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CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 16, Issue, 06, pp.345-349, June 2025

International Journal of Recent Scientific Research

ISSN: 0976-3031

Subject Area : Public Health Dentistry

FROM BENCH TO CLINIC: A REVIEW OF EVOLVING LANDSCAPE OF REGENERATIVE DENTISTRY

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DOI: http://dx.doi.org/10.24327/ijrsr.20251606.006

ARTICLE INFO

Article History:

Received 13th May 2025
Received in revised form 27th May 2025
Accepted 17th June 2025
Published online 28th June 2025

Key words:

Bioengineering, Multipotent Stem Cells, Tissue Engineering, Tissue Scaffolds

ABSTRACT

Regenerative dentistry is an emerging and interdisciplinary field that seeks to restore the structure and function of damaged dental tissues using principles derived from stem cell biology, tissue engineering, and molecular science. This review paper offers an in-depth overview of the development, ideas, and prospects of regenerative dentistry treatments. By integrating biologically driven approaches with clinical practice, regenerative dentistry offers promising alternatives to conventional dental treatments such as root canals, implants, and prosthetics. The key components of regenerative procedures—stem cells, scaffolds, and growth factors—form the triad of tissue engineering, enabling the regeneration of dentin-pulp complexes, periodontal tissues, and even whole teeth. Various types of stem cells, including dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHED), and mesenchymal stem cells (MSCs), have shown potent differentiation capabilities critical for oral tissue regeneration. Scaffolds, both natural and synthetic, play a vital role in promoting cellular proliferation and matrix deposition, while growth factors such as BMPs, TGF-β, and platelet-derived concentrates further enhance tissue healing and integration. The article also traces the historical milestones that have shaped this specialty and highlights pivotal clinical studies that support its efficacy. Although significant advancements have been made, challenges remain in standardizing protocols and translating laboratory successes into predictable, routine clinical applications. Nonetheless, regenerative dentistry holds immense potential to revolutionize dental care, offering biologically sound, patient-specific, and minimally invasive treatment modalities. Continued interdisciplinary research and clinical trials are imperative to fully realize its trans formative impact in oral healthcare.

INTRODUCTION

Regenerative dentistry is a new and creative field that uses biologically based techniques to replace or repair damaged oral and dental tissues by combining concepts from stem cell biology, tissue engineering, and molecular science. Unlike traditional dental procedures that rely on synthetic materials or prosthetics, regenerative dentistry focuses on natural tissue regeneration, offering solutions such as pulp revitalization, dentin and enamel regeneration, and periodontal tissue repair. Its scope includes the use of stem cells, biomimetic scaffolds, and growth factors to facilitate healing and reestablish function in oral structures (Yelick& Sharpe, 2019; American Association of Endodontists, 2020).

The importance and relevance of regenerative dentistry are rapidly increasing in modern clinical practice. As oral diseases continue to affect over 3.5 billion people globally and impose significant healthcare costs, there is a pressing need for advanced, cost-effective, and minimally invasive alternatives to conventional treatments (Langer et al., 1995). Regenerative dentistry not only addresses these needs but also holds great promise for use in under-resourced regions, where access to dental care is limited and extractions are often favored over restoration (Diogenes et al., 2016). Additionally, its principles and technologies have broader implications in regenerative medicine, potentially contributing to organ repair and systemic health improvements (Gronthos S et al., 2000).

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However, the field arises in response to several challenges in traditional dental treatments. Conventional methods often involve mechanical or artificial replacements that do not truly restore biological function. These approaches may be costly, invasive, and offer limited long-term success, especially in cases involving extensive tissue damage. Regenerative dentistry offers a paradigm shift—aiming not just to repair, but to biologically heal and restore the natural structure and vitality of dental tissues (Petersen et al., 2005; Östby, 1961).

