Review Article

Role of Periostin in Oral Squamous Cell Carcinoma: A Systematic Review

Sandhya Sundar, Pratibha Ramani, Herald J. Sherlin, Gifrina Jayaraj

Department of Oral Pathology, Saveetha Dental College and Hospitals, Saveetha University, Chennai, Tamil Nadu, India

Abstract

Background: Like any other cancer, tumor microenvironment of oral squamous cell carcinoma (OSCC) is closely connected to every step of its tumorigenesis. Periostin is a unique multifunctional extracellular matrix protein found to be overexpressed in various types of human cancers. **Objective:** The objective of this systematic review is to critically analyze various studies in literature that have reported the expression of emerging novel tumor marker "PERIOSTIN" and to determine its role in OSCC. **Materials and Methods:** Articles on periostin in relation to OSCC were searched in PubMed, EMBASE, MEDLINE, and a thorough Google search was done. Hand search of Journals was also performed. Of nine potentially relevant articles, four were excluded on the grounds of exclusion criteria, and one was excluded being a review article. However, one article was included by internet search and hand search. Of the total of five relevant articles reviewed, the resulting data were collected and tabulated. **Results:** All the five studies reviewed demonstrated an upregulation of periostin in OSCC. Among the five, two studies showed a positive correlation of periostin with the invasive patterns of OSCC. Two of the studies correlated the expression of periostin with angiogenesis and lymphangiogenesis. Four of the five articles reviewed, showed a significant correlation of periostin expression with metastasis of OSCC. **Conclusion:** The inference drawn from this systematic review is that the periostin plays an important role in tumor progression including invasion, angiogenesis, and metastasis of OSCC raising the possibility that it could be used as a molecular target in the therapy of OSCC patients.

Keywords: *Oral squamous cell carcinoma, osteoblast-specific factor-2, prognosis, periostin*

Received: April, 2019.
Accepted: April, 2019.

Introduction

Oral squamous cell carcinoma (OSCC) is the malignant neoplasm with increased propensity for local invasion and early lymph node metastasis. The recent trends have shown its increased incidence among younger patients (<40 years), females and are typically associated with risk factors such as smoking, alcohol consumption, and betel-quid chewing.[1]

Oral carcinogenesis is a complex and dynamic process with the tumor environment (formed by extracellular matrix [ECM] and stromal cells) playing an important role in every step of tumorigenesis. ECM has complementary effects on development and metastasis of tumors in diverse ways: through extracellular secretion, altering phenotype of stromal or tumor cells, getting away with immune surveillance, and providing hypoxic environment.[2]

Periostin is a unique ECM protein found in collagen-rich connective tissues and encoded by POSTN gene. It belongs to the superfamily of transforming growth factor-beta (TGF-β)-inducible proteins.[3] As a secreted protein, periostin is mainly expressed by fibroblasts in the

Access this article online

Quick Response Code:

Website: www.ijofb.org

DOI: 10.4103/ijofb.ijofb_2_19

Address for correspondence:
Dr. Sandhya Sundar, E-mail: sandhyasundar0402@gmail.com

How to cite this article: Sundar S, Ramani P, Sherlin HJ, Jayaraj G. Role of periostin in oral squamous cell carcinoma: A systematic review. Int J Orofac Biol 2018;2:35-40.

stroma; other bone marrow-derived mesenchymal stromal cells and mesenchymal stem cells and their derivatives.

Recently, periostin was found to be overexpressed in various types of human cancers such as non-small cell lung carcinoma, breast cancer, colon cancer, head and neck cancer, ovarian cancer, and pancreatic ductal adenocarcinoma. Periostin expression was well correlated with their malignant behavior such as invasion, metastasis, and poor survival. Although periostin may play an important role for tumor progression in various types of cancer, some studies have reported it to be tumor suppressor in bladder carcinoma and osteosarcoma.[4]

Hence, this Systematic review aims to critically analyze various studies on the expression of periostin in OSCC and determine its role in tumor progression, prognosis, and its possibility as a therapeutic target.

Materials and Methods

Search strategy for identification of the studies

The Search strategy was in accordance with the Cochrane guideline for the systematic review. A search in PubMed.gov and embase.com was performed, using identical search strings till the year 2017. Search strategy used terms for two categories – OSCC and periostin. Due to scarcity of studies relating periostin to OSCC, a timeline was not included in the search, and all the possible articles were exhausted. The article search included only those studies done on humans that are published in the English literature.

