Regenerative Therapy
A Periodontal-Endodontic Perspective

Bassam Michael Kinaia, DDS, MS[a,b,c,*], Sami M.A. Chogle, BDS, DMD, MSD[d,e,f], Atheel M. Kinaia, DDS[g], Harold E. Goodis, DDS[e,h,i]

KEY POINTS

- Periodontal and endodontic diseases are inflammatory responses to microorganisms leading to periodontal and pulpal tissue damage and loss. Regenerative therapies aim to restore the lost structures to vitality and function.
- Various materials and treatments methods, such as bone grafts, guided tissue regeneration, enamel materials derivatives, growth and differentiation factors, and stem cells research, have been used.
- Although the current materials and methods demonstrated favorable clinical results, true and complete biological regeneration of the damaged or injured structures is not yet attainable.

INTRODUCTION

Periodontal disease is a destructive inflammatory process affecting the periodontal attachment apparatus of the teeth, leading to irreversible loss of bone and periodontal ligament (PDL).[1] Similarly in endodontics, a progressive injury (ie, caries) to the dental

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[a] Postgraduate Periodontology Program, Periodontology Department, The Boston University Institute for Dental Research and Education, PO Box 505097, Dubai Healthcare City, Dubai, United Arab Emirates; [b] Department of Periodontology and Oral Biology, The Goldman School of Dental Medicine, Boston, MA, USA; [c] University of Detroit Mercy - School of Dentistry, Detroit, MI, USA; [d] Postgraduate Program in Endodontics, Endodontics Department, The Boston University Institute for Dental Research and Education, PO Box 505097, Dubai Healthcare City, Dubai, United Arab Emirates; [e] Department of Endodontics, The Goldman School of Dental Medicine, Boston, MA, USA; [f] Department of Endodontics, Case School of Dental Medicine, Cleveland, OH, USA; [g] Advanced Education in General Dentistry Program, The European University, PO Box 505097, Dubai Healthcare City, Dubai, United Arab Emirates; [h] The Boston University Institute for Dental Research and Education, PO Box 505097, Dubai Healthcare City, Dubai, United Arab Emirates; [i] Department of Endodontics, The University of California School of Dentistry, San Francisco, CA, USA
* Corresponding author. 2452 Westmont Cr. Sterling Heights, MI 48310.
E-mail address: kinaia@perio.org

pulp stimulates an inflammatory response leading to pulpal necrosis and periapical tissue involvement manifested in periradicular tissue breakdown. Various treatment methods have been proposed for the treatment of periodontal disease. In the 1950s and 1960s, treatments ranged from conservative therapy, such as curettage and open flap debridement, to surgical treatment procedures, such as gingivectomy, root amputation, hemi-section, and tunneling. Regardless of the treatment method used, healing occurred by repair (ie, long junctional epithelium) rather than regeneration of the lost tissues of the periodontal attachment apparatus. The introduction of bone grafts[2–4] in the 1970s and 1980s and the concept of guided tissue regeneration (GTR)[5–7] offered new treatment options to regenerate lost periodontal tissues.[8–10] In the 1990s and 2000s, enamel matrix derivatives (EMDs),[11] platelet-derived growth factor (PDGF),[12,13] insulinlike growth factor (IGF-I),[14] and bone morphogenetic proteins (BMPs)[15] have given a new dimension to periodontal regeneration with promising clinical results. The aim of periodontal treatment is complete regeneration of the lost or damaged tissues. Despite the success of the above-mentioned materials and methods, this aim has been partially but not completely established. At present, stem cells (SCs) represent a new era in regenerative therapy with the aim of complete regeneration. This article chronologically reviews the regenerative therapies used in periodontal and endodontic fields with emphasis on periodontal regeneration.

HEALING
Endodontic Repair Versus Regeneration

In pulpal injury, if the original odontoblasts survive and react by secreting tertiary dentin matrices, complete regeneration and return of the damaged vital pulp tissue to its normal form and function is possible via reactionary dentinogenesis.[16] Conversely, reparative dentin formation occurs in response to deep dentinal caries and represents a much more complex sequence of biologic events beginning with apoptosis of the odontoblasts in the area of injury, including progenitor cell recruitment and differentiation.[17] When the pulp is exposed in advanced lesions, reparative dentinogenesis may result in dentin bridge formation, which restores only the functional integrity of the pulpodentin complex. In the case of a periradicular lesion due to pulpal necrosis, usually the lesion would heal to form and function after conventional endodontic therapy. However, in some instances, the lesion may persist or not completely heal despite adequate therapy. Generally, a persistent periapical radiolucent lesion would indicate ongoing disease. On occasion, unresolved periapical radiolucency may represent healing by remnants of the lesion, which may be mistaken as a sign of failed endodontic treatment.[18,19] These types of lesions usually occur when the lesion penetrates both the buccal and lingual cortical plates (ie, communicating lesion). In such cases, the form and functional healing of the periradicular tissues are replaced by a fibrous tissue repair of the area, which persists as a radiolucency alluding to persistent disease of the apical region.

