



Regenerative Endodontics: Biologically Based Treatment Strategy for Management of Immature Necrotic Permanent teeth - A Paradigm Shift in Endodontics

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Abstract

It is well known fact that management of an immature, necrotic permanent teeth which result due to dental trauma or caries, pose a great challenge among dental specialist. It is difficult to treat such teeth using conventional endodontic procedures because of presence of wide periapical apex, thin root dentine walls, and wide root canal space. To manage such teeth traditional methods of treatment including CaOH₂ apexification and MTA apexification have been introduced. However, both of these procedures are associated with their own drawbacks. Therefore, tissue engineering technology engulfed this field which resulted in inception of a novel treatment strategy termed as "Regenerative Endodontic Procedures." For the successful outcome of this novel treatment modality, triad of tissue engineering critical factors are highly essential without these factors, an empty canal space will not support new growth of tissue from the periapical area into the root canal space. These critical factors are stem cells, growth factors and bioactive biomimetic physical scaffolds. The aim of the present research paper is to enlighten about a promising technology which results in regeneration of new pulp-dentine complex.

Keywords: Apexification procedure, Immature permanent tooth, Necrotic teeth, Non-vital tooth, Open apex, Regenerative Endodontic procedure.

INTRODUCTION

Endodontics is a dental specialty that treats trauma and infections involving the dental pulp, dentin, and periapical lesions. During this 21st century endodontics is being reinvented and redefined as a result of advances in cellular biology, microscopy and digital technology along with reconceptualization of how to clean and shape the root canals [1]. The primary purpose of endodontic therapy is the prevention or treatment of pulpal diseases. Although traditional endodontic procedures that treat apical periodontitis by disinfection of the root canal system followed by placing an intracanal restoration called as obturation, is not considered a biologically based procedure and hence would not focus on regenerating a functional pulp-dentin complex. Therefore, 'Regenerative Endodontics' is emerged as a novel domain in the endodontics arena which is the creation and delivery of tissues to replace diseased, missing, and traumatized pulp [2]. The regenerative capability of a living creature was recorded as early as 330 BC, when Aristotle observed that a lizard could grow back the lost tip of its tail. Since then, there have been slow but steady attempts at understanding the regenerative capabilities of human being [3].

Regenerative endodontic procedure can be defined as biologically based procedures designed to replace damaged structures, including dentin and root structures, as well as pulp dentin complex. Regenerative dental procedure has a long history originating around 1952, when Dr. Hermann reported application of Ca (OH)₂ in case of vital pulp amputation [4]. Presently two concepts exist in regenerative endodontics to treat non vital infected teeth or the vital teeth. One is the active pursuit of pulp-dentine regeneration to implant or regrow pulp based on tissue engineering technology and the other in which new living tissue is expected to form from the tissue present in the teeth itself, allowing continued root development which is termed as revascularization [5].

Revascularization method assumes that the root canal space has been disinfected and the formation of blood clot yields a matrix like fibrin that traps cells capable of initiating new tissue formation. Regenerative endodontic procedures and revascularization of the root canal in the teeth with infected root canal systems have been termed as a paradigm shift in the treatment protocol for endodontic management [5].

Recently, there has been a substantial and growing public and scientific awareness of a relatively new field of applied biological research called tissue engineering, which is increasingly being viewed as having enormous clinical potential. This field builds an interface between materials science and biocompatibility, and integrates cells, natural or synthetic scaffolds, and specific signals to create new tissues [6]. In the field of tooth engineering encompassing regenerative endodontics, efforts have been made to explore mesenchymal stem cells (MSCs) such as stem cells from human exfoliated deciduous teeth (SHEDs), adult dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), stem cells from apical part of the papilla (SCAPs), stem cells from dental follicle (DFSCs), bone marrow derived mesenchymal stem cells (BMSCs) and epithelium originated stem cells. In addition to stem cells, different types of physical scaffolds are available which is one among the three major factors needed for regeneration of pulp-dentine complex. The third major factor that is also essential in this intricate process of regeneration is growth factors. Therefore, the aim of the present article is to briefly review the available literature pertaining to regenerative endodontics which represents a paradigm shift in conventional endodontics domain [7].

Discussion

Review of Literature

Biological solutions to the repair and regeneration of the dental tissues

Regenerative medicine offers many advantages for the treatment of disease with its aim of replacing or regenerating human cells, tissues or organs to restore or establish normal function. And within dentistry there is exciting future potential for engineering whole teeth. Nevertheless, several challenges still exist before such tooth replacement therapies can be clinically implemented in dental practice. Paramount among these challenges is programmed development of appropriate crown and cuspal morphology for occlusal function and engineering of the tooth/periodontium interface to allow normal oral function.

Use of scaffolds of defined morphology may assist with overcoming some of the morphologic challenges. Considerable recent interest in the concept of regenerative endodontics has led to reports of engineering of individual dental component tissues, which provides a more achievable goal in the shorter term. Seeding of pulp cells isolated from exfoliated primary teeth in a simple polylactic acid scaffold within a dentine slice before subcutaneous implantation in vivo has allowed engineering of tissue with the same appearance and structure as normal pulp [8].

