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REVIEW

The multifaceted role of periostin in tumorigenesis

Kai Ruan · Shideng Bao · Gaoliang Ouyang

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Abstract Periostin, also called osteoblast-specific factor 2 (OSF-2), is a member of the fasciclin family and a disulfide-linked cell adhesion protein that has been shown to be expressed preferentially in the periosteum and periodontal ligaments, where it acts as a critical regulator of bone and tooth formation and maintenance. Furthermore, periostin plays an important role in cardiac development. Recent clinical evidence has also revealed that periostin is involved in the development of various tumors, such as breast, lung, colon, pancreatic, and ovarian cancers. Periostin interacts with multiple cell-surface receptors, most notably integrins, and signals mainly via the PI3-K/Akt and other pathways to promote cancer cell survival, epithelial–mesenchymal transition (EMT), invasion, and metastasis. In this review, aspects related to the function of periostin in tumorigenesis are summarized.

Keywords Periostin · Cancer · Tumorigenesis · Extracellular matrix (ECM) · Epithelial–mesenchymal transition (EMT) · Metastasis

K. Ruan · S. Bao · G. Ouyang (✉)
Key Laboratory of the Ministry of Education for Cell Biology and Tumor Cell Engineering, School of Life Sciences, Xiamen University, 361005 Xiamen, China
e-mail: oygldz@yahoo.com.cn

Present Address:
S. Bao
Stem Cell Biology and Regenerative Medicine, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, USA

Introduction

Periostin, originally designated osteoblast-specific factor 2 (OSF-2), was first identified in a mouse osteoblastic cell line as a cell adhesion protein for pre-osteoblasts [1, 2]. Thereafter, orthologous genes in human, rat, and zebrafish were also cloned [3–5]. Most current studies of periostin's role in development have focused on its expression and function in bones, teeth, and the heart. Periostin has been shown to be highly expressed in early osteoblastic cells in vitro and in periosteum and periodontal ligaments in vivo and to play a potential role in formation and structural maintenance of bones and teeth [2]. During their development, periostin is expressed in teeth and surrounding tissues. Mice lacking periostin exhibit dwarfism, incisor enamel defects, and an early-onset periodontal disease-like phenotype [6]. As an important developmental factor and a secreted adhesion molecule, periostin has also been shown to be involved in the development of heart valves and other tissues [7–9]. Periostin is also re-expressed in adults after myocardial [7, 10, 11], vascular [12], and skeletal muscle [13] injuries or bone fracture [14]. In addition, recent studies have reported that periostin is frequently found to be highly expressed in various types of human cancer cell lines in vitro and human cancer tissues in vivo [15–18].

In this review, we will focus on findings related to the current understanding of the role of periostin in tumorigenesis and summarize the molecular mechanisms of periostin in these activities.

Structure of periostin

The murine periostin gene is located on chromosome 3, while human periostin is found on chromosome 13q [19].

The length of mouse periostin cDNA is 3,187 bp, with an 18-bp 5′ untranslated region, a 733-bp 3′ untranslated region, and a 2,436-bp open-reading frame, which encodes a protein of 811 amino acids with a MW of 90.2 kDa [1]. Currently, five different forms of human periostin have been isolated, due to multiple splicing events that can occur within the C-terminal domain. Alternative splicing of the C-terminus gives rise to periostin isoforms [1]. Isoforms lacking the entire carboxyl domain have been shown to inhibit cell motility and migration [20]. The first two isolated human periostin cDNAs were screened from placental and osteosarcoma cDNA libraries, using mouse periostin cDNA as a probe. The human placental periostin open-reading frame encodes a protein of 779 amino acids, with a MW of 87.0 kDa, while the human osteosarcoma periostin open-reading frame encodes a protein of 836 amino acids with a MW of 93.3 kDa. Homology analysis shows that periostin is highly conserved between mouse and human. The amino acid identity between the two species is 89.2% for the entire protein and 90.1% for the mature form. However, as compared to other regions within the mature periostin protein, the C-terminal region shows slightly less conservation, with 85.5% identity.

Periostin is a unique, evolutionarily conserved extracellular matrix (ECM) protein that shares high homology with the insect axon guidance protein fasciclin 1 (FAS1). In *Drosophila*, the ancestral fasciclin domain functions as an adhesion molecule linked to axonal guidance, migration, and differentiation [1, 19, 21]. FAS1-like domains exist in many proteins from various species, including bacteria and plants, suggesting that this domain represents an evolutionarily ancient adhesion domain. Therefore, periostin has been assigned to the fasciclin family, which includes βig-h3 (TGF-β-induced gene clone 3), stabling I and II, MBP-70, algal-CAM, and periostin-like factor (PLF) [22]. These proteins all contain repeats of the FAS1 domain, each consisting of 150 amino acids. Periostin protein contains a typical N-terminal secretory signal sequence but lacks a typical transmembrane domain. Adjacent to the signal sequence is a cysteine-rich domain, followed by four internal homologous repeat regions which precede the C-terminal hydrophilic domain [1, 2]. The four internal homologous repeats in periostin are homologous to FAS1 and are thought to be important for periostin's adhesive activity.

