Expression of periostin according to endometrial cancer grade

DILSAD HERKILOGLU 1, SEFIK GOKCE 1, ECMEL ISIK KAYGUSUZ 2 and OZGE CEVIK 3

1Department of Obstetrics and Gynaecology, Gaziosmanpasa Hospital, Yeni Yuzyl University, Istanbul 34245; 2Department of Pathology, Zeynep Kamil Training and Research Hospital, Istanbul 2022; 3Department of Biochemistry, School of Medicine, Aydin Adnan Menderes University, Aydin 09010, Turkey

Received January 18, 2022; Accepted April 21, 2022

DOI: 10.3892/ol.2022.13335

Abstract. While various molecular profiling methods have been described for the early diagnosis and prognostic process of endometrial cancer, the most common gynaecological cancer, the obtained data remain insufficient. The present study aimed to investigate the protein and gene expression of periostin and its role as a new biomarker in the diagnosis, treatment and prognosis of endometrial cancer. A total of 15 patients diagnosed with endometrial cancer at the Department of Pathology, Zeynep Kamil Training and Research Hospital (Istanbul, Turkey) and 15 patients who were operated on for non-tumour-related reasons, between December 2019 and May 2020, were included in the study. The cases diagnosed with endometrial cancer were divided into three groups: International Federation of Gynaecology and Obstetrics grades I, II and III. Pathology tumour blocks were selected for enzyme-linked immunosorbent assay and PCR studies in which periostin gene expression and protein levels were measured, respectively. A significant increase in periostin gene expression was observed in the endometrial cancer samples compared with that in the controls (3.40±0.66 vs. 2.23±0.47). The protein level of periostin in the tissues was found to be higher in the endometrial cancer samples than that in the control group (1.59±0.31 vs. 0.94±0.22). The levels of periostin protein and gene expression detected in the endometrial cancer samples increased as the grade increased. To the best of our knowledge, the current study is the first to determine the levels of periostin protein and gene expression in endometrial cancer. The results suggested that periostin may be used as a biomarker in the determination of higher histological grade in endometrial cancer.

Introduction

Endometrial cancer is the most common gynaecological cancer and is diagnosed in one out of 35 women in developed countries (1). When diagnosis of endometrial cancer is made, the first-line treatment is surgery, and then adjuvant treatment is recommended; however, adjuvant treatment is determined according to the tumour invasion depth, histological grade, patient age and lymph-vascular space invasion, which have an important role in the staging of endometrial cancer (2,3). While a high quality of life and improved clinical outcomes have recently been achieved for patients following use of chemotherapy and radiotherapy, the literature shows that 8% of patients with endometrial cancer in the high-risk group may develop distant metastases despite all treatment efforts (4,5). The early diagnosis of endometrial cancer will have a great impact on treatment management, the prognostic process and cost. While a number of molecular profiling studies indicate its value in the diagnosis and prognosis of endometrial cancer and its place in the risk classification of patients, the data available remain insufficient (6-9). This situation has driven researchers to seek novel biomarkers and target gene therapies.

Periostin (POSTN), a component of the extracellular matrix (ECM) produced by fibroblasts, interacts with integrin receptors and transmits signals to affect the cellular differentiation, adhesion and migration regulated by cytokines (10). The important role of POSTN in physiological processes has been demonstrated in a number of studies. For example, it has been shown that abnormal expression of POSTN is associated with the pathophysiology of asthma, myocardial damage and, most importantly, cancer (11-13). In cancer, POSTN interacts with integrin αvβ3 in endothelial cells and activates the focal adhesion kinase pathway, resulting in tumour angiogenesis through vascular endothelial growth factor (VEGF) regulating receptor-2 (VEGFR-2) (14).

Hiroi et al (15) first discovered that the expression of POSTN in the human endometrium varies according to the menstrual cycle, and is regulated by the oestrogen and progesterone released from the ovary. The present study aimed to investigate the protein and gene expression of POSTN and its utility as a biomarker in the determination of higher histological grade in endometrial cancer.

