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REVIEW

Periostin function in communication with extracellular matrices

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Abstract Periostin is a secretory protein with a multi-domain
structure, comprising an amino-terminal cysteine-rich EMI
domain, four internal FAS 1 domains, and a carboxyl-
terminal hydrophilic domain. These adjacent domains bind
to extracellular matrix proteins (type I collagen, fibronectin,
tenascin-C, and laminin $\gamma2$), and BMP-1 that catalyzes
crosslinking of type I collagen, and proteoglycans, which play
a role in cell adhesion. The binding sites on periostin have
been demonstrated to contribute to the mechanical strength
of connective tissues, enhancing intermolecular interactions
in close proximity and their assembly into extracellular matrix
architectures, where periostin plays further essential roles in
physiological maintenance and pathological progression.
Furthermore, periostin also binds to Notch 1 and CCN3,
which have functions in maintenance of stemness, thus open-
ing up a new field of periostin action.

Introduction

Periostin was originally identified as osteoblast-specific fac-
tor-2 (Osf-2) (Sugiura et al. 1995), with its roles being dem-
onstrated as regulation of cell adhesion, cell differentiation,
and organization of extracellular matrix. Periostin is a
matricellular protein of 90 kDa, having a secretory signal pep-
tide, followed by an amino-terminal cysteine-rich EMI do-
main, four internal FAS 1 domains, and a carboxyl-terminal
domain (CTD) (Horiuchi et al. 1999; Kudo 2011; Sugiura
et al. 1995) the sequence of which varies as a result of alter-
native splicing (Horiuchi et al. 1999; Hoersch and Andrade-
Navarro 2010). Periostin has been demonstrated to behave as
a scaffold for assembly of extracellular matrix proteins (type I
collagen, fibronectin, tenascin-C, and laminin $\gamma2$) and acces-
sory proteins (BMP-1 and CCN3), underlying sophisticated
extracellular matrix architectures (Elliott and Hamilton 2011;
Kii et al. 2010; Maruhashi et al. 2010; Snider et al. 2008). This
scaffold function is made possible by the multi-domain struc-
ture of periostin, thereby enabling interacting proteins in close
proximity to assemble into a large interacting complex. The
contribution of periostin to the mechanical strength of tissues
is due to the adjacent domains of periostin that interact with
the different extracellular and accessory proteins, which func-
tion to maintain pathophysiological conditions.

The localization of periostin in mouse and human tissues
has been examined by employing antibodies against the
periostin domains (Horiuchi et al. 1999; Shimazaki et al.
2008), demonstrating that periostin physiologically localizes
at collagen-rich regions in connective tissues such as the peri-
odontal ligament (Horiuchi et al. 1999; Kii et al. 2006; Rios

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et al. 2005; Suzuki et al. 2004), periosteum (Horiuchi et al. 1999; Rios et al. 2005), cardiac valve (Hakuno et al. 2010; Norris et al. 2009a, b), and lung (Bozyk et al. 2012; Kondoh et al. 2016; Okamoto et al. 2011). Pathologically, periostin has also been localized in infarcted myocardium (Shimazaki et al. 2008; Oka et al. 2007), fibrosis (Okamoto et al. 2011; Ishikawa et al. 2014; Naik et al. 2012; Takayama et al. 2006; Uchida et al. 2012), tissues undergoing wound healing (Nishiyama et al. 2011; Norris et al. 2007; Ontsuka et al. 2012; Zhou et al. 2010), and cancer-associated stroma (Fukushima et al. 2008; Kashima et al. 2009; Kikuchi et al. 2008, 2014; Liu et al. 2014; Nitsche et al. 2016; Oskarsson and Massague 2012; Qin et al. 2016; Ruan et al. 2009; Sung et al. 2016; Tian et al. 2015; Underwood et al. 2015; Wang and Ouyang 2012). Taken together, periostin expression is well correlated with tissue regeneration (Conway et al. 2014).

