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REGENERATIVE ENDODONTICS

Veeramma Patil[1]*, R. Vinaychandra[2] and Geeta I. B.[3]

[1]Postgraduate Student, Department of Conservative Dentistry and Endodontics, Rajareswari Dental College and Hospital, Bengaluru Karnataka, India.
[2]Professor, Department of Conservative Dentistry and Endodontics, Rajareswari Dental College and Hospital, Bengaluru Karnataka, India.
[3]Professor and Head of the Department Department of Conservative Dentistry and Endodontics, Rajareswari Dental College and Hospital, Bengaluru Karnataka, India.

***Corresponding Author: Dr. Veeramma Patil**
Postgraduate Student, Department of Conservative Dentistry and Endodontics, Rajareswari Dental College and Hospital, Bengaluru Karnataka, India.

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ABSTRACT
Regenerativeendodontics is an exciting and developing field in the treatment of immatureteeth with infected root canals that has been described as a "paradigm shift"in the management of these teeth and can result in continued root maturationand apical closure. Traditional approaches of calcium hydroxide apexificationand apical barrier techniques with mineral trioxide aggregate (MTA) have beenused in the treatment of immature teeth with pulp necrosis though generallythere is no further root development so the roots remain thin and fragile witha higher risk of fracture and tooth loss. The treatment of immature teeth withREPs has been described as a 'paradigm shift' as there is the potential forfurther root maturation. Clinically, REPs involve disinfection of the rootcanal system without damaging the endogenous stem cell potential present in theapical papilla and other tissues. These stems cells are introduced into theroot canal space by inducing a blood clot followed by placement of anintracanal barrier to prevent microleakage. The biological concept of REPsinvolves the triad of stem cells, scaffold and signalling molecules.

KEYWORDS: Regenerative, Stem cells, Tissue engineering, Scaffold, Bioengineering, revascularization.

INTRODUCTION
Regenerative endodontics is defined as "biologically based procedures designed to replace damaged tooth structures, including dentin e and root structures, as well as cells of the pulp -dentin e complex" (Murray et al. 2007).[1] Based on this definition, regenerative endodontic therapy (RET) is aimed to regenerate the pulp -dentin e complex damaged by infection, trauma or developmental anomaly of immature permanent teeth with necrotic pulp. The vitality of the dentin-pulp complex is fundamental to the life of the tooth and it is a priority for targeting clinical management strategies. The pulp cells not only maintain tissue homeostasis after the tooth development, but they also underpin the defense reactions taking place in response to the injury and the reparative events leading to the tissue regeneration. The overall response of tooth to injury represents complex interplay between injury, defense and the regenerative process. Interplay and the relative balance among these processes will be primary determinant of tissue vitality and tooth survival.[2] In case of immature permanent teeth, maintaining the pulp vitality is essential for continuous root development and apical closure. If the pulp of immature permanent teeth is infected, apexification that includes removal of the infected pulp and application of calcium hydroxide has been performed traditionally.[3] In apexification, calcium hydroxide is used as an intracanal medication, which should be replaced every 3 months, and a long-term follow-up is necessary. Long-term application of the intra-canal medication increases the possibility of root fracture and developing defects in the root walls due to its porous characteristics. On the other hand, regenerative endodontic treatment can result in complete root development after a short-term treatment procedure. Thus, regenerative endodontic treatment causes an increase in root length and thickness.[4]

Tissue engineering
The term **"Tissue engineering"** was coined by Langer and Vacanti in 1993 and was defined as "an inter disciplinary field that applies the principles of engineering and life sciences towards the development of biological substitute that restore maintain or improve tissue function." Tissue engineering is an interdisciplinary field that integrates the principles of biology and engineering to develop biological substitutes

that replace or regenerate human cells, tissue or organs in order to restore or establish normal function. It aims at the regeneration of affected or lost pulp tissue using stem cell therapy.[1]

Triads of tissue engineering

There are three key elements for tissue engineering: stem cells, scaffolds and growth factors.