Selection of studies

The selection of qualified studies was performed in three stages. The first stage was based on the title alone. The second stage was based on the abstract using the inclusion criteria, and the third stage of selection was based on the full-text article.

The hand search was carried out of the reference lists of the studies entering the review, in order to identify studies not found in the original search. The data were then extracted, tabulated, and analyzed. The process is shown in Figure 1.

Level of evidence

Each study was evaluated for the level of evidence as per Oxford Centre for Evidence-Based Medicine levels of evidence (March 2009). The level of evidence for all the included studies is summarized in Table 1.

Results

The search strategy identified five studies[5-9] that determine the expression and various roles of periostin in the pathogenesis of OSCC. The studies have been done either using tumor tissue samples or serum from oral cancer patients. All the five included studies[5-9] have shown increased expression of periostin in OSCC and its association with poor prognosis in OSCC. In two studies, the expression of periostin was compared with the invasive histopathology patterns.[5,6] Studies have shown the expression of periostin in relation to angiogenesis[5] and lymphangiogenesis.[8] Four studies have shown that increased expression of periostin is associated with metastasis.[5-8] The detailed description of the studies is summarized in Table 2. Description of excluded studies[10-13] are given in Table 3.

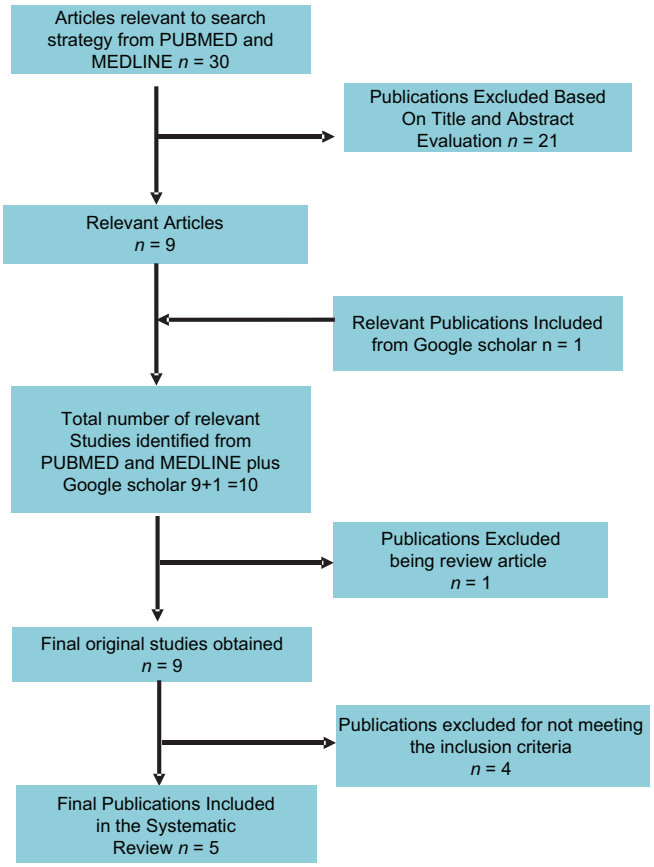

Figure 1: Search flowchart

Table 1: Level of evidence as per oxford centre for evidence-based medicine levels of evidence (March 2009)

Author	Study design	Evidence level
BSMS Siriwardena *et al*. 2006[17]	Retrospective cohort study	2b*
Kudo Y *et al*. 2006[18]	Retrospective cohort study	2b*
Peter choi *et al*. 2008[19]	Retrospective cohort study	2b*
Kudo Y *et al*. 2012[20]	Retrospective cohort study	2b*
Xing Qin *et al*. 2016[21]	Retrospective cohort study	2b*

*Oxford Centre for Evidence-Based Medicine Levels of Evidence (March 2009)