Periostin interacts with extracellular matrix proteins

The EMI domain of periostin interacts with fibronectin as shown in Fig. 1. Periostin directly binds to fibronectin (Kii et al. 2010; Norris et al. 2007). A proximal localization between periostin and fibronectin was observed in the endoplasmic reticulum of fibroblastic cells (Kii et al. 2016), implying that periostin interacts with fibronectin before its secretion. Furthermore, periostin enhances secretion of fibronectin from the endoplasmic reticulum to the extracellular milieu (Kii et al. 2016), indicating an important role of periostin in fibronectin secretion. Periostin was detected in the Golgi apparatus and the endoplasmic reticulum in fibroblastic cells, suggesting a role in the protein secretory pathway (Kii et al. 2010, 2016; Kim et al. 2009). The mechanism of alternative splicing is essential for the regulation of periostin secretion followed by localization at ECMs as a determinant of differentiation (Horiuchi et al. 1999; Hoersch and Andrade-Navarro 2010). Similarly, splice variants of fibronectin containing either EDA or EDB domains can augment osteoblast differentiation or

enhance mineralization by induced differentiation of osteoblasts, respectively (Sens et al. 2016). In periostin, the alternatively spliced region in the CTD has not been demonstrated as a target of any protein in biological analyses; thus its molecular function is not well understood.

Periostin also interacts with collagens, which is in good agreement with its localization on collagen fibrils (Kii et al. 2006; Suzuki et al. 2004; Norris et al. 2007). Periostin was found to form a complex with collagen type I (Norris et al. 2007), and directly binds to collagen type V (Takayama et al. 2006), although the binding site for collagens has not been identified, marking the need for further studies on this interaction. Fibronectin has several interaction sites for collagens, suggesting that the EMI domain of periostin may indirectly interact with collagens. As a consequence of its interaction with fibronectin, which is a crucial factor for collagen fibrillogenesis (Kadler et al. 2008), periostin plays an important role in collagen fibrillogenesis (Norris et al. 2007).

Collagen fibrillogenesis is a complicated multi-step process that is poorly understood (Canty and Kadler 2005). Molecular level studies on the interaction of periostin with collagen and fibronectin, both inside and outside cells, would contribute to elucidating the mechanism of collagen fibrillogenesis as shown in Fig. 2. At the first event of periostin regulation, the expression of TGFβ and/or IL-4 and IL-13 is induced in inflammation or mechanical stress. These cytokines trigger the expression of periostin and its splice variants together with primarily splice variants of fibronectin and tenascin-C. The splice variant of periostin is secreted and localized outside of the cell in the ECM, where it interacts with integrin αvβ3 on fibroblastic cells to induce their cell migration through downstream Akt and FAK phosphorylation. These fibroblastic cells produce type I collagen to repair tissues.