Periodontal Repair Versus Regeneration

Periodontally, repair is healing of a wound by tissue that does not fully restore the architecture or the function of the lost part as in healing by long junctional epithelium.[1] Regeneration constitutes the reproduction of a lost or injured part. Periodontally, GTR is a procedure that attempts to regenerate the lost periodontal structures through differential tissue responses by using a barrier (ie, membrane).[1] Thus, restoration of the periodontal apparatus occurs by the regeneration of connective tissue, cementum, and alveolar bone rather than epithelium. Healing by regeneration is favorable compared

with repair because the goal of periodontal therapy is to restore the periodontal tissues to their original biological structure. Many materials and methods have been used to accomplish regeneration, including bone grafts, GTR, EMDs, growth factors, and SCs.

REGENERATIVE THERAPY
Bone Grafts

Bone grafts are used as fillers in periodontal defects and aid in healing by repair. Bone grafts are used because of their osteogenic (autograft), osteoinductive (allograft), or osteoconductive (xenograft/alloplast) properties.[20] Osteogenic materials stimulate the formation of new bones because they contain bone-forming cells and progenitor cells. Osteoinductive materials stimulate progenitor SCs in the surrounding tissue immediately adjacent to the defect to regenerate the lost structures.[21,22] In contrast, osteoconductive materials serve as scaffolds for bone growth within the existing bony walls and passively promote healing.[3] Although bone grafts demonstrated adequate clinical results, the healing mainly occurred by repair (long junctional epithelium), rather than regeneration of the PDL (**Fig. 1**).[6,23]

Bone grafts are also used in the treatment of apical periodontitis and more specifically, in periradicular surgery. Freeze-dried bone allografts (FDBA) were used in osseous defects after the removal of periapical lesions. The results showed that FDBA had an osteogenic potential and, for the most part, bone regeneration occurred.[24] Although the previously mentioned studies were beneficial in healing of periodontal and periradicular defects, complete true regeneration did not occur.
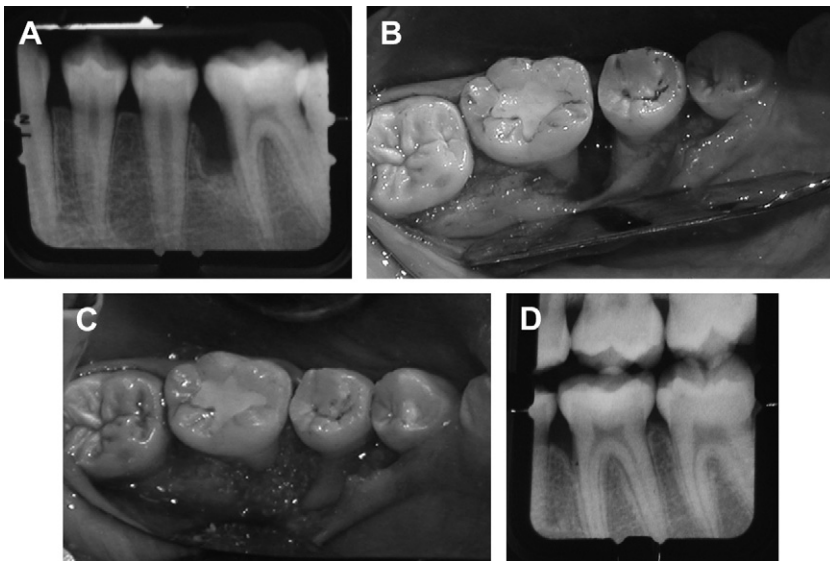

Fig. 1. Bone allograft material for treatment of intrabony periodontal defect. (*A*) Preoperative radiograph of intrabony periodontal defect #19. (*B*) Clinical picture showing surgical exposure of the defect extending mesiolingually. (*C*) Bone allograft material filling the defect. (*D*) Follow-up radiograph (18 months) showing the presence of adequate bone fill. (*Courtesy of* Bassam M. Kinaia, DDS, MS, Boston University Institute for Dental Research and Education, Dubai Healthcare City, Dubai, UAE.)