Table 2: Description of included studies

Author	Year	Sample used	No of samples	Method	Result	Significance
BSMS Siriwardena *et al*.[17]	2006	Human oral squamous cell carcinoma tissue Human oral squamous cell carcinoma tissue Human oral squamous cell carcinoma tissue Human oral squamous cell carcinoma tissue	31 74 74 74	RT-PCR Immunohistochemistry Correlation of positive periostin expression with invasive patterns (Grade I &II- low invasion Grade III & IV- high invasion) Clinicopathological Correlation of periostin expression with lymph node metastasis	In 68% (21 of 31of cases) high expression of Periostin mRNA observed In 69% (51 out of 74 cases), higher expression of periostin has been observed (P<0.005) High expression of Periostin observed in 100% Pattern IV invasion cases (23 cases) and 75.7%(28 out of 37 cases) with pattern III. Pattern I & II were completely negative for Periostin. (P<0.005) 91.9% (34 out of 37 cases) with lymph node metastasis showed higher expression of Periostin (P<0.005)	Periostin expression was correlated with tumor development in OSCC Periostin expression was correlated with tumor development in OSCC Periostin expression can enhance the invasiveness of OSCC Periostin expressing tumors frequently underwent lymph node metastasis
Kudo Y *et al*.[18]	2006	Human oral squamous cell carcinoma tissue Human oral squamous cell carcinoma tissue Human oral squamous cell carcinoma tissue Human oral squamous cell carcinoma tissue	102 102 62 41	Immunohistochemistry Correlation of positive periostin expression with invasive patterns (Grade I &II- low invasion Grade III & IV- high invasion) Clinicopathological Correlation of periostin expression with lymph node metastasis Microarray analysis	80.4% (82 out of 102 cases) showed positive expression of periostin (P=0.0001) 86.25% of cases with high invasive grading and 59% of low invasive grading showed periostin expression (P=0.01) 90.6% of cases with metastasis showed positive expression of periostin (P=0.28) Periostin expressed at higher levels in OSCC cases compared to 13 normal controls. OSCC cases with angiolymphatic invasion showed higher expression of periostin	Periostin expression was correlated with tumor development in OSCC Periostin enhanced invasion and anchorage-independent growth in OSCC cells Periostin expressing tumors frequently underwent lymph node metastasis. OSCC cases with metastasis showed higher Periostin expression correlated with angiolymphatic invasion
Peter Choi *et al*.[19]	2008	Human oral squamous cell carcinoma tissue	24	Immunohistochemistry of TMA sections Clinicopathological Correlation of periostin expression with cervical lymph node metastasis Clinicopathological Correlation of periostin expression with tumor stage	In 58.3% cases Periostin is highly expressed in cancer samples than normal controls (P<0.005). Periostin staining was localized primarily to the stroma 23.5% of cervical metastatic tumors showed periostin positivity 65% of the stage III/IV OSCC tumors, including 100% of T4 tumors were positive for epithelial periostin immunostaining, compared to only 25% of the stage I/II tumors	Periostin expression was correlated with tumor development in OSCC Periostin expression in primary tumor may be necessary but not sufficient for its presence in metastatic tumors Epithelial expression of periostin may be associated with a more aggressive tumor phenotype in OSCC

Contd...

Table 2: Contd...

Author	Year	Sample used	No of samples	Method	Result	Significance
Kudo *et al*.[20]	2012	Human oral squamous cell carcinoma tissue	54	Immunohistochemistry	High expression of periostin was observed in 72.2%(39 of 54 cases)	Periostin expression was correlated with tumor development in OSCC
		Serum of oral squamous cell carcinoma patients	81	ELISA	Periostin expression was observed in 92.6% cases (25 of 27) with lymphatic invasion	Periostin expression was significantly correlated with lymphatic invasion
					84.6% (33 of 39) OSCC cases with periostin expression expressed VEGF-C (P<0.0001)	Periostin induced up regulation of VEGF-C promoted lymphangiogenesis
					32.4% of periostin-positive cases	Periostin correlated with lymphatic invasion.
					The percentage of Periostin-positive cases increased with the stage of progression and with lymph node metastasis	Periostin expression was correlated with tumor progression and metastasis in OSCC
Xing Qin *et al*.[21]	2016	Human oral squamous cell carcinoma tissue	29	Real time PCR	POSTN was up regulated in 79.3% (23 of 29) of the cases. Higher expression of periostin was observed in tissues with lymph node metastasis	Periostin expression was correlated with tumor development in OSCC
		Human oral squamous cell carcinoma tissue	73	Immunohistochemistry		CAF derived POSTN play an important role in tumor progression
					Periostin was highly enriched in stroma of cancer tissues and produced mainly by cancer associated fibroblasts (CAFs)	

