

REGENERATIVE ENDODONTICS

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ABSTRACT

Regenerative endodontics is a rapidly evolving discipline focused on biologically restoring the pulp dentin complex to revive vitality in non-vital teeth. Unlike traditional endodontic therapies that rely on inert materials to preserve structure, regenerative techniques, aim to re-establish natural structure and function by harnessing advancements in tissue engineering. This narrative review examines recent progress in stem cell applications, scaffold development, signalling molecules and protocols that contribute to successful regenerative outcomes. Advances in stem cell sources, biomimetic scaffolds and growth factor delivery systems have shown promising results, though challenges such as variability in outcome and the need for standardized clinical protocol remain. This review also highlights future directions, including gene therapy and 3-D bioprinting, which holds the potential to overcome current limitations and pave the way for effective and reliable biologically restorative dental treatments.

Key Words: - Regeneration, Scaffolds, Stemp Cells

INTRODUCTION:

It has been called a "paradigm shift" in the treatment of immature teeth with infected root canals, and regenerative endodontics is an interesting and emerging discipline that can lead to apical closure and continuing root development (1, 2, 3). Immature teeth with pulp necrosis have traditionally been treated with calcium hydroxide apexification and apical barrier techniques with mineral trioxide aggregate (MTA). However, since there is typically no further root development, the roots remain thin and fragile, increasing the risk of fracture and tooth loss. Regenerative endodontic procedures (REPs) that use endogenous stem cells that are inserted into the canal by cutting the periapical tissues to fill the empty space have recently been proposed. Traditionally, apexification procedures involving calcium hydroxide to induce apical hard tissue barrier formation or apical MTA plugs prior to root canal filling are used to treat immature permanent teeth with necrotic pulp/apical periodontitis (Frank 1966, Heithersay 1975, Rafter 2005). Long-term exposure to calciumhydroxide dressings on immature permanent teeth may raise the risk of root fracture (Andreasen et al. 2002). It seems that the apical MTA plug and calcium hydroxide apexification treatment outcomes are compatible (Rafter 2005, Chala et al. 2011).

However, an apexification procedure has no potential to restore the vitality of damaged tissue in the canal space and promote root maturation (thickening of the root canal walls

and/or apical closure) of immature permanent teeth with necrotic pulp.

In the year 2001, a new treatment option termed 'revascularization' was introduced in endodontics to manage an immature permanent tooth with apical periodontitis and sinus tract (Iwaya et al. 2001).

The term 'revascularization' was first used by Iwaya et al. (2001). Later, revitalization instead of revascularization was proposed as a more applicable term as the tissues regenerated in the canal space were not both hard and soft tissues, in addition to blood vessels (Huang & Lin 2008).

Based on a tissue engineering approach, the American Association of Endodontists accepted the term "regenerative endodontics" in 2007 (Murray et al. 2007).

In order to repair pulp tissue injured by infection, trauma, or developmental abnormalities, regenerative endodontics uses the trinity of tissue engineering, stem cells, biomimetic scaffold, and bioactive growth factors in the canal space (Nakashima & Akamine 2005).

The European Society of Endodontology (ESE) utilized the term "revitalization" in their 2016 position statement. Revascularization, revitalization, and regenerative endodontics are terms that are used interchangeably and synonymously in the endodontic literature.

"Biologically based procedures designed to replace damaged tooth structures, including dentine and root structures, as well as cells of the pulp–dentine complex" is the definition of

regenerative endodontics (Murray et al. 2007).

According to this definition, the goal of regenerative endodontic therapy (RET) is to repair the pulp-dentine complex in immature permanent teeth with necrotic pulp that has been harmed by infection, trauma, or developmental abnormalities.

TERMINOLOGY

In the endodontic literature, the term "revascularization" is widely used to describe the restoration of vascularity in the pulp space following severe lesions that cut off the blood supply to the pulp of juvenile teeth (4, 5).

Previous studies on this novel technique defined the insertion of a blood clot into the root canal as "revascularization" and demonstrated renewed root maturation in infected young teeth 6, 7.

According to regenerative endodontics, the pulp-dentine complex is restored as a result of further root development.

Numerous investigations demonstrate that this is not the case, as various tissues detected in teeth treated with regenerative endodontic protocols—including dentine, cementum, periodontal ligament, bone, osteoid, and possibly pulp—indicate "repair" rather than "regeneration" (8–9).

'Since "revitalization" refers to non-specific vital tissue rather than merely blood vessels, as the term "revascularization" suggests, it has been proposed (21).