PRINCIPLES OF REGENERATIVE DENTISTRY

Triad of Tissue Engineering

Regenerative dentistry is grounded in the tissue engineering triad—stem cells, scaffolds, and growth factors (Langer et al., 1995).Stem cells serve as the regenerative engine, offering self-renewal and multipotent differentiation. Scaffolds, either natural (e.g., platelet-rich fibrin) or synthetic (e.g., β-tricalcium phosphate), provide structural support for cellular activity (Diogenes et al., 2016). Growth factors, such as BMPs, TGF-β1, and PDGF, guide cell proliferation, differentiation, and migration, essential for tissue formation (Diogenes et al., 2016; Iwaya et al., 2001).

Core Concepts

Revascularization was first successfully applied clinically by Iwaya et al., Stimulating blood supply restoration in immature permanent teeth (Iwaya et al., 2001).Regenerative Endodontic Procedures (REPs) were formally described by Murray et al. in 2007, emphasizing a tissue engineering approach to replace damaged dentin and pulp (Murray et al., 2007). Revitalization refers to biological reactivation of the pulp space, often through bleeding induction or scaffold-based techniques (Huang et al., 2008). These procedures are now recognized in guidelines by the American Association of Endodontists and European Society of Endodontology (American Association of Endodontists, 2020; Rutherford et al., 1993).

HISTORICAL BACKGROUND

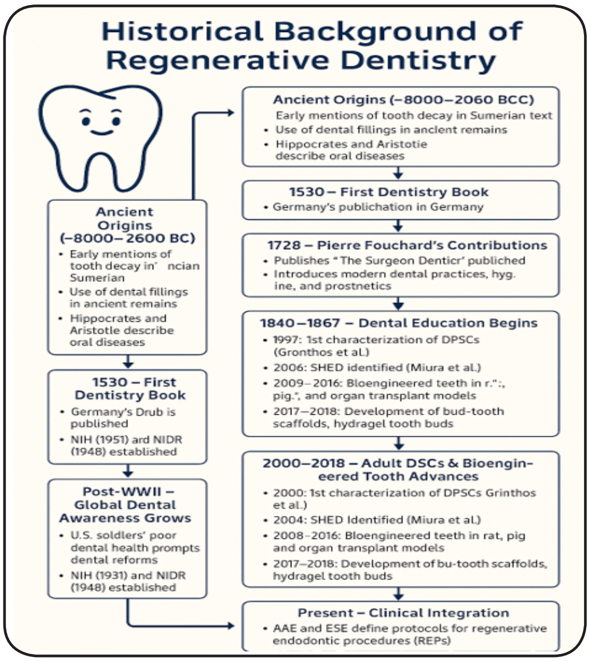

Figure 1. Historical Background of Regenerative Dentistry (Miura et al., 2003; Duailibi et al., 2004).

Abbreviations: **DSCs**: Dental Stem Cells, **NIH**: National Institutes of Health, **NIDR**: National Institute of Dental Research, **DPSCs**: Dental Pulp Stem Cells, **SHED**: Stem cells from Human Exfoliated Deciduous teeth, **AAE**: American Association of Endodontists, **ESE**: European Society of Endodontology, **REPs**: Regenerative Endodontic Procedures.

STEM CELLS IN DENTAL REGENERATION

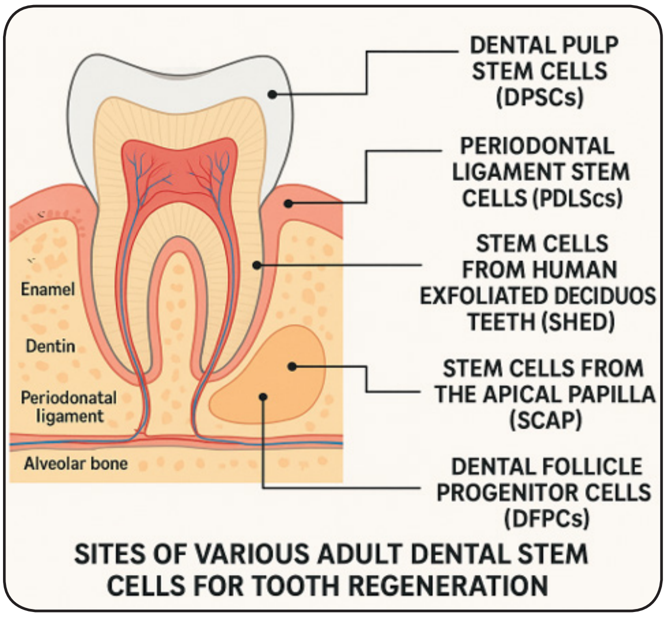

Figure 2. Stem Cells in Dental Regeneration (Yelick& Sharpe, 2019; American Association of Endodontists, 2020).

