Commentary

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Towards truly Regenerative Endodontic Procedures

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During the last ten years, many research articles have been published on the potential use of Clinical Endodontic Procedures to induce regeneration of dental pulp. Written and published under the umbrella of Regenerative Endodontic Procedures (REPs), these articles do not show enough histological or molecular results which demonstrate the achievement of such a goal, but a partial tissue recovery known as re-vascularization of the dental pulp. In a recent review published in Journal of Endodontics [1], we have addressed this issue comparing available histological information from pre-clinical and clinical REP studies.

The review analyses results from a variety of different in vivo assays using human stem cells from tooth and other sources combined with different growth factors and natural or artificial scaffolds in pre-clinical experiments with animal models. Most of these studies show poor histological results in which odontoblast or sub-odontoblast layers are not recovered completely, abnormal vascularization is obtained and ectopic dentin, bone or cement tissue is formed within the dental pulp complex. Only a few of these studies show appropriate histological recovery in root canal and none of them induce a correct regeneration of the crown dental pulp.

In this work [1], we have also reviewed recent cellular and molecular studies on this topic to provide cues for future developments of REPs. Developmental cell and molecular biology is providing an enormous experimental background from studies on the development or regeneration of several animal species that can be used to support such a clinical transference. Many transcription factors and signal molecules have been studied in their expression during tooth development and the function of only a few of them have been analyzed in knock-out mice. We have focused our attention in those genes potentially involved in dental pulp patterning and growth. HOX and TALE genes, molecular signatures of many developing tissues, are some of these genes expressed in dental tissues, and a knock-out mouse line of TWIST gene shows dental pulp phenotypes similar to those poor results obtained by current REPs. Moreover, several trophic factors have been studied to sustain vitality of dental pulp cells in vitro and in vivo that also provides alternatives to previous procedures.

Our approach in this study is to discuss these results under the concept of positional memory [2] of dental pulp cells and its dependence on a correct molecular signalling from dental pulp niches. During current REPs, such signalling must be provided to circulating or resident stem cells by the blood clot, the Platelet-Rich Plasma (PRP), Platelet-Rich Fibrin (PRF) or the collagen sponge techniques, in order to drive a correct restoration of absent positional cues. During many years, clinical and pre-clinical molecular studies [3-7] have been published to suggest that these signal molecules are entrapped into the dentine matrix during tooth development. If this entrapping preserves the chemical/functional properties and concentrations of many these molecules in the extracellular matrix of the dental pulp, they could represent a library of positional memory signalling potentially useful for new developments of REPs [1,7]. Several treatments have been described which release functional signalling molecules from dentin [5-6,8-11] but scaffolds have not been developed yet to enhance and promote the functional biomimicking of this molecular information.

Other authors have published an interesting example last month in Nature [12], with a new-innovation in REPs that would be benefited with this approach. Antagonists of GSK3, a natural repressor of Wnt positional signalling pathway, were added to collagen sponges and sealed with glass ionomer in an experimental tooth damage model in mouse. After 6 weeks, complete natural dentin repair and dental pulp vitality was obtained but histology of the dental pulp and repaired dentine was still incomplete [12]. This type of experiments could be benefited by the use of appropriate positional molecular markers and/or controlled signal molecule release from dentin.

In conclusion, the point of view presented in our review in Journal of Endodontics [1], clearly opens new developmental venues for REPs. The use of positional memory genes as histological markers, the search of appropriate biomimetic scaffolds to store positional cues to dental stem cells and the

search for appropriate trophic factors to maintain dental stem cells alive could be good steeping stones in the route map towards a true Regenerative Endodontic Procedure.

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