Guided Tissue Regeneration

Melcher[5] suggested that there are 4 different cell types dictating the type of periodontal healing that occurs. These cells originate from the gingival epithelial tissue, lamina propria of connective tissue, alveolar bone, and PDL. Cells derived from PDL and bone posses the potential to heal by true regeneration when compared with cells from lamina propria of gingiva or gingival epithelial tissue that heal by repair (**Fig. 2**).[5] Understanding barrier mediated selective cell repopulation gave rise to the concept of epithelial exclusion to restore lost periodontal tissue and obtain new attachment. Bowers and colleagues[6] published a histologic report on the formation of new periodontal attachment apparatus in humans. The study included teeth with intrabony defects that needed to be extracted because of advanced periodontal disease. The investigators performed flap curettage, crown removal, and submersion of the vital root beneath the mucosa with biopsies obtained at 6 months after treatment. The submersion of the teeth allowed epithelial exclusion similar to GTR. New attachment occurred in the submerged group indicating regeneration. Healing by long junctional epithelium was observed on the nonsubmerged teeth, indicating repair. Further, regeneration of new attachment apparatus, cementum, and bone was more likely in submerged, intrabony grafted defects with demineralized FDBA. New attachment in
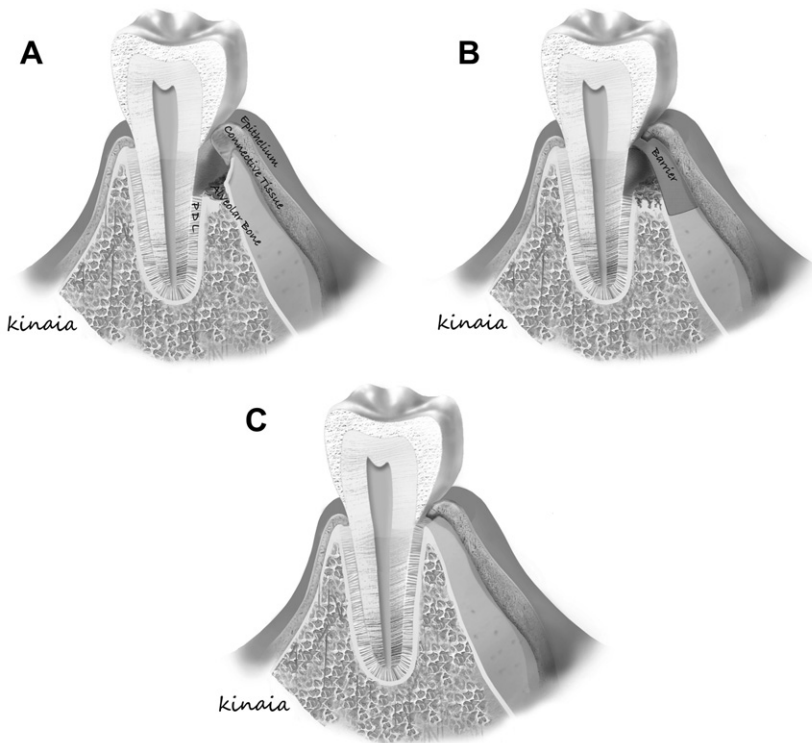

Fig. 2. Illustration of GTR for periodontal intrabony defect. (*A*) Epithelium and connective tissue migration into periodontal intrabony defect with PDL tissue and alveolar bone loss. (*B*) Membrane to exclude the soft tissue coronally to allow selective PDL and alveolar bone regeneration. (*C*) Ideal outcome of GTR showing complete reconstruction of the periodontal attachment apparatus. (*Courtesy of* Bassam M. Kinaia, DDS, MS, Boston University Institute for Dental Research and Education, Dubai Healthcare City, Dubai, UAE.)

grafted sites measured 1.76 mm compared with 0.76 mm in nongrafted sites. The investigators concluded that healing with a new attachment was more predictable for submerged teeth and more likely when a bone graft was added.[23] The literature demonstrated that GTR was biologically possible with promising clinical results in intrabony and furcation defects.[9,10]

