Growth Factors in Periodontal Complex Regeneration

Fazele ATARBASHI-MOGHADAM[1], Maryam REZAI RAD[2], Sorane SIJANIVANDI[2], Pouya KHODAYARI[2], Masoumeh MAHMOUM[2]

The ultimate goal of periodontal treatments is the regeneration of all lost periodontal tissues including bone, cementum and the periodontal ligament (PDL). Until now, the clinical methods for periodontal regeneration have been associated with significant failure or incomplete success. Various studies have reported the promising effects of growth factors/cytokines on periodontal regeneration. Growth factors/cytokines include proteins or steroid hormones that bind to cellular receptors, known as signalling molecules, and that trigger cellular responses that eventually stimulate cell proliferation and differentiation. The present review aims to provide an overview of the main growth factors that play an important role in and have been used in the regeneration of periodontal components.

Key words: growth factors, cementogenesis, osteogenesis, periodontal regeneration, stem cells
Chin J Dent Res 2022;25(2):85–92; doi: 10.3290/j.cjdr.b3086335

The supporting structure of the teeth, i.e, the periodontium, is composed of alveolar bone, root cementum, the periodontal ligament (PDL) and the gingiva which cover other components[1]. After completion of tooth crown development, root formation begins and dental follicle stem cells (DFSCs) differentiate to fibroblasts, cementoblasts and osteoblasts to form the PDL, cementum and alveolar bone, respectively[2]. These structures function as a unit[1] in which the principal PDL fibre connects the cementum to the alveolar bone and provides an apparatus to control all forces and support the dentition[1,3]. Destructive chronic inflammation of these supporting tooth structures, known as periodontitis, eventually results in tooth loss[4]. The ultimate goal of periodontal treatments is the regeneration of all lost periodontal tissue[4]. Until now, the clinical methods for periodontal regeneration have been associated with significant failure or incomplete success, and most have been technique sensitive[5].

Growth factors/cytokines include proteins or steroid hormones that bind to cellular receptors, known as signalling molecules, and result in cellular responses that eventually stimulate proliferation and differentiation[6,7]. Various studies have reported the promising effects of these signalling molecules on periodontal regeneration[3,6]. The present review aimed to provide an overview of the main growth factors that play an important role in and have been used in the regeneration of periodontal components.

Table 1 summarises the included studies and Fig 1 illustrates the main growth factors that play an important role in the regeneration of each periodontal component.

1 Department of Periodontics, Dental School of Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2 Dental Research Centre, Research Institute of Dental Sciences, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Corresponding author: Dr Maryam REZAI RAD, Dental Research Centre, Research Institute of Dental Sciences, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel: 98-22413897; Fax: 98-22427753; Email: m.rezai.rad@gmail.com

Table 1 Growth factors used in periodontal complex regeneration.

Location	Growth factor	Effect
Bone	BMPs	BMP-7 induces PDLSCs and DFSCs towards the osteoblast/cementoblast in a dose- and time-dependent manner[14].
		BMP-7 increases the expression of osteoblastic genes in human gingiva-derived MSCs[16].
		BMP-9 promotes osteogenesis in DFSCs[17].
		BMP-2, 6 and 7 increase biomineralisation of hPDLSCs[18].
		The most pronounced induction of biomineralisation of hPDLSCs occurs in BMP-6[18].
	PTH	Regulates the differentiation of DFSCs into osteoblasts[19,21].
	IGF	Increases the volume of newly formed bone following tooth extraction[26]. Promotes osteogenic differentiation and osteogenesis but decreases the odontogenic differentiation and dentinogenesis capacity[62].
	Vit D	Stimulates osteoblastic differentiation with the subsequent increase of bone mineral matrix deposition[27,30].
Cementum	EMD	Affects both proliferation and differentiation of PDLSCs[32-34]. Induces DFSCs towards the cementoblast phenotype[38]. Induces the formation of cementum-like structures on teeth affected by periodontal disease[40].
	PTH	Is essential for cementoblast differentiation[54,55]. Improves the stability of tooth movement by promoting periodontal regeneration[56].
	CP-23	Differentiates both DFSCs and PDLSCs to the cementoblast lineage[52,53].
	BMP	BMP-7 mediates cementogenesis of PDLSCs and DFSCs in a dose- and time-dependent manner[14,49]. BMP-3 inhibits BMP-2 mediated osteoblastic differentiation and enables maintenance of the PDL and root cementum[44,47].
PDL	FGF2	Decreases the expression of osteo/cementogenic markers in hPDLCs[59,70]. Increases the expression of teno/ligamentogenic markers in PDLSCs[59]. Induces PDLSCs towards fibroblastic differentiation and inhibits mineralisation[60]. Stimulates and maintains the fibroblastic feature in hPDLSCs[59].
	TGF-β	TGF-β1 suppresses the proliferation of PDL cells and contributes to fibroblastic differentiation[71], and increases tenomodulin but decreases scleraxis[59]. TGF-β3 enhances periodontal tissue regeneration significantly[67].
	PDGF	PDGF-BB enhances mitogenesis and matrix biosynthesis in PDLSCs[74,77], and enhances alveolar bone formation and cementogenesis in large periodontal bone defects[75].