For regeneration to occur in the dentin-pulp complex, there is both a requirement for cells to secrete new tissue and for appropriate molecular and cellular signaling to occur, to enable cells to secrete the newly regenerated tissue. One can therefore envisage regeneration being determined by the following [9]:

- A permissive environment in which regeneration can occur
- Cells capable of secreting the extracellular matrices of the dentin-pulp complex
- Secretion of molecular signals and cell-cell interactions to occur for up regulation of cellular synthesis and secretion of new dentin-pulp tissue.

Molecular events in Dentin-Pulp Regeneration [10-14]

The signaling of cellular differentiation and secretory regulation for dentinogenesis is closely controlled in temporospatial terms through epithelial-mesenchymal interactions between the cells of the tooth germ [10]. These interactions, many of which are recapitulated during repair and regeneration in the mature tooth, have a molecular basis. Understanding these molecular signaling events is crucial to not only initiating pulpal regeneration but also to controlling subsequent cellular activity in the tissue, where overall tooth architecture must be maintained if pulp-canal obliteration is to be avoided. Several aspects of molecular signaling of cellular events are of critical importance in regenerative endodontics as mentioned below:

- Recruitment of stem/progenitor cells
- Induction of odontoblast-like cell differentiation
- Upregulation of odontoblast-like cell synthetic and secretory activity
- Stimulation of pulpal revascularization
- Control of odontoblast-like cell activity to preserve crown and root architecture.

It seems likely that several molecules can provide a stimulus for cellular migration in the pulp, including various growth factors, cytokines, and extracellular matrix molecules. Once recruited, the differentiation of these cells perhaps shows close parallels to tooth development whereby signals from the inner-enamel epithelium induce odontoblast differentiation in cells at the periphery of the dental papilla through the intermediary action of the dental basement membrane [15].

Although an epithelial-derived source of signaling is absent in the mature tooth, an alternative source can be found within the dentin matrix. Isolated dentin-matrix components have been demonstrated to induce reparative dentinogenesis in a pulp-capping situation, which reflects a long-recognized observation that dentin chips have similar effects. Dentin matrix, in fact, contains a plethora of non-collagenous components in addition to the collagen and mineral generally recognized to comprise this matrix. Many of these non-collagenous components have significant biological activities, and dentin should therefore be considered as a bioactive matrix rather than the more traditional view of it as an inert tissue with primarily a mechanical role [16].

Many growth factors and cytokines are reported as sequestered within dentin matrix during its secretion, and it is probable that many others will be identified too. Release of these growth factors during carious demineralization of the tissue may signal odontoblast-like cell differentiation for dentin-pulp regeneration in a parallel manner to the role of enamel organ signaling during tooth development. The presence of angiogenic growth factors in dentin and the demonstration of the action of these matrix-derived molecules in signaling angiogenic events suggest ways by which pulpal revascularization may be promoted, which will be of fundamental importance to pulpal regeneration. Regulation of odontoblast or odontoblast-like cell secretion during reactionary and reparative dentinogenesis, respectively, is critical to maintenance of the tooth's normal architecture and avoidance of pulp-canal obliteration [17].

Translational opportunities for Dentin-Pulp Regeneration [18-21]

Stimulation of regeneration in the inflamed pulp following caries or trauma, however, provides the opportunity to make significant contributions to preservation of pulp vitality and improvements to the currently unsatisfactory long-term survival rates for many dental restorations. The challenge, however, perhaps lies in assessing the disease status of each individual case and tailoring treatment planning to reflect this. There is commonly an assumption that pulp regeneration should only be attempted in immature teeth with open apices, and there may be merit in being a little more ambitious than this in case selection. More focused control of bacteria and inflammation may also aid in the realization of such a goal [21].

Potential complications/Undesired outcomes of regenerative endodontics procedure

Although revitalization procedures are designed to heal bone and promote root development, potential complications and undesired outcomes must be addressed with patients and guardians before treatment. These complications include potential tooth discoloration, adverse reaction to intracanal antibiotics, and treatment failure [22].

Tooth discoloration after revitalization procedures has been demonstrated in several case reports/series. The likely cause for bluish-gray discoloration reported in some cases is minocycline from medicaments placed in the canal space; the removal of which eliminated tooth discoloration. Another approach to prevent discoloration is to place a root canal projector (CJM Engineering Inc, Santa Barbara, CA, USA) into the access, seal the coronal dentin with composite, and then remove the projector and place the triple antibiotic paste in the canal. Discoloration can also be avoided by using Ca (OH)₂ paste. If discoloration does occur after the placement of a minocycline-containing paste in the canal, sodium perborate bleach can be used in the tooth internally [23-25].

