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Dental Pulp Stem cells and its application in Regenerative Endodontic Therapy- Literature review

[1]Shaima Shafiq, BDS, Goregaon Dental Centre

[2]Naval Ghule, BDS, Goregaon Dental Centre

[3]Amar Shaw, MDS Public Health Dentistry, Goregaon Dental Centre

Corresponding Author: Shaima Shafiq, BDS, Goregaon Dental Centre

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Introduction

Dental caries is a global burden that millions suffer from.[1] The World Health Organization (WHO) defines dental caries as a local pathological process of the extra-somatic background that results in enamel decalcification, decomposition of dental hard tissue, and, as a result, the formation of a dental cavity.[2] The Global Burden of Disease (GBD) study has consistently shown that oral health is a major neglected global population health challenge.[3] According to the WHO Global Oral Health Status Report (2022), oral diseases affect approximately 3.5 billion people worldwide, with three out of every four people affected living in middle-income countries.[4] Furthermore, caries of permanent teeth affect an estimated 2 billion people worldwide, while primary tooth caries affects 514 million children.[4] Estimates from the Global Burden of Disease Study (2019) revealed permanent dentition has a lower caries prevalence than deciduous dentition in more developed countries.[5] Restoring this defect has been a long-standing problem in the field of restorative dentistry.[1]

Currently, pulp capping (direct or indirect) is the only clinical option for preserving pulp vitality.[1] Vital pulp therapy/pulp capping procedures aim to treat compromised dental pulp by utilizing synthetic materials such as MTA and Ca(OH)2 to stimulate reparative dentine formation without complete removal of the healthy pulp.[6] This technique however has shown variable outcomes, frequently associated with reinfection and irreversible inflammation of the pulp.[1] Most vital pulp therapies are reported to have a failure rate of 45% after five years and can go up to 80% after ten years.[1]

When the pulp is beyond repair, root canal treatment (RCT) is performed, which involves the removal of the pulp and replacement with inorganic biomaterials (gutta-percha and sealer cement).[7] Endodontic therapy has a high success rate and currently considered the most practical treatment protocol available.[8] This treatment, however, renders the tooth non-vital and brittle, along with many other clinical complications like periapical lesions due to incomplete pulp removal or recontamination of the root canal.[1,8]

Limitations of these current clinical therapies and interventions to restore the damaged tissues and failure to overcome them have paved the way for an alternative approach for the progressive regeneration of injured tissues which has piqued the interest of many in the field of endodontics.[1,7,9]

This new alternative of tissue engineering that involves the use of living cells or living cells combined with natural or inert extracellular components in the development of biological substitutes for replacements is becoming available to clinicians.[10] The use of tissue engineering therapies is the foundation of regenerative endodontic treatments (RET).[6,8]

According to the American Association of Endodontists' Clinical Considerations for a Regenerative Procedure, the primary goal of the regenerative procedure is the elimination of clinical symptoms and the resolution of apical periodontitis.[11] As a result, regenerative endodontics and traditional non-surgical root canal therapy share the same primary goal.[11]

Dental tissue regeneration has been an exciting area of research for many years.[6] Many regenerative procedures that include guided tissue or bone regeneration(GTR, GBR) have been developed over the years.[8] In 1952, Hermann reported the use of Ca(OH)2 in a case report of vital pulp amputation.[8] Operative dentistry techniques have been attempting regenerative treatment for a long time, using materials like MTA and Ca(OH)2 to stimulate reparative/reactionary dentine formation, with varying degrees of success.[8,6]

The concept of pulp regeneration first appeared in 1963, when Ostby demonstrated tissue ingrowth into an empty pulp space following the introduction of a blood clot.[6]

Advances in tissue engineering and biotechnology have opened up new avenues for developing biological pulp treatment methods.[6] Based on several studies, dental pulp regeneration could be achieved by cell transplantation and cell homing techniques.[9] The former approach being a cell-based therapy, however, involved many complex procedures such as tooth extraction, pulp extirpation, isolation of stem cells, in-vitro cell culture, and ex vivo cell expansion along with its storage and shipping.[6] Therefore, the cell-based approach exhibited questionable clinical and economic viability despite its scientific validity.[9,6]