BMP, bone morphogenic protein; CP-23, human cementum protein 1 (also CEMP-1); DFSCs, dental follicle stem cells; EMD, enamel matrix derivative; FGF2, fibroblast growth factor 2; hPDLSCs, human PDL stem cells; IGF, insulin-like growth factor; MSCs, mesenchymal stem cells; PDGF, platelet-derived growth factor; PDLScs, PDL stem cells; PTH, parathyroid hormone; TGF-β, transforming growth factor β; Vit D, vitamin D.

Growth factors used in alveolar bone regeneration

Bone morphogenetic proteins (BMPs)

Bone morphogenetic proteins (BMPs) are multifunctional growth factors that are so-called due to their osteoinductive properties and are part of the transforming growth factor-beta (TGF-β) superfamily which enhances mineralisation in several tissues[8]. The effect of BMPs in bone formation occurs through their involvement in the differentiation of mesenchymal stem cells (MSCs) and osteoprogenitors to osteoblasts[9]. BMPs can also recruit endogenous MSCs and osteoblasts to defect sites[10]. Over 20 types of BMPs have been shown to differentiate MSCs into osteoblasts; however, the most potent factors among them include BMP-2, 4, 6, 7, 9 and 13[9,11]. In a study by Cheng et al[12] on different types of BMPs on the osteogenic activity of MSCs and osteoblastic cells, it was shown that BMP-2, 6 and 9 may play an important role in inducing osteoblast differentiation of MSCs. BMPs have been found to regulate the differentiation of MSCs mainly through Smad proteins[13]. Moreover, BMPs can function in the form of heterodimers, including BMP-4/7, 2/7 and 2/6/99.

Açil et al[14] found that BMP-7 induces osteoblast/cementoblast differentiation of PDL stem cells (PDLSCs) and DFSCs in a dose- and time-dependent manner. In a similar study, they indicated that compared to DFSCs, PDLSCs exhibited a slightly higher response to BMP-7[15]. Lee et al[16] evaluated the effects of short-term application BMP-7 on human gingiva–derived MSCs and recorded increased expression of target genes for osteoblastic differentiation. Li et al[17] showed that DFSCs transfected with BMP-9 could significantly promote osteogenesis. Hakki et al[18] demonstrated the regulatory effect of BMPs on the proliferation, mineralisation and expression of bone/mineralised tissue-

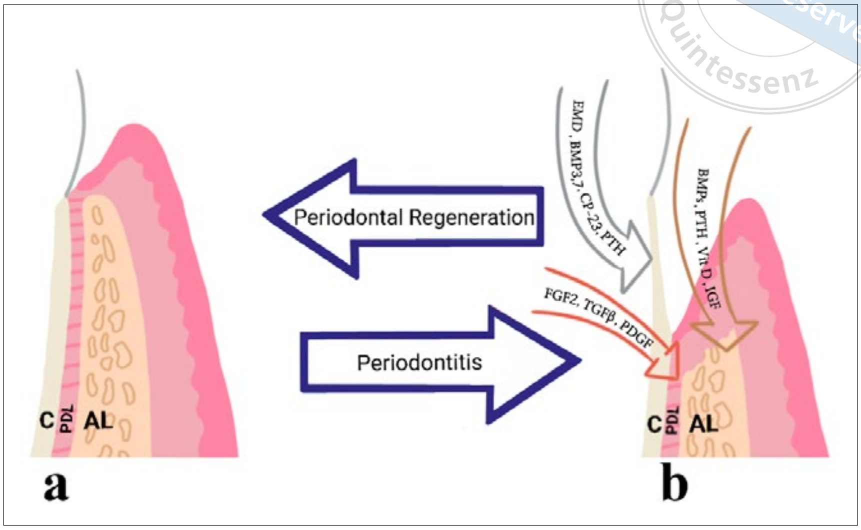

Fig 1 The main growth factors that play an important role in the regeneration of each periodontal component. **(a)** Healthy periodontium; **(b)** destroyed periodontium due to periodontitis. The red arrow shows growth factors related to PDL regeneration, the grey arrow indicates growth factors related to regeneration of cementum, and the brown arrow shows growth factors related to alveolar bone regeneration. AL, alveolar bone; BMPs, bone morphogenic proteins; C, cementum; CP-23, human cementum protein 1 (also CEMP-1); EMD, enamel matrix derivative; FGF2, fibroblast growth factor 2; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; PTH, parathyroid hormone; TGF-β, transforming growth factor β; Vit D, vitamin D.

associated genes in human PDLSCs in a time and dose-dependent manner. They suggested that BMP-2, 6 and 7 are potent regulators for gene expression and biomineralisation of human PDLSCs; however, the effect of BMP-6 on mediating the mineralisation of human PDLSCs was superior to BMP-2 and 7[18].