Materials and methods

Patients. A total of 15 patients diagnosed with endometrial cancer and treated at the Department of Pathology Zeynep Kamil Training and Research Hospital (Istanbul, Turkey) and 15 patients who received surgery for non-tumour-related
results between December 2019 and May 2020 were included in the present study. Three groups, International Federation of Gynaecology and Obstetrics grades I, II and III, were collected from the cases diagnosed with endometrial cancer via archive screening, with 5 patients in each group (16). All patients underwent a hysterectomy and bilateral salpingo-oophorectomy, as well as pelvic and/or paraaortic lymphadenectomy operations according to the pathology results obtained from frozen tissue samples. Tumour preparations of the cases from the pathology archive were re-evaluated, and endometrial cancer, non-tumour-related reason diagnosed blocks were selected for ELISA and PCR studies.

The control group consisted of patients who underwent a hysterectomy due to the indication of abnormal uterine bleeding; no cancer cells were detected in the endometrial sampling before the hysterectomy operation, and treatment-resistant bleeding continued.

Patients diagnosed with leiomyosarcoma, ovarian cancer and cervical cancer were excluded from the study.

Ethics. The present retrospective study was approved by the Ethics Committee of Zeynep Kamil Training and Research Hospital (Istanbul, Turkey; approval no. 116). All patients consented to treatment in accordance with institutional guidelines, and provided written informed consent at the time of the treatment. The present study was performed in accordance with the Declaration of Helsinki and the guidelines of the Ethics Committee of Zeynep Kamil Training and Research Hospital (Istanbul, Turkey).

Gene expression of POSTN by reverse transcription-quantitative (RT-q)PCR. From each paraffin block, five tissue sections (each 10-µm thick) were collected in 1.5-ml microfuge tubes. Extraction of total RNA from paraffin-embedded tissues was performed in duplicate using an FFPE RNA isolation kit (catalogue no. K156002; Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer’s instructions. RNA (1 µg) was reverse transcribed to cDNA with the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems; Thermo Fisher Scientific, Inc.) according to the manufacturer’s instructions. The following primers were used: POSTN forward, 5'-TGC TCGAATCATCCATGGGAA-3' and reverse, 5'-TGTGTA AGCACAGGCAATG-3'; and GAPDH forward, 5'-AGG GCTGCTTTTAACTCTGTTG-3' and reverse 5'-CCCCAC TTGATTTTGGAGGGA-3' (Merck KGaA). Amplification was performed with an ABI StepOnePlus detection system using SYBR Green PCR Master Mix (Applied Biosystems; Thermo Fisher Scientific, Inc.). The reaction conditions were as follows: 95°C for 10 min, followed by 40 cycles of 95°C for 15 sec and 60°C for 1 min. The results were analysed using StepOne Software v2.3 (Applied Biosystems; Thermo Fisher Scientific, Inc.) and using the 2-ΔΔCt method (17) and normalized to GAPDH mRNA. Data are expressed as fold-change relative to the control.

Protein levels of POSTN as determined by ELISA. A total of four formalin-fixed, paraffin-embedded tissue sections (each 10- to 15-µm thick) were placed in a 1.5 ml centrifuge tube. Samples were incubated with 250 µl buffer (pH 7.5; 0.05 M Tris, 1 mM EDTA and 0.5% Tween 20). The tube was placed at 100°C for 10 min and immediately placed into a dry ice ethanol slurry until frozen. Protein extraction of all samples was performed as previously described (18). Protein concentrations were measured using the Bradford method (19). POSTN levels were measured with the sandwich ELISA method following the kit manufacturer's instructions (cat. no. EH0255; Wuhan Fine Biotech Co., Ltd.) with an inter-assay coefficients of variability (cv) of <12% and an intra-assay cv of <10%, respectively. The mean minimum detectable quantity of human POSTN was 0.094 ng/ml. POSTN values are presented as ng/µg protein. All ELISA measurements were performed using a microplate reader (BioTek Instruments, Inc.).

