SOX2 knockdown inhibits the migration and invasion of basal cell carcinoma cells by targeting the SRPK1-mediated PI3K/AKT signaling pathway

ZHUO-RAN LI¹, YONG JIANG¹, JIAN-ZHONG HU², YANG CHEN³ and QUAN-ZHONG LIU²

¹Department of Dermatology, The Second Hospital of Tianjin Medical University, Tianjin 300211; ²Department of Dermatology, Tianjin Medical University General Hospital, Tianjin 300052; ³Department of Orthopedics Institute, Tianjin Hospital, Tianjin 300211, P.R. China

Received August 12, 2017; Accepted February 1, 2018

DOI: 10.3892/ol.2018.9810

Abstract. Basal cell carcinoma (BCC) is the most common type of human skin cancer, which is driven by the aberrant activation of Hedgehog signaling. Previous evidence indicated that sex determining region Y-box 2 (SOX2) is associated with the tumor metastasis. However, the expression and role of SOX2 in BCC remain unknown. Therefore, the aim of the current study was to analyze the possible mechanism of SOX2 in the progression of BCC. The levels of SOX2 in BCC cells were detected by reverse transcription-quantitative polymerase chain reaction. Transwell assays were also used to determine the migration and invasion of BCC cells. Immunoblotting and immunofluorescence were used for analyzing the role of SOX2 knockdown in the serine-arginine protein kinase 1 (SRPK1)-mediated phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling pathway in BCC cells. The results demonstrated that SOX2 is overexpressed in BCC tissues and cells. In addition, SOX2 knockdown inhibited the migration and invasion of BCC cells, and the epithelial-mesenchymal transition (EMT) progress of BCC cells. It was also observed that SOX2 knockdown decreased SRPK1 expression, which further led to the downregulation of PI3K and AKT expression levels in BCC cells. Furthermore, SRPK1 transfection or PI3K/AKT pathway activation abolished the inhibitory effects of SOX2 knockdown on the migration, invasion and EMT progress of BCC cells. In conclusion, these results indicated that SOX2 may potentially serve as a target for BCC therapy by targeting the SRPK1-mediated PI3K/AKT signaling pathway.

Introduction

Basal cell carcinoma (BCC) is one of the most common types of human skin cancer, which is characterized by mutations in the patched and/or smoothened genes, and aberrant expression of the Hedgehog signaling pathway (1). Epidemiological studies have reported that BCC is associated with exposure to radiation in various populations, including atomic bomb survivors, radiologists and interventional cardiologists (2,3). Currently, exposure to UV rays is the most common cause of BCC onset in the general population, and numerous possible mechanisms have been proposed for the pathogenesis of BC, such as DNA damage and certain cell signaling pathways (4–6). However, various regulatory factors involved in the chronological progression of BCC lesions also require further investigation.

Sex determining region Y (SRY)-box 2 (SOX2) is a member of the SRY-related high mobility group box family that has been widely reported to be involved in human carcinogenesis and several malignancies (7,8). More recently, it has been observed that SOX2 presented completely distinct effects for different tumor types (9–11). Previous studies have indicated that SOX2 promoted the development of certain types of cancer, including osteosarcomas (12), colorectal cancer (13), glioblastomas (14), prostate cancer (15), breast cancer (16) and ovarian cancer (17), while it exhibited inhibitory roles in gastric cancer (18) and squamous cell lung cancer (19). These findings suggested that SOX2 may be regarded as a tumor-associated gene in human cancer. In addition, multivariate analysis further demonstrated that the SOX2 expression may be a prognostic factor in cancer patients (20,21). However, the regulatory roles and potential mechanisms of SOX2 remain elusive in BCC.

A previous study has indicated that epithelial-mesenchymal transition (EMT) signaling is implicated in the invasion and metastasis of various types of human cancer (22,23). In addition, it has been reported that inhibition of serine-arginine protein kinase 1 (SRPK1) suppressed prostate cancer progression by modulation of VEGF alternative splicing (24). Furthermore, phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling pathway participates in the signal transduction in tumor cells (25,26). Therefore, the present study investigated...
the role of SOX2 in the invasion and metastasis of BCC cells, and hypothesized that the regulatory effect of SOX2 was exerted through the SRPK1-mediated PI3K/AKT signaling pathway.