Table 3: Description of excluded studies

Citation	Reasons for exclusion
Kudo Y *et al*, 2007[4]	Does not satisfy our inclusion criteria being a review article
Deraz EM *et al*., 2011[10]	Does not satisfy our inclusion criteria being a cell line study
Gihan E.H.Gawish *et al*. 2013[11]	Does not satisfy our inclusion criteria being a cell line study done on human oral squamous cell carcinoma cells
M.G. Cristofaro *et al*., 2014[12]	No patient sample size was mentioned
Gonzalez HE *et al*., 2003[13]	Does not satisfy our inclusion criteria. Has very less sample size (3 patients)

Discussion

OSCC is one of the most common types of human cancer with very high mortality rate and failure of treatment options, despite advances of diagnostic and therapeutic strategies. The identification of novel invasion and metastasis-related molecules in OSCC and better understanding of mechanisms by which carcinoma cells undergo invasion and metastasis are of fundamental importance for better treat this disease.[4]

The knowledge of periostin has expanded from its recognized functions in embryogenesis, bone metabolism, to role in tissue repair and implications in cancer. For the last few years, numerous studies have described the role of periostin in the process of oncogenesis. The exact mechanism responsible for the effect of periostin on the progression of cancer and its metastasis is still subject of intense research.[14]

The systematic review analyzed a total of five studies which were selected based on inclusion and exclusion criteria in which various variables such as periostin protein and POSTN gene have been studied to ascertain the role of periostin protein in OSCC using human tumor tissue samples and serum samples. The pooled data were taken into consideration to determine the significant role of periostin and its potential as a novel prognostic indicator in OSCC.

Expression of periostin in oral squamous cell carcinoma

On analysis of the selected articles, all the five relevant articles by Siriwardena *et al*.,[5] Kudo *et al*.,[6] Choi *et al*.,[7] Kudo *et al*.,[8] and Qin[9] *et al*., highlighted increased expression of periostin with the mean expression level of 71.84%. Cumulative findings suggest that high expression of Periostin is associated with tumor progression in OSCC. Periostin binds to integrin through its FAS1 domain. This interaction leads to tumor progression by the activation of cytosolic

signaling cascades to mediate cell proliferation, cell survival, and cell migration.[4] This tumor progression confers with the phenotypic attributes of excessive growth, local invasiveness, and the ability to form distant metastases.[15]

Peter Choi *et al*.[7] and Xing Qin *et al*.[9] showed that periostin expression was mainly localization to the tumor stroma while Siriwardena *et al*.,[5] Kudo Y *et al*.[6] and Kudo Y *et al*.[8] demonstrated periostin expression in the cytoplasm of the carcinoma cells. Although the expression of periostin was slightly increased in tumor cells, Xing *et al*.[9] showed that periostin was highly enriched in the stroma of cancer tissues and produced mainly by cancer-associated fibroblasts (CAF). The TGF-β3 regulated production of periostin by CAF modulated a tumor-supportive microenvironment resulting in the cancer cell proliferation, colonization, invasion, and migration leading to metastasis.

Role of periostin in invasiveness of oral squamous cell carcinoma

Invasion forms an important step in the spread of tumors. Invasive tumors are more aggressive and frequently associated with metastases and poor prognosis. Cancer-associated fibroblasts (CAFs), ECM macromolecules, and neovascularization within the stroma of the tumor can have profound effects on the invasion of cancer cells.[16,17] With recent attempts to identify markers of invasion and metastases, the clinician's ability to target them therapeutically will be greatly enhanced.

Siriwardena *et al*.[5] and Kudo Y *et al*.[6] correlated levels of periostin expression with Jacobsson's invasive histopathology patterns[18] in OSCC cases. On an average, 85.6% of periostin expressing tumors showed highly invasive histopathology pattern (pattern III and pattern IV) suggesting that periostin positive cases frequently detaches from the tumor nests. Kudo Y *et al*.[6] showed that periostin-integrin interaction may inhibit ECM-integrin interaction and trigger intracellular signaling and activation of certain genes involved in invasion and anchorage-independent growth of OSCC. This periostin promoted invasion and anchorage-independent growth are important for cancer metastasis. Siriwardena *et al*.[5] identified periostin as an invasion-promoting factor by demonstrating the highest fold change expression of periostin in the invasive clones of OSCC cells.