The main objective of regenerative endodontics procedures is designed to replace the cells of the pulp dentin complex with viable cells, preferably of the same origin to restore the physiologic unit.[12] Recent studies done in an ectopic animal model (Kim et al. 2010) have shown cell homing as a better alternative to the former cell-based approach as it may avoid many of the challenges associated with cell transplantation.[9] As there is no need to isolate and manipulate stem cells in vitro, it may be easier to perform clinically.[7,9]

Following early attempts at pulp regeneration, several new studies based on Langer and Vacanti's tissue engineering concept were done, which involves the triad of stem/progenitor cells, scaffolds for cell growth, and growth factors.[6] The possible cell sources used include dental pulp stem cells (DPSCs), apical papilla stem cells (SCAP), and bone blood stem cells (BMSCs).[6]

Stem cells are considered primitive cells with progenitor cell properties such as self-replication and multi-directional differential potentiality, and this novel approach uses progenitor pulp stem cells from induced periapical bleeding and extracellular matrix scaffolds introducing platelet-derived growth factors into the canal space for possible pulp tissue regeneration.[9,8,13,14] Stem cells are considered the key to tissue generation, about ten years after the discovery of dental pulp stem cells pulp/dentine regeneration was achieved in small and

large animals using exogenously transplanted dental stem cells.[7]

Although introducing endodontic tissue engineering therapies poses significant challenges, the potential benefits to patients and the profession are equally revolutionary, giving patients a clear alternative to the currently available treatment plans.[8,15]

The objective of this review article is to discuss the current state of knowledge, goals, and challenges of regenerative endodontics, as well as descriptions of potential techniques that will make RET a possible reality.[8]

Triad of Tissue Engineering

Pulp is regarded as one of the most difficult tissues to regenerate because of its unique anatomic and physiological nature.[13] Tissue engineering offers possibilities to restore the natural function of the tooth and over the years various new ideas have been proposed leading to advancements in regenerative endodontic techniques.[15] Various biological methods have been studied that use certain bioactive factors to create regenerative therapies.[14]

In 1993, Langer and Vacanti described the triad of stem/ progenitor cells, scaffolds for cell growth, and growth factors, and these factors have been major areas of research (Fig. 1).[6,8] These three biological elements are often combined to create a favorable microenvironment for the regeneration to take place.[15]

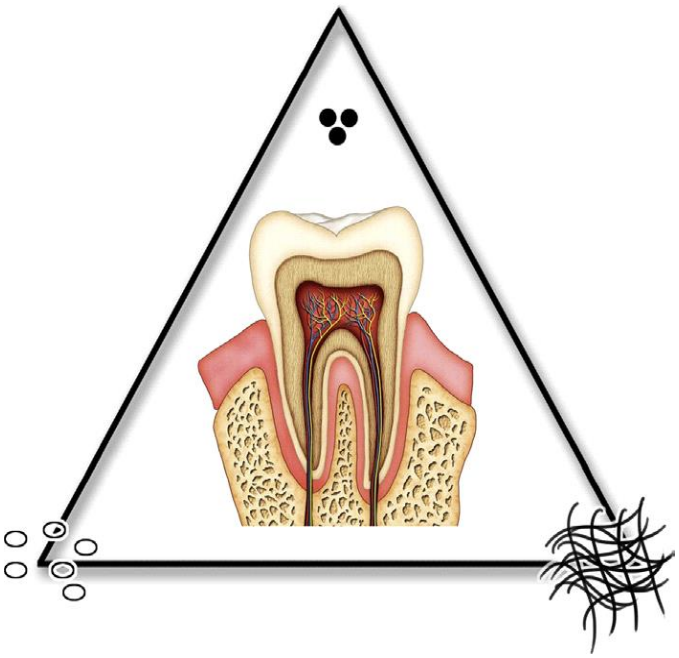

Figure 1: Triad of tissue engineering.

