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MULTI-AUTHOR REVIEW

Periostin and its interacting proteins in the construction of extracellular architectures

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Abstract Periostin is a matricellular protein that is composed of a multi-domain structure with an amino-terminal EMI domain, a tandem repeat of four FAS 1 domains, and a carboxyl-terminal domain. These distinct domains have been demonstrated to bind to many proteins including extracellular matrix proteins (Collagen type I and V, fibronectin, tenascin, and laminin), matricellular proteins (CCN3 and βig-h3), and enzymes that catalyze covalent crosslinking between extracellular matrix proteins (lysyl oxidase and BMP-1). Adjacent binding sites on periostin have been suggested to put the interacting proteins in close proximity, promoting intermolecular interactions between each protein, and leading to their assembly into extracellular architectures. These extracellular architectures determine the mechanochemical properties of connective tissues, in which periostin plays an important role in physiological homeostasis and disease progression. In this review, we introduce the proteins that interact with periostin, and discuss how the multi-domain structure of periostin functions as a scaffold for the assembly of interacting proteins, and how it underlies construction of highly sophisticated extracellular architectures.

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Introduction

Periostin is a secretory protein of around 90 kDa with a multi-domain structure that is composed of an amino-terminal EMI domain, a tandem repeat of four FAS 1 domains, and a carboxyl-terminal domain (CTD) [1–3]. The CTD amino acid sequence varies as a result of alternative splicing [1, 4]. Periostin has been suggested to function as a scaffold for the assembly of several extracellular matrix proteins as well as its accessory proteins, which underlie highly sophisticated extracellular meshwork architectures [5–8]. This scaffold function is likely due to periostin's multi-domain structure, which puts the interacting proteins in close proximity and assembles them into a large complex. In accordance with the requirements of the mechanochemical properties of living tissues, the adjacent domains of periostin interact with different kinds of proteins, which serves to maintain pathophysiological states.

Kudo and colleagues developed rabbit polyclonal antibodies against the first FAS 1 domain and the carboxyl-terminal end of the CTD [1, 9], and have revealed the spatiotemporal distribution of periostin in mouse and human tissue. Commercially available antibodies against periostin were also used to investigate periostin localization. Immunohistochemical analyses using these antibodies demonstrated that periostin physiologically localizes at collagen-dense areas in connective tissue, including in the periodontal ligament [1, 10–12], periosteum [1, 11], cardiac valve [13–15], and alveolar wall in the lung [16–18]. Periostin has also been found to pathologically localize in infarcted myocardium [9, 19], fibrosis [18, 20–23], the wound healing process [24–27],

and cancer-associated stroma [28–40]. Thus, expression of periostin is also closely associated with tissue regeneration post-injury [41].

Immuno-electron microscopic analyses verified that periostin is localized on the cytoplasmic processes of fibroblasts in the mouse periodontal ligament, and is largely confined to their cell membranes tightly associated with the bundles of surrounding collagen fibers [10, 12]. The cell-surface localization of periostin was also observed in pericryptal fibroblasts in mouse colonic mucosa [30]. Immuno-reactivity for periostin was also detected on collagen bundles in the mouse periodontal ligament [10, 12]. Additionally, immuno-gold transmission electron microscopic localization of periostin was observed on collagen bundles of the mouse atria-ventricular valve [25]. Taken together, these reports suggest that periostin binds to the proteins localized in the extracellular matrix and on the cell surface.

In this review, we introduce the proteins that interact with each of the adjacent domains in periostin (Fig. 1), and discuss that the multi-domain structure of periostin functions as a scaffold for the assembly of these interacting proteins. This scaffold function of periostin likely underlies the construction of highly sophisticated extracellular architectures.