Moreover, periostin-transfected cells showed morphological changes as well as an increase in the expression of mesenchymal markers. This suggests that periostin confers an invasive phenotype to periostin expressing tumors through epithelial mesenchymal transformation.[19-21]

Role of periostin in lymphangiogenesis and angiogenesis of oral squamous cell carcinoma

The most important poor prognostic indicator of OSCC is the cervical lymph node involvement. Lymphangiogenesis can occur adjacent to or within cancers and correlates with lymph node metastasis.[22] The number of lymph vessels in both intratumoral and peritumoral areas are associated with an increased tendency for nodal metastasis. Kudo *et al*.[8] showed periostin to be direct/indirect promoter of tumor lymphangiogenesis. The periostin mediated activation of the vascular endothelial growth factor-C (VEGF-C)/Flt-4 axis in lymphatic endothelial cells increases the formation of lymphatic vessels within and around tumors.

Siriwardena *et al*.[5] reported that periostin expression was well associated with blood vessels density. Periostin secreted by tumor cells acts in a paracrine manner to augment the survival of endothelial cells and induce neovascularization.[5] In endothelial cells, periostin promotes angiogenesis through the upregulation of VEGF-A/Flk-1/KDR expression through the integrin avb3-FAK-mediated signaling pathway.[23] This periostin-integrin interaction-mediated activation of angiogenesis is another mode through which metastasis occurs in OSCC.

Thus, Mutual interactions between periostin and VEGFs, VEGF-A, and VEGF-C play the key role in the initiation of new blood vessel and lymphatic vessel formation within and around tumors respectively that can facilitate metastasis.

Role of periostin in metastasis of oral squamous cell carcinoma

Metastasis is the leading cause of death in cancer patients. Attempts to identify the genes and proteins involved in the metastasis are pivotal for early detection of cancer behavior. Siriwardena *et al*.,[5] Kudo Y *et al*.,[6] Peter Choi *et al*.,[7] Kudo Y *et al*.,[8] and Xing Qin *et al*.[9] demonstrated higher expression of periostin in OSCC tissue of patients with lymph node metastasis confirming that overexpression of periostin might contribute to malignant potential. Similar to the study results of Bao *et al*.[24] and Sasaki *et al*.[25] All the five articles[5-9] reviewed gave a good clinicopathological correlation of metastasis in periostin-positive cases of OSCC with mean metastasis level of 90.25% observed in periostin expressing tumors.

Thus, this suggests invasion, cellular survival, and angiogenesis mediated by periostin may be involved in the process of metastasis and periostin may be a candidate for early prediction of metastasis in cancer.

From these, we evince that elevated levels of periostin lead to tumor growth by subsequent angiogenesis, lymphangiogenesis, cancer cell survival, increased invasion through epithelial-mesenchymal transition process, and metastasis substantiating their potential as a poor prognostic indicator of OSCC.

Conclusion

This systematic review identified that periostin plays a significant role in tumor progression including invasion, angiogenesis, and metastasis in OSCC and may be considered a potential therapeutic target.

Implications for practice

Periostin plays an important role in tumor progression, invasion, angiogenesis, and metastasis. Thus, it can be a useful marker to predict the prognosis of OSCC.

