Cell. Mol. Life Sci. (2017) 74:4279–4286
DOI 10.1007/s00018-017-2645-3

Cellular and Molecular Life Sciences

MULTI-AUTHOR REVIEW

Functions of Periostin in dental tissues and its role in periodontal tissues' regeneration

Juan Du[1] · **Minqi Li**[1]

Received: 24 August 2017 / Accepted: 4 September 2017 / Published online: 9 September 2017

Abstract The goal of periodontal regenerative therapy is to predictably restore the tooth's supporting periodontal tissues and form a new connective tissue attachment of periodontal ligament (PDL) fibers and new alveolar bone. Periostin is a matricellular protein so named for its expression primarily in the periosteum and PDL of adult mice. Its biological functions have been widely studied in areas such as cardiovascular physiology and oncology. Despite being initially identified in the dental tissues and bone, investigations of Periostin functions in PDL and alveolar-bone-related physiopathology are less abundant. 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 pivotal part in regeneration of the PDL and alveolar bone following periodontal surgery. The aim of this article is to provide an extensive review of the implications of Periostin in periodontal tissue biology and its potential use in periodontal tissue regeneration.

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

Periostin and periodontium

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

The periodontium is a specialized tissue that surrounds and also supports teeth, maintaining them in the maxillary and mandibular bones. It provides the support necessary to maintain the function of teeth. Periodontium consists of four principal components: gingiva, PDL, cementum, and alveolar bone. By definition, periodontal tissue engineering/regeneration must achieve regeneration of all tooth-supporting structures, including the alveolar bone, cementum, and PDL, and adequate sealing by the gingival tissue [3].

Structure of Periostin

The Periostin protein consists of a signal sequence followed by an EMILIN-like (EMI) domain rich in cysteine, four repeated and conserved fasciclin-1 (Fas-1) domains, and a C-terminal hydrophilic and variable domain including a heparin-binding site. Periostin is classified as a member of the fasciclin 1 family by possessing these typical Fas-1 domains, which involved in cell adhesion functions [4]. Each Fas-1 domain, rich in glutamate residues, has an N-terminal recognition site for γ-glutamyl carboxylase. It also contains a cell adhesion site that interacts with tenascin-C and bone morphogenetic protein (BMP)-1 [2, 5]. In addition, the N-terminal site could recognize the vitamin K-dependent γ-glutamyl carboxylase, in order to modify glutamic residues

✉ Minqi Li
liminqi@sdu.edu.cn

[1] Department of Bone Metabolism, School of Stomatology, Shandong Provincial Key Laboratory of Oral Tissue Regeneration, Shandong University, Jinan 250012, China

to γ-carboxyglutamate post-translationally [6]. The EMI domain at the N-terminus is a cysteine residue-rich site for protein–protein interactions through which Periostin directly interacts with type-I collagen and fibronectin [7, 8]. The C-terminal domain could alternatively split to generate at least five different human isoforms [9].

Expression of Periostin in dental tissues

Periostin expression in the PDL was initially demonstrated by immunohistochemistry of sections of a 5-week-old mouse mandible [2]. Spatiotemporal localization of Periostin expression was then revealed within developing and maturing dental tissues. Kruzynska-Frejtag et al. found that during early interactions between epithelial and mesenchymal, the mRNA and protein of Periostin were asymmetrically localized to the lingual/palatal and buccal side [10]. Suzuki et al. found that, Periostin expressed in the interface between the inner enamel epithelium and preodontoblasts in tooth germs at the cap stage. It was also expressed in mesenchymal tissues around the cervical loop and dental follicles. And they also found that Periostin presented in dental papilla cells and trans-differentiating odontoblasts during the bell and hard tissue formation stages of tooth development [11].

In the adult rodent, Periostin expression appears to be restricted to the periodontium. After postnatal day 7, immunoreactions of Periostin become uniformly localized to fibrous bundles in the PDL in accordance with the organization of the periodontal fibers, indicating its role in morphogenesis of the PDL. In the incisors of both 7- and 21-day-old mice, Periostin immunoreactions are discernible in the lingual PDL and labial fibrous tissue adjacent to the papillary layer [11]. 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 [12]. Most importantly, the expression of Periostin was also found in the alveolar bone surface by both immunoreactivity and in situ hybridization [11, 12]. Furthermore, the immunoelectron microscopy analysis demonstrated that Periostin presented in the cytoplasmic extensions of periodontal fibroblasts membrane, but neither in the cytoplasm nor the mature PDL [11]. The Periostin protein is markedly present in the extracellular matrix (ECM) and secreted possibly from periodontal fibroblasts. In addition, there is no positive reaction observed in enamel, dentin, cementum, dental pulp, or alveolar bone [13]. This finding suggests that Periostin might regulate the deposition of ECM and effect with other adhesion molecules during tooth development. It is possible that Periostin modulates and maintains the integrity of adult teeth by mediating cell-to-matrix interactions, particularly at sites of hard-soft tissue interfaces (Fig. 1).