The amino-terminal EMI domain of periostin interacts with extracellular matrix proteins

The EMI domain, named after its presence in the EMILIN family [42], is composed of approximately 80 amino acid residues, and includes six highly conserved cysteine residues. These cysteine residues are likely to be responsible for multimer formation via a disulfide bond. In a similar manner, periostin forms disulfide-bonded multimers (dimer to hexamer) [6]. The EMI domain is always a single copy

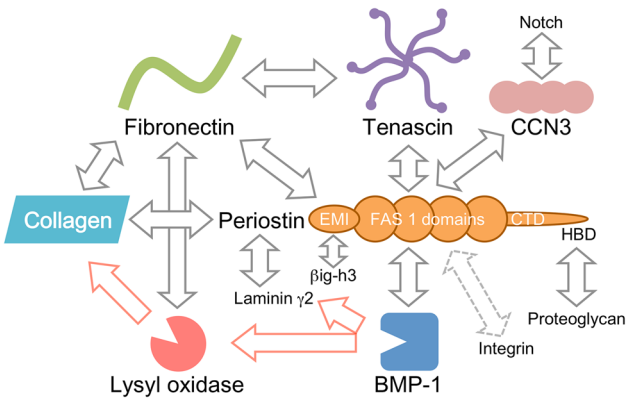

Fig. 1 Periostin and its interacting proteins. The known interacting proteins of periostin are depicted based on the multi-domain structure of periostin. *CTD* carboxyl-terminal domain, *HBD* heparin-binding domain

located at the amino-terminus of secretory proteins [43]. EMILIN-1 is an extracellular matrix protein involved in elastin deposition [44]. The EMI domain of EMILIN-1 was reported to interact with the C1q domain of EMILIN-2 [45, 46], indicating heterogeneous multimerization between EMILIN-1 and EMILIN-2. It has been demonstrated that the EMI domain of EMILIN-1 and EMILIN-3 binds to pro-TGF-β1 [47, 48]. These reports suggest that the EMI domain is a protein–protein interaction module.

The EMI domain of periostin has been demonstrated to interact with fibronectin. Purified periostin bound to fibronectin-coated microtiter plates [6, 25], indicating a direct interaction. The EMI domain that fused to Fc was co-immunoprecipitated with fibronectin in 293T cells transfected with the expression vectors of EMI-Fc and fibronectin [6]. In addition, a close proximity between periostin and fibronectin was detected inside fibroblastic C3H10T12 cells [49], possibly indicating that the interaction between periostin and fibronectin occurs before its secretion. Furthermore, this interaction in the secretory pathway enhanced secretion of fibronectin into the extracellular milieu [49], suggesting an undetermined role for periostin in protein secretion. Periostin was localized preferentially in the Golgi apparatus and the endoplasmic reticulum, indicating its function in the secretory pathway [6, 49, 50]. The EMI domain possesses a conserved tryptophan residue between the second and third cysteine residue [6, 42]. In periostin, this conserved tryptophan residue locates to position 65. The substitution of this tryptophan to alanine caused loss of the interaction with fibronectin [6], clearly demonstrating that the EMI domain is the interaction domain for fibronectin and that this conserved tryptophan residue is essential for the interaction.

Periostin has also been shown to interact with collagens, which is consistent with the localization of periostin on collagen bundles [10, 12, 25]. Periostin was co-immunoprecipitated with collagen type I [25], and purified periostin protein bound to collagen type V-coated microtiter plates [22]. However, the binding site for collagen has not yet been identified and further studies of this interaction are required.

Fibronectin has several binding regions for collagen, possibly indicating that periostin directly and indirectly interacts with collagens via the EMI domain. As consequence of the interaction of periostin with collagen and fibronectin that is an essential factor for collagen fibrillogenesis [51], periostin plays a role in promoting collagen fibrillogenesis [25]. Collagen fibrillogenesis is a complicated multi-step process that is still poorly understood [52]. Molecular studies on the interaction of periostin with collagen and fibronectin, both inside and outside cells, would contribute to clarifying the mechanism of collagen fibrillogenesis.

The EMI domain of periostin interacts with the EMI domain of βig-h3 (also known as keratoepithelin and

RGD-CAP), which is a protein with structural and sequence homology to periostin [53]. βig-h3 is coded in the *TGFBI* (transforming growth factor-β-induced) gene, mutations of which are associated with corneal dystrophies, progressive eye disorders [54]. The interaction between periostin and βig-h3 likely results from hetero-multimerization via their EMI domains [50]. This interaction was found to be essential for the proper secretion of a periostin/βig-h3 hetero-multimer [50]. Further, it has been demonstrated that βig-h3 directly binds to collagens type I, II, and IV [55], and localizes to the Golgi apparatus as periostin [50]. These similarities between periostin and βig-h3 suggest redundancy in the molecular functions of these matricellular proteins.

