7 Functions of Periostin in Dental Tissues and Its Role in Periodontal Tissue Regeneration

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Abstract

The goal of periodontal regeneration therapy is to reliably restore teeth's supporting periodontal tissue, while aiding the formation of new connective tissue attached to the periodontal ligament (PDL) fibers and new alveolar bone. Periostin is a matricellular protein, primarily expressed in the periosteum and PDL of adult mice. Its biological functions have been extensively studied in the fields of cardiovascular physiology and oncology. Despite being initially identified in bone and dental tissue, the function of Periostin in PDL and the pathophysiology associated with alveolar bone are scarcely studied. Recently, several studies have suggested that Periostin may be an important regulator of periodontal tissue formation. By promoting collagen fibrillogenesis and the migration of fibroblasts and osteoblasts, Periostin might play a key role in the regeneration of PDL and alveolar bone after periodontal surgery. In this chapter, the implications of Periostin in periodontal tissue biology and its potential use in periodontal tissue regeneration are reviewed.

Keywords

Periostin · Periodontium · Periodontal ligament · Alveolar bone · Periodontal regeneration

7.1 Periostin and the Periodontium

Periostin is a 90-kDa glutamate-containing matricellular protein. It was identified in the mouse osteoblastic cell line MC3T3-E1 and initially named osteoblast-specific factor 2 (OSF-2) [1]. Subsequently, OSF-2 was renamed as Periostin, based on its localization in the periosteum and periodontal ligament [2]. Periostin is preferentially expressed in collagen-rich fibrous connective tissue which undergoes constant mechanical strain, such as the periosteum, PDL, tendons, heart valves, and skin. As a multifunctional protein, Periostin is thought to be involved in tissue remodeling by promoting cell adhesion, cellular differentiation, cell survival, and fibrogenesis.

The periodontium is a specialized tissue that surrounds and supports the teeth, ensuring their

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stability in the maxillary and mandibular bones. The periodontium consists of four principal components: gingiva, PDL, cementum, and alveolar bone. By definition, periodontal tissue engineering/regeneration must achieve the regeneration of all tooth-supporting structures, supporting the reproduction of alveolar bone, cementum, and PDL, and ensuring adequate sealing by gingival tissue [3]. As Periostin is abundantly expressed in the periodontal ligament, it may become a potential stock in promoting periodontal tissue regeneration.

7.2 Expression of Periostin in Dental Tissues

The expression of Periostin in PDLs was initially demonstrated by immunohistochemistry of 5-week-old mice mandible in 1999 [2]. The spatiotemporal localization of Periostin was then revealed within developing and maturing dental tissues. Kruzynska-Frejtag et al. [4] found that both its mRNA and protein were asymmetrically expressed at the lingual/palatal and buccal side during early epithelial-to-mesenchymal interactions. Meanwhile, Suzuki et al. [5] found that, in tooth germs at the cap stage, Periostin immunoreactivity was recognizable at the interface between the inner enamel epithelium and preodontoblasts, as well as in mesenchymal tissues around the cervical loop and dental follicles. They also found that Periostin is present in dental papilla cells and within trans-differentiating odontoblasts during the bell and hard tissue formation stages of tooth development. Additionally, the expression level of Periostin in periodontal tissue was found to vary directly with the maturation stage of the periodontal ligament [6]. Therefore, it seems that the distribution of Periostin is shifting in space over time, during dental tissue development. However, further research is needed to determine the underlying mechanisms of this diversification.