Materials and methods

Clinical tissues. A total of 12 (male/female, 6/6) BCC tissues and matched adjacent non-tumor tissues were collected at the Department of Dermatology, The Second Hospital of Tianjin Medical University (Tianjin, China) between May 2008 and June 2016. The pathological diagnosis of the BCC patients (mean age, 48.6 years; range, 42.2-54.5) was performed according to the World Health Organization criteria (27). Patients with a history of cancer were excluded from the present study. The BCC tissues were stored at -80°C and then embedded in paraffin. None of the patients received chemotherapy, radiotherapy or other treatments prior to tumor resection. All patients were required to provide written informed consent. This study also approved by Ethics committee of Tianjin Medical University General Hospital.

Cell culture. BCC and normal cells were obtained from the 12 BCC tissues and matched adjacent non-tumor tissues, respectively, as described previously (28). Cells were maintained in Dulbecco's modified Eagle's medium (DMEM; Sigma-Aldrich; Merck KGaA, Darmstadt, Germany) supplemented with 10% fetal bovine serum (FBS; Sigma-Aldrich; Merck KGaA), 100 U/ml penicillin, 100 µg/ml streptomycin, sodium pyruvate and L-glutamine at 37°C in an atmosphere with 5% CO2.

Immunohistochemical (IHC) analysis. The BCC and normal tissue sections (4 µm) obtained from patients were deparaffinized in xylene and rehydrated through graded ethanol. Following blocking of endogenous peroxidase activity in 3% hydrogen peroxide for 10 min at room temperature, the samples were analyzed for SOX2 expression using immunostaining, as described previously (29). Briefly, tumor sections were incubated with specific primary antibodies for anti-SOX2 (1:1,000; Abcam, Cambridge, MA, USA) for 12 h at 4°C. Tumor tissues were then incubated with a monoclonal horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG antibody (PV-6001; OriGene Technologies, Inc.) for 24 h at 4°C. A Ventana Benchmark automated staining system (Tucson, AZ, USA) was used for analyzing the protein expression.

Small interfering RNA (siRNA) transfection. BCC cells (4x10^4 cells/well) were seeded into 6-well and incubated for 24 h at 37°C. Next, the medium was removed and Opti-MEM (Invitrogen; Thermo Fisher Scientific, Inc.) was added for 24 h at 37°C. The siRNA sequences corresponding to each gene were designed and synthesized by GenePharma Co., Ltd. (Shanghai, China), and were as follows: siRNA-SOX2, 5'-CUG CAG UAC AAC UCC AUG ATT-3'; siRNA-vector (control), 5'-CUC GUC AAC UCC AUG ATT-3'; siRNA-SRPK1, 5'-CCA UTG GUU CGG UGG UCA ATT-3'; siRNA-PI3K, 5'-CGG ATT TGG TC-3', and reverse, 5'-AGC CTT CTC CAT GGT TCA AGG CAG AGA-3'; siRNA-AKT, 5'-AGC CTT CTC CAT GGT TCA AGG CAG AGA-3', and reverse, 5'-CAG GAG TTG TCA AGG CAG AGA-3'; and reverse, 5'-CAGGAGTTG TCAAGGCAGAGA-3'. The PCR thermocycling conditions included 45 amplification cycles, of denaturation at 95°C for 15 sec, primer annealing at 66°C for 20 sec and primer extension at 72°C for 15 sec. Relative levels of mRNA expression were calculated using the 2^-ΔΔCq method (30). The results were expressed as a fold change relative to the normal controls by comparing the levels of target mRNA expression to that of the β-actin control group.