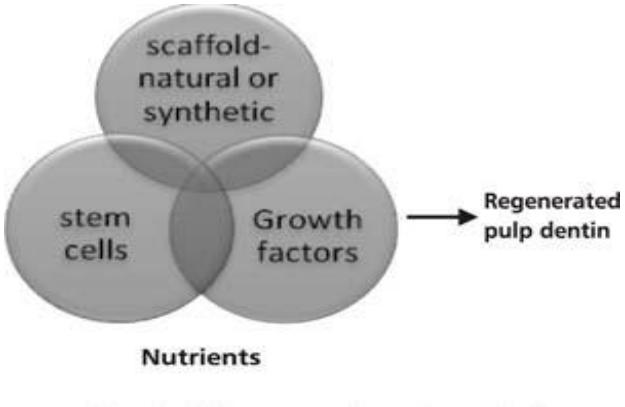


Fig. 1: Triad of tissue engineering.

i. **Stem cells:** Stem cells are undifferentiated cells that continuously divide. There are two main types: embryonic, and adult or postnatal.

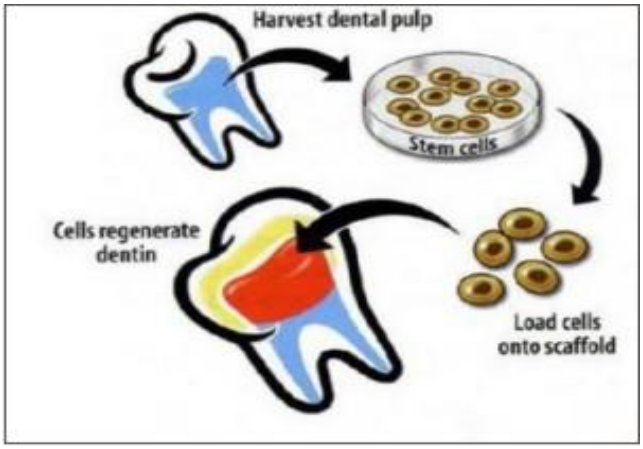


Figure 2: Stem cells.

Pulp stem cells

The dental pulp contains a population of stem cells, called pulp stem cells [5][6] or, in the case of immature teeth, stem cells from human exfoliated deciduous teeth (SHED) [7][8]. Sometimes pulp stem cells are called odontoblastoid cells, because these cells appear to synthesize and secrete dentin matrix like the odontoblast cells they replace.[9]

Stem cells from exfoliated deciduous teeth

The exfoliated deciduous tooth contains living pulp remnants consisting of connective tissue, blood vessels, and odontoblasts. This tissue contains special kind of cells known as Stem Cells from Human Exfoliated Deciduous Teeth (SHED). SHED can differentiate into odontoblast like cells that form small dentin like structures, SHEDs are distinctive from DPSCs with respect to odontogenic differentiation and osteogenic induction.[10]

Periodontal ligament stem cells

The periodontal ligament connects the cementum to alveolar bone and functions primarily to support the tooth in the alveolar socket. A recent report identified stem cells in the human PDL (PDLSCs) and found that PDLSCs implanted into nude mice generated cementum/ PDL like structures that resemble the native PDL as a thin layer of cementum that interfaced with dense collagen fibers, similar to Sharpey's fibers. Thus, the PDLSCs have the ability of forming periodontal structures, including cementum and PDL.[10]

ii. Scaffolds

Scaffolds provide support for cell organization, proliferation, differentiation and vascularisation.[11] Current REPs have utilized dentin as well as the blood clot[4] or platelet-rich plasma[12] to provide scaffolds in the root canal.

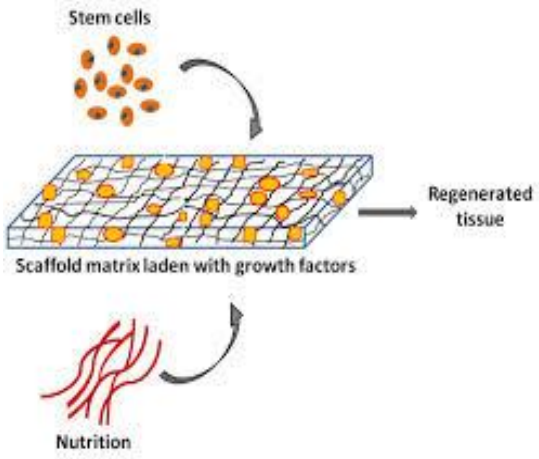


Fig. 3: Scaffold matrix.

