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Regenerative Endodontics

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Abstract

Despite root canals are a successful treatment for many disorders today regenerative therapies in which healthy pulp tissues are substituted for damaged or necrotic pulp tissues to revitalise the teeth may be an optimal form of therapy. It's crucial to develop a regeneration therapy for the dentin-pulp complex to get around the problems with currently available treatments.

Keywords: Pulp–dentine complex, regenerative endodontics, stem cell, scaffold, tissue engineering

Introduction

Although many diseases can be successfully treated with root canals today, an ideal form of therapy might include regenerative methods whereas healthy pulp tissues are substituted for diseased or necrotic pulp tissues to revitalize the teeth. Due to the significant risk of problems, such as root fracture or the unintentional injection of fluids or filling materials beyond the wide root apex, conventional endodontic treatment of permanent teeth with incomplete root development is not possible[1]. Two techniques-apexogenesis and apexification are generally accepted in the endodontic care of immature teeth.

There is currently a lot of interest in the regenerative endodontic technique, which Banchs and Trope proposed in 2004. The phrases revitalization and revascularization are frequently used interchangeably in the literature. These terms refer to biological processes that promote the regeneration of tooth tissues, including the development of the pulp-dentine complex and the roots. A framework for developing tissue, stem cells, and growth factors is required in the root canal for this process to take place. After regenerative procedures, angiogenesis, reinnervation, and the differentiation of cells responsible for root formation are the main activities that take place in the root canal. As a result, living pulp, bone, cementum, or periodontal-like tissue forms in the canal and roots begin to form.

Numerous techniques, including pulp implantatiorevascularization, and postnatal stem cell therapy, have been developed by regenerative endodontics. Revascularization has been effectively used in clinical settings recently, giving dentists amazing outcomes. Regenerative endodontics is crucial in resolving these issues because root canal therapy failure and posttreatment problems are on the rise. Preventing aggressive, intrusive instrumentation and radiography exposure must be the objective. The reimposition of B $ T lymphocytes, which support defence against the pathogens causing pulp damage, is how this is accomplished. The tooth's vitality is

maintained and the canal is entirely sealed, preventing periapical reinfection and tooth fracture. The idea of tissue engineering is used in regenerative endodontic procedures (REPs) to repair the root canal system to a healthy state, enabling the continuity of development and regeneration of the root and the tissues around it (He et al., 2017).

The main goals of regenerative endodontic procedures primarily target the resolution of Apical Periodontitis (AP), induction of apical closure, and increased root canal wall thickness and length of juvenile teeth, to conserve and preserve the remaining tooth structure as well as enhancing its survival (Endodontistso AAo, 2016). Regarding these goals, the conservation and preservation of teeth in a functional state is a substantially equivalent goal shared by regenerative endodontic procedures and Minimally invasive endodontics (MIEs) endodontic ideas. In other words, whereas Minimally invasive endodontics seek to maintain the original tooth structure, Regenerative endodontic procedures attempt to restore it.

The study of tissue engineering focuses on the functional restoration of tissue structure and physiology in tissues that have been harmed or hindered by cancer, disease, or trauma. Revascularization is the process through which the original vascularity of the pulp of a wounded immature tooth is restored after injury. On the other hand, revitalization refers to general vital tissues rather than only blood vessels. Such revascularization/ revitalization therapy for developing teeth with non-vital pulp produces apexogenesis, which leads to tissue regeneration. By restoring root development and strengthening dentinal walls, the strength of the root and long-term retention of the tooth are strengthened. Such a treatment method is an effective substitute for traditional apexification techniques[2].