Another potential source of discoloration resulting from revitalization procedures is the placement of mineral trioxide aggregate (MTA). Both gray and white MTA have been shown to discolour dentin following placement in the canal. To avoid potential discoloration from MTA, the MTA could be placed apical to the esthetic zone, but this placement would necessarily decrease the potential for revitalization in the coronal portion of the canal, thus eliminating the potential for increased root wall thickness in the cervical area. Alternatively, a different pulp space barrier, such as glass-ionomer could be used [26].

A potentially more serious consequence of using antibiotics in the canal space is an allergic reaction. Allergic reactions have been reported after topical use of the antibiotics in the triple antibiotic paste. There are no reports, however, of allergic reactions after the use of these antibiotics in root canals. Nonetheless, patients and guardians should be informed of the possibility of a reaction and asked about related allergies [27].

Another potential outcome of the revitalization procedure is the failure of the apical bone to heal and/or tissue to grow into the canal space, or apical bone to heal. This may be evidenced radiographically by a persistent or enlarging apical radiolucency, and/or the lack of root development. Persistent pain, swelling, or sinus tract would also indicate failure of the treatment. If any of these signs or symptoms should occur, alternative treatments should be considered, including apexification, nonsurgical root canal treatment, or extraction [28].

Dental regenerative treatments and guided tissue regeneration already save millions of teeth each year. Researchers are aiming to develop enhanced regenerative therapies that have the capability to regenerate teeth and tissues beyond current limits. This will require the development of new protocols using stem cells, scaffolds, and growth factors. Several

bioengineering approaches involving stem cells, scaffolds, and growth factors can be combined to regenerate the different tissues needed to generate a tooth and its supporting tissues [29].

Despite the initial promise, regenerative endodontics has encountered substantial barriers in clinical translation. Dental pulp stem cells may seem to be a priority choice for dental pulp regeneration. However, dental pulp stem cells may not be available in patients who are in need of pulp/dentin regeneration therapy. Even if dental pulp stem cells are available autologous or perhaps allogeneically, one must address a multitude of scientific, regulatory, and commercialization barriers; unless these issues are resolved, the transplantation of dental pulp stem cells for dental pulp regeneration will remain a scientific exercise rather than a clinical reality [30]. These barriers include cell isolation; ex vivo manipulation with the potential for changing cell phenotype; and safety issues, including immune-rejection, potential contamination, pathogen transmission, and potential tumorigenesis. Excessive costs associated with these issues in addition to shipping; storage; handling issues; and regulatory difficulties, including unclear pathway and the general inability to ensure batch-to-batch consistency in cell quality, cast multidimensional questions for the practicality of cell transplantation. Cell homing offers an alternative to cell transplantation for dental pulp/ dentin regeneration. Biomaterial scaffolds are another area of innovation in regenerative endodontics. Several natural and synthetic polymers have shown positive results in vivo. Preclinical animal models and randomized clinical trials that test novel therapies are indispensable for translating regenerative technologies into clinical therapies [10-15].

The ready availability of DSCs makes them a viable source of adult MSCs for regenerative medicine applications. Human dental stem/progenitor cells that have been isolated and characterized include DPSCs, SHED cells, SCAP cells, PDLSCs, and DFPCs. Although much work is required for the translation of data from in vitro and animal studies to viable clinical applications, there are exciting possibilities for the use of DPSCs in tissue engineering and regenerative medicine applications within the root canal, the oral cavity, and in other parts of the body [18-20].

Finally, the relative ease with which DSCs can be obtained, coupled with interest in stem cell banking, will likely drive research that further elucidates their characteristics and potential applications.

Finally, in order to apply stem-cell-based therapies to the treatment of diseases, the appropriate microenvironment must be identified to guide the development of stem cells through the following 6 steps [30-32]:

1. To increase survival of stem cells in the recipient/transplant.
2. To integrate the transplanted cells into the surrounding tissue without harming the recipient; research strategies must be created to avoid the problem of immune rejection without long-term use of immunosuppressive drugs.
3. To increase the proliferation of stem cells to generate sufficient amounts of tissue.
4. To induce the differentiation of stem cells into the desired cell types.
5. To maintain the differentiated cells and retain their functions throughout the recipient's life.
6. To remove unwanted cells.

CONCLUSION

With today's 21st century technological advancements, it is expected that individuals will like to either retain their natural teeth or obtain functional tooth replacements throughout their entire life. There is a need for biologically based endodontic procedures that offer the potential to replace tissue lost because of trauma or disease. Although there are still significant scientific hurdles to overcome, it now seems more certain that, with the continued growth in the knowledge base and armamentarium, a regenerative endodontic concept that was once was only imagined will become reality constituting a fully functional regenerated pulp-dentin complex. The development of regenerative endodontics may make those other procedures not needed such as extraction and implant replacement, especially with the expectation that both hard tissues like dentin and enamel and soft tissue like innervated and vascularised dental pulp tissues would become a normal and successful following regenerative endodontic procedure. Therefore, the domain regenerative endodontics definitely represents a paradigm shift from the conventional/traditional endodontic procedure like apexification procedures.

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