figure 4. Relative protein levels of ANXA1 in Tca-8113 and SCC-9 cells transfected with the ANXA1-pcDNA3.1 plasmid and treated with TGFβ1/EGF. *P<0.01 compared with the normal + vector control group; #P<0.01 compared with the TGFβ1/EGF + vector control group. Lanes: 1, normal + vector control; 2, normal + ANXA1; 3, TGFβ1/EGF + vector control; 4, TGFβ1/EGF + ANXA1. ANXA1, Annexin A1; TGFβ1, transforming growth factor β1; EGF, epidermal growth factor.

ANXA1 overexpression inhibits Tca-8113 and SCC-9 cell proliferation. An MTT assay was performed on ANXA1-overexpressing Tca-8113 and SCC-9 cells to investigate the effect of ANXA1 on OSCC cell proliferation. The results demonstrated that pcDNA3.1 vector control did not affect Tca-8113 and SCC-9 cell growth. In ANXA1-overexpressing Tca-8113 and SCC-9 cells, the cell survival rate was significantly decreased compared with that in the vector control-transfected cells (Fig. 2).

ANXA1 overexpression reduces Tca-8113 and SCC-9 cell invasion. The Transwell-Matrigel invasion assay was performed using ANXA1-overexpressing Tca-8113 and SCC-9 cells to investigate the effect of ANXA1 on OSCC cell invasion. As presented in Fig. 3, there was no significant difference in the number of invasive cells between the vector control and blank groups. Of note, ANXA1 overexpression significantly suppressed the invasiveness of each of the two OSCC cell lines.

Effect of ANXA1 overexpression on TGFβ1/EGF-induced EMT. The Tca-8113 and SCC-9 cells were treated with TGFβ1 and EGF for 6 h, and the ANXA1 protein levels was determined by western blot analysis. As presented in Fig. 4, TGFβ1 and EGF treatment resulted in a decreased expression of ANXA1 in Tca-8113 and SCC-9 cells.

Subsequently, the effect of ANXA1 on the expression of EMT markers in Tca-8113 and SCC-9 cells in the presence or absence of TGFβ1/EGF was examined. As demonstrated in Fig. 5, TGFβ1 and EGF treatment induced EMT in OSCC cells by downregulating E-cadherin expression, and upregulating N-cadherin and vimentin expression. ANXA1 overexpression led to an upregulation of E-cadherin expression, and a downregulation of N-cadherin and vimentin expression in untreated as well as TGFβ1/EGF-treated Tca-8113 and SCC-9 cells.

Discussion

ANXA1 was suggested to be a prognostic biomarker for OSCC in several clinical studies. Zhu *et al* (24,25) and