The dental pulp is enclosed by highly structured mineralized tissues that make up the complex organ known as the tooth. Different mineralized tissues can regenerate in various ways. The odontoblasts promote the enamel-producing ameloblasts, which are derived from ectoderm. After the creation of the enamel matrix, these cells experience apoptosis since they cannot regenerate[3]. Ectomesenchyme gives rise to odontoblasts and cementoblasts, which produce dentin and cementum, respectively. These cells can only regenerate to a certain extent. At the pulp-dentin interface, progenitor cells generated from the pulp produce tertiary dentin in cases of minor injuries. By separating the pulp from the injured tooth structure, secondary dentin aids in protecting the vitality of the pulp. To make up for the passive eruption of the tooth, cellular cementum is also deposited at the root apex throughout life, much like dentin.

Regenerative endodontics is regarded as a different treatment option from apexification in human dentistry and is now a branch of therapeutic endodontics.

Dentin/Pulp Complex

The development of dentin/pulplike tissue is one of the crucial requirements for successful dentin/pulp regeneration, but angiogenesis and neurogenesis are also necessary. It should be emphasised that the freshly differentiated odontoblasts from the dentinal wall are responsible for generating the deposited dentin-like tissues on the existing dentin structure. within the limits of the root canal. Currently, two main goals are being pursued by prospective techniques for improving stem cell-mediated dentin/pulp regeneration: first, inducing angiogenesis, and second, promoting tissue mineralization.

1. Limitations of Conventional Therapy for Preservation of Dental Pulp.

The dental pulp is sometimes affected by external stimuli such as caries infection or traumatic injury. Preservation of dental pulp and maintenance of its viability are essential to avoid tooth loss, and dentists carry out restorative procedures with pulp capping to regulate inflammatory responses of dental pulp, or cement lining on a cavity floor to block external stimuli. Reversible damage induces pulp wound healing, and direct pulp capping and pulpotomy with calcium hydroxide are known to be effective to induce pulp wound healing mechanisms. After external stimuli such as cavity preparation, apoptosis of pulp cells including odontoblasts is induced followed by pulp wound healing including reactionary and reparative dentinogenesis. Reactionary dentin is formed by surviving odontoblasts, whereas reparative dentin is formed by odontoblast-like cells that are differentiated from

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pulp cells of the residual dental pulp, resulting in a reduction in dental pulp size and vitality[4].

When external damage to dental pulp induces irreversible changes in the pulp, dentists carry out pulpectomy. Generally, a root canal after pulpectomy is tightly filled with biomaterials such as gutta-percha to prevent reinfection by bacteria. However, a tooth without vital dental pulp has lost its defensive ability, which is often followed by severe damage such as the progression of deep radicular caries or tooth fracture, resulting in the extraction of the tooth. Furthermore, a treated tooth is often reinfected by bacteria because of its complicated anatomical structure or inadequate treatment by a dentist, resulting in the formation of a lesion around the root apex with bone resorption. The success rate of endodontic retreatment is lower than that of pulpectomy. To overcome these limitations of the present endodontic treatment, the preservation of the dentin pulp complex is the clear strategy.

2. Regeneration of the Dentin-Pulp Complex.

It is well known that growth factors, such as bone morphogenetic proteins (BMPs) and fibroblast growth factors (FGFs), stem cells, and scaffolds, are essential for tissue engineering to regenerate tissues. During regeneration processes, stem cells differentiate into specific cells for tissue defects, growth factors such as BMPs and FGFs induce proliferation and differentiation of stem cells, and scaffolds with properties of extracellular matrix temporally support structures for cell growth, differentiation, and tissue formation. In studies to develop the regeneration therapy of the dentin-pulp complex, three strategies that utilize these essential three factors have been proposed; regeneration of the entire tooth, local regeneration of the dentin-pulp complex in dentin defect area from residual dental pulp, and regeneration of dental pulp from apical dental pulp or periapical tissues including the periodontal ligament and bone.

Tissue Engineering In Endodontics

The discovery of biological substitutes that can preserve, restore, or enhance tissue function is the goal of the newly growing multidisciplinary area known as tissue engineering. Dentin, pulp, cementum, and periodontal tissues are among the tissues of interest in regenerative endodontics. To replace unhealthy, diseased, or dead tissues, the field of tissue engineering has grown over the past ten years. Hard and soft tissue deformities owing to trauma (such as vehicle accidents), congenital defects (such as cleft palate), and acquired diseases (such as cancer, and periodontal disease), as they relate to the oral-maxillofacial apparatus, constitute a serious health issue An extracellular matrix scaffold, morphogens, or growth factors, and stem cells are the main components of tissue engineering.