Western blotting. BCC cells were homogenized in lysis buffer containing protease inhibitor (Sigma-Aldrich; Merck KGaA) and centrifuged at 8,000 x g at 4°C for 10 min. SDS assays were performed as described previously (31). Subsequent to blocking in 5% skimmed milk for 1 h at 37°C, the following primary antibodies at a dilution of 1:1,000 were added to membranes: PI3K (ab86714), AKT (ab8805), SOX2 (ab92494), SRPK1 (ab90527), E-cadherin (ab40772), Vimentin (ab92547), Fibronectin (ab2413) and β-actin (ab5694; all purchased from Abcam). Membranes were then incubated with monoclonal HRP-conjugated goat anti-rabbit IgG secondary antibodies (PV-6001; OriGene Technologies, Inc.) for 24 h at 4°C. A Ventana Benchmark automated staining system (Tucson, AZ, USA) was used for analyzing the protein expression.

Lentivirus production and cell transduction. The packaging plasmid psPAX2 and the envelope plasmid pMD2.G were purchased from Invitrogen (Thermo Fisher Scientific, Inc.). pWPXLSOX2 (pSOX2), pWPXLSRPK1 (pSRPK1) or pWPXLP (pvector) vector was transfected into BCC cells or siRNA-SOX2-transfected BCC cells using Lipofectamine 2000 (Invitrogen; Thermo Fisher Scientific, Inc.). Following incubation for 48 h at 37°C, cells were used for further analysis.

Cell proliferation assays. BCC cells transfected with pSOX2, pvector, siRNA-vector or siRNA-SOX2 vector were seeded into 6-well plates (2x10^4 cells/well) and cultured at 37°C for 14 days. Following incubation, the medium was removed, and the cells were fixed with 100% methanol and stained with 0.1% (v/v) crystal violet (Sigma-Aldrich; Merck KGaA). Cell viability was determined by microscopy and quantified using ImageJ software (NIH, USA).
colonies were counted using Image-Pro Plus version 5.0 software (Media Cybernetics, Inc., Bethesda, MD, USA).

**Cell migration and invasion analysis.** BCC cells were transfected with pSOX2, pSRPK1, siRNA-SOX2 or siRNA-SRPK1, and BCC or transfected BCC cells were treated with MK2206 (2 mg, Sigma-Aldrich; Merck KGaA) for 12 h at 37˚C. For the migration and invasion assay, BCC cells with 150 µl serum-free DMEM were placed into the upper chamber of 6-well plates at a density of 1x10^4 cells/well, and DMEM in the lower chamber supplemented with 10% FBS (Sigma-Aldrich; Merck KGaA). Transwell inserts (pore size, 8 µm; EMD Millipore, Billerica, MA, USA) that were uncoated or coated with Matrigel were used to evaluate the cell migration and invasion, respectively. After 24 h, BCC cells in the lower chamber were fixed in 4% paraformaldehyde for 15 min at 37˚C and stained with 0.1% crystal violet dye (Sigma-Aldrich) for 20 min at 37˚C. Subsequently, the cells were counted in 3 randomly selected fields of view using a light microscope (Olympus BX51; Olympus Corporation).

**Statistical analysis.** Data are expressed as the mean ± standard deviation of at least three independent replicates. All data were analyzed by SPSS software, version 19.0 (IBM Corp., Armonk, NY, USA) and Graphpad Prism version 5.0 (GraphPad Software, Inc., La Jolla, CA, USA) using one-way analysis of variance, followed by Tukey’s multiple comparison post hoc tests. P<0.05 and P<0.01 values were considered to indicate differences that were statistically significant.

**Results**

**Expression of SOX2 in BCC tissues and cell lines.** BCC tissue samples (12 patients) and BCC cell lines were used to analyze the expression of SOX2. It was demonstrated that SOX2 was overexpressed in BCC tissue samples when compared with normal basal tissue, as determined by immunohistochemical staining (magnification, x40). (B) Gene and (C) protein expression levels of SOX2 were upregulated in BCC cell lines as compared with those in normal cells. (D) SOX2 protein expression levels in BCC cells and the normal basal cells. **P<0.01. SOX2, sex determining region Y-box 2; BCC, basal cell carcinoma; NB, normal basal.

Abcam). Cells were then treated with fluorescein isothiocyanate-conjugated donkey anti-rabbit IgG polyclonal antibodies (Jackson ImmunoResearch Laboratories, Inc., West Grove, PA, USA) for 2 h at 37˚C. Finally, the cells were examined using a microscope (Leica DMi4000 B; Leica Microsystems GmbH, Wetzlar, Germany).

