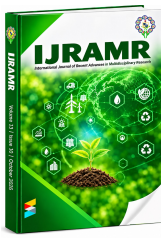
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REVIEW ARTICLE

CELL FREE/HOMING IN REGENERATIVE ENDODONTICS – A NOVEL TREATMENT STRATEGY FOR MANAGEMENT OF TRAUMATIZED ANTERIOR TEETH OPEN APICES

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ABSTRACT

Regenerative Endodontics" has revolutionized as an alternative, innovative, biologically based- treatment strategy for the treatment of traumatized necrotic young permanent anterior teeth with open apex representing a 'paradigm shift' in conventional root canal procedure. Gradually this treatment approach modified in various strategies including different scaffolds, growth factors, medicaments and stem cells. "Cell free or homing" is a recent novel promising technique based on stem cells belonging to host and their potential to regenerate functional pulp-dentin tissue complex and revolutionized the arena of regenerative endodontics. Extensive review of endodontic literature revealed paucity of literature pertaining to this new era of endodontics. Therefore, the aim of this research paper is to enlighten the domain of 'cell homing' in regenerative endodontics highlighting its mechanism, principle, advantages, clinical applications, limitations and challenges including future perspectives. The current article also helps to address the fact that the transition from "damaged to healing" utilising cell homing treatment strategy is not just a possibility, it is the inevitable future of regenerative endodontics in dental health science.

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INTRODUCTION

"Regenerative Endodontics" is a biological based treatment strategy representing a novel transformative alternative for the treatment of traumatized non-vital permanent teeth with open apex which comprises regeneration of the damaged pulp-dentin complex.[1-3]For the success of regenerative endodontic treatment procedure three critical factors are essential which consists mainly stem cells, physical scaffold and growth factors. Without these three factors, regeneration of damaged pulp tissue is highly impossible. Various modifications and advancements happened among these factors for the successful superior results.[4-8]Regeneration of the diseased pulp tissue usually consists of two different strategies like 'cell transplantation' and 'cell free or homing' approach.[9]

Cell transplantation stands out a vital approach in-vivo preclinical experimental set-up for the pulp tissue regeneration strategy using progenitor/stem cells mainly from dental pulp tissue. Sometimes these cells are recruited from other origins. In this technique, the transplanted stem/progenitor cells, irrespective of their origins, are presumed to participate in the regeneration/repair process of damaged pulp tissue not only by supplying cells per se but also by providing growth factors or signaling molecules released from transplanted cells as trophic factors to accelerate the cellular activity of endogenous as well as transplanted cells (Table 1).[10-14]In comparison to cell transplantation, cell homing completely depends on the recruitment of host-derived stem cells to the site of injury, making it a clinically feasible and minimally invasive approach.[15] Therefore, Cell free or homing represents a promising recently emerged innovative

technique encompassing endogenous stem cell recruitment and differentiation to restore and regenerate functional pulp-dentin complex. Cell homing is characterized by a process involving migration of endogenous cells from the host and their concentration into the targeted cite. The force behind this phenomenon includes either biological stimuli or physiochemical signalling from the apical tissue (Table 1).[16-18]There is paucity of scientific literature evidence pertaining to cell homing concept in the available endodontic literature. Therefore, the current research article was planned and designed to explore the conceptuality, technique, mechanism, advantages, limitations and future perspectives about the interesting era of cell homing in the futuristic science of tissue engineering for the restoration of pulp-dentin complex and to preserve the vitality of the tooth.

Table 1. Comparative Evaluation of Cell homing versus Cell Transplantation[10-15]