Stem Cells

Stem cells are undifferentiated embryonic or adult cells that divide continuously.[12]

post-natal stem cells derived from the umbilical cord, bone marrow, peripheral blood, and body tissues including pulp tissues of teeth have been studied over the years.[15]

Teeth can be considered the most natural, non-invasive source of stem cells which can be collected in a comparatively easy and affordable manner.[16]

Since their discovery, many other varieties of multipotent dental stem cells capable of differentiating into odontoblast-like cells have been reported.[17]

The five types of postnatal mesenchymal stem cells (MSCs) reported are:[18]

- Dental pulp stem cells (DPSC)
- Stem cells of human exfoliated deciduous teeth (SHED
- Stem cells of apical papilla (SCAP)
- Dental follicle progenitor cells (DFPC)
- Periodontal ligament stem cells (PDLSCs)

Dental pulp stem cells (DPSC)

The breakthrough for the use of stem cells in dentistry was when Gronthos (2000) isolated these odontogenic stem cells from the dental pulp of wisdom teeth and referred to them as dental pulp stem cells (DPSCs).[16,19] DPSCs are multipotent stem cells and can be used for various dental and medical therapies.[20] Several studies have also been done on animals that have demonstrated dentin-pulp complex regeneration using DPSCs acquired from permanent teeth.[17]

The function of DPSCs can be attributed to the regenerative potential of the dental pulp.[16] Human DPSCs (HDPSCs) have been studied due to their ability to differentiate into odontoblasts and osteoblasts.[11] These 2 cells are known to have the ability to replace damaged bone and dentin-pulp tissues with healthy ones.[11]

Features of DPSCs

- Potential to form densely calcified nodules [16]
- Even after cryopreservation, DPSCs retain their stem cell properties.[16]
- Capable of regenerating pulp and dentin.[16]
- Can be expanded in vitro and differentiated into osteoblasts chondrocytes and adipocytes.[16]
- Low morbidity rate after being extracted from the pulp. [16]
- Viable after crypreservation.[21]
- Non-immunogenic and favorable anti-inflammatory abilities.[16]

Collection and isolation of DPSCs

DPSCs can be acquired easily from orthodontic extracted teeth like premolars and wisdom teeth.[14] Various techniques can be used to isolate these cells from the pulp.[14] This includes a small-sized cell population isolated by enzymatic digestion of whole pulp tissue, using immune magnetic methods or separating cells based on fluorescence.[17]

SHED Cells

In 2003, Miura M reported that SHED cells can be isolated from exfoliated deciduous teeth and are capable of inducing dentin and bone formation.[19] Like DPSCs these cells are also capable of differentiating into osteoblasts, odontoblasts, and adipocytes along with neural cells.[19]

After in-vivo transplantation, they were seen to differentiate into dentin-like tissues suggesting their potential for pulp generation.[21]

When compared to DPSCs, these cells have shown a higher proliferation rate and osteogenic differentiation.[21] SHEDs have also exhibited gene expression profiles that were different from the formerly mentioned cells.[19] Due to these features they may be considered excellent sources of regenerative endodontic therapies.[19]

Collection and isolation of SHED cells

SHED cells can be collected from primary teeth that have no pathology or even those extracted early for orthodontics reasons.[16] After collecting this freshly extracted tooth, they are carefully sealed into a thermette.[16] This is done to maintain their hypothermic state while transporting.[16] These cells are then isolated from the pulp chamber after the tissue digestion is done using collagenase Type 1 and dispase.[16]

SCAP cells

This variety of MSCs was first isolated by Sonoyama W (2006) from the apical papilla of human immature permanent teeth.[22] These cells exist only during the stage of root development and are found at the tips of these roots.[21] Like DPSCs and SHEDs, these cells can also differentiate into osteo/dentinogenic, neurogenic, and adipogenic cells.[23] More in vivo studies are thus required to confirm their potential in pulp regeneration.[23]