The tandem repeat of four FAS 1 domains binds to tenascin, BMP-1, and CCN3

The FAS 1 domain was originally identified in an insect neural cell adhesion molecule, *Drosophila* fasciclin I, consisting of the tandem repeat of four FAS 1 domains [56, 57]. The crystal structure of the third and fourth FAS 1 domains of *Drosophila* fasciclin I revealed a unique domain fold, consisting of a seven-stranded β wedge and a number of α helices [57]. Nuclear magnetic resonance spectroscopy was also used to solve the structure of the FAS 1 domain of *Mycobacterium bovis* secretory protein MPB70, which has structural homology to the FAS 1 domain of fasciclin I [58].

The tandem repeat of four FAS 1 domains of periostin has been demonstrated to bind to tenascin [6]. Tenascin is an extracellular matrix protein, the amino-terminus of which forms a disulfide-bonded hexamer, resulting in a six-armed oligomer, termed a hexabrachion [59]. Co-immunoprecipitation analysis confirmed the interaction of the FAS 1 domains of periostin and tenascin [6]. The purified FAS 1 domains of periostin bound to tenascin-coated microtiter plates [6], clearly demonstrating direct binding. Interestingly, the interaction between the FAS 1 domains and tenascin required cleavage of the CTD of periostin [6]. The CTD of periostin is likely to be cleaved in the secretory pathway, especially in the Golgi apparatus [6]. Although the inhibitory mechanism of the CTD on the FAS 1 domain-tenascin interaction is not currently well understood, inter- and intra-molecular interactions in periostin have been reported [22, 60]. It was shown that recombinant periostin CTD bound to the recombinant tandem repeat of four FAS 1 domains in a solid-phase binding assay [60], suggesting that this intra- or inter-molecular interaction in periostin inhibits interaction of the FAS 1 domains and tenascin. Structural analysis of periostin would clarify this auto-inhibitory mechanism.

The four FAS 1 domains of periostin have been reported to interact with bone morphogenetic protein-1 (BMP-1), which is the pro-collagen C-proteinase that cleaves the carboxyl-terminal propeptides of procollagens I, II, and III [61]. Co-immunoprecipitation analysis revealed that the tandem repeat of the four FAS 1 domains of periostin interacted with the metalloproteinase domain of BMP-1 [7]. In addition, a solid-phase binding assay using purified proteins confirmed direct binding between periostin and BMP-1 [7, 62]. Furthermore, three-dimensional docking simulation was performed between the FAS 1 domains of periostin and BMP-1, implicating their binding sites [62].

This direct interaction between the FAS 1 domains and BMP-1 promoted proteolytic activation of lysyl oxidase (LOX), which was indirectly associated with the EMI domain of periostin through fibronectin [7, 63]. LOX is an enzyme that catalyzes the formation of highly reactive aldehydes from peptidyl lysine residues in collagen molecules [64]. These aldehydes spontaneously react with other aldehydes or with intact lysine residues intermolecularly, resulting in the crosslinking of collagen molecules, which is essential for the stabilization of collagen fibrils. Consequently, targeted deletion of the *periostin* gene in mice caused the reduction of cross-links in collagens [6, 9, 25]. Thus, the periostin-BMP-1-LOX axis underlies the mechanochemical property of the collagen matrix.

The tandem repeat of four FAS 1 domains in periostin has also been reported to interact with CCN3 [65]. CCN3 is a matricellular protein that belongs to the CCN family. CCN3 consists 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). A co-immunoprecipitation experiment revealed that the four FAS 1 domains of periostin interacted with TSP1 and CT of CCN3 [65]. Periostin acted as an anchor of CCN3 for its localization in the extracellular matrix in the mouse periodontal ligament [65]. Similarly to tenascin, BMP-1, and CCN3, periostin is likely to act as an anchor for the FAS 1 domain-interacting proteins to the extracellular matrix through the EMI domain.