The main goals of current clinical methods for tissue replacement and reconstruction were to reduce discomfort and to regain mechanical stability and function. Autogenous grafts, allografts, and synthetic materials (alloplastic) are some of the current treatment options for missing tissues. Even though each of these medical advancements and treatment philosophies has been successful, they all have their drawbacks, Because humans do not have considerable reserves of extra tissue for transplantation, one of the main drawbacks of both autografts and allografts is this. Morbidity at the donor site, structural and anatomical issues, and high levels of resorption after healing are some additional limitations, especially those about restoring missing bone[5].

The use of medical devices and whole tissue grafts has undergone a clear and noticeable hypothetical shift in regenerative medicine to a more explicit approach that uses specific bioactive, biodegradable synthetic or natural scaffolds combined with cells and/or biological molecules to create a functional replacement tissue in a diseased or damaged site.

Over the past 50 years, there have been several phases in medical research involving the use of biomaterials to replace tissue function, each of which has been characterised by a set of materials and developmental achievements. For instance, in the 1950s, metal implants and related devices were widely used, and the consequences on the surrounding tissues, much alone the cells, were not given much consideration. Researchers considered both biological and synthetic materials when using polymers and synthetic materials during the 1970s and 1980s. material characteristics. More recently, a clear and focused effort has been made to design and employ both natural and biodegradable scaffolds, as well as to provide the materials with advanced biological consideration[6].

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Stem cells

The most valuable cells for regenerative medicine are thought to be stem cells. Advancements in our understanding of how an organism grows from a single cell and how healthy cells replace damaged ones in adult creatures are being made possible by research on stem cells[7].

Stem cells can divide repeatedly to replicate themselves (self-replication) or to create specialised cells that can develop into a variety of other cell or tissue types (multilineage differentiation).

Classification Of Stem Cells

1. Based on origin-:
    1. Embryogenic stem cells
    2. Stomatic/adult/postnatal/mesenchymal stem cells
2. Based on the source-:
    1. Autologous: obtained from the same individual to whom they will be implanted.
    2. Allogenic: obtained from the donor of the same species.
    3. Xenogenic: obtained from a donor of another species.
    4. Syngenic: obtained from genetically identical organisms; twins; clones research animal.
3. Based on potency (range of differentiation)-:
    1. Totipotent: can differentiate into all embryonic and extra-embryonic cell types.
    2. Pluripotent: can differentiate into all types of cells except cells of the embryonic membrane.
    3. Multipotent: can differentiate into more than one mature cell.
    4. Unipotent: can differentiate into only one type of cells.

Types Of Stem Cells

1. Early Embryonic Stem Cells

The first step in human development occurs when the newly fertilized egg or zygote begins to divide, producing a group of stem cells called an embryo. These early stem cells are totipotent, i.e. possess the ability to become any kind of cell in the body.

2. Blastocyst Embryonic Stem Cells

Five days after fertilization, the embryo forms a hollow ball-like structure known as a blastocyst. Embryos at the blastocyst stage contain two types of cells: an outer layer of trophoblasts that eventually form the placenta and an inner cluster of cells known as the inner cell mass that becomes the embryo and then develops into a mature organism. The embryonic stem cells in the blastocyst are pluripotent, i.e. having the ability to become almost any kind of cell in the body.

Scientists can induce these cells to replicate themselves in an undifferentiated state for very long periods before stimulating them with appropriate signalling molecules to create specialized cells. However, the sourcing of embryonic stem cells is controversial and associated with ethical and legal issues, thus reducing their appeal for the development of new therapies[8.]