Classification

Scaffolds can be classified mainly into two:

I. NATURAL: Collagen, platelet- rich plasma, fibrin and glucosamine.

II. II SYNTHETIC: Polylactic acid, polyglycolic acid (PGA) and poly (lactic-co-glycolic) acid (PLGA).

Requirements of a scaffold

It should be effective for transport of nutrients, oxygen, and waste.

It should be gradually degraded and replaced by regenerative tissue, retaining the feature of the final tissue structure.

It should be biocompatible, non toxic and should have proper physical and mechanical strength.

Easy cell penetration, distribution and proliferation.

Permeability of culture medium.

In vivo vascularisation (once implanted).

Maintenance of osteoblastic cell phenotypes.

Adequate mechanical stiffness.

Ease of fabrication.

iii. Growth Factors/Morphogens/Signalling molecules

Growth factors are proteins that bind to receptors on the cell and act as signals to induce cellular proliferation and/or differentiation.[13] Examples of key growth factors in pulp and dentin formation include bone morphogenetic protein,[14] transforming growth factor–beta [15] and fibroblastic growth factor.[16] Current REPs aim to utilize growth factors found in platelets and dentin. Recent studies have shown that dentin contains a number of bioactive molecules that, when released, play an important role in regenerative procedures.[17]

Abbreviation	Factor	Primary Source	Activity	Usefulness
BMP	Bone morphogenetic proteins	Bone matrix	BMP induces differentiation of osteoblasts and mineralization of bone	BMP is used to make stem cells synthesize and secrete mineral matrix
CSF	Colony stimulating factor	A wide range of cells	CSFs are cytokines that stimulate the proliferation of specific pluripotent bone stem cells	CSF can be used to increase stem cell numbers
EGF	Epidermal growth factor	Submaxillary glands	EGF promotes proliferation of mesenchymal, glial and epithelial cells	EGF can be used to increase stem cell numbers
FGF	Fibroblast growth factor	A wide range of cells	FGF promotes proliferation of many cells	FGF can be used to increase stem cell numbers
IGF	Insulin-like growth factor-I or II	I - liver II–variety of cells	IGF promotes proliferation of many cell types	IGF can be used to increase stem cell numbers
IL	Interleukins IL-1 to IL-13	Leukocytes	IL are cytokines which stimulate the humoral and cellular immune responses	Promotes inflammatory cell activity
PDGF	Platelet-derived growth factor	Platelets, endothelial cells, placenta	PDGF promotes proliferation of connective tissue, glial and smooth muscle cells	PDGF can be used to increase stem cell numbers
TGF-α	Transforming growth factor-alpha	Macrophages, brain cells, and keratinocytes	TGF-α may be important for normal wound healing	Induces epithelial and tissue structure development
TGF-β	Transforming growth factor-beta	Dentin matrix, activated TH_1 cells (T-helper) and natural killer (NK) cells	TGF-β is anti-inflammatory, promotes wound healing, inhibits macrophage and lymphocyte proliferation	TGF-β1 is present in dentin matrix and has been used to promote mineralization of pulp tissue
NGF	Nerve growth factor	A protein secreted by a neuron's target tissue	NGF is critical for the survival and maintenance of sympathetic and sensory neurons.	Promotes neuron outgrowth and neural cell survival

Table 1: A summary of the source, activity and usefulness of common growth factors *functions.*

To stimulate division of neighbouring cells and those infiltrating the defect (example: growth factors- PDGF)
To stimulate the differentiation of certain cells along a specified pathway (example: Differentiation Factors – BMP)
To stimulate angiogenesis
To act as chemo attractants for specific cell types.