In the same study, An et al. [6] observed that Periostin expression was restricted to the periodontium in adult rodents. Following postnatal day 7, immunoreactions of Periostin become uniformly localized to fibrous bundles in the PDLs in accordance with the organization of the periodontal fibers, indicating its role in the morphogenesis of PDLs. In the incisors of both 7- and 21-day-old mice, Periostin immunoreactions were discernible in the lingual PDL and labial fibrous tissue adjacent to the papillary layer [5]. During physiological tooth movement, Periostin mRNA expression was found to be uniformly distributed in the PDL surrounding the mesial and distal roots of molars in 7-week-old Sprague-Dawley rats [7]. Most importantly, Periostin was also found to be expressed on the alveolar bone surface by both methods of immunoreactivity and in-situ hybridization [5–7]. Furthermore, regarding its distribution in cellular substructures, immunoelectron microscopy showed immunolocalization of Periostin in the membrane of cytoplasmic extensions of periodontal fibroblasts, but not in their cytoplasm or the ground substance of mature PDL. Periostin is present at sites of close association between cells, including periodontal fibroblasts and cementoblasts, as well as in the adjacent collagen fibrils [5]. The Periostin protein is markedly present in the extracellular matrix (ECM), and possibly secreted by periodontal fibroblasts. In contrast, there is no detectable Periostin in the enamel, dentin, cementum, dental pulp, or alveolar bone [8]. This finding suggests that Periostin plays a key role in tooth development, and may be linked to the deposition and organization of other ECM adhesion molecules. Moreover, Periostin might modulate and maintain the integrity of adult teeth by mediating cell-to-matrix interactions, particularly at sites of hard-soft tissue interfaces (Fig. 7.1).

7.3 Functions of Periostin in Dental Tissues

The functions of Periostin have been classified into two major categories based on its molecular properties and protein interactions [9]. One is fibrillogenesis, which occurs inside the cell; the other is cell migration, which includes its extracellular activity [9, 10]. First, Periostin promotes

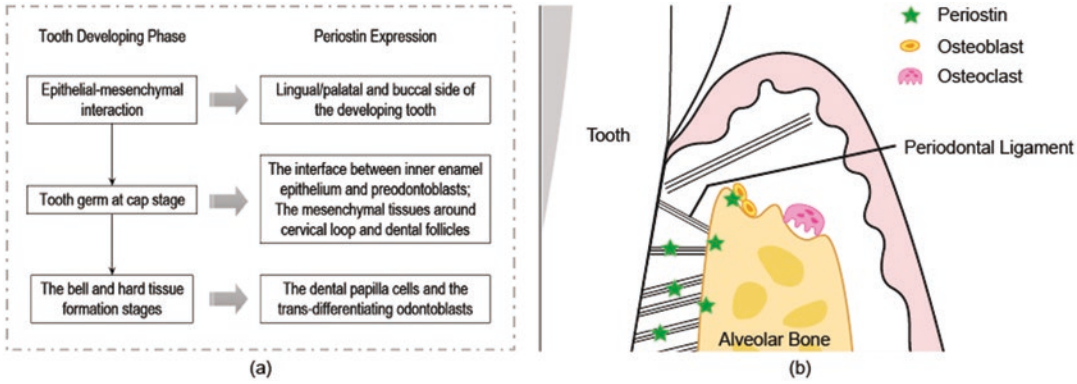

Fig. 7.1 The expressions of Periostin in dental tissues. (**a**) The expression of Periostin during dental development. (**b**) The expression of Periostin in periodontal tissues

the proteolytic activation of lysyl oxidase for collagen crosslinking. This process is mediated by the ability of Periostin to directly interact with type I collagen [11], fibronectin [12], and Notch1 [10] through its EMI domain, as well as with tenascin-C [12] and BMP-1 [13] through the Fas-1 domain. Periostin also serves as a ligand of integrins αvβ3 and αvβ5, facilitating cell motility by activating the actin/myosin contractile machinery [14]. Thus, it is reasonable to assume that Periostin could serve as an adhesive between these cells and collagen fibers, bearing mechanical stress in mature tissues and determining the strength and rigidity of these tissue.

7.3.1 Periostin Affects Dental Tissue Development as a Fetal Protein

Periostin has been regarded as a fetal protein involved in the morphogenesis and subsequent development of various tissues, including bone and periodontal tissues [4, 15, 16]. Periostin expression has demonstrated intense immunoreactivity in the cervical loop and dental follicles of molar tooth germs at cap and bell stages, which then disappears in the advance stages of tooth development [5]. In addition, Periostin immunoreactions have been found in the dental follicles of developing teeth, as well as in the developing sites of incisors, suggesting that this protein could be widely distributed in various fetal tissues in which the ECM undergoes active remodeling. Moreover, Periostin could inhibit precocious cell differentiation to maintain the proliferative potential of these cellular elements at the fetal stage. This change in the expression pattern of Periostin may be explained by the theory that Periostin is produced as a kind of fetal protein [5].

