*Asian Journal of Dental Sciences*

*2(1): 34-39, 2019; Article no.AJDS.52102*

# Periostin: A Potential Biomarker for Periodontitis

**Zeinab Rezaei Esfahrood[1] and Setareh Kazemi Veysari[2*]**

*[1]Department of Periodontics, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
*[2]Dental Research Center, Dentistry Research Institute, Tehran University of Medical Sciences, Tehran, Iran.*

***Authors' contributions***

*This work was carried out in collaboration between both authors. Author SKV wrote the protocol and wrote the first draft of the manuscript. Author ZRE designed the study and managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.*

***Article Information***

Editor(s):
(1) Dr. José Francisco Gómez Clavel, Professor, Facultad de Estudios Superiores Iztacala, UNAM, Universidad Nacional Autónoma de México, México.
Reviewers:
(1) Josué Martos, Federal University of Pelotas, Brazil.
(2) Abdul Samad Aziz, Maharashtra University of Health Sciences, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/52102

***Review Article***

***Received 09 August 2019***
***Accepted 15 October 2019***
***Published 28 October 2019***

## ABSTRACT

**Background:** Periostin is among the most important extracellular matrix proteins, that seems to play a role in the healing of periodontal defects as a modulator of periodontal ligament (PDL) hemostasis. This study aims to review the available literature on this protein and its role in the healing of periodontal defects.
**Methods:** An electronic search of the literature was carried out in PubMed and Google Scholar using the keywords "periostin", "gingival crevicular fluid", "saliva" and "periodontitis".
**Results:** Periostin, as an extracellular matrix protein, was found to play a key role as a modulator of critical cellular interactions in disease conditions. It is necessary for tissue integrity and plays a critical role in wound healing.
**Conclusion:** The role of periostin in cell proliferation, differentiation, migration and signalling to maintain hemostasis has yet to be identified. Further studies are warranted in this respect.

*Keywords: Periostin; gingival crevicular fluid; saliva; periodontitis.*

**Corresponding author: Email: S.kazemiveysari@gmail.com;*

## 1. INTRODUCTION

Regeneration and healing of the injured tissues in periodontitis and periodontal defects occur via intracellular and extracellular matrix interactions, and complex molecules present in the matrix play a role in this respect. Therefore, the integrity of the extracellular matrix is a prerequisite to maintain the normal structure and function of tissues. The extracellular matrix locally releases molecules and proteins that work together as a complex network to physically protect the cells, tissues and organs. In the past, researchers used to believe that the extracellular matrix only serves as a scaffold. But today, it is known as a fact that several cells and molecules are involved in cellular aspects such as cell morphology and differentiation by sending specific signals. The PDL around teeth is an ideal system to dynamically entrap the proteins and complex molecules of the extracellular matrix during wound healing [1].

Periostin is among the most important proteins that play a key role in the healing of wounds and periodontal defects. It serves as a modulator of hemostasis in the PDL. In other words, periostin is a type of cellular matrix protein secreted by fibroblasts into the PDL and is necessary for health and maturation of tissues [2,3]. It is also required for tissue integrity and plays an important role in tooth support and skeletal maturity [4]. In addition to the PDL, periostin is also expressed in the periosteum and plays a critical role in collagen fibrillogenesis pathway [5]. In chronic periodontal disease, the proliferation and differentiation of the PDL cells significantly decrease, the tissue integrity is impaired and tissue regeneration and healing are seriously compromised. Under such circumstances, periostin serves as a marker for reconstructive cellular matrix interactions and cell behaviour in matrix biomechanics. It preserves hemostasis and protects the integrity of the connective tissue [2]. This study aims to review the available literature on periostin and its role in the regeneration and repair of the PDL.

## 2. MATERIALS AND METHODS

An electronic search of the literature was carried out in PubMed and Google Scholar using the keywords “periostin”, “gingival crevicular fluid”, “saliva” and “periodontitis” for relevant studies published in English from 1990 and 2018 was performed.