Functions of Periostin in dental tissues

Periostin actions has been classified into two major functional categories by Kudo in regard of their molecular properties of protein interactions. First is fibrillogenesis, which occurs inside the cell. And another is cell migration, which including the extracellular action outside the cells [14, 15]. Through its EMI domain, Periostin could interact directly with type I collagen [8], fibronectin [5], and Notch1 [15], as well as with tenascin-C [5] and BMP-1 [16] through the Fas-1 domain. These functions fulfil Periostin to promote proteolytic activation of lysyl oxidase for collagen crosslinking. Periostin also acts as a ligand of integrins αvβ3 and αvβ5 to facilitate cell motility by activation of actin/myosin contractile machinery [17]. Thus, Periostin might serve as an adhesive device by connecting these cells and collagen

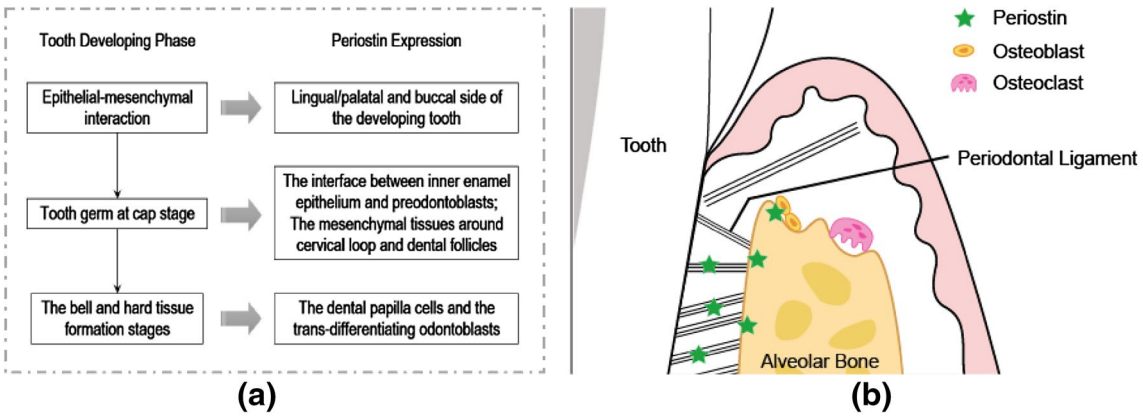

Fig. 1 The expressions of Periostin in dental tissues. **a** The expression of Periostin during dental development. **b** The expression of Periostin in periodontal tissues

fibers, in order to undertake the mechanical stress in mature tissues, provide the strength and rigidity for this tissue.

Periostin affects dental tissue development as a fetal protein

Periostin is supposed to be a fetal protein, which effected the morphogenesis and development of bone and periodontal tissues, et al. [10, 18, 19]. The expression Periostin has been demonstrated in the cervical loop and dental follicles of incisors and the molar tooth germs at cap and bell stages, which then disappear in advance of tooth development [11]. Protein extensively distributed in the active of ECMs where the remodeling takes place in various fetal tissues, suggesting it might effect in extracellular matrix deposition and tissue remodeling. In addition, in order to preserve the proliferative potentiality in these cellular elements, Periostin might probably prevent precocious cell differentiation at the fetal stage [11].

Periostin functions in the PDL

The PDL lies between the tooth and alveolar bone, and is important for many functions such as proprioception, tooth support, and tissue remodeling in response to physiological or pathological conditions. It consists of cells and an extracellular compartment of dense fibrous connective tissue that bears mechanical stress fibers. The cells are fibroblasts, epithelial cells, mesenchymal cells, and bone and cementum cells. The extracellular compartment consists 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 keep the local histological architectures by the integrity of ECM. And several ECM-associated proteins could play pivotal parts in regulating cell proliferation, adhesion, migration, differentiation, and survival, et al. [20].

Periostin is crucial to maintain the integrity of the PDL. Periostin null mice develop an early onset periodontal disease-like phenotype [21]. Widened PDLs and disturbing alveolar bone were discovered in the Periostin null mouse incisors, as well as enhanced osteoclast activity leading to abnormal remodeling. There were drawbacks of ameloblast functions in Periostin null mice, leading to improper amorphous matrix secretion postnatally. Subsequently, the compressed and disordered enamel and dentin of the incisors were found, as well as the abnormal jaw bone, which ultimately resulted in enhanced tooth wear [21]. Furthermore, the Periostin null mice periosteum exhibits altered collagen fibrillogenesis, manifest as alteration in fibril diameter and collagen crosslinking as observed in the skin, tendons, and heart [8, 22]. Similar findings from Kii et al. using Periostin null mice showed inappropriate incisors' eruption. And their results also suggested that Periostin has crucial functions during the remodeling of collagen matrix in the shear zone; deletion of Periostin led to disappearance of the shear zone [23]. Another experiment applied by Norris et al., also with Periostin mutant mice demonstrated reduced diameters of collagen fibrils compared with wild-type mice. And their results indicate aberrant collagen fibril maturation and assembly, as well as disorganized collagen crosslinking [8]. Several crucial ECM proteins (type-I collagen, fibronectin, and tenascin C) in the PDL of Periostin null mice also manifested an alteration of distribution [24]. The collagen bundle organization was random in different directions with abnormal localization of fibronectin and tenascin C without Periostin. In addition, the expressions of several non-collagenous proteins, such as dentin sialophosphoprotein, dentin matrix acidic phosphoprotein-1, bone sialoprotein, and osteopontin, in the incisor dentin were also found changed in the Periostin mutant mice compared to the wild-type ones [24]. Taken together, Periostin might play a crucial part in the cross linkage and distribution of ECM proteins, collagenous or non-collagenous, suggesting that Periostin is critical to preserve the integrity of PDLs and is very significant for postnatal development.

