Histol Histopathol (2025) 40: 687-696

Histology and Histopathology
From Cell Biology to Tissue Engineering

ORIGINAL ARTICLE Open Access

Periostin acts as an oncogene to promote laryngeal cancer progression by activating decorin

Chao Wu, Bo Yang and Jiusheng Chu

Department of Otolaryngology Head and Neck Surgery, Taizhou People's Hospital, Taizhou, Jiangsu Province, China

Summary. Laryngeal carcinoma (LC) is the second most common malignancy of the head and neck worldwide, with increasing incidence every year. However, the mechanism of its development is not completely clear. Periostin (POSTN) has been reported to be involved in various aspects of tumorigenesis. To determine the influence of POSTN on LC tumorigenesis, we first examined the expression of POSTN in tissues from patients with LC through immunohistochemistry, western blot, and qRT-PCR. Besides, we demonstrated that POSTN promoted LC cell migration, invasion, and proliferation *in vitro* by CCK-8, colony formation, and Transwell assays, and tumor growth *in vivo* by immunohistochemistry. Furthermore, the interaction between POSTN and decorin (DCN) was further verified by bioinformatics analysis and immunoprecipitation (IP), finding that POSTN promoted the malignant progression of LC by targeting DCN. Our findings support the idea that the level of POSTN expression and accumulation in tumors correlated with the malignancy degree of LC, suggesting that POSTN may play a potential role in improving laryngeal cancer treatment strategies.

Key words: Periostin, Oncogene, Laryngeal cancer, Decorin

Introduction

Laryngeal carcinoma (LC) is the second most common malignancy of the head and neck worldwide (Chu and Kim, 2008), among which laryngeal squamous cell carcinoma (LSCC) is the commonest, with significant differences in morbidity and mortality across the globe (Dobrossy, 2005). Overall, mortality and morbidity are high in the later stages of LSCC. Current standards of nursing management of LSCC aim to improve disease control, survival, and preservation of respiratory, speech, and laryngeal functions. Depending on the stage of the tumor, surgery, radiation, and chemotherapy are preferred alone or in combination. To improve survival in patients with LSCC, clinical trials are needed that effectively assess the benefits of new treatment regimens and identify molecular markers and novel therapeutic targets (Lefebvre et al., 2009). With the increasing incidence of LSCC, it is urgent to develop new techniques for diagnosis and treatment.

Periostin (POSTN), also known as osteoblast-specific factor 2 (OSF-2), is an extracellular secreted matrix protein that induces adhesion and aggregation of periosteal osteoblast precursor cells, as well as the proliferation and differentiation of osteoblasts (Contie et al., 2010). In addition, POSTN takes part in the progression of tumors through Akt/PI3K, integrin, and Wnt-1 (Baril et al., 2007; Malanchi et al., 2011). Additionally, POSTN plays a considerable part in increasing tumor growth, invasion, and metastasis (Bao et al., 2004; Michaylira et al., 2010; Malanchi et al., 2011). For example, induction of mesenchymal POSTN by TGF-β1 facilitates metastasis and aggression of ovarian cancer (Yue et al., 2021). Similarly, POSTN was found to play an important role in the progression and prognosis of gastric cancer and may serve as a useful biomarker for predicting the survival of gastric cancer patients (Lu et al., 2022). However, the role of POSTN in LC has not been reported. Therefore, we aimed to detect the functions of POSTN in LC progression in the study.

Decorin (DCN), a typical small proteoglycan rich in leucine, is a crucial component of the cellular microenvironment or extracellular matrix (ECM) (Sofeu Feugaing et al., 2013) and is a potential natural anticancer agent (Santra et al., 2002). Explicitly, DCN cancels out the biological activity of transforming growth factor-β1 (TGF-β1), which is an autocrine element that activates the growth of cancer cells (Yamaguchi et al., 1990; Wu et al., 2010). Overall, the group of proteins interacting with DCN (the "interaction group") produces a powerful anti-tumor signal by effectively inhibiting tumor cell proliferation, survival,

Corresponding Author: Chao Wu, Department of Otolaryngology Head and Neck Surgery, Taizhou People's Hospital. No. 366, Taihu Road, Pharmaceutical High-tech Zone, Hailing District, Taizhou City 225300, Jiangsu Province. e-mail: doctorwu521@126.com

www.hh.um.es. DOI: 10.14670/HH-18-804

migration, and angiogenesis (Neill et al., 2012). It was found that DCN deficiency contributes to epithelial-mesenchymal transition and colon cancer metastasis (Mao et al., 2021). However, studies on DCN in LC have not been reported, and the purpose of our study was to investigate the relationship between DCN and POSTN in the development of LC.

Materials and methods

Ethics statement

All human experiments were conducted according to the guidelines approved by the Ethics Committee of Taizhou People's Hospital, and preoperative written informed consent was obtained from each patient.

Patients and tissue samples

The 40 LC tissue specimens (LSCC specimens and paired normal tissues) analyzed in this study were obtained from the Department of Otolaryngology, Taizhou People's Hospital during 2021-2022. All patients in the study had either a total or partial laryngectomy. None of the patients received chemotherapy or radiation before surgery. Inclusion criteria (Wang et al., 2021): (I) A definitive pathological diagnosis of LC; (II) New cases of LC; (III) The patient did not receive any radiotherapy, chemotherapy, or other anti-cancer treatment before surgery. Exclusion criteria: (I) Unclear diagnosis, such as atypical hyperplasia, keratosis of the larynx, and other non-cancerous lesions; (II) Recurrent cases; (III) Cases receiving treatment other than surgery. Tissue samples for subsequent experiments were rapidly frozen in liquid nitrogen and stored at -80°C or formalin-fixed and paraffin-embedded.

Cell culture and transfection

Human Hep-2 and AMC-HN-8 cells were purchased from ATCC (Manassas, VA, USA), and cultured in Roswell Park Memorial Institute (RPMI) medium at 37°C in 5% CO_2, which contained 10% fetal bovine serum (FBS). SiRNA sequences were integrated by Invitrogen (Shanghai, China) for POSTN and negative control (NC) according to the manufacturer's agreement. As previously, the plasmid PCDNA3.1A-DCN was replicated in *Escherichia coli* DH5.α, and its reliability was examined and verified by sequencing (Wu et al., 2008). Lipofectamine RNAiMAX (Invitrogen) was transfected with siRNA. Quantitative real-time polymerase chain reaction (RT-PCR) was performed to detect the efficiency.