## 3. RESULTS

### 3.1 History of Periostin

Periostin is a 90 kD protein that was first identified in mice. It has 811 amino acids with EMI domain at one end of the chain followed by 4 FAS-1 domains and a carboxyl-terminal domain. There is a C-terminal sequence at the other end of the chain. It was first named the osteoblast-specific factor-2 but was later renamed as periostin due to its presence in the periosteum and the PDL [6-13].

It is a fetal protein present in the cervical loop and dental follicle of incisor and molar teeth in cap stage and bell stage, which disappears before tooth eruption. The active role of periostin in tissue regeneration and its potential role in the proliferation of fetal cells related to tooth structure further highlight its significance in morphogenesis and development of bone and periodontal tissue [14-18].

Periostin has two main functions namely intracellular fibrillogenesis and extracellular migration. It also has a close relationship with type I collagen, fibronectin and Notch-1, and bonds to collagen by proteolytic activation of lysine oxidase [19-21]. Periostin is present in collagen-rich tissues such as the heart, tendons and skin, which are affected by mechanical loads as well as the PDL around teeth, which is constantly subjected to occlusal forces. It plays a supporting role in cell adhesion, proliferation, survival and fibrillogenesis in all four components of the periodontium namely the PDL, bone, cementum and gingiva. The periostin expression is up-regulated by increased mechanical stresses and leads to tissue regeneration [21,22].

Thus, evidence shows that periostin is a multi-functional protein present in different tissues in different forms. However, comprehensive information about this protein is still lacking.

### 3.2 Periostin in the Gingival Crevicular Fluid (GCF), Saliva and Serum

Kumaresan et al., in 2016 evaluated the level of periostin in GCF of healthy individuals and chronic periodontitis patients who underwent non-surgical periodontal therapy. They showed that the level of periostin in the GCF of these patients can serve as a possible biomarker for assessment of treatment outcome [5]. Padial-

Molina et al., in 2015 evaluated the changes in the level of periostin in tissues, GCF and serum following periodontal surgery. Histological results showed a lower level of periostin in periodontal patients. The level of periostin in both groups increased over time; this increase was significant in patients with periodontitis. A slight transient change was noted in serum level of periostin. The periostin mRNA had an inverse correlation with the level of periostin, which indicates post-transcription regulation in chronic inflammation. They discussed that the local transient increase in GCF level of periostin after eliminating the local etiologic factors in affected areas indicates its significant role in maturation and stability of the connective tissue [1]. Aral et al. assessed the level of periostin in the GCF and saliva of patients with chronic and aggressive periodontitis and found a negative correlation between the level of periostin and clinical periodontal parameters ($P<0.01$). Also, their results revealed that periostin in the GCF can play a protective role against periodontal disease but its level decreases in disease conditions. Furthermore, salivary level of periostin can yield promising results in the detection of aggressive periodontitis [23]. In our previous study, the level of periostin in the saliva of patients with chronic periodontitis was significantly lower than that in healthy controls [24]. Bulli et al. showed that the GCF level of periostin significantly decreases by the progression of periodontal disease while no significant change occurs in the serum level of periostin. They discussed that the GCF level of periostin may serve as a reliable marker for assessment of the severity of the periodontal disease [4].