Periostin binds to tenascin, BMP-1, and CCN3

The FAS 1 domains of periostin bind to tenascin-C (Kii et al. 2010). Tenascin-C is an extracellular matrix protein, forming a hexamer by disulfide bond in the amino-terminal region. This disulfide-bonded multimerization results in a six-armed oligomer, accordingly termed a hexabrachion (Midwood et al. 2016). Immunoprecipitation experiments revealed the interaction of the FAS 1 domains with tenascin-C (Kii et al. 2010). Purified FAS 1 domains directly bind to tenascin-C. Notably, cleavage of the CTD of periostin is required for the interaction between the FAS 1 domains and tenascin-C (Kii et al. 2010). The CTD of periostin may be processed in the Golgi apparatus (Kii et al. 2010). Although this auto-inhibitory mechanism has not been understood, the intra-molecular interaction in periostin has been indicated (Takayama et al. 2006, 2009). Recombinant protein studies showed that CTD of periostin
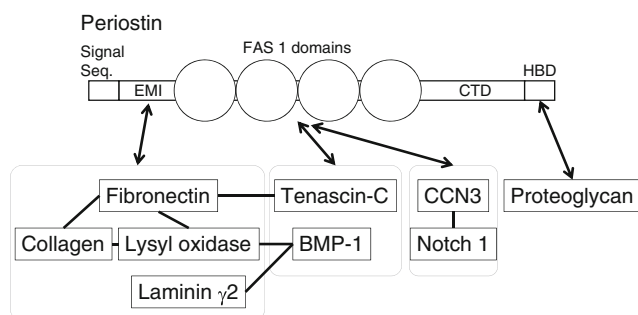
Fig. 1 Periostin interacts with multiple extracellular proteins. The interactions of periostin with the extracellular/secretory proteins are depicted based on the multi-domain structure of periostin. CTD; carboxyl-terminal domain, HBD: heparin-binding domain
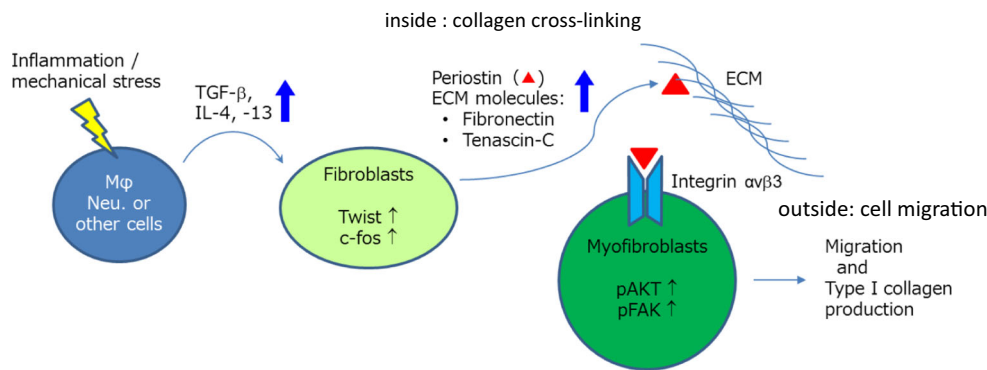
Fig. 2 Periostin function at the inside or outside of cells. Inflammation or mechanical stress induces the expression of TGFβ and/or IL-4 and IL-13 in macrophages and neutrophils for inflammation or in other types of cells for mechanical stress. These cytokines induce the expression of periostin and other ECM molecules such as fibronectin and tenascin-C in fibroblasts, which proteins are mainly splice variants. The splice variant of periostin is secreted and localized outside the cell in the ECM, where it interacts with integrin αvβ3 on myofibroblasts to induce their cell migration through downstream signals of Akt and FAK phosphorylation. These myofibroblasts produce type I collagen to repair tissues. In this collagen production, periostin together with tenascin-C inside the cell forms a meshwork structure with fibronectin to constitute a scaffold for the cross-linking of type I collagen. This cross-linking is activated by periostin in association with BMP-1 to generate the active lysyl oxidase (LOX) for enhancement of cross-linking inside the cells

directly binds to the four FAS 1 domains (Takayama et al. 2009), suggesting that this intra-molecular interaction in periostin inhibits the interaction between the FAS 1 domains and tenascin-C.

The four FAS 1 domains interact with bone morphogenetic protein-1 (BMP-1). BMP-1 is a pro-collagen processing enzyme that removes the carboxyl-terminal propeptides (Vadon-Le Goff et al. 2015). Immunoprecipitation experiments have shown that the four FAS 1 domains interact with BMP-1 (Maruhashi et al. 2010). Moreover, in silico structural analysis indicated possible direct binding between the FAS 1 domains and BMP-1 (Hwang et al. 2014). This interaction enhances proteolytic activation of lysyl oxidase (LOX), which is associated with the EMI domain of periostin via fibronectin (Maruhashi et al. 2010; Garnero 2012). LOX is an enzyme that catalyzes intermolecular crosslinking between collagen molecules (Trackman 2016), which is crucial for collagen fibrillogenesis. Similarly, knockout of the *periostin* gene in mice caused reduction of cross-linking in collagens (Kii et al. 2010; Shimazaki et al. 2008; Norris et al. 2007). Taken together, the formation of the periostin-BMP-1-LOX complex may underlie the mechanical property of collagen fibers. Interestingly, the same FAS 1 domain (the first or third FAS 1 domain) of periostin can bind to BMP-1 and BMP-2, though the binding affinity for BMP-2 is lower (Hwang et al. 2014), suggesting a possible mechanism of binding switch due to the developmental stage.