Quantitative RT-PCR

Total RNA was extracted with Trizol. The 5×PrimeScript® RT Master Mix kit was adopted for reverse transcription (10 μL). The GoTaq qPCR master mix (Promega) kit was performed for quantitative PCR with the primers shown in Table 1. The $2^{-\Delta\Delta Ct}$ approach was used to calculate and normalize the relative expression levels of each gene. All gene primer sequences are shown in Table 1.

Immunohistochemistry

Paraffin-embedded tissue was sectioned to 5 μm thickness. Then, sections were dewaxed and the endogenous peroxidase was sealed with 3% H_2O_2. The tissue was heated in a microwave oven for 10 min to extract the antigen. Subsequently, the tissue was then incubated overnight with primary antibodies (anti-POSTN, anti-Ki67, anti-caspase-3) at 4°C. A biotinylated secondary antibody was added and incubated at 37°C for 15 min, followed by treatment with 3,3'-diaminobenzidine (DAB) dye. Finally, the tissue was stained with hematoxylin and observed under a microscope.

Western blotting

Cells were dissolved in a radioimmunoprecipitation analysis (RIPA) buffer supplemented with protease inhibitor (Roche Diagnostics, Mannheim, Germany). Briefly, protein samples were electrophoresis on a 10% denatured SDS-polyacrylamide gel and transferred to a nitrocellulose membrane, then blocked in 5% defatted milk for 1h, and incubated with the primary antibodies: anti-POSTN, anti-DCN, and anti-GAPDH. Then, horseradish peroxide (HRP) conjugated secondary antibodies (Amersham Biosciences, BaiedUrfe, QC) were used to incubate membranes. The ECL system (Amersham Biosciences) was used to detect the antigen-antibody complexes.

Colony formation assays

Hep-2 and AMC-HN-8 cells were inoculated on a 6-well cell culture plate, treated according to the specified conditions, fixed with 4% polyformaldehyde, washed with PBS, and stained with crystal violet, and the colony formation of cells in each group was calculated.

Cell viability test

The CCK-8 kit was used, according to the manufacturer's instructions, to test cell viability. In

Table 1. Primer sequence for genes used in RT-PCR experiments.

Gene name	Primer sequence (5'-3')
DCN-F	CGAGTGGTCCAGTGTTCTGA
DCN-R	AAAGCCCCATTTTCAATTCC
POSTN-F	GATGGAGTGCCTGTGGAAAT
POSTN-R	AACTTCCTCACGGGTGTGTC
GAPDH-F	ACATCATCCCTGCCTCTACTGG
GAPDH-R	AGTGGGTGTCGCTGTTGAAGTC

detail, 10 μl of CCK-8 solution was added to the cell culture medium and incubated for 2-3h. Subsequently, the viability rate of CCK-8 was gauged at 450 nm OD using an EPOCH digitizer (BioTek).

Transwell assay

Hep-2 and AMC-HN-8 cells were inoculated in a stromal gel-coated upper cavity with pores (50 uL stromal gel, BD Bioscience, USA) with 10% FBS. The migratory and aggressive cells on the surface of the inferior membrane were incubated for 24h, then fixed and stained with 20% Giemsa solution. Five random fields in each chamber were calculated using an inverted microscope (Olympus, Japan).

Flow cytometry analysis

Human Hep-2 and AMC-HN-8 cells were inoculated in a 12-well plate at a density of 40,000 cells and incubated overnight in 1 mL complete medium. Then, cells were collected and washed in cold phosphate buffer (PBS). According to the manufacturer's protocol, cell microspheres were stained with propidium iodide and APC-conjugated Annexin V (eBioscience, San Diego, CA). The quantitative analysis was performed on a FACS (BD Biosciences) with the use of CellQuest software.

Animal model

The male BALB/C Nu/Nu mice (SLC Co., Ltd, Shizuoka, Japan) weighed about 20 g at six weeks of age and were kept under specific pathogen-free conditions, the room temperature was constant, and the day and night cycle lasted 12 h. After anesthesia, the cells were subcutaneously injected into the back skin of mice (200 μL medium, 5×10^6 cells per mouse). Tumor growth was recorded once a week for five weeks. Tumor volume was counted as length×width^2×0.5. Animal experiments for this study were permitted by the Taizhou People's Hospital Animal Ethics Committee.

Transplanted tumor volume and inhibition rate

Except for the control group, each group was given a corresponding solution of 50 μL, twice a week, for three weeks, weighing twice a week and measuring the maximum length (a) and width (b) of the tumor with a vernier caliper. Tumor volume=verticality×width×height×0.5236. On the second day after the last treatment, the mice were killed and solid tumors were collected and weighed.

Immunoprecipitation (IP)

Iced cells were lysed using a buffer with the co-IP kit (ABS955; Absin Bioscience Inc., Shanghai, China) containing protease inhibitors. After centrifugation at 4°C for 10 min at 14000×g, the lysate was incubated with protein A/G agarose beads to clarify the soluble part. In the cleared supernatant, the protein was immunoprecipitated overnight with an indicated primary antibody at 4°C for 12h. The immunoprecipitated complexes were rinsed thoroughly and western blotting was performed. The input was the positive control.

Statistical analysis

All data in this study were presented as mean ± standard deviation (SD). The student t-test was used to determine the *P* value between different groups.

Results

Aberrant high expression of POSTN correlates with poor prognosis in LC patients

POSTN is a secreted ECM protein, correlating with the development and progression of cancer in bone and heart (Dobreva et al., 2012). POSTN is a predictor of poor prognosis or tumor progression. Gene Expression Profiling Interactive Analysis (GEPIA) indicated that POSTN was highly expressed in head and neck squamous cell carcinoma (HNSC, including LC, Fig. 1A). To verify the degree of accuracy of the above results, we performed immunohistochemical staining for POSTN expression in tissues from LC patients. We found a significantly higher level of POSTN in tumor tissues compared with normal tissues (Fig. 1B). Also, we collected 18 pairs of clinical samples from each group for RT-PCR analysis and found elevated levels of POSTN mRNA in tumor tissues (Fig. 1C). Consistently, western blotting showed that POSTN protein expression was upregulated in tumor tissues compared with the normal levels of six pairs of randomly selected clinical samples (Fig. 1D). Furthermore, survival analysis found that the lower the expression of POSTN, the longer the survival time, which is consistent with the results of the DriverDBv3 database (Fig. 1E,F). Together, these results suggested that high expression of POSTN in LC patients may be correlated with poor prognosis.