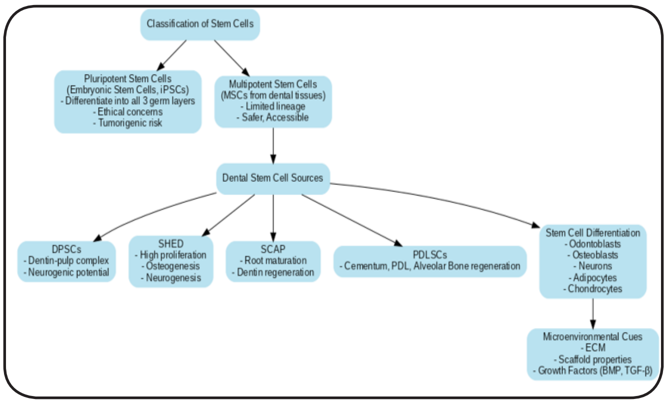

Figure 3. Classification of Stem Cells(Yelick& Sharpe, 2019; American Association of Endodontists, 2020; Langer et al., 1995; Diogenes et al., 2016 & Gronthos S et al., 2000).

Abbreviations: iPSCs – Induced Pluripotent Stem Cells, MSCs – Mesenchymal Stem Cells, DPSCs – Dental Pulp Stem Cells, SHED – Stem Cells from Human Exfoliated Deciduous Teeth, SCAP – Stem Cells from the Apical Papilla, PDLSCs – Periodontal Ligament Stem Cells, PDL – Periodontal Ligament, ECM – Extracellular Matrix, BMP – Bone Morphogenetic Protein, TGF-β – Transforming Growth Factor Beta

Current Clinical and Preclinical Applications

Preclinical studies using DPSCs and SCAP have shown success in regenerating pulp-dentin complexes, root elongation, and periodontal repair in animal models(Diogenes et al., 2016).Clinical applications include Regenerative Endodontic Procedures (REPs), which use stem cells and biological scaffolds to restore function in immature teeth with necrotic pulp (American Association of Endodontists, 2020). Tissue regeneration trials with SHED and DPSCs are being explored for craniofacial bone defects, pulp necrosis, and even neurological disorders (Yelick& Sharpe, 2019).Ongoing innovations include stem cell banking, injectable cell-based therapies, and 3D-bioprinted scaffolds for future personalized dental treatments.

SCAFFOLD MATERIALS IN REGENERATIVE DENTISTRY

Natural Scaffolds: Blood Clots, PRP, PRF

Natural scaffolds are biologically derived and widely used due to their biocompatibility and regenerative potential.

Blood clots form in the root canal space during regenerative endodontic procedures and serve as a natural scaffold that traps stem cells and releases growth factors, aiding in tissue regeneration (Östby, 1961 & Iwaya et al., 2001).

Platelet-Rich Plasma (PRP) and Platelet-Rich Fibrin (PRF) are autologous blood-derived materials containing platelets and leukocytes that release growth factors such as PDGF, VEGF, and TGF-β, essential for cell recruitment and angiogenesis (Yelick& Sharpe, 2019).

PRF has advantages over PRP due to its longer-lasting release of bioactive molecules and simplified preparation without anticoagulants

Synthetic Scaffolds and Biomaterials

Synthetic scaffolds offer controlled composition, structure, and degradation profiles, making them ideal for experimental and customized tissue engineering applications. Materials such as polylactic acid (PLA), polyglycolic acid (PGA), PLGA, and hydrogels have been studied extensively for their compatibility and ability to mimic the extracellular matrix (Langer et al., 1995).