Parathyroid hormone (PTH)

Both parathyroid hormone (PTH) and PTH receptor (PTHrp) are important signals that regulate osteoblastic differentiation[8]. PTHrp is required for several different regulations of enchondral bone development, differentiation of bone precursor cells and development of craniofacial tissues.

The dental follicle, which is involved in tooth eruption and alveolar bone regeneration, has been found to express a large amount of PTH[19]. Klingelhöffer et al[19] showed that PTH participates in the early phase of osteogenic differentiation in DFSCs. The PTH-PTHrp autocrine signal maintains the physiological cell fates of DFSCs to establish the functional periodontal attachment apparatus and orchestrates tooth eruption[20]. Moreover, Pieles et al[21] reported that PTH supports the expression of BMP-2, which is strongly involved in the osteogenic differentiation of DFSCs.

Insulin-like growth factor (IGF)

Insulin-like growth factor (IGF) is signalling through type 1 receptor that stimulates cell proliferation, function and survival of osteoblasts[22]. IGF-1 can regulate osteogenic differentiation in an endocrine, paracrine or autocrine manner which is regulated by a family of six IGF binding proteins (IGFBPs). IGFBP-3 and 5 have been shown to stimulate the actions of IGF-1, whereas IGFBP-1, 2, 4 and 6 are known inhibitors of IGF 1 in bone[23].

In a study by Wang et al[24], stem cells from the apical papilla (SCAPs) treated with IGF-1 showed an increase in osteogenic differentiation; however, the odontogenic differentiation and dentinogenesis capacity of SCAPs was reduced significantly. A similar study by Feng et al[25] showed that IGF-1 triggers early-stage osteogenic differentiation and maintains the later-stage osteogenic differentiation of dental pulp stem cells (DPSCs). IGF-1 was also administrated following tooth extraction in a diabetic rat model, and the results showed that IGF-1 not only increased new bone formation but also normalised the expression of glucose transporter 1 in diabetic rats[26].

Vitamin D (Vit D)

Vitamin D (Vit D) is crucial for bone mineralisation as well as maintenance of calcium homeostasis. It has also been shown to play an important role in the proliferation and differentiation of MSCs to osteoblasts[27,28]. Vit D is an important regulator of Runt-related transcription factor 2 (RUNX2), with which it cooperates in inducing the expression of osteocalcin, which is also a key protein that regulates osteoblastic differentiation[29]. Posa et al[30] showed that Vit D treatment increases osteogenic differentiation of tooth bud stem cells (DBSCs).

Growth factors used in cementum regeneration

Enamel matrix derivative (EMD)

Enamel matrix derivative (EMD) is an enamel matrix extract that mainly contains amelogenins, which have been shown to be involved not only in formation of enamel but also in that of the periodontal attachment[31]. Several studies have illustrated the effect of EMD on the proliferation and differentiation of PDLSCs[32-34]. Davenport et al[32] showed that in the presence of EMD, human PDL fibroblasts differentiate to cells more similar to cementoblasts than fibroblasts. The amelogenins can form an insoluble extracellular matrix that has a high affinity for collagens and hydroxyapatite[35,36], and histological evaluation has shown that it can form acellular cementum which is essential for PDL fibre attachment[37]. Kenmour et al[38] found that EMD induced human DFSCs towards the cementoblastic phenotype through BMP-dependent pathways. Moreover, two in vivo studies confirmed that new cementum was formed following administration of EMD[39,40]. Bosshardt et al[40] showed that EMD can induce the formation of cementum-like structures on teeth affected by periodontal disease.

BMPs

BMPs are best known for their potential in osteoblastic differentiation[41,42]; however, several studies have indicated the effect of BMP-7 and BMP-3 on cementoblastic differentiation[41,43-48]. Bozic et al[43] showed the BMP-7 mechanism induces differentiation and mineralisation of cementoblasts, and does so via inducing procollagen COOH-terminal proteinase enhancer 1 (PCPE1) and BMP-1. Torii et al[49] showed that BMP-7 mediates cementogenesis of PDLSCs via activation of protein tyrosine phosphatase-like, member A/cementum attachment protein (PTPLA/CAP) and cementum-derived protein (CEMP1). Similarly, it has been shown that BMP-7 can induce cementoblast differentiation of PDLSCs and DFSCs in a dose- and time-dependent manner[14]. In the analysis of tooth development by Aberg et al[50], it was reported that BMP-3 is involved in cementum development. Another study showed that BMP-3 inhibits BMP-2–mediated osteoblastic differentiation[44]. The negative regulation of BMP-3 in mineralisation enables the maintenance of the PDL between bone and root cementum[47].