DFPC cells

Experiments using implants found these cells to differentiate into cementum in vivo and in vitro.[21] These cells not only regenerate periodontal ligament-like tissues in vivo, but they also regenerate periodontal tissues via epithelial-mesenchymal interactions.[21] Due to these features they are fast gaining popularity in the field of regenerative medicine.[21]

PDLSC cells

In vitro studies suggested that these cells are capable of repair and regeneration of the PDL structure.[21] PDLSCs differentiated into cementoblast-like cells, adipocytes, and collagen-forming cells under controlled conditions.[24] These cells, therefore, hold the potential for the reconstruction of tissues lost by periodontal diseases.[24]

SCAFFOLDS

Scaffolds if the second component of tissue engineering.[8] The American Society for Testing Materials (ASTM) defines scaffold as "the delivery vehicle or matrix that can promote binding, migration or transport of bioactive molecules used for tissue regeneration".[6] It's a 3-D structure in which pulp stem cells can be organized to create a more practical endodontic tissue engineering therapy.[8]

These porous scaffolds are seeded with PSCs providing structural support to aid faster tissue development.[15] These scaffolds may also contain nutrients and antibiotics that can promote cell growth and prevention of microbial growth within the canal space.[15]

Requirements for scaffolds:

- Should be biocompatible[6]
- Incorporate growth factors to help the proliferation and differentiation of stem cells.[8]
- Undergo gradual biodegradation.[6]
- Should have high porosity and enough pore size to facilitate the seeding and diffusion of stem cells.[8]
- Surface adhesion for cell regeneration/differentiation into various dental tissues.[6]
- Should be able to alter mechanical, physical, and biological properties when required.[6]
- Should not cause an inflammatory reaction and is non-cytotoxic.[18]
- Must be able to replicate the original extracellular matrix of the tissue from which it is derived.[21]

Scaffolds materials

Bleeding is provoked intentionally within the periapical tissues to provide blood clots as a scaffold.[9] This is done to introduce platelet-derived growth factors and mesenchymal stem cells into the canal space to regenerate pulp tissue.[9]

Earlier it was suggested to use blood clots from within the canal space as matrix/scaffold to promote pulp tissue healing.[17] Later on, clinical procedures done on immature teeth by T.W. Lovelace (2011) showed that evoked periapical bleeding brings fibrin scaffold along with the delivery of MSCs and growth factors into the canal space.[17] However, it was not always possible to induce periapical bleeding into the canal space as it might lead to severe tissue destruction.[9]

Platelet-rich plasmas (PRP) have therefore been used as an alternative to the blood clot.[9] It was thought that these alternative scaffolds might improve the regeneration process as they are rich in growth factors.[9] These, however, have not shown any superior outcomes in RETs.[9]

This eventually led to the introduction of various other scaffold materials that showed improved outcomes.[6]

Natural (derived from plants, animals, microbes)

These scaffolds are known to mimic the extra-cellular matrix.[6] Although they have the advantages of good structural strength, bioactivity, and biodegradability,

they are often difficult to process and carry the risk of immune reaction.[6]

Natural scaffolds can be classified as:[6]

1. Materials inspired by the extracellular matrix

E.g.: hyaluronic acid, gelatin, collagen

2. Based on structure:[6]

a. Proteins and peptides

E.g.: Fibrin, silk protein, Self-assembling peptides

b. Polysaccharides

E.g.: alginate, cellulose, chitosan

Synthetic (artificial materials)

These scaffolds offer good biocompatibility and structural strength and can be altered to possess a wide range of structural, mechanical, and chemical properties depending on the applications.[6]

1. Synthetic polymeric scaffolds

E.g.: Polylactic acid (PLA), polyglycolic acid (PGA), and polylactide-coglycolide

(PLGA)

2 Bioactive ceramic scaffolds

E.g.: Calcium phosphate ceramics, bioactive glasses, and glass ceramics

3. Composite scaffolds

Hydrogels

They have been shown to improve the proliferation and differentiation of stem cells along with the formation of mineralized tissues.[6]

