Prognostic significance of periostin in colorectal cancer

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Abstract

Accumulating evidence suggests that periostin is frequently upregulated in tissue injury, inflammation, fibrosis and tumor progression. Periostin expression in cancer cells can promote metastatic potential of colorectal cancer (CRC) via activating PI3K/Akt signaling pathway. Moreover, periostin is observed mainly in tumor stroma and cytoplasm of cancer cells, which may facilitate aggressiveness of CRC. In this review, we summarize information regarding periostin to emphasize its role as a prognostic marker of CRC.

Keywords: Periostin; prognostic functionality; stromal cells; colorectal cancer

Introduction

Colorectal cancer (CRC) is one of the most common gastrointestinal malignancies worldwide, and the major factor contributing to its poor prognosis and CRC-related death is the development of lymph node and/or distance metastases (1). Noninvasive imaging modalities, such as computed tomography, magnetic resonance imaging and endorectal ultrasonography, are frequently used for the preoperative diagnosis of lymph node and/or distance metastases. However, these imaging approaches are generally unreliable and inadequate at identifying metastasis (2-5).

In the past, biomarker discovery has mainly focused on the identification of transcriptional mRNAs, non-coding RNAs or methylated DNAs and proteins in tumor tissues. While a series of pioneering studies conducted on CRC prognosis have identified gene signatures that are prognostics for CRC patients, most proposed biomarkers for CRC are not clinically implemented due to their lack of reproducibility and/or standardization (6). Recently, periostin has attracted substantial interest as a helpful prognostic factor of CRC.

Periostin, originally named osteoblast-specific factor 2 (OSF-2), is a secreted protein that shares structural homology with the insect cell adhesion molecule fasciclin I (FAS1). Initially categorized into the inducible transforming growth factor (TGF)-β superfamily of proteins (7), periostin was also recently classified as a novel matricellular protein that mediates cell activation by binding to receptors on the cell surface (8). Periostin regulates cell function by binding to integrins at the plasma membrane via its N-terminal region, while its C-terminal region regulates cell-matrix organization and binds interactions with extracellular matrix (ECM) proteins (9). Some reports have indicated that periostin is physiologically expressed in a wide variety of normal adult tissues and fetal tissues, including mammary gland, lung, thyroid, skin and ovarian tissue, as well as periosteum and periodontal ligaments (10-12). Periostin was also found to play important roles in the formation and maintenance of normal bone structure, heart development and healing after acute myocardial infarction (8,13-15).

Recent studies in animal models and patients have demonstrated that periostin also functions in adult tissues under stressed conditions and in the pathobiology of various diseases, such as heart tissue under pressure or volume overload, skeletal muscle after injury, inflammatory diseases, and even tumorigenesis and metastasis. Overexpression of periostin has frequently been detected in

various types of human cancer and is consequently defined as a tumor-enhancing factor (16,17). Periostin's overexpression in cancer stroma and/or neoplasm epithelia is typically correlated with the most malignant phenotypes and poorest outcomes (16). Although the role of periostin in physiopathology has been demonstrated in recent years, its function in the metastatic process remains unclear. In this review, we summarize the current main opinions regarding the characteristics of periostin in metastatic process and discuss its prognostic functional roles in CRC.

Structure and isoforms of periostin

The genes encoding periostin have been cloned from multiple species. In humans, the periostin gene is located at locus 13q13.3 (13) and has 23 exons, with a genomic footprint covering approximately 36 kilobases. The open reading frame of human placental periostin encodes a protein 779 amino acids long (87.0 kD MW), while that of human osteosarcoma periostin encodes a protein 836 amino acids long (93.3 kD MW) (18). The periostin structure is composed of an N-terminal region, which includes a secretory signaling peptide followed by an EMILIN-like (EMI) domain rich in cysteines, 4 internal repeats and conserved FAS-1 domains, and a C-terminal variable hydrophilic domain (10,18). The N-terminal region contains a signaling peptide to promote periostin secretion and regulates cell functions by binding to integrins at the plasma membrane via FAS domains (19,20). Periostin was previously classified into the FAS family. The presence of integrin-binding motifs, which have been shown to mediate adhesion of TGF-β members [including gene clone 3 (big-h3)] to α3β1 (21) in FAS-1 domains, suggests that periostin is implicated in cell adhesion. In addition, the FAS-1 domains contain an N-terminal recognition site for γ-glutamyl carboxylase, which mediates the posttranslational modification of glutamate to γ-carboxyglutamate (22).

