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The Future of Endodontic Therapy: Factors Involved In Pulp Regeneration

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Three factors are implicated in the regeneration of a wounded dental pulp. The interplay between stem cells, scaffold and growth factor constitutes the biological basis for pulp regeneration, a therapeutic approach that will be probably the next future for endodontic treatments, despite all the difficulties still encountered (Nakashima, Akmine 2005; Huang, 2012).

1) Six categories of Stem Cells may be used for the dental pulp regenerative dentistry. Stem cells (SC) are characterized by their properties: they retain their 'stemness', are highly proliferative and capable of regenerating a tissue, they control the self-renewal, have clonogenic properties, and progeny production, by using asymmetric or symmetric divisions. They have a potential for terminal differentiation. Cells such as odontoblasts, osteoblasts, chondrocytes, adipocytes, blood vessels (angiogenesis) and neurons underwent terminal differentiation. They may be used for pulp regeneration. Embryonic stem cells were isolated from the inner cell mass of blastocytes, but ethical considerations arise and they are difficult to obtain. Postnatal or adult pulp stem cells have been characterized. They are issued from mesenchymal stem cells (MSC) or from dental pulp stem cells (DPSC). Permanent human teeth and exfoliated immature primary teeth (SHED) provide the cellular partner necessary to the triad leading to pulp regeneration. Stem cells can also be obtained from the apical papilla (SCAP), the periodontal ligament stem cells (PDLSC), and dental follicle progenitor cells (DFSC). In case of problems due to the restricted supply, induced pluripotent stem cells (IPSs) may be used. Different transcription factors (Oct4, Sox2, Klf4, Myc), contribute to reprogram the adult human cells. This procedure generates embryonic stem-like cells, shown to be efficient for pulp regeneration. The gene expression is positive for MSC markers (CD73, CD90, CD105, and CD146). They are significantly upregulated, whereas the negative MSC marker CD45 is downregulated (Huang 2012; Chrepa *et al*. 2015, Nör & Cucco 2016).

2) Scaffolds are serving as an extracellular matrix for a finite period of time, allowing cell migration and proliferation. Natural and synthetic polymers provide physicochemical characteristics, including the size of the pore, microstructure, interconnectivity to guide tissue formation and the formation of a network of vessels. Scaffolds are three-dimensional structures that provide an initial framework for cells, and can be used to deliver morphogenic molecules. The tooth slice/scaffold model using poly-l-lactic acid (PLLA) has become a very useful model for mechanistic studies. Another approach involves their use of a co-polymer, i.e. poly-lactic-co-glycolic acid (PLGA) in the tooth slice/scaffold. The degradation rate of the scaffold and incorporation of morphogenic molecules constitutes important properties when using the scaffold as a slow release device. Self-assembly peptide hydrogels have several features that make them attractive for dental pulp tissue engineering purposes. They form a nanofiber mesh in a controllable manner, and have relatively low cost. Puramatrix (Bioscience, San Jose, CA, USA), a peptide matrix composed by multiple sequences of arginine (R), alanine (A), aspartate (D) and alanine (A). This scaffold has have been used successfully and promote cell growth and differentiation (Demarco et al., 2011).

3) Morphogenetic signaling molecules: Growth factors (GFs) are proteins that bind to specific cell membrane receptors and induce a cascade of processes. As morphogens, they are regulating cell division and proliferation. Cytokines (TNF-a, TNF-b) are associated with inflammation and immune reactions. Growth factors (amelogenin, TGFs, BMPs) orchestrate epithelial/mesenchymal interactions, regulating the differentiation of adult cells. GFs recapitulate events occurring during embryonic development. GF are released from dentin. They regulate the migration and terminal differentiation of odontoblasts. Growth factors such as TGF β1, PDGF, BMPs, VEGF displayed regenerative properties when they are implanted in dental pulp these proteins have an important role. They include epidermal growth factor (EGF), fibroblast growth factor (FGF), IFN, KGF, VEGF, that enhance the vascularization, and stimulate angiogenesis, granulocyte macrophage colony stimulating factor (GM-CSF), TGF α and β thromboxane A2, the tumor necrosis factor-α family (TNF). The transforming growth factor (TGF)-beta family was originally identified as regulators of cartilage and bone formation and they play an important role in embryogenesis and morphogenesis of various organs and tissues, including teeth. It now established that human recombinant BMPs (rhBMP-2, rhBMP-7) induce dentinogenesis.

The response of dental pulp cells to BMPs suggests that the cells provide receptors for these bioactive molecules. BMP receptors (BMPR) are serine/threonine kinases, including type I receptors (BMPR-IA, BMPR-IB) and the type II receptor (BMPR-II). It was established that dental pulp cells (SHED, DPSC, fibroblasts) express BMPR-IA, BMPR-IB and BMP-II receptor. Bone Marrow Mesenchymal Stem Cells (BMMSC) have the potential to differentiate into osteoblasts, chondrocytes, and adipocytes. MSC appear to be more oriented to odontogenic rather than to osteogenic development. Polyesters of naturally occurring alpha-hydroxy acids, amino-acid based polymers, alginate and natural materials such as collagen and reconstituted extracellular matrix proteins.

Using a similar strategy as that one which was used for isolation of DPSCs, SHED demonstrated to be a population highly proliferative, composed by clonogenic cells, able to differentiate into a diversity of cell types including neural cells, adipocytes, and odontoblasts. SHED express STRO-1 and CD146, two MSC markers also present in DPSC, but SHED exhibited higher proliferation rates than DPSC. SHED differentiated into odontoblast-like cells, expressing three putative markers of odontoblastic differentiation (DSPP, DMP1, and MEPE). The obstruction of bone morphogenetic protein 2 (BMP-2) signaling inhibited the differentiation of SHED into odontoblasts. The growth factors BMP-2, BMP-4, BMP-6, BMP-7 and Gdf11 play an important role in the biology of pulp cells. Studies have shown that the expression of BMP-2 is increased during the terminal differentiation of odontoblasts, and that BMP-7 promotes the formation of reparative dentin mineralization in animal models. Dentin-derived BMP-2 is required for the differentiation of SHED into odontoblasts (Bottino *et al*., 2013).

MMPs and their inhibitors are metalloproteinases that comprise serralysins, astacins, adamalysins (a disintegrin and metalloproteinase domain or ADAMs), and matrixins (matrix metalloproteinases or MMPs). MMPs comprise 25 members. The established functions for MMPs include ECM cleavage of growth factor receptors, shedding of cell adhesion molecules, and activation of other MMPs, which display non-catabolic functions. ADAMs contain a distintegrin or integrin-binding domain, and a metalloproteinase domain that is similar to the conserved Zn2+-binding catalytic domain of MMPs (Hattori., *et al*. 2009). MMP1 facilitates keratinocyte migration over the dermal matrix by decreasing the affinity of collagen-integrin contacts. MMP7 regulates re-epithelialization by cleavage of the E-cadherin within the adherens junctions.

The tissue inhibitors of MMPs (TIMPs) include four family members, TIMP-1 to -4. TIMPs inhibit MMPs in a 1:1 inhibitor to enzyme ratio, through interaction of the N-terminal domain of the TIMP molecule with the active site of the MMP. Degradation of cell adhesion molecules by MMPs is also necessary during the repair phase, where MMP 1, 7, 9, and 10 are required for cell migration, while the addition of a synthetic metalloproteinase inhibitor leads to impaired cell migration. Resorbable materials such as alginate beads include also hyaluronate, chitosan, and collagen scaffold.

Combined altogether, or using cellular or acellular strategies constitute the successful steps for the pulp regenerative therapy, the future of endodontic treatment.

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