Periostin expression and epithelial-mesenchymal transition in cancer: a review and an update

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Abstract Periostin, also called osteoblast-specific factor 2, is a secreted cell adhesion protein, which shares a homology with the insect cell adhesion molecule fasciclin I. It has been shown to be an important regulator of bone and tooth formation and maintenance, and of cardiac development and healing. Recent studies revealed that periostin plays an important role in tumor development and is upregulated in a wide variety of cancers such as colon, pancreatic, ovarian, breast, head and neck, thyroid, and gastric cancer as well as in neuroblastoma. Periostin binding to the integrins activates the Akt/PKB- and FAK-mediated signaling pathways which lead to increased cell survival, angiogenesis, invasion, metastasis, and importantly, epithelial-mesenchymal transition of carcinoma cells. In this review we summarize recent clinicopathological studies that have investigated periostin expression in lung, kidney, prostate, liver cancer, and malignant pleural mesothelioma and discuss the role of periostin isoforms in tumorigenesis and their potential as targets for stroma-targeted anticancer therapy.

Keywords Periostin · EMT · Isoform · Stroma · Target

Background

Periostin, also termed osteoblast-specific factor 2, is a 93.3-kDa secreted protein and shares a homology with the insect cell adhesion molecule fasciclin I. It promotes integrin-dependent cell adhesion and motility and belongs to the superfamily of TGF-β-inducible proteins [1, 2]. Its N-terminal region contains a signal peptide (SP) for its secretion, and a cysteine-rich region (EMI domain) which promotes the formation of multimers in non-reducing conditions. Adjacent to the SP and the EMI domains, four internal homologous repeats (FAS domains) are located; these are homologous to the insect cell adhesion protein fasciclin I and act as ligands for the integrins [1, 2]. The C-terminal region of periostin consists of a hydrophilic domain. The N-terminal region of periostin is highly conserved, while the C-terminal region of the protein varies depending on the isoform [1, 3]. The N-terminal region regulates the cell function by binding to integrins at the plasma membrane of the cells through its FAS domains. The C-terminal region of the protein regulates the cell–matrix organization and interactions by binding extracellular matrix (ECM) proteins such as collagen I/V, fibronectin, tenascin C, acid mucopolysaccharides, such as heparin and periostin itself [4]. Periostin was shown to be able to bind the integrins αvβ3, αvβ5, and α6β4, promoting the recruitment of the epidermal growth factor receptor (EGFR) and the activation of the Akt/PKB and FAK-mediated signaling pathways. Periostin-activated signaling pathways promote cellular survival, angiogenesis, and resistance to hypoxia-induced cell death. Additionally, periostin can be upregulated in response to the stress of hypoxia in the human A549 non-small cell lung cancer cell line and in rat pulmonary arterial smooth muscle cells (PASMCs) [5, 6]. The study of Li et al. demonstrated that upregulation of periostin in PASMCs is mediated through Ras signaling [6] (Fig. 1).

The desmoplastic tumor stroma constitutes the so-called tumor microenvironment, which supports growth, invasion, and immune evasion of the tumor. It is formed by a stromal matrix in which cancer cells and the peri-tumoral stromal...
cells are embedded. The tumor stromal cells consist of tumor-associated endothelial cells (TECs), cancer-associated fibroblasts (CAFs), and tumor-associated macrophages, as well as distinct sets of tumor-directed lymphocytes. All these cell types produce growth factors, angiogenic factors, and proteolytic enzymes which sustain the tumor growth and angiogenesis and degrade the ECM, enhancing the tumor cell invasion and metastasis [7]. Furthermore, an excessive production of ECM proteins such as periostin, collagen, and fibronectin may contribute to the generation of a tumor-supportive microenvironment (Fig. 2). Within this context, the matrix protein periostin (gene POSTN) plays an important role, regulating cell function and cell–matrix interactions.

Periostin probably exerts its pro-tumorigenic effect not only through its binding to the integrins and the consequent activation of intracellular pathways which determine an enhanced invasiveness, but also through its effect on the ECM fibrillogenesis. The C-terminal region of periostin has been shown to interact with ECM molecules by immunoprecipitation and binding assays [4, 8]. Together with those studies showing colocalization of periostin with fibronectin, collagen, and tenascin C [8], these findings suggest that periostin regulates collagen fibrillogenesis and biomechanical properties of connective tissues, forming reticular structures. Considering that alterations in the ECM components of the tumor microenvironment have a remarkable impact on the invasive and metastatic process, it is possible that periostin promotes an ECM organization that supports invasion and metastasis (Fig. 3).