Periostin has been shown to interact with other ECM proteins, such as fibronectin, tenascin-C, collagen V, and periostin itself [23, 24]. Periostin co-localizes with fibronectin, tenascin-C, and collagens, known components of subepithelial fibrosis of bronchial asthma, indicating that periostin forms a reticular structure by binding to these ECM proteins [24]. Functionally, periostin interacts with integrins to support cell adhesion and the spreading of chondrocytes, fibroblasts, and cancer cells.

Expression of periostin in clinical cancers

Periostin is a unique ECM protein found in collagen-rich connective tissues and is highly expressed in the embryonic periosteum, cardiac valves, placenta, and periodontal ligaments, as well as in many adult tissues, and its deposition is augmented by an increase in mechanical pressure [6, 25, 26]. Recently, periostin was found to be overexpressed in various types of human cancer, such as non-small-cell lung carcinoma, breast cancer, colon cancer, head and neck cancer, ovarian cancer, and pancreatic ductal adenocarcinoma. Here, we focus on the expression of periostin in five prevalent human cancers: breast, lung, colon, pancreatic, and ovarian cancers (Fig. 1).

Breast cancer

High levels of periostin expression are associated with human breast cancers [18, 27]. The level of periostin expression is undetectable in normal breast tissues or in an immortalized cell line derived from normal mammary epithelial cells. However, the expression of periostin is readily detectable in the vast majority of breast tumor samples, with an average level of periostin expression 20-fold higher than the baseline expression, defined by gene array data obtained from normal breast tissues [27]. Another report shows that serum periostin levels are elevated in breast cancer patients with bone metastases from breast, but not lung cancer [28].

Lung cancer

A recent report showed that periostin was expressed in 42% of 88 patients with non-small-cell lung cancer (NSCLC). Its expression was significantly correlated with tumor size, disease stage, metastasis, and lymph node and lymphatic invasion [29]. Another report also demonstrated that high expression of periostin in either stroma or tumor epithelia, correlated with male gender, higher stage, higher pT category, and larger tumor size; similarly, periostin expression in stroma also correlated with tumor relapse [30]. There also was a significant relationship between periostin expression and density of both circulatory and lymphatic microvessels. NSCLC patients with periostin expression have significantly poorer survival rates than patients showing no periostin expression [3, 29]. In addition, the serum periostin level may serve as a prognostic marker for NSCLC [31]. These data indicate that periostin correlates with increased tumor progression, angiogenesis, and lymphangiogenesis, as well as a worse prognosis for NSCLC patients.