Comparative Parameter	Cell homing	Cell transplantation
Source of cells	From endogenous cells (Patient's or host own cells)	From exogenous cells (Transplanted cells/external cells)
Immune risk	Low (as autologous cells are used)	High (due to allogenic)
Invasiveness	Minimally invasive	Sometimes require surgery
Advantages	Utilises the patient's innate healing potential Practitioners don't require any training for recruitment and delivery of growth factors or signaling molecules. It is very easy to deliver growth factors into the root canals. No immune rejection is seen FDA approved cell homing products like growth factors are commercialized and easily available in the market.	Control over cell number maintenance Control over maintenance of cell type (various derivatives of stem cells)
Disadvantages	Scarcity of available endogenous cells at the defective sites	There are chances of patient's immune rejection, transmission of pathogens and tumor occurrence. Practitionersrequire knowledge in proper handling and application of stem cell products.
Limitations	Existing FDA approval pathways (growth factors)	High cost required for manufacturing stem cell products
Cost Effectiveness	Low cost as cell culture is not required	Associated with high cost due to requirement of cell processingprocedures like sophisticated storage procedures of cell homing contents such as cell cryopreservation/banking system, packaging, and shipping procedures.
Regulatory issues	None	FDA approval is required

REVIEW OF LITERATURE

'Cell homing' in context with pulp dentin complex applies to the concept of recruitment of host-derived stem cells to a specific targeted site using biochemical molecules such as chemokines, cytokines and growth factors.[1-5,12-17] Cell transplantation mainly involves introducing exogenous stem cells to the targeted damaged tissue site. In contrast, cell homing leverages the host's own innate reparative potential by stimulating the migration, proliferation, and differentiation of local stem cells.[18-21]The three critical key factors as mentioned in Table 1 are highly essential for the outstanding results of regenerative endodontic procedure following cell homing approach.

Table 2. Key components of Cell Homing [13-17]

Key Factors	Purpose
Physical Scaffolds	Provide a 3-dimensional structure for cell attachment and tissue growth. Scaffolds also provide structural support and release bioactive molecules to guide cell function. They are natural or synthetic scaffolds. Natural Scaffolds - Collagen, Fibrin, Chitosan Synthetic Scaffolds - PLGA, PCL Hydrogels and 3 dimensional printed scaffolds enhance cell infiltration and vascularization.
Chemo-attractants	Cell Homing efficiency depends on the microenvironment and signaling cues. They are signaling molecules like stromal-derived factor – (SDF-1) that direct stem cell migration. Dental pulp stem cells (DPSC), stem cells from apical papilla (SCAP), and periodontal ligament stem cells (PDLSC) are mobilized from periapical and periodontal tissues.
Growth Factors	Growth factors guide stem cell recruitment and differentiation. Different types of growth factors are employed. Growth Factors: Different proteins such as platelet-derived growth factor, vascular endothelial growth factor, fibroblast growth factor and bone morphogenetic proteins are released to energize stem cells. Cytokines:some cytokines like transforming growth factor beta and stromal derived factor – 1 play major roles in stem cell migration.

Mechanisms of Cell homingStrategy in Regenerative Endodontic Procedure: According to American Association of Endodontists, 'Cell homing'being a novel concept is referred to the "process involving the migration of host cells like stem cells or progenitor cells, to targeted tissue.In this therapeutic novel approach, the movement of these cells occurs to the injured targeted site with the continuous stimulation of biological signaling molecules.[12-16] In order to enhance the innate healing potential of host endogenous cells, wide array of signaling molecules associated with different varieties of physical scaffolds are introduced to the damaged tissue region which ultimately does intricate process of tissue regeneration. Cell homing comprises molecules that drive therapeutic efficacy, and may be less sensitive to procedural and patient variations. This innovative approach uses either natural or synthetic scaffolds that can deliver a wide array of bioactive pharmacological epigenetic modulators like HDACis, DNMTis, and ncRNAs, which are cost-effective and easily applied to stimulate pulp tissue regrowth.[10-14, 18-22]In addition to this, an array of proteins, peptides, and chemical compounds that are need to be identified may orchestrate endogenous cells to regenerate dental pulp-dentin complex.

Table 3. Scientific Molecular Principlesof Cell homing [21-28]

Molecular Stages	Action Happened
Recruitment of Stem cells	Bioactive singling proteinsare released in the root canal to attract mesenchymal stem cells, stem cells from the apical papilla and dental pulp stem cells.
Dentin-PulpComplex Regeneration	Differentiated odontoblast-like cells secrete new dentin, restoring tooth structure.
Neurogenesis and Angiogenesis	Growth factors result innew blood vessel formation (angiogenesis) and nerve regeneration, essential for pulp tissue functionality.