POSTN promotes LC cell proliferation, migration, and invasion in vitro

To discover the impact of POSTN on LC tumorigenesis, small interfering RNA was used to knock down the expression of POSTN in Hep-2 and AMC-HN-8 cells. First, the interference efficiency was verified by RT-PCR and western blot analyses, which revealed a significant reduction in mRNA and protein levels of POSTN expression in the si-POSTN group (Fig. 2A). The CCK-8 assay showed that cell proliferation was diminished in the si-POSTN group compared with the si-NC group, which depended on the culture time (Fig.

2B). The colony formation assay also showed a substantial inhibitory impact on proliferation by si-POSTN compared with si-NC (Fig. 2C). Furthermore, knockdown of POSTN in Hep-2 and AMC-HN-8 cells inhibited metastasis and invasion (Fig. 2D,E). Flow cytometry showed that silencing POSTN was effective in promoting the apoptosis of Hep-2 and AMC-HN-8 cells compared with the negative control group (Fig. 2F).

POSTN promotes the growth of xenograft tumors of LC cells in vivo

To investigate the significance of POSTN in cancer tumorigenesis *in vivo*, nude mice were subcutaneously injected with Hep-2 cells to generate tumors. Firstly, we found that silencing of POSTN significantly inhibited tumor growth compared with the si-NC group (Fig. 3A). Furthermore, compared with the si-NC group, the tumor weight and volume in the interfering POSTN application group decreased significantly (Fig. 3B,C). Additionally, immunohistochemical staining of proliferated protein Ki67 and apoptotic protein cleaved caspase-3 in tumor tissues acknowledged the effect of POSTN on tumor growth and apoptosis (Fig. 3D), that is, knocking down POSTN inhibited tumor growth and promoted tumor cell apoptosis.

POSTN interacts with DCN

To explore the molecular mechanism of POSTN in LC progression, we predicted the POSTN-interacting proteins based on the STRING database and identified several potential proteins, including DCN (Fig. 4A). Then we attempted to investigate the significant function of the mutual effect between DCN and POSTN, both of which are secreted proteins. By co-immunoprecipitation of these proteins from Hep-2 and AMC-HN-8 lysates, we found that endogenous DCN and POSTN interacted

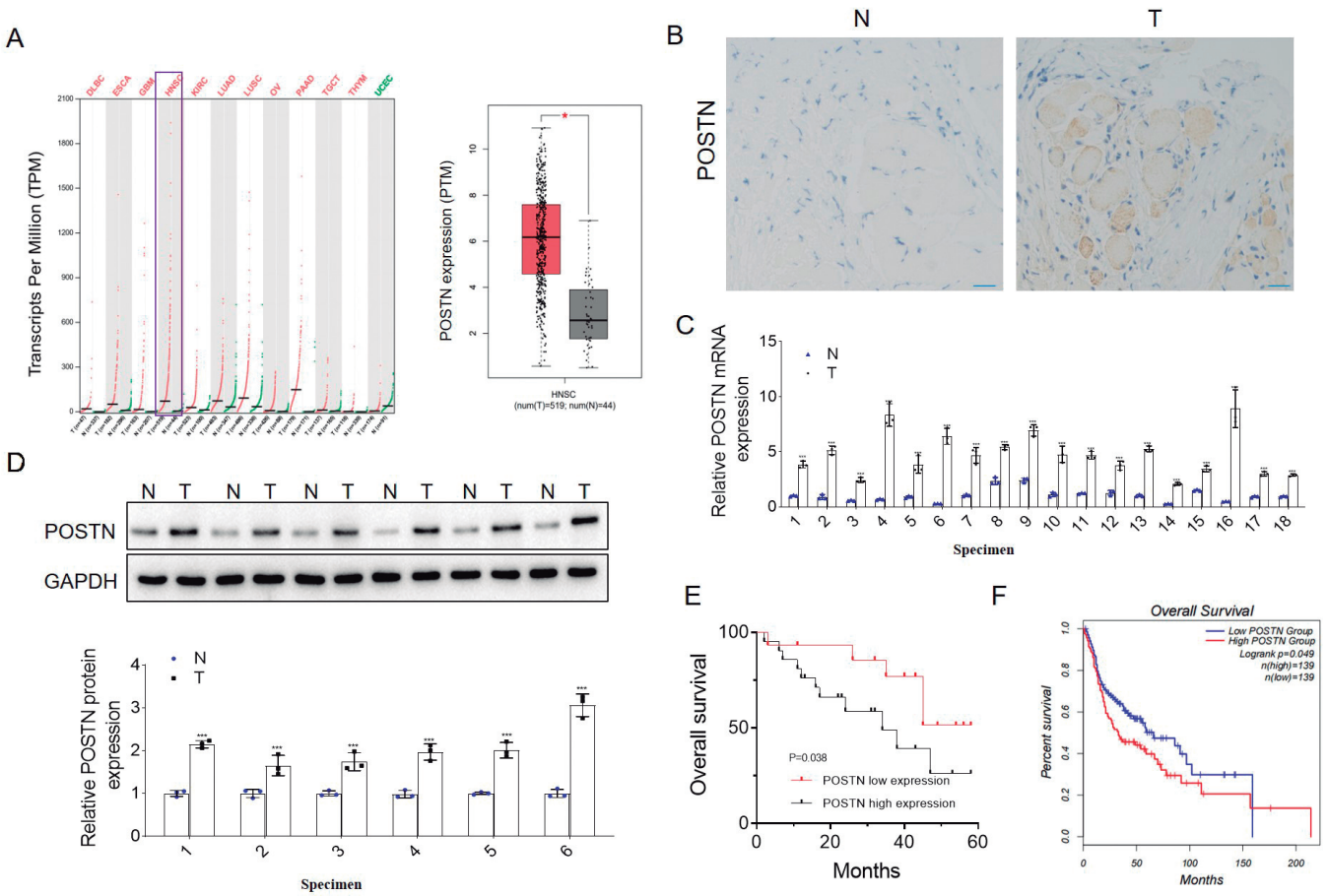

Fig. 1. Aberrant high expression of POSTN correlates with poor prognosis in LC patients. **A.** Gene Expression Profiling Interactive Analysis (GEPIA) indicated the expression of POSTN in various kinds of tumors. **B.** Representative immunohistochemical staining images of POSTN expression in normal and tumor tissues. **C, D.** Western blot and RT-PCR analyses showed the levels of POSTN in normal and tumor tissues. **E.** Kaplan-Meier analysis for overall survival (OS) of LC patients with low and high POSTN expression. **F.** OS of LC patients obtained from the DriverDBv3 database. **p*<0.05, ****p*<0.001. n=3.

directly or indirectly in these cells (Fig. 4B). Furthermore, the GEPIA database indicated a positive correlation between DCN and POSTN in HNSC (Fig. 4C); western blot analysis showed that the level of DCN protein expression was reduced after silencing POSTN (Fig. 4D). Meanwhile, the DCN protein was increased in LC tumor tissues (Fig. 4E).

