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Research Article

A NEW INNOVATION IN DENTISTRY: REGENERATIVE ENDODONTICS

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ABSTRACT

Aim: The aim of this article is to review regenerative endodontics.
Background: Tissue regeneration and engineering is the most challenging part of a tissue repair/regeneration program. The emergence of this branch in medicine has shed new light on the treatment of the patients with degenerative disorders. The approach for the completion of the requirements of this field, combines tools from a variety of fields such as stem cell biology, biomaterials and developmental biology. The field of tissue engineering requires an appropriate microenvironment for proper development of stem cells. With the advancement of the tissue engineering field, though lately introduced in the field of dentistry can look forward to the development of the oral tissues and regeneration of whole tooth.
Conclusion: The emergence of this branch in medicine has shed new light on the treatment of the patients with degenerative disorders. With the advancement of the tissue engineering field, it was lately introduced in the field of dentistry can look forward to the development of the oral tissues and regeneration of whole tooth. Regeneration in endodontics can change the entire outlook of endodontic therapy which can lead to new innovations in this era of dentistry.

INTRODUCTION

Regenerative medicine holds the promise for the restoration of organ and tissues damaged by diseases, trauma, cancer, or congenital deformity. This includes thousands of organ transplants, joint replacements to major reconstruction of facial soft and remineralised tissues. 'Regenerative Endodontics' is a branch of regenerative medicine and has been defined as biological procedures designed to replace damaged, diseased or missing dental structures, including dentine and root as well as cells of the pulp-dentine complex, with living, viable tissues, preferably of the same origin, that restore the normal physiological functions of the pulp dentine complex.[1] The first step towards regenerative endodontics could be attributed to Dr B.W.Hermann (1952), when he reported a case on the application of calcium hydroxide for vital pulp amputation. The other in which new living tissue is expected to form, from the tissue present in the teeth itself, allowing continued root development (revascularization).[2]

The ultimate goal and objective of regenerative endodontics is to regenerate dental pulp-like tissue as an alternative to conventional root canal treatment, maintain pulp health in pulpal inflammation, regenerate damaged coronal dentin following a carious destruction, regenerate resorbed root, cervical or apical dentin and induce biological replacement of dental tissues.[3-5]

Tissue Engineering

The term 'Tissue engineering' was coined by the National Science Foundation (NSF) in 1987. It was defined formally by Skalak and Fox as 'the application of the principles and methods of engineering and life sciences to obtain a fundamental understanding of structure function relationship in novel and pathological mammalian tissues and the development of biological substitutes to restore, maintain or improve tissue function'.[6] Later in 1993, Langer and Vacanti defined 'Tissue Engineering' as an interdisciplinary field that applies the principles of engineering and life sciences towards

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the development of biological substitutes that restores, maintain or improve tissue functions. The key components for tissue engineering are: stem cells, scaffold of extracellular matrix (ECM), growth factors and gene therapy.[7]

Steps for Tissue Regeneration

There are 8 key elements to create and use tissue constructs for tissue regeneration:

Step #1. The size, shape of tooth needs to be assessed using cone beam microcomputer tomography and radiographs.
Step #2. Stem cells, such as dental pulp stem cells from an exfoliated baby tooth, need to be obtained from the host patient or a donor to serve as the building blocks for tissue regeneration.
Step #3.Surface marker are used to identify stem cells which are isolated from donor cells using fluorescent cell sorting
Step #4. Millions of stem cells are needed to create functional tissues; this requires that they be expanded using cell culture.
Step #5. The activity of the stem cells must be controlled by growth factors during cell culture to ensure that the stem cells differentiate into a useful cell type (e.g., pulp, periodontal ligament and bone).
Step #6. Cells grown in culture lack a 3-dimensional scaffold necessary to function and have the correct size and shape to generate a tissue; therefore, the cells need to be seeded onto a scaffold to form a tissue construct which gives the cells the characteristics of a tissue, such as dental pulp stem cells seeded onto polymer and collagen scaffolds to generate replacement pulp tissue.
Step #7. The tissue construct is maintained in cell culture until a functional tissue is generated.
Step #8. The tissue construct is grafted or implanted into the donor site, where the regenerated tissue is required. [8]

Stem Cells

Stem cells are non-specialized cells that continuously divide, have the ability of self-renewal, and are capable of generating complex tissues and organs. Gronthos *et al* defined it as clonogenic cells capable of both self-renewal and multilineage differentiation since they are thought to be undifferentiated cells with varying degrees of potency and plasticity.[9]Duailibi *et al* defined stem cells as "quiescent cell populations present in low numbers in normal tissue, which exhibit the distinct characteristic of asymmetric cell division, resulting in the formation of two distinct daughter cells - a new progenitor/ stem cell and another daughter cell capable of forming a differentiated tissue". [10]