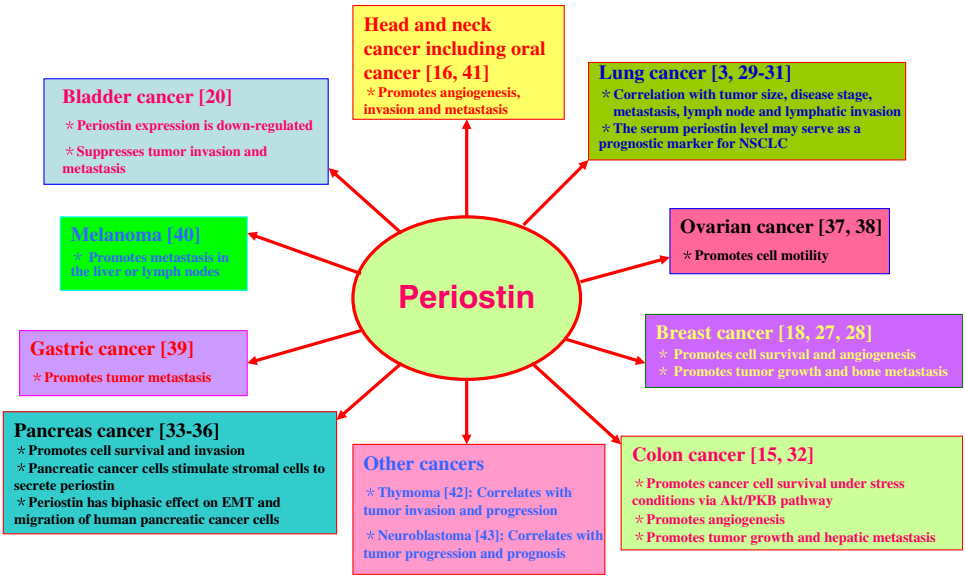

Fig. 1 Expression and function of periostin in human cancers

Colon cancer

We have previously found that periostin is differentially overexpressed in more than 80% of human primary colon cancer samples [15]. Quantitative analysis indicates that two-thirds (20 of 29 cases) of examined primary colon carcinomas show a tumor/normal (T/N) ratio of periostin message expression higher than 5-fold, with one-third of these primary tumors having a T/N ratio higher than 10-fold. Furthermore, periostin is overexpressed in all cases of colon metastatic tumors in the liver. Importantly, the expression level of periostin in hepatic metastases, derived mostly from patients with relapses of their colon cancers, is noticeably higher than in matched primary colon tumors from the same patients (eight of nine cases) [15]. Another report also demonstrated that periostin is upregulated in primary colorectal cancers and liver metastases [32]. These results suggest that late-stage metastatic tumors express higher levels of periostin, which may play a role during the metastatic stage of colon cancer progression [15].

Pancreatic cancer

Periostin is overexpressed in a large set of pancreatic cancer tissues. Although the periostin transcript is exclusively expressed in tumor cells, the protein product is only detected in the extracellular matrix adjacent to cancer cells. There are significantly increased levels of periostin in the sera of pancreatic cancer patients, compared to non-cancer controls. Furthermore, periostin promotes the invasiveness of tumor cells and enhances the survival of tumor cells exposed to hypoxic conditions [33]. Several other reports dealing with pancreatic cancer have shown that the periostin protein is secreted from pancreatic stromal cells rather than cancer cells [34–36]. Therefore, the interaction between cancer cells and stromal cells plays a critical role in pancreatic cancer development, and periostin from pancreatic satellite cells might create a tumor-supportive microenvironment in the pancreas [35].

Ovarian cancer

Periostin transcription is up-regulated in epithelial ovarian tumors [37]. While periostin transcripts are expressed in several normal tissues and highly expressed in fetal tissues, they are not found in normal ovaries. Ovarian cancer cells secrete periostin, which can accumulate in malignant ascites in patients with ovarian cancer. There are not any significant changes in the serum levels of periostin in women with ovarian cancer, when compared with controls. However, the majority of ascites from ovarian cancer patients contain high levels of periostin [37, 38].

Other cancers

Periostin is also highly expressed in tumors from patients suffering from other cancers, including melanoma, gastric cancer, head and neck squamous cell carcinoma, oral squamous cell carcinoma, thymoma, and neuroblastoma, although it is not expressed in the patients' normal tissues [3, 16, 39–43]. However, other studies have reported a down-regulation of periostin transcription in bladder carcinoma [20].

Role of periostin in the hallmarks of cancer

The development of human cancer, ultimately caused by genomic instability, involves a complex series of

processes. During tumorigenesis, cancer cells can acquire some special capabilities, such as the ability to overcome the restraints of the microenvironment of nearby normal tissue, self-sufficiency for mitogenic signals, deregulation of the cell cycle, escape from apoptosis, and the potential for unlimited replication [44, 45]. Within a growing tumor mass, the genetic and epigenetic alterations generated also enable cancer cells to gain the ability to induce angiogenesis, invade neighboring tissues, and metastasize to distant organs [15]. Current reports have demonstrated that periostin plays a critical role in the acquisition of most of these hallmarks of cancer cells (Table 1).

Promoting or inhibiting cell proliferation

Cell proliferation is strictly regulated by the concerted actions of both mitogenic growth signals and anti-proliferative signals that converge on regulators of the cell cycle [44, 45]. Periostin has been reported to promote re-entry of differentiated mononucleated cardiomyocytes into the cell cycle, where such cell cycle re-entry required integrins and the PI3-K/Akt pathway [7]. Exposure of MIF101 colorectal cancer cells to periostin-induced a dramatic increase in cell proliferation [32]. To reveal the role of periostin in the progression of tumor development, Shao et al. [27] used three tumor cell lines, 293T, the highly invasive mouse melanoma cell B16F1, and the metastatic human breast cancer cell MDA-MB-231, to engineer stable cell lines that overexpress periostin. Interestingly, the proliferation rate of these periostin-producing cells was noticeably slower than that of the control cells in culture, suggesting that periostin does not promote proliferation of tumor cells in vitro. However, these periostin-overexpressing tumor cell lines showed a phenotype of accelerated growth and angiogenesis when planted as xenografts in immunocompromised SCID-Beige mice [27]. Kudo et al. [41] also demonstrated that periostin overexpression does not promote cell proliferation, but it dramatically enhances the invasiveness of the head and neck cancer cell lines HSC2 and HSC3. Since the activities of this mesenchyme-specific gene product may not be exclusively associated with the promotion of cell proliferation, evaluation of the potential contribution of periostin to the progression of tumorigenesis must be based on an assessment of its ability to promote tumorigenesis in in vivo studies of xenografts or transgenic animal model systems, rather than solely on in vitro studies in cell culture [27].