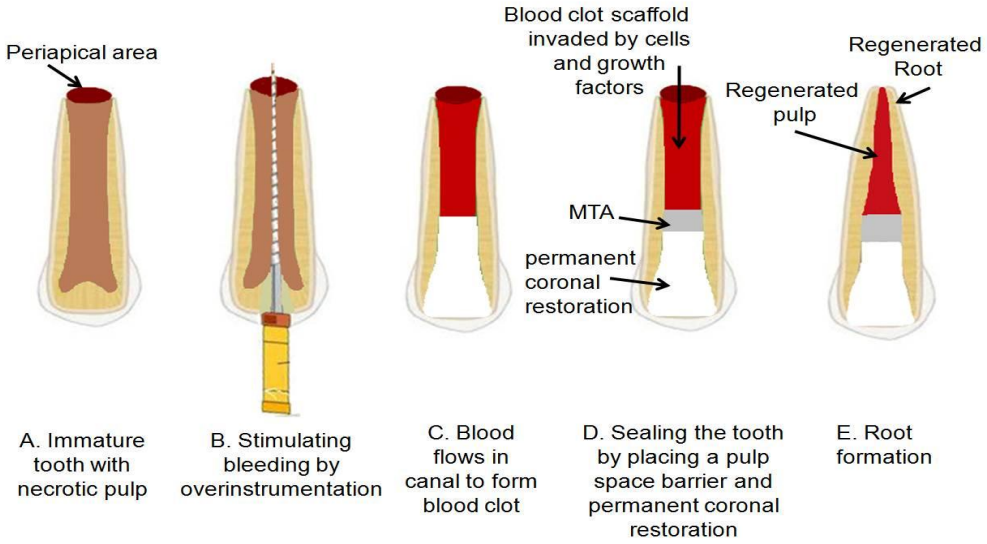


Fig 4: Schematic representation of simple regenerative procedure.

Potential technologies for regenrative endodontics
Several major areas of research have been identified that might have application in the development of regenerative endodontic techniques.
These techniques are

- Root canal revascularization via blood clotting,
- Postnatal stem cell therapy,
- Three-dimensional cell printing,
- Gene delivery.
- Pulp implantation,
- Scaffold implantation,
- Injectable scaffold delivery,

These regenerative endodontic techniques are based on the basic tissue engineering principles already described and include specific consideration of cells, growth factors, and scaffolds.

I. Revascularization
Several case reports have documented revascularization of necrotic root canal systems by disinfection followed by establishing bleeding into the canal system via over instrumentation.[18] An important aspect of these cases is the use of intracanal irrigants (NaOCl and chlorhexdine) with placement of antibiotics (e.g. a mixture of ciprofloxacin, metronidazole, and minocycline paste) for several weeks. This particular combination of antibiotics effectively disinfects root canal systems.[19] and increases revascularization of avulsed and necrotic teeth, suggesting that this is a critical step in revascularization. Revascularization of necrotic pulps with fully formed (closed) apices might require instrumentation of the tooth apex to approximately 1 to 2 mm in apical diameter to allow systemic bleeding into root canal systems.