Researchers have studied various types of stem cells and concluded that stem cells can be harvested from the following source

1. Permanent teeth - Dental pulp stem cells (DPSC)
2. Deciduous teeth - Stem cells from human-exfoliated deciduous teeth (SHED): stem cells are present within the pulp tissue of deciduous teeth,
3. Periodontal ligament - Periodontal ligament stem cells (PDLSC).
4. Stem Cells from apical papilla (SCAP).
5. Stem cells from supernumerary tooth
6. Dental follicle progenitor cells.
7. Stem cells from human natal dental pulp- (hNDP) [2,12]

Dental Pulp stem cells (DPSC)

DPSCs were first isolated from human permanent third molars in 2000.[11] The cells were characterized as clonogenic and highly proliferative. These human pulp cells can be isolated invitro by inducing them to differentiate into cells of odontoblastic phenotype, characterized by polarized cell bodies and accumulation of mineralized nodules.[13-16] Studies have confirmed that DPSCs can also differentiate into osteoblast, chondrocyte, and myoblast like cells and demonstrate axon guidance. DPSCs have also been shown to express the bacterial recognition toll-like receptors, TLR4 and TLR2, and vascular endothelial growth determine the outcome. This notion is supported by in vitro observations of DPSCs factor in response to lipopolysaccharide, a product of gram-negative bacteria. When compared with normal pulps, DPSCs in inflamed pulp tissues have reduced migrating from the perivasculature toward the dentin surface following injury to the dentin matrix and differentiating into functional odontoblasts in response to dentinogenesis activity, and an in vitro investigation has shown reduced dentinogenic potential of DPSCs exposed to a high bacterial load that can be recovered after the inhibition of the bacterial recognition toll-like receptor.[11]

Stem Cells of Human exfoliated teeth

Miura *et al* discovered stem cell in deciduous teeth and stated its characteristics for tissue engineering. The obvious advantages of SHEDs (stem cells from human exfoliated deciduous teeth) are: higher proliferation rate compared with stem cells from permanent teeth, easy to be expanded in vitro, high plasticity since they can differentiate into neurons, adipocytes, osteoblasts and odontoblasts, readily accessible in young patient, especially suitable for young patients with mix dentition. SHEDs cells can not differentiate directly into osteoblasts but did induce new bone formation by forming a template to recruit murine host osteogenic cells. SHEDs are distinctive with the osteoinductive ability and high plasticity.[17] However, SHED cells have a higher proliferation rate than DPSCs and BMMSCs, suggesting that they represent a more immature population of multipotent stem cells. SHED cells have shown different gene expression profiles from DPSCs and BMMSCs; genes related to cell proliferation and extracellular matrix formation, such as transforming growth factor (TGF-β), fibroblast growth factor (FGF-2), collagen (Col) I, and Col III, are more highly expressed in SHED cells compared with DPSCs.

Stem Cells from the Apical Papilla (SCAP)

SCAP cells are present in the apical papilla located at the apices of developing teeth at the junction of the apical papilla and dental pulp. The apical papilla is essential for root development and were first isolated in human root apical papilla collected from extracted human third molars. [18] This tissue is loosely attached to the apex of the developing root and can be easily detached. SCAP, similarly to DPSCs and SHEDs, comprise a heterogeneous population capable of osteoblastic and odontoblastic differentiation, and to a lesser extend adipogenic differentiation.[19] They are also capable of expressing neurogenic and myogenic markers, and shows consistent capacity for dentin regeneration. The discovery of

SCAP explained a clinical phenomenon that was presented in a number of recent clinical case reports showing that apexogenesis can occur in infected immature permanent teeth with apical periodontitis or abscess. It is most likely that SCAP residing in the apical papilla had survived the infection due to their proximity to the periapical tissues. This tissue may be benefited by its collateral circulation, which enables it to survive during the process of pulp necrosis. Perhaps, after endodontic disinfection, these cells give rise to primary odontoblasts for complete root formation. When compared with DPSCs, SCAP cells show higher proliferation rates and greater expression of CD24, which is lost as SCAP cells differentiate and increase alkaline phosphate expression. [20]

Periodontal Ligament Stem Cells (PDLSCs)