Evasion of apoptosis

It is well known that tumors grow in an uncontrolled manner, resulting from an imbalance between cell proliferation and death [45]. In contrast to normal cells, cancer cells can break the balance between pro- and anti-apoptotic factors to promote cell survival under conditions of environmental stress [15]. Our previous work has revealed that cancer cells can induce the expression of some secreted ECM proteins, such as periostin and OPN, to prevent apoptosis in the context of a tumor [15, 46–48]. Periostin can dramatically enhance the metastatic growth of colon cancer by promoting survival of both cancer cells and endothelial cells under stress conditions that are commonly associated with metastatic tumors and fast-growing tumor masses, such as hypoxia, nutrient depletion, and loss of

Table 1 Periostin and the hallmarks of cancer

Hallmarks of cancer	Functions of periostin in hallmarks of cancer	Cancer types or cancer cell lines
Resistance to anti-proliferation signals and independence from exogenous growth factor signals	Pro-proliferation	Colon cancer, colorectal cancer MIF101 cells
	Anti-proliferation	293T, mouse melanoma B16F1 cells, MDA-MB-231
Evasion of apoptosis	Anti-apoptosis	Colon cancer, pancreatic cancer, breast cancer cells
Limitless replicative potential	Regulation of immortalization or senescence	None reported
Induction of angiogenesis	Pro-angiogenesis	Colon cancer, breast cancer, NSCLC, oral cancer
Evasion of the immune system	Escape from immunosurveillance	None reported
Tissue invasion and metastasis	Pro-metastasis	Colon cancer, NSCLC, oral cancer, breast cancer, head and neck cancer, oral cancer, gastric cancer, neuroblastoma, thymoma, pancreatic cancer cells
	Anti-metastasis	Bladder carcinoma, pancreatic cancer cells
Genomic instability	Genomic instability results in overexpression of periostin	Breast cancer

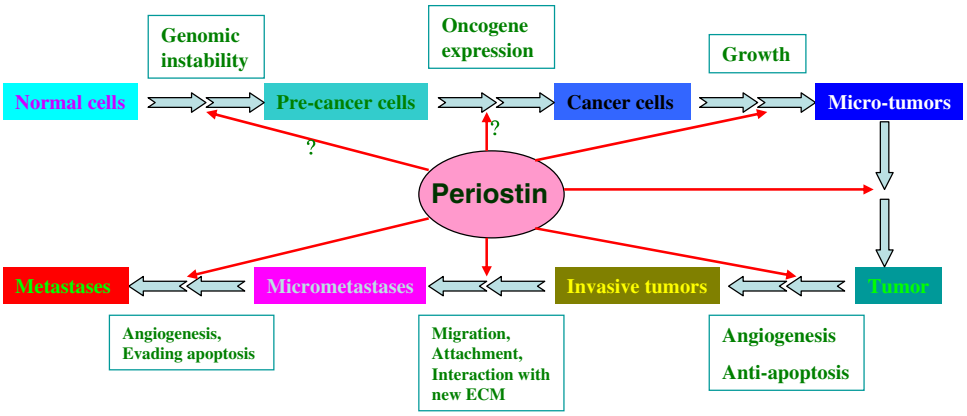

Fig. 2 Hypothetical illustration of the role of periostin in tumorigenesis. This model depicts the potential role of periostin in regulating the transformation of normal cells into malignant cancer cells and, eventually, metastatic tumors. Periostin, which is highly expressed in various malignancies, interacts with integrins or other receptors to induce a variety of cellular events. Current reports have revealed that periostin contributes to malignancies mainly by preventing apoptosis and promoting angiogenesis, invasion, and metastasis. The roles of periostin in regulating cell proliferation, evasion of senescence and immunosurveillance, and genomic instability of cancer cells during tumorigenesis still require further investigation

adhesion [15]. In addition, periostin promotes the survival of human breast cancer cells under several stress conditions, including hypoxia, serum starvation, and acid conditions (our unpublished data). Periostin can also promote the survival of pancreatic cancer cells under hypoxic conditions [33]. Interestingly, pancreatic stellate cells can secrete periostin to perpetuate fibrogenic activity and support tumor cell growth under serum deprivation and hypoxia [35]. As a result of periostin's promotion of cell survival, requirements for the establishment of metastatic colonies would be less stringent. Therefore, promoting cell survival or evading apoptosis might be one of the key mechanisms of periostin-enhanced tumor growth.