Periostin protein is physiologically expressed in a wide variety of normal adult tissues and fetal tissues, such as embryonic periosteum, periodontal ligament, placenta, cardiac valves, adrenal glands, lung, thyroid, stomach, colon, vagina, ovary, testis, prostate, and breast [1, 9]. Moreover, periostin is expressed in tissues under stress conditions, such as heart under pressure or volume overload, skeletal muscle after injury, and in pulmonary aortic smooth muscle cells in response to hypoxia [6, 10, 11]. Periostin has been shown to be essential for bone and tooth formation and maintenance [2], for heart develop-
Periostin-deficient mice have a mild phenotype characterized by alterations in periodontal ligament and craniofacial ECM, structural valvular anomalies, and reduced fibrosis after myocardial infarction. Periostin upregulation has been reported for many cancer types, as non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), malignant pleural mesothelioma (MPM), and others and is consequently defined as a tumor-enhancing factor. Only a few reports in bladder cancer and osteosarcoma have described periostin as a tumor-inhibiting factor. Moreover periostin upregulation has been reported also for chronic sinusitis and recent studies suggest that periostin may be part of a negative-feedback loop regulating allergic airway inflammation. Importantly, periostin is involved in the epithelial-mesenchymal transition (EMT) of carcinoma cells.

In this review, we summarize the current knowledge about the role of periostin in the process of EMT and discuss its potential as a target for anticancer therapies directed against the tumor stroma. Furthermore, we summarize current knowledge about periostin expression in the different tumor components of NSCLC, MPM, prostate cancer (PC), RCC, hepatocellular carcinoma (HCC), and bile duct carcinoma (BDC) (Table 1).

Epithelial-mesenchymal transition and periostin

It is well known that the EMT process is fundamental during the embryonic development of multicellular organisms. In addition to embryonic development, the EMT also participates in tumor progression. This is not unexpected, considering that analogies between the two processes (embryonic development and tumor progression) frequently occur. An increasing number of genes and signaling pathways that are involved in embryonic development are also found to be involved in tumorigenesis. However there is much evidence that the EMT process is responsible for dissemination of primary tumor epithelial cells to the sites of metastasis and for the dedifferentiation program that leads to increased malignant behavior of the tumor (Fig. 4).

On a morphologic basis, EMT in vitro can be recognized by the presence of spindle-shaped cells, emission of pseudopodia, and increased intercellular separation, which reflects the acquisition of a mesenchymal phenotype, increased motility, and loss of cell–cell adhesion. Furthermore, the EMT of cancer cells is characterized by an upregulation of mesenchymal proteins such as periostin, vimentin, fibronectin, and N-cadherin, accompanied by a downregulation of epithelial markers such as E-cadherin.
On a functional basis, gain of N-cadherin expression, together with loss of E-cadherin, leads to alterations in the epithelial cell shape and motility by dissociation of intercellular adherens junctions, promoting only weak homophilic cell adhesion interactions [30, 31]. In vitro, lack of E-cadherin determines acquisition of a mesenchymal phenotype and invasive behavior, which can be reversed if E-cadherin is restored and constitutively expressed [32]. In vivo, it has been shown that E-cadherin-negative cell lines have an increased tumorigenic potential when implanted as xenografts in nude mice [30]. Clinical studies showed that E-cadherin expression is inversely correlated with high-grade cancers or with poor survival [33, 34]. On a molecular basis, E-cadherin is

![Diagram of Periostin](image)