7.3.2 Functions of Periostin in the PDL

The PDL, which lies between the tooth and alveolar bone, is important for many functions such as proprioception, tooth support, and tissue remodeling in response to physiological or pathological conditions. The PDL consists of cells (*e.g.* fibroblasts, epithelial cells, mesenchymal cells, and bone and cementum cells) and extracellular compartments of dense fibrous connective tissue that confer resistance against mechanical stress. The extracellular compartments are formed of type I, III, and V collagen fibers, fibronectin, and tenascin-C embedded in the intercellular substance. It is important for bone and PDL to maintain the local histological architectures and the integrity of the ECM, and several ECM-associated proteins could play pivotal parts in regulating cell proliferation, adhesion, migration, differentiation, survival, *etc*. [17].

Periostin has been reported to be part of the ECM and contribute to the regulation of bone homeostasis, which is crucial in maintaining the integrity of PDL as well as that of the neighboring alveolar bone. Periostin null mice develop an early onset periodontal disease-like phenotype [18]. Widened PDLs and damaged alveolar bone coupled with enhanced osteoclast activity were discovered in Periostin null mouse incisors, leading to abnormal remodeling. Moreover, ameloblast functions are abnormal in Periostin null mice, leading to improper amorphous matrix secretion postnatally. These mice also present with compressed and disordered enamel and dentin of the incisors, and abnormal jaw bone, which ultimately result in enhanced tooth wear [18]. Furthermore, the periosteum of Periostin null mice exhibits alterations in collagen fibrillogenesis, fibril diameter and collagen crosslinking as observed in the skin, tendons, and heart [11, 19]. Similar findings from Kii et al. [20] using Periostin null mice showed abnormal incisor eruption. Their results also suggested that Periostin has crucial functions during the remodeling of the collagen matrix in the shear zone. Another experiment using Periostin mutant mice performed by Norris et al. [11] demonstrated the reduced diameters of collagen fibrils compared with those of wild-type mice. These results indicate aberrant collagen fibril maturation and assembly, as well as disorganized collagen crosslinking. Several crucial ECM proteins (type-I collagen, fibronectin, and tenascin C) in the PDL of Periostin null mice also showed altered distribution [21]. In the absence of Periostin, the collagen bundle organization was random, with abnormal localization of fibronectin and tenascin C. In addition, the expressions in the incisor dentin of several non-collagenous proteins, such as dentin sialophosphoprotein, dentin matrix acidic phosphoprotein-1, bone sialoprotein, and osteopontin, were also found to be altered in Periostin mutant mice compared to the wild-type mice [21]. Furthermore, soluble Periostin treatment increases the expression of osteogenic markers in bone marrow mesenchymal stem cells, including Runx2, collagen 1, osteocalcin, osterix, alkaline phosphatase and calcium nodules, and this effect was weakened when the soluble Periostin was neutralized [22]. Taken together, these findings suggest that Periostin might play a crucial role in the cross-linkage and distribution of collagenous and non-collagenous ECM proteins, implying that Periostin is critical in preserving the integrity of PDLs and plays a significant role in the postnatal development.