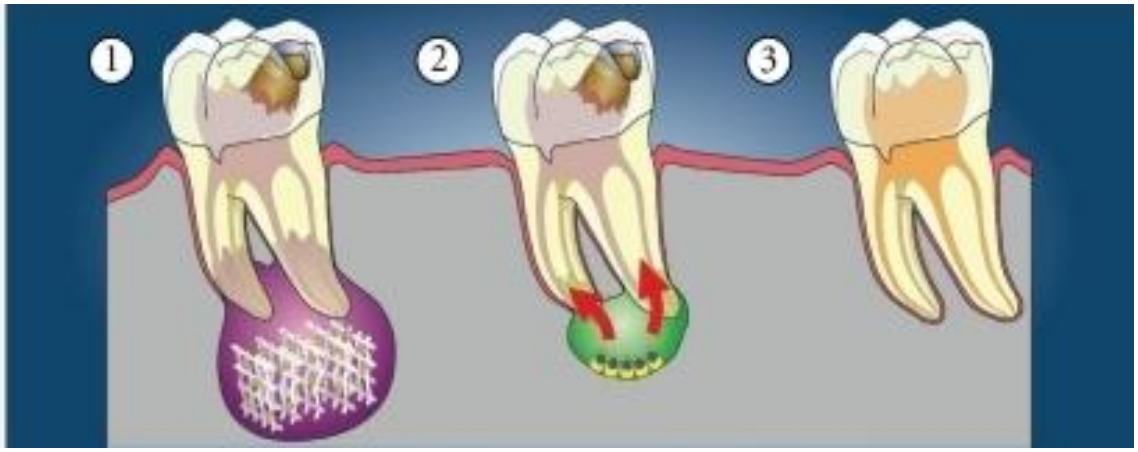
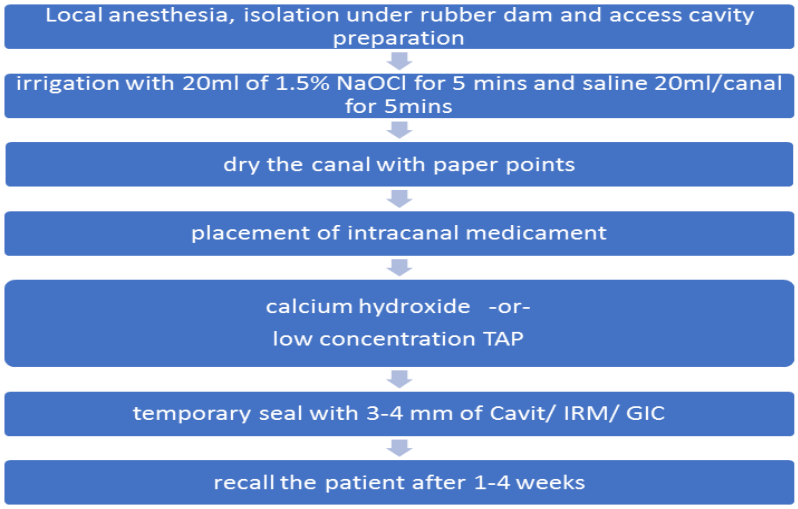


Fig. 5: Local regeneration of dentin pulp from apical pulp or periapical tissues.

- A few vital pulp cells remaining at the apical end of the root canal might proliferate into the newly formed matrix and differentiate into odontoblasts
- Continued root development could be due to multipotent dental pulp stem cells, which are present in immature permanent teeth
- Stem cells in the periodontal ligament can proliferate and grow into the apical end and within the root canal. They may deposit hard tissue both at the apical end and on the lateral root walls
- The blood clot is a rich source of growth factors such as platelet- derived growth factor, vascular endothelial growth factor, platelet derived epithelial growth factor and tissue growth factor. These could play an important role in regeneration.

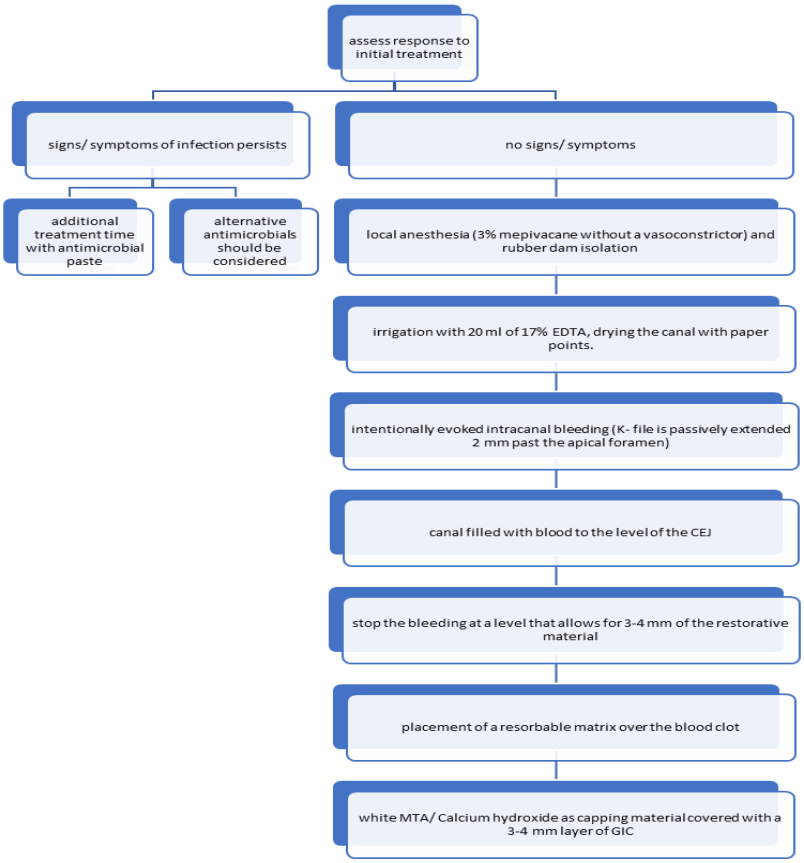
- **Clinical protocol**

Regenerative endodontic therapy (first appointment)