The CTD possesses an Arg-rich region responsible for binding to proteoglycans

The CTD of periostin has been demonstrated to interact with heparin [3]. Heparin is a highly acidic polysaccharide with a sulfate group, which is conjugated on transmembrane proteins and secretory proteins called heparan sulfate proteoglycans. The CTD contains basic amino acid residues in its terminal end (Arg–Arg–Arg–Leu–Arg in human) [3], which is a motif common in heparin-binding proteins as B_1–B_2–X–B_3, where B represents a basic residue. This basic amino acid sequence is highly conserved in periostin among species [4], indicating its importance. Thus, periostin is

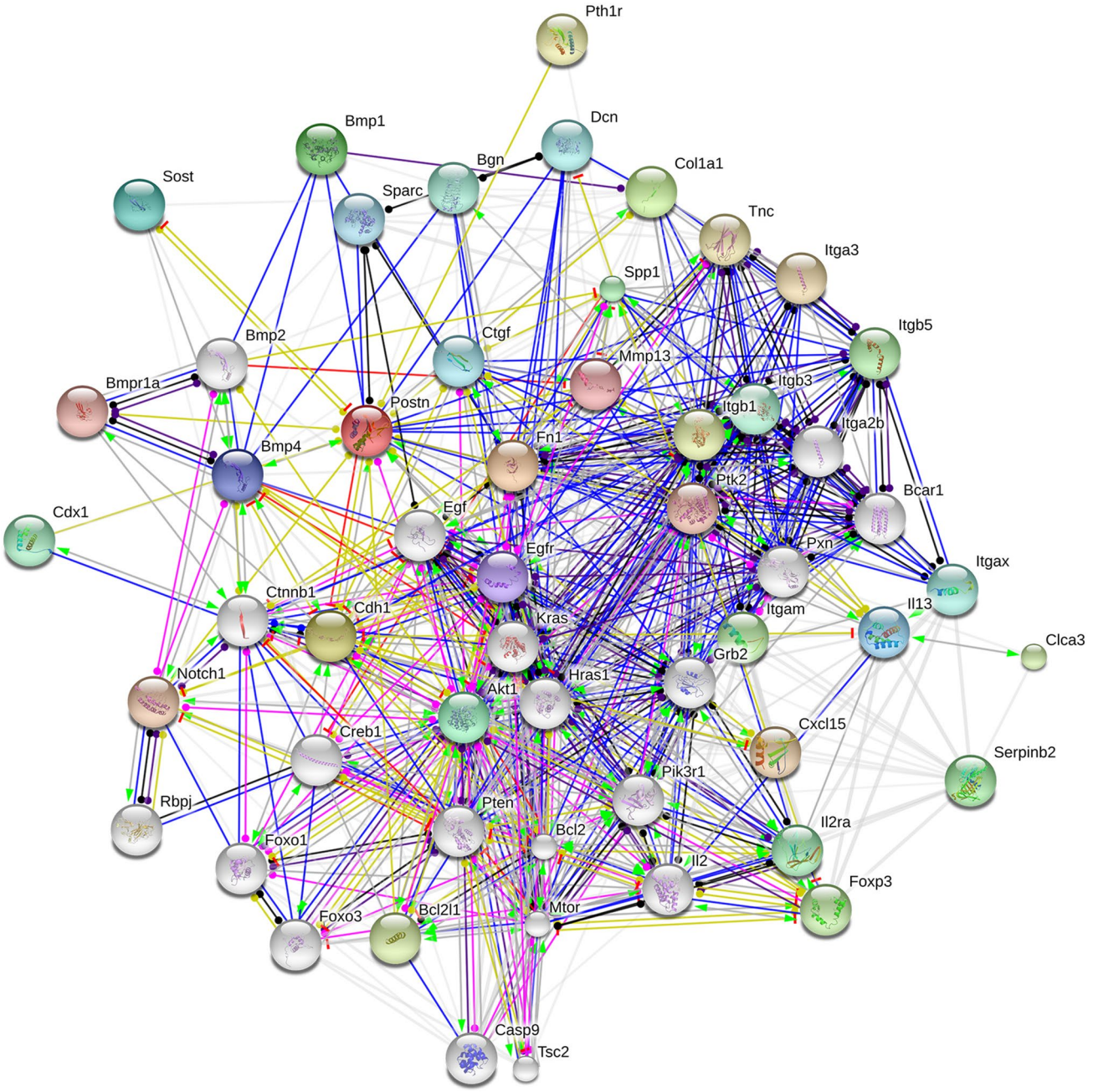

Fig. 2 The interactome map for periostin in STRING. Protein interactome map of periostin, as obtained from the STRING database. STRING analysis of known and predicted protein–protein associations is shown. STRING Version 10.5 was used

likely to interact with cell-surface heparan sulfate proteoglycans and to regulate cellular processes such as cell migration and growth factor signaling [66]. These interactions have not been extensively investigated, but are likely involved in connective tissue development and disease progression.