Cementum-derived protein (CEMP1)

CEMP1, also known as CP23, is well-known as a key marker for cementoblast differentiation; however, it has been shown to be expressed not only in cementoblasts, but also in PDLSCs[51]. An immunohistological evaluation by Alvarez-Pérez et al[52] showed the distribution of CEMP1 throughout the entire root surface, including acellular and cellular cementum, cementocytes and cells located near the blood vessels in the PDL. Further studies showed that the application of CEMP1 on both DFSCs and PDLSCs differentiate them to the cementoblast lineage, indicating that CEMP1 is a key protein in cementoblast differentiation[52,53].

PTH

PTH, which is involved in mediating several important biological actions, such as endochondral bone development, promotes cementogenesis in a protein kinase A (PKA) and extracellular signal-regulated mitogen-activated protein kinase 1/2 (ERK1/2)-dependent manner[50,54]. It has been speculated that PTH could promote cementoblastic differentiation and cementogenesis[50]. Most of the cells expressing PTH are in the dental follicle and on the root surface. The deletion of this peptide receptor (PPR) in these progenitors leads to failure of eruption and significantly truncated roots lacking PDLs. PPR is likely to orchestrate cementoblast differentiation of the progenitors, as the PPR-deficient cells fail to form the acellular cementum, and rather form irregular cellular cementum on the root surface. This phenotype can be interpreted as accelerated and disordered differentiation[55]. Li et al[56] showed that intermittent PTH administration could promote cementogenesis and regeneration of the tooth root caused by resorption.

Growth factors used in PDL regeneration

Fibroblast growth factor 2 (FGF2)

Fibroblast growth factor 2 (FGF2), also known as the basic FGF, is a heparin-biding cytokine that plays a role in the inflammatory phase as an anti-inflammatory cytokine, and the proliferative phase of wound healing[57]. Its angiogenic and fibrous tissue forming activity, along with its ability to stimulate proliferation and differentiation of MSCs, make it suitable to be used in wound healing and periodontal regeneration[57,58].

Hyun et al[59] showed have shown that FGF2 acts as a signalling molecule and increases the expression of scleraxis and tenomodulin, early and late teno/ligamentogenic markers, respectively, in human PDLCs[5] and that FGF2 decreases the expression of osteo/cementogenic markers on hPDLCs and has an antagonist effect on BMPs. A similar observation was made by

Murakami et al[60], who found that FGF2 decreased collagen 1 (COL1) expression and calcification. It therefore appears that FGF2 guides human PDLSCs towards fibroblastic differentiation and inhibits mineralisation; however, administration of FGF2 in combination with BMP-2 was found to enhance bone regeneration both in vitro and in vivo[61,62].

Nagayasu-Tanaka et al[63], in a dog model, showed that periodontal regeneration in the presence of FGF2 was revealed to promote disappearance of blood clots and granulation tissue formation, which are replaced rapidly with new bone; thus, bone formation is more accelerated. Besides, the vascularised connective tissue with tight collagen fibres on the root surface extends coronally from the existing PDL and forms new cementum and PDL with Sharpey's fibres. Rapid dense connective tissue formation in the presence of FGF2 maintains gingival tissue at higher levels and consequently creates a regenerative space and inhibits further periodontal collapse. The clinical application of FGF2 shows its effectiveness in bone regeneration of periodontal defects; however, there is still a lack of clinical attachment[64,65].

TGF-β

TGF-β is a superfamily of growth factors with multifunctional effects. Its role in wound healing occurs through its effect on cell proliferation, differentiation and migration. Three isoforms, i.e., TGF-β1, 2 and 3, with significant homology have been detected for TGF-β. It has been reported that the isoforms 1 and 3 which signal through the same receptor complex, TGF-β receptor type II (TβRII)[66], play roles in periodontal regeneration[67,68].

TGF-β1 has long been recognised as a prerequisite for the differentiation of myofibroblasts that play a key role in the remodelling and reconstruction of connective tissue by the secretion and organisation of the extracellular matrix and by endowing tissue with contractile forces[69]. Moreover, Fujii et al[70] showed the exclusive distribution of TGF-β1 throughout the PDL tissues and proved that the amount of TGF-β1 in PDL tissues is greater than that in pulp tissues or alveolar bone tissues, indicating the important physiological role played by TGF-β1 in PDL cells.

TGF-β1 has been shown to suppress the proliferation of PDL cells, while its upregulation of actin alpha 2 (ACTA2), COL1 and fibrillin-1 encoding gene (FBN1) contributes to their fibroblastic differentiation[71]. Besides, TGF-β1 has been shown to increase tenomodulin but decrease scleraxis[59]. Hence, subsequent administration of TGF-β1 after FGF2 on the differentiation of PDLSCs into fibroblastic cells has been suggested to accelerate the regeneration of functional periodontium[71]. TGF-β3 is of particular interest due to its association with dermal wound and tendon healing promotion without fibrotic scar formation[72]. TGF-β3 has been shown to enhance the proliferation and early differentiation of MSCs into osteoblasts, chondrocytes, adipocytes and tendon cells[66]. In a study by Moshaverinia et al[72], in a mouse model, PDLSCs and gingival stem cells encapsulated in TGF-β3–loaded RGD-modified alginate microspheres showed the successful differentiation of given cells into tendon-like tissue.