Bio-ceramics like hydroxyapatite (HA) and tricalcium phosphate (TCP) promote mineralized tissue regeneration and are often used in bone and periodontal regeneration.Emerging smart scaffolds, including drug-loaded, thermos-responsive, or pH-sensitive materials, are being developed to enhance regeneration outcomes (Yelick& Sharpe, 2019).

Role in Supporting Cell Functions

Scaffolds play an essential biological and structural role by:

- Facilitating cell adhesion, enabling stem cells to anchor and establish contact.
- Supporting proliferation, maintaining a sufficient number of active cells.
- Directing differentiation through biochemical signals and scaffold architecture, helping form tissue-specific lineages such as dentin, pulp, and bone (Langer et al., 1995; Diogenes et al., 2016).

REGENERATIVE ENDODONTIC PROCEDURES (REPS)

Development and Standardization of REPs

Regenerative Endodontic Procedures (REPs) emerged as a biologically based treatment alternative to conventional root canal therapy, especially for immature permanent teeth with necrotic pulp. The concept began evolving in the 1960s with Nygaard-Østby's early work on pulp regeneration, and gained clinical traction in the early 2000s with case reports demonstrating revascularization techniques (Östby, 1961 & Iwaya et al., 2001). REPs aim not just to disinfect but to restore vital tissue, allowing for continued root development, apical closure, and thickening of dentinal walls. By the late 2000s, tissue engineering principles—stem cells, scaffolds, and growth factors—were formally incorporated into REP protocols (Murray et al., 2007).

Clinical Protocols and Guidelines (AAE, ESE)

Leading dental organizations have established standardized protocols to improve the predictability and success of REPs:

The American Association of Endodontists (AAE) recommends a three-phase approach: disinfection, induction of bleeding, and sealing of the canal. Disinfection is often achieved using low-concentration sodium hypochlorite and intracanal medicaments like calcium hydroxide or triple antibiotic paste (TAP) (American Association of Endodontists, 2020).

The European Society of Endodontology (ESE) also supports REPs, highlighting the importance of aseptic technique, biocompatible scaffolds, and the avoidance of cytotoxic irrigants and medicaments. Both organizations emphasize the importance of case selection, particularly in young permanent teeth with open apices (Galler et al., 2016).

Success Stories and Clinical Trials

Numerous clinical case reports and trials have demonstrated the success of REPs in promoting:

- Root lengthening
- Apical closure
- Thickening of canal walls
- Return of pulp vitality (in some cases)

A landmark study by Diogenes et al. Reported high rates of radiographic healing and root development in immature teeth treated with REPs (Diogenes et al., 2016).

Continued follow-ups in many cases have shown long-term retention of function, with no need for prosthetic intervention. Additionally, stem cell-based and scaffold-enhanced REP trials are ongoing to further improve tissue regeneration and standardization in broader clinical contexts (Yelick& Sharpe, 2019).

CLINICAL APPLICATIONS AND CURRENT TECHNOLOGIES IN REGENERATIVE DENTISTRY

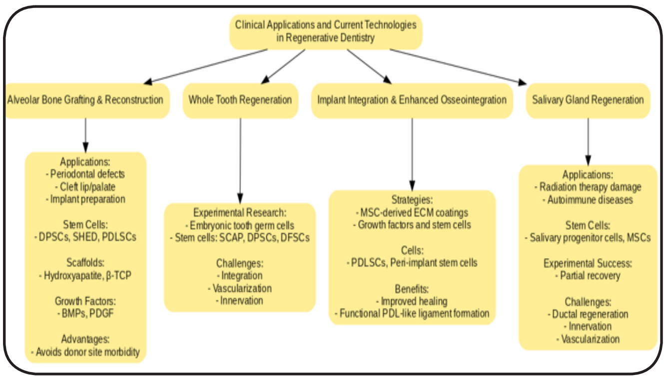

Figure 4. Clinical Applications and Current Technologies in Regenerative Dentistry(Yelick& Sharpe, 2019;Langer et al., 1995; Diogenes et al., 2016; Yu & Klein, 2020 & Ikeda et al., 2009).