Histopathological evaluation. Histopathological evaluation was performed on the samples of each of the 30 subjects. One sample per tumor centimeter was taken from each tumor and the samples were embedded in paraffin blocks and cut into 5-µm-thick sections using a Leica RM2125 RTS microtome device (Leica Microsystems GmbH). The selected paraffin sections were stained with haematoxylin and eosin (H/E) at room temperature for morphological evaluation (Figs. 1 and 2). One sample from each endometrial tumor was selected according to the WHO classification of tumors, 5th edition (16). A single sample was placed in each paraffin block. Proliferative endometrium samples were taken from hysterectomy materials that were surgically resected for reasons other than endometrial pathologies. All slides were examined under a light microscope (Olympus BX51; Olympus Corporation).

Statistical analysis. SPSS version 18.0 (SPSS, Inc.) was used for the statistical analysis. Values are expressed as the mean ± standard deviation for age, and as the mean ± standard error for the POSTN gene expression and protein levels. One-way ANOVA was used to analyse the differences among multiple groups, and an unpaired Student’s t-test was used to compare data between two groups. Post-hoc tests analyses were performed using Tukey’s test to compare the groups after one-way ANOVA, as the variances were homogeneous. Spearman's correlation analysis was used to analyse the correlations between cancer grade and POSTN protein levels and gene expression. P<0.05 was considered to indicate a statistically significant difference.

Results

The mean age was 55.6±9.0 years for the total patient cohort, with high similarity between the endometrial cancer and non-pathological control groups (58.8±8.8 vs. 52.4±8.3 years, respectively; P=0.05). H/E staining for endometrial cancer in Fig. 1; confluent glandular, cribriform pattern and intervening loss of stroma were observed. For proliferative endometrium (control) in Fig. 2; endometrial glands were observed to be uniform and widely spaced, and glandular epithelium consisted of low columnar cells.

To explore the role of POSTN in endometrial cancer tissues, the difference in expression was compared in the 15 endometrial cancer tissues and the 15 non-pathologically diagnosed hysterectomy tissues (control). Significantly increased POSTN gene expression was observed in cancer tissues compared with...
that in tissues without a pathological diagnosis (3.40±0.66 vs. 2.23±0.47, respectively) (Fig. 3A).

When the mean value for the protein level of POSTN was examined, it was found to be higher in endometrial cancer (1.59±0.31) compared with that in the control (0.94±0.22) (Fig. 3B).

Gene expression (P=0.005) and protein levels (P=0.003) were found to be significantly higher in the endometrial cancer group compared with those in the control group. Moreover, gene expression (P=0.007; Fig. 4A) and protein (P=0.015; Fig. 4B) levels were found to be significantly higher in the grade III patient group compared with those in the other grade groups and the control group. Grade I and II and the control groups were similar in terms of the mean gene expression and protein levels (P>0.05 for each).

In the results obtained in terms of demographic data, the median age in the endometrial cancer group was 57 years (range, 46-75 years) and the median age in the control group was 49 years (range, 43-67 years). The median age was 57 years (range, 53-75 years) in those with grade I disease, 52 years (range, 46-65 years) in those with grade II disease and 59 years (range, 50-73 years) in those with grade III disease.

The endometrial cancer grade was found to be significantly correlated with POSTN protein (P=0.003; Rho=0.719) and gene expression (P=0.010; Rho=0.643) levels (Fig. 5A and B).

**Discussion**

Epithelial-mesenchymal transition (EMT) is known as an important stage in cancer invasion and metastasis, and POSTN is a demonstrated factor in cell migration and transformation via EMT during cell differentiation and pathological progression (20). It has been shown that the effect of POSTN on EMT is mediated by the PI3K/AKT signalling pathway, which is regulated by cytokines, such as TGF-β1 (21,22). While POSTN is a marker of EMT, it is also an inducer of EMT (23). Previous studies have indicated that POSTN is expressed in large quantities in the tumour microenvironment and is one of the factors that mediate the communication between tumour cells and the ECM (21-23). The present study showed an increase in the protein level and gene expression of POSTN in endometrial cancer, and to the best of our knowledge, it is the first study reporting on this subject.