3. Fetal Stem Cells

After 8 weeks of development, the embryo is referred to as a fetus. By this time it has developed a human-like form. Stem cells in the fetus are responsible for the initial development of all tissues before birth. Like embryonic stem cells, fetal stem cells are pluripotent.

4. Umbilical Cord Stem Cells

The umbilical cord is the lifeline that transports nutrients and oxygen-rich blood from the placenta to the fetus. Blood from the umbilical cord contains stem cells that are genetically identical to the newborn baby. Umbilical cord stem cells are multipotent, i.e. they can differentiate into a limited range of cell types. Umbilical cord stem cells can be stored cryogenically after birth for use in future medical therapy.

5. Adult Stem Cells

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This name is rather misleading because infants and children also have stem cells. Thus the term Postnatal Stem Cells is preferable. These stem cells reside in tissues that have already developed, directing their growth and maintenance throughout life. These cells are also multipotent.

Adult stem cells typically generate the cell types of the tissue in which they reside. However, some experiments over the last few years have raised the possibility of a phenomenon known as plasticity, in which stem cells from one tissue may be able to generate cell types of completely different tissue.

Postnatal stem cells have been found in almost all body tissues, including dental tissues. To date, four types of human dental stem cells have been isolated and characterized: i) Dental pulp stem cells (DPSCs) (10), ii) Stem cells from human exfoliated deciduous teeth (SHED) (11), iii) Stem cells from apical papillae (SCAP), and iv) Periodontal ligament stem cells (PDLSCs).

Among them, all except SHED are from permanent teeth. The identification of these dental stem cells provides a better understanding of the biology of the pulp and periodontal ligament tissues and their regenerative potential after tissue damage.

6. Progenitor Cells.

Stem cells generate intermediate cell types before they achieve their fully differentiated state. The intermediate cell is known as a precursor or progenitor cell. It is believed that such cells usually differentiate along a particular cellular development pathway. Generally, undifferentiated cells are considered to be progenitor cells until their multi-tissue differentiation and self-renewal properties are demonstrated and they become designated as stem cells

7. Dental Pulp Stem Cells.

In the dental pulp of adult teeth, there is a population of clonogenic cells with a high proliferative capacity – the DPSCs. These cells were successfully isolated by enzymatic digestion of pulp tissue after separating the crown from the root.

Dental pulp stem cells are multipotent cells that proliferate extensively (maintained for at least 25 passages), can be safely cryopreserved, possess immunosuppressive properties, and express markers such as CD13, CD29, CD44, CD59, CD73, CD90, CD105, CD146 and STRO-1, but do not express CD14, CD24, CD34, CD45, CD19 and HLA-DR.

The plasticity of DPSCs has been verified through in vitro and in vivo studies. DPSCs can differentiate into odontoblast-like cells, osteoblasts, adipocytes, neural cells, cardiomyocytes, myocytes and chondrocytes.DPSCs can form mineralized nodules with a dentine-like structure under osteoinductive conditions in vitro and reparative dentine-like tissue on the surface of human dentine in vivo. DPSCs transplanted with the carrier hydroxyapatite/tricalcium phosphate (HA/TCP) produce a dentine-like structure lined with human odontoblast-like cells and surrounded by pulp-like interstitial tissue. Thus, DPSCs can differentiate into osteoblasts in Vivo and produce bone-like tissue.

8. Stem cells from human exfoliated deciduous teeth.

Miura et al. (2003) reported the potential to obtain stem cells from human deciduous teeth. As DPSCs, these multipotent cells are derived from dental pulp explants or by digestion of dental pulp tissue and have immune suppressive properties.

The morphology of SHEDs, also termed immature, is similar to that of DPSCs, SCAPs and DFPSCs. SHEDs have a higher proliferation rate than bone marrow mesenchymal stem cells (BMMSCs) and DPSCs and express Oct4, CD13, CD29, CD44, CD73, CD90, CD105, CD146 and CD166, but do not express CD14, CD34, or CD45.