Periostin regulates alveolar bone cells

Bone tissue, including alveolar bone, is continuously remodeled through the concerted actions of bone cells. This process consists of bone formation by osteoblasts and bone resorption by osteoclasts, while the osteocytes serve as mechanosensors and orchestrators during the bone-remodeling process [25]. The expression of Periostin was first identified in the mouse osteoblastic cell line MC3T3-E1 [1] and found in the alveolar bone surface in vivo, suggesting its role in regulation of osteoblasts functions. In Periostin-deficient mice, the crestal alveolar bone is decreased, and the PDL appears to be enlarged. In addition, despite not belonging to the periodontal tissue, the basal bone of the mutant mice was also affected caused by the decreased bone volume on tissue volume (BV/TV) and enhanced fibrous areas [26]. Consistent with these observations, other studies of long bone osteoblasts show that Periostin mutation caused the impeded attachment of osteoblasts to the bone matrix, as well as severe reduced expression of type I collagen, osteocalcin, osteopontin, and alkaline phosphatase. These alternations of the weakened functions result in the obstacle of their differentiation into mature osteoblasts, as well as the decrease in mineralization processes in vitro [27, 28]. Conversely, Cobo and co-workers demonstrated that in MC3T3-E1 osteoblastic cells, overexpression of Periostin inhibits their migratory capacity but increases the adhesion capacity. The analysis of the effect of Periostin overexpression on the alternation of the RNA expression

profile of MC3T3-E1 cells confirmed that many genes that associated in processes such as cell migration, adhesion, and bone metabolism are changed, but not the gene in bone differentiation [29]. In addition, Periostin overexpressing in rats by injection of an adenovirus could upregulate the bone formation rate and bone mass [30]. Further studies are necessary in order to interpret whether Periostin could directly regulate osteoblastic cell functions.

Different from osteoblasts, studies of osteoclasts are not advanced well. There is currently no direct evidence of Periostin expression in osteoclasts of alveolar bone. However, Periostin null mouse incisors showed a significant enhancement of osteoclast activity in the periodontium of null mice, with abnormal bone remodeling and defection of alveolar bone [21], suggesting that Periostin affects osteoclast function. Recently, an in vitro study suggests that osteoclasts from mouse long bones could express low level of Periostin during osteoclastogenesis, while its expression tendency assumed to increase with differentiation [31]. In addition, Periostin-deficient mice have a higher number and activity of osteoclasts with lower bone formation indices in alveolar bone (jaw) [26] and femurs in response to unloading [32].

Periostin is considered to be a marker of immature osteocytes because its mRNA expression is not observed in osteocytes [2, 12]. Consistently, Periostin mRNA has been shown to be expressed in a preosteocyte-like cell line MLO-A5 cells, but not in an osteocyte cell line MLO-Y4 cells [33]. However, increased basal sclerostin expression, abrogation of sclerostin down-regulation with loading, and reduced load-related bone formation are observed in Periostin knockout mice [34]. Sclerostin is an osteocyte-specific factor. By antagonizing the canonical Wnt pathway in osteocytes, sclerostin reduces bone formation [35]. The Periostin knockout mice have demonstrated abnormal skeleton and decreased alveolar bone volumes, which are the results of the increased expression of sclerostin. Moreover, the disordered alveolar bone phenotype of the Periostin knockout mice could be normalized though crossbreeding with sclerostin knockout mice [36]. Similarly, Bonnet demonstrated that Periostin mutant mice showed higher apoptosis of osteoblasts and osteocytes. And intermittent parathyroid hormone (PTH)-stimulated could upregulate Periostin expression at the periosteal surface and in osteocytes, but reduce sclerostin in osteocytes [27]. In addition, the number of osteocytes in Periostin knockout mice could be decreased and the number of empty osteocyte lacunae increased with administration of high-dose zoledronate [26]. Although much evidence as above indicates that Periostin may act as an anti-apoptotic role in osteocytes, whether Periostin affects other functions of osteocytes still needs to be elucidated.

Periostin functions in periodontium responses to mechanical loading

Orthodontic tooth movement is achieved by reiterated alveolar bone resorption on the pressure side and new bone formation on the tension side. Cells from the bone and ECM architecture as well as PDL activate mechanosensory signaling systems and adjust cytoskeletal form in order to respond to mechanical force stimulation. In terms of the functions of Periostin in the PDL matrix structure, as well as in osteoblast and osteocyte, it 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. Periostin null mice have severe periodontal defects after tooth eruption [21]. Alleviating mechanical strain on the PDL by removing masticatory forces with a soft diet could partially rescue both the enamel and periodontal disease-like phenotypes [37]. 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 [38].

