AAP Centennial Commentary: Theme 9

Treatment of Periodontitis: Destroyed Periodontal Tissues Can Be Regenerated Under Certain Conditions

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It is well accepted that a major goal of periodontal therapy is the preservation of the dentition in a state of health and, when indicated, regeneration of attachment apparatus structures lost as a result of the disease.[1] However, over the last century, periodontology's path toward regeneration of a previously destroyed periodontal apparatus has been challenged, even today where debates continue if clinicians should even attempt periodontal regeneration. Periodontal–restorative dilemmas exist as to whether to save a tooth with limited periodontium or extract it and place a dental implant. This American Academy of Periodontology Centennial reflection highlights some of the advances that have paved the way to make periodontal regeneration a clinical reality.

Prior to the era of modern periodontology, the general belief in the field was that the diseased supporting bone around the teeth in periodontitis was infected or necrotic and that it should be eliminated. Given that periodontitis was considered an irreversible loss of connective tissue and supporting alveolar bone, the approaches were primarily resective to remove such contaminated osseous tissue. In 1935, Rudolf Kronfeld demonstrated that the alveolar bone in disease was neither necrotic nor infected.[2] He emphasized that inflammation control was the key to the treatment of periodontitis. Kronfeld, a student of Bernhard Gottlieb, represented one of the first of the group of eminent physician–dentist scientists from Austria who left the University of Vienna to populate dental schools in the United States. During the late 1920s to late 1930s, the Viennese exodus included founders of modern periodontology such as Bernhard Gottlieb, Balint Orban, Peter Weinmann, and Harry Sicher.[3] It was these academicians who greatly influenced the more biologic basis of periodontal diseases and synergized with Chicago-based clinical scholars who had expertise in restorative dentistry. They were able to exploit recent advances in microscopic anatomy and histology to unravel some of the key issues involved in periodontal diseases at that time.

Following Kronfeld's work, Orban (another student of Gottlieb's) extended this approach of targeting inflammation with the surgical treatment of the gingivae and removal of the diseased tissue via gingivectomy.[4] Further along the lines of resection, Saul Schluger emphasized the renewed focus on alveolar bone with his well-recognized concepts on osseous resective surgery.[5] It was his theory which idealized that reshaping the bony topography, not the infection itself, was critically important to a better long-term stability of both osseous and gingival architecture after disease. At the same time, Jens Waerhaug demonstrated that scaling and root planing of a diseased root surface could lead to the resolution of inflammation and re-formation of a normal epithelial cuff.[6] Waerhaug's study was an early example of periodontal "repair," whereby the lost periodontium resulted in healing by tissue that does not fully restore the architecture or the function of the part. In most cases, a long junctional epithelial attachment forms without corresponding supporting structures after therapy. The concept of periodontal "regeneration" was not considered possible as defined as the reproduction or reconstitution of a lost or injured part, i.e., the re-formation of supporting alveolar bone, periodontal ligament (PDL), and cementum.[7]

Despite some of the controversies regarding the possibility, the field began to embrace the concept that the periodontium had regenerative capabilities limited not only to the soft tissue, but that periodontal support could be "repaired" following microbial contamination of the tooth surface. It was believed that once the root was infected, the supporting apparatus in its totality could not be re-formed. The repair concept was demonstrated by Jack Caton, Sture Nyman, and Helmut Zander in a classic histologic study.[8] They evaluated the healing after scaling and root planing or modified Widman flap surgery with/without bone replacement grafts (i.e., autografts or alloplasts). They showed that these "regenerative" treatments failed to result in a new attachment to the diseased root surface, only an epithelial lining.[8]

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The classic *Journal of Periodontology* paper by Tony Melcher, "On the Repair Potential of Periodontal Tissues" (Google Scholar, April 21, 2014; 739 citations), was part of a lecture presentation at the 50th anniversary of the New York University College of Dentistry.[9] Melcher's paper was more of a hypothesis than a study on the compartmentalization of wound healing as a fundamental underpinning that eventually became guided tissue regeneration (GTR). He illuminated the field on the concept that the periodontium's key components of alveolar bone, cementum, PDL, and lamina propria of the gingiva all play crucial roles in periodontal healing and regeneration. He assimilated what was to become stem cell biology for application to periodontal development and repair. Melcher made the analogy of the regenerative capacity within the endosteum of the bone marrow to the lining of the alveolus by the periodontal ligament. He highlighted how both compartments were rich sources of cells possessing a regenerative stem capacity; he also emphasized how the PDL contributed in a major way to the healing that occurs at the periodontal wound site, much like the corresponding bone-covering periosteum with the cambial and fibrous layers. These components are rich sources of determined osteogenic progenitor cells identified by Friedenstein for much of the regenerative capacity of the periodontium.[10] Much later, Seo and coworkers confirmed Melcher's prediction of the multipotent nature of PDL stem cells and their capacity to form different tissues including bone, cartilage, and ligament (Google Scholar, April 21, 2014; 1,334 citations).[11] This notion laid the groundwork for the focus on directed wound regeneration via the exclusion of the lamina propria of the gingiva and epithelium with the progenitor cells present in the PDL.

