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Review Article

Regenerative endodontics: A new era of clinical protocol

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ABSTRACT:

The high susceptibility of teeth to damage combined with non-regenerative nature of dental tissue emphasize the need for replacement tooth therapy. Until the present time the field of restorative dentistry and material sciences have combined efforts to produce a variety of synthetic materials for use in restoration of damaged dental hard tissue. With advances in dentistry such as improved irrigation protocols, better visibility to the operating site andincreased skills of endodontists, regenerative endodontic procedures have come into the limelight. These potential approaches include root-canal revascularization, stem cell therapy, scaffoldimplant, tissue engineering. This article gives an in-depth detail of various regenerative approaches.

Keyword: non-regenerative nature, regenerative endodontic procedures, stem cells, scaffoldimplant.

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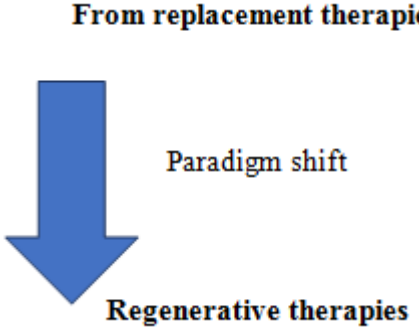
INTRODUCTION

Every year uncountable teeth are saved by root canal therapy. Eventhough current treatment mode offer high level of success, yet an ideal form of therapy consists of regenerative approaches in which diseased pulp tissue is removed and replaced with healthy pulp tissue to revitalize it. It is defined as a biologically based procedure to replace damaged structures as dentin, root structure and cells of pulp dentin complex[1] (Murray). It is a treatment of immature teeth is considered as a "Paradigm shift" as there is the potential for further root maturation. Clinically, regenerative endodontic procedures (REPs) involve disinfection of the root canal system without damaging the endogenous stem cell. Once the tooth becomes non-vital, growth of root stops making the tooth weak. As a result of which it is unable to bear normal physiological forces of mastication and hence, high root fracture rate with poor prognosis in long term. About 50% of such teeth will be lost in the first ten years following trauma despite being endodontic treated[2]. REP uses the concept of tissue engineering to replace the root canals and surrounding tissue[3]. Other name for regenerative endodontics is revascularisation, revitalisation, maturogenesis.



OBJECTIVE

REPs have main aim of inducing further root development and thickening of root dentinal walls and to replace damaged tooth structures including dentin, root structures.

1. To regenerate pulp like tissue - of the pulp–dentin complex.
2. To regenerate damaged coronal dentin.
3. To regenerate resorbed root, cervical or apical dentin.