Periostin is essential during orthodontic tooth movement processes, and deletion of this gene significantly alters collagen and bone remodeling in periodontium. Divergent expression of Periostin mRNA was observed comparing with control specimens during experimental tooth movement from 3 to 96 h. It is reported the expression of Periostin staining in pressure sites is stronger than that in tension sites [12]. When Periostin has been deleted, the mutant mice showed a wider residually compressed PDL compared to wild-type littermates, while several bone-remodeling-related factors have been effected [39–41]. Immunolocalization of cathepsin K, matrix metalloproteinase (MMP) 1, and MMP2 decreases greatly in the compressed PDL of Periostin null mice after orthodontic tooth movement at 1 and 3 days [39]. High mobility group box 1 (HMGB1), a late inflammatory cytokine, could be regulated by PDL cells during tooth movement. HMGB1 in the Periostin knockout mice was demonstrated a high basal level, but a weak response level in the compression site compared with the wild-type mice, suggesting a correlation between HMGB1 and Periostin with mechanical force [40]. Furthermore, during tooth movement, sclerostin in alveolar bone displayed divergent expression with an increase in the compression side and a decrease in the tension side. However, this phenomena vanished in Periostin knockout mice, which suggests an interaction between Periostin and sclerostin during tooth movement [41]. The mRNA expression of Periostin and twist, which is an upstream signal regulating Periostin, in the PDL could be inhibited by removing mechanical forces [13]. In addition, the delayed bone remodeling in compression side during tooth movement might be attributed to the

reduced osteoclast activity in the Periostin null mice [36]. However, a further study of the same group showed expression of both RANKL (a potent stimulator of osteoclasts) and osteoprotegerin (a strong inhibitor of osteoclasts) decreased in Periostin null mice, which complicates the mechanism of the reduced osteoclast number in Periostin knockout mice [41]. Taken together, it is apparent that Periostin is essential for the periodontium in response to orthodontic tooth movement. However, further studies are required to illustrate the role of Periostin during this process (Fig. 2).

Periostin and periodontal tissue regeneration

The inflammatory response to bacteria can initiate the destructive process of periodontitis, leading to loss of connective tissue and alveolar bone around teeth, as well as an apical shift of the junctional epithelium. Untreated periodontitis results in loss of function, tissue destruction, loosening, and subsequent loss of teeth [42]. The preferential expression of Periostin in collagen-rich tissues submitted to mechanical strains, such as the PDL, as well as the increment during fracture healing, suggests that it might act as a critical role in periodontium maintenance and regeneration. As indicated above, Periostin has been used as a successful periodontal regeneration marker [43–45]. Padial-Molina et al. designed a case control study to gain the expression profile of Periostin that facilities wound stability and maturation [46]. They found that Periostin increases 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 surgical procedure could be the interpretation of Periostin increment. Moreover, the expression levels of Periostin in GCF/wound fluid moderates to baseline levels along with the wound matures, possibly resulting by an increase of Periostin deposit in the ECM as the collagen structure matures [46].

By definition, periodontal tissue engineering/regeneration must achieve regeneration of all tooth-supporting structures, including the alveolar bone, cementum, and PDL, and adequate sealing by the gingival tissue [3]. In this particular healing process, a temporal sequence and specific spatial distribution of multiple cells, scaffold, matrix interactions, as well as the involved signaling molecules must be followed [47]. The application of biological agents can regulate and promote the activity of the natural events in the healing area to promote tissue regeneration [48]. Periostin is a matricellular protein, indicating that it is an extracellular protein. Thus it is predicted that Periostin plays a part in the cell–matrix interactions and cell functions, but not act directly with the formation of structural elements [49]. In terms 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 part in the remodeling of the PDL and its surrounding bone.