POSTN promotes the malignant progression of LC cells by targeting DCN

DCN was originally discovered as an essential collagen-binding protein, crucial for proper fiber formation, which could influence tissue integrity by regulating key biomechanical parameters of tendons and skin (Neill et al., 2016). DCN interacts with matrix and cell membrane components, which are involved in matrix organization, signal transduction, cell migration, inhibitory metastasis, and so on (Jarvelainen et al., 2015). To investigate the consequences of DCN in laryngeal tumorigenesis, we assessed the role of DCN in Hep-2 and AMC-HN-8 cells using DCN plasmids. First, we verified the efficiency of DCN-overexpression plasmids in Hep-2 and AMC-HN-8 cells by RT-PCR analysis (Fig. 5A). As shown in Figure 5B,C, overexpression of DCN caused an increase in cell activity and cell proliferation compared with negative controls. Overexpression of DCN alleviated the prohibitive influence of si-POSTN on LC cell activity and proliferation. Moreover, Transwell analysis showed that overexpression of DCN not only accelerated the migration of LC cells compared with the NC group but also reversed the impact of silencing POSTN on cell migration (Fig. 5D). Equally, overexpression of DCN effectively inhibited apoptosis in Hep-2 and AMC-HN-8 cells and partially attenuated the apoptosis-promoting effect of knockdown POSTN (Fig. 5E).

Discussion

In this study, we characterized the impact of DCN and POSTN on LC. POSTN, a secretory cell adhesion protein, that is highly expressed in collagen fibers (Zhao et al., 2013), plays a part in cell adhesion and the progression and maintenance of mechanical stress structures (Silvers et al., 2016). POSTN has been found and studied in tissue wound repair (Hamilton, 2008; Elliott et al., 2012; Ontsuka et al., 2012), atherosclerosis (Hixson et al., 2011; Schwanekamp et al., 2016), scleroderma (Terao et al., 2015), allergic inflammation (Izuhara et al., 2017), polycystic kidney disease (Wallace et al., 2014), and various tumors. Our study found abnormally high expression of POSTN in LC, suggesting the possibility of POSTN being involved in

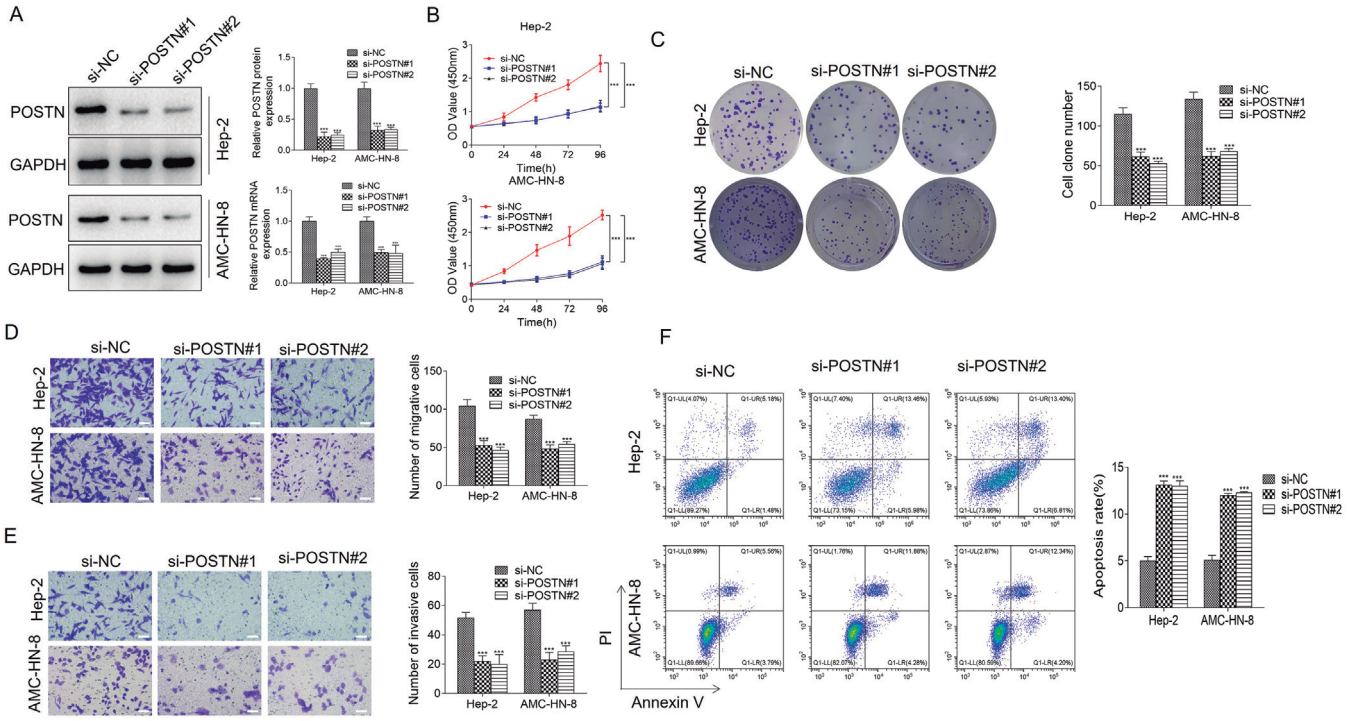

Fig. 2. POSTN promotes LC cell proliferation, migration, and invasion *in vitro*. **A.** The efficiency of knockdown POSTN was verified by RT-PCR and western blot analyses. **B.** The CCK-8 assay showed cell proliferation. **C.** Images showed cell proliferation by the colony formation assay. **D, E.** Transwell analysis indicated cell migration and invasion. **F.** Flow cytometry analysis indicated apoptosis of cancer cells. ***p<0.001. n=3.

the occurrence and progression of LC. Previous studies have shown upregulated POSTN expression in the tumor stroma of various metastatic tumors, such as hepatocellular carcinoma (Zhang et al., 2017), intrahepatic cholangiocarcinoma (Sirica et al., 2014), esophageal squamous cell carcinoma (Lv et al., 2017), breast cancer (Wang et al., 2013), head and neck cancer (Qin et al., 2016), and prostate cancer (Nuzzo et al., 2012). Recent findings also suggest that POSTN enhances angiogenesis by upregulating vascular

