Clin Oral Invest (2011) 15:1–2
DOI 10.1007/s00784-010-0503-x

EDITORIAL

Toward a strategic plan for pulp healing: from repair to regeneration

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Received: 5 October 2010 / Accepted: 28 December 2010 / Published online: 14 January 2011

Although the terminology used for repair and regeneration of the dental pulp covers two distinct series of events, implying different therapeutic approaches, quite often the two words are mixed up or used in a very confusing way, suggesting that they are virtually indistinguishable. However, the differences between these two terms underlined here are not only semantic but refer to clinical realities that are not overlapping. Therefore, we feel that there is a need for a clear-cut utilization of these terms.

Challenge 1: pulp repair

The term *pulp repair* should be used for therapies aiming to promote the healing of a pulp that is still alive. This is for instance the case if a carious lesion enters the dentin or after tooth trauma involving the dentin with and without pulp exposure. Clinical symptoms should indicate a reversible lesion. In such cases, repair is occurring after treatment of the injury by indirect or direct pulp capping followed by the placement of a biocompatible restorative material.

If there is no pulp exposure and no clinical signs of irreversible damage, the odontoblasts (and potentially the cells of the Hoehl's layer) synthesize a reactionary dentin, and beneath this dentin-like deposit, the pulp may gradually heal.

After a moderate pulp exposure, direct capping with calcium hydroxide or MTA promotes the recruitment and differentiation of pulp progenitor cells. Stem cells or pluripotent cells taking origin in the pulp are implicated in the production of a reparative dentinal bridge. Due to the efficiency of the capping agent, again, the pulp may recover and spontaneous repair is initiated. This is possible only in the absence of an acute inflammatory process and with a pulp showing sufficient blood supply to promote healing (mainly in teeth of young patients). After a direct pulp capping with $Ca(OH)_2$, under a superficial scar, pulp cells contribute to the formation of a dentinal bridge. Afterwards, the pulp that is still vascularized and alive, isolated from the deleterious agents present in the oral cavity, may resolve gradually the noxious effects of the lesion.

In this context, it has been shown that full-length bioactive molecules such as Bone SialoProtein, or small peptides released after enzymatic cleavage (either as spliced forms of amelogenins: A+/−4, or Dentonin, a peptide of MEPE), are involved in the commitment, proliferation, migration, and terminal differentiation of pulp progenitor cells into odonto/osteoblast-like pulp cells which produce ECM molecules involved in the pulp repair and in the formation of reparative dentin. This phenomenon includes the gradual development of small foci of mineralization within the pulp, merging to form a dentinal bridge. This cascade of events eventually leads to pulp healing. The end point of this process may be the mineralization of the whole pulp chamber or even more.

Generally, pulp repair is up to now an accepted treatment aim in Endodontics with a rather predictable treatment outcome. However, despite the absence of inflammation or other pathological signs, mainly no *restitutio ad integrum* is achieved.

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Challenge 2: pulp regeneration

If the lesion is not treated, the presence of bacteria/toxins and endogenous proteases may lead to extensive inflammatory processes and then to the total degradation of the pulp, which constitutes a non-reversible pulp alteration. Similar situations occur if the pulp is exposed after trauma and not treated in due time. Necrotic debris, pulp remnants, and bacteria/toxins within the root canal need to be eliminated and the lumen cleaned before a classical endodontic treatment, i.e. the tight mechanical filling of the lumen. Such therapy is not biological. The other option still largely speculative at the moment is to regenerate a new pulp. Tissue engineering technologies provide new tools and, in theory, potential answers. Building an "artificial pulp" constitutes a developing option within the scope of regenerative dentistry.

At this point, we are facing several options.

- The first project is to regenerate a pulp that is alive, bearing almost all the functional properties of the original tissue. This strategy intends to produce a non-mineralized tissue with a vascular network and possibly innervated. The clinical relevance of this option has yet to be established, but presumably the presence of such a fully vascularized tissue (artificial pulp) may for instance maintain dentin wetness. As a consequence, this may contribute to preserve the root(s) from perpendicular fractures.
- Following the regeneration of an artificial pulp, as a consecutive step, an optional cascade of events may favor its gradual mineralization. An initial homogeneous mineralized layer forms along the walls of the lumen and finally fills in entirety the root canals. This prospect could be regarded as a perfect filling of the root canal with a densely mineralized homogeneous structure. At the moment, we are not too far from a future clinical application at the chair side.
- Another option, however, would be the generation of an artificial pulp which is able to well control dentin generation. This could be useful for teeth with immature root development at the time of therapy or even for the regeneration of dentin which had been lost, e.g., due to caries. A *restitutio ad integrum* would be possible.

Identification of the genuine cells or bioactive molecules, appropriate 3D scaffolds, cocktails of hormones, growth factors, and signaling factors are still under investigation. In any case, pulp biology and endodontic treatment are coming closer together, and it is time to think about new strategic concepts.