Limitless replicative potential

Oncogene-induced senescence is an important mechanism of tumor suppression that restricts the progression of benign tumors in the absence of additional cooperating mutations. It has been demonstrated that many genes trigger oncogene-induced senescence in vitro and in vivo [49]. Periostin has been shown to be highly expressed in immortalized human microvascular endothelial cells [50] and TesPDL cells, derived from miniature swine periodontal ligaments [51], where these cells are transfected with hTERT to prevent cell senescence. However, there are no reports on the direct role of periostin as an oncogene product that results in the unlimited replicative potential of cancer cells. We also do not know whether overexpression of periostin is sufficient to induce senescence in vitro and in vivo. Further studies are required to reveal the role of periostin in cell immortalization and evasion of senescence during tumorigenesis (Fig. 2).

Induction of angiogenesis

It is now well established that unrestricted growth of tumors is dependent upon angiogenesis [45, 52]. There is accumulating evidence indicating that many molecules can promote angiogenic signaling cascades in endothelial cells [53]. VEGF, which acts through its membrane tyrosine kinase receptors VEGF receptor 1 (Flt-1) and receptor 2 (Flk-1/KDR) is one of the most potent angiogenic molecules. As a mesenchyme-specific gene product, periostin has also been defined as a novel potent angiogenic factor for tumor growth [27, 50]. One of the mechanisms by which periostin dramatically enhances metastatic growth of colon cancer is through augmentation of human endothelial cell survival, which promotes angiogenesis [15]. Overexpression of periostin in human breast cancers leads to a significant enhancement of angiogenesis. The underlying mechanism of periostin-mediated induction of angiogenesis has been found to derive, in part, from the upregulation of Flk-1/KDR by endothelial cells through an integrin $\alpha v\beta 3$-focal adhesion kinase (FAK)-mediated signaling pathway [27]. Thus, although periostin may confer a growth advantage to breast tumors in vivo by altering the microenvironment through promotion of angiogenesis, its overexpression may impose a growth disadvantage when the tumor cells are grown in culture [27]. In oral cancers and NSCLC, periostin is also frequently overexpressed and enhances angiogenesis and invasion [16, 29]. Therefore, epithelial cell-derived tumors may gain the ability to generate more blood vessels, invade, and metastasize during late stages of tumorigenesis via the acquired expression of genes that normally are associated only with mesenchymal cells [27].

Tissue invasion and metastasis

Tumor invasion and metastasis is a multifaceted, controlled, and complicated process in the final phases of tumor development; it includes intravasation, survival in the circulatory system, arrest and extravasation into a new tissue, initiation and maintenance of growth, and reactivation of angiogenesis, in order to successfully establish metastatic colonies in the parenchyma of distant organs [15]. To complete this journey, cancer cells utilize numerous strategies, all of which lead to the same goal: the establishment of secondary sites of tumor growth [54]. In this multistep process, metastasis requires interactions between cancer and stromal cells, as well as between cancer cells and the ECM. Alterations of components in the ECM within the tumor microenvironment exert a considerable impact on the metastatic process [55].

Periostin, a fasciclin-containing adhesive ECM glycoprotein, promotes tumor metastasis not only in breast, lung, and colon cancers, as mentioned above, but also in melanoma, gastric cancer, head and neck squamous cell carcinoma, thymoma, and neuroblastoma. In melanoma samples, the average periostin expression is not increased in primary tumors, whereas periostin overexpression is detected in about 60% of metastatic melanoma tumors in the liver or lymph nodes [40]. Periostin is also overexpressed in gastric cancer and lymph node metastases [39]. Overexpression of periostin is frequently observed in head and neck squamous cell carcinoma and is believed to promote angiogenesis, tumor invasion, and metastasis of oral squamous cell carcinoma cases [16, 41]. In addition, periostin mRNA levels correlate with neuroblastoma tumor progression and prognosis [43]. Serum periostin levels are not significantly different between most thymoma patients and controls; however, the serum periostin level of stage IV thymoma patients is significantly higher than that of controls, suggesting that serum periostin level may indicate tumor invasion and progression of thymoma [42].

One critical step in tumor metastasis is termed epithelial–mesenchymal transition (EMT), which enables epithelial cancer cells to acquire invasive and metastatic potential [56–59]. Periostin has been shown to facilitate the migration and differentiation of cells that have undergone EMT, both during embryogenesis and in pathological conditions [60]. Furthermore, periostin is associated with EMT during cardiac development [19, 61]. Periostin is expressed throughout all stages of murine tooth development, especially in the embryonic sites of epithelial-mesenchymal interaction and in later newborn cells that transdifferentiate from one phenotype to another [62]. Various aggressive tumors are characterized by overexpression of periostin. As a mesenchyme-specific gene product, periostin is a potential contributor to metastasis and EMT in tumor progression. Stable expression of periostin in tumorigenic, but nonmetastatic, 293T cells induces those cells to undergo EMT and promotes cell migration, invasion, and adhesion [63]. High expression of periostin is also noted during EMT of cancer cells in NSCLC [30].