The C-terminal region of periostin regulates cell matrix organization. Periostin interacts with ECM proteins via its EMI domain and with tenascin-C (23) and bone morphogenetic protein (BMP)-1 via its FAS-1 domains (24). Periostin also possesses 4 putative N-glycosylation sites and a heparin-binding domain and binds glycoproteins, glycosaminoglycans and proteoglycans via its C-terminal region (25). Evolutionary analysis suggests that the C-terminal region of periostin is more variable among vertebrates in comparison to other parts of this protein (21),

indicating its functional importance of this region by mediating protein-protein interaction.

Interactions with ECM proteins and alternative splicing domains generate different isoforms of human periostin. Currently, the full-length variants of four different periostin isoforms have been sequenced and annotated, and the isoforms vary in length between 751 and 836 amino acids. The periostin N-terminus is conserved, while its C-terminal sequences, characterized by the individual presence or absence of cassette exons (10,16,18-20), vary. Alternative splicing of the C-terminal sequences gives rise to the four known periostin isoforms, including periostin 1 or OSF-2OS (full-length variant with all exons), periostin 2 or OSF-2p1 (exons 17 and 18 are absent), periostin 3 or periostin-like factor (PLF) (exons 17 and 21 are absent), and periostin 4 (exons 17, 18 and 21 are absent). The four isoforms were identified from different tissues (isoform 1 from human osteosarcoma, isoform 2 from human placenta, isoform 3 from epithelial ovarian carcinoma, and isoforms 2 and 4 from normal and cancerous human bladder tissues). The isolation of different periostin isoforms from different tissues indicates that their expression processes are tissue-specific (10,26,27).

Periostin promotes tumor progression

Periostin was found to be upregulated in multiple types of human cancers, suggesting its crucial role in the acquisition of most cancer cell imprinting functions, such as the promotion of solid tumor angiogenesis, migration and metastasis (28-34).

As members of the transmembrane receptor family, integrins are involved in cell-cell and cell-ECM interactions (35). The FAS-1 domain in the N-terminal region of periostin acts as a ligand for integrins, inducing metastasis via the activation of protein kinase B (Akt/PKB) signaling in cancer cells (12,36). The FAS-1 domain also promotes angiogenesis via the signaling pathways mediated by focal adhesion kinase (FAK) (37), TGF-β/SMAD (38) and Erk/VEGF (39) in endothelial cells. Activated integrin receptors, including αvβ3, αvβ5 and α6β4, are also thought to be involved in carcinogenesis (40,41). In CRC, periostin exerts pro-metastatic effects by binding to integrin αvβ3 and/or αvβ5 receptors, thus increasing cell motility and survival (36). In ovarian cancer, periostin has been shown to serve as a ligand for the αvβ3 and αvβ5 integrins, resulting in cell adhesion and migration (40,42). Moreover, downregulating periostin expression inhibited bone

metastasis by blocking the αvβ3 integrin signaling pathway in lung cancer cells (43). In addition, the αvβ3 integrin complex acts as a receptor for periostin and is involved in activating the Akt/PKB survival pathway in breast cancer and endothelial cells (37). Furthermore, pancreatic stellate cells can be activated via a periostin autocrine loop. The stromal secretion of periostin facilitates invasiveness via α6β4 integrin-FAK signaling and promotes the survival of pancreatic adenocarcinoma cells (44). The interaction between periostin and integrin was shown to enable the phosphorylation of FAK and Akt by activating the phosphatidylinositol3-kinase (PI3K)/Akt pathway (44).