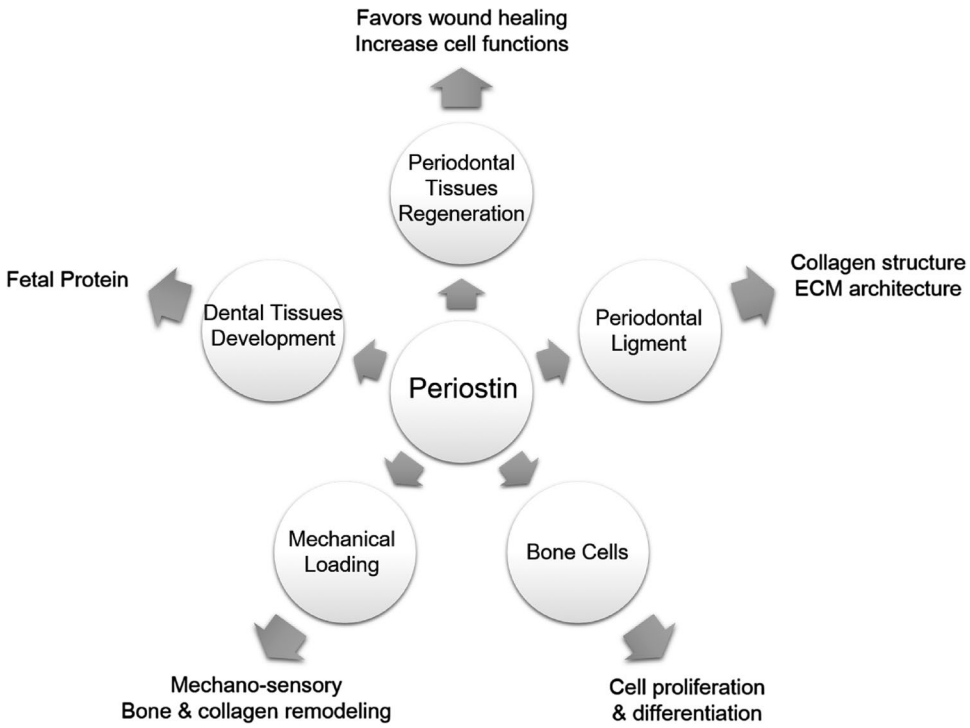

Fig. 2 The multiple functions of Periostin in dental tissues

Periostin could regulate cell functions to favor tissue regeneration through several signaling pathways. Periostin enhances migration and proliferation of human PDL fibroblasts subjected to tumor necrosis factor-α and *Porphyromonas gingivalis* lipopolysaccharides through the PI3K/Akt/mTOR pathway [50]. 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 [51]. Additionally, Periostin regulates angiogenesis through the enhancement of vascular endothelial growth factor (VEGF) and MMP-2, which could be expressed though the activation of αvβ3 integrin/extracellular-related kinase signaling pathway in human PDL cells [52].

THE mRNA and protein levels Periostin rapidly enhanced during fracture healing [53, 54], 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 [28, 55]. These data indicate that Periostin could be expressed by immature osteoblasts and associate with the differentiation process, which favors bone regeneration. Recently, a study using murine calvarial defect model showed Periostin administration was able to promote survival and bone healing capacity of transplanted human adipose tissue-derived mesenchymal stem cells (hASCs) [56]. In addition, Periostin expression has been found 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 modulation of postnatal tooth formation [57].

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 in these tissues, Periostin may become a promising agent to promote the regeneration of periodontal tissues in the future.

Acknowledgements This study was partially supported by the National Nature Science Foundation of China (Grant Nos. 81470719; 81611140133) to Li M.