The endometrium consists of stromal and epithelial cells with eutopic and ectopic localization. In a previous study on the intrauterine physiological endometrium, POSTN expression was reported to increase significantly in the mid-proliferative and early secretory phases, while downregulated expression was observed in the late-proliferative, mid-secretory and late-secretory phases (15). The data obtained showed a strong association between oestrogen and progesterone supplementation and POSTN expression (15). POSTN expression is controlled by ovarian steroid hormones, and this may have a strong effect on physiological pregnancy and pathological processes (15). In other studies, POSTN was found to be overexpressed in tumour metastases, similar to certain mesenchymal cell markers, such as fibronectin and cadherin (24,25). POSTN interacts with integrin receptors to regulate the adhesion, differentiation and migration of undifferentiated cells with their characteristic fascin I domains (26). Cancer-associated fibroblasts are known as a major ECM component in the tumour microenvironment, and POSTN is partially produced by fibroblasts in metastatic lesions (27,28). In a previous study, it was determined that active fibroblasts secrete POSTN and support the differentiation, adhesion and migration of cholangiocarcinoma cells (29). Moreover, increased expression of POSTN has been shown to affect the tumour microenvironment by remodelling the ECM and interacting with integrins or other signalling molecules (10). The present study measured the protein level and gene expression of POSTN with regard to all three grades of endometrial cancer, and found that endometrial cancer grade was significantly correlated with gene expression and protein level, showing an increase in POSTN level as the grade increased. The present data support the results of previous studies indicating increased POSTN expression in malignant tissues such as colon, esophageal, nasopharyngeal carcinoma and pancreatic cancer (21-24).

In a large study conducted on patients diagnosed with ovarian cancer, POSTN was associated with drug resistance in epithelial ovarian cancer and gene expression profiling revealed a correlation between POSTN expression and chemotherapy resistance (30). In a previous study showing...
increased resistance to chemotherapy in chemosensitive ovarian cells under the influence of recombinant POSTN (31), it was reported that the proliferation and spread of non-small cell lung cancer cells could be inhibited, while sensitivity to chemotherapy was increased (32). In conclusion, targeting POSTN represents a novel therapeutic strategy for minimizing chemoresistance. There have been attempts to demonstrate the efficacy of targeting POSTN in the detection and treatment of tumours in several preclinical models. One of them used near-infrared fluorescence imaging with upper gastrointestinal endoscopy to detect preneoplastic lesions via optical imaging of POSTN (33). Kyutoku et al (34) reported that treatment with PNI-Ab, an anti-POSTN antibody in breast cancer, was able to significantly inhibit the growth of primary tumours and the formation of lung metastases in an experimental study.

The present study has certain limitations. For example, patient serum samples were not assessed, as paraffin-embedded tissues were used. The aim of the study was to demonstrate the POSTN changes at the tissue level before proceeding with measuring changes in the serum in larger groups in future studies and the fact that the sample size was small was another limitation of the study.

The data obtained in the present study suggest that POSTN may be used as a biomarker in the early detection of...
endometrial cancer and determination of higher histological grade. Further comprehensive studies are required to fully elucidate the clinical value and prognostic impact of POSTN.

Acknowledgements

The authors would like to thank Professor Canan Kabaca (Zeynep Kamil Training and Research Hospital, Istanbul, Turkey) for sharing her experience and knowledge and for her contribution to this study by surgical techniques and literature review.

Funding

No funding was received.

Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

DH: Project development and manuscript writing, SG: Data management, data analysis and manuscript writing, EK: Data collection and management and data analysis, OC: Data analysis, manuscript writing and editing. DH and OC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Zeynep Kamil Training and Research Hospital (Istanbul, Turkey; approval no. 116). All patients consented to treatment in accordance with institutional guidelines, and all provided written informed consent at the time of the treatment.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jamal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68: 394-424, 2018.
2. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsten JJ, Wârlâm-Rodenhuis CC, De Winter KA, Luftgens LC, van den Bergh AC, de Steen-Banasik EM, et al.: Surgery and postoperative radiotherapy versus surgery alone for patients with stage-I endometrial carcinoma: Multicentre randomised trial. PORTEC study group. Post operative radiation therapy in endometrial cancer. Lancet 355: 1404-1411, 2000.
3. Nout RA, Smit VT, Putter H, Jürgenliemk-Schulz IM, Jobsten JJ, Luftgens LC, van de Steen-Banasik EM, Mens JW, Slot A, Kroese MC, et al.: Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): An open-label, non-inferiority, randomised trial. Lancet 375: 816-823, 2010.
4. Örtoft G, Hansen ES and Bertelsen K: Omitting adjuvant radiotherapy in endometrial cancer increases the rate of locoregional recurrences but has no effect on long-term survival: The danish endometrial cancer study. Int J Gynecol Cancer 23: 1429-1437, 2013.
5. Thomas GM: A role for adjuvant radiation in clinically early carcinoma of the endometrium? Int J Gynecol Cancer 20 (11 Suppl 2): S64-S66, 2010.
6. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pushtian J, Shen R, et al.: Integrated genomic characterization of endometrial carcinoma. Nature 497: 67-73, 2013.
7. Talhouk A, McConathy MK, Leung S, Li-Chang HH, Kwon JS, Melnyk N, Yang W, Senz J, Boyd N, Karnezis AN, et al.: A clinically applicable molecular-based classification for endometrial cancers. Br J Cancer 113: 290-310, 2015.
8. Talhouk A and McAlpine IN: New classification of endometrial cancers: The development and potential applications of genomic-based classification in research and clinical care. Gynecol Oncol Res Pract 3: 14, 2016.
9. Talhouk A, McConathy MK, Leung S, Yang W, Lum A, Senz J, Boyd N, Pike J, Anglesio M, Kwon JS, et al.: Confirmation of ProMisE: A simple, genomics-based classifier for endometrial cancer. Cancer 123: 802-813, 2017.
10. Liu AY, Zheng H and Ouyang G: Periostin, a multifunctional matricellular protein in inflammatory and tumor microenvironments. Matrix Biol 37: 150-156, 2014.
11. Woodruff PF, Boussekey HA, Dolganov GM, Barker CS, Yang YH, Donnelly S, Ellwanger A, Sidhu SS, Dao-Pick TP, Pantoca J, et al.: Genome-wide profiling identifies epithelial cell genes associated with asthma and with treatment response to corticosteroids. Proc Natl Acad Sci USA 104: 15858-15863, 2007.
12. Duan GW II: Periostin and myocardial repair, regeneration, and recovery. N Engl J Med 357: 1552-1554, 2007.
13. Sasaki H, Dai M, Auclair D, Kaji M, Fukai I, Kiriyama Y, Yamakawa Y, Fujii Y and Chen LB: Serum level of the periostin, a homologue of an insect cell adhesion molecule, in thymoma patients. Cancer Lett 172: 37-42, 2001.
14. Shao R, Bao S, Bai X, Blanchette C, Anderson RM, Tang D, Gishizky ML, Marks JR and Wang XF: 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 24: 3992-4003, 2004.
15. Hino H, Momoeada M, Nakazawa F, Koizumi M, Tsutsui R, Hosokawa Y, Osuga Y, Yano T, Tsutsui O and Taketani Y: Expression and regulation of periostin/OSF-2 gene in rat uterus and human endometrium. Endocr J 55: 183-189, 2008.
16. Creasman WT, Ondico F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, Heintz AP, Ngan HY and Pecorelli S: Carcinoma of the corpus uteri. FIGO 26th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet 95 (Suppl 1): S105-S143, 2006.
17. Livak KJ and Schmittgen TD: Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta CT(T)) method. Methods 23: 402-408, 2001.
18. Nicholson EM, Greenlee JJ and Hamir AN: PrPSc detection in formalin-fixed paraffin-embedded tissue by ELISA. BMC Res Notes 4: 432, 2011.
19. Bradford MM: A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 72: 248-254, 1976.
20. Lindsley A, Snider P, Zhou H, Rogers R, Wang J, Olaopa M, Kruyznska-Freitag A, Koushik SV, Lily B, Burch JB, et al.: Identification and characterization of a novel Schwann and outflow tract endocardial cushion lineage-restricted peristin enhancer. Dev Biol 307: 340-355, 2007.
21. Bao S, Ouyang G, Bai X, Huang Z, Ma C, Liu M, Anderson RM, Bao S, Ouyang G, Bai X, Huang Z, Ma C, Liu M, Anderson RM, et al.: Periostin, a multifunctional matricellular protein in inflammatory and tumor microenvironments. Matrix Biol 37: 150-156, 2014.
22. Hillier R, Snider P, Zhou H, Rogers R, Wang J, Olaopa M, Kruyznska-Freitag A, Koushik SV, Lily B, Burch JB, et al.: Identification and characterization of a novel Schwann and outflow tract endocardial cushion lineage-restricted peristin enhancer. Dev Biol 307: 340-355, 2007.
23. Michaylira CZ, Wong GS, Miller CG, Gutierrez CM, Nakagawa H, Hammond R, Klein-Szanto AJ, Lee JS, Kim SB, Herlyn M, et al: 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, 2010.