The Akt/PKB pathway is now recognized as one of the most important regulators of cell proliferation and survival. In CRC, the periostin-activated Akt/PKB pathway can remarkably increase tumor growth by augmenting cancer and endothelial cell survival and preventing stress-induced apoptosis (36). Treatment with an Akt/PKB paralyzer was sufficient to abolish the effects of periostin on inducing cancer cell resistance to unfavorable microenvironments.

Although periostin alone does not significantly affect cell proliferation, the upregulation of periostin can induce invasion and anchorage-independent growth by allowing cancer cells to survive by inhibiting the anoikis-related apoptotic pathway in tumors (45,46). Furthermore, as a major contributor to epithelial-mesenchymal transition (EMT), periostin possesses relevant metastatic potential because it increases cancer cell motility, migration, invasion and adhesion, which enhances angiogenesis via the upregulation of vascular endothelial growth factor receptor VEGFR-2 (Flk-1/KDA) expressed via the integrin αvβ3-FAK-mediated signaling pathway. Highly dense blood vessels and high enrichment of VEGFR are correlated with periostin-producing tumor cells. Treating periostin-overexpressing cells with an anti-αvβ3 antibody was shown to block Flk-1/KDA receptor induction and induce capillary formation. Periostin also commonly mediates angiogenesis and lymphangiogenesis in non-small cell lung cancer (47). In a recent study on head and neck cancer, lymphangiogenesis was reportedly promoted by periostin itself and by periostin-induced overexpression of VEGF-C (46).

Recently, a histopathological study showed that high levels of periostin were vitally associated with advanced clinical stages, lymph node metastasis and decreased overall survival in nasopharyngeal cancer patients (48). Serum periostin levels in patients correlate well with malignant tumor behaviors, including tumor stage and lymph node metastasis (46,47). In invasive melanoma, periostin is highly expressed compared with that in normal tissues, and its expression is restricted to stromal tissues (49).

Periostin plays an important role in regulating the maintenance and expression of cancer stem cells (CSCs) during metastatic colonization. CSCs are a subpopulation of tumor cells that have the potential to initiate metastatic growth; however, metastatic colonization is limited by many factors. The secretion of periostin from stromal cells was also shown to be critical for metastatic colonization by regulating the interaction between CSCs and their metastatic microenvironment. Periostin increases Wnt signaling by interacting with Wnt1 and Wnt3A, thus contributing to a favorable CSC microenvironment that promotes metastatic formation (50-52).

Considering that periostin overexpression has been correlated with tumor progression, especially during lymph node and distant metastases (36,37,53-56), periostin can serve as a potential diagnostic and therapeutic target to treatment of cancer.

Role of periostin in formation of metastases of CRC

Although periostin has been found to promote cancer metastasis in a variety of cancer types (43,57,58), its function has been highlighted in CRC. For the last few years, a lot of reports have described that periostin was found increased in more than 80% of human primary CRC specimens in numerous studies, and periostin over-expression was shown to be accompanied by formation of CRC metastasis (2,32,59). Bao et al. (36) demonstrated that a CRC cell line with low metastatic potential displayed accelerated metastatic growth when subjected to periostin overexpression mediated by retrovirus infection. Moreover, periostin expression levels were markedly higher in hepatic metastases relative to that in CRC primary tumors. In addition, periostin was observed mainly in areas containing cancer cells of primary colon tumors and metastatic tumors in the liver, whereas the levels in normal colon mucosa were undetectable (59). Supporting the above evidence, retrospective analyses of clinical studies have also shown that periostin expression is correlated with trends for CRC metastasis (36).

Role of periostin in metastatic microenvironments

Tumor progression is strongly influenced by the

complicated interactions between tumor cells and peritumoral stromal cells, and periostin functions as a matricellular protein that mediates communication between cells and their extracellular microenvironment. In the local niche, secreted periostin induces phenotypic changes in tumor cells by binding to the αvβ3 and αvβ5 integrins to activate PI3K/Akt, TGF-β or FAK signaling (36,42,44). This potential mechanism of periostin may contribute to its function in metastatic microenvironments (12,50,60).