7.3.3 Periostin Regulates Alveolar Bone Cells

Bone tissue, including alveolar bone, is continuously remodeled through the concerted action of bone cells. This process consists of bone formation by osteoblasts and bone resorption by osteoclasts, while the osteocytes serve as a mechanosensor and an orchestrator during bone remodeling [23]. Periostin was found to be expressed on the alveolar bone surface *in vivo*, suggesting its role in the regulation of osteoblast functions. In Periostin-deficient mice, the crestal alveolar bone was decreased, and the PDL appeared to be enlarged. In addition, despite not belonging to the periodontal tissue, the basal bone of the mutant mice was also affected, causing a decrease in bone volume on tissue volume (BV/TV) and enhanced fibrous areas [24]. Consistent with these observations, other studies of osteoblasts in long bone show that Periostin deficiency results in defective attachment of osteoblasts to the bone matrix, which affects their differentiation into mature osteoblasts as shown by a severe reduction in the expression of type I collagen, osteocalcin, osteopontin, and alkaline phosphatase, and by a decrease in mineralization processes *in vitro* [25, 26]. Conversely, Cobo and colleagues demonstrated that the overexpression of Periostin inhibited the migratory capacity of MC3T3-E1 osteoblastic cells, but increased their adhesion capacity [27]. The results of Periostin overexpression affecting the RNA expression profiles of MC3T3-E1 cells confirmed that many genes associated with processes such as cell migration, adhesion, and bone metabolism have impaired expression, except for the genes involved in bone differentiation [27]. In addition,

Periostin overexpression in rats by injection of an adenovirus could increase the bone formation rate and bone mass [28]. Further studies are necessary to determine whether Periostin could directly regulate the osteoblastic cell functions.

Different from osteoblasts, studies on osteoclasts are scarce. There is currently no direct evidence of Periostin expression in osteoclasts of alveolar bone. However, Periostin null mice incisors showed a significant enhancement of osteoclast activity in the periodontium, with abnormal bone remodeling and a defect of alveolar bone [18], suggesting that Periostin affects osteoclast function. Recently, an *in vitro* study suggested that osteoclasts from mouse long bones could express a low level of Periostin during osteoclastogenesis, and the expression level is assumed to increase with the stage of differentiation [29]. In addition, Periostin-deficient mice have a higher number and activity of osteoclasts, with lower bone formation indices in alveolar bone (jaw) [24] and femurs in response to unloading [30].

Periostin is considered to be a marker of immature osteocytes because its mRNA expression is not observed in osteocytes [2, 7]. Consistently, Periostin mRNA has been shown to be expressed in preosteocyte-like cell line MLO-A5 cells, but not in osteocyte cell line MLO-Y4 cells [31]. However, increased basal sclerostin expression, abrogation of sclerostin down-regulation with loading, and reduced load-related bone formation were observed in Periostin knockout mice [32]. Sclerostin is an osteocyte-specific factor. By antagonizing the canonical Wnt pathway in osteocytes, sclerostin reduces bone formation [33]. Periostin knockout mice have shown abnormal skeletons and decreased alveolar bone volumes, which are the results of an increased expression of sclerostin. Moreover, the disordered alveolar bone phenotype of Periostin knockout mice could be normalized by crossbreeding with sclerostin knockout mice [34]. Similarly, Bonnet demonstrated that Periostin mutant mice show higher apoptosis levels of osteoblasts and osteocytes. Stimulated intermittent parathyroid hormone (PTH) can upregulate Periostin expression at the periosteal surface and in osteocytes, but reduces the expression of sclerostin [25]. In addition, the number of osteocytes in Periostin knockout mice decreased, while the number of empty osteocyte lacunae increased with the administration of high-dose zoledronate [24]. Although the above-mentioned evidence indicates that Periostin may play an anti-apoptotic role in osteocytes, it remains to be determined whether Periostin affects other functions of osteocytes.

7.3.4 Role of Periostin in Periodontium Responses to Mechanical Loading

Mechanical forces are prevalent in various biological processes, stretching the cytoskeleton within cells, assembling the original fibers that connect the cells, and regulating ligand-receptor binding on the cell surface. Cells from the bone, ECM architecture and PDL can activate mechanosensory signaling systems and adjust the cytoskeleton in order to respond to mechanical force stimulation. Accordingly, there are many proteins involved in this process. Considering its functions in osteoblasts, osteocytes, and the PDL matrix structure, Periostin is expected to be involved in periodontium remodeling in response to mechanical stress. It has been proved that Periostin withstands mechanical forces loaded onto the PDL, such as occlusal forces and/or tooth eruption. Consequently, Periostin null mice have severe periodontal defects after tooth eruption [18]. Alleviating the mechanical strain on the PDL by removing masticatory forces with a soft diet could partially rescue both the enamel and periodontal-disease-like phenotypes [35]. Similarly, a study of 45 Wistar rats showed that the PDL fiber system undergoes degradation and Periostin levels decrease in the absence of mechanical stress [36].

