Group C
Reactor Paper
Periodontal regeneration - fact or fiction?

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Introduction

In the comprehensive and elegantly written review by Bartold *et al.* in Periodontology 2000, the authors have reviewed all different aspects of periodontal regeneration. At first, the principles of periodontal regeneration are defined as:

1. A functional epithelial seal that should be no more than 2 mm in length.
2. Connective tissue fibers that are inserted into the previously exposed root surface to reproduce both periodontal ligament and the dentogingival fiber complex.
3. New acellular, extrinsic fiber cementum must be reformed on the previously exposed root surface.
4. Alveolar bone height must be restored to within 2 mm of the cemento-enamel junction.

In general, periodontal regeneration is part of the healing process of the periodontal tissues after surgical intervention. Thus, the events and interactions that occur during healing have a substantial impact on the healing result, which normally is characterized by a long junctional epithelial attachment (Caffesse *et al.,* 1995; Beaumont *et al.,* 1984). In order to change the results of healing, which is one of the major goals of regenerative therapy, our understanding of the basic events has to be substantially improved. In several reviews the involvement of growth factors, their interactions and the different cell types have driven knowledge about healing events and the organization of the blood clot, but still the precise mechanisms in periodontal healing and regeneration have not been elucidated (Aukhil, 2000; Caffesse and Quinones, 1993). During the initial phase a fibrin meshwork is established and later organized. Even during these steps variations may occur: recently it has been detected that the properties of the fibrin meshwork change considerably as a reaction to mechanical stress (Weisel, 2008; Weisel, 2007; Weisel, 2011; Varju *et al.,* 2011).

Early periodontal regeneration studies investigated the importance of different components of the periodontal tissues in a series of animal experiments. Based on the results of these studies the concept of guided tissue regeneration (GTR) was established (Nyman *et al.,* 1982a; Nyman *et al.,* 1982b; Nyman *et al.,* 1981; Nyman *et al.,* 1980; Karring *et al.,* 1980; Ellegaard *et al.,* 1974b; Ellegaard *et al.,* 1974a; Ellegaard *et al.,* 1973). This concept introduced the use of a physical barrier in order to guide and change events after periodontal surgery. Even though this clinical concept was established, the basic biological events associated with the noted periodontal regeneration were unknown and not further investigated for many years.

When the GTR concept was introduced into clinical practice failures were experienced and, as a result, some people concluded that the basic biological concept did not work. This was mostly due to the fact that in many cases the original concept and protocols were not meticulously followed and the properties of the materials which were introduced into the periodontal wound were not known. The first human experimental study for periodontal regeneration used a filter paper made of cellulose, which was fixed around the diseased root surface and then the tissues were closed (Nyman, *et al.,* 1982). Afterwards a block biopsy sample was taken and the tooth together with the surrounding tissues was removed. Later on a different barrier was manufactured and was introduced in general practice, which was not made of cellulose but of expanded tetrafluorethylene, which has completely different properties with regard to diffusion, adhesion and wettability. From then on the concept of tissue regeneration was largely based on mechanical interventions.

The first approach to introduce biological factors was based on systematic investigations and observations of the early events of root and ligament formation (Slavkin *et al.,* 1989; Gestrelius *et al.,* 1997; Gestrelius *et al.,* 2000).

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From these studies it was noted that secretion and deposition of enamel matrix proteins on the dentin surface was based on the activity of cells arising from the Hertwig's epithelial root sheath. Hammarstrom (1997) was able to demonstrate a layer of enamel matrix proteins in histological sections in different animals and experimental studies. Enamel matrix proteins would then initiate the differentiation of cells from the dental follicle into cementoblasts (Hammarstrom, 1997; Hammarstrom *et al.,* 1997).

In contrast to these results, others were not able to demonstrate any secretion of enamel matrix proteins by epithelial root sheath cells and questioned this early concept of enamel matrix proteins (Bosshardt, 2008; Nanci and Bosshardt, 2006).

To date, the precise steps of cementoblast differentiation and the importance of enamel matrix proteins in this process are still not known; however, there is an ongoing discussion based on the basic cellular and molecular biological effects leading to the deposition of enamel matrix proteins on the root surface (Nanci and Bosshardt, 2006; Bosshardt and Sculean, 2009).

Despite this fact, there is a very large number of growth factors that have been identified as being important in wound healing and tissue regeneration. Further research so far has not resulted in any major breakthrough with regard to using these biological agents for periodontal tissue regeneration, and the influence of the orchestration of the different cell types that are involved in these complex healing events.

The introduction of the enamel matrix proteins into clinical practice resulted in a large number of clinical studies where it was demonstrated that indeed regenerative therapy using these proteins resulted in clinical gain of attachment and bone healing (Sculean *et al.,* 1999a; Sculean *et al.,* 1999b; Sculean *et al.,* 1999c; Sculean *et al.,* 2000; Sculean *et al.,* 2001; Sculean *et al.,* 2002; Ebersole *et al.,* 1982; Jepsen *et al.,* 2004; Meyle *et al.,* 2004; Jepsen *et al.,* 2008; Meyle *et al.,* 2011; Needleman *et al.,* 2001; Needleman *et al.,* 2005; Needleman *et al.,* 2006). But still the postulates that were formulated as the basis of periodontal regeneration could not be fulfilled, as already stated in the initiator's review (Bartold).

In addition, it is known that during the development of periodontal ligament and root formation, the first events are the interactions of the fiber systems between the periodontal ligament and the dentin (Bosshardt and Schroeder, 1992). These interactions are the result of very complex cellular activity originating from cementoblasts sitting on the fiber system of dentin that is not yet mineralized and connecting the fiber systems in order to achieve a mechanically resistant connection. After the fiber systems have been connected with each other, the whole system mineralizes during the following years, thus leading to the well known periodontal ligament and anchorage of the root in acellular extrinsic fiber cementum (Bosshardt and Selvig, 1997).

Despite the demineralization of the root surface by acids or chelating agents during regenerative therapy, the dentin itself is still mineralized and thus a real interconnection of the different fiber systems does not take place even though a new cementum layer is deposited on top of the cleaned, previously diseased root surface. According to some investigators, regenerative cementogenesis along established but formerly diseased and denatured root surfaces is not achieved in the true sense of the term (Schroeder, 1992).

In many histological samples it is obvious that during sample preparation the covering layer of newly formed cementum is (artificially) separated from the root surface. This does not occur when a natural periodontal ligament is handled in the same way and prepared for histological analysis (Bosshardt and Sculean, 2009). In some specimens, bacteria have been detected on the dentin surface, indicating that this contamination could also be responsible for the gap formation (Bosshardt *et al.,* 2005).

Thus the question arises of how strong the interconnection is between the newly formed cementum layer and the root surface. In addition, the type of mineralized tissue formed is another point of discussion: according to Bosshardt this resembles newly formed bone and not acellular extrinsic fiber cementum (Bosshardt *et al.,* 2006).

Assessment of human histological samples from regenerative procedures have demonstrated periodontal regeneration in terms of new cementum, bone and periodontal ligament. Furthermore, clinical measurements and radiographs have also demonstrated the clinical success of this type of therapy by a combination of reduced probing depths together with gain of clinical attachment. However, to date, it has not been proven that regenerative treatment is really improving the anchorage of the tooth in the surrounding tissues.

As another conceptual problem for this treatment approach, data are missing that demonstrate that through regenerative therapy, either using mechanical barriers or biologically active proteins, the longevity of the tooth is improved, i.e., that this type of treatment avoids tooth loss.

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