**Table 1** Overview of correlations found, by immunohistochemical studies on NSCLC, MPM, PC, RCC, and BDC tissue microarrays (TMAs), between epithelial and stromal periostin expression and clinicopathological parameters

| Tumor type          | Poor survival       | Differentiation grade | Stage of disease                   | Reference            |
|---------------------|---------------------|-----------------------|------------------------------------|----------------------|
| Non-small cell lung cancer | Stromal expression |                      | Epithelial and stromal expression  | Soltermann et al. [16] |
| Malignant pleural mesothelioma | Epithelial expression |                      | Epithelial expression              | Schramm et al. [20]  |
| Prostate cancer     | Stromal expression  | Epithelial and stromal expression | Epithelial expression           | Tischler et al. [28] |
| Renal cell carcinoma | Epithelial expression | Epithelial and stromal expression | Epithelial expression            | Dahinden et al. [21] |
| Bile duct carcinoma | Epithelial expression |                      | Epithelial and stromal expression  | Riener et al. [29]   |
downregulated by epigenetic mechanisms, such as pro-
moter hypermethylation and transcriptional repression. 
Transcriptional repressors of E-cadherin are the zinc 
finger proteins Snail and SIP1 and the basic helix-loop-helix 
transcription factor Twist, all of which have the ability to 
recognize and bind E boxes in the E-cadherin promoter 
[35–37]. Snail, SIP1, and Twist are therefore inducers of 
EMT and promote tumor cell invasion. Activation of 
several growth factor receptors, including tyrosine kinase 
receptors such as the hepatocyte growth factor receptor c-
Met, the ErbB protein family, and the fibroblast growth 
factor, the insulin growth factor, and the transforming 
growth factor-β (TGF-β) receptors, have been found to 
induce EMT in vitro and in vivo [38–41]. Downstream 
effectors of these activated receptors belong to the Ras and 
the mitogen-activated protein kinase pathway, the phos-
phoinositide 3-kinase pathway, or to the TGF-β-SMAD 
pathway, which all lead to Snail expression [30, 31, 35]. 
Recently, the DNA binding factor LIV1 has been found to 
promote activation of Snail through a STAT3-dependent 
pathway [42] (Fig. 4).

The matrix protein periostin was shown to be not only a 
marker of EMT, but to be itself an inducer of this 
phenomenon [26, 27]. Indeed Yan et al. demonstrated that 
ectopic expression of periostin in tumorigenic but non-
metastatic 293T cells can induce EMT and promote 
invasion and metastasis in vivo [26]. Upregulation of 
periostin was accompanied by upregulation of vimentin, 
fibronectin, and active MMP-9, while E-cadherin and N-
cadherin expression was una 
ltered. Periostin signaling 
pathway in 293T cells seems to require interaction with 
αvβ5 integrin and recruitment of EGFR, as demonstrated 
by the fact that periostin-induced increase in cell adhesion, 
migration and invasion can be blocked by incubation with 
anti-integrin αvβ5 antibody or with tyrphostin 25, an 
EGFR kinase inhibitor.

Kim et al. found that periostin was able to induce EMT 
and an increased invasiveness in prostate cancer cell lines 
by downregulation of E-cadherin via Snail and increased 
phosphorylation of Akt [27]. Opposite effects were ob-
served using bladder cancer cell lines, indicating that 
periostin regulates E-cadherin in a cell-type-dependent 
way. Furthermore, the C-terminal region of periostin was 
not sufficient for induction of EMT in prostate cancer cells, 
indicating that the induction of EMT is mediated by the N-
terminal region of periostin.

However, examination of the expression pattern of EMT 
markers (such as periostin, vimentin, fibronectin, N-
cadherin, E-cadherin, and β-catenin) or members of the Akt/PKB signaling pathway allows determination of their occurrence and clinical significance in vivo. Therefore, an increasing number of immunohistochemical studies aim to characterize EMT expression profiles and their prognostic significance.

**Periostin expression in different tumor types**

Upregulation of periostin has been observed in many cancer types, such as neuroblastoma [43], head and neck [44], nasopharyngeal [45], thyroid [46], oral [47], breast [48], and ovarian cancer [19]. Elevated periostin levels were also detected in the serum from thymoma [49] and breast [50] cancer patients as well as in serum and pleural effusions of lung cancer patients [51, 52]. In the following, recent data on periostin expression will be described for different tumor types.

