



## EDITORIAL

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Regeneration of the periodontium has remained as an enigma for clinicians over years. Although a large body of studies has been able to unravel critical issues concerning cell differentiation, signaling pathways and growth factors involved in periodontal development and regeneration, we are still far away from a predictable treatment that may result in the complete regeneration of periodontal tissues lost by periodontitis. The periodontium is a complex tissue conformed by the gingiva, periodontal ligament, cementum and alveolar bone. Specific cell consortiums and a complex extracellular matrix contribute to the organization of this tissue. The nature and differentiation pathways of cells conforming the periodontium are still an unresolved puzzle. The restricted knowledge concerning the biology of the periodontium has limited advances in this arena. In this editorial I describe some of the main findings concerning periodontal regeneration and future lines of research in this area. It is important to clarify that this is not a complete review of periodontal regeneration, but a concise commentary concerning important issues that might be interesting for clinicians and researchers in this field.

After periodontal debridement the most common response is the formation of a long junctional epithelium. However, periodontal regeneration may be observed in the most apical areas of the lesion, particularly when considering intra-alveolar defects<sup>1</sup>. Moreover, seminal studies showed that when root surfaces are adequately debrided and submerged within the tissues periodontal regeneration occurs<sup>2</sup>. This proof of concept experiment led to important advances in the field. During the early 80's, the first clinical approaches to achieve periodontal regeneration comprised the use of membranes designed to guide the migration and proliferation of soft tissues giving a chance for the re-growth of cementum, alveolar bone and periodontal ligament. In those days the profession embraced the concept of guided periodontal regeneration and several studies followed the initial descriptions performed by

## How far are we from periodontal regeneration?

Nyman, Karring and Lindhe among others<sup>3</sup>. However, clinical application of these concepts showed to be technically demanding and a great variability in treatment response was observed, probably due to differences in the surgical skills of the clinicians and the selection of the clinical case (furcation defects or intra-alveolar defects). These studies stimulated the development of technologies that included non-resorbable / resorbable and structurally reinforced membranes, to support the surgical protocols. One important development derived from these inventions was the application of periodontal membrane to guide bone growth associated or not with implant surgery. With time the initial application of membranes for periodontal regeneration has remained as a specific treatment option with limited application, mainly for experienced surgeons and particular clinical cases.

Studies from Ulf Wikesjö's group have been critically important for the understanding of periodontal regeneration and its limitations<sup>4</sup>. This prolific group has been able to establish several important facts concerning periodontal wound healing. First they showed that the more important effect of membranes is to stabilize the wound allowing an adequate and secure interaction between the blood clot and the tooth surface. This response is probably important for the colonization of the root surface by the remaining periodontal ligament. Second, periodontal wound healing is a relatively fast process and regeneration may be complete in the dog model in about 14 days. Although extrapolation to the human model is not obvious, healing times for periodontal tissues are probably faster than our initial concept about this process.

Another important approach in periodontal regeneration has been the use of enamel matrix proteins. This concept has an interesting biological basis since cementum development is associated with the proliferation and differentiation of cells derived from the enamel organ, namely the Hertwig's Epithelial Root Sheet (HERS). During root formation, the HERS cells that synthesize enamel matrix proteins covers ra-



dicular dentin. By analogy, researchers thought that enamel matrix proteins might be important for the differentiation of cementoblasts<sup>5</sup>. With time, enamel matrix proteins have been shown to be important for cell proliferation and mineralization of tissues. Although a specific effect of enamel matrix proteins on cementum formation is still unclear, the market product Emdogain® has gained a space in the clinical field with different applications. However, clinicians are aware of the unknown effects of this product on true periodontal regeneration.

In recent years, a large amount of studies have been devoted to the identification and application of recombinant growth factors for the regeneration of periodontal tissues<sup>6</sup>. The biological idea behind this concept is interesting but several unsolved issues remain as important challenges in this field. One important question is why the application of one or two growth factors might be so strong to potentiate the differentiation of cells and tissues that may conform the periodontium. Periodontal wound healing, as any wound in the organism, is a complex process and several growth factors, cytokines and matrix proteins may be important to allow tissue regeneration. It is difficult to think that the key resides in only one factor and not in the concert interaction between different cells, signaling molecules and matrix proteins.

Another important area of research concerns with the role of adult stem cells in the periodontium<sup>7</sup>. Several studies have been able to show that stem cells reside in periodontal tissues of adult individuals and may play an important role in the preservation of tissue homeostasis, cell differentiation and proliferation<sup>8</sup>. Given this relevant role for this cell population, pre-clinical and probably clinical studies concerning the utilization of stem cells should give important information for the advancement in this field.

In recent years we have performed studies to identify the role of aging in the wound healing process in gingival tissues. Our studies have identified important defects in wound healing in aging rats and human cells. These deficiencies include a reduced proliferation of fibroblasts, altered granulation tissue remodeling and defects in cell migration<sup>9</sup>. Importantly, future studies should consider whether defects in periodontal regeneration reside in specific deficits associated with genetic abnormalities, aging or diseases that may comprise the wound healing and inflammatory response in the periodontium.

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