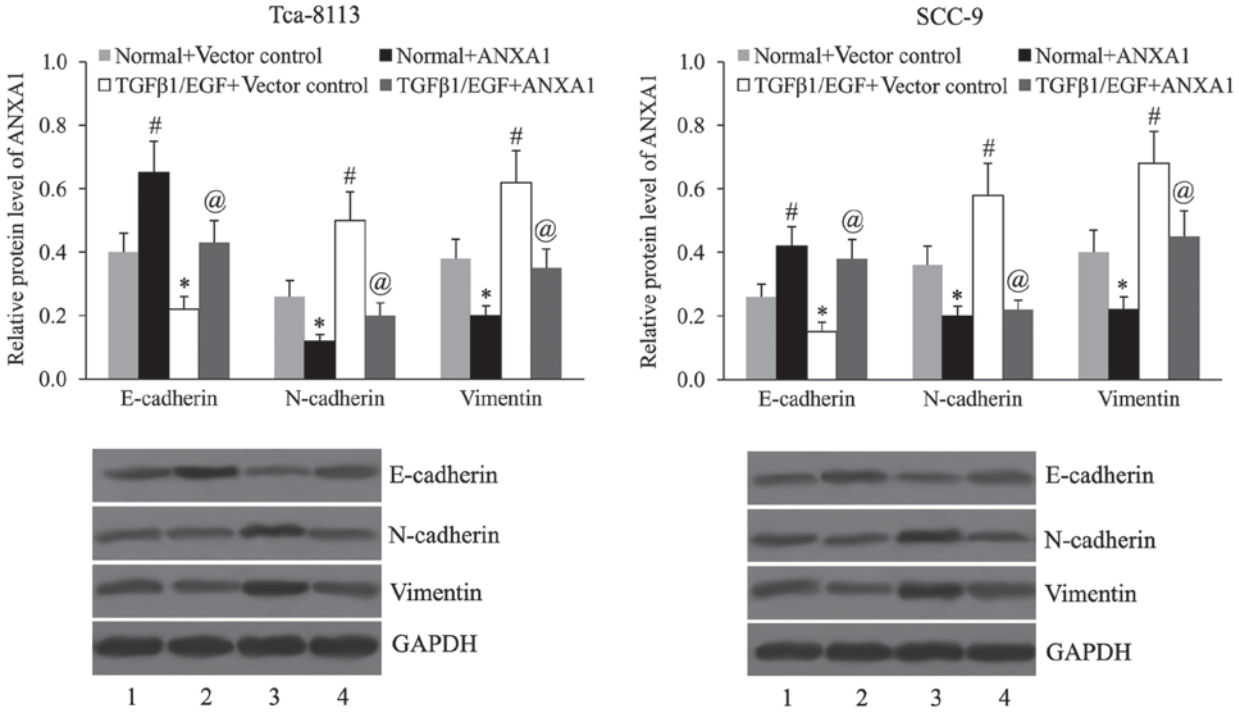

Figure 5. Effect of ANXA1 overexpression on TGFβ1/EGF-induced epithelial-mesenchymal transition. *P<0.05, #P<0.01 compared with the normal + vector control group; @P<0.01 compared with the TGFβ1/EGF + vector control group. Lanes: 1, normal + vector control; 2, normal + ANXA1; 3, TGFβ1/EGF + vector control; 4, TGFβ1/EGF + ANXA1. ANXA1, Annexin A1; TGFβ1, transforming growth factor β1; EGF, epidermal growth factor.

Zhang *et al* (26) reported that ANXA1 expression is significantly correlated with the pathological differentiation grade in OSCC patients. A lower ANXA1 expression in OSCC tissues correlates to a poorer pathologic differentiation grade (25,26). ANXA1 mRNA is downregulated in peripheral blood from OSCC patients compared with that in negative control individuals (18). In addition, patients with moderate or poorly differentiated OSCC as well as low ANXA1 expression may benefit from induction chemotherapy (24). All of these clinical studies revealed that ANXA1 is associated with OSCC development. In the present study, *in vitro* studies on Tca-8113 and SCC-9 cells were performed to investigate the role of ANXA1 in OSCC cell proliferation and invasion. The results demonstrated that vector-mediated overexpression of ANXA1 in Tca-8113 and SCC-9 cells induced a significant decrease in cell growth and invasiveness, suggesting that ANXA1 inhibits OSCC cell proliferation and invasion. Accumulating evidence has indicated that the tumor-advancing effect of ANXA1 is tissue type-specific (9,10). Through gain-of-function experiments, the present study was the first to demonstrate that ANXA1 may act as a tumor suppressor in OSCC, to the best of our knowledge. This finding is consistent with those of previous clinical studies. Further studies may be performed to investigate the effect of ANXA1 knockdown on OSCC progression.

EMT is a critical process in the development of numerous types of tissue and organs (27). The importance of EMT in mediating aggressiveness during carcinoma progression has attracted much attention in recent years (28). During EMT, epithelial cells lose their epithelial characteristics and gain invasive properties to become mesenchymal-like cells (29). ANXA1 has been demonstrated to be important for epithelial differentiation in OSCC (19). Nomura *et al* (19) found that loss of ANXA1 occurs frequently during oral carcinogenesis, and the loss of membranous ANXA1 is correlated with a poor differentiation status of OSCC cells. OSCC patients with nuclear localization of ANXA1 had poor overall survival (30). TGFβ1 and EGF are important regulators of the EMT. Previous studies have demonstrated that EMT in OSCC is mediated by multiple growth factors, and TGFβ1 and EGF co-stimulation induced phenotype transition in OSCC cells (31,32). The present study we further confirmed the involvement of ANXA1 in TGFβ1/EGF-induced EMT. It was found that the expression of E-cadherin, which is a key marker of the epithelial phenotype, was increased in ANXA1-overexpressing Tca-8113 and SCC-9 cells. By contrast, the expression of vimentin and N-cadherin, which are mesenchymal cell markers, was decreased in ANXA1-overexpressing Tca-8113 and SCC-9 cells. These results suggested that ANXA1 contributes to mesenchymal-to-epithelial transition, which is the reverse process of EMT, in OSCC cells. TGFβ1/EGF treatment led to downregulation of ANXA1 expression in OSCC cells. Furthermore, it was found that TGFβ1/EGF-induced EMT in OSCC was attenuated by ANXA1 overexpression. This finding is consistent with the role of ANXA1 in EMT in breast cancer (23).

In conclusion, to the best of our knowledge, the present study provided the first evidence that ANXA1 suppresses cell proliferation and invasion of human OSCC cells *in vitro*. Furthermore, it was demonstrated that TGFβ1/EGF-induced EMT was reversed by ANXA1 in OSCC. ANXA1 was suggested to be a potential marker for OSCC as well as a novel treatment. However, further studies are required regarding the molecular mechanisms by which ANXA1 exerts its role in OSCC.

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