Immunofluorescence assay. Immunofluorescence was performed as previously described (32). Briefly, the siRNA-SOX2-transfected BCC cells were cultured in 6-well plates for 24 h at 37˚C. The BCC cells were then washed with phosphate-buffered saline and fixed with 4% paraformaldehyde (Sigma-Aldrich) at 4˚C for 10 min. The cells were again rinsed with phosphate-buffered saline and permeabilized with 1% Triton X-100 at 4˚C for 10 min. Subsequently, the cells were incubated for 2 h at 37˚C with the indicated antibodies as follows: E-cadherin (1:1,000; ab40772), Vimentin (1:1,000; ab92547), Fibronectin (1:1,000; ab2413; all purchased from Abcam).
It was observed that SOX2 knockdown by siRNA targeting SOX2 markedly downregulated the expression of SOX2, while SOX2 overexpression by pSOX2 transfection markedly upregulated SOX2 expression in BCC cells, indicating that the transfections were successfully performed (Fig. 2A and B). The results then demonstrated that SOX2 overexpression promoted the cell migration and invasion (Fig. 2C and D), while SOX2 knockdown inhibited the migration and invasion of BCC cells (Fig. 2E and F). These results suggest that SOX2 expression is associated with BCC cell migration and invasion.

**SOX2 knockdown inhibits the EMT process and the growth of BCC cells.** A previous study has suggested that the EMT process is a critical regulator in the progression of cancer metastasis (33). Therefore, the effects of SOX2 on EMT processes in BCC cells were further analyzed. The results revealed that overexpression of SOX2 promoted BCC cell proliferation, whereas knockdown of SOX2 inhibited BCC cell proliferation (Fig. 3A and B). In addition, SOX2 knockdown upregulated the expression of the epithelial marker E-cadherin, and inhibited the levels of the mesenchymal markers Vimentin and Fibronectin in BCC cells. By contrast, SOX2 overexpression caused the reverse effects on the EMT process markers in BCC cells (Fig. 3C and D). The immunofluorescence assay also confirmed the effects of SOX2 knockdown and overexpression on the epithelial and mesenchymal marker expression levels in BCC cells (Fig. 3E and F). These results indicate that SOX2 expression regulates the EMT processes and proliferation of BCC cells.
SRPK1 is a direct target of SOX2 in BCC cells. A previous study has indicated that SRPK1 is associated with human cancer metastasis (34). To elucidate the potential molecular mechanisms mediated by SOX2, SRPK1 expression was analyzed in BCC cells. The results demonstrated that SOX2 transfection promoted SRPK1 expression, while SOX2 knockdown inhibited SRPK1 expression in BCC cells (Fig. 4A and B). In addition, SRPK1 knockdown was observed to result in a marked reduction of cell migration and invasion (Fig. 4C and D). However, SRPK1 overexpression prominently canceled the SOX2 knockdown-inhibited migration and invasion of BCC cells compared to control (Fig. 4E and F). Furthermore, SRPK1 knockdown downregulated the EMT processes of BCC cells as observed by the increased E-cadherin and decreased the levels of Vimentin and Fibronectin (Fig. 4G). By contrast, SRPK1 overexpression canceled the SOX2 knockdown-inhibited EMT processes of BCC cells (Fig. 4H). These data suggest that SRPK1 is a direct target of SOX2-induced EMT processes in BCC cells.

SOX2 knockdown inhibits BCC cell invasion through the PI3K/AKT signaling pathway. A previous study has indicated that SRPK1 promotes the activation of PI3K/AKT signaling in the metastasis of human cancer (35). In the present study, the association between SOX2 and the PI3K/AKT signaling pathway was explored in BCC cells. As shown in Fig. 5A and B, SOX2 knockdown markedly decreased the expression levels of PI3K and AKT in BCC cells, whereas SRPK1 overexpression increased these levels (Fig. 5C and D). However, activation of the PI3K/AKT pathway by MK2206 abrogated the inhibitory effects of SOX2 knockdown on BCC cell migration and invasion (Fig. 5E and F). Thus, these results suggest that SOX2 knockdown inhibits BCC cell invasion through the PI3K/AKT signaling pathway.