Although the concept of GTR was primarily established in periodontal regeneration, it also has been applied in surgical endodontic treatment (**Fig. 3**). A recent systematic review by Tsesis and colleagues[25] evaluated the efficacy of GTR in endodontic surgery. They found that large communicating lesions healed better with GTR compared with those without GTR (*P* = .02). However, GTR in small confined lesions was of no added benefit (*P* = .27). The use of a resorbable membrane was more favorable than nonresorbable membranes (*P* = .02), a finding that was similar to that obtained in the regeneration of periodontal furcation defects.[10] Therefore, when a periapical lesion is confined, GTR may not be necessary. If there is a large communication of the periapical lesion, GTR would be of potential benefit.[26] Despite the success of GTR in periodontal and endodontic treatments, complete regeneration of the periodontal attachment apparatus is not always predictable.[25] Thus, advances in molecular biology, such as EMDs and growth factors, offer a new area of research with the hope of complete regeneration.
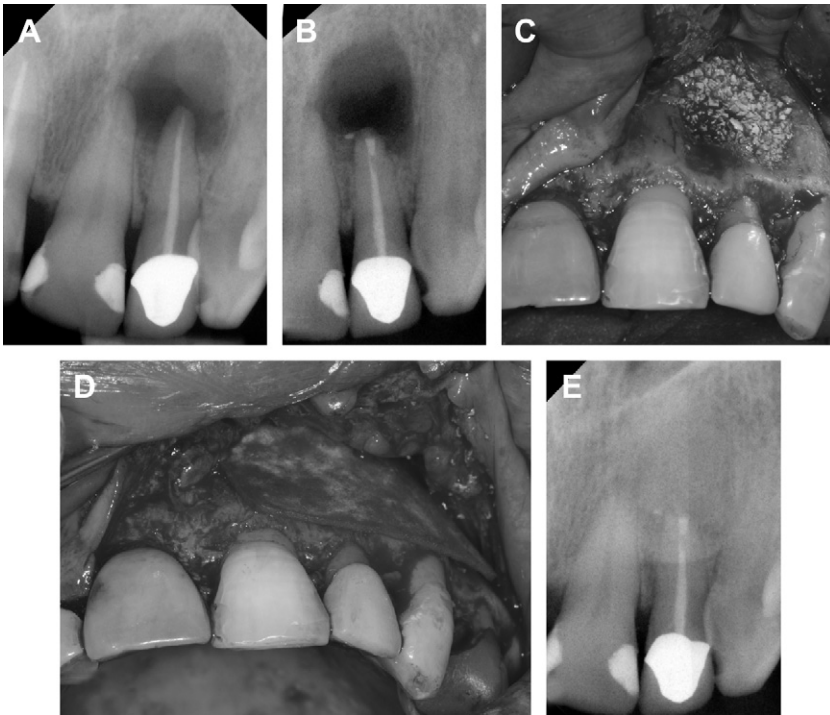

Fig. 3. Combination of bone allograft material and resorbable membrane (GTR) for the treatment of apical periodontitis. (*A*) Periapical radiolucency on #10 after treatment (RCT completed 15 years ago). (*B*) Immediate postsurgical radiograph showing retrograde fill. (*C*) Bone allograft material added. (*D*) Resorbable membrane placed. (*E*) Follow-up radiograph (6 months) showing adequate bone fill. (*Courtesy of* Bassam M. Kinaia, DDS, MS, and Sami Chogle, BDS, DMD, MSD, Boston University Institute for Dental Research and Education, Dubai Healthcare City, Dubai, UAE.)