Tumor metastasis is an invalid cascade, and only a few tumor cells possess the ability to survive in the new, unfit organ condition and colonize in the metastatic niche (50,60). First, accumulating data suggest that premetastatic microenvironments are created in prospective metastatic target organs to permit the colonization and outgrowth of disseminated tumor cells. The premetastatic micro-environments are established prior to the arrival of tumor cells in the predetermined metastatic locations (61,62). Bone marrow-derived VEGFR1-positive hematopoietic progenitor cells are recruited to target organ sites (63). Hematopoietic progenitor cells and other cellular factors alter the ECM composition to convert target sites into hospitable microenvironments for disseminated tumor cells. Myeloid-derived suppressor cells are generally localized in the tumor microenvironment and exert immunosuppressive functions as an immature myeloid cell lineage, contributing to the formation of premetastatic niche for tumor metastatic outgrowth (52,61). Periostin may also be sent to secondary metastatic sites by exosomes and directly promote metastasis by shaping tumor microenvironment before the arrival of tumor cells (64).

Moreover, cancer-associated fibroblasts (CAFs), predominant stromal cells that produce ECM components, can be activated by paracrine cues from nearby cancer cells and peritumoral stromal cells or by autocrine factors themselves. CAFs act in concert with other stromal cells to establish and remodel the metastatic niche and promote tumor metastasis by secreting cytokines, growth factors and other components. Previous studies revealed that periostin is often secreted by CAFs in metastatic tissues. Ouyang demonstrated that periostin expression at distant secondary sites is higher than that at primary CRC sites (36). Xu et al. (65) demonstrated that stromal periostin expression gradually increased from normal tissues, to primary CRC tissues and to metastatic CRC tissue, which indicated that stromal periostin expression accumulates consecutively during CRC progression. Apparently, colonic fibroblast-

derived periostin markedly promotes invasion and chemo-resistance of CRC in a paracrine-dependent manner and migration and growth of fibroblasts themselves via autocrine signaling in CRC (65). The abovementioned evidence highlights the functional demand of stromal periostin for establishment of premetastatic and tumor metastasis microenvironments.

CSC niches are involved in tumor microenvironments that maintain the CSC pool and regulate their self-renewal, differentiation and carcinogenesis abilities. CSCs that disseminate from primary sites represent a small number of tumor cells that can self-renew, differentiate and colonize at secondary sites. Malanchi et al. found that CD90+CD24+ CSCs isolated from primary tumors in an MMTV-PyMT animal model can metastasize to lung tissues (50). Moreover, the infiltrating CSCs educate CAFs at the metastatic sites to produce periostin via TGF-β3 stimulation. Stromal periostin recruits Wnt ligands to CSCs and consequently augments inner CSC Wnt signaling, which leads to CSC spreading and metastatic colonization at the secondary sites. Periostin potentially induces mesenchymal stem cells (MSC)-like or CSC-like properties in mammary epithelial cells, and periostin upregulation induces tumor metastasis (66). High levels of periostin are closely correlated with poor chemotherapy results and can be used as an independent prognostic factor for cancer. Further analysis revealed that basal-like CSC-derived periostin forms a CSC niche to maintain the stemness of CSCs via the IL-6/STAT3 signaling pathway (67). Evidence demonstrates that periostin functions as a critical component of CSC niche to maintain stemness and metastatic colonization.