24. Luo W and Yao K: Molecular characterization and clinical implications of spindle cells in nasopharyngeal carcinoma: A novel molecule-morphology model of tumor progression proposed. PLoS One 8: e83135, 2013.

25. Soltermann A, Tischler V, Arbogast S, Braun J, Probst-Hensch N, Weder W, Moch H and Kristiansen G: Prognostic significance of epithelial-mesenchymal and mesenchymal-epithelial transition protein expression in non-small cell lung cancer. Clin Cancer Res 14: 7430-7437, 2008.

26. Seifert GJ: Fascinating fasciclins: A surprisingly widespread family of proteins that mediate interactions between the cell exterior and the cell surface. Int J Mol Sci 19: 1628, 2018.

27. Malanchi I, Santamaria-Martínez A, Susanto E, Peng H, Lehr HA, Delaloye JF and Huelsken J: Interactions between cancer stem cells and their niche govern metastatic colonization. Nature 481: 85-89, 2011.

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

29. Utispan K, Thuwajit P, Abiko Y, Charrngkaew K, Paupairoj A, Chau-in S and Thuwajit C: Gene expression profiling of cholangiocarcinoma-derived fibroblast reveals alterations related to tumor progression and indicates periostin as a poor prognostic marker. Mol Cancer 9: 13, 2010.

30. Ryner L, Guan Y, Firestein R, Xiao Y, Choi Y, Rabe C, Lu S, Fuentes E, Huw LY, Lackner MR, et al: Upregulation of periostin and reactive stroma is associated with primary chemoresistance and predicts clinical outcomes in epithelial ovarian cancer. Clin Cancer Res 21: 2941-2951, 2015.

31. Sung PL, Jan YH, Lin SC, Huang CC, Lin H, Wen KC, Chao KC, Lai CR, Wang PH, Chuang CM, et al: Periostin in tumor microenvironment is associated with poor prognosis and platinum resistance in epithelial ovarian carcinoma. Oncotarget 7: 4036-4047, 2016.

32. Hu W, Jin P and Liu W: Periostin contributes to cisplatin resistance in human non-small cell lung cancer A549 cells via activation of Stat3 and Akt and upregulation of survivin. Cell Physiol Biochem 38: 1199-1208, 2016.

33. Wong GS, Habibollahi P, Heidari P, Lee JS, Klein-Szanto AJ, Waldron TJ, Gimotty P, Nakagawa H, Taylor PR, Wang TC, et al: Optical imaging of periostin enables early endoscopic detection and characterization of esophageal cancer in mice. Gastroenterology 144: 294-297, 2013.

34. Kyutoku M, Taniyama Y, Katsuragi N, Shimizu H, Kunugiza Y, Iekushi K, Koibuchi N, Sanada F, Oshita Y and Morishita R: Role of periostin in cancer progression and metastasis: Inhibition of breast cancer progression and metastasis by anti-periostin antibody in a murine. Int J Mol Med 28: 181-186, 2011.

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