The CTD has a variation in amino acid sequence as a result of alternative splicing [1, 4]. The alternatively spliced region in the CTD has not been a target of biological analyses, and thus its molecular function is not well understood. The periostin paralogue βig-h3 lacks an extended region equivalent to the CTD, suggesting that the CTD is of functional relevance and could modulate periostin function. The CTD was shown to inhibit the interaction of the FAS 1 domains with tenascin-C, and cleavage of the CTD was required for the interaction [6]. This cleavage mechanism would underlie the spatiotemporal regulation of the interaction between periostin and tenascin in the secretory pathway. Identification of the enzymes that catalyze this CTD

cleavage would clarify the periostin-specific regulation mechanism for the assembly of extracellular matrix proteins.

The predicted protein interactome of periostin

A system-wide functional association for the specific and functionally productive interaction of proteins has been investigated with knowledge-based approaches based on known and predicted protein–protein association data [67]. STRING is a database of protein–protein interactions, including physical and functional associations from computational prediction, knowledge transfer, and interactions of other databases [68]. The interactome map of periostin that was generated by STRING is shown in Fig. 2. This map shows the known interacting proteins of periostin such as fibronectin (fn1), collagen (Col1a1), tenascin (Tnc), and BMP-1 (Bmp1). The map also indicates strong associations between periostin and integrin (Itga2b, Itga3, Itgam, Itgax, Itgb1, Itgb3, and Itgb5). Interestingly, these interactions seem to congregate at Akt1, which is a down-stream cell-survival signal mediator of integrin, consistent with the hypothesis that periostin activates Akt signaling [9, 39, 69–74]. Thus, this knowledge-based approach would be useful for molecular studies of periostin.

Other databases are also useful. The BioPlex is a network of the building blocks based on the immunopurification of tagged proteins and the detection of associated proteins by mass spectrometry [75, 76]. The BioPlex database gives us a physical interaction dataset for proteins of interest. Unfortunately, periostin was not found in the BioPlex. However, the interacting proteins of periostin (fibronectin, BMP-1 and so on) were found, which are useful for understanding the functions of periostin. It would be valuable to identify all of the interacting proteins of periostin by quantitative mass spectrometry-based proteomics in combination with affinity purification protocols, as this would accelerate molecular studies of periostin.

Concluding remarks

In addition to the proteins described in this review, periostin has been reported to interact with the integrin superfamily. Although periostin is thought to interact with integrins, including αVβ3, αVβ5, and α6β4, which promote cell proliferation, cell migration, epithelial to mesenchymal transformation, and modulation of the biomechanical properties of connective tissues [39, 69, 77–82], evidence of the direct interaction between periostin and integrins has not been demonstrated. Periostin has also been found to interact with notch and laminin γ2 [24, 83], and to function as a regulator of these proteins; however, the interacting domain of periostin has not been identified. To understand the relationship between the interacting proteins and periostin, it is necessary to map the interaction sites on the multi-domain structure of periostin.

The pathological roles of periostin have been the focus of a number of published papers. In most cases, inhibition of periostin function has shown a beneficial effect on the prevention and treatment of disease, such as cardiac remodeling, fibrosis, and cancer progression [16, 19, 20, 23, 74, 82, 84–96]. Development of a small organic molecule drug targeting periostin could be useful for disease prevention and treatment. However, structural analyses have not identified a pocket for drug binding in periostin. In addition, drug discovery targeting the protein–protein interaction surface is a promising approach; however, this is still difficult to perform. The interacting proteins of periostin described in this review may be potential drug discovery targets. For example, BMP-1 is an enzyme that has been targeted by small molecule inhibitors [97]. Inhibitors of LOX have been tested as a drug for cancer metastasis [98–100]. Enzymes such as BMP-1 and LOX are involved in the large protein complex based on periostin, and are attractive targets of drug discovery for periostin-related diseases.

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