However, periostin may play a role as a suppressor of invasion and metastasis in the progression of human bladder cancers [20, 64]. The induced expression of periostin in pancreatic cancer cells (to levels of 150 ng/ml) can inhibit EMT and reduce cell migration in vitro as well as lead to formation of smaller tumors and suppression of metastasis in vivo. On the other hand, a high concentration of recombinant periostin (1 μg/ml) promotes cell migration with Akt activation [34]. Periostin can bind different integrin receptors, and different cancers express specific integrins. In addition, there are different spliced periostin isoforms in different tissues. These isoforms are not expressed uniformly but are differentially expressed in various cells [1, 2, 64]. Taken together, these results suggest that context influences the function of periostin, as related to tumor invasion and metastasis.

Genomic instability

It is crucial for cells to maintain their genomic integrity and stability because the DNA contained in every mammalian cell is under constant attack by many stresses and damaging agents [65, 66]. It is well known that genomic instability, one of the hallmarks of human cancer, is responsible for cellular changes that confer progressive transformation on cancer cells [45]. Genetic defects in DNA repair mechanisms and cell cycle checkpoints result in increased genomic instability and cancer predisposition [67, 68]. The genetic instability of tumorigenesis allows cancer cells to frequently bypass these systems. A recent paper has shown that periostin is overexpressed in Brca1 mutant cancer cells [69]. The Brca1 tumor suppressor, a checkpoint protein, plays a role in homologous recombination and may function in DNA repair by serving as a scaffold for ATM and ATR, thereby facilitating phosphorylation of downstream targets [70, 71]. Inherited mutations in Brca1 predispose individuals to breast and ovarian cancer; for carriers, the lifetime risk of breast cancer is 60–80%, and the risk of ovarian cancer is 25–50% [71–74]. Quaresima et al. [69] used microarray analysis to explore the gene expression pattern produced by the cancer-associated Brca1 5083del19 founder mutation. They found that periostin was significantly upregulated in HeLa/(5083del19)Brca1 cells, compared with both HeLa/(pcDNA3.1/empty) and HeLa/(wt)Brca1 cells. This finding was confirmed both in vitro, in breast cancer cell lines harboring mutations in Brca1, and in vivo, in breast

cancer specimens bearing the 5083del19 Brca1 mutation as well as sera obtained from patients and healthy carriers of the same mutation [69]. Since cancer is caused by a multistep process of sequential alterations in several oncogenes and tumor suppressor genes, periostin overexpression, together with Brca1 mutations, may be key steps in tumorigenesis of some breast and ovarian cancers.

Periostin activation of intracellular signaling pathways in tumorigenesis

Integrins: versatile integrators of periostin-mediated cell signaling

Integrins are transmembrane, heterodimeric receptors with noncovalently associated α and β subunits and are involved in both cell–cell and cell–ECM interactions [75]. Through integrins, cells can sense dimensionality and other physical and biochemical properties of the glycoproteins in the extracellular matrix, either in basement membranes or the interstitial matrix, or sense other ligands on the surface of neighboring cells [76]. Hence, integrins constitute the majority of receptors for sensing the environment of the cell. In addition to sensing the environment through their extracellular region, integrins are also able to engage several effectors on their cytosolic side. Through coupling to kinases, scaffolding proteins, or small GTPases, integrins modulate intracellular signaling pathways to determine adhesion, migration, polarity, survival, growth, or death of the cell [77].

The expression of integrins is frequently altered in tumors [78]. Cancer cells that express a wide variety of integrins can constitutively activate signaling pathways to promote tumor cell growth, survival, and migration [45, 79]. Current studies have shown that periostin is upregulated in various tumors and enhances cancer cell proliferation, survival, angiogenesis, and metastasis. Identified integrin receptors of periostin that play a role in tumorigenesis include $\alpha v\beta 3$, $\alpha v\beta 5$, and $\alpha 6\beta 4$. Receptors $\alpha v\beta 3$ and/or $\alpha v\beta 5$ are thought to regulate adhesion and migration of ovarian, breast, colon, and oral cancer cells [15, 38]. Gillan et al. [38] have found that purified recombinant periostin protein supports the adhesion of ovarian epithelial cells, which can be inhibited by monoclonal antibodies against $\alpha v\beta 3$ or $\alpha v\beta 5$ integrin, but not by anti-$\beta 1$ integrin antibody. Furthermore, $\alpha v\beta 3$ integrins, but not $\beta 1$ integrin, co-localize with the focal adhesion plaques formed on periostin. Cells plated on periostin form fewer stress fibers and are more motile than those plated on fibronectin. Therefore, periostin functions as a ligand for $\alpha v\beta 3$ and $\alpha v\beta 5$ integrins to support the adhesion and migration of ovarian epithelial cells [38].