As a potent pro-angiogenic factor, periostin reportedly binds the integrin αvβ3 and upregulates the expression of VEGFR (Flk-1/KDR) via the FAK signaling pathway to promote tumor angiogenesis (37). The overexpression of periostin in CRC cells may induce angiogenesis in metastatic liver tissues (36) and has been reported to promote angiogenesis in pancreatic (39) and oral cancers. Interestingly, periostin is also involved in remodeling the perivascular niche to modulate tumor cell dormancy or induce micrometastatic results (68). Endothelial cells in the mature microvasculature express high levels of thrombospondin-1 (TSP-1), and other secreted factors to form a perivascular niche, thus maintaining cancer cell latency. However, endothelial cells in the sprouting neovasculature produce periostin, TGF-β and versican to establish a different perivascular microenvironment,

accelerating tumor metastatic outgrowth (68). This means that periostin and other factors surrounding neovasculature tip cells can arouse dormant disseminated tumor cells and augment tumor growth. These studies highlight the important role of periostin in the perivascular niche during tumor progression.

Periostin is also reportedly involved in the formation of fibrotic microenvironment. The colon stroma is a dynamic mechanical microenvironment, and mechanical signals arising from increased ECM density in the tissue micro-environment can transduce signaling via mechanosensory proteins to modulate cell proliferation, differentiation, survival and motility. Increased ECM deposition, crosslinking and remodeling reportedly contribute to increased stiffness, which is associated with tumor progression (69). As an important component of the tissue microenvironment, the ECM can be modulated by matricellular proteins, matrix metalloproteinases (MMPs) and other extracellular proteinases to maintain homeostasis or be remodeled during tissue repair, fibrosis, tumorigenesis and metastasis.

For instance, periostin is considered a key factor in regulating mutual interactions between stromal cells and prostate cancer (PCa) cells by forming a positive feedback loop to alter the tumor microenvironment via ECM remodeling. Recently, additional research revealed that the recruitment of inflammatory monocytes to the liver is pivotal for the liver metastasis of PCa. These macrophages stimulate myofibroblasts to increase the production of periostin (70), consequently leading to the formation of a fibrotic microenvironment for metastatic cancer cell growth in the liver. Periostin can directly interact with fibronectin and collagen I via its EMI domain and with tenascin-C and BMP-1 via its FAS-1 domains (8,71). These data suggest that a massive periostin deposit in a metastatic microenvironment may act as a scaffold to aid collagen crosslinking and accelerate tumor metastasis by creating a collagen-rich fibrotic niche within the metastatic microenvironment.

Considering these findings together, periostin production is generally low in most adult tissues; however, at tumor sites within adult organisms, periostin is often highly secreted by stromal cells, which are stimulated by TGF-β and other local cytokines or growth factors produced by epithelial cells and other cells. Secreted periostin contributes to tumor progression by binding to various ECM proteins to remodel the local micro-environment and interacting with cell surface integrin receptors to regulate the PI3K-Akt pathway and/or other cellular pathways.

Periostin and EMT

EMT is the main mechanism responsible for tumor metastasis, facilitating the acquisition of invasive and metastatic potential by epithelial cells. EMT, initially recognized as a crucial step in morphogenesis during embryonic development, is characterized by the loss of epithelial cell marker expression, the gain of mesenchymal cell marker expression and increased MMP activity (72). Emerging evidence indicates that EMT is an important developmental process promoting tumor recurrence and metastasis that is associated with poor clinical outcomes for cancer patients. The histological analysis of periostin expression strongly implicates that CAFs are the primary source of periostin. Periostin establishes the premetastatic microenvironment and facilitates cancer cell migration, invasion and adhesion by contributing to EMT.

During EMT, cancer cells secrete more periostin, which dramatically promotes the expression of vementin, fibronectin and other mesenchymal molecular markers but does not affect cytokeratin, E-cadherin or N-cadherin epithelial marker expression. Ectopic periostin expression during tumorigenesis is a strong inducer of EMT via the interaction with integrin αvβ5 (47) and recruits and activates epidermal growth factor receptor (EGFR), as demonstrated by the fact that periostin-induced increases in cell adhesion and invasion can be blocked by incubation with anti-integrin αvβ5 or an EGFR kinase inhibitor. The crosstalk between integrins and EGFR activates the intracellular signaling pathway, thus regulating the expression of multiple genes involved in the acquisition of mesenchymal phenotype. In addition, periostin is one of the main factors affecting the regulation of intracellular pathway associated with PI3K and Akt/PKB (36,73).