E.g.: Fibrin, hyaluronic acid, collagen, alginate Poly (ethylene glycol) (PEG), polyfumarate Collagen with poly (ethylene glycol)

SAP (self-assembling peptide hydrogel)

Advanced scaffold materials[1]

Polyelectrolyte-coated polymeric scaffolds

Cell adhesive-nonadhesive scaffolds

Spatially-controlled stimuli-responsive scaffolds

Multifunctional recombinant polymer scaffolds

Growth Factors

The third component of tissue engineering is growth factors/morphogens.[6] Growth factors are extracellular matrix-bound polypeptides or proteins produced by immune-inflammatory and tissue cells.[9]

If regenerative endodontics is to have a significant impact on clinical practice, it must first and foremost focus on providing effective therapies for restoring lost dentinal structure and regenerating functioning pulp tissue.[15] Many studies have reported that dentin may be considered a reservoir of a variety of growth factors that can stimulate tissue responses.[15,18] Dentin and pulp contain a variety of bioactive molecules, including cytokines, growth factors, and matrix molecules, which are thought to promote reparative and regenerative events after injury.[18] Recent REPs emphasize the use of growth factors derived from dentine and platelets.[18] Once released, these growth factors may play a key role in signalling pulp-dentin repair.[15]

Morphogens can be used to control various stem cell activities by binding to specific receptors on the surface of target cells.[8,12,18] This includes stem cell proliferation, differentiation, chemotaxis, or stimulation of stem cells to synthesize and secrete mineralized matrix.[8] These biological molecules can be delivered along with the stem cells to the root canal space via apical bleeding.[13] The blood clot when used as a scaffold allows the controlled release of these morphogens.[9]

Growth factors can be pretty flexible, stimulating cellular division in a wide range of cell types, whereas others are more cell-specific.[25]Many growth factors like platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF), colony-stimulating factor (CSF), and epidermal growth factor (EGF) can be used to mediate stem cell proliferation,

whereas, factors like vascular endothelial growth factor (VEGF) can be used as regulators of angiogenesis.[25]

Platelet-Derived Growth Factor (PDGF)

PDGF is a growth factor released by platelets that promote angiogenesis and cell proliferation.[26] PGDF in the injury site can induce chemotaxis and proliferation of mesenchymal stem/progenitor cells.[26] Induced blood clot formation in dental pulp causes the platelets to release PDGF-containing a-granules and attract neutrophils and macrophages.[26]

Studies done by Yokose S (2004) on rat DPSCs reported PDGFs do not have much effect on the formation of the dentin-like nodules.[26] These factors, however, can be seen to stimulate fibroblast proliferation and dentin matrix protein synthesis.[26]

In vivo studies done using root canal treated human teeth have shown de novo formation of dental pulp–like tissues when implanted in rats. (Kim JY et al,2010).[26]

Bone Morphogenic Proteins (BMPs)

BMPs are a subgroup of the TGFb superfamily that is involved in a variety of biological activities such as cell proliferation, differentiation, and apoptosis.[26] They also have strong osteoinductive and chondrogenic effects.[26] BMPs and BMP receptors (BMPRs) direct mesenchymal stem cell differentiation, which modulates the development of calcified tissues.[27] Several BMP-like molecules have been identified in vertebrates and invertebrates, many of which are crucial in dental engineering.[27] The successful retrieval of growth factors and BMPs from mammalian teeth could provide a significant alternative for effective tooth engineering.[27]

In vivo and in vitro, BMP2 can be seen to stimulate the differentiation of dental pulp stem/progenitor cells into odontoblasts.[26] BMP2 has been used as a surface coating on scaffolds, causing a reduction in pore size and improved adhesion and proliferation of BMP-MSCs.[27]

During crown formation, BMP4 is secreted by MSCs and regulates cell differentiation in the dental epithelium.[28] It also promotes elongation and cell proliferation in HERS cells, implying that it could be used as a root-formation agent in tissue engineering applications.[28]