Implications for research

Periostin should be studied prospectively for its prognostic value and the role as a therapeutic target in OSCC.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Hussein AA, Helder MN, de Visscher JG, Leemans CR, Braakhuis BJ, de Vet HC, *et al.* Global incidence of oral and oropharynx cancer in patients younger than 45 years versus older patients: A systematic review. Eur J Cancer 2017;82:115-27.
2. Wang M, Zhao J, Zhang L, Wei F, Lian Y, Wu Y, *et al.* Role of tumor microenvironment in tumorigenesis. J Cancer 2017;8:761-73.
3. Horiuchi K, Amizuka N, Takeshita S, Takamatsu H, Katsuura M, Ozawa H, *et al.* Identification and characterization of a novel protein, periostin, with restricted expression to periosteum and periodontal ligament and increased expression by transforming growth factor beta. J Bone Miner Res 1999;14:1239-49.
4. Kudo Y, Siriwardena BS, Hatano H, Ogawa I, Takata T. Periostin: Novel diagnostic and therapeutic target for cancer. Histol Histopathol 2007;22:1167-74.
5. Siriwardena BS, Kudo Y, Ogawa I, Kitagawa M, Kitajima S, Hatano H, *et al.* Periostin is frequently overexpressed and enhances invasion and angiogenesis in oral cancer. Br J Cancer 2006;95:1396-403.
6. Kudo Y, Ogawa I, Kitajima S, Kitagawa M, Kawai H, Gaffney PM, *et al.* Periostin promotes invasion and anchorage-independent growth in the metastatic process of head and neck cancer. Cancer Res 2006;66:6928-35.
7. Choi P, Jordan CD, Mendez E, Houck J, Yueh B, Farwell DG, *et al.* Examination of oral cancer biomarkers by tissue microarray analysis. Arch Otolaryngol Head Neck Surg 2008;134:539-46.
8. Kudo Y, Iizuka S, Yoshida M, Nguyen PT, Siriwardena SB, Tsunematsu T, *et al.* Periostin directly and indirectly promotes tumor lymphangiogenesis of head and neck cancer. PLoS One 2012;7:e44488.
9. Qin X, Yan M, Zhang J, Wang X, Shen Z, Lv Z, *et al.* TGFβ3-mediated induction of periostin facilitates head and neck cancer growth and is associated with metastasis. Sci Rep 2016;6:20587.
10. Deraz EM, Kudo Y, Yoshida M, Obayashi M, Tsunematsu T, Tani H, *et al.* MMP-10/stromelysin-2 promotes invasion of head and neck cancer. PLoS One 2011;6:e25438.
11. Gawish GEH, Alomar HA. The role of periostin in regulation of early tumorigenesis in oral squamous cell carcinoma. Biochem Anal Biochem 2013;2:4.
12. Cristofaro MG, Scumaci D, Fiumara CV, Di Sanzo M, Zuccalà V, Donato G, *et al.* Identification of prognosis-related proteins in gingival squamous cell carcinoma by twodimensional gel electrophoresis and mass spectrometry-based proteomics. Ann Ital Chir 2014;85:518-24.
13. Gonzalez HE, Gujrati M, Frederick M, Henderson Y, Arumugam J, Spring PW, *et al.* Identification of 9 genes differentially expressed in head and neck squamous cell carcinoma. Arch Otolaryngol Head Neck Surg 2003;129:754-9.
14. Rosselli-Murai LK, Almeida LO, Zagni C, Galindo-Moreno P, Padial-Molina M, Volk SL, *et al.* Periostin responds to mechanical stress and tension by activating the MTOR signaling pathway. PLoS One 2013;8:e83580.
15. Goubran HA, Kotb RR, Stakiw J, Emara ME, Burnouf T. Regulation of tumor growth and metastasis: The role of tumor microenvironment. Cancer Growth Metastasis 2014;7:9-18.
16. Mueller MM, Fusenig NE. Friends or foes – Bipolar effects of the tumour stroma in cancer. Nat Rev Cancer 2004;4:839-49.
17. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell 2011;144:646-74.
18. Jakobsson PA, Eneroth CM, Killander D, Moberger G, Mårtensson B. Histologic classification and grading of malignancy in carcinoma of the larynx. Acta Radiol Ther Phys Biol 1973;12:1-8.
19. Toruner GA, Ulger C, Alkan M, Galante AT, Rinaggio J, Wilk R, *et al.* Association between gene expression profile and tumor invasion in oral squamous cell carcinoma. Cancer Genet Cytogenet 2004;154:27-35.
20. Gillan L, Matei D, Fishman DA, Gerbin CS, Karlan BY, Chang DD. Periostin secreted by epithelial ovarian carcinoma is a ligand for alpha(V)beta(3) and alpha(V)beta(5) integrins and promotes cell motility. Cancer Res 2002;62:5358-64.
21. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. J Clin Invest 2009;119:1420-8.
22. Kudo Y, Kitajjma S, Sato S, Miyauchi M, Ogawa I, Takata T. Establishment of an oral squamous cell carcinoma cell line with high invasive and p27 degradation activities from a lymph node metastasis. Oral Oncol 2003;39:515-20.
23. Shao R, Bao S, Bai X, Blanchette C, Anderson RM, Dang T, *et al.* Acquired expression of periostin by human breast cancers promotes tumor angiogenesis through up-regulation of vascular endothelial growth factor receptor 2 expression. Mol Cell Biol 2004;24:3992-4003.
24. Bao S, Ouyang G, Bai X, Huang Z, Ma C, Liu M, *et al.* Periostin potently promotes metastatic growth of colon cancer by augmenting cell survival via the Akt/PKB pathway. Cancer Cell 2004;5:329-39.
25. Sasaki H, Yu CY, Dai M, Tam C, Loda M, Auclair D, *et al.* Elevated serum periostin levels in patients with bone metastases from breast but not lung cancer. Breast Cancer Res Treat 2003;77:245-52.