Table 4. Research Publications on Cell Free approach in Regenerative Endodontics

Author & Year	Type of the Publication	Aim/Objective	Conclusion	Published Journal
Kim et al, 2013 [9]	Original Research (In-vitro study)	To assess the release of active growth factors in experimental model.	Cell homing associated with number of advantages. These can be compared with development of clinical treatment procedures for regeneration of pulp-dentin.	Endodontics Topics
Saoud et al, 2016 [23]	Case series	To illustrate the potential of regenerative endodontic treatment strategies for mature permanent teeth associated with necrotic pulps and apical periodontitis.	Shows the potential of using regenerative endodontic procedure for mature non-vital permanent teeth with necrotic pulp or apical periodontitis.	Journal of Endodontics
He et al, 2017 [13]	Review	To update and benchmark other therapies with cell homing.	Cell homing uses new molecules that attract therapeutic efficacy, and may be less sensitive to procedural and patient variations.	Dental Clinics of North America
Jiang et al, 2017 [17]	Randomized Controlled Clinical Trial	To evaluatewhether a Bio-Gide collagen membrane has efficacy in promoting dentin formation in regenerative endodontic treatment.	The use of the Bio-Gide collagen membrane promoted the development of the dentin wall in the middle third of the root.	Journal of Endodontics
Shivashankar et al, 2017 [18]	A Triple Blind randomized controlled clinical trial	To compare the effect of platelet rich fibrin, induced bleeding technique and platelet rich plasma in the revascularization of tooth with necrotic pulp and open apex.	It is advantageous to perform induced bleeding technique as a standard endodontic procedure for revascularization of a non-vital immature permanent tooth	Journal of Clinical and Diagnostic Research
Nagesh et al, 2018 [24]	A clinical study	To evaluate the possibility of regaining pulp sensibility in mature necrotic teeth using modified regenerative endodontic procedures by inducing bleeding in root canals and using platelet-rich fibrin.	The presence of sensibility is indicative of the formation of vital pulplike tissue. Re-establishing real pulp tissue after regenerative endodontic treatment is debatable and still needs high level of evidence with large-scale investigations.	Journal of Endodontics
Duncan et al, 2018 [25]	Review	To summarize current views on the role and therapeutic potential of growth factors within endodontic cell homing.	-	Curr Oral Health Rep
Lin et al, 2017 [21]	Randomized controlled trial	To compare the results of regenerative endodontic treatment in comparison to apexificationin immature permanent teeth with pulp necrosis and apical periodontitis.	Regenerative endodontic treatment and apexification achieved a comparable outcome in regard to the resolution of symptoms and apical healing. Regenerative endodontic treatment showed a better outcome than apexification regarding increased root thickness and root length.	Journal of Endodontics
Eramo et al, 2018 [12]	Systematic Review	To examine cell homing pertaining to dental pulp regeneration, selecting articles on in vitroexperiments, in vivo ectopic transplantation modelsand in situ pulp revascularization.	Cell homing strategiesfor pulp regeneration need further understanding andimprovement if they are to become a reliable andeffective approach in endodontics.	International Endodontic Journal
Meschi et al, 2018 [16]	Retrospective case series	To evaluate the outcome of regenerative endodontic procedures of immatureand infected permanent teeth pertaining to periapical bone healing, root development, and pulp vitality.	Thirty-six months following regenerative endodontic treatment procedure more favourable results were obtained pertaining to periapical bone healing, root development, and pulp vitality.	Journal of Endodontics
Widbiller et al, 2018 [31]	In vitro study	To evaluate whether pulplike tissue formation in empty root canals following application of the stem cells is possible and whether this could be bombarded by dentin-derived growth factors.	The new cell homing model provides evidence that fibrin derivatives make applicable scaffolds and that dentin-derived proteins induce chemotaxis and pulplike tissue formation.	Journal of Endodontics
Ulusoy et al, 2019 [19]	Prospective Randomized trial	To compare the clinical and radiographic outcome of regenerative endodontic treatment using platelet-rich plasma (PRP), platelet-rich fibrin (PRF), a platelet pellet (PP), and an induced blot clot (BC).	PRP, PRF, and PP can provide similar clinical and radiographic outcomes to BC without the need for prior apical bleeding and with significantly less tendency for root canal obliteration.	Journal of Endodontics
Arslan et al, 2019 [22]	Randomized controlled trial	To compare clinical and radiographic outcomes of regenerative endodontic procedures with that of conventional root canal treatment in necrotic mature teeth with periapicalradiolucencies.	Regenerative endodontic procedures have the potential to be used as a treatment option for mature teeth with large periapicalradiolucencies.	Journal of Endodontics

Continue ….