Enamel Matrix Derivatives

Advances in molecular biology set the stage for a new era in periodontal regeneration for complete regeneration (**Fig. 4**). Studies reported that treatment of intrabony defects with EMDs led to decreased probing depth, increased clinical attachment level (CAL), increased bone-fill, and periodontal regeneration.[27] EMD contains amelogenins among other enamel matrix proteins that mimic the cementogenesis process during root formation.[28] These proteins, in primate studies, have demonstrated stimulation of the surrounding undifferentiated mesenchymal cells into cementoblasts to form acellular cementum, a process similar to the formation of the inner layer of Hertwig epithelial root sheath during tooth development.[29] Once the cementum is formed, collagen fibers attach from the adjacent PDL leading to the restoration of the periodontal attachment apparatus.[28] Although not consistent, EMD creates a favorable environment at the cellular level for periodontal regeneration by improving the attachment as well as differentiation of PDL fibroblasts compared with gingival fibroblasts.[30] Similarly, the amelogenins are involved in the differentiation of odontoblasts during development indicating that they may play a role in odontogenesis. Nakamura and colleagues[31] examined the effect of EMD on pulpal wound healing in an animal study using premolars. They found that EMD formed dentinlike hard tissue with the presence
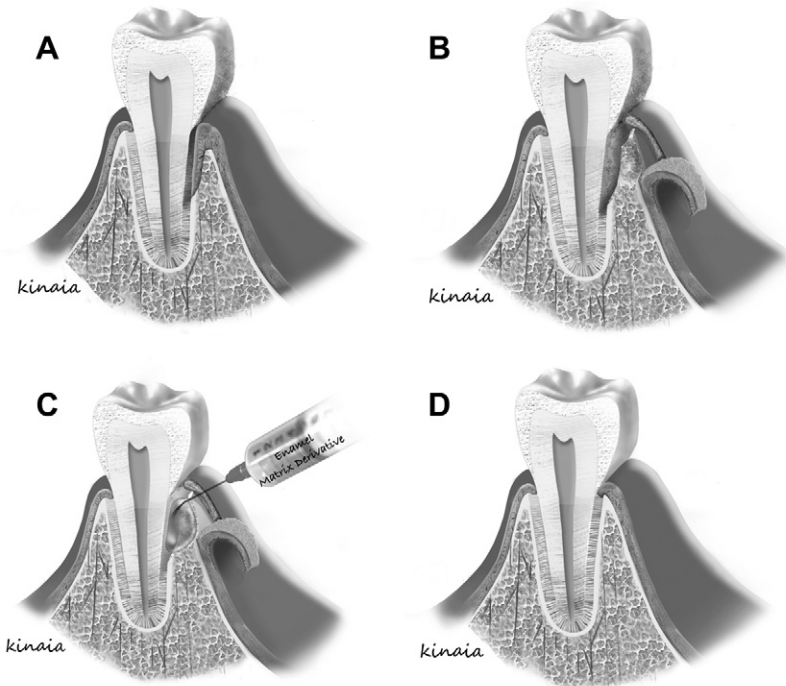

Fig. 4. Illustration of EMD for treatment of periodontal intrabony defect. (*A*) Apical migration of epithelium and connective tissue into periodontal intrabony defect with PDL tissue and alveolar bone loss. (*B*) Diseased root surface and periodontal defect are surgically exposed. (*C*) Enamel matrix derivatives added to repair the defect. (*D*) Ideal outcome showing complete reconstruction of the periodontal attachment apparatus. (*Courtesy of Bassam M. Kinaia, DDS, MS, Boston University Institute for Dental Research and Education, Dubai Healthcare City, Dubai, UAE.*)

of formative cells outlining the pulpal wound. EMD had a 2-fold better reparative potential of the pulpal wound compared with the control (calcium-hydroxide) group. At the microbiological level, EMD selectively inhibited the growth of gram-negative pathogens although exhibiting no effect on gram-positive pathogens.[32] EMD mainly creates a positive environment, but it does not contain a specific growth factor that can be useful to enhance regeneration.[33] More recent advances in regenerative therapies include the use of growth and differentiation factors for periodontal and endodontic regeneration.

Growth and Differentiation Factors

Growth and differentiation factors play an important role in regulating wound-healing events, such as chemotaxis, cell adhesion, proliferation, and differentiation.[34] These factors include platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factors (TGF) α and β, acidic and basic fibroblast growth factors, epidermal growth factor, IGF-I, IGF-II, cementum-derived growth factor, parathyroid hormone-related protein, and BMPs.[35] See the article by Kim and colleagues in this issue for further details on growth and differentiation factors.

At present, the most used factors are PDGF, IGF, and BMPs. PDGFs are dimeric glycoproteins comprising 2 A (-AA), 2 B (-BB) chains, or a combination of the 2 (-AB) chains. PDGF-BB has been used in intrabony periodontal defects with significant improvement in clinical outcomes demonstrated as CAL gain, bone growth, and percentage bone fill.[13,36] IGF is a protein with 2 ligands (IGF-1 and IGF-2). Howell and colleagues[14] reported CAL gain, periodontal probing depth (PPD) reduction, and bone gain with use of a combination of IGF-1 and PDGF-BB. Further, a pulp-capping study in rat molars by Lovschall and colleagues[37] reported a positive effect of IGF-1 in dentin repair. IGF-1 improved the reparative dentinogenesis in injured dental pulps. Contrary to the Lovschall study, Regan and colleagues[38] evaluated the use of the PDGF and IGF combination in periapical surgery and reported no regeneration of the periapical tissues. PDGF and IGF have shown promising results in periodontal regeneration but their results are controversial in endodontic regeneration.[13,14,36–38]