The four FAS 1 domains have been demonstrated to interact with CCN3 (Takayama et al. 2017). CCN3 is composed of four domains: the insulin-like growth factor-binding protein-like domain (IGFBP), the von Willebrand type C-like domain (VWC), the thrombospondin type 1-like domain (TSP1), and the carboxyl-terminal domain (CT). The four FAS 1 domains interact with TSP1 and CT of CCN3 (Takayama et al. 2017). The role of periostin has been elucidated as an enhancer for the deposition of CCN3 on the extracellular matrix (Takayama et al. 2017). Similar to tenascin-C, BMP-1 and CCN3, periostin may function as the anchor for these proteins to the extracellular matrix.

The CTD of periostin was shown to inhibit the interaction of the FAS 1 domains with tenascin-C, and this interaction requires the cleavage of the CTD (Kii et al. 2010). This cleavage mechanism underlies the regulation of the interaction between periostin and tenascin-C. Identification of the enzymes that catalyze the CTD cleavage would shed light on the periostin-specific regulatory mechanism for construction of the extracellular architecture.

Periostin paralogue, TGFBI (βig-h3)

The interaction between periostin and the periostin paralogue, TGFBI (βig-h3) likely results from hetero-multimerization via their EMI domains (Kim et al. 2009). This interaction was found to be essential for the proper secretion of a periostin/βig-h3 hetero-multimer. Furthermore, it has been demonstrated that βig-h3 directly binds to collagens type I, II and IV (Hashimoto et al. 1997), and localizes to the Golgi apparatus like periostin (Kim et al. 2009). These similarities in both proteins suggest the molecular function of these matricellular proteins as a modulator.

Periostin and βig-h3 generally have different expression patterns. However, in bone cells, periostin and βig-h3 are expressed in both osteoblasts and osteoclasts in vitro (Merie et al. 2014), suggesting that both genes possibly act cooperatively in bone formation. By contrast, after myocardial

infarction, deletion of βig-h3 did not alter cardiac disease, in contrast to periostin-deficient mice, indicating a distinct action of βig-h3 (Schwanekamp et al. 2017). In addition, βig-h3 lacks an extended region equivalent to the CTD, suggesting that the CTD is of functional relevance and could modulate periostin function.
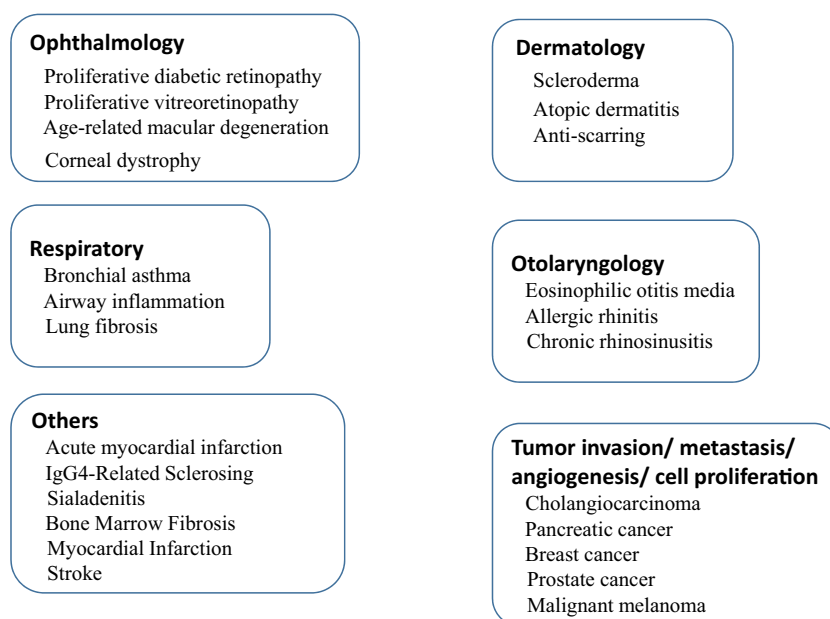
Periostin function in stemness