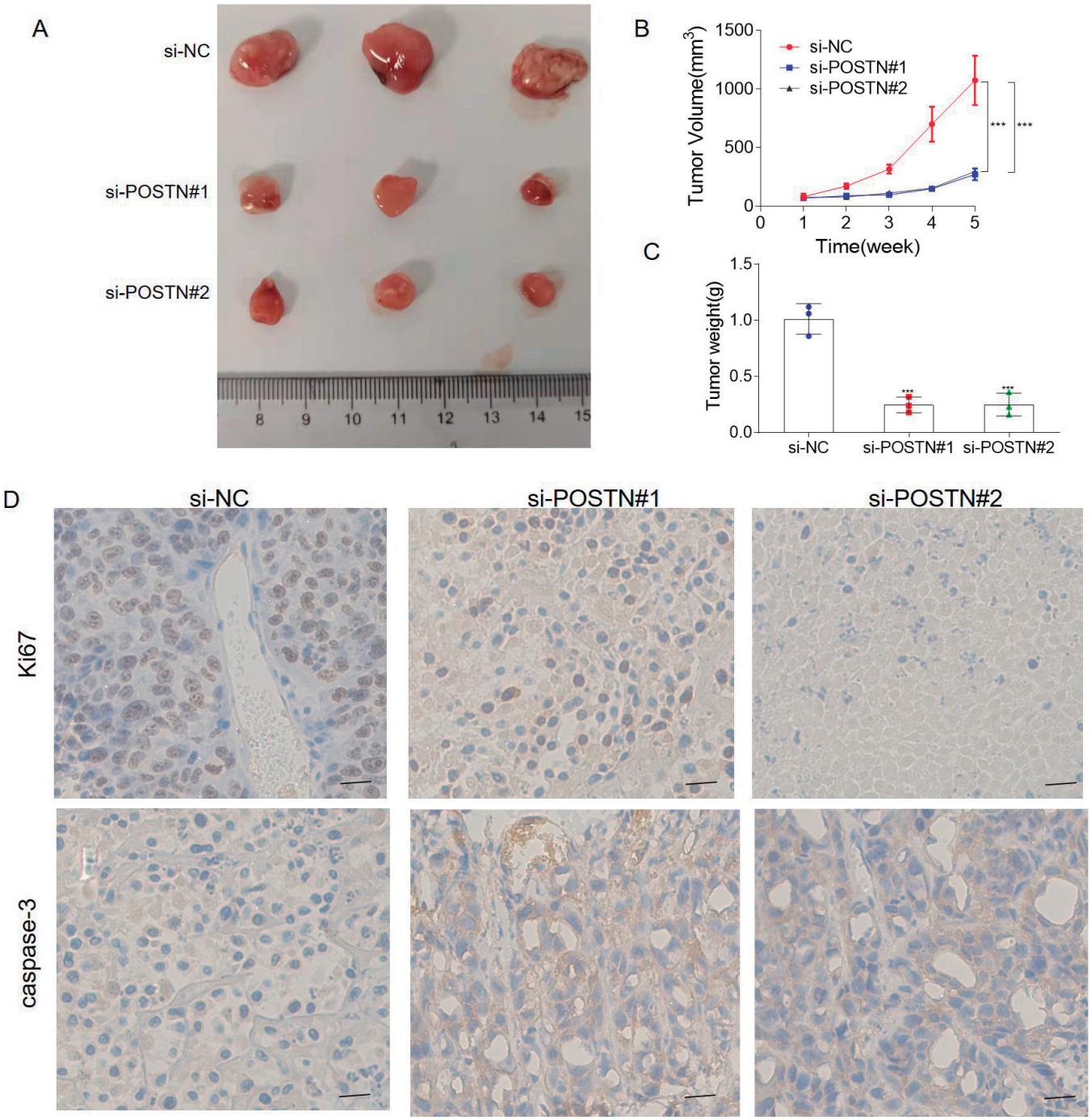

Fig. 3. POSTN promotes the growth of xenograft tumors of LC cells *in vivo*. **A-C.** Images show tumor volume and weights in treatment with silencing POSTN. **D.** Images showed Ki67 or cleaved caspase-3 positive cells in xenografted tumors. ***$p<0.001$. n=3.

endothelial growth factors through a focal adhesion kinase-mediated signaling pathway (Kuhn et al., 2007). These data suggest that POSTN is a key stromal cell component in remodeling the tissue microenvironment during tumor growth and metastasis. Our findings demonstrated that POSTN was more abundant in laryngeal tumor tissues, and that endogenous POSTN resulted in the promotion of cell proliferation, migration, and invasion *in vitro*.

To explore the molecular mechanism of POSTN in LC progression, we predicted the POSTN-interacting proteins based on the STRING database and identified several potential proteins including DCN. DCN is an SLRP, known to be a valid tumor cell growth inhibitor, which is present in both glycosylated and unglycosylated forms, with a significant increase in DCN in comparison with normal larynx with LSCC progression. Previous studies have shown that DCN holds back tumor growth by impeding angiogenesis via vascular endothelial growth factor receptor 2 (VEGFR2) and the concurrent activation of protracted endothelial cell autophagy (Xie et al., 2022). In this report, we described the function and relationship between DCN and POSTN in LC cells in which POSTN forms a complex with DCN. Our data indicates the feasibility that POSTN knockdown in cancer cells caused an impact on cell proliferation, migration, and invasion by using both laryngeal tumor tissues and LC cells.

DCN protects against cell migration and invasion. Consistent with this, paracancerous matrix DCN expression was significantly weaker in invasive breast cancer tumors than in ductal carcinoma *in situ* alone (Oda et al., 2012). In mouse models harboring A431 orthotopic tumor xenografts, it was demonstrated that DCN, through its targeting of EGFR, significantly reverses tumorigenic growth *in vivo* (Csordas et al., 2000). Our results suggested the value of POSTN as an underlying therapeutic target for cancer cells. Our mechanistic studies demonstrated that POSTN binds and interacts with DCN, thereby reducing the level of cell proliferation, migration, and invasion in LC cells.