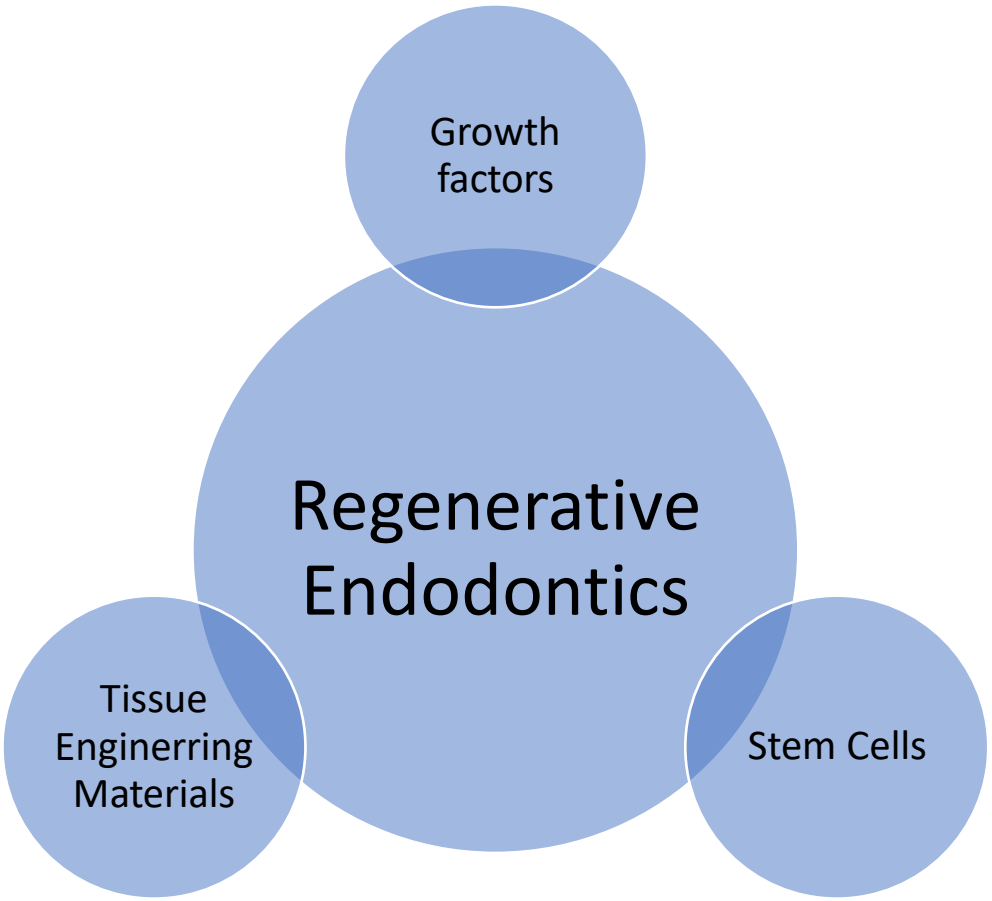
HISTORY

Regenerative dental procedures have a long history[4,5,6]

S.No	Name	Year	Invention
1.	Dr. B. W. Hermann	1952	the application of Ca(OH)2[4]
2.	Dr. Nygaard-Ostby	1961	Use a blood clot to re-vascularize tissue within the root canals of Teeth[6] as blood clot play similar role of clot in healing of other area.
3.	Rule DC, 1966	Rule DC, 1966	Use of double antibiotic paste
4.	Hoshino	1993	Use of triple antibiotic paste
5.	Iwaya	2001	Evoked intracanal bleeding step
6.	Branchs& Trope	2004	Case report on immature mandibular reports

PRINCIPLE

The principles of regenerative medicine can be applied to endodontic tissue engineering. Regenerative endodontics comprises research in adult stem cells, growth factors, organ-tissue culture, and tissue engineering materials.



GOALS

- **Primary**-elimination of symptoms and evidence of bone healing.
- **Secondary**-increased root length along with increased root thickness
- **Tertiary**-positive response to vitality test

- **Pinnacle of regenerative goals-** histologic confirmation for structural and restoration functional

GROWTH FACTORS

These are the proteins which attach to the receptors present on the cell and promote cellular proliferation and/or differentiation.

FUNCTION

- To stimulate angiogenesis
- To stimulate division of neighbouring cells.
- Dentin being a reservoir of growth factor and cytokines. These factors released during dentinogenesis become sequestrated and fossilized into the dentin after biomineralization[7].

FOLLOWING TABLE ELUCIDATED VARIOUS GROWTH FACTORS AND THEIR FUNCTIONS[8]

S. No	Growth Factors	Functions
1.	Fibroblast Growth Factors	Chemotaxis and Angiogenesis
2.	Vascular endothelial growth factors	Chemotaxis, Mitogenesis, and Angiogenesis
3.	Platelet-derived growth factors	Angiogenesis
4.	Nerve growth factors	for survival and growth of nerve fibers
5.	Bone morphogenetic protein-7	Mineralized tissue formation
6.	Transforming growth factor-alpha	Induces epithelial and tissue structure development
7.	Transforming growth factor-beta	It is present in dentin matrix and has been used to promote mineralization of pulp tissue.

STEM CELLS

It is defined as a clonogenic cells capable of both self-renewal and multi lineage differentiation. They are classified on the basis of their origin under two categories – embryonic/fetal or adult/ post-natal[9].

ON THE BASIS OF THEIR SOURCE

- allogenic
- autologous
- xenogenic
- syngenic.

ON THE BASIS OF POTENCY

- Totipotent
- Pluripotent
- Multipotent
- Unipotent

S. No	Stem cells	Function
1.	Stem cells from human exfoliated deciduous teeth(SHED)	Differentiate into odontonblast-like cells that form dentin like structures.
2	Periodontal ligament stem cells (PDLSCs)[13]	Present in enzymatically digested PDL. Can form cementum / PDL like structures.
3	Stem cells from apical papilla (SCAPs)	Found at apices of developing teeth at junction of apical papilla and dental pulp. They can undergo odontoblastic, osteogenic, neurogenic differentiation.
4	DPSCs[10]	Responsible for dental repair. Can regenerate pulp-dentin like complex.
5.	bone marrow stem cells (BMSCs)[11,12]	Dentinogenic, Osteogenic, Angiogenic, and Neurogenic differentiation potential