References

1. Takeshita S, Kikuno R, Tezuka K, Amann E (1993) Osteoblast-specific factor 2: cloning of a putative bone adhesion protein with homology with the insect protein fasciclin I. Biochem J 294(Pt 1):271–278
2. Horiuchi K, Amizuka N, Takeshita S, Takamatsu H, Katsuura M, Ozawa H, Toyama Y, Bonewald LF, Kudo A (1999) Identification and characterization of a novel protein, Periostin, with restricted expression to periosteum and periodontal ligament and increased expression by transforming growth factor beta. J Bone Miner Res 14(7):1239–1249. doi:10.1359/jbmr.1999.14.7.1239
3. Padial-Molina M, Marchesan JT, Taut AD, Jin Q, Giannobile WV, Rios HF (2012) Methods to validate tooth-supporting regenerative therapies. Methods Mol Biol 887:135–148. doi:10.1007/978-1-61779-860-3_13
4. Kim JE, Kim SJ, Lee BH, Park RW, Kim KS, Kim IS (2000) Identification of motifs for cell adhesion within the repeated domains of transforming growth factor-beta-induced gene, betaig-h3. J Biol Chem 275(40):30907–30915. doi:10.1074/jbc.M002752200
5. Kii I, Nishiyama T, Li M, Matsumoto K, Saito M, Amizuka N, Kudo A (2010) Incorporation of tenascin-C into the extracellular matrix by Periostin underlies an extracellular meshwork architecture. J Biol Chem 285(3):2028–2039. doi:10.1074/jbc.M109.051961
6. Coutu DL, Wu JH, Monette A, Rivard GE, Blostein MD, Galipeau J (2008) Periostin, a member of a novel family of vitamin K-dependent proteins, is expressed by mesenchymal stromal cells. J Biol Chem 283(26):17991–18001. doi:10.1074/jbc.M708029200
7. Kii I, Nishiyama T, Kudo A (2016) Periostin promotes secretion of fibronectin from the endoplasmic reticulum. Biochem Biophys Res Commun 470(4):888–893. doi:10.1016/j.bbrc.2016.01.139
8. Norris RA, Damon B, Mironov V, Kasyanov V, Ramamurthi A, Moreno-Rodriguez R, Trusk T, Potts JD, Goodwin RL, Davis J, Hoffman S, Wen X, Sugi Y, Kern CB, Mjaatvedt CH, Turner DK, Oka T, Conway SJ, Molkentin JD, Forgacs G, Markwald RR (2007) Periostin regulates collagen fibrillogenesis and the biomechanical properties of connective tissues. J Cell Biochem 101(3):695–711. doi:10.1002/jcb.21224
9. Hoersch S, Andrade-Navarro MA (2010) Periostin shows increased evolutionary plasticity in its alternatively spliced region. BMC Evol Biol 10:30. doi:10.1186/1471-2148-10-30
10. Kruzynska-Frejtag A, Wang J, Maeda M, Rogers R, Krug E, Hoffman S, Markwald RR, Conway SJ (2004) Periostin is expressed within the developing teeth at the sites of epithelial-mesenchymal interaction. Dev Dynam 229(4):857–868. doi:10.1002/dvdy.10453
11. Suzuki H, Amizuka N, Kii I, Kawano Y, Nozawa-Inoue K, Suzuki A, Yoshie H, Kudo A, Maeda T (2004) Immunohistochemical localization of Periostin in tooth and its surrounding tissues in mouse mandibles during development. Anat Rec A Discov Mol Cell Evol Biol 281(2):1264–1275. doi:10.1002/ar.a.20080
12. Wilde J, Yokozeki M, Terai K, Kudo A, Moriyama K (2003) The divergent expression of Periostin mRNA in the periodontal ligament during experimental tooth movement. Cell Tissue Res 312(3):345–351. doi:10.1007/s00441-002-0664-2
13. Afanador E, Yokozeki M, Oba Y, Kitase Y, Takahashi T, Kudo A, Moriyama K (2005) Messenger RNA expression of Periostin and Twist transiently decrease by occlusal hypofunction in mouse periodontal ligament. Arch Oral Biol 50(12):1023–1031. doi:10.1016/j.archoralbio.2005.04.002
14. Kudo A (2011) Periostin in fibrillogenesis for tissue regeneration: Periostin actions inside and outside the cell. Cell Mol Life Sci 68(19):3201–3207. doi:10.1007/s00018-011-0784-5
15. Tanabe H, Takayama I, Nishiyama T, Shimazaki M, Kii I, Li M, Amizuka N, Katsube K, Kudo A (2010) Periostin associates with Notch1 precursor to maintain Notch1 expression under a stress condition in mouse cells. PLoS ONE 5(8):e12234. doi:10.1371/journal.pone.0012234
16. Maruhashi T, Kii I, Saito M, Kudo A (2010) Interaction between Periostin and BMP-1 promotes proteolytic activation of lysyl