BMPs are differentiating factors belonging to the TGF-β superfamily. They play a major role in differentiation, cell migration, proliferation, and apoptosis. At present, there are more than 20 BMPs with BMP-2 (osteogenic protein-2 [OP-2]), BMP-3 (osteogenin), and BMP-7 (osteogenic protein-1 [OP-1]) being the most useful in regenerative therapy.[39] In 2007, the Food and Drug Administration approved the use of INFUSE Bone Graft containing BMP in dental regeneration.[40] BMP-2 and -3 have shown potential in correcting intrabony and furcation bone loss. However, BMP-2 has been associated with ankylosis histologically.[15] Therefore, these molecules are generally reserved for use around implants or for guided bone regeneration.[41] However, BMP-7 has been used successfully in periodontal regeneration with no ankylosis.[42] Similarly, animal studies reported the differentiation of pulp cells into odontoblasts leading to the formation of osteodentin when using BMP-2[43] and BMP-7.[44] The current regenerative methods have shown adequate clinical results, but complete regeneration as of yet is not predictably achievable. New research emphasizes the use of SCs with the aim and hope of complete regeneration of the original periodontal and endodontic tissues.

Stem Cells

Although growth and differentiating factors have shown positive clinical results, they possess a short biologic half-life that may limit their use in complete regeneration of lost or damaged tissues. Therefore, constant release of these factors may be essential

for complete periodontal regeneration. SCs are readily present in human tissues offering new horizons for complete regeneration. Dental SCs are primarily found in the dental pulp and PDL. Three dental SC populations have been identified based on their origin: dental pulp SCs (DPSCs), SCs from human exfoliated deciduous teeth (SHED), and PDLSCs .[45,46] DPSC's and SHEDs are further discussed in the article by Sedgley and colleagues in this issue.

Several preclinical studies have been reported on PDLSCs. In 1 study, PDLSCs were isolated from extracted human third molar PDLs and transplanted into immuno-compromised mice and rats.[47] PDLSCs differentiated into cementoblastlike cells, adipocytes, and collagen-forming cells and generated cementum/PDLlike tissues. PDLSCs are similar to DPSCs and SHED in their expression of surface markers of STRO-1 and CD146/MUC18. Further, they are superior to bone mesenchymal stromal SCs (BMSSCs) in their high proliferation rate and differentiation capacity.[46] Lin and colleagues[48] examined human periodontium of molar teeth. The investigators used SC markers STRO-1, CD146, and CD44, and were able to identify PDLSCs in the regenerated tissue, indicating their involvement in periodontal regeneration. Another marker that has been seen in BMSSCs recruitment is stromal cell–derived factor-1 (SDF-1). A recent study by Du and colleagues,[49] reported significant proliferation and stimulated the migration of PDLSCs at concentrations of 100 and 400 ng/mL of SDF-1. This process suggests that SDF-1 may play a role in periodontal tissue regeneration in addition to the previous cell markers mentioned. PDLSCs require a scaffold such as hydroxyapatite/tricalcium phosphate to generate periodontal tissues.

PDL progenitor cells (PDLPs) are alternative cell sources to PDLSCs. PDLPs have been shown to play a role in periodontal regeneration because both are driven from the PDL. SCs differentiate into progenitor cells, which are more developmentally committed, yet are undifferentiated in comparison to those cells that have differentiated into specialized tissue cells. Fen and colleagues[50] examined the use of PDLPs in the treatment of human intrabony periodontal defects and compared it to PDLSCs. PDLPs were transplanted in defects measuring more than 6 mm depth in 3 patients. PDLPs were similar to PDLSCs in their high proliferation rate and multipotent differentiation, resulting in therapeutic periodontal regeneration.[50] This study represents one of the early clinical studies examining the use of stem/progenitor cells in periodontal regeneration in humans.

FUTURE DIRECTIONS

Although the current research in regenerative therapy is very promising, complete biological regeneration of periodontal and endodontic tissues is not yet predictably obtained. Bone grafts generally result in repair rather than regeneration. GTR is a sound principle, but it does not always regenerate the lost tissues predictably and completely. EMDs and growth and differentiation factors have a short biological half-life limiting their use for complete regeneration. SCs possess great potential for complete regeneration but still needs to be demonstrated as effective in human clinical trials. Future directions involve the fabrication of vehicles and scaffolds that are able to have a sustained release of growth factors and SCs with the aim of complete and true biological regeneration to restore the original tissues. See the article by Goodis and colleagues in this issue for an update on scaffolds for pulp regeneration.