When placed over amputated dental pulp in macaque teeth, BMP7, also known as osteogenic protein 1, was seen to promote dentin formation.[29,30] BMP7 has been shown to have a dentinogenic effect on amputated dental pulp in several other animal models, including rats, ferrets, and miniature swine.[26]

Transplantation of BMP11 in amputated dental pulp in dogs was reported to induce the formation of dentin-like tissues.[26] Ultrasound-mediated gene delivery of BMP11 stimulated odontoblastic differentiation of DPSCs in vitro and reparative dentin formation in vivo.[26]

Cytokines

Cytokines also known as immunomodulatory proteins or polypeptides are often used interchangeably with growth factors as share similar actions.[26] The effects of pro-inflammatory cytokines, such as IL-1 and TNF, were investigated by Xuechao Yang and associates (2012).[31] It was found that these cytokines had the potential to induce odontogenic differentiation of DPSCs.[31]It was also suggested that IL-1 and TNF produced in the early inflammatory reaction might be able to induce the mineralization of DPSCs.[31]

Delivery of Biological Molecules

Growth factors can be released in a controlled manner using scaffolds.[13] If these biological molecules are not released using a carrier or scaffold, their biological effect might wear off quickly.[13] As a result, the biological molecules involved in cell differentiation and tissue formation should have a controlled release profile for the

biological effects to be sustained in the later stages of regeneration process.[13]

To be functional throughout the process of regeneration, growth factors can either be delivered by being incorporated within scaffolds or by using microspheres as the delivery vehicle.[13]

Cell Homing

The infected dental pulp is traditionally treated with RCT, in which all dental pulp is removed and the pulp space is filled with artificial inorganic materials.[21] These teeth however have lost their vitality and eventually become brittle, making them prone to post-operative fracture.[21] Thus, coming up with alternatives to preserve the pulp vitality has become crucial.[21]

The basic idea behind cell homing for dental regeneration is to promote tissue regeneration by directing host endogenous cells to damaged pulp tissue via signaling molecules.[21]Pulp revascularization and cell homing-based RET are the 2 strategies proposed for pulp regeneration.[21]Both of these are considered cell-free RET because they are performed without the use of exogenous cells.[21]

Pulp revascularization of permanent teeth could be thought of as a cell-homing strategy for pulp regeneration.[7] It includes a 2-step protocol that has been studied over the past decade.[7] In this technique blood acts not only as a scaffold but also as a source for signaling.[21]

In this method, bleeding was induced within the canal of immature teeth.[6] These studies show radiographic evidence of continued root end development and formation; however, histologically, the regenerated tissue is cementum-like or osseous-like tissue rather than dentin.[6]

In cell- homing based RET, however, bioactive cues encapsulated into biodegradable scaffolds are used.[6] And when these are released into endodontically treated root canals, stem/progenitor cells migrate and are homed in vivo into the root canal, resulting in pulp regeneration.[6]

Apart from many in vitro studies published over the years, preclinical research on immunocompromised animal models has also been carried out to address the clinical potential of stem cell transplantation.[32] Complete pulp regeneration with adequate vasculature and innervation has been observed in pulpectomized root canals of dogs.[32] In 2008, Cordeiro and his associates did a study involving SHED cells.[33] These cells were seeded in biodegradable scaffolds which were transplanted into immunocompromised mice.[33] It was observed that the architecture and cellularity of the resulting tissue closely resembled dental pulp.[33] Moreover, in 2013 pre-clinical efficacy and safety tests were performed in dogs using mobilized DPSCs, which resulted in complete pulp regeneration with the formation of coronal dentin in the pulpectomized root canal and no evidence of toxicity.[32] Thus, scientific evidence of the safety and efficacy critical for clinical applications has been presented based on the findings of these pre-clinical trials.[32] In vivo experiments used various cell-homing molecules in both mature and immature teeth from humans or animals.[7] Almost all of the studies obtained regenerated connective pulp-like tissues in the emptied root canals and pulp chambers without the use of transplanted cells, relying solely on host endogenous cells.[7]