Possibility of using periostin as a prognostic CRC biomarker

As described previously, periostin has been proposed to be not only a potential prognostic marker but also a putative therapeutic target for genitourinary cancer (7). Clinical investigation indicates that the level of periostin correlates with CRC advancement and five-year survival rates (74). Study using serum periostin from 108 CRC patients suggests that this protein has the potential to be a

diagnostic and prognostic marker for CRC (75). Furthermore, mechanistically, accumulating evidence has shown that stromal periostin expression is gradually increased from normal tissues to metastatic CRC, suggesting that periostin is consecutively secreted during CRC progression. Importantly, stromal periostin expression in primary CRC tissues dose-dependently predicted poor postoperative prognoses and had a higher discriminatory performance than epithelial periostin expression (32,63). Stromal periostin expression upregulation, rather than epithelial periostin expression, predicted unfavorable postoperative prognoses independently in two China cohort studies (76). Furthermore, the abilities of medium-level stromal periostin expression and CRC cell-derived gene signature are comparable for predicting the 5-year disease-free and disease-specific survival rates of CRC patients. Thus, stromal periostin expression in surgically removed tumors should be a powerful and robust prognostic biomarker for CRC (76).

The effects of periostin are elucidated via monitoring its interactions with αv-integrin receptors in CRC cell lines. External periostin could induce the phosphorylation of Akt and FAK after binding to its receptors, activating the PI3K/Akt, NF-κB/STAT3 and Erk signaling pathways and inducing the expression of multiple downstream genes. Periostin also acts as a driver of EMT and induces the expression of MMP 9, MMP 10, and MMP 13, resulting in the degradation of ECM and promotion of tumor cell spreading and metastasis (36,39,77). Thus, stromal periostin accumulates during CRC progression, promoting cancer cell invasiveness via the activation of oncogenic pathways. In primary CRC tissues, stromal periostin expression dose-dependently predicted the unfavorable prognoses of stage III CRC patients who underwent postoperative chemotherapy (63). Periostin expression in CD133+ cells is significantly higher than that in CD133- CRC cells (57). Targeting PI3K/Akt or Erk signaling pathways can attenuate the growth of CRC cells and sensitize CRC cell lines to 5-fluorouracil chemotherapy, respectively (78,79). Targeting periostin and the abovementioned pathways can potentially serve as therapeutic options for metastatic CRC.

It is well established that chronic inflammation promotes the development of CRC, and some proinflammatory or immunosuppressive molecules can induce the expression of periostin in a cell-specific context. Some conditional media from CRC cell lines can induce periostin production via the secretion of TGF-β1, VEGF, IL-4, IL-6, IL-10 and prostaglandin E2 from fibroblasts, etc (80). These CRC cell-derived factors can induce the expression of periostin in colonic fibroblasts, and autocrine periostin can change the cellular phenotype independent of colonic fibroblast growth. Cancer cells can induce fibroblast-mediated accumulation of stromal periostin, and periostin derived from CSCs can recruit M2 tumor-associated macrophages, indicating that periostin can bridge cancer cells and cancer-supportive stromal cells (81,82). Like other cancer biomarkers, periostin is actively expressed in a specific temporal and spatial pattern during embryogenesis, silenced after birth, and re-expressed in response to mechanical stress or carcinogenesis (8).

Conclusions

Stromal periostin expression in primary tumor tissues independently predicted unfavorable prognosis of CRC patients. Stromal periostin secretion also dose-dependently predicted the poor prognosis of CRC patients who underwent postoperative chemotherapy. Periostin may facilitate evolution and development of CRC via creating a favorable CSC microenvironment. Thus, the stromal periostin level is a prognostic biomarker for CRC and is worthy of clinical translation for prediction of CRC metastasis. Furthermore, targeting periostin-mediated signaling pathways could better serve as a therapeutic option for metastatic CRC.

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Footnote

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