### 3.3 Periostin in the Gingival Tissue

An in vitro study showed that interleukins 4 and 13 significantly induced the production of periostin by gingival fibroblasts and PDL cells while they did not affect gingival epithelial cells. The tumour necrosis factor-alpha and lipopolysaccharides of Porphyromonas gingivalis did not affect the production of periostin. The effect of periostin on inflammatory cytokines released by gingival fibroblasts was weak and it did not affect PDL or epithelial cells. Periostin had no significant effect on the expression of genes related to protein matrix. Evidence shows that gingival fibroblasts are the source of periostin in periodontal defects. However, periostin has a limited role in inflammatory response or matrix protein metabolism [25]. Padial-Molina et al. demonstrated that long-term exposure of human PDL fibroblasts to pro-inflammatory cytokines (tumour necrosis factor-alpha) and bacterial virulence factors (Porphyromonas gingivalis lipopolysaccharide) significantly decreased the level of periostin in the culture medium.[2] Padial-Molina et al. evaluated PDL samples of rats and noticed that the level of periostin decreased in response to inflammation. Thus, the level of periostin in PDL tissue significantly decreases as the result of chronic inflammatory responses and is associated with adverse changes in the periodontium over time [3].

## 4. DISCUSSION

Recent advances in the pathogenesis of periodontal disease and its diagnosis have mainly focused on the role of genes, proteins and metabolic products in the periodontal system and are attempting to find factors responsible for initiation and progression of periodontal disease. In this respect, periostin as a cellular matrix protein plays an important role as a modulator of critical cellular interactions in disease conditions. Periostin is a key biological factor that maintains the integrity of the periodontal tissue and can be used as a new marker with high diagnostic potential and sensitivity for the detection of periodontal disease. Periostin can provide information about biochemical reactions that occur in healthy tissue and changes that lead to a disease condition [3].

Knowledge about periostin can reveal its association with the dynamic course of healing. Further understanding of the role of this protein in the cellular matrix and periodontal hemostasis can reveal new metabolic pathways to expand treatment protocols in this respect. It can also help predict the outcome of regenerative treatments [25]. For instance, considering the important role of periostin in the course of healing from the granulation phase to increased angiogenesis and cell proliferation, it may serve as a specific biomarker for the healing of periodontal defects and maturation and stabilization of wounds [1].

The role of periostin as a modulator of periodontal tissue during inflammatory responses has been previously confirmed. It has been demonstrated that periostin regulates tissue integrity and plays a role in tooth development and eruption by proliferation and differentiation of osteoblasts. Also, interleukins 3 and 4 affect the PDL cells and fibroblasts and slightly increase

the level of periostin in tissues with the help of HGF and HPDL [11,26-31]. This finding can also be used as a new therapeutic approach for the treatment of periodontal defects.

Considering the highly significant protective role of periostin in tissues, it can be used as a reliable inflammatory biomarker for the detection of diseases. It can also be used as a diagnostic biomarker for postoperative evaluation of the efficacy of interventions [5].

Since GCF and saliva are rich in molecules, proteins, enzymes and pro-inflammatory cytokines, assessment of their components such as periostin can reveal information about the health of periodontal tissue. Thus, periostin can be used as an effective diagnostic marker for assessment of the health of periodontal tissue or severity and progression of periodontal disease [32,33]. Moreover, the level of periostin decreases in the GCF following periodontal disease; thus, it can be used as a reliable biomarker to determine the severity of the periodontal disease [4].

## 5. CONCLUSION

In vitro and animal studies have evaluated the diagnostic value of periostin as a new biomarker; however, its role in cell proliferation, differentiation, migration and signalling to maintain hemostasis has yet to be identified. Further studies on the mechanism of signalling, periostin concentration and its correlation with other constituents of the GCF and saliva are warranted to further elucidate the role of this protein in the process of wound healing.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES


1. Padial-Molina M, Volk SL, Rios HF. Preliminary insight into the periostin leverage during periodontal tissue healing. J Clin Periodontol. 2015;42(8):764-72.
2. Padial-Molina M, Volk SL, Rios HF. Periostin increases migration and proliferation of human periodontal ligament fibroblasts challenged by tumour necrosis factor-α and Porphyromonas gingivalis lipopolysaccharides. J Periodontal Res. 2014;49(3):405-14.
3. Padial-Molina M, Volk SL, Taut AD, Giannobile WV, Rios HF. Periostin is down- regulated during periodontal inflammation. J Dent Res. 2012;91(11): 1078-84.
4. Balli U, Keles ZP, Avci B, Guler S, Cetinkaya BO, Keles GC. Assessment of periostin levels in serum and gingival crevicular fluid of patients with periodontal disease. J Periodontal Res. 2015;50(6): 707-13.
5. Kumaresan D, Balasundaram A, Naik VK, Appukuttan DP. Gingival crevicular fluid periostin levels in chronic periodontitis patients following nonsurgical periodontal treatment with low-level laser therapy. Eur J Cancer. 2016;10(4):546.
6. Ben QW, Zhao Z, Ge SF, Zhou J, Yuan F, Yuan YZ. Circulating levels of periostin may help identify patients with more aggressive colorectal cancer. Int J Oncol 2009;34(3):821-8.
7. Fujimoto K, Kawaguchi T, Nakashima O, Ono J, Ohta S, Kawaguchi A, et al. Periostin, a matrix protein, has potential as a novel serodiagnostic marker for cholangiocarcinoma. Oncology Reports. 2011;25(5):1211-6.
8. Nuzzo PV, Buzzatti G, Ricci F, Rubagotti A, Argellati F, Zinoli L, *et al*. Periostin: a novel prognostic and therapeutic target for genitourinary cancer?. Clin Genitourin Cancer. 2014;12(5):301-11.
9. Okamoto M, Hoshino T, Kitasato Y, Sakazaki Y, Kawayama T, Fujimoto K, *et al*. Periostin, a matrix protein, is a novel biomarker for idiopathic interstitial pneumonias. Eur Respir J. 2011;37(5): 1119-27.
10. Takeshita S, Kikuno R, Tezuka KI, Amann E. Osteoblast-specific factor 2: cloning of a putative bone adhesion protein with homology with the insect protein fasciclin I. Biochemical Journal. 1993; 294(1):271-8.
11. Horiuchi K, Amizuka N, Takeshita S, Takamatsu H, Katsuura M, Ozawa H, et al. Identification and characterization of a novel protein, periostin, with restricted expression to periosteum and periodontal