Sture Nyman, Jan Lindhe, Thorkild Karring, and Harald Rylander tested Melcher's hypothesis in a human case as a proof-of-principle experiment. They questioned whether epithelial exclusion (and now known to also consider wound stabilization) of gingival connective tissue and overlying epithelium could promote regeneration on a previously diseased tooth root surface.[12] In this study (Google Scholar, April 21, 2014; 1,028 citations), a single mandibular incisor with advanced periodontal destruction was treated using a cell-occlusive filter paper between the osseous defect and a full-thickness flap comprising the epithelium and connective tissue. A histologic biopsy specimen was retrieved 3 months after the surgical operation. Based on the microscopic evidence, the authors concluded that the "...new attachment can be achieved by cells originating from the PDL and demonstrates the concept that the periodontitis affected root surface is a major preventive factor for new attachment is invalid."[12] This landmark case report set the stage for more expanded clinical studies in humans.[13,14] The GTR concept has been adapted into the clinical practice setting by the use of non-resorbable and resorbable barrier biomaterials. Cell-occlusive membranes are now used for tooth-related defects and for guided bone regeneration (GBR) of the resorbed alveolar bone ridge.[15,16]

Coinciding with the advances occurring with GTR, regenerative biology was being considered at all levels of periodontal therapy, leaving behind the previously more commonplace resective or reparative surgical approaches.[17] The use of bone grafts and transplants (autografts, allografts, or synthetic biomaterials) had been ongoing. Schallhorn, Hiatt, Froum, and others were showing cases of significant osseous defect fill by bone grafts or transplants in humans.[18,19] However, it was not until the classic three-part series by Bowers and coworkers in the late 1980s whereby more definitive evidence was shown with exquisite histologic characterization of the periodontal apparatus that was regenerated on the previously diseased root surface.[20-22] In this series of studies, bone allografts demonstrated the ability to promote true periodontal regeneration in humans. New attachment including bone, ligament, and cementum was shown at the histologic level, providing the "proof" by definition of periodontal regeneration.

In the late 1990s and early 2000s, the concept of enhancing the regeneration of the periodontium using either purified or molecularly cloned biologic factors was applied to the human clinical scenario. Early application of these modifiers included enamel matrix derivative, a partially purified material from the developing porcine tooth bud applied to periodontal lesions to stimulate cementogenesis and periodontal regeneration.[23-25] Other recombinant molecules were also shown to promote periodontal repair or regeneration in humans including platelet-derived growth factor-BB,[26-28] fibroblast growth factor-2,[29,30] growth and differentiation factor-5,[31] and teriparatide.[32] The use of biologic factors as biomimetic molecules to enhance the regenerative response is based on the rationale of the local enrichment of natural biomolecules that may be deficient in chronic periodontal wound sites. Bioengineering concepts applied tissue engineering[33] (Google Scholar, April 25, 2014; 1,580 citations) for translation to the oral, dental, and craniofacial complex, including the periodontium. There continues to be the study of multi-pronged approaches using cell transplantation, biologics, and scaffolding matrices for the regeneration of tooth-supporting periodontium.[34]

In summary, there have been major advances in periodontal biology for regeneration as a recapitulation of the developmental process.[35] The clinical reality that periodontal structures lost due to chronic microbial biofilms and uncontrolled inflammation can be regenerated offers a strong basis for long-term tooth retention. The future suggests that new regenerative innovations built on this solid foundation can lead to greater predictability and a new era of conservative preservation of the dentition.