Stem cells isolated from the pulp tissue of exfoliated deciduous teeth are capable of differentiating into a variety of cells, such as neural cells, osteoblasts, chondrocytes, adipocytes and myocytes.

After transplantation subcutaneously on the dorsum of immune-compromised mice, SHEDs form ectopic dentine-like tissue but are unable to regenerate the dentine/pulp-like complex. These results suggest that SHEDs can differentiate into odontoblasts in vivo. Thus, the mineralized tissue generated by SHED in the pulp space of tooth-slice scaffolds had morphological features of dentine, including the presence of dentinal tubules and predentine, which distinguishes it from osteoid tissue.

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Stem cells from human exfoliated deciduous teeth are also capable of repairing critical-size parietal defects in immune-compromised mice; however, the bone generated by these cells lacks haematopoietic marrow elements.

In addition, the neural developmental potential was studied by injecting SHEDs into the dentate gyrus of the hippocampus of immune-compromised mice. These studies showed that SHEDs can survive for more than 10 days inside the mouse brain microenvironment and express neural markers such as neurofilament M (NFM).

9. Stem cells from Apical Papilla

A potentially new type of stem cell has been discovered in the apical papilla of human immature permanent teeth. The distinction between the dental pulp and the apical papilla is that the apical papilla represents a precursor tissue for the radicular pulp.SCAPs obtained by explant cultures or enzymatic digestion of apical pulp tissue are derived from a developing tissue that may represent a population of early stem/progenitor cells. SCAPs may thus be a superior cell source for tissue regeneration. SCAPs express mesenchymal markers, such as CD13,CD24,CD29,CD44,CD73,CD90,CD105,CD106 and CD146and do not express CD18, CD34, CD45, or CD150

Stem cells from the apical papilla also can undergo osteo/dentinogenic, neurogenic, and adipogenic differentiation. SCAPs display an expression pattern of osteo/dentinogenic markers and growth factor receptors similar to that observed in DPSCs, but these markers are expressed at lower levels in SCAPs than in DPSCs. Despite these findings, the myogenic and chondrogenic differentiation potential of SCAPs has not been determined. Furthermore, in several cases of apexogenesis in an infected immature tooth with periradicular periodontitis or abscess, SCAPs could induce root formation.

When ex vivo-expanded human SCAPs were transplanted into immune-compromised mice with HA/TCP as a carrier, the typical dentine structure was regenerated. Dentine-forming cells were stained with antihuman-specific mitochondrial antibodies, suggesting that the donor-derived human SCAPs contributed to dentine formation.

10. Periodontal ligament stem cells.

Human PDL contains a population of postnatal multipotent stem cells that can be isolated using explant cultures or enzymatic digestion and expanded in vitro. PDLSCs express MSC markers such as CD10, CD13, CD29, CD44, CD59, CD73, CD90 and CD105, and do not express CD14,CD34,CD45,HLA-DR.

Periodontal ligament stem cells can differentiate into cells similar to cementoblasts and collagen-forming cells. The formation of calcified nodules is less prominent than that observed with DPSCs and SHEDs. Furthermore, PDLSCs can differentiate in vitro into adipogenic, osteogenic and chondrogenic cells.

In vivo, PDLSCs can differentiate into functional cementoblasts when transplanted subcutaneously on the dorsum of immune-compromised mice and could form collagen fibres embedded in the cementum-like tissue, suggesting the potential to regenerate the cementum/PDL-like tissue in vivo.

Goals Of Stem Cell Therapy In Tissue Engineering

1. Proliferate extensively and generate sufficient quantities of tissue.
2. Differentiate into the desired cell type(s).
3. Survive in the recipient after transplant.
4. Integrate into the surrounding tissue after transplant.
5. Function appropriately for the duration of the recipient's life.
6. Avoid harming the recipient in any way.