Discussion

Several studies have indicated that SOX2 expression is markedly increased in human cancer tissues compared with that in normal tissues, including in ovarian and prostate cancer (36,37). In the present study, SOX2 expression in BCC tissues and cell lines was determined, and the results indicated that SOX2 is overexpressed in BCC tissues and cell lines. More recently, SOX2 expression was reported to be associated with lymph node metastases and distant invasion in right-sided colon cancer, suggesting that SOX2 also regulates tumorigenesis (38). Findings in the current study indicated that SOX2 regulated BCC cell migration and invasion through targeting the SRPK1-mediated EMT and the PI3K/AKT signaling pathway.

Although the association of SOX2 expression with the progression of several human cancer cells has been reported (39-41), the functional roles and potential mechanisms in BCC have not been examined previously. Currently, the role of SOX2 remains controversial in different cancer types (42).

Several studies have indicated that SOX2 expression is markedly increased in human cancer tissues compared with that in normal tissues, including in ovarian and prostate cancer (36,37). In the present study, SOX2 expression in BCC tissues and cell lines was determined, and the results indicated that SOX2 is overexpressed in BCC tissues and cell lines. More recently, SOX2 expression was reported to be associated with lymph node metastases and distant invasion in right-sided colon cancer, suggesting that SOX2 also regulates tumorigenesis (38). Findings in the current study indicated that SOX2 regulated BCC cell migration and invasion through targeting the SRPK1-mediated EMT and the PI3K/AKT signaling pathway.

Although the association of SOX2 expression with the progression of several human cancer cells has been reported (39-41), the functional roles and potential mechanisms in BCC have not been examined previously. Currently, the role of SOX2 remains controversial in different cancer types (42).
in BCC. The differences between SOX gene and protein expression may have resulted from the translational efficiency of SOX in BCC tissue and cells. Yang et al (43) reported that SOX2 promoted the migration and invasion of laryngeal cancer cells by induction of matrix metalloproteinase-2 via the PI3K/AKT/mechanistic target of rapamycin pathway. However, Yoon et al (44) indicated that overexpression of SOX2 is associated with better overall survival in squamous cell lung cancer patients treated with adjuvant radiotherapy. The present study reported that SOX2 knockdown inhibited BCC cell migration and invasion by downregulation of the SRPK1-induced EMT signaling pathway.

SRPK1 is a highly conserved protein that is dysregulated in different types of cancer. SRPK1 inhibition has been regarded as a potential targeted therapeutic strategy for prostate cancer therapy (45). A previous study has indicated that SRPK1 serves a critical role in the EMT process of human glioblastoma (46). In the current study, it was demonstrated...
that SRPK1 is a potential target of SOX2, and its expression was decreased by SOX2 knockdown in BCC cells. In addition, this SRPK1 downregulation mediated by SOX2 knockdown further regulated the EMT process in BCC cells, resulting in inhibition of migration and invasion. Furthermore, it also reported that SRPK1 downregulation inhibited the PI3K/AKT signaling pathway. Therefore, reduced expression of SOX2 may lead to suppression of BCC metastasis.

A previous study has demonstrated that SRPK1 functions as an oncogene via promoting the activation of PI3K/AKT signaling (35). Numerous reports have also suggested that the activation of PI3K/AKT signaling pathway is involved in the development and progression of human cancer, and regulates the invasion of cancer cells (47-49). The current study results demonstrated that SOX2 knockdown downregulated the PI3K/AKT signaling pathway in BCC cells. Notably, PI3K/AKT serves a crucial role in the EMT process and in the proliferation and invasion of lung cancer cells (50). SOX2 was also involved in paclitaxel resistance of the prostate cancer cell line PC-3 via the PI3K/AKT pathway (51). The current study reported that activation of PI3K/AKT signaling pathway abrogated the effects of SOX2 knockdown on BCC cell migration and invasion. Therefore, the SRPK1/PI3K/AKT pathway may be involved in the role of SOX2 in the migration and invasion of BCC cells.