Periostin is regarded as a critical molecule that plays a progressive role in severe diseases, such as fibrosis in asthma, scar formation in infarcted myocardium, and tumorigenesis (Conway et al. 2014), as summarized in Fig. 3. Interestingly, there are several recent reports of periostin function in stem cells. Periostin has been shown to maintain hematopoietic stem cells (HSC) in a quiescent state through its interaction with integrin-αv of HSC in the bone marrow niche (Khurana et al. 2016); and another recent report showed that periostin secreted from stromal fibroblastic cells supports not only normal hematopoietic precursor cells but also leukemia-initiating cells (Tanaka et al. 2016). It has also been reported that periostin associates with a matricellular protein, CCN3 (also termed NOV), and that a functional relationship was observed in the periodontal ligament (Djokic et al. 2013). In this regard, CCN3 acts as a regulator of human HSC or hematopoietic progenitor cells as demonstrated by the loss of CCN3, which diminishes the functional capacity of the primitive hematopoietic compartment (Horiguchi et al. 2009). In mice, CCN3 plays a role in the HSC maintenance (Ishihara et al. 2014), suggesting a cooperative function of periostin together with CCN3 for HSC maintenance. In addition, the Notch signaling pathway is involved in HSC maintenance, and periostin-Notch1 and periostin-CCN3 interactions indicate a possible contribution of the functional complex of these three molecules, periostin-CCN3-Notch1, in HSC stemness. Periostin is secreted from mesenchymal stem cells to support tendon formation (Noack et al. 2014), characterized by the overexpression of periostin. Taken together, it can be speculated that periostin-CCN3 has become functional inside the bone after landing of animals (Gupta et al. 2007), initiating the building of the bone marrow microenvironment that supports hematopoietic stem cells by maintaining the hematopoietic compartment.

Periostin in mechanical stress

From expression profiling of periostin in periosteum and periodontal ligament, periostin has been expected to be mechanical stress-sensitive (Horiuchi et al. 1999), since the periosteum on the bone and the periodontal ligament in teeth are very sensitive to mechanical stress in order to aid tissue regeneration and development; however, no direct evidence of stress sensitivity has been reported. Interestingly, cathepsin K controls cortical bone formation by degrading periostin (Bonnet et al. 2017), since osteocytes expressing cathepsin K play a central role in the regulation of the biomechanical response in bone tissues, and degradation of periostin by cathepsin K occurs in osteocytes. Hence, cortical bone formation is regulated by the periostin-mediated blocking of random bone formation. Since peiostin is now known as an essential marker of periodontal ligament, the knowledge of which has helped to develop researches on periodontal ligament, and has clinical

Fig. 3 Periostin and related diseases

Ophthalmology
Proliferative diabetic retinopathy
Proliferative vitreoretinopathy
Age-related macular degeneration
Corneal dystrophy

Dermatology
Scleroderma
Atopic dermatitis
Anti-scarring

Respiratory
Bronchial asthma
Airway inflammation
Lung fibrosis

Otolaryngology
Eosinophilic otitis media
Allergic rhinitis
Chronic rhinosinusitis

Others
Acute myocardial infarction
IgG4-Related Sclerosing
Sialadenitis
Bone Marrow Fibrosis
Myocardial Infarction
Stroke

Tumor invasion/ metastasis/ angiogenesis/ cell proliferation
Cholangiocarcinoma
Pancreatic cancer
Breast cancer
Prostate cancer
Malignant melanoma

applications for periodontal diseases. A recent study demonstrated that periostin maintains stemness of periodontal ligament mesenchymal stem cells, and then promotes them into osteogenic differentiation through the JNK pathway under inflammatory conditions (Tang et al. 2017).