The periodontal ligament (PDL) is a specialized connective tissue, derived from dental follicle and originated from neural crest cells. McCulloch reported the presence of progenitor/stem cells in the periodontal ligament of mice in 1985. Subsequently, the isolation and identification of multipotent MSCs in human periodontal ligaments were first reported in 2004 by Seo and colleagues, demonstrated the presence of clonogenic stem cells in enzymatically digested PDL and further showed that human PDLSCs transplanted into immunodeficient rodents generated a cementum/PDL-like structure that contributed to periodontal tissue repair. [21] PDLSCs display cell surface marker characteristics and differentiation potential which is similar to bone marrow stem cells and DPSCs.[22-24]

Dental follicle precursor cells (DFPCs)

The dental follicle forms at the cap stage by ectomesenchymal progenitor cells. It is a loose vascular connective tissue that contains the developing tooth germ, DFPCs come from developing tissue, it is considered that they might exhibit a greater plasticity than other DSCs. [25] Indeed, different cloned DFPCs lines have demonstrated great heterogeneity. Studies have proven that DFPCs are able to differentiate into odontoblasts after combining rat DFPCs with treated dentin matrix the root-like tissues stained positive for markers of dental pulp. Both DFPCs and SHED cells can differentiate into neural cells; however, these are differentially expressed when the cells are grown under the same culture conditions.[26]

SCAFFOLD

Scaffolds are three-dimensional structures that provide an initial framework for the cells and can be used to deliver morphogenic molecules. Few terms which are used synonymously and interchangeably with biomaterial are: Bioabsorbable material (material whose breakdown products are incorporated into the normal physiologic and biochemical process), Biocompatible material (function in biologic environment without known or significant detrimental effects on either the material or the living system), Biodegradable material (break down when placed in a biologic environment), Bioabsorbable material (material that is broken down in vivo and removed from the implant site).[27-29]

Ideal requirements of a scaffold[30]

1. It should provide support for delivering cells and/or growth factors to the proposed sites of tissue regeneration.
2. It should provide the framework for cell growth, differentiation and organization at a local site.
3. It should reflect the microenvironment of target tissues/organs to facilitate cell growth and ultimately integration to the host.
4. It should be porous to allow placement of cells and growth factors.
5. It should allow effective transport of nutrients, oxygen, and waste.
6. It should be biodegradable, leaving no toxic byproducts.
7. It should be replaced by regenerative tissue while retaining the shape and form of the final tissue structure.
8. It should be biocompatible.
9. It should have adequate physical and mechanical strength.

These requirements are important features and should be considered during scaffold selection, including the physical and mechanical aspects of the material, its biocompatibility, and its degradation timeline. These physical aspects of a 3D scaffold include the porosity (pore volume fraction of the scaffold), pore size (pore diameter), pore structure (shape), and all aspects that can influence how well the cells adhere to the material.The important mechanical properties of a scaffold material are viscoelasticity and the tensile strength, [31-33]

A beneficial clinical feature for dental pulp regeneration would be if the scaffold is injectable, as are some of the natural scaffold materials and hydrogels. [34]

Classification of scaffolds

Synthetic Scaffolds

Biodegradable

- Polyglycolic acid (PGA)
- Polylactic acid (PLA)
- Polylactic-glycolic acid (PLGA)
- Poly ε-caprolactone
- Arginine
- Agarose
- Hydroxy apatite
- Tricalcium Phosphate
- Bioceramics
- Titanium Hydrogel

Nonbiodegradable

- Polymethyl methacrylate (PMMA)
- Polytetrafluroethylene (PTFE)
- Polydimethylsiloxane (PDMS)

Natural

- Collagen
- Gelatin
- Chitosan
- Hyaluronic acid

- Fibrin
- Emdogain
- PRP
- Blood clot

Growth Factors

Growth factors are proteins that bind to receptors on the cell and induce cellular proliferation andor differentiation. [35] They are extracellularly secreted signals governing morphogenesis ororganogenesis during epithelial mesenchymal interactions and regulate the division or specialization of stem cells to the desirable cell type, and mediate key cellular events in tissue regeneration including cell proliferation, chemotaxis, differentiation, and matrix synthesis.[36] They regulate either transplanted cells or endogenously homed cells in pulp-dentin regeneration. [37] Growth factors and cytokines may act as signaling molecules that modulate cell behavior by mediating intracellular communication. Growth factors are polypeptides or proteins that bind to specific receptors on the surface of target cells. Growth factors can initiate a cascade of intracellular signaling and act in either an autocrine or paracrine manner. Cytokines are typically referred to as immunomodulatory proteins or polypeptides.[38] Cytokines are often used interchangeably with growth factors because many cytokines share similar actions with growth factors. As opposed to systemic effects by hormones on target cells, growth factors or cytokines typically act locally on target cells. Many growth factors are quite versatile, simulating cellular division in numerous cell types, while others are more cells specific. Two important families of growth factors that play a vital role are the transforming growth factor-beta (TGF-β) family and bone morphogenic proteins (BMPs). Many growth factors are quite versatile, stimulating cellular division in numerous cell types, while others are more cell-specific. The growth factors that play an important role in endodontic regeneration are:

1. Platelet derived growth factor (P.D.G.F.),
2. Transforming Growth Factor- β (T.G.F.-β),
3. Bone Morphogenetic Proteins (B.M.P.s).
4. Vascular Endothelial Growth factor (VEGF)
5. Fibroblast Growth Factor (FGF)
6. Insulin-like growth factor (I.G.F.),
7. Nerve Growth Factor (NGF)
8. Stromal cell Derived Factor 1 (SDF-1)
9. Dentonin

Tooth Regeneration

A tooth is a complex biological organ and consists of multiple tissues including the enamel, dentin, cementum and pulp. Tooth loss is the most common organ failure. The only vascularized tissue of the tooth is the dental pulp that is encased in the mineralized dentin. Tooth regeneration represents a revolution in stomatology as a shift in the paradigm from repair to regeneration. Tooth regeneration is an extension of the concepts in the broad field of regenerative medicine to restore a tissue defect to its original form and function by biological substitutes. Current research efforts in whole tooth tissue engineering are focused on three areas: [46]

1. Molecular profiling of epithelial and mesenchymal PNDSC to define the genes whose coordinated expression confers on these cells the ability to adopt dental cell differentiation fates;
2. Defining methods of manipulating PNDSC via cell-cell and cell scaffold interactions to generate bioengineered tooth tissues of predetermined size and shape that exhibit similar physical and mechanical properties to those exhibited by naturally formed dental tissues; and
3. Promotingthe formation of bioengineered tooth root structures, including cementum, periodontal ligament, and alveolar bone. Progress in each of these areas that will facilitate whole tooth tissue engineering efforts is described briefly Regeneration of teeth can be broadly divided into several areas as listed below. It is divided into following areas:

Table 1 Primary effects and interactions of signaling molecules for regenerative endodontics. [36]

Signaling Molecules	Target Cells	Primary Effects	Interactions
PDGF	Dental pulp cells	• Cell proliferation • Dentin matrix synthesis • Odontoblastic differentiation • Dentinogenesis	• Combined with IGF-1 or dexamethasone, increased cell proliferation • Combined with PDGF, increased cell proliferation
TGFβ1	Dental pulp cells/ Dental pulp stem cells	• Cell proliferation • Extracellular matrix synthesis • Odontoblastic differentiation • Dentinogenesis	
BMP2	Dental pulp cells	• Odontoblastic differentiation, • Dentinogenesis	
BMP4	Dental Pulp Cells	•Odontoblastic differentiation, • Dentinogenesis	
BMP7 (OP-1)	Dental Pulp cells	Dentinogenesis	
BMP11 (GDF11)	Dental pulp stem cells	•Odontoblastic differentiation, • Dentinogenesis	
VEGF	Dental pulp stem cells	• Odontoblastic Differentiation • Cell proliferation	• Under osteogenic conditions, • increased osteogenic differentiation
FGF2 (bFGF)	Dental pulp stem cells/ Dental Pulp	• Chemotaxis • Cell proliferation	• Combined with TGFb1 • Increased odontoblastic differentiation
IGF	Dental pulp cells	• Cell proliferation • Odontoblastic differentiation	• Combined with PDGF, • increased cell proliferation

- Regeneration or de novo formation of the entire, anatomically correct teeth.
- Regeneration of dental pulp.
- Regeneration of dentin based on biological approaches and potentially as biological fillers that may replace current synthetic materials for restorative dentistry.
- Regeneration of cementum as a part of periodontium regeneration or for loss of cementum and/or dentin resulting from trauma or orthodontic tooth movement
- Regeneration of the periodontium including cementum, periodontal ligament and alveolar bone.
- Regeneration or synthesis of enamel-like structures that may be used as biological substitute for lost enamel.