In conclusion, the present study findings indicated that SOX2 served a pivotal role in BCC cell migration and invasion through targeting the SRPK1-mediated PI3K/AKT signaling pathway, suggesting that SOX2 may be a novel potential therapeutic target for BCC.

Acknowledgements
Not applicable.

Funding
Not funding was received.

Availability of data and materials
The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Authors’ contributions
ZL and YJ performed all experiments in the present study. JH and YC analyzed the data, and QL designed all experiments in the present study.

Ethics approval and consent to participate
The present study was approved by the Ethics Committee of Tianjin Medical University General Hospital.
Consent for publication

The study participants provided consent for the publication of this data.

Competing interests

The authors declare that they have no competing interests.

References

1. Jacobsen AA, Aldahan AS, Hughes OB, Shah VV and Strasswimmer J: Hedgehog pathway inhibitor therapy for locally advanced and metastatic basal cell carcinoma: A systematic review and pooled analysis of interventional studies. JAMA Dermatol 152: 816-824, 2016.

2. Ericson MB, Wennberg AM and Larkö O: Review of photodynamic therapy in actinic keratosis and basal cell carcinoma. Ther Clin Risk Manag 4: 1-9, 2008.

3. Ionescu DN, Arida M and Jukic DM: Metastatic basal cell carcinoma: Four case reports, review of literature, and immunohistochemical evaluation. Arch Pathol Lab Med 130: 45-51, 2006.

4. Chen L, Silapunt S and Migden MR: Sonidegib for the treatment of advanced basal cell carcinoma: A comprehensive review of sonidegib and the BOLT trial with 12-month update. Future Zhao X, Sun D, Liu T, Che N, Gu Q, Dong X, Li R, Liu Y and Li J: Slug promotes hepatocellular cancer cell progression by increasing SOX2 and Nanog expression. Oncol Rep 33: 149-156, 2015.

5. Hou W, Pan C, Sun J, Gilbert C, Dreas-Elger K, Azzam DJ, Picon-Ruiz M, Kim M, Ullmer W, El-Ashry D, et al: VEGF drives cancer-initiating stem cells through VEGFR-2/Stat3 signaling to upregulate Myc and Sox2. Oncogene 34: 3107-3119, 2015.

6. Basu-Roy U, Seo E, Ramanathanurup L, Rapp TB, Perry JA, Orkin SH, Mansukhani A and Basilico C: Sox2 maintains self renewal of tumour-initiating cells in osteosarcomas. Oncogene 31: 2270-2282, 2012.

7. Li Y, Lv Z, He G, Wang J, Zhang X, Lu G, Ren X, Wang F, Zhu H, Ding Y, et al: The SOX17/miR-371-5p/SOX2 axis inhibits EMT, stem cell properties and metastasis in colorectal cancer. Oncotarget 6: 20019-20025, 2015.

8. van Roosmalen W, De Lévédec SE, Golani O, Smid M, Pulyakchina I, Timmermans AM, Look MP, Zi D, Pont C, de Graauw M, et al: Tumor cell migration screen identifies SRPK1 as breast cancer metastasis determinant. J Clin Invest 125: 1648-1664, 2015.

9. Chang Y, Wu Q, Tian T, Li L, Guo X, Feng Z, Zhou J, Zhang L, Zhou S, Feng G, Han F, et al: The influence of SRPK1 on glioma apoptosis, metastasis, and angiogenesis through the PI3K/Akt signaling pathway under normoxia. Tumour Biol 36: 6083-6093, 2015.

10. Bae KM, Dai Y, Vieweg J and Siemann DW: Hypoxia promotes SOX2 expression to promote prostate cancer cell invasion and sphere formation. Am J Cancer Res 6: 1078-1088, 2016.
37. Belotte J, Fletcher NM, Alexis M, Morris RT, Munkarah AR, Diamond MP and Saed GM: Sox2 gene amplification significantly impacts overall survival in serous epithelial ovarian cancer. Reprod Sci 22: 38-46, 2015.

