Tissue Injury and Pulp Regeneration

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INVITED EDITORIAL

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Tissue Injury and Pulp Regeneration

Despite the high success rate of traditional root canal therapy, up to 95% under optimal clinical conditions, the idea of pulp (and dentin) regeneration is tempting, at least from the philosophical point of view that a true *restitutio ad integrum* is the ultimate goal of medical therapy. Further reasons for approaches to the regeneration of a functional dental pulp include the wetting of dentin, new dentin formation after caries attack, transmission of pain as an indicator of tissue damage, and active tissue defense mechanisms against invading micro-organisms.

REGENERATION *vs.* VASCULARIZATION

The idea of pulp regeneration is not new: Östby already (in 1961) demonstrated tissue ingrowth into an empty pulp space. However, the term 'pulp regeneration' is justified only if—besides the presence of a vascularized connective tissue—new and functional odontoblast-like cells line the dentin walls of the pulp chamber, which is still a matter of discussion. Recently, clinicians have reported the completion of root formation in immature teeth with necrotic pulps after anti-infectious treatment followed by provocation of bleeding into the root canal. However, the newly formed hard tissue could also be cementum- or osteoid-like, and thus the presence of odontoblasts remains uncertain.

After the early attempts at pulp regeneration, the scene was set for a number of new studies. The tissue engineering concept, delineated by Langer and Vacanti in 1993, which involves stem/progenitor cells, scaffolds for cell growth, and signaling molecules, became the center of interest. Pulp-derived stem/progenitor cells with the potential to differentiate into odontoblast-like cells, among other cell types, are available. More recently, induced pluripotent stem cells (iPS) have been established from dental pulp cells (Tamaoki *et al*., 2010), and cell banking of different HLA-types could provide a match for 80% of the local population for clinical applications (Nakatsuji, 2010).

Various scaffold materials are in use, and numerous relevant signaling molecules have been identified, which can be extracted from their natural reservoir: dentin. However, regenerative approaches for dental pulp or dentin after tissue injury are hampered by the presence of bacteria and inflammation.

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PULP BIOLOGY AND REGENERATION GROUP SYMPOSIUM

Within the Pulp Biology and Regeneration Group (PBRG) of the IADR, this setting sparked the idea of organizing a symposium entitled "Tissue Injury and Pulp Regeneration", which was held in Geneva, Switzerland, in July 2010, with 100 participants from 25 different countries. Thirteen manuscripts based on the oral presentations given at the symposium are now available in *Advances of Dental Research*. Mainly constructed as review articles, they include original data to point out different facets of the interplay between tissue injury and pulp regeneration. The following brief descriptions highlight some of the aspects discussed at the symposium.

STEM CELLS AND CELLULAR DIFFERENTIATION

The treatment aim may be repair, *e.g*., reparative dentin, where the resulting tissue is nearly identical to the original, or regeneration, *e.g*., construction of a new, functional pulp. Along the way, control over ongoing processes (*e.g*., of mineralization) is essential (Goldberg, 2011). Stem cells in conjunction with their respective microenvironment (niche) play an important role, and the exploitation of adult stem cell sources is challenging. Repair processes in the pulp are triggered by apoptotic cells as a consequence of cell injury, and Notch proteins might be important regulators (Mitsiadis *et al*., 2011). The replication of permissive signals for the generation of tubular dentin *via* genetic manipulation of dental stem cells and overexpression of TWIST1 is proposed (Li *et al*., 2011), which stimulates late markers of mineralization such as DSPP.

BACTERIA AND INFLAMMATION

Bacterial infection by oral and food-borne micro-organisms of pulp space and dentinal tubules may impair regeneration or repair. A comparison of specific antibiotics *vs*. non-specific disinfectants is presented (Fouad, 2011). An ambiguous relation

between pulp inflammation and (dentin) regeneration/repair exists: Inflammation may impair or may support dentinogenesis (Cooper *et al*., 2011). The pleiotropic hormone adrenomedullin (ADM) may be a link between both processes. Pattern-recognition receptors (PRR) recognize microbial target molecules; they belong to the TLR and NOD families, and are present on odontoblasts, pulp fibroblasts, and immunocompetent cells. Excessive pulp inflammation may be controlled by receptor antagonists (Staquet *et al*., 2011). Dental monomers like TEGDMA may interfere with the cellular defense system (Schmalz *et al*., 2011). The LPS-triggered cell response is attenuated by TEGDMA, which may affect repair and regeneration due to insufficient bacterial clearance.

DENTIN REGENERATION

Amelogenin and its alternatively spliced forms as signaling molecules or multipotent stem cells derived from tooth germs of transgenic mice for dentin regeneration can induce osteodentin formation (Harichane *et al*., 2011). The specific role of supportive cells (pulp fibroblast or endothelial cells) is shown in several *in vitro* models such as explant tooth cultures; these cells secrete growth factors involved in stem cell activation, migration, differentiation, and neoangiogenesis (About, 2011).

PULP REGENERATION

Impressive data are presented on pulp regeneration in dogs after pulpotomy and pulpectomy (Nakashima and Iohara, 2011). The experiments are based on the isolation of a specific sub-fraction of dental pulp cells that possess angiogenic and neurogenic potential. Successful pulp engineering is described; after removal of the original pulp in a tooth slice, the void is filled with a scaffold laden with pulp-derived stem/progenitor cells (Sakai *et al*., 2011). After implantation into immunocompromised mice, the generated tissue shows a pulp-like morphology with odontoblasts and newly formed tubular dentin. Microvessel formation can be induced by the addition of VEGF, which stimulates the differentiation of pulp-derived stem cells into endothelial cells. Different scaffolds for pulp regeneration are reviewed (Galler *et al*., 2011). Self-assembling peptide hydrogels are described as a model system for a tailor-made matrix carrying growth factors and stem cells, which could be injected into the root canal space to induce pulp regeneration.

FROM BENCH TO CLINIC

Finally, the integration and translation of new information into clinical strategies are discussed (Simon *et al*., 2011). For pulp therapies, the generation of new, tubular dentin and the delineation between reversible and irreversible inflammation are still a challenge. After the loss of dental pulp, the aim is the regeneration of a new pulp-like tissue. Besides many open scientific questions (Goldberg, 2011), strategic concerns also need to be addressed, *e.g*., do we really need odontoblasts, or is a connective tissue inside the pulp chamber an acceptable compromise? Is complete mineralization of the root canal a satisfactory treatment outcome? These and other controversies arising from the existing data and opinions set the starting point for additional research.

CONCLUSIONS

Analysis of the new data presented and the vivid discussion at the symposium illustrate that pulp/dentin regeneration is a highly relevant and active area of research. The elements for dental pulp engineering, namely, stem cells, scaffolds, and differentiation factors, are available, and the interplay among these elements needs to be evaluated further for optimized strategies. Studies as presented here demonstrate proof of principle. At this point, the time for the design and implementation of clinical studies has come, to develop novel therapies within the emerging field of regenerative endodontics.

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