Emerging evidence about POSTN allows us to speculate that understanding the mechanisms involved in these diseases is essential for the advancement of novel therapeutic strategies to prevent or reverse them. To determine the precise functional properties of POSTN, which will greatly improve our understanding of its pathogenic role, detailed phenotypic and functional analysis of the protein is necessary. Our findings support the idea that the level of POSTN expression and accumulation in tumors correlated with the progression of LC, suggesting that POSTN may play a potential role

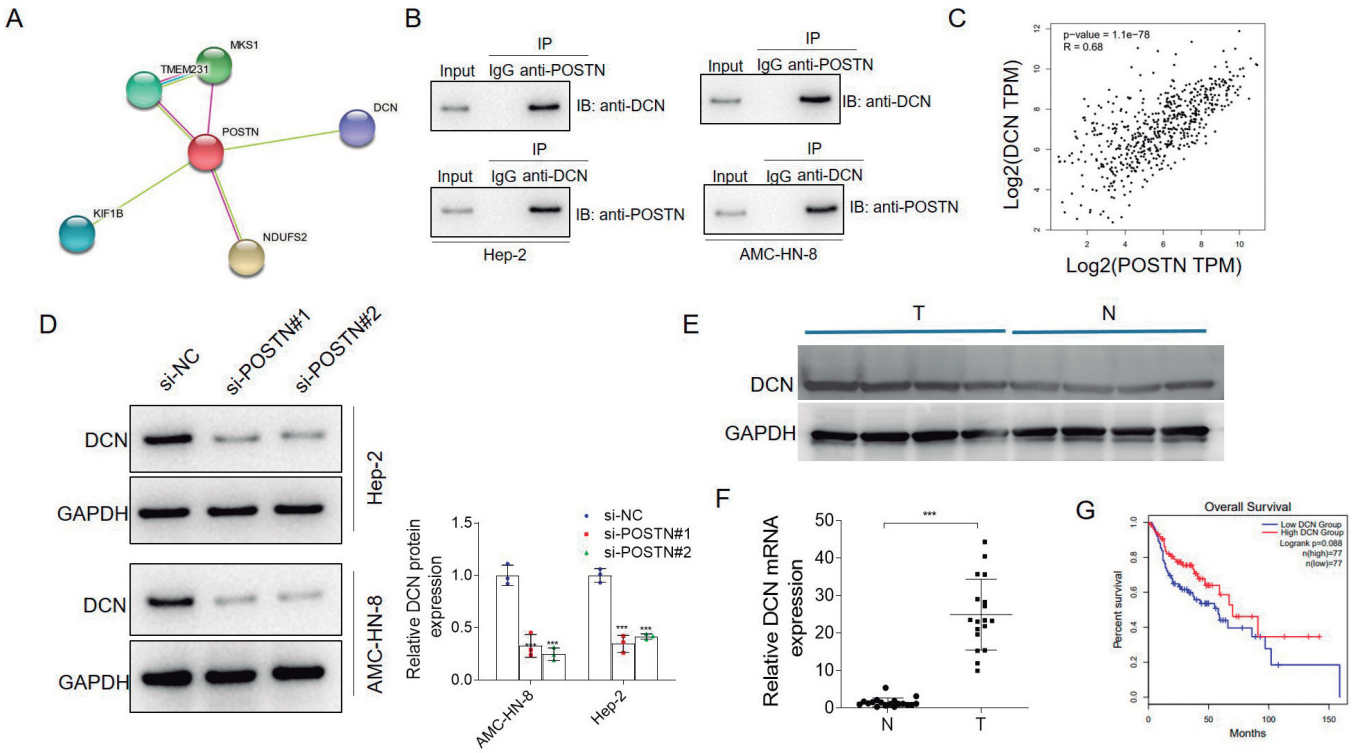

Fig. 4. POSTN interacts with DCN. **A.** The interacting protein network of POSTN was predicted by STRING. **B.** The bands showed an interaction between POSTN and DCN by immunoprecipitation analysis. **C.** The correlation between POSTN and DCN was analyzed by the GEPIA database. **D.** Images showed the expression of DCN in silencing POSTN. **E.** The bar graph shows the expression level of DCN in tumor tissues. ***p<0.001. n=3.