Regenerative endodontic therapy – first appointment procedures

Regenerative endodontic therapy (second appointment)



Regenerative endodontic therapy – Second appointment procedures

II. Post-natal stem cell therapy

The simplest method to administer cells of appropriate regenerative potential is to inject postnatal stem cells into disinfected root canal systems after the apex is opened. Postnatal stem cells can be derived from multiple tissues, including skin, buccal mucosa, fat, and Bone.[20]

III. 3-D Cell printing

Another approach for creating replacement pulp tissue may be to create it using a three-dimensional cell printing technique.[21] In theory, an ink-jet-like device is used to dispense layers of cells suspended in a hydrogel [22] to recreate the structure of the tooth pulp tissue. The three-dimensional cell printing technique can be used to precisely position cells, and this method has the potential to create tissue constructs that mimic the natural tooth pulp tissue structure.

IV. Gene therapy

New techniques involving viral or non-viral vectors can deliver genes for growth factors, morphogens, transcription factors, and extracellular matrix molecules into target cell populations, such as the salivary gland [23]. A recent review has discussed the use of gene delivery in regenerative endodontics. One use of gene delivery in endodontics would be to deliver mineralizing genes into pulp tissue to promote tissue mineralization.[24]

V. Pulp implantation

The majority of in vitro cell cultures grow as a single monolayer attached to the base of culture flasks. However, some stem cells do not survive unless they are grown on top of a layer of feeder cells [25]. In all of these cases, the stem cells are grown in two dimensions. In theory, to take two-dimensional cell cultures and make them three-dimensional, the pulp cells can be grown on biodegradable membrane filters.

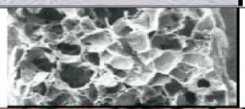
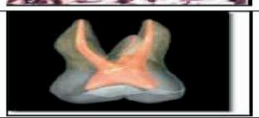
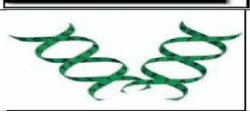
VI. Scaffold implantation

To create a more practical endodontic tissue engineering therapy, pulp stem cells must be organized into a three-dimensional structure that can support cell organization and vascularization. This can be accomplished using a porous polymer scaffold seeded with pulp stem cells.[26] A scaffold should contain growth factors to aid stem cell proliferation and differentiation, leading to improved and faster tissue development.[27] Growth factors were described in the previous section. The scaffold may also contain nutrients promoting cell survival and growth, and possibly antibiotics to prevent any bacterial in-growth in the canal systems. The engineering of nano scaffolds may be useful in the delivery of pharmaceutical drugs to specific tissues.[28]

VII. Injectable scaffold delivery

Hydrogels are injectable scaffolds that can be delivered by syringe. Hydrogels have the potential to be noninvasive and easy to deliver into root canal systems. In theory, the hydrogel may promote pulp regeneration by providing a substrate for cell proliferation and differentiation into an organized tissue structure.[29] Past problems with hydrogels included limited control over tissue formation and development, but advances in formulation have dramatically improved their ability to support cell survival.

Table 2: Potential technologies for regenerative endodontic procedures.