Source Of Pulp Stem Cells

The source of odontoblastic cells that repair dentinal bridges has proved to be controversial. Initially, the replacement of irreversibly injured odontoblasts by predetermined odontoblastic cells that do not replicate DNA after induction was suggested, researchers proposed that the cells within the sub-odontoblast cell-rich layer of Hohl adjacent to odontoblasts differentiate into odontoblasts. the purpose of these cells seems to be limited to an odontoblast-supporting role, however, because the survival of these cells is linked to the survival of the odontoblasts., no proliferative or regenerative activity was observed.

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Future Directions.

The last decade has proved to be an exciting time for pulp biology and has led to rapid advances in our knowledge of repair in this tissue. At the start of a new millennium, the use of biological molecules for the development of novel restorative treatment modalities in clinical dentistry is in sight. These approaches have potential applications in unexposed cavity preparations for the protection of the pulp from harmful effects of dental materials by increasing the residual dentin thickness through reactionary dentinogenesis, as well as in exposed pulp situations for restoration of the structural integrity of the dentin wall by reparative dentinogenesis. In the severely compromised pulp, it may even be possible to use biological approaches in endodontic therapy to seal the root canal[9].

Scaffold Biomaterial.

A scaffold surrounds cells and provides structural support for the formation and maintenance of tissues and organs. The scaffold is mainly composed of extracellular matrix proteins (ECMPs). The key ECMPs are collagen, vitronectin, and laminin, which provide the cell with anchorage, sequestration of growth factors, and signal cells to migrate, differentiate and proliferate through integrin receptor-mediated signalling pathways. ECMPs have an important role in dental regeneration. COLLAGEN is the predominant structural factor to regulate cell proliferation and differentiation. LAMININ promotes odontoblast differentiation, and a recent study by Howard and colleagues claims it to be an important factor in dental pulp stem cell migration. FIBRONECTIN is known to increase ameloblast growth and differentiation, VITRONECTIN provides a structural framework[10].

Natural ECMP scaffolds have varying chemical and physical characteristics which contribute to the specific functions of the tissue in which they reside. The physical properties include porosity, pore size, weight and hydration capacity. High porosity and sufficient pore size are necessary to facilitate cell seeding and diffusion of cells and nutrients throughout the scaffold. Other important properties are biocompatibility and biodegradability[11]. Some scaffolds are permanent, while others are absorbed by the surrounding tissues to avoid interference with the regenerated tissue. The rate of degradation should coincide with the rate of tissue formation.

Growth Factors

To restore the vitality and functions of the pulp dentin complex that has been lost to trauma or infections, another alternative approach is present, apart from the regular practice of delivering dental or non-dental stem/progenitor cells. This alternative approach for pulp-dentin regeneration relies on growth factor delivery[12].

The growth factors and cytokines may act as signalling molecules that modulate cell behaviour by mediating intracellular communication. Growth factors are polypeptides or proteins that bind to specific receptors on the surface of target cells. They can initiate a cascade of intracellular signalling, an act in either an autocrine or paracrine manner. Morphogens regulate the rate of tissue proliferation, cell differentiation into another cell type and matrix production[13].

Cytokines are typically referred to as immune modulatory proteins or polypeptides. They are used interchangeably with growth factors. The growth factors and cytokines, act locally on target cells. Stem cells require external stimuli to undergo differentiation. Morphogens or signalling molecules are the protein that binds to the specific cell membrane receptor and induces a cascade of processes that result in the generation of new tissue. Dentin contains many proteins capable of stimulating tissue responses. Demineralization of dentinal tissue can lead to the release of growth factors following the application of cavity etching agents, restorative materials and even caries[14].

Growth factors especially belonging to the transforming growth factor beta (TGFβ) family are important in cellular signalling for odontoblast differentiation and stimulation of dentin matrix secretion. Another important family of growth factors in tooth development and regeneration consists of bone morphogenic protein. (BMPS). Seven types of bone morphogenic proteins are identified, from BMP1 to BMP7. Recombitant human BMP2 stimulates the differentiation of adult pulp stem cells into odontoblastoid morphology in culture. Recombitant BMP2-4 and 7 induce the formation of reparative dentin in-vivo[15].