**Non-small cell lung cancer**

Periostin expression in normal healthy lung tissue has been observed [9] and its upregulation in cancerous lung tissue has been reported [16, 53] and associated with EMT [16]. Recently, periostin was identified in malignant pleural effusions from lung adenocarcinoma by mass spectrometric N-glycoprotein profiling [52] and its serum levels were shown to be higher compared with the normal control in NSCLC. The normal control consisted of pleural effusions from patients with cardiac disease but no neoplasia. Soltermann et al. compared the expression of EMT proteins such as periostin and vimentin, the MET protein versican, and classical desmoplasia markers such as collagen and elastin, in NSCLC by immunohistochemical analysis of tissue microarrays (TMAs). From these studies, it was derived that stromal periostin is a prognostic factor for decreased progression-free survival in NSCLC, and together with epithelial periostin, it was also significantly associated with several clinicopathological parameters such as squamous cell carcinoma histotype, higher stage, higher pT, higher pM, larger tumor size, and vessel infiltration, as well as with male gender [16]. Moreover, stromal periostin expression was significantly associated with epithelial cytoplasmic expression of vimentin and with collagen, but not with elastin, suggesting that during tumor progression the stromal fibrillogenesis in NSCLC may switch from elastin to periostin [16]. However, periostin stromal expression in NSCLC is mostly due to the intra-tumoral component, rather than to the peritumoral component of the stroma (own unpublished data). Interestingly, periostin was also correlated with the MET marker versican [16]; the expression of versican has been shown to be associated with tumor recurrence and more advanced disease in NSCLC [54].

**Malignant pleural mesothelioma**

MPM consists of different histotypes, including epithelioid, sarcomatoid, and biphasic. The biphasic MPM is a mixed histotype which is associated with both epithelial and mesenchymal phenotypes. The sarcomatoid and epithelioid histotypes resemble the EMT–MET transdifferentiation, being associated with the epithelial and mesenchymal differentiation state of the cell, respectively.

Schramm et al. conducted an immunohistochemical study on more than 350 MPM patients. Members of a putative MPM–EMT signaling cascade were analyzed: the EMT marker periostin, the EGFR, integrin β1, the inhibitor of Akt signaling pathway phosphatase and tensin homolog (PTEN), the integrin-linked kinase (ILK), and the two cell cycle regulators, p21 and p27. The results showed that expression of periostin in tumor cells can be considered as an independent prognostic factor for overall survival [20]. Indeed high periostin levels in tumor cells correlated with poor survival, whereas high cytoplasmic PTEN, ILK, or nuclear p21 and p27 correlated with better survival.

Interestingly, both stromal and tumor cell periostin expression was associated with the sarcomatoid histotype, indicating that periostin is associated with the mesenchymal differentiation state of the cell [20]. Contrary to periostin, high EGFR and integrin β1 expression nuclear p27 were associated with the epithelioid histotype of MPM.

**Prostate cancer**

A limited number of studies have investigated periostin expression in prostate cancer [9, 28, 55]. Periostin expression in normal prostate tissue has been detected by western blot analysis [9]. Tsunoda et al. detected periostin among several genes by a screening for three-dimensional culture (3DC)-associated genes. Non-malignant prostate epithelial cells, cultured in two-dimensional culture (2DC) and 3DC, were compared with 40 PC samples and their matched non-neoplastic prostate epithelium. Candidate genes were further validated by quantitative real time (RT)-PCR. Since periostin mRNA showed the highest levels among all the genes upregulated in 3DC, its protein expression was further evaluated by immunohistochemistry (IHC). Cancer cells of early stage but not advanced stage prostate cancer had an increased periostin expression compared with normal glands [55]. Tischler et al. [28] analyzed periostin expression by IHC in more than 400 prostate tumors. Contrary to Tsunoda et al., both stromal
and epithelial periostin expression was found to be increased in advanced and metastatic tumors [28]. They also reported increased periostin expression in the tumor stroma compared with the stroma around normal prostate glands. Furthermore, they showed that stromal periostin is upregulated in high-grade prostate cancers and affirmed stromal periostin as a progression factor for prostate-specific antigen relapse-free survival.