REFERENCES

1. The American Academy of Periodontology. Glossary of periodontal terms. 4th edition. Chicago; 2001. p. 42–7.

2. Schallhorn RG, Hiatt WH, Boyce W. Iliac transplants in periodontal therapy. J Periodontol 1970;41(10):566–80.

3. Schallhorn RG. Present status of osseous grafting procedures. J Periodontol 1977;48(9):570–6.

4. Mellonig JT, Bowers GM, Bright RW, et al. Clinical evaluation of freeze-dried bone allografts in periodontal osseous defects. J Periodontol 1976;47(3):125–31.

5. Melcher AH. On the repair potential of periodontal tissues. J Periodontol 1976; 47(5):256–60.

6. Bowers GM, Chadroff B, Carnevale R, et al. Histologic evaluation of new attachment apparatus formation in humans. Part I. J Periodontol 1989;60(12):664–74.

7. Becker W, Becker BE, Berg L, et al. New attachment after treatment with root isolation procedures: report for treated Class III and Class II furcations and vertical osseous defects. Int J Periodontics Restorative Dent 1988;8(3):8–23.

8. Reynolds MA, Aichelmann-Reidy ME, Branch-Mays GL, et al. The efficacy of bone replacement grafts in the treatment of periodontal osseous defects. A systematic review. Ann Periodontol 2003;8(1):227–65.

9. Murphy KG, Gunsolley JC. Guided tissue regeneration for the treatment of periodontal intrabony and furcation defects. A systematic review. Ann Periodontol 2003;8(1):266–302.

10. Kinaia BM, Steiger J, Neely AL, et al. Treatment of Class II molar furcation involvement: meta-analyses of reentry results. J Periodontol 2011;82(3):413–28.

11. Esposito M, Grusovin MG, Papanikolaou N, et al. Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects. A Cochrane systematic review. Eur J Oral Implantol 2009;2(4):247–66.

12. Nevins M, Camelo M, Nevins ML, et al. Periodontal regeneration in humans using recombinant human platelet-derived growth factor-BB (rhPDGF-BB) and allogenic bone. J Periodontol 2003;74(9):1282–92.

13. Jayakumar A, Rajababu P, Rohini S, et al. Multi-centre, randomized clinical trial on the efficacy and safety of recombinant human platelet-derived growth factor with β-tricalcium phosphate in human intra-osseous periodontal defects. J Clin Periodontol 2011;38(2):163–72.

14. Howell TH, Fiorellini JP, Paquette DW, et al. 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(12):1186–93.

15. Sigurdsson TJ, Lee MB, Kubota K, et al. Periodontal repair in dogs: recombinant human bone morphogenetic protein-2 significantly enhances periodontal regeneration. J Periodontol 1995;66(2):131–8.

16. Duque C, Hebling J, Smith AJ, et al. Reactionary dentinogenesis after applying restorative materials and bioactive dentin matrix molecules as liners in deep cavities prepared in nonhuman primate teeth. J Oral Rehabil 2006;33(6):452–61.

17. Sloan AJ, Smith AJ. Stem cells and the dental pulp: potential roles in dentine regeneration and repair. Oral Dis 2007;13(2):151–7.

18. Nair PN, Sjogren U, Figdor D, et al. Persistent periapical radiolucencies of root-filled human teeth, failed endodontic treatments, and periapical scars. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;87(5):617–27.

19. Love RM, Firth N. Histopathological profile of surgically removed persistent periapical radiolucent lesions of endodontic origin. Int Endod J 2009;42(3): 198–202.

20. Lindhe J, Karring T, Lang NP. Clinical periodontology and implant dentistry. Oxford (United Kingdom): Blackwell Munksgaard; 2003. p. 667.

21. Ellegaard B, Karring T, Listgarten M, et al. New attachment after treatment of interradicular lesions. J Periodontol 1973;44(4):209–17.

22. Ellegaard B. Bone grafts in periodontal attachment procedures. J Clin Periodontol 1976;3(5):1–54.

23. Bowers GM, Chadroff B, Carnevale R, et al. Histologic evaluation of new attachment apparatus formation in humans. Part II. J Periodontol 1989;60(12):675–82.

24. Saad AY, Abdellatief EM. Healing assessment of osseous defects of periapical lesions associated with failed endodontically treated teeth with use of freeze-dried bone allograft. Oral Surg Oral Med Oral Pathol 1991;71(5):612–7.

25. Tsesis I, Rosen E, Tamse A, et al. Effect of guided tissue regeneration on the outcome of surgical endodontic treatment: a systematic review and meta-analysis. J Endod 2011;37(8):1039–45.

26. Bashutski JD, Wang HL. Periodontal and endodontic regeneration. J Endod 2009;35(3):321–8.

27. Kalpidis CD, Ruben MP. Treatment of intrabony periodontal defects with enamel matrix derivative: a literature review. J Periodontol 2002;73(11):1360–76.