A small population of competent progenitor stem cells may exist within the dental pulp throughout life and are called as pulp stem cells or in case of immature teeth human exfoliated deciduous teeth (SHED). Pulpal stem cells were first derived from permanent third molar in 2000 by Gronthos. Sometimes pulp stem cells are called odontoblastoid cell as they appear to synthesis and secrete dentin matrix[14]. It is more economical when compared to cord blood and may be complementary to cord cell banking. Ideally suited for young patients with mixed dentition who had suffered trauma in immature permanent teeth. After severe pulp damage or mechanical or caries exposure,the odontoblasts are often irreversibly injured beneath the woundsite [15,16]. Odontoblasts are postmitotic terminally differentiatedcells, and cannot proliferate to replace subjacent irreversibly injuredodontoblasts[17].According to Chrepa et al. in 2015 bleeding-induction inside the root canals of mature teeth with periradicular lesions expressed Multipotent Stem Cell (MSC) markers and demonstrated intense mineralizing differentiation potential with humoral and cellular components of immunity.[18]

One of the major obstacles is to obtain stem cells that will continually divide and produce cells or pulp cells that can be implanted into the root canal systems. Possibilities are the development of an autogenous human pulp stem cell line that isdisease- and pathogen-free, and/or the development of a tissue biopsy transplantation technique using cells from the oral mucosa, as examples.

The use of a human pulp stem cell line has the advantage that patients do not need to provide their own cells through a biopsy, and that pulp tissue constructs can be premade for quick implantation when they are needed. If a patient provides their own tissue to be used to create a pulp tissue construct, it is possible that the patient will have to wait some time until the cells have been purified and/or expanded in number.This is because it is found that many adult tissues contain only 1 to 4% stem cells, so purification is needed[19].

Different techniques of tissue engineering[20]

- Scaffold implantation
- Injectable scaffold delivery

SCAFFLOLD IMPLANTATION

Three dimensional porous solid biomaterials that provide physio-chemical and biological three-dimensional micro-environment for cell growth and differentiation, promoting cell adhesion, and migration[21]. Serve as a carrier for morphogens in cell and in protein therapy.

Cells are often implanted or seeded into an artificial structure capable of supporting three- dimensional tissue formation. Its degradation rate coincides rate of tissue formation. A high porosity and an adequate pore size facilitates cell seeding and diffusion throughout the whole structure of both cells and nutrients[22].These structures are known as scaffold. It usually serves at least one the following function:-

- Allow cell attachment and migration
- Deliver and retain cells and biochemical factors
- Provide structural support and shape to construct
- Enable diffusion of vital cell nutrients and expressed products[23]

CLASSIFICATION

1. Based on form-
- Solid blocks
- Sheet
- Porous sponges

2. Based on presence or absence of cells-
- Cell free scaffold
- Scaffold loaded with stem calls

3. Based on degrability of matrices:-
- Biodegradable
- Permanent or biostatable

Natural scaffolds include PRP, PRF, Collagen, blood clot etc. Cell homing by intracanal bleeding evoked by the instrumentation of periapical tissues is the most simplistic endodontic approach in clinical practice. During dental pulp regeneration, an ideal scaffold shouldalso ensure good neurovascular supply to new pulp tissue.Eg. DPSCs are seeded on 3-D polyglycolic acid matrix,grown in vitro and surgically implanted.

DISADVANTAGES

- low cell survivals after implantation
- must be engineered to fit root canal precisely

INJECTABLE SCAFFOLD DELIVERY

Rigid tissue engineered scaffold structures provide excellent support for cells used in bone. However, in root canal systems a tissue engineered pulp is not required to provide structural support of the tooth. This will allow tissue engineered pulp tissue to be administered in a soft three-dimensional scaffold matrix, such as a polymer hydrogel. Polymerizable hydrogel alone / containing cell suspensions are delivered by injections[24]. It may provide regeneration by providing substitute for extracellular matrix (ECM).Hydrogels have the potential to be non-invasive and easy to deliver into root canal systems. They promote pulp regeneration by providing a substrate for cellproliferation and differentiation into an organized tissue structure.

DISADVANTAGES[25]

- low cell survivals
- limited control over tissue formation
- Early stage research has yet to prove functional in vivo

CONCLUSION

Regenerative endodontics strategies have tremendous potential to be an effective, safe, biological mode to save teeth. These procedure presents a new era in biologicaland clinical endodontics. The success of regenerative procedures contributes to 90%[26]. Eventhough these procedures are widely available, yet their success depends on tissue engineering therapies to regenerate pulp dentin tissue. The proposed therapies involving stem cells, growth factors, and tissue engineering all require pulp re- vascularization, in itself an enormous challenge. It has certain disadvantages such as discoloration of teeth. In future, large-scale clinical studies should be performed with patients of different ages, more complex tooth types and with longer follow-up periods.

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