Platelet-derived growth factor (PDGF)

Platelets can produce and release growth factors and cytokines involved in angiogenesis, inflammation and immune response which eventually enhance tissue repair. PDGF is one of the growth factors stored in platelets[73] that are actively involved in tissue regeneration and wound healing[74]. Various studies have confirmed the effect of PDGF on the proliferation of PDL fibroblasts[75-77]. Three different forms of PDGF, i.e., PDGF-AA, PDGF-AB and PDGF-BB, have been identified[74,78]. Of these, the efficacy of PDGF-BB in both soft and hard tissue regeneration of the periodontium has been demonstrated most clearly. Studies have shown that PDGF-BB is the most effective form, enhancing PDL cell mitogenesis and matrix biosynthesis[74,77]. Jin et al[75] also demonstrated enhanced alveolar bone formation and cementogenesis in large periodontal bone defects using gene therapy with a mode of PDGF-BB delivery in vivo. Furthermore, the use of PDGF-BB in combination with IGF[79] or FGF[74] has been shown to improve periodontal regeneration.

Conclusion

Optimal periodontal regeneration includes restoration of all periodontium components, i.e., alveolar bone, cementum and PDL. Knowledge regarding specific growth factors and cytokines involved in regeneration of each of them may serve as a basis for development of the therapeutic methods targeting all periodontium components. Future studies in this field should be dedicated to designing a combination of these factors in a single smart delivery system and evaluating the effectiveness of their periodontal complex regeneration.

Acknowledgements

The authors thank Melika Tofighi for her assistance with Fig 1. They also thank the Research Institute of Dental Research of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Drs Fazele ATARBASHI-MOGHADAM and Maryam REZAI RAD contributed to the data analysis; Drs Soran SIJANIVANDI, Pouya KHODAYARI and Masoumeh MAHMOUM were involved in the data gathering. All authors contributed to the writing and editing of the manuscript.

(Received Feb 4 2021; accepted Dec 14, 2021)