Renal cell carcinoma

Periostin was identified as an accessible biomarker from the blood stream after ex vivo perfusion and biotinylation of Surgically resected human kidney carcinoma [56]. Its tumor specificity was further confirmed by IHC. Periostin showed a prominent vascular and stromal staining pattern [56]. Interestingly, the MET protein versican and the EMT protein periostin were found to have similar stromal expression patterns in RCC [56] as well as in NSCLC [16]. A bioinformatic network modeling approach, comparing immunohistochemical stainings from TMA of RCC patients, analyzed periostin along with several other proteins to elucidate molecular pathways influenced by the von Hippel-Lindau (VHL) gene and the PTEN gene, which are often deregulated in clear cell RCC [21]. Both epithelial and a stromal periostin staining was observed. In particular, epithelial periostin was significantly increased in high-grade and high-stage tumors and was significantly associated with poor overall survival [21]. In an estimated graphical log-linear model, periostin was also found to be positively associated with nuclear PTEN, phosphorylated ribosomal protein p-S6, and nuclear p21, whereas cytoplasmic PTEN and inactive non-phosphorylated ribosomal protein S6 correlated with a prolonged survival [21]. Recently, we identified several periostin isoforms in renal tissue by direct sequencing, one of which was found to be tumor associated [57].

Hepatocellular and bile duct carcinomas

Periostin has been found to enhance tumor progression in several gastrointestinal cancers such as colon, gastric, and pancreatic cancer [17, 58, 59]. Few studies have investigated periostin expression in human liver [18, 29, 60]. Tilman et al. analyzed periostin mRNA levels by quantitative RT-PCR in six HCC and five normal liver samples. Periostin mRNA levels were increased by an average 65-fold in tumor [60]. Additionally, among various tumor types, strong periostin upregulation was mostly observed in liver and pancreatic tumors [60]. Baril et al. analyzed periostin expression by IHC in multiple tumor types including 11 HCC: liver tumors showed the highest periostin levels, together with breast, pancreatic, colon and larynx tumors. Recently, Riener et al. [29] performed the first immunohistochemical analysis on a large number of liver cancer patients (91 HCC and 116 BDC), which represented also the first report on periostin expression in BDC. Their study showed that expression of epithelial periostin was increased in higher-grade HCC and was shown to be an independent prognostic marker for poor overall survival in BDC. Periostin expression was also detected in the stroma of both HCC and BDC but did not correlate with clinicopathological parameters. Periostin expression was also analyzed in normal bile ducts, gallbladder epithelium, and hepatocytes, which showed a weak periostin cytoplasmic expression.

These immunohistochemical studies show that, depending on the cancer type, either epithelial or stromal periostin expression is associated with different tumor behavior (Table 1). One might hypothesize the existence of an autocrine/paracrine periostin loop between stromal and epithelial tumor cells and that the protein is secreted at a site where it can exert its strongest effect, namely at the interface between tumor and stroma. Furthermore, different splice variants of periostin might result in different biological effects, if they are secreted either by tumor stromal cells or by tumor epithelial cells.

Periostin isoforms and alternative splicing

Up to six different splice isoforms of periostin have been reported, four of which have been fully sequenced and annotated [3, 56] (Table 2). The isoforms of periostin are between 83 and 93 kDa in mass and differ in their C-terminal sequences, characterized by individual presence or absence of cassette exons 17–21 (UniProtKB/Swiss-Prot, March 2011); its N-terminus is conserved. Periostin isoforms were initially detected in pre-osteoblast cells, and it has been shown that the levels of osteoblast-specific differentiation markers were markedly reduced when the activity of these proteins was blocked in the mouse

Table 2 Schematic representation of the periostin cassette exons in the four known isoforms (isoforms 1–4)

| Isoform | Exon  |
|---------|-------|
| 1       | 1–16  |
| 2       | 1–16  |
| 3       | 1–16  |
| 4       | 1–16  |

Periostin splice isoforms are characterized by an individual presence or absence of cassette exons 17–21.
osteoblast cell line MC3T3-E1. These results suggest that these proteins play a role in the differentiation of osteoblasts [3].