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REFERENCES

1. Wang HL, Greenwell H, Fiorellini J, et al. Periodontal regeneration. *J Periodontol* 2005;76:1601-1622.
2. Kronfeld R. The condition of the alveolar bone underlying periodontal pockets. *J Periodontol* 1935;6:22-29.
3. Kremenak NW, Squier CA. Pioneers in oral biology: The migrations of Gottlieb, Kronfeld, Orban, Weinmann, and Sicher from Vienna to America. *Crit Rev Oral Biol Med* 1997;8:108-128.
4. Orban B. Gingivectomy or flap operation? *J Am Dent Assoc* 1939;26:1276-1283.
5. Schluger S. Osseous resection; a basic principle in periodontal surgery. *Oral Surg Oral Med Oral Pathol* 1949;2:316-325.
6. Waerhaug J. Microscopic demonstration of tissue reaction incident to removal of subgingival calculus. *J Periodontol* 1955;26:26-29.
7. American Academy of Periodontology. *Glossary of Periodontal Terms*, 4th ed. Chicago: American Academy of Periodontology; 2001:44.
8. Caton J, Nyman S, Zander H. Histometric evaluation of periodontal surgery. II. Connective tissue attachment levels after four regenerative procedures. *J Clin Periodontol* 1980;7:224-231.
9. Melcher AH. On the repair potential of periodontal tissues. *J Periodontol* 1976;47:256-260.
10. Friedenstein AJ, Chailakhyan RK, Latsinik NV, Panasyuk AF, Keiliss-Borok IV. Stromal cells responsible for transferring the microenvironment of the hemopoietic tissues. Cloning in vitro and retransplantation in vivo. *Transplantation* 1974;17:331-340.
11. Seo BM, Miura M, Gronthos S, et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet* 2004;364:149-155.
12. Nyman S, Lindhe J, Karring T, Rylander H. New attachment following surgical treatment of human periodontal disease. *J Clin Periodontol* 1982;9:290-296.
13. Cortellini P, Pini Prato G, Tonetti MS. Periodontal regeneration of human intrabony defects with bioresorbable membranes. A controlled clinical trial. *J Periodontol* 1996;67:217-223.
14. Gottlow J, Nyman S, Lindhe J, Karring T, Wennström J. New attachment formation in the human periodontium by guided tissue regeneration. Case reports. *J Clin Periodontol* 1986;13:604-616.
15. Buser D, Bragger U, Lang NP, Nyman S. Regeneration and enlargement of jaw bone using guided tissue regeneration. *Clin Oral Implants Res* 1990;1:22-32.
16. Dahlin C, Linde A, Gottlow J, Nyman S. Healing of bone defects by guided tissue regeneration. *Plast Reconstr Surg* 1988;81:672-676.
17. Polson AM, Caton J. Factors influencing periodontal repair and regeneration. *J Periodontol* 1982;53:617-625.
18. Froum SJ, Thaler R, Scopp IW, Stahl SS. Osseous autografts. I. Clinical responses to bone blend or hip marrow grafts. *J Periodontol* 1975;46:515-521.
19. Schallhorn RG, Hiatt WH. Human allografts of iliac cancellous bone and marrow in periodontal osseous defects. II. Clinical observations. *J Periodontol* 1972;43:67-81.
20. Bowers GM, Chadroff B, Carnevale R, et al. Histologic evaluation of new attachment apparatus formation in humans. Part III. *J Periodontol* 1989;60:683-693.
21. Bowers GM, Chadroff B, Carnevale R, et al. Histologic evaluation of new attachment apparatus formation in humans. Part II. *J Periodontol* 1989;60:675-682.
22. Bowers GM, Chadroff B, Carnevale R, et al. Histologic evaluation of new attachment apparatus formation in humans. Part I. *J Periodontol* 1989;60:664-674.
23. Hammarström L. Enamel matrix, cementum development and regeneration. *J Clin Periodontol* 1997;24:658-668.
24. Heijl L, Heden G, Svardstrom G, Ostgren A. Enamel matrix derivative in the treatment of intrabony periodontal defects. *J Clin Periodontol* 1997;24:705-714.
25. Tonetti MS, Lang NP, Cortellini P, et al. Enamel matrix proteins in the regenerative therapy of deep intrabony defects. *J Clin Periodontol* 2002;29:317-325.
26. 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.
27. Jayakumar A, Rajababu P, Rohini S, et al. Multi-center, randomized clinical trial on the efficacy and safety of recombinant human platelet-derived growth factor with beta-tricalcium phosphate in human intra-osseous periodontal defects. *J Clin Periodontol* 2011;38:163-172.
28. Nevins M, Kao RT, McGuire MK, et al. Platelet-derived growth factor promotes periodontal regeneration in localized osseous defects: 36-month extension results from a randomized, controlled, double-masked clinical trial. *J Periodontol* 2013;84:456-464.
29. 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.
30. 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.
31. Stavropoulos A, Windisch P, Gera I, Capsius B, Sculean A, Wikesjö UM. A phase IIa randomized controlled clinical and histological pilot study evaluating rhGDF-5/beta-TCP for periodontal regeneration. *J Clin Periodontol* 2011;38:1044-1054.
32. Bashutski JD, Eber RM, Kinney JS, et al. Teriparatide and osseous regeneration in the oral cavity. *N Engl J Med* 2010;363:2396-2405.
33. Griffith LG, Naughton G. Tissue engineering—current challenges and expanding opportunities. *Science* 2002;295:1009-1014.

34. Rios HF, Lin Z, Oh B, Park CH, Giannobile WV. Cell- and gene-based therapeutic strategies for periodontal regenerative medicine. *J Periodontol* 2011;82:1223-1237.
35. Ripamonti U. Recapitulating development: A template for periodontal tissue engineering. *Tissue Eng* 2007;13: 51-71.

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