References

1. Cho MI, Garant PR. Development and general structure of the periodontium. Periodontol 2000 2000;24:9–27.
2. de Jong T, Bakker AD, Everts V, Smit TH. The intricate anatomy of the periodontal ligament and its development: Lessons for periodontal regeneration. J Periodontal Res 2017;52:965–974.
3. Ripamonti U. Developmental pathways of periodontal tissue regeneration: Developmental diversities of tooth morphogenesis do also map capacity of periodontal tissue regeneration? J Periodontal Res 2019;54:10–26.
4. Ivanovski S. Periodontal regeneration. Aust Dent J 2009;54(suppl 1): S118–S128.
5. Cortellini P, Tonetti MS. Clinical concepts for regenerative therapy in intrabony defects. Periodontol 2000 2015;68:282–307.
6. Smith PC, Martínez C, Cáceres M, Martínez J. Research on growth factors in periodontology. Periodontology 2000 2015;67:234–250.
7. Song IS, Han YS, Lee JH, Um S, Kim HY, Seo BM. Periodontal ligament stem cells for periodontal regeneration. Curr Oral Health Rep 2015;2:236–244.
8. Blair HC, Larrouture QC, Li Y et al. Osteoblast differentiation and bone matrix formation in vivo and in vitro. Tissue Eng Part B Rev 2017;23:268–280.
9. Garg P, Mazur MM, Buck AC, Wandtke ME, Liu J, Ebraheim NA. Prospective review of mesenchymal stem cells differentiation into osteoblasts. Orthop Surg 2017;9:13–19.
10. Gonnerman KN, Brown LS, Chu TMG. Effects of growth factors on cell migration and alkaline phosphatase release. Biomed Sci Instrum 2006;42:60–65.
11. Pettipher R, Hansel TT, Armer R. Antagonism of the prostaglandin D2 receptors DP1 and CRTH2 as an approach to treat allergic diseases. Nat Rev Drug Discov 2007;6:313–325.
12. Cheng H, Jiang W, Phillips FM, et al. Osteogenic activity of the fourteen types of human bone morphogenetic proteins (BMPs). J Bone Joint Surg Am 2003;85:1544–1552.
13. Miyazono K, Kusanagi K, Inoue H. Divergence and convergence of TGF-beta/BMP signaling. J Cell Physiol 2001;187:265–276.
14. Açil Y, Yang F, Gulses A, Ayna M, Wiltfang J, Gierloff M. Isolation, characterization and investigation of differentiation potential of human periodontal ligament cells and dental follicle progenitor cells and their response to BMP-7 in vitro. Odontology 2016;104:123–135.
15. Açil Y, Ghoniem AA, Wiltfang J, Gierloff M. Optimizing the osteogenic differentiation of human mesenchymal stromal cells by the synergistic action of growth factors. J Craniomaxillofac Surg 2014;42:2002–2009.
16. Lee H, Min SK, Song Y, Park YH, Park JB. Bone morphogenetic protein-7 upregulates genes associated with osteoblast differentiation, including collagen I, Sp7 and IBSP in gingiva-derived stem cells. Exp Ther Med 2019;18:2867–2876.
17. Li C, Yang X, He Y, et al. Bone morphogenetic protein-9 induces osteogenic differentiation of rat dental follicle stem cells in P38 and ERK1/2 MAPK dependent manner. Int J Med Sci 2012;9:862–871.
18. Hakki SS, Bozkurt B, Hakki EE, et al. Bone morphogenetic protein-2, -6, and -7 differently regulate osteogenic differentiation of human periodontal ligament stem cells. J Biomed Mater Res B Appl Biomater 2014;102:119–130.
19. Klingelhöffer C, Reck A, Ettl T, Morsczeck C. The parathyroid hormone-related protein is secreted during the osteogenic differentiation of human dental follicle cells and inhibits the alkaline phosphatase activity and the expression of DLX3. Tissue Cell 2016;48:334–339.
20. Takahashi A, Nagata M, Gupta A, et al. Autocrine regulation of mesenchymal progenitor cell fates orchestrates tooth eruption. Proc Natl Acad Sci U S A 2019;116:575–580.
21. Pieles O, Reck A, Morsczeck C. High endogenous expression of parathyroid hormone-related protein (PTHrP) supports osteogenic differentiation in human dental follicle cells. Histochem Cell Biol 2020;154:397–403.
22. Govoni KE. Insulin-like growth factor-I molecular pathways in osteoblasts: Potential targets for pharmacological manipulation. Curr Mol Pharmacol 2012;5:143–152.
23. Parra-Torres AY, Valdés-Flores M, Orozco L, Velázquez-Cruz R. Molecular aspects of bone remodeling. In Valdés-Flores M (ed). Topics in Osteoporosis. London: IntechOpen, 2013:1–27.
24. Wang S, Mu J, Fan Z, et al. Insulin-like growth factor 1 can promote the osteogenic differentiation and osteogenesis of stem cells from apical papilla. Stem Cell Res 2012;8:346–356.
25. Feng X, Huang D, Lu X, et al. Insulin-like growth factor 1 can promote proliferation and osteogenic differentiation of human dental pulp stem cells via mTOR pathway. Dev Growth Differ 2014;56: 615–624.
26. Fang Y, Wang LP, Du FL, Liu WJ, Ren GL. Effects of insulin-like growth factor I on alveolar bone remodeling in diabetic rats. J Periodontal Res 2013;48:144–150.
27. Geng S, Zhou S, Glowacki J. Effects of 25-hydroxyvitamin D(3) on proliferation and osteoblast differentiation of human marrow stromal cells require CYP27B1/1α-hydroxylase. J Bone Miner Res 2011;26:1145–1153.
28. Liu P, Oyajobi BO, Russell RG, Scutt A. Regulation of osteogenic differentiation of human bone marrow stromal cells: interaction between transforming growth factor-beta and 1,25(OH)(2) vitamin D(3) in vitro. Calcif Tissue Int 1999;65:173–180.
29. Li YL, Xiao ZS. Advances in Runx2 regulation and its isoforms. Med Hypotheses 2007;68:169–175.
30. Posa F, Di Benedetto A, Colaianni G, et al. Vitamin D effects on osteoblastic differentiation of mesenchymal stem cells from dental tissues. Stem Cells Int 2016;2016:9150819.
31. Esposito M, Grusovin MG, Papanikolaou N, Coulthard P, Worthington HV. Enamel matrix derivative (Emdogain(R)) for periodontal tissue regeneration in intrabony defects. Cochrane Database Syst Rev 2009;2009:CD003875.