oxidase. J Biol Chem 285(17):13294–13303. doi:10.1074/jbc.M109.088864
17. Gillan L, Matei D, Fishman DA, Gerbin CS, Karlan BY, Chang DD (2002) Periostin secreted by epithelial ovarian carcinoma is a ligand for alpha(V)beta(3) and alpha(V)beta(5) integrins and promotes cell motility. Can Res 62(18):5358–5364
18. Ito T, Suzuki A, Imai E, Horimoto N, Ohnishi T, Daikuhara Y, Hori M (2002) Tornado extraction: a method to enrich and purify RNA from the nephrogenic zone of the neonatal rat kidney. Kidney Int 62(3):763–769. doi:10.1046/j.1523-1755.2002.00533.x
19. Kruzynska-Frejtag A, Machnicki M, Rogers R, Markwald RR, Conway SJ (2001) Periostin (an osteoblast-specific factor) is expressed within the embryonic mouse heart during valve formation. Mech Dev 103(1–2):183–188
20. Moussad EE, Brigstock DR (2000) Connective tissue growth factor: what's in a name? Mol Genet Metab 71(1–2):276–292. doi:10.1006/mgme.2000.3059
21. Rios H, Koushik SV, Wang H, Wang J, Zhou HM, Lindsley A, Rogers R, Chen Z, Maeda M, Kruzynska-Frejtag A, Feng JQ, Conway SJ (2005) Periostin null mice exhibit dwarfism, incisor enamel defects, and an early-onset periodontal disease-like phenotype. Mol Cell Biol 25(24):11131–11144. doi:10.1128/MCB.25.24.11131-11144.2005
22. Shimazaki M, Nakamura K, Kii I, Kashima T, Amizuka N, Li M, Saito M, Fukuda K, Nishiyama T, Kitajima S, Saga Y, Fukayama M, Sata M, Kudo A (2008) Periostin is essential for cardiac healing after acute myocardial infarction. J Exp Med 205(2):295–303. doi:10.1084/jem.20071297
23. Kii I, Amizuka N, Minqi L, Kitajima S, Saga Y, Kudo A (2006) Periostin is an extracellular matrix protein required for eruption of incisors in mice. Biochem Biophys Res Commun 342(3):766–772. doi:10.1016/j.bbrc.2006.02.016
24. Tabata C, Hongo H, Sasaki M, Hasegawa T, de Freitas PH, Yamada T, Yamamoto T, Suzuki R, Yamamoto T, Oda K, Li M, Kudo A, Iida J, Amizuka N (2014) Altered distribution of extracellular matrix proteins in the periodontal ligament of Periostin-deficient mice. Histol Histopathol 29(6):731–742. doi:10.14670/HH-29.731
25. Florencio-Silva R, Sasso GR, Sasso-Cerri E, Simoes MJ, Cerri PS (2015) Biology of bone tissue: structure, function, and factors that influence bone cells. Biomed Res Int 2015:421746. doi:10.1155/2015/421746
26. Bonnet N, Lesclous P, Saffar JL, Ferrari S (2013) Zoledronate effects on systemic and jaw osteopenias in ovariectomized Periostin-deficient mice. PLoS ONE 8(3):e58726. doi:10.1371/journal.pone.0058726
27. Bonnet N, Conway SJ, Ferrari SL (2012) Regulation of beta catenin signaling and parathyroid hormone anabolic effects in bone by the matricellular protein Periostin. P Natl Acad Sci USA 109(37):15048–15053. doi:10.1073/pnas.1203085109
28. Litvin J, Selim AH, Montgomery MO, Lehmann K, Rico MC, Devlin H, Bednarik DP, Safadi FF (2004) Expression and function of Periostin-isoforms in bone. J Cell Biochem 92(5):1044–1061. doi:10.1002/jcb.20115
29. Cobo T, Viloria CG, Solares L, Fontanil T, Gonzalez-Chamorro E, De Carlos F, Cobo J, Cal S, Obaya AJ (2016) Role of periostin in adhesion and migration of bone remodeling cells. PLoS ONE 11(1):e0147837. doi:10.1371/journal.pone.0147837
30. Zhu S, Barbe MF, Amin N, Rani S, Popoff SN, Safadi FF, Litvin J (2008) Immunolocalization of Periostin-like factor and Periostin during embryogenesis. J Histochem Cytochem 56(4):329–345. doi:10.1369/jhc.7A7321.2007
31. Merle B, Bouet G, Rousseau JC, Bertholon C, Garnero P (2014) Periostin and transforming growth factor beta-induced protein (TGFbetaIp) are both expressed by osteoblasts and osteoclasts. Cell Biol Int 38(3):398–404. doi:10.1002/cbin.10219
32. Gerbaix M, Vico L, Ferrari SL, Bonnet N (2015) Periostin expression contributes to cortical bone loss during unloading. Bone 71:94–100. doi:10.1016/j.bone.2014.10.011
33. Kato Y, Boskey A, Spevak L, Dallas M, Hori M, Bonewald LF (2001) Establishment of an osteoid preosteocyte-like cell MLO-A5 that spontaneously mineralizes in culture. J Bone Miner Res 16(9):1622–1633. doi:10.1359/jbmr.2001.16.9.1622
34. Bonnet N, Standley KN, Bianchi EN, Stadelmann V, Foti M, Conway SJ, Ferrari SL (2009) The matricellular protein Periostin is required for sost inhibition and the anabolic response to mechanical loading and physical activity. J Biol Chem 284(51):35939–35950. doi:10.1074/jbc.M109.060335
35. Robling AG, Niziolek PJ, Baldridge LA, Condon KW, Allen MR, Alam I, Mantila SM, Gluhak-Heinrich J, Bellido TM, Harris SE, Turner CH (2008) Mechanical stimulation of bone in vivo reduces osteocyte expression of Sost/sclerostin. J Biol Chem 283(9):5866–5875. doi:10.1074/jbc.M705092200
36. Ren Y, Han X, Ho SP, Harris SE, Cao Z, Economides AN, Qin C, Ke H, Liu M, Feng JQ (2015) Removal of SOST or blocking its product sclerostin rescues defects in the periodontitis mouse model. FASEB J Off Publ Federation Am Soc Exp Biol 29(7):2702–2711. doi:10.1096/fj.14-265496
37. Rios HF, Ma D, Xie Y, Giannobile WV, Bonewald LF, Conway SJ, Feng JQ (2008) Periostin is essential for the integrity and function of the periodontal ligament during occlusal loading in mice. J Periodontol 79(8):1480–1490. doi:10.1902/jop.2008.070624
38. Choi JW, Arai C, Ishikawa M, Shimoda S, Nakamura Y (2011) Fiber system degradation, and Periostin and connective tissue growth factor level reduction, in the periodontal ligament of teeth in the absence of masticatory load. J Periodontal Res 46(5):513–521. doi:10.1111/j.1600-0765.2011.01351.x
39. Lv S, Liu H, Cui J, Hasegawa T, Hongo H, Feng W, Li J, Sun B, Kudo A, Amizuka N, Li M (2014) Histochemical examination of cathepsin K, MMP1 and MMP2 in compressed periodontal ligament during orthodontic tooth movement in Periostin deficient mice. J Mol Histol 45(3):303–309. doi:10.1007/s10735-013-9548-x
40. Li J, Feng W, Liu B, Sun B, Han X, Du J, Sun J, Yimin Cui J, Guo J, Kudo A, Amizuka N, Li M (2015) Altered distribution of HMGB1 in the periodontal ligament of Periostin-deficient mice subjected to Waldo's orthodontic tooth movement. J Mol Histol 46(3):303–311. doi:10.1007/s10735-015-9619-2
41. Rangiani A, Jing Y, Ren Y, Yadav S, Taylor R, Feng JQ (2016) Critical roles of Periostin in the process of orthodontic tooth movement. Eur J Orthod 38(4):373–378. doi:10.1093/ejo/cjv071
42. Savage A, Eaton KA, Moles DR, Needleman I (2009) A systematic review of definitions of periodontitis and methods that have been used to identify this disease. J Clin Periodontol 36(6):458–467. doi:10.1111/j.1600-051X.2009.01408.x
43. Park CH, Rios HF, Jin Q, Sugai JV, Padial-Molina M, Taut AD, Flanagan CL, Hollister SJ, Giannobile WV (2012) Tissue engineering bone-ligament complexes using fiber-guiding scaffolds. Biomaterials 33(1):137–145. doi:10.1016/j.biomaterials.2011.09.057
44. Berahim Z, Moharamzadeh K, Jowett AK, Rawlinson A (2015) Evaluation of osteogenic and cementogenic potential of periodontal ligament fibroblast spheroids using a three-dimensional in vitro model of periodontium. Int J Dent 2015:605813. doi:10.1155/2015/605813
45. Panduwawala CP, Zhan X, Dissanayaka WL, Samaranayake LP, Jin L, Zhang C (2017) In vivo periodontal tissue regeneration by periodontal ligament stem cells and endothelial cells in three-dimensional cell sheet constructs. J Periodontal Res 52(3):408–418. doi:10.1111/jre.12405

