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Paediatric endodontics Part 2: Pulp regeneration: current approaches

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Abstract

Dental pulp regeneration: An overview of the current approaches

Regenerative Endodontic Procedures (REPs) are biologically based procedures aimed at restoring the damaged structures and physiological functions of the pulp-dentine complex. Clinically, two strategies have been proposed so far to induce REP: cell transplantation and cell homing. REPs success relies primarily on the clinical and biological conditions of the tooth; therefore, cell homing strategies will not be consistently successful in every condition. Root canal treatment remains the standard of care for mature teeth with necrotic pulps and closed apex.

KEYWORDS Dental pulp regeneration; Cell transplantation; Cell homing.

Introduction

Traumas and dental caries, or variability of dentinal substrate, that compromise adhesion [Campanella, Gallusi, Nardi et al., 2020; Campanella, Gallusi, Di Taranto et al., 2020] in immature teeth may result in pulp damage through bacterial infection [Pinna et al., 2017; Libonati et al., 2019; Gallusi et al., 2020]. In these cases, the tissue also become inflamed, and necrosis can occur. As a result, odontoblast necrosis disturbs root development [Nagata et al., 2014]. After proper and efficient endodontic manual and rotary instrumentation [Libonati et al., 2018; Severino et al., 2019; Campanella, Gianni et al., 2020], traditionally these teeth undergo apexification therapy [American Association of Endodontics,2003]. In this regard, calcium hydroxide and mineral trioxide aggregate (MTA) have been widely used to induce mineralisation and apical barrier formation [Milia et al., 2012; Pinna et al., 2015; Usai et al., 2019; Campanella, Di Taranto, et al., 2020]. However, while apexification promotes apical closure, it does not allow for root development [Damle et al., 2012]. With the aim to provide an apical healing and root maturation, tissue engineering and biotechnology have suggested biological methods [Chieruzzi et al., 2016]. Regenerative Endodontic Procedures (REPs) are biologically based procedures aimed at restoring the damaged structures and physiological functions of the pulp-dentine complex finally leading to apical closure [Eramo et al., 2018]. Nevertheless, the clinical status of the teeth in need of treatment is to be considered in order to achieve the desired outcome [Schmalz et al., 2000]. REPs are based on the combination and interplay of three key elements: appropriate cells (stem or progenitor cells), appropriate signaling molecules to regulate the cellular processes, and a matrix (scaffold) that allows for cellular growth [Diogenes et al., 2013, Schmalz et al., 2017]. In this context, the dental pulp stem cells (DPSCs), the stem cells from the apical papilla (SCAP), stem cells from human exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSC), dental-follicle-derived stem cells (DFSC), and the bone marrow stem cells (BMSCs) have been largely explored [Campanella, 2018] (Table 1). Concerning the signaling molecules, a great number of molecules have been evaluated using several types of *in vitro* assays and animal models with the purpose to induce chemotaxis of endogenous cells, proliferation and differentiation of stem/progenitor cells [Maioli et al., 2015; Moretti et al., 2015; Smith et al., 2016; Wang et al., 2017]. Signaling models have been mainly represented by the stromal cell-derived factor, basic fibroblast growth factor, vascular endothelial growth factor, platelet-derived growth factor, stem cell factor, and granulocyte colony-stimulating factor [Eramo et al., 2017] (Table 2). Regarding the scaffolds, they serve as transient, three-dimensional, extracellular-matrix-mimicking porous templates, which provide mechanical support and regulate cell functions [Li et al., 2005; Bottino et al., 2012]. A wide range of polymer scaffolds have been used with this purpose. Among them, synthetic (i.e. polylactic acid) and natural scaffolds (i.e. collagen), ranging from macroporous structures obtained through salt leaching/solvent casting [Cordeiro et al., 2008] and gas foaming [Huang et al., 2010], to nanofibrous scaffolds processed via electrospinning, self-assembly, and phase-separation. However, there is no single implantable scaffold that can evenly coordinate the growth and development of the different tissue types involved in the functional regeneration of the pulp-dentin complex so far.

Stem Cell Type	Source	Multipotentiality	Main applications
DPSC	Pulp	Osteogenetic, Odontogenetic, Dentinogenetic, Adipogenetic, Condrogenetic, Miogenetic, Neurogenetic	Pulp dentin regeneration
SHED	Pulp	Osteogenetic, Dentinogenetic, Adipogenetic, Condrogenetic, Miogenetic, Neurogenetic	Pulp–dentin-like tissue formation
SCAP	Apical papilla	Odontogenetic, Dentinogenetic, Adipogenetic, Neurogenetic	Pulp–dentin-like tissue regeneration Odontoblast like cells formation
PDLSC	Periodontal ligament	Osteogenetic, Cementogenic, Adipogenetic, Condrogenetic, Neurogenetic	Root and periodontium-like tissue formation
DFSC	Follicle	Osteogenetic, Odontogenic, Cementogenic, Adipogenetic, Condrogenetic, Miogenetic,	Root and periodontium-like tissue formation

TABLE 1 Main types of dental derived stem cells and their applications in REPs.

Strategies in REPs

Clinically, two strategies have been proposed to induce REP: cell transplantation and cell homing.

Cell transplantation is a cell-based approach, which involves the transplantation into the root canal system of exogenous stem cells together with signaling molecules loaded in scaffolds. Collection of cells can be obtained from the host (autologous) or from other individuals (allogenic). Then, the cells are either processed or grown in cultures to increase their numbers. However, this technique involves very complex procedures and the risk of potential contamination and tumorigenesis [Yildirim et al., 2011; Kim et al., 2012].

In the case of cell homing, the tissue repair/regeneration is achieved through chemotaxis of host endogenous cells via biological signaling molecules [Laird et al., 2008; Mao et al., 2010]. Compared with stem cell transplantation, cell homing is easier to perform, because there is no need to isolate and manipulate stem cells *in vitro* [Kim et al., 2013; Huang and Garcia-Godoy, 2014]. Bioactive scaffolds impregnated with growth factors are injected into the pulpless root canal to induce migration, proliferation and differentiation of endogenous stem/progenitor cells from the root apex [Kao et al., 2009; Chieruzzi et al., 2016]. The stem cells from the apical papilla may play an important role in this technique. At the base of the process, however, an effective root canal disinfection and appropriate size of the apical foramen are required to allow cell migration, new vascularisation and innervation [Laureys et al., 2013]. Existing cells, biomaterials, and the oral cavity's natural chemistry are used to synthesize a natural-like microenvironment needed for REP.

Conclusion

Despite significant progress, vasculogenesis/angiogenesis and neurogenesis/re-innervation remain a significant challenge in REPs treatments. The success relies primarily on the clinical and biological conditions of the tooth needing the treatment; therefore, cell homing strategies will not be consistently successful in every condition. Techniques using nanofibrous scaffolds added to antibiotics are promising in this field, but further investigations are required. Currently, root canal treatment remains the standard of care for mature teeth with necrotic pulp and closed apex.

DPSC	Recombinant human Bone Morphogenetic Proteins 2 or 4
SDF-1	Stromal cell Derived Factor
BFGF	Basic Fibroblast Growth Factor
PDGF	Platelet Derived Growth Factor
SCF	Stem Cells Factor
G-CSF	Granulocyte Colony-Stimulating Factor
VEGF	Vascular Endothelial Growth Factor
TGFβ1	Transforming Growth Factor beta 1

TABLE 2 Main types of Growth Factors used in REPs.

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