Orthodontic tooth movement is achieved by reiterated alveolar bone resorption on the pressure side and new bone formation on the tension side. Periostin is essential during orthodontic tooth movement processes, and deletion of this gene significantly alters collagen and bone remodeling in the periodontium. Divergent expression of

Periostin mRNA was observed, compared with control specimens, during experimental tooth movement from 3 to 96 h. It has been reported that the expression of Periostin protein on pressure sides is stronger than that on tension sides [7]. In studies involving Periostin silencing, the mutant mice showed a wider residually-compressed PDL compared to wild-type littermates, while several bone-remodeling-related factors were also affected [37–39]. Immunolocalization of cathepsin K, matrix metalloproteinase (MMP) 1, and MMP2 decreased greatly in the compressed PDL of Periostin null mice after orthodontic tooth movement at 1 and 3 days [37]. High mobility group box 1 (HMGB1), a late inflammatory cytokine, could be regulated by PDL cells during tooth movement. HMGB1 expression in Periostin knockout mice was found to have a high basal level, but on the compression side, a weak response level was shown compared with the wild-type mice, suggesting a correlation between HMGB1 and Periostin following the action of a mechanical force [38]. Furthermore, during tooth movement, sclerostin in alveolar bone displayed divergent expression, with an increase on the compression side and a decrease on the tension side. However, this phenomenon was not observed in Periostin knockout mice, which suggests an interaction between Periostin and sclerostin during tooth movement [39]. The mRNA expressions of Periostin and twist, which is an upstream molecule regulating Periostin in the PDL, could be inhibited by removing mechanical forces [8]. In addition, the delayed bone remodeling on the compression side during tooth movement might be attributed to the reduced osteoclast activity in Periostin null mice [34]. However, a subsequent study of the same group showed that the expressions of both RANKL (a potent stimulator of osteoclasts) and osteoprotegerin (a strong inhibitor of osteoclasts) decreased in Periostin null mice, which complicates the mechanism underlying the reduced osteoclast number in Periostin null mice [39]. Taken together, these results suggest that Periostin is essential for the periodontium in response to orthodontic tooth movement. However, further studies are required to fully elucidate the role of Periostin during this process (Fig. 7.2).

7.4 Periostin and Periodontal Tissue Regeneration

Inflammatory responses to bacteria can initiate the destructive process of periodontitis, leading to both a loss of connective tissue and alveolar bone around teeth and an apical shift of the junc-