A functional link between the signaling cascades in mechanical stress and periostin gene expression was reported; it was found that both periostin and mammalian target of rapamycin (mTOR) are coordinately up-regulated by mechanical stress during the wound healing process to induce cell migration and proliferation (Rosselli-Murai et al. 2013), suggesting that the same signal originating from mechanical stress enhances both periostin and mTOR expression, after which periostin activates mTOR signals probably via integrin. Coincidently, the activated mTOR signaling pathway promotes osteoclast formation for bone remodeling (Dai et al. 2017), which reasonably suggests that periostin plays a role in the maintenance of bone mass (Kii et al. 2010). One of the candidate signals linking the mTOR and periostin activation is neuronal nitric oxide synthase (nNOS). In overload-induced skeletal muscle hypertrophy in mice, nNOS is transiently activated in a very short period after overloading, which activates the transient receptor potential cation channel, subfamily V member 1 (TRPV1), resulting in increased intracellular Ca^{2+} concentration that subsequently triggers mTOR activation (Ito et al. 2013).

DDR1 (Discoidin domain receptor 1) is a receptor tyrosine kinase that shows similar functions to periostin physiologically, and is pathologically specific to chronic kidney disease (CKD). Notch 1 is an interacting partner of DDR1, while type I collagen is a ligand of DDR1, indicating that activation of DDR1 receptor kinase through type I collagen binding induces Notch 1 signaling to promote cell survival (Kim et al. 2011). This activity is highly similar to periostin function (Tanabe et al. 2010) and probably involves CCN3 (Takayama et al. 2017). Further analyses of the synergy functioning between DDR1 and periostin would be very important to understand apoptosis induced by mechanical stress. In CKD, both periostin and DDR1 are involved in the regulation of inflammation and fibrosis. Thus, both proteins are novel biomarkers and therapeutic targets in CKD (Prakoura and Chatziantoniou 2017).

Clinical trials on periostin

Due to the increase in the number for periostin-related diseases (Fig. 3), some clinical trials have already underway. The first trial for clinical application of periostin demonstrated that gelform disks loaded with a recombinant periostin introduced into the pericardial cavity of pigs lead to increased cardiomyocyte cell cycle activity and angiogenesis (Polizzotti et al. 2012). Thereafter, inhibition of periostin action has been getting popular as clinical trials, because excessive activity of periostin induces severe fibrosis, generating deficiency of organ function. In this concept, a new RNAi agent had a pronounced inhibitory effect on lung fibrosis (Tomaru et al. 2017), choroidal neovascularization and choroidal fibrosis (Nakama et al. 2015) as well as retinal neovascularization (Nakama et al. 2017) and adhesion formation of abraded cecum after surgery (Takai et al. 2017). Similarly, intraperitoneal administration of the periostin-binding DNA aptamer significantly abrogated peritoneal fibrosis (Nam et al. 2017). In a new therapeutic method, overexpression of miR-599, which down-regulates periostin, inhibited glioma cell migration and invasion (Zhang et al. 2017).

In diagnostic applications, periostin is a useful marker of severe bronchial asthma. In patients with asthma, the high-Th2 phenotype has been associated with a high level of circulating periostin, which is induced by interleukin-13 (IL-13) and expressed by airway structural cells, and was detected by anti-periostin antibodies (Kraft 2011). The effect of anti-IL-13 antibody-based drug, termed lebrikizumab, on asthma was reported (Corren et al. 2011). Although there was a beneficial effect on airflow obstruction in all the patients treated with lebrikizumab, the effect was greater in patients who had circulating levels of periostin, indicating that periostin is a good biomarker for determining candidates for lebrikizumab treatment (Zhu et al. 2017). With regards to mechanical stress, under microgravity, periostin can be utilized as a marker of periosteal metabolism because of the fact that periostin concentration in serum increased transiently along with 15% increase in cortical porosity, which indicates that periostin is a good marker of cortical porosity (Vico et al. 2017).

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