The periostin C-terminal domain probably modulates the protein function by binding to ECM molecules such as fibronectin and collagen [61]. Indeed, Norris et al. demonstrated that the C-terminal domain of periostin binds collagen I, concluding that it is involved in fibrillogenesis and influences the biomechanical properties of fibrinous connective tissues [4]. On the basis of comparative studies of periostin sequences among vertebrates, Hoersch and Andrade-Navarro suggested that the C-terminal domain of periostin is able to bind the matrix proteins collagen and fibronectin, and that each isoform may exert its influence on the ECM fibrillogenesis differently [61]. Therefore, alternative splicing of periostin isoforms seems to reflect the differential modulation of the periostin function in the ECM. This hypothesis is supported by the finding that downregulation and/or loss by alternative splicing of the periostin non-spliced form, together with expression of variant I (isoform 4 in UniProtKB/Swiss-Prot database), promotes increased invasiveness in in vitro and in vivo experiments using the human bladder cancer cell line SBT991, the mouse malignant melanoma cell line B16F10, and nude mice [22, 62]. Given that periostin isoforms have a differential invasive potential, it remains to be clarified how exactly periostin isoforms modulate the ECM formation and if this periostin-isoform-modulated ECM formation has an influence on the global invasive and metastatic potential of the protein.

Alternative splicing contributes to the expansion of transcriptomic diversity. It is achieved by the interplay of several RNA-binding proteins that associate with pre-mRNA transcripts, determining an exon skipping or inclusion in the mature RNA transcript [63]. Several ubiquitous families of proteins that regulate splicing have been identified and they act in cooperation with tissue-specific regulators of splicing [64]. Warzecha et al. identified the epithelial splicing regulatory proteins 1 and 2 (ESRP1 and ESRP2) as cell-type-specific regulators of transcripts that switch splicing during the EMT [65]. Those two RNA-binding proteins promote alternative splicing events with function in cell–cell adhesion, polarity, and migration, influencing the phenotypic morphological changes that are observed in the EMT. This complex alternative splicing network reveals an important post-transcriptional aspect in addition to the changes in gene expression that underlie the EMT. In particular, it was shown that downregulation of the ESRPs leads to an increase in exon skipping events in the penultimate exons of the C-terminal transcript regions of all analyzed proteins. These events are thought to be functionally relevant because the skipped exons were in multiples of three nucleotides, allowing translation into different protein isoforms. Even though periostin was not identified among the transcripts regulated by ESRP1 and ESRP2, periostin isoforms are generated by alternative splicing in the penultimate exons of the C-terminal transcript region and the skipped exons are in multiples of three. Therefore it is possible that periostin transcripts are regulated during EMT by specific splice-regulatory proteins and that these transcripts have an influence on the morphologic and functional changes associated with the EMT.

**Periostin as a target for immunotherapy**

In RCC, periostin was found to be overexpressed in the subendothelial stroma of the tumor neovasculature [56]. It was suggested that periostin represents a potential target for anticancer therapies directed against the subendothelial stroma (so called “tumor vascular targeting” [66]). Indeed, the tumor neovasculature is tumor specific and discrete from normal adult tissue, except for a local and transient angiogenesis that occurs during specific processes such as tissue regeneration and inflammation [67].

Castronovo et al. found periostin to be an accessible antigen from the blood stream after ex vivo perfusion and biotinylation of surgically resected human renal carcinomas [56]. The ex vivo biotinylation of surgically resected renal carcinomas allowed a selective labeling of tumor vascular structures. Subsequent proteomic analysis of the biotinylated specimens allowed the identification of several proteins in the tumor portions, including periostin, which was the most abundant tumor-associated protein identified in RCC [56]. Validation of periostin as a tumor-associated antigen was performed by IHC and PCR. IHC showed overexpression of periostin in tumor samples, with a prominent vascular and stromal pattern of staining. PCR analysis yielded stronger periostin expression in fetal and tumor specimens [56]. These data suggested that oncofetal periostin variants might represent even more specific tumor targets.

In conclusion, upregulation in tissues and body fluids of many tumor types, accessibility from the blood stream, and correlation with malignant behavior and with poor prognosis speak in favor of the potential usefulness of periostin as a target for immunotherapy. Further, ECM proteins such as periostin, fibronectin, or tenascin C belong to a class of proteins that can be considered suitable tumor antigens for targeted delivery of therapeutic agents because of their accessibility, specificity, stability, and abundance [56, 66]. The therapeutic potential of periostin has recently been evaluated by Castronovo et al. [56] and by Kudo et al. [68], with the conclusion that stroma-targeting represents a valid option in anticancer therapy.
Conflict of interests  The authors declare no conflict of interest.

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