28. Hammarstrom L. Enamel matrix, cementum development and regeneration. J Clin Periodontol 1997;24(9 Pt 2):658–68.

29. Lindskog S. Formation of intermediate cementum. II: a scanning electron microscopic study of the epithelial root sheath of Hertwig in monkey. J Craniofac Genet Dev Biol 1982;2(2):161–9.

30. Lyngstadaas SP, Lundberg E, Ekdahl H, et al. Autocrine growth factors in human periodontal ligament cells cultured on enamel matrix derivative. J Clin Periodontol 2001;28(2):181–8.

31. Nakamura Y, Hammarstrom L, Lundberg E, et al. Enamel matrix derivative promotes reparative processes in the dental pulp. Adv Dent Res 2001;15:105–7.

32. Spahr A, Lyngstadaas SP, Boeckh C, et al. Effect of the enamel matrix derivative Emdogain on the growth of periodontal pathogens in vitro. J Clin Periodontol 2002;29(1):62–72.

33. Haase HR, Bartold PM. Enamel matrix derivative induces matrix synthesis by cultured human periodontal fibroblast cells. J Periodontol 2001;72(3):341–8.

34. Narayanan AS, Bartold PM. Biology of the periodontal connective tissues. Carol Stream (IL): Quintessence; 1998. p. 245–6.

35. AAP Position Paper. The potential role of growth and differentiation factors in periodontal regeneration. J Periodontol 1996;67(5):545–53.

36. Nevins M, Giannobile WV, McGuire MK, et al. Platelet-derived growth factor stimulates bone fill and rate of attachment level gain: results of a large multicenter randomized controlled trial. J Periodontol 2005;76(12):2205–15.

37. Lovschall H, Fejerskov O, Flyvbjerg A. Pulp-capping with recombinant human insulin-like growth factor I (rhIGF-I) in rat molars. Adv Dent Res 2001;15:108–12.

38. Regan JD, Gutmann JL, Iacopino AM, et al. Response of periradicular tissues to growth factors introduced into the surgical site in the root-end filling material. Int Endod J 1999;32(3):171–82.

39. Reddi AH. Bone morphogenetic proteins: from basic science to clinical applications. J Bone Joint Surg Am 2001;83(Suppl Pt 1):S1–6.

40. Wikesjo UM, Huang YH, Polimeni G, et al. Bone morphogenetic proteins: a realistic alternative to bone grafting for alveolar reconstruction. Oral Maxillofac Surg Clin North Am 2007;19(4):535–51, vi–vii.

41. Cochran DL, Schenk R, Buser D, et al. Recombinant human bone morphogenetic protein-2 stimulation of bone formation around endosseous dental implants. J Periodontol 1999;70(2):139–50.

42. van den Bergh JP, ten Bruggenkate CM, Groeneveld HH, et al. Recombinant human bone morphogenetic protein-7 in maxillary sinus floor elevation surgery in 3 patients compared to autogenous bone grafts. A clinical pilot study. J Clin Periodontol 2000;27(9):627–36.
43. Nakashima M. Induction of dentin formation on canine amputated pulp by recombinant human bone morphogenetic proteins (BMP)-2 and -4. J Dent Res 1994;73(9):1515–22.
44. Six N, Decup F, Lasfargues JJ, et al. Osteogenic proteins (bone sialoprotein and bone morphogenetic protein-7) and dental pulp mineralization. J Mater Sci Mater Med 2002;13(2):225–32.
45. Gronthos S, Mankani M, Brahim J, et al. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Proc Natl Acad Sci U S A 2000;97(25):13625–30.
46. Seo BM, Miura M, Gronthos S, et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. Lancet 2004;364(9429):149–55.
47. Seo BM, Miura M, Sonoyama W, et al. Recovery of stem cells from cryopreserved periodontal ligament. J Dent Res 2005;84(10):907–12.
48. Lin NH, Menicanin D, Mrozik K, et al. Putative stem cells in regenerating human periodontium. J Periodontal Res 2008;43(5):514–23.
49. Du L, Yang P, Ge S. Stromal cell-derived factor-1 significantly induces proliferation, migration, and collagen type I expression in a human periodontal ligament stem cell subpopulation. J Periodontol 2012;83(3):379–88.
50. Feng F, Akiyama K, Liu Y, et al. Utility of PDL progenitors for in vivo tissue regeneration: a report of 3 cases. Oral Dis 2010;16(1):20–8.