All operations aimed at achieving organized restoration of the tooth pulp, including future therapies that have not yet been developed in the field of regenerative endodontics, are referred to by the widely accepted name "regenerative endodontic procedures" (REPs) (6).

After receiving the proper care, tissue damage brought on by trauma or infection will heal through either repair or regeneration (22). Regeneration is the process by which injured tissue is replaced by tissue that is identical to the original tissue and biological functions are restored (22, 23).

Repair is the process of replacing injured tissue with a new tissue that preserves biological functioning (22, 23).

The ability of the dental pulp to regenerate is limited (24). Following EDTA treatment, a large number of growth factors

embedded in the dentin matrix are released into the canal space during regenerative endodontic treatments (25).

It has been demonstrated that these growth factors can instruct pulp stem cells to develop into cells resembling odontoblasts and create reparative dentin (26–29).

In regenerative endodontics, pulp tissue regeneration is currently accomplished in two ways: cell-free and cell-based. The idea of tissue engineering using stem cells, bioactive growth/differentiation agents, and biomimetic scaffolds is the foundation of both strategies.

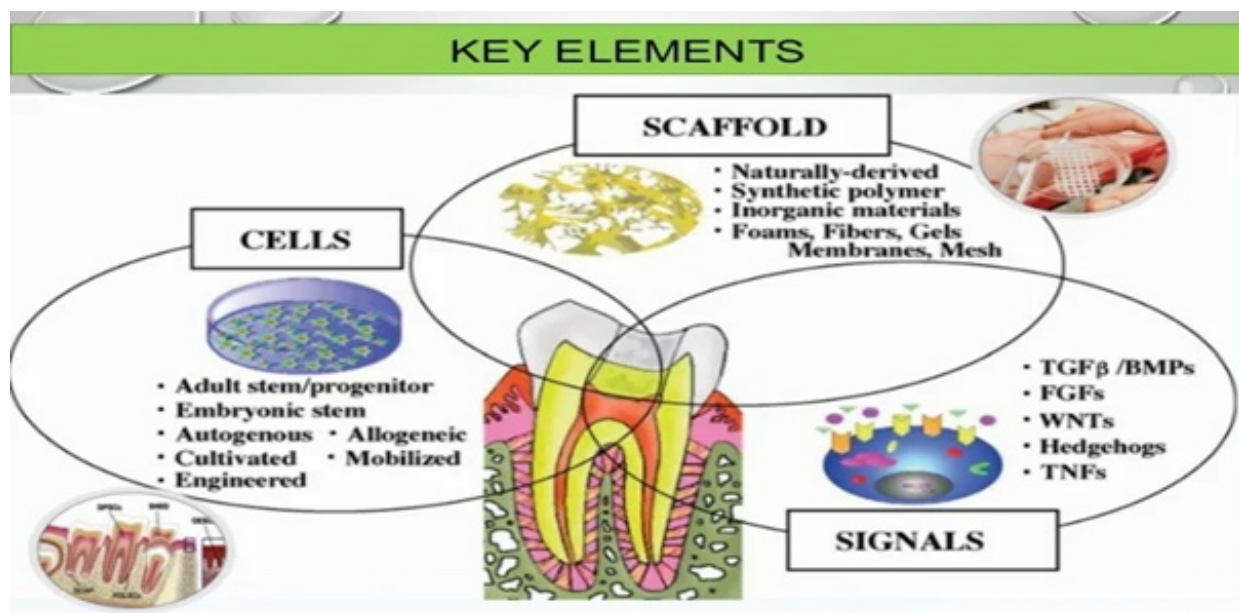
One could think of clinical regenerative endodontic techniques as a cell-free method. Isolation and ex vivo proliferation of stem cells seeded in the scaffold and subsequently transplanted into the canal space are prerequisites for the cell-based strategy (73, 74, 75, 76, 77, 78, 79).

Technically, the cell-free approach is simpler than cell-based approach because the former does not have to be concerned about stem cell source, and isolation. However, in the cell-free approach the endogenous stem cells are not pulp tissue specific and can be from apical papilla, periodontal ligament or bone marrow. The cell-based approach employs pulp tissue specific stem cells, such as dental pulp stem cells (DPSCs) (80), stem cells from exfoliated deciduous teeth (81), and stem cells from apical papilla (82). These stem cells have been shown to be capable of differentiating into odontoblast-like cells and produce dentine-like mineralized tissue (80, 81, 82).