Since a tooth is a biological organ, it is unavoidable that regeneration of various components of the tooth is highly inter-connected. Two major cell types are involved in dental hard tissue formation: the mesenchyme-originated odontoblasts that are responsible for the production of dentin and the epithelium-derived ameloblasts that form the enamel. Odontoblasts are columnar post-mitotic cells that form a layer in contact with the dentin. Odontoblastic processes are formed at their distal part, penetrate the dentin and participate in the secretion of dentin matrix and minerals. The matrix is composed of collagen (90%) and noncollagenous proteins such as Dentin Sialophosphoprotein (DSPP) and Dentin Matrix Protein 1 (DMP-1). Recently, the therapeutically viable approaches for tooth regeneration by contrasting cell transplantation and cell homing approaches. [47]

effect of caries or a restorative procedure on the pulp is the result of a complex interaction of many factors. These factors include the thickness and permeability of the intervening dentin, the health of the underlying pulp, mechanical injury to odontoblast processes during cavity preparation, the possible toxicity of the restorative material, and microbial leakage.[44] The goal of modern restorative dentistry is to restore tooth structure functionally and cosmetically which is destroyed due to various mechanical applications and from dental caries. The currently used restorative materials include metal and polymer-based materials; primarily silver amalgam, resin-based composites and metal or porcelain crowns. With this thought of regeneration researchers introduce new materials which have potential for regeneration of pulp and hard tissue formation.[42] When tooth with extensive caries are planned for treatment, the treatment plan could be altered from certain extraction to being properly restored as a result of the regeneration of dentinal tooth structure, endodontists would have engineered a more desirable outcome. The reestablishment of vitality and a functional immune response may allow the body to better fight the presence of any remaining bacteria within the canal system. Thus, future efforts must focus on a more biologic and scientific approach to these endodontic procedures. Regenerative endodontics is a high priority for the specialty of endodontics. Revascularization can occur but requires a particular set of circumstances that, until recently, were thought to be exclusive to the avulsed immature permanent tooth. First, the exclusion of bacteria is the key factor in the success of this process.

Table 2 Developmental approaches for regenerative endodontic procedures [1]

Technique	Advantages	Disadvantages
Root canal Re-vascularisation: Open up tooth apex to 1mm to allow bleeding into root canals	• Lowers risk of immune rejection. • Lowers the risk of pathogen transmission	• Minimal case reports have been published till date • Potential risk of necrosis if tissue becomes re-infected.
Stem cell Therapy: Autologous or allogenic stem or cells are delivered to teeth via injectable matrix	• Procedure is quick • Easy delivery • Least painful • Cells are easy to harvest	• Low cell survival • Cells do not produce new functioning pulp. • High risk of complications.
Pulp Implant: Pulp tissue is grown in laboratory in sheets and implanted surgically.	• Sheets of cells are easy to grow. • More stable than an injection of dissociated cells.	• Sheets lack of vascularity so only small constructs are possible. • Must be engineered to fill root canal precisely.
Scaffold Implant: Pulp cells are seeded onto 3-D scaffold made up of polymers and surgically implanted	• Structures support cell organisation. • Some materials promote vascularization	• Low cell survival after implantation. • Must be engineered to fill root canal space precisely.
3-D printing: Ink-jet-like device dispenses layers of cells in hydrogel which is surgically implanted.	• Multiple cell types can be precisely positioned	• Must be engineered to fill root canal space precisely. • Early Stage research has yet to prove functional in vivo.
Injectable Scaffolds: Polymerizable hydrogels, alone or containing cell suspension are delivered by injection	• Easy delivery • May promote regeneration by providing substitute for extracellular matrix	• Limited control over tissue formation. • Low cell survival • Early Stage research has yet to prove functional in vivo.

Endodontic Application of Regenerative Procedures

Dentin-pulp complex is a dynamic tissue that responds to mechanical, bacterial, or chemical irritation in several ways to decrease irritation.[39] The vitality and dentin repair potential of the pulp are dependent on the survival of the odontoblasts beneath the site of injury.[40] The most common cause of injury to the pulp-dentin complex is the carious breakdown of the enamel and dentin, leading to pathologic changes in the pulp and peri-radicular area. [40] Apart from dentinogenesis, odontoblasts also play important roles as defence cells and as thermal and mechanical sensory receptors.[41-43] Thus, the net

Second, the combination of an open apex and a short root allows the ingrowth of well vascularized tissue. Third, the devitalized uninfected pulp is also thought to act as a scaffold for the ingress of apical tissue. Successful revascularization of the pulp leads to the maturation of the root and deposition of hard tissue within the root, both of which improve the probability of long-term retention of the tooth. [45]

CONCLUSION

The emergence of this branch in medicine has shed new light on the treatment of the patients with degenerative

disorders.With the advancement of the tissue engineering field, it was lately introduced in the field of dentistry can look forward to the development of the oral tissues and regeneration of whole tooth. Regeneration in endodontics can change the entire outlook of endodontic therapy which can lead to new innovations in this era of dentistry.

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