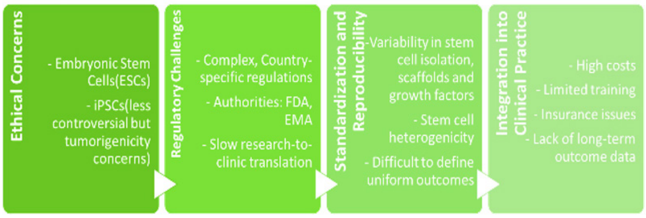

Figure 5. Ethical Concerns and Regulatory Issues (Yelick& Sharpe, 2019; American Association of Endodontists, 2020; Langer et al., 1995; Diogenes et al., 2016).

FUTURE DIRECTIONS IN REGENERATIVE DENTISTRY

Bioengineered Whole Teeth

The goal of whole-tooth regeneration involves replicating the natural tooth structure using a combination of epithelial and mesenchymal stem cells. Research has successfully generated tooth-like structures in animal models, showing functional characteristics such as enamel, dentin, and pulp formation (Yu & Klein, 2020; Ikeda et al., 2009).

Challenges include achieving functional integration, vascularization, innervation, and appropriate eruption. Recent advances include the use of tooth germ organoids and bioprinting of dental tissues (Otsu et al., 2014; Shopova et al., 2023).

Scaffold-Free Approaches

Scaffold-free tissue engineering, such as cell sheet technology and spheroid-based self-assembly, avoids complications related to scaffold biocompatibility and degradation. These techniques allow direct cell-cell interactions, promote natural ECM production, and improve tissue integration (da Silva, 2023).For example, DPSC - derived cell sheets have been used for pulp regeneration in vivo without the need for scaffolds (Huang et al., 2008).

Personalized Regenerative Dental Therapy

Advancements in genomics, bioprinting, and stem cell banking enable the development of patient-specific regenerative strategies. Using autologous cells like SHED or DPSCs ensures immune compatibility and reduces rejection risk. Technologies such as CRISPR gene editing, 3D-bioprinted scaffolds, and tailored growth factor delivery systems are being tested to create custom solutions for tissue loss or defect repair (Tsutsui, 2020; Wrzyszcz-Kowalczyk et al., 2021).

Interdisciplinary Collaboration for Innovation

The future of regenerative dentistry depends on synergistic collaboration across disciplines-including dentistry, bioengineering, material science, and stem cell biology. Research in smart biomaterials, nanotechnology-based scaffolds, and real-time regenerative imaging is driving innovation. Organizations like the National Institute of Dental and Craniofacial Research (NIDCR) promote interdisciplinary frameworks to bridge lab discoveries and clinical application (Wrzyszcz-Kowalczyk et al., 2021).

CONCLUSION

Regenerative dentistry marks a trans formative evolution in oral healthcare, shifting from conventional repair-based methods to biologically inspired therapies that aim to restore the form, function, and vitality of dental tissues. Through the use of stem cells, scaffolds, and growth factors, it holds immense promise for regenerating structures such as the pulp-dentin complex, periodontium, alveolar bone, and even whole teeth. While clinical procedures like REPs have shown encouraging outcomes, the field still requires extensive research, standardization, and cost-effective solutions to enhance its clinical viability. Future advancements in cell-free therapies, bioprinting, and gene editing, supported by interdisciplinary collaboration, will be vital to overcoming current limitations. Ultimately, the vision is to achieve personalized, minimally invasive, regenerative dental care that not only repairs but truly restores oral health, contributing to a higher quality of life for patients worldwide.

STATEMENTS AND DECLARATION

(a) Funding: This research received no external funding.

(b) Conflicts of Interest: The authors declare no conflict of interest.

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How to cite this article:

Apeksha Suryawanshi, Vikram Garcha, Vittaldas Shetty, Kadambari Ambildhok and Asawari Shidhore. (2025). From Bench to Clinic: A Review of Evolving Landscape of Regenerative Dentistry. *Int J Recent Sci Res*.16(05), pp.345-349.

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