Data analysis of RET clinical protocols was done in 2015 and it was revealed that RET protocols varied significantly throughout all studies.[9] The treatment outcomes seemed to differ depending on the protocol used.[9] This has made the evaluation of true outcomes of RET in the literature quite impossible.[9] Therefore, from both a clinical and research standpoint, RET requires a

standardized clinical protocol and strict outcome criteria.[9]

Challenges of RET

Regenerative therapy promises numerous clinical dental benefits, including biological strategies for tooth repair and tooth regeneration.[34] Regardless of the impressive growth in RETs, there are several drawbacks that must be addressed in to improve the treatment's quality and efficiency.[34]

Some of the challenges include:

- Crown discoloration after RETs.[35] According to Kim et al, tooth discoloration is primarily caused by the use of minocycline in the triple antibiotic paste.[36]
- From a practical standpoint, obtaining autologous dental stem cells is quite difficult, and even more so from a subpopulation of stem cells.[34] Although stem cells are present in all teeth, only a small number of teeth meet the criteria for stem cell extraction.[34]
- Stem cells isolated from adult tissues are frequently difficult to expand in vitro and do not retain their phenotype.[8]
- The need for a suitable vascularized scaffold to promote the formation of large tissue constructs.[34] Requirement of an appropriate vascularized scaffold study using scaffold-based approaches often relies upon *in vivo* maturation of a small scaffold.[34]
- The main disadvantage of growth factors is that it takes a different set of growth factors to induce stem cells from different sources to differentiate.[34] Along with safety, the quantity and timing of growth factors are significant challenges.[34]
- Another issue that has been reported after regenerative endodontic treatment of necrotic immature teeth disinfected with calcium hydroxide is root canal calcification/obliteration.[37]
- Unpredictable histological outcomes of current treatment protocols of animal studies.[36]
- Finally, patient compliance with the multiple appointments.[35] The required time for disinfection of the root canal space with triple antibiotic paste or calcium hydroxide and an increased number of clinical sessions.[36]

Many theoretical mechanisms must still be investigated for clinical applications and real tissue regeneration to be successful.[14] Existing in vivo animal studies have yet to identify a viable pathway applicable to humans.[7] By overcoming these barriers, regenerative endodontics by cell homing might be clinically easier to perform and also economically convenient.[7]

Conclusion

The main goal of endodontic therapies is to be able to maintain pulp vitality which is essential to the tooth's functional life. For many years, operative dentistry techniques have experimented with regenerative treatments. Regenerative endodontic strategies are constantly being updated and improved in order to benefit the field of dentistry. RET is capable of resolving apical periodontitis and eliminating clinical symptoms/signs in patients. Furthermore, they have also shown the potential to promote continued root maturation of immature permanent teeth affected by necrotic pulp/apical periodontitis.

Despite the developments of the last few years, they are still in the preclinical stage. The procedures attempted were able to successfully produce root development but have failed to re-establish real pulp tissue and have presented unpredictable results. Further research is needed to achieve clinical translation of pulp regeneration via cell homing strategy.

Apart from the various studies on ectopic animal models being done, cell-homing strategies must also be tested in orthotopic models, first in animals and then in humans. Randomized, prospective clinical trials are needed to compare the clinical outcomes of regenerative endodontic therapy and non-surgical root canal therapy for immature and mature teeth with necrotic pulps. Also, from both a clinical and research standpoint, RET requires a standardized clinical protocol and strict outcome criteria.

To a certain extent, the topic of regeneration of pulp-dentin complex has been very obscure. And this is due to the diverse, and complicated structural and functional characteristics of dental tissues.

Although the concept of tissue engineering is very different from traditional endodontic therapies, it is hoped that this new approach of using dental stem cells, scaffolds, and signaling molecules for pulp generation will one day be accomplished. While there are still some challenges to overcome in regenerative endodontics, there are several advantages and benefits for patients in terms of tooth maintenance, function, and longevity.

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