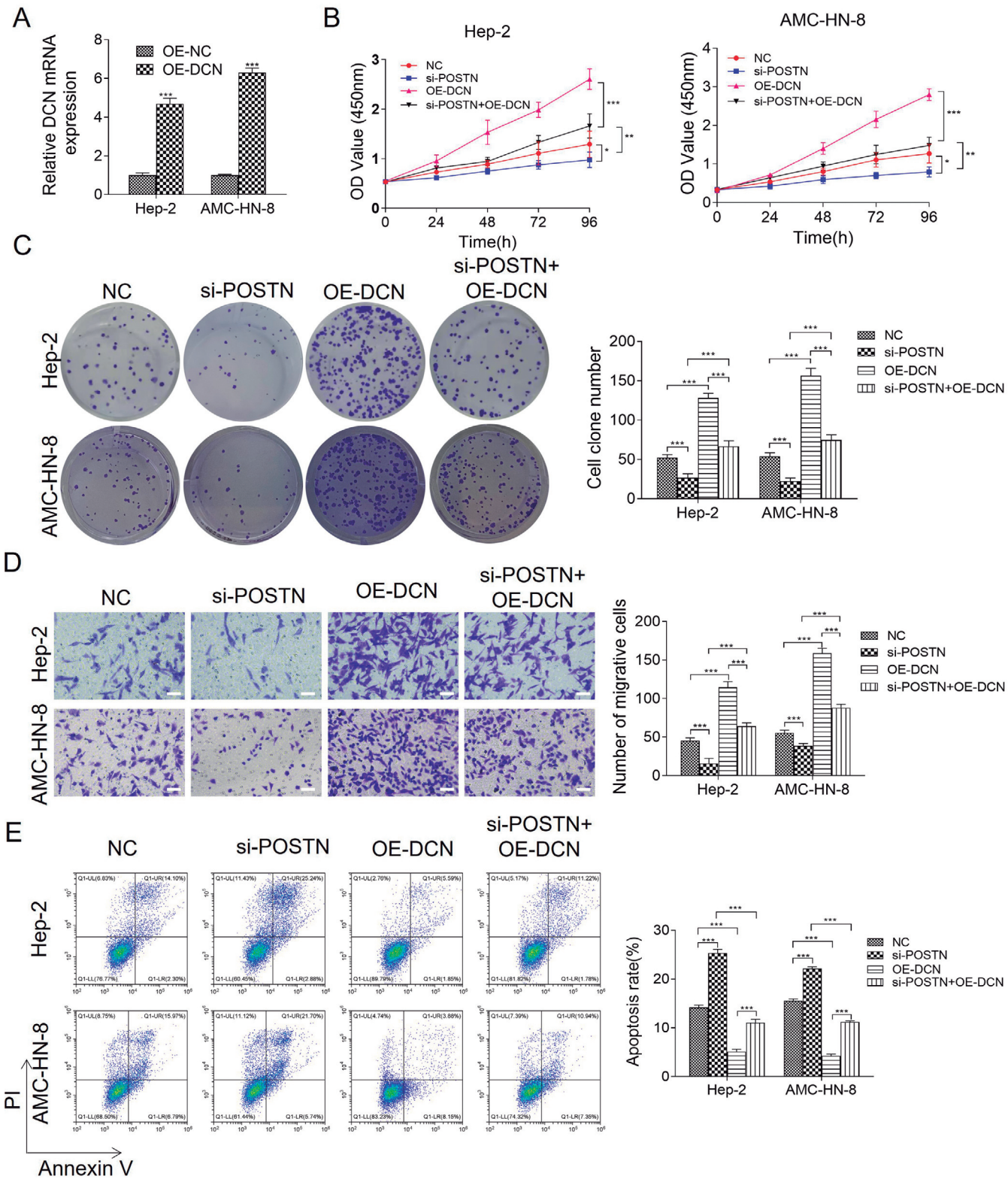

Fig. 5. POSTN facilitates the malignant progression of LC cells by targeting DCN. **A.** The efficiency of DCN overexpression was verified by RT-PCR analyses. **B.** The CCK-8 assay showed cell proliferation. **C.** Images show cell proliferation by the colony formation assay. **D.** Transwell analysis indicated cell migration. **E.** Flow cytometry analysis indicated apoptosis of cancer cells. *p<0.05, **p<0.01, ***p<0.001. n=3.

in improving LC treatment strategies.

Acknowledgements. N/A
Authors' contributions. WC: Methodology, Formal Analysis, and Paper Writing; YB: Validation software and review & editing; CJH; Supervision and Funding acquisition.
Ethics approval and consent to participate. This research was approved by the ethics community of Taizhou People's Hospital (KY202022401).
Consent for publication. Approved by all authors.
Patient consent for publication. N/A
Availability of data and materials. N/A
Competing interests. The authors declare no conflicts of interest.
Funding. Supported by the Science and Technology Development Project of Taizhou People's Hospital (ZL202038).

References

Bao S., Ouyang G., Bai X., Huang Z., Ma C., Liu M., Shao R., Anderson R.M., Rich J.N. and Wang X.F. (2004). Periostin potently promotes metastatic growth of colon cancer by augmenting cell survival via the Akt/PKB pathway. Cancer Cell 5, 329-339.

Baril P., Gangeswaran R., Mahon P.C., Caulee K., Kocher H.M., Harada T., Zhu M., Kalthoff H., Crnogorac-Jurcevic T. and Lemoine N.R. (2007). Periostin promotes invasiveness and resistance of pancreatic cancer cells to hypoxia-induced cell death: Role of the beta4 integrin and the PI3k pathway. Oncogene 26, 2082-2094.

Chu E.A. and Kim Y.J. (2008). Laryngeal cancer: Diagnosis and preoperative work-up. Otolaryngol. Clin. North Am. 41, 673-695, v.

Contie S., Voorzanger-Rousselot N., Litvin J., Bonnet N., Ferrari S., Clezardin P. and Garnero P. (2010). Development of a new ELISA for serum periostin: Evaluation of growth-related changes and bisphosphonate treatment in mice. Calcif. Tissue Int. 87, 341-350.

Csordas G., Santra M., Reed C.C., Eichstetter I., McQuillan D.J., Gross D., Nugent M.A., Hajnoczky G. and Iozzo R.V. (2000). Sustained down-regulation of the epidermal growth factor receptor by decorin. A mechanism for controlling tumor growth *in vivo*. J. Biol. Chem. 275, 32879-32887.

Dobreva M.P., Lhoest L., Pereira P.N., Umans L., Camus A., Chuva de Sousa Lopes S.M. and Zwijsen A. (2012). Periostin as a biomarker of the amniotic membrane. Stem Cells Int. 2012, 987185.

Döbrossy L. (2005). Epidemiology of head and neck cancer: Magnitude of the problem. Cancer Metastasis Rev. 24, 9-17.

Elliott C.G., Wang J., Guo X., Xu S.W., Eastwood M., Guan J., Leask A., Conway S.J. and Hamilton D.W. (2012). Periostin modulates myofibroblast differentiation during full-thickness cutaneous wound repair. J. Cell Sci. 125, 121-132.

Hamilton D.W. (2008). Functional role of periostin in development and wound repair: Implications for connective tissue disease. J. Cell Commun. Signal. 2, 9-17.

Hixson J.E., Shimmin L.C., Montasser M.E., Kim D.K., Zhong Y., Ibarguen H., Follis J., Malcom G., Strong J., Howard T., Langefeld C., Liu Y., Rotter J.I., Johnson C. and Herrington D. (2011). Common variants in the periostin gene influence development of atherosclerosis in young persons. Arterioscler. Thromb. Vasc. Biol. 31, 1661-1667.

Izuhara K., Nunomura S., Nanri Y., Ogawa M., Ono J., Mitamura Y. and Yoshihara T. (2017). Periostin in inflammation and allergy. Cell. Mol. Life Sci. 74, 4293-4303.

Jarvelainen H., Sainio A. and Wight T.N. (2015). Pivotal role for decorin in angiogenesis. Matrix Biol. 43, 15-26.

Kuhn B., del Monte F., Hajjar R.J., Chang Y.S., Lebeche D., Arab S. and Keating M.T. (2007). Periostin induces proliferation of differentiated cardiomyocytes and promotes cardiac repair. Nat. Med. 13, 962-969.

Lefebvre J.L., Ang K.K. and Larynx Preservation Consensus P. (2009). Larynx preservation clinical trial design: Key issues and recommendations--a consensus panel summary. Head Neck 31, 429-441.

Lu S., Peng L., Ma F., Chai J., Hua Y., Yang W. and Zhang Z. (2022). Increased expression of POSTN predicts poor prognosis: A potential therapeutic target for gastric cancer. J. Gastrointest. Surg. 27, 233-249.

Lv Y.J., Wang W., Ji C.S., Jia, Xie M.R. and Hu B. (2017). Association between periostin and epithelial-mesenchymal transition in esophageal squamous cell carcinoma and its clinical significance. Oncol. Lett. 14, 376-382.

Malanchi I., Santamaria-Martinez A., Susanto E., Peng H., Lehr H.A., Delaloye J.F. and Huelsken J. (2011). Interactions between cancer stem cells and their niche govern metastatic colonization. Nature 481, 85-89.

Mao L., Yang J., Yue J., Chen Y., Zhou H., Fan D., Zhang Q., Buraschi S., Iozzo R.V. and Bi X. (2021). Decorin deficiency promotes epithelial-mesenchymal transition and colon cancer metastasis. Matrix Biol. 95, 1-14.