In determining whether integrins are involved in the activity of periostin to promote survival of human colon cancer cells (CX-1NS) and microvessel endothelial cells (HMVECs), we have found that the activation of the Akt/PKB survival pathway by periostin is mediated primarily through the $\alpha v\beta 3$ integrin signaling pathway [15]. The angiogenic activity of periostin has been correlated with the increased expression of the VEGF receptor Flk-1/KDR on endothelial cells via an integrin $\alpha v\beta 3$-FAK-mediated signaling pathway [27]. In addition, the $\alpha 6\beta 4$ integrin complex acts as the receptor for periostin in pancreatic cancer cells [33]. At the mechanistic level, it is not surprising that periostin exerts its effect via integrins, because current reports have demonstrated that integrins on the surface of tumor cells and adhesion molecules in the ECM microenvironment are extremely important for tumor cell survival, growth, and migration [15, 80–82]. One recent report has shown that secreted periostin interacts with $\alpha v\beta 5$ integrins, and the intracellular signaling activation via cross-talk between integrins, and EGFR promotes the cell to undergo EMT, resulting in tumor invasion and metastasis [63]. Nonetheless, we cannot yet rule out the existence of other receptors that transduce periostin signals in tumorigenesis.

PI3-K/Akt: a critical pathway in regulating periostin-induced tumorigenesis

Signals from the ECM are based on the engagement of integrins with specific matrix proteins to stimulate cell survival signaling molecules, including the extracellular signal-regulated kinases 1 and 2 (ERK1/2) and PI3-K in the MAP kinase cascade [83, 84]. It is now generally accepted that the PI3-K/Akt survival pathway is a central regulator of cell survival and proliferation [48, 85]. Akt functions as a cardinal node for transduction of extracellular and intracellular signals. It is positively regulated by PI3-K and negatively regulated by PTEN. Akt plays a critical role in a variety of cellular events including cell growth, motility, and survival, in both normal and cancer cells. The PI3-K/Akt pathway is also instrumental in EMT and angiogenesis during tumorigenesis. Deregulation of the PI3-K/Akt pathway is one of the most common signaling alterations in human malignancy [85]. Our previous work has revealed that periostin can dramatically enhance metastatic growth of colon cancer both by preventing stress-induced apoptosis in cancer cells and by augmenting endothelial cell survival via the Akt/PKB pathway [15]. Interestingly, OPN and SPARC are other secreted matrix-cellular proteins that play important roles in the progression of tumor development [86–88]. Our recent results suggest that the underlying mechanism of OPN-mediated promotion of tumor development is largely associated with Akt

activation, which enhances cell survival under stress [15, 46–48]. In addition, periostin can induce Akt phosphorylation via binding to $\alpha 6\beta 4$ integrins and can activate the PI3-K/Akt pathway, rather than the RAF/MEK/ERK pathway, to promote the survival of pancreas cancer cells [33]. In this regard, acquired expression of periostin, OPN, SPARC, and similar types of proteins may enable tumor cells to thrive in a tumor microenvironment.

Regulators of periostin in tumorigenesis

Periostin expression has previously been shown to be significantly increased by both TGF-β and bone morphogenetic protein (BMP)-2 [2, 89]. BMP-2 induces cell migration and periostin expression during atrioventricular valvulogenesis [90]. Since TGF-β has been revealed to promote EMT and tumor metastasis, it is possible that periostin acts as an effector that mediates the pro-metastatic activity of TGF-β in certain cancers. Besides TGF-β and BMP-2, PDGF-bb, PDGF-aa, FGF-B, and FGF-A are also potent secretagogues for periostin in pancreatic stellate cells [35]. Periostin has also been shown to be regulated by twist, which is a basic helix–loop–helix (bHLH) transcription factor important for cell proliferation, migration, and differentiation in embryonic progenitor cell populations and transformed tumor cells. Twist can bind the periostin promoter in undifferentiated pre-osteoblasts and upregulate periostin expression [91]. The hypoxia-responsive growth factors FGF-1 and angiotensin II enhance periostin expression in pulmonary arterial smooth muscle cells by activation of the PI3-K/Akt/p70S6K, Ras/MEK1/2/ERK1/2, and Ras/p38MAPK signaling pathways, but not the Ras/JNK pathway [92]. We have also found that TGF-α and bFGF upregulate the expression of periostin to promote the survival of A549 lung cancer cells in a hypoxic microenvironment via activation of PI3-K/Akt pathway (our unpublished data). In addition, periostin can be regulated by Wnt-3 in mouse mammary epithelial cells [93] and by IL-4 or IL-13 in lung fibroblasts [24]. However, most of the data about the regulators of periostin have come from studies on embryonic or adult development. Further studies are necessary to identify the regulators of periostin in tumorigenesis.