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Conclusion

Significant advances in our understanding of the biological processes involved in tooth development and repair at the cellular and molecular levels have underpinned the newly emerging area of regenerative endodontics.

Regenerative endodontics uses the concept of tissue engineering to restore root canals to a healthy state. As tooth retention, rather than extraction or replacement', is the ultimate goal of endodontic treatment, achieving a healthy root canal in this way could provide dentists with the holy grail of endodontic treatment. In 2006, the US National Institutes of Health defined regenerative medicine as the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects. The distinction between repair and regeneration is also highlighted. Regenerative endodontics provides more of a reparative than a regenerative therapeutic strategy.

Thus, applying tissue engineering principles has been shown to result in the preservation of tissue vitality in the dental pulp. Interestingly, these tissue engineering and wound healing treatments are by nature more medical and do not require the same mechanical skill as current RCT procedures.

The proposed tissue engineering therapies involve the interplay of stem cells, growth factors and scaffolds in a conducive environment to aid in the engineering of dental tissues (regenerative endodontics). The modern development of tissue engineering started in the late 1980s when synthetic biodegradable materials were introduced as scaffolds for cell expansion. However, further use in regenerative endodontics was halted due to the lack of isolation of specific dental stem cells. This was until the first human dental pulp stem cells were isolated in 2000. Currently, at least five different types of mesenchymal stem cells have been isolated from dental tissues, including dental pulp stem cells.

(DPSC), stem cells of human exfoliated deciduous teeth (SHED), stem cells of the apical papilla (SCAP), dental follicle progenitor cells(DFPC) and stem cells from periodontal ligament. Among these, DPSC, SHED and SCAP show stronger potential for pulp regeneration. In the last decade, a variety of biomaterials have been developed as the scaffold to support pulp regeneration. These include natural polymers, synthetic polymers, hydrogels and bioceramics. Scaffolds not only support stem cell proliferation and differentiation but also can integrate and provide a sustained release of growth factors to guide cell differentiation. Numerous animal models and preclinical studies have shown the success of regenerating pulp-like tissues via tissue engineering in invitro and invivo.

A variety of techniques have been discussed with each having its clinical applications and shortcomings. Some of the techniques are already in use, some at an early stage of development and others just hypothetical. Also, a combination of different therapies (like gene therapy with tissue engineering) is required for regenerative procedures/techniques to be predictable and widely available, to regenerate pulp-dentin tissue.

Current regenerative endodontic protocols rely on:

1. Irrigants to disinfect the canal and release growth factors found in dentin
2. Bleeding from the peri apical area to bring cells and growth factors into the root canal
3. The blood clot and dentin walls provide scaffolds for the generation of new tissue.

It is clear that the many possible clinical variables do not give the clinician control of the stem cell/growth factors/scaffold compositionIt is evident that recent rapid advances have opened the door to exciting new opportunities in the quest for healing immature teeth with pulpal necrosis. Extension of these advances to the treatment of mature teeth with pulpal necrosis would provide significant therapeutic benefits by enabling retention of the natural dentition in a larger patient pool. Recent reports describing the presence of mesenchymal stem/progenitor cells with regenerative capabilities in human inflamed pulps and inflamed periapical tissue present intriguing possibilities yet to be explored for the treatment of the mature tooth with pulpal necrosis and apical periodontitis. While current protocols have undergone rapid evolution to improve outcomes, it is likely that future REPs will differ from current practice and have the potential to provide benefits for a larger proportion of the population.

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Endodontists, knowledge in the fields of pulp biology, dental trauma and tissue engineering can be applied to deliver biologically based regenerative endodontic treatment of necrotic immature permanent teeth resulting in continued root development, increased thickness in the dentinal walls and apical closure. These developments in the regeneration of a functional pulp-dentin complex have a promising impact on efforts to retain the natural dentition, the ultimate goal of endodontic treatment.

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