ligament and increased expression by transforming growth factor β. J Bone Miner Res. 1999;14(7):1239-49.
12. Kim JE, Kim SJ, Lee BH, Park RW, Kim KS, Kim IS. Identification of motifs for cell adhesion within the repeated domains of transforming growth factor-β-induced gene, βig-h3**.** J Biol Chem. 2000;275(40):30907-15.
13. Kudo A. Introductory review: Periostin—gene and protein structure. Cell Mol Life Sci. 2017;74(23):4259-68.
14. Kruzynska-Frejtag A, Wang J, Maeda M, Rogers R, Krug E, Hoffman S, *et al*. Periostin is expressed within the developing teeth at the sites of epithelial–mesenchymal interaction. Developmental dynamics: An official publication of the American Association of Anatomists. 2004; 229(4):857-68.
15. Suzuki H, Amizuka N, Kii I, Kawano Y, Nozawa-Inoue K, Suzuki A, et al. Immunohistochemical localization of periostin in tooth and its surrounding tissues in mouse mandibles during development. Anat Rec (Hoboken). 2004; 281(2):1264-75.
16. Ito T, Suzuki A, Imai E, Horimoto N, Ohnishi T, Daikuhara Y, et al. Tornado extraction: A method to enrich and purify RNA from the nephrogenic zone of the neonatal rat kidney. Kidney International. 2002;62(3):763-9.
17. Kruzynska-Frejtag A, Machnicki M, Rogers R, Markwald RR, Conway SJ. Periostin (an osteoblast-specific factor) is expressed within the embryonic mouse heart during valve formation. Mech Dev. 2001; 103(1-2):183-8.
18. Romanos GE, Asnani KP, Hingorani D, Deshmukh VL. Periostin: Role in formation and maintenance of dental tissues**.** J Cell Physiol. 2014;229(1):1-5.
19. Kudo A. Periostin in fibrillogenesis for tissue regeneration: periostin actions inside and outside the cell. Cell Mol Life Sci. 2011;68(19):3201
20. Tanabe H, Takayama I, Nishiyama T, Shimazaki M, Kii I, Li M, et al. Periostin associates with Notch1 precursor to maintain Notch1 expression under a stress condition in mouse cells. PloS One. 2010;5(8):e12234
21. Du J, Li M. Functions of Periostin in dental tissues and its role in periodontal tissues' regeneration. Cell Mol Life Sci. 2017; 74(23):4279-86.
22. Padial-Molina, Marchesan JT, Taut AD, Jin Q, Giannobile WV, Rios HF et al. Methods to validate tooth-supporting regenerative therapies. *Odontogenesis*. Humana Press. 2012;135-148.
23. Aral CA, Köseoğlu S, Sağlam M, Pekbağrıyanık T, Savran L.Gingival crevicular fluid and salivary periostin levels in non-smoker. Subjects with Chronic and Aggressive Periodontitis. Inflammation 2016;39(3): 986-93.
24. Esfahrood ZR, Vardian ST, Yadegari Z, Adhim M, Saravi NS. Periostin levels in saliva of patients with chronic periodontitis. J Indian Soc Periodontol. 2018;22(1): 25.
25. Nakajima M, Honda T, Miyauchi S, Yamazaki K. Th2 cytokines efficiently stimulate periostin production in gingival fibroblasts but periostin does not induce an inflammatory response in gingival epithelial cells. Arch Oral Biol. 2014;59(2): 93-101.
26. Rios H, Koushik SV, Wang H, Wang J, Zhou HM, Lindsley A, et al. Periostin null mice exhibit dwarfism, incisor enamel defects, and an early-onset periodontal disease-like phenotype. Molecular and Cellular Biology. 2005;25(24):11131-44.
27. Takayama G, Arima K, Kanaji T, Toda S, Tanaka H, Shoji S, et al. Periostin: A novel component of subepithelial fibrosis of bronchial asthma downstream of IL-4 and IL-13 signals. J Allergy Clin Immunol. 2006;118(1):98-104.
28. Masuoka M, Shiraishi H, Ohta S, Suzuki S, Arima K, Aoki S, *et al*. Periostin promotes chronic allergic inflammation in response to Th2 cytokines. J Clin Invest. 2012; 122(7):2590-600.
29. Kruzynska-Frejtag A, Wang J, Maeda M, Rogers R, Krug E, Hoffman S, *et al*. Periostin is expressed within the developing teeth at the sites of epithelial–mesenchymal interaction. Dev Dyn. 2004; 229(4):857-68.
30. Ríos HF, Ma D, Xie Y, Giannobile WV, Bonewald LF, Conway SJ, *et al*. Periostin is essential for the integrity and function of the periodontal ligament during occlusal loading in mice. J Periodontol. 2008;79(8): 1480-90.
31. Afanador E, Yokozeki M, Oba Y, Kitase Y, Takahashi T, Kudo A, et al. Messenger RNA expression of periostin and Twist transiently decrease by occlusal hypofunction in mouse periodontal

ligament. Arch Oral Biol. 2005;50(12): 1023-31.

32. Adonogianaki E, Mooney J, Kinane DF. The ability of gingival crevicular fluid acute phase proteins to distinguish healthy, gingivitis and periodontitis sites. J Clin Periodontol. 1992;19(2):98-102.

33. Salazar MG, Jehmlich N, Murr A, Dhople VM, Holtfreter B, Hammer E, et al. Identification of periodontitis associated changes in the proteome of whole human saliva by mass spectrometric analysis. J Clin Periodontol. 2013;40(9): 825-32.



*Peer-review history:*
*The peer review history for this paper can be accessed here:*
*http://www.sdiarticle4.com/review-history/52102*