32. Davenport DR, Mailhot JM, Wataha JC, Billman MA, Sharawy MM, Shrout MK. Effects of enamel matrix protein application on the viability, proliferation, and attachment of human periodontal ligament fibroblasts to diseased root surfaces in vitro. J Clin Periodontol 2003;30:125–131.
33. Lyngstadaas SP, Lundberg E, Ekdahl H, Andersson C, Gestrelius S. Autocrine growth factors in human periodontal ligament cells cultured on enamel matrix derivative. J Clin Periodontol 2001;28:181–188.
34. Tokiyasu Y, Takata T, Saygin E, Somerman M. Enamel factors regulate expression of genes associated with cementoblasts. J Periodontol 2000;71:1829–1839.
35. Fincham AG, Moradian-Oldak J, Simmer JP, et al. Self-assembly of a recombinant amelogenin protein generates supramolecular structures. J Struct Biol 1994;112:103–109.
36. Gestrelius S, Andersson C, Johansson AC, et al. Formulation of enamel matrix derivative for surface coating. Kinetics and cell colonization. J Clin Periodontol 1997;24:678–684.
37. Sculean A, Alessandri R, Miron R, Salvi GE, Bosshardt DD. Enamel matrix proteins and periodontal wound healing and regeneration. Clin Adv Periodontics 2011;1:101–117.
38. Kémoun P, Laurencin-Dalicieux S, Rue J, et al. Human dental follicle cells acquire cementoblast features under stimulation by BMP-2/-7 and enamel matrix derivatives (EMD) in vitro. Cell Tissue Res 2007;329:283–294.
39. França-Grohmann IL, Sangiorgio JPM, Bueno MR, et al. Treatment of dehiscence-type defects with collagen matrix and/or enamel matrix derivative: Histomorphometric study in minipigs. J Periodontol 2020;91:967–974.
40. Bosshardt DD, Sculean A, Windisch P, Pjetursson BE, Lang NP. Effects of enamel matrix proteins on tissue formation along the roots of human teeth. J Periodontal Res 2005;40:158–167.
41. Ripamonti U, Renton L. Bone morphogenetic proteins and the induction of periodontal tissue regeneration. Periodontol 2000 2006;41:73–87.
42. Sasikumar KP, Elavarasu S, Gadagi JS. The application of bone morphogenetic proteins to periodontal and peri-implant tissue regeneration: A literature review. J Pharm Bioallied Sci 2012;4(suppl 2):S427–S430.
43. Bozic D, Grgurevic L, Erjavec I, et al. The proteome and gene expression profile of cementoblastic cells treated by bone morphogenetic protein-7 in vitro. J Clin Periodontol 2012;39:80–90.
44. Daluiski A, Engstrand T, Bahamonde ME, et al. Bone morphogenetic protein-3 is a negative regulator of bone density. Nat Genet 2001;27:84–88.
45. Giannobile WV, Ryan S, Shih MS, Su DL, Kaplan PL, Chan TC. Recombinant human osteogenic protein-1 (OP-1) stimulates periodontal wound healing in class III furcation defects. J Periodontol 1998;69:129–137.
46. Hakki SS, Bozkurt BS, Hakki EE. Boron regulates mineralized tissue-associated proteins in osteoblasts (MC3T3-E1). J Trace Elem Med Biol 2010;24:243–250.
47. Popowics T, Foster BL, Swanson EC, Fong H, Somerman MJ. Defining the roots of cementum formation. Cells Tissues Organs 2005;181:248–257.
48. Ripamonti U, Heliotis M, Rueger DC, Sampath TK. Induction of cementogenesis by recombinant human osteogenic protein-1 (hop-1/bmp-7) in the baboon (Papio ursinus). Arch Oral Biol 1996;41:121–126.
49. Torii D, Tsutsui TW, Watanabe N, Konishi K. Bone morphogenetic protein 7 induces cementogenic differentiation of human periodontal ligament-derived mesenchymal stem cells. Odontology 2016;104:1–9.
50. Aberg T, Wozney J, Thesleff I. Expression patterns of bone morphogenetic proteins (Bmps) in the developing mouse tooth suggest roles in morphogenesis and cell differentiation. Dev Dyn 1997;210:383396.
51. Komaki M, Iwasaki K, Arzate H, Narayanan AS, Izumi Y, Morita I. Cementum protein 1 (CEMP1) induces a cementoblastic phenotype and reduces osteoblastic differentiation in periodontal ligament cells. J Cell Physiol 2012;227:649–657.
52. Alvarez-Pérez MA, Narayanan S, Zeichner-David M, Rodríguez Carmona B, Arzate H. Molecular cloning, expression and immunolocalization of a novel human cementum-derived protein (CP-23). Bone 2006;38:409–419.
53. Sowmya S, Chennazhi KP, Arzate H, Jayachandran P, Nair SV, Jayakumar R. Periodontal specific differentiation of dental follicle stem cells into osteoblast, fibroblast, and cementoblast. Tissue Eng Part C Methods 2015;21:1044–1058.
54. Xu Y, Lv C, Zhang J, et al. Intermittent parathyroid hormone promotes cementogenesis in a PKA- and ERK1/2-dependent manner. J Periodontol 2019;90:1002–1013.
55. Ono W, Sakagami N, Nishimori S, Ono N, Kronenberg HM. Parathyroid hormone receptor signalling in osterix-expressing mesenchymal progenitors is essential for tooth root formation. Nat Commun 2016;7:11277.
56. Li T, Yan Z, He S, et al. Intermittent parathyroid hormone improves orthodontic retention via insulin-like growth factor-1. Oral Dis 2021;27:290–300.
57. Fujihara C, Kanai Y, Masumoto R, et al. Fibroblast growth factor-2 inhibits CD40-mediated periodontal inflammation. J Cell Physiol 2019;234:7149–7160.
58. Tavelli L, McGuire MK, Zucchelli G, et al. Biologics-based regenerative technologies for periodontal soft tissue engineering. J Periodontol 2020;91:147–154.
59. Hyun SY, Lee JH, Kang KJ, Jang YJ. Effect of FGF-2, TGF-β-1, and BMPs on teno/ligamentogenesis and osteo/cementogenesis of human periodontal ligament stem cells. Mol Cells 2017;40:550–557.
60. Murakami S, Takayama S, Ikezawa K, et al. Regeneration of periodontal tissues by basic fibroblast growth factor. J Periodontal Res 1999;34:425–430.
61. Lee AR, Choi H, Kim JH, Cho SW, Park YB. Effect of serial use of bone morphogenetic protein 2 and fibroblast growth factor 2 on periodontal tissue regeneration. Implant Dent 2017;26:664–673.
62. Wang L, Huang Y, Pan K, Jiang X, Liu C. Osteogenic responses to different concentrations/ratios of BMP-2 and bFGF in bone formation. Ann Biomed Eng 2010;38:77–87.
63. Nagayasu-Tanaka T, Anzai J, Takaki S, et al. Action mechanism of fibroblast growth factor-2 (FGF-2) in the promotion of periodontal regeneration in beagle dogs. PLoS One 2015;10:e0131870.
64. Kitamura M, Akamatsu M, Machigashira M, et al. FGF-2 stimulates periodontal regeneration: Results of a multi-center randomized clinical trial. J Dent Res 2011;90:35–40.
65. Kitamura M, Nakashima K, Kowashi Y, et al. Periodontal tissue regeneration using fibroblast growth factor-2: Randomized controlled phase II clinical trial. PLoS One 2008;3:e2611.
66. Grafe I, Alexander S, Peterson JR, et al. TGF-β family signaling in mesenchymal differentiation. Cold Spring Harb Perspect Biol 2018;10:a022202.
67. Teare JA, Ramoshebi LN, Ripamonti U. Periodontal tissue regeneration by recombinant human transforming growth factor-beta 3 in Papio ursinus. J Periodontal Res 2008;43:1–8.
68. Mohammed S, Pack AR, Kardos TB. The effect of transforming growth factor beta one (TGF-beta 1) on wound healing, with or without barrier membranes, in a Class II furcation defect in sheep. J Periodontal Res 1998;33:335-344.
69. Xu H, He Y, Feng JQ, et al. Wnt3α and transforming growth factor-β induce myofibroblast differentiation from periodontal ligament cells via different pathways. Exp Cell Res 2017;353:55–62.
70. Fujii S, Maeda H, Tomokiyo A, et al. Effects of TGF-β1 on the proliferation and differentiation of human periodontal ligament cells and a human periodontal ligament stem/progenitor cell line. Cell Tissue Res 2010;342:233–242.
71. Kono K, Maeda H, Fujii S, et al. Exposure to transforming growth factor-β1 after basic fibroblast growth factor promotes the fibroblastic differentiation of human periodontal ligament stem/progenitor cell lines. Cell Tissue Res 2013;352:249–263.