Concluding remarks

A tumor-supportive microenvironment is critical for tumor cell proliferation, survival, angiogenesis, invasion, and metastasis because tumors require essential growth factors, survival signals, pro-angiogenic factors, and various adhesion molecules [94]. It is well accepted that tumors are composed of several distinct cell types, including cancer cells, immune cells, fibroblasts, and endothelial cells. Tumorigenesis largely depends on alterations in the heterotypic interactions between incipient cancer cells and their normal neighbors [45]. Cancer cells can modify the composition of the adjacent stroma by secreting their own ECM proteins to create a permissive and supportive environment for their growth [33, 95, 96]. However, it is still not well understood how cancer cells manipulate periostin and other ECM proteins to cooperate with other cell types within tumors to promote their own survival and growth under stressful microenvironments. A recent report demonstrated that once stimulated by pancreatic cancer cells, pancreatic stellate cells remain active via an autocrine periostin loop. This process is exacerbated by even radiotherapy, resulting in the production of an excess of ECM proteins, creating a tumor-supportive microenvironment. Therefore, pancreatic stellate cells can secrete excessive amounts of ECM proteins, including periostin, collagen-1, and fibronectin, which promote tumor growth under serum deprivation, hypoxia, and chemotherapeutic pressure [35]. The class of nonstructural ECM proteins, including SPARC, osteopontin, thrombospondin, and tenascin-C, is structurally diverse, but regulates similar biological functions during embryonic development, tissue injury, and tumorigenesis by promoting the adhesion, migration, and survival of cancer cells [33, 88, 97, 98]. In contrast to many defined oncogenes, the normal functions of this type of gene are not often associated with the promotion of cell proliferation. Instead, this group of proteins may exert their influence on tumorigenesis by changing the microenvironment through the regulation or alteration of cell adhesion, composition of the extracellular matrix, and the activities of stromal cells within and surrounding the tumor mass [27]. As an adhesive protein, periostin is highly expressed in the embryonic tissues and in several normal adult tissues, predominantly bone, and is strongly upregulated in some adult tissues after injury [6, 7]. Furthermore, periostin has been found to potently promote adhesive interaction through desmoplastic stroma and to enhance metastatic development of various cancers. Therefore, periostin can be regarded as a new member of the matrixcellular proteins; increased periostin expression may confer a selective advantage to cancer cells during the process of metastasis and reflect a more aggressive tumor phenotype.

It is important to note that the data obtained from reports on βig-h3 may also provide important clues about the role of periostin in development and tumorigenesis. βig-h3 and periostin are both TGF-β-induced ECM proteins, both have FAS1 domains, and both are assigned to the FAS1 family. βig-h3 contains a signal sequence at the N-terminus, an Arg-Gly-Asp (RGD) sequence at the C-terminus, and four FAS1 domains; it shares a significant structural homology with

periostin [55, 99]. However, the RGD motif (an integrin recognition site) near the C-terminus in βig-h3 can be deleted without affecting cell adhesion [100]. βig-h3 does not contain any sequence homologous to the C-terminal hydrophilic domain in periostin, while periostin does not contain an RGD motif, suggesting that functional differences may exist between the two proteins during development and tumorigenesis [15, 17, 55]. As a secreted protein, the major function of βig-h3 is to mediate cell spreading, adhesion, proliferation, migration, and the promotion of tumorigenesis. Current studies have revealed that these functions are mediated through interactions between the FAS1 domains and integrin receptors, such as α3β1, αvβ5, αvβ3, and α6β4 [19]. Interestingly, although βig-h3 and periostin share significant sequence and structural homology, these two ECM proteins are involved in different processes in tumorigenesis. βig-h3 appears to promote colon cancer metastasis primarily during extravasation, a critical step in the metastatic dissemination of cancer cells, by inducing the dissociation of VE-cadherin junctions between endothelial cells via activation of the integrin αvβ5-Src signaling pathway [55]. However, as noted earlier, periostin has been shown to promote metastatic development of colon tumors by activation of the Akt/PKB signaling pathway through αvβ3 integrins to increase cell survival [15]. Therefore, the differences in their C-terminal domains may contribute to their differential integrin binding specificities, which, in turn, may result in differing impacts on tumor progression [15, 55].

Considering the key role periostin plays in bone and tooth formation, cardiac development, cardiovascular disease, oncogenesis, and tumor metastasis, this secreted protein could serve as a potential therapeutic target. Further studies will facilitate a deeper understanding of the mechanisms involved in the function, regulation, and biological activities of periostin in embryonic development and tumorigenesis.

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