38. Neumann J, Bahr F, Horst D, Kriegl L, Engel J, Luque RM, Gerhard M, Kirchner T and Jung A: SOX2 expression correlates with lymph-node metastases and distant spread in right-sided colon cancer. BMC Cancer 11: 518, 2011.

39. Liu XF, Yang WT, Xu R, Liu JT and Zheng PS: Cervical cancer cells with positive Sox2 expression exhibit the properties of cancer stem cells. PLoS One 9: e87092, 2014.

40. Herreros-Villanueva M, Zhang JS, Koening A, Abel EV, Smyrk TC, Bamlet WR, de Narvajas AA, Gomez TS, Simeone DM, Bujanda L and Billadeau DD: SOX2 promotes dedifferentiation and imparts stem cell-like features to pancreatic cancer cells. Oncogenesis 2: e61, 2013.

41. Chen S, Xu Y, Chen Y, Li X, Mou W, Wang L, Liu Y, Reisfeld RA, Xiang R, Lv D and Li N: SOX2 gene regulates the transcriptional network of oncogenes and affects tumorigenesis of human lung cancer cells. PLoS One 7: e36326, 2012.

42. Weinak K and Utikal J: SOX2 and cancer: Current research and its implications in the clinic. Clin Transl Med 3: 19, 2014.

43. Yang N, Hui L, Wang Y, Yang H and Jiang X: SOX2 promotes the migration and invasion of laryngeal cancer cells by induction of MMP-2 via the PI3K/Akt/mTOR pathway. Oncol Rep 31: 2651-2659, 2014.

44. Yoon HI, Park KH, Lee EJ, Keum KC, Lee CG, Kim CH and Kim YB: Overexpression of SOX2 is associated with better overall survival in squamous cell lung cancer patients treated with adjuvant radiotherapy. Cancer Res Treat 48: 473-482, 2016.

45. Mavrou A, Brakspear K, Hamdollah-Zadeh M, Damodaran G, Babaei-Jadidi R, Oxley J, Gillatt DA, Ladomery MR, Harper SJ, Bates DO and Oltean S: Serine-arginine protein kinase 1 (SRPK1) inhibition as a potential novel targeted therapeutic strategy in prostate cancer. Oncogene 34: 4311-4319, 2015.

46. Liao Z, Wu J, Wu M, Yan Y, Wang H, Cheng C and Tang W: The critical role of SRPK1 in EMT of human glioblastoma in the spinal cord. Mol Neurobiol 54: 1818-1824, 2017.

47. Liu JF, Tsao YT and Hou CH: Fractalkine/CX3CL1 induced intercellular adhesion molecule-1-dependent tumor metastasis through the CX3CR1/PI3K/Akt/NF-κB pathway in human osteosarcoma. Oncotarget 8: 54136-54148, 2016.

48. Cui H, Wu S, Shang Y, Li Z, Chen M, Li F and Wang C: Pleurutus nebiodensis polysaccharide(PNS0G) evokes A549 cell apoptosis by the ROS/AMPK/PI3K/AKT/mTOR pathway to suppress tumor growth. Food Funct 7: 1616-1627, 2016.

49. Sun Y, Tu Y, He L, Ji C and Cheng BO: High mobility group box 1 regulates tumor metastasis in cutaneous squamous cell carcinoma via the PI3K/AKT and MAPK signaling pathways. Oncol Lett 11: 59-62, 2016.

50. Meng J, Zhang XT, Liu XL, Fan L, Li C, Sun Y, Liang XH, Wang JB, Mei QB, Zhang F and Zhang T: WSTF promotes proliferation and invasion of lung cancer cells by inducing EMT via PI3K/Akt and IL-6/STAT3 signaling pathways. Cell Signal 28: 1673-1682, 2016.

51. Li D, Zhao LN, Zheng XL, Lin P, Lin F, Li Y, Zou HF, Cui RJ, Chen H and Yu XG: Sox2 is involved in paclitaxel resistance of the prostate cancer cell line PC-3 via the PI3K/Akt pathway. Mol Med Rep 10: 3169-3176, 2014.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.