Technique	Image	Advantages	Disadvantages
Root-canal revascularization: open up tooth apex to 1 mm to allow bleeding into root canals		✓ Lowest risk of immune rejection ✓ Lowest risk of pathogen transmission	➢ Minimal case reports published to date ➢ Potential risk of necrosis if tissue becomes reinfected
Stem cell therapy: autologous or allogenic stem or cells are delivered to teeth via injectable matrix		✓ 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 the laboratory in sheets and implanted surgically		✓ Sheets of cells are easy to grow ✓ More stable than an injection of dissociated cells	➢ Sheets lack vascularity so only small constructs are possible ➢ Must be engineered to fit root canal precisely
Scaffold implant: pulp cells are seeded onto a 3-D scaffold made of polymers and surgically implanted		✓ Structure supports cell organization ✓ Some materials may promote vascularization	➢ Low cell survival after implantation ➢ Must be engineered to fit root canal precisely
3-D cell printing: ink-jet-like device dispenses layers of cells in a hydrogel which is surgically implanted		✓ Multiple cell types can be precisely positioned	➢ Must be engineered to fit root canal 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
Gene therapy: mineralizing genes are transfected into the vital pulp cells of necrotic and symptomatic teeth		✓ May avoid cleaning and shaping root canals ✓ May avoid the need to implant stem cells	➢ Most cells in a necrotic tooth are already dead ➢ Difficult to control ➢ Risk of health hazards ➢ Not approved by the FDA

Whole-tooth bioengineering

Whole-tooth bioengineering has always been the ultimate goal of regenerative dentistry. Despite recent progress in this field, we are still facing a number of difficult challenges to overcome. The basic principle of this "organ engineering" approach is understanding the mechanisms that regulate the embryonic tooth development and recreating these events in vitro, mimicking the natural cascade of signaling that occurs during organ formation.[30] Due to its non-essential function and accessibility, it represents an important model to study organogenesis. In common with other ectodermal appendages, like hair follicles and exocrine glands (mammary, sweat, and salivary), tooth morphogenesis is guided by reciprocal interactions between epithelial and mesenchymal tissues and progresses through distinct stages.[31,32] The knowledge gained in bio-tooth engineering potentially could have a broader impact in the field of regenerative medicine and the repair of different organs.

Enamel regeneration

The first synthetic generation of apatite nanorods was based on an aqueous solution of hydroxyapatite titrated to pH 2 in conjunction with surfactant docusate sodium salt as a colloidal suspension solution.Adjusting this solution to only slightly acidic conditions (pH 5.8) resulted in the precipitation of 200–400 nm long apatite crystals with a Ca/P (Calcium/Phosphate) ratio of 1.6, fairly close to atomic Ca/P ratio of hydroxyapatite at 1.67.28 This study represented the first successful approach toward the synthetic generation of parallel-aligned and elongated enamel-like apatite crystals.[33] Recently, a three-step synthetic process was conceived to mimic key aspects of initial enamel formation, including (i) conjugation of carboxymethyl chitosan (CMC) with alendronate (ALN) to stabilize amorphous calcium phosphate (ACP) and form CMC/ACP nanoparticles, (ii) application of sodium hypochlorite (NaClO) to degrade the CMC-ALN matrix generated in step (i), and (iii) use of 10 nmol•L−1 glycine (Gly) to guide HAP/ACP (hydroxyapatite/ amorphous calcium phosphate) nanoparticles to organize into well-ordered rod-like apatite crystals. This process is based on a polysaccharide/bisphosphonate matrix (chitosan/alendronate) and mimics key steps of initial amelogenesis, including (i) formation of a Ca/P-rich amelogenin protein matrix, (ii) enzymatic degradation and continued crystal growth, and (iii) crystal elongation as facilitated by elongated amelogenin fragments.[34]

Future directions

To this date, enamel tissue engineering remains a unique biotechnology challenge. Progress in enamel bioengineering is limited partially due to the high level of specialization and interconnectivity of the cells involved in enamel deposition, and also because of the highly evolved materials properties of biological enamel

Drawbacks of regerative endodontics

Discoloration
Poor root development
Insufficient bleeding
Root canal calcification/obliteration

CONCLUSION

We have entered a new era in the regeneration of orofacial structures, where molecular enhancement by osteoinductive materials and stem-cell-based therapies can be used to improve and expedite clinical outcomes. Current active research areas of stem-cell-based therapy in dentistry are focused on tissue engineering and chair-side cellular grafting approaches that may result in more predictable regenerative outcomes in the future. The success of regenerative endodontics will depend on how closely multidisciplinary teams of clinicians, engineers, scientists, and technicians can work, each contributing his own area of expertise to expand research. There is an extensive need to translate preclinical research in to clinical realities. Even though it is a long way to go, once the potential of regenerative endodontics is unleashed, it would be of immense clinical advantage and benefit to the millions of patients in the field of dentistry.

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