72. Moshaverinia A, Xu X, Chen C, et al. Application of stem cells derived from the periodontal ligament or gingival tissue sources for tendon tissue regeneration. Biomaterials 2014;35:2642–2650.
73. Andrade SS, de Sousa Faria AV, de Paulo Queluz D, Ferreira-Halder CV. Platelets as a ‘natural factory’ for growth factor production that sustains normal (and pathological) cell biology. Biol Chem 2020;401:471–476.
74. Li F, Yu F, Xu X, et al. Evaluation of recombinant human FGF-2 and PDGF-BB in periodontal regeneration: A systematic review and meta-analysis. Sci Rep 2017;7:65.
75. Jin Q, Anusaksathien O, Webb SA, Printz MA, Giannobile WV. Engineering of tooth-supporting structures by delivery of PDGF gene therapy vectors. Mol Ther 2004;9:519–526.
76. Kaigler D, Avila G, Wisner-Lynch L, et al. Platelet-derived growth factor applications in periodontal and peri-implant bone regeneration. Expert Opin Biol Ther 2011;11:375–385.
77. Kaigler D, Cirelli JA, Giannobile WV. Growth factor delivery for oral and periodontal tissue engineering. Expert Opin Drug Deliv 2006;3:647–662.
78. Hoch RV, Soriano P. Roles of PDGF in animal development. Development 2003;130:4769–4784.
79. Howell TH, Fiorellini JP, Paquette DW, Offenbacher S, Giannobile WV, Lynch SE. A phase I/II clinical trial to evaluate a combination of recombinant human platelet-derived growth factor-BB and recombinant human insulin-like growth factor-I in patients with periodontal disease. J Periodontol 1997;68:1186–1193.