46. Padial-Molina M, Volk SL, Rios HF (2015) Preliminary insight into the Periostin leverage during periodontal tissue healing. J Clin Periodontol. doi:10.1111/jcpe.12432
47. Larsson L, Decker AM, Nibali L, Pilipchuk SP, Berglundh T, Giannobile WV (2016) Regenerative medicine for periodontal and peri-implant diseases. J Dent Res 95(3):255–266. doi:10.1177/0022034515618887
48. Suarez-Lopez Del Amo F, Monje A, Padial-Molina M, Tang Z, Wang HL (2015) Biologic agents for periodontal regeneration and implant site development. Biomed Res Int 2015:957518. doi:10.1155/2015/957518
49. Bornstein P, Sage EH (2002) Matricellular proteins: extracellular modulators of cell function. Curr Opin Cell Biol 14(5):608–616
50. Padial-Molina M, Volk SL, Rios HF (2014) Periostin increases migration and proliferation of human periodontal ligament fibroblasts challenged by tumor necrosis factor -alpha and Porphyromonas gingivalis lipopolysaccharides. J Periodontal Res 49(3):405–414. doi:10.1111/jre.12120
51. Matsuzawa M, Arai C, Nomura Y, Murata T, Yamakoshi Y, Oida S, Hanada N, Nakamura Y (2015) Periostin of human periodontal ligament fibroblasts promotes migration of human mesenchymal stem cell through the alphavbeta3 integrin/FAK/PI3 K/Akt pathway. J Periodontal Res 50(6):855–863. doi:10.1111/jre.12277
52. Watanabe T, Yasue A, Fujihara S, Tanaka E (2012) PERIOSTIN regulates MMP-2 expression via the alphavbeta3 integrin/ERK pathway in human periodontal ligament cells. Arch Oral Biol 57(1):52–59. doi:10.1016/j.archoralbio.2011.07.010
53. Nakazawa T, Nakajima A, Seki N, Okawa A, Kato M, Moriya H, Amizuka N, Einhorn TA, Yamazaki M (2004) Gene expression of Periostin in the early stage of fracture healing detected by cDNA microarray analysis. J Orthop Res Off Publ Orthop Res Soc 22(3):520–525. doi:10.1016/j.orthres.2003.10.007
54. Zhu S, Barbe MF, Liu C, Hadjiargyrou M, Popoff SN, Rani S, Safadi FF, Litvin J (2009) Periostin-like-factor in osteogenesis. J Cell Physiol 218(3):584–592. doi:10.1002/jcp.21633
55. Rani S, Barbe MF, Barr AE, Litivn J (2010) Role of TNF alpha and PLF in bone remodeling in a rat model of repetitive reaching and grasping. J Cell Physiol 225(1):152–167. doi:10.1002/jcp.22208
56. Heo SC, Shin WC, Lee MJ, Kim BR, Jang IH, Choi EJ, Lee JS, Kim JH (2015) Periostin accelerates bone healing mediated by human mesenchymal stem cell-embedded hydroxyapatite/tricalcium phosphate scaffold. PLoS ONE 10(3):e0116698. doi:10.1371/journal.pone.0116698
57. Ma D, Zhang R, Sun Y, Rios HF, Haruyama N, Han X, Kulkarni AB, Qin C, Feng JQ (2011) A novel role of Periostin in postnatal tooth formation and mineralization. J Biol Chem 286(6):4302–4309. doi:10.1074/jbc.M110.140202