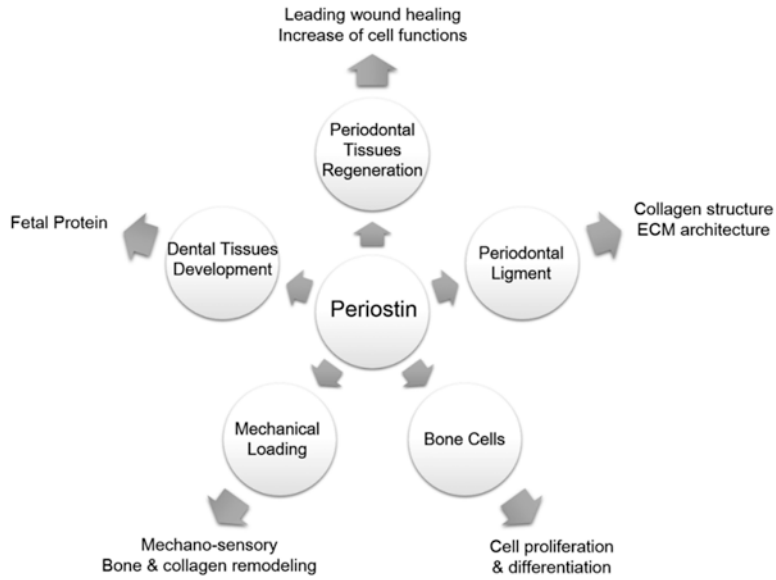

Fig. 7.2 The multiple functions of Periostin in dental tissues

tional epithelium. Untreated periodontitis results in loss of function, tissue destruction, loosening, and subsequent loss of teeth [40]. The preferential expression of Periostin in collagen-rich tissues submitted to mechanical strains, such as the PDL, and its increase during fracture healing, suggest that it might play a critical role in periodontium maintenance and regeneration. Periostin has successfully been used as a periodontal regeneration marker [41–43]. Padial-Molina et al. [44] designed a case-control study to determine the expression profile of Periostin that facilities wound stability and maturation. Periostin increased after periodontal surgery in gingival crevicular fluid (GCF)/wound fluid, which is higher in periodontitis patients. The decline of chronic inflammatory stimuli and bacterial challenge caused by the periodontal surgical procedure could potentially explain the Periostin increment. Moreover, the expression levels of Periostin in GCF/wound fluid moderated to baseline levels as the wound matured, possibly resulting from an increase in Periostin deposits in the ECM as the collagen structure matures [44].

As indicated above, periodontal tissue engineering/regeneration must achieve the regeneration of all tooth-supporting structures [3]. In this particular healing process, a temporal sequence and specific spatial distribution of multiple cells, scaffolds, matrix interactions, and signaling molecules must be followed [45]. The application of biological agents can regulate and promote the natural processes in the healing area, facilitating tissue regeneration [46]. Periostin is a matricellular protein, thus an extracellular protein. Consequently, it is assumed that Periostin plays a part in the cell–matrix interactions and cell functions, but is not directly involved in the formation of structural elements [47]. In light of these characteristics, Periostin is supposed to regulate cell migration, recruitment, adhesion, proliferation and attachment to healing areas of various tissues. By promoting the migration of fibroblasts and osteoblasts, Periostin might play an essential role in the remodeling of the PDL and its surrounding bone.

Periostin could regulate cell functions to favor tissue regeneration through several signaling pathways. For example, Periostin enhances the migration and proliferation of human PDL fibroblasts subjected to tumor necrosis factor-α and *Porphyromonas gingivalis* lipopolysaccharides through the PI3K/Akt/mTOR pathway [48]. Moreover, Periostin expression in human PDL fibroblasts promotes the migration of human mesenchymal stem cells through the αvβ3 integrin/FAK/PI3K/Akt pathway *in vitro* [49]. Additionally, Periostin regulates angiogenesis through the enhancement of vascular endothelial growth factor and MMP-2, which could occur through the activation of the αvβ3 integrin/extracellular-related kinase signaling pathway in human PDL cells [50].

At both mRNA and protein levels, Periostin expression is rapidly enhanced during fracture healing [51, 52], suggesting its role in bone regeneration at various phases. Despite its initial identification in the MC3T3-E1 osteoblastic cell line, the functions of Periostin have not been sufficiently studied in bone-remodeling cells (osteoblasts and osteoclasts). In MC3T3-E1 cells and primary rat osteoblasts, Periostin promotes proliferation and differentiation by increasing Runx2, alkaline phosphatase, and osteocalcin levels [26, 53]. These data indicate that Periostin could be expressed by immature osteoblasts and participate in the differentiation process, which favors bone regeneration. Recently, a study using a murine calvarial defect model showed that Periostin administration was able to promote the survival and bone-healing capacity of transplanted human adipose tissue-derived mesenchymal stem cells [54]. In addition, Periostin has been found to be expressed in ameloblasts, subodontoblasts, and odontoblasts. An enormous increase of dentin mass in Periostin null incisors and defects of enamel in these null molars support its direct role in the modulation of postnatal tooth formation [55].

7.5 Conclusion

Considering its spatial localization in both the PDL and alveolar bone of the periodontium, and its pivotal role in the regulation of the functions of these tissues, Periostin may become a promising agent to promote the regeneration of periodontal tissues in the future.

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