Michaylira C.Z., Wong G.S., Miller C.G., Gutierrez C.M., Nakagawa H., Hammond R., Klein-Szanto A.J., Lee J.S., Kim S.B., Herlyn M., Diehl J.A., Gimotty P. and Rustgi A.K. (2010). Periostin, a cell adhesion molecule, facilitates invasion in the tumor microenvironment and annotates a novel tumor-invasive signature in esophageal cancer. Cancer Res. 70, 5281-5292.

Neill T., Painter H., Buraschi S., Owens R.T., Lisanti M.P., Schaefer L. and Iozzo R.V. (2012). Decorin antagonizes the angiogenic network: Concurrent inhibition of Met, hypoxia inducible factor 1α, vascular endothelial growth factor A, and induction of thrombospondin-1 and TIMP3. J. Biol. Chem. 287, 5492-5506.

Neill T., Schaefer L. and Iozzo R.V. (2016). Decorin as a multivalent therapeutic agent against cancer. Adv. Drug Deliv. Rev. 97, 174-185.

Nuzzo P.V., Rubagotti A., Zinoli L., Ricci F., Salvi S., Boccardo S. and Boccardo F. (2012). Prognostic value of stromal and epithelial periostin expression in human prostate cancer: Correlation with clinical pathological features and the risk of biochemical relapse or death. BMC Cancer 12, 625.

Oda G., Sato T., Ishikawa T., Kawachi H., Nakagawa T., Kuwayama T., Ishiguro M., Iida S., Uetake H. and Sugihara K. (2012). Significance of stromal decorin expression during the progression of breast cancer. Oncol. Rep. 28, 2003-2008.

Ontsuka K., Kotobuki Y., Shiraishi H., Serada S., Ohta S., Tanemura A., Yang L., Fujimoto M., Arima K., Suzuki S., Murota H., Toda S., Kudo A., Conway S.J., Narisawa Y., Katayama I., Izuhara K. and Naka T. (2012). Periostin, a matricellular protein, accelerates cutaneous wound repair by activating dermal fibroblasts. Exp. Dermatol. 21, 331-336.

Qin X., Yan M., Zhang J., Wang X., Shen Z., Lv Z., Li Z., Wei W. and Chen W. (2016). TGFβ3-mediated induction of periostin facilitates head and neck cancer growth and is associated with metastasis. Sci. Rep. 6, 20587.

Santra M., Reed C.C. and Iozzo R.V. (2002). Decorin binds to a narrow region of the epidermal growth factor (EGF) receptor, partially overlapping but distinct from the EGF-binding epitope. J. Biol. Chem. 277, 35671-35681.

Schwanekamp J.A., Lorts A., Vagnozzi R.J., Vanhoutte D. and Molkentin J.D. (2016). Deletion of periostin protects against atherosclerosis in mice by altering inflammation and extracellular matrix remodeling. Arterioscler. Thromb. Vasc. Biol. 36, 60-68.

Silvers C.R., Liu Y.R., Wu C.H., Miyamoto H., Messing E.M. and Lee Y.F. (2016). Identification of extracellular vesicle-borne periostin as a feature of muscle-invasive bladder cancer. Oncotarget 7, 23335-23345.

Sirica A.E., Almenara J.A. and Li C. (2014). Periostin in intrahepatic cholangiocarcinoma: Pathobiological insights and clinical implications. Exp. Mol. Pathol. 97, 515-524.

Sofeu Feugaing D.D., Gotte M. and Viola M. (2013). More than matrix: The multifaceted role of decorin in cancer. Eur. J. Cell Biol. 92, 1-11.

Terao M., Yang L., Matsumura S., Yutani M., Murota H. and Katayama I. (2015). A vitamin D analog inhibits Th2 cytokine- and TGFβ - induced periostin production in fibroblasts: A potential role for vitamin D in skin sclerosis. Dermatoendocrinol. 7, e1010983.

Wallace D.P., White C., Savinkova L., Nivens E., Reif G.A., Pinto C.S., Raman A., Parnell S.C., Conway S.J. and Fields T.A. (2014). Periostin promotes renal cyst growth and interstitial fibrosis in polycystic kidney disease. Kidney Int. 85, 845-854.

Wang X., Liu J., Wang Z., Huang Y., Liu W., Zhu X., Cai Y., Fang X., Lin S., Yuan L. and Ouyang G. (2013). Periostin contributes to the acquisition of multipotent stem cell-like properties in human mammary epithelial cells and breast cancer cells. PLoS One 8, e72962.

Wang Z., Gu J., Yan A. and Li K. (2021). Downregulation of circ-RANBP9 in laryngeal cancer and its clinical significance. Ann. Transl. Med. 9, 484.

Wu H., Wang S., Xue A., Liu Y., Liu Y., Wang H., Chen Q., Guo M. and Zhang Z. (2008). Overexpression of decorin induces apoptosis and cell growth arrest in cultured rat mesangial cells *in vitro*. Nephrology 13, 607-615.

Wu H., Jiang W., Zhang Y., Liu Y., Zhao Z., Guo M., Ma D. and Zhang Z. (2010). Regulation of intracellular decorin via proteasome degradation in rat mesangial cells. J. Cell. Biochem. 111, 1010-1019.

Xie C., Mondal D.K., Ulas M., Neill T. and Iozzo R.V. (2022). Oncosuppressive roles of decorin through regulation of multiple receptors and diverse signaling pathways. Am. J. Physiol. Cell Physiol. 322, C554-C566.

Yamaguchi Y., Mann D.M. and Ruoslahti E. (1990). Negative regulation of transforming growth factor-beta by the proteoglycan decorin. Nature 346, 281-284.

Yue H., Li W., Chen R., Wang J., Lu X. and Li J. (2021). Stromal POSTN induced by TGF-β1 facilitates the migration and invasion of ovarian cancer. Gynecol. Oncol. 160, 530-538.

Zhang R., Yao R.R., Li J.H., Dong G., Ma M., Zheng Q.D., Gao D.M., Cui J.F., Ren Z.G. and Chen R.X. (2017). Activated hepatic stellate cells secrete periostin to induce stem cell-like phenotype of residual hepatocellular carcinoma cells after heat treatment. Sci. Rep. 7, 2164.

Zhao Y., Wang S., Sorenson C.M., Teixeira L., Dubielzig R.R., Peters D.M., Conway S.J., Jefcoate C.R. and Sheibani N. (2013). Cyp1b1 mediates periostin regulation of trabecular meshwork development by suppression of oxidative stress. Mol. Cell. Biol. 33, 4225-4240.

Accepted August 26, 2024