Both cell-free and cell-based approaches to pulp tissue regeneration are still in the preclinical stage of experiments (84), but from a future perspective, pulp tissue regeneration sounds like an achievable goal based on the concept of stem cell-based pulp tissue engineering (85). Therefore, this approach has more promise to result in true regeneration. However, there are a number of issues associated with the cell-based approach that need to be resolved, including limited availability of stem cell source, isolation and ex vivo expansion of stem cells, good manufacturing practice facilities, contamination, stem cell bank, cost, regulatory issues, and clinicians' capacity to perform stem cell transplantation (83, 84).

Table 3. Characteristics and applications of stem cell types in regenerative endodontics

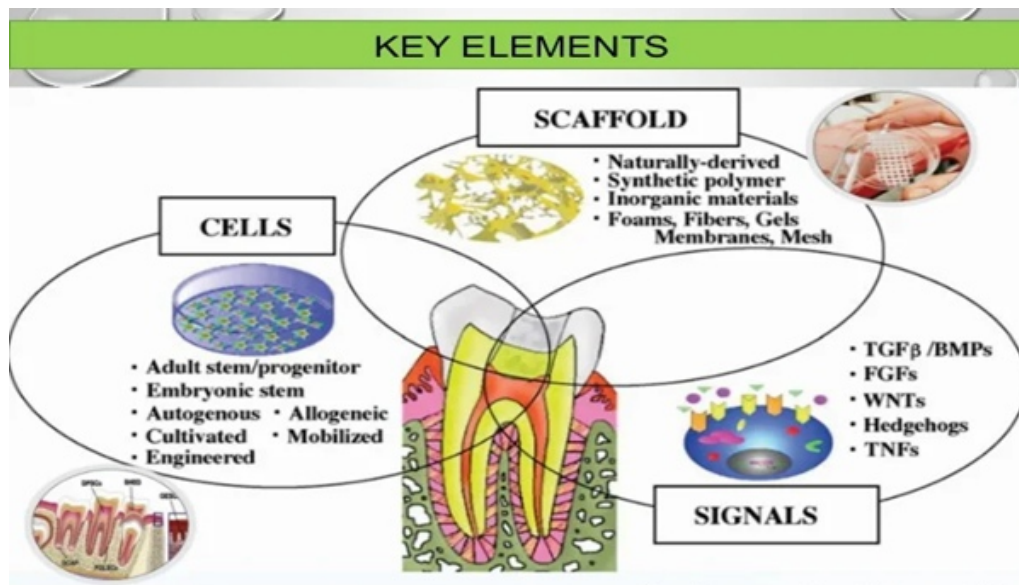
Type of stem cell	Source	Use in endodontics	Advantages
Dental pulp stem cells (DPSCs)	pulp tissue	Dentin regeneration and pulp tissue formation	odontogenic potential is higher
Stem cells from apical papilla (SCAPs)	Apical papilla	Root dentin is formed, root lengthening in immature teeth	Vitality in immature teeth
Periodontal ligament stem cells (PDLSCs)	PDL	Pulp repair	Pulp tissue repair
Dental follicle progenitor cells (DFPCs)	follicle	Pulp-dentin complex regeneration	Proliferation



Scaffolds in Regenerative Dentistry

Because they offer a supporting matrix that encourages cellular development, differentiation, and structure, scaffolds are essential in regenerative endodontics. The perfect scaffold should resemble the extracellular matrix found naturally in pulp tissue and be biocompatible and biodegradable. Hydrogels, polycaprolactone, polylactic acid, and natural polymers like collagen and chitosan are examples of common scaffold types [4]. Because collagen-based scaffolds are biocompatible and structurally comparable to pulp tissue, they are frequently utilized to promote cell migration and adhesion.

Because of their high water content, which promotes waste elimination and nutrient diffusion and creates the ideal environment for cellular activity, hydrogels have become more and more popular in regenerative endodontics.



Signaling Molecules:

Since they control tissue growth and stem cell differentiation, signaling molecules are essential to regenerative endodontics. Bone morphogenetic proteins (BMPs), vascular endothelial growth factor (VEGF), and transforming growth factor-beta (TGF- β) are significant signaling molecules in this area.

Gene therapy:

One intriguing method for obtaining reliable delivery of signaling molecules is gene therapy, which involves directly introducing genes encoding particular growth factors into cells [5]. Although this method is yet experimental, it might offer a controlled and prolonged release of chemicals necessary for regeneration.

Conclusion:

Regenerative endodontics is one of the most exciting developments in dentistry today and endodontists are at the forefront of this cutting-edge research. 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 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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