Shetty et al, 2021 [20]	A Prospective clinical study	Qualitative and quantitative evaluation of the outcomes of regenerative endodontic procedure (REP) on human immature necrotic teeth with apical periodontitis using cone-beam computed tomography (CBCT)	This study highlighted that the expected outcome of radiographic root development was less predictable when immature permanent teeth with periradicularpathosis were treated with REP.	Clinical Oral Investigation
Cui et al, 2021 [28]	Review	To summarize current understanding of the biological basis of clinical treatments for immature necrotic permanent teeth and the roles of dental mesenchymal stem cells during cell homing process	-	Front Cell DevBiol
Ahmed et al, 2021 [26]	Review	Elaborating on cell homing and cell transplantation techniques in the treatment of irreversibly inflamed or necrotic pulp, which is aimed at regenerating a fully functional pulp-dentin complex.	-	Stem Cells International
Tirez E et al, 2022 [10]	Systematic Review	To compare the apical healing, root maturation and histological characteristics of teeth treated with cell-based versus cell-free techniques.	Currently, the number of randomized clinical trials on this topic are very scarce. This is probably due to the limited infrastructure and lack of resources to apply the cell-based technique.	Materials (Basel)
Yan H, et al, 2023 [11]	Review	To provide an overview of vital pulp tissue and various strategies to promote regeneration of damaged pulp tissue. The cell homing technique will be reviewed through clinical trials.	Regenerative endodontics using the cell-homing technique shows promising results that can be translated into clinical practice.	Journal of Endodontics
Fouad et al, 2024 [27]	Histo-morphological study	To evaluate the regenerative potential of photobiomodulation (PBM) on RET in immature roots when photodynamic therapy (PDT) protocol is implemented for root canal disinfection in canine model.	The disinfection protocol of PDT and subsequent irradiation with low power laser in PBM protocol pose a promising potential for regenerative endodontics in immature teeth.	BMC Oral Health
Quigley et al, 2024 [29]	Review	To describe the current state of bioactive-biomaterial/scaffold-based engineering strategies to stimulate dentine-pulp regeneration, explicitly focusing on epigenetic modulators and therapeutic pharmacological inhibition.	-	Bioactive Materials
Alharbi et al, 2024 [30]	Comprehensive review	To describe the intricate processes of cell homing in the context of regenerative endodontics, particularly focusing on its application in immature teeth with open apices.	-	Cureus
Kim et al, 2025 [14]	Review	To explore how biomolecules and scaffold materials enhance the recruitment of endogenous stem cells to the site of damaged dental pulp tissue, thereby promoting repair and regeneration.	-	Cells
Shi et al, 2025 [15]	Review	To present a panorama of emerging potential tissue engineering strategies for pulp-dentin complex regeneration from cell transplantation and cell homing perspectives, emphasizing the critical regenerative components of stem cells, biomaterials, and conducive microenvironments.	-	Journal of Advanced Research

Although both cell transplantation and cell homing are scientifically tested valid approachescell homing possess a greater number of advantages which are essential for the development of alternative clinical therapies for the regeneration of dental pulp-dentin tissue.[2-6] The scientific molecular principles/mechanism established behind the process of cell homing comprises three important critical steps as described in Table 2.

DISCUSSION

Behind the heart of innovative, transformative approach of cell homing with regard to regeneration of pulp-dentin complex recruiting of endogenous stem cells to the site of damaged pulp tissue takes place by harnessing the body's own healing mechanisms.[9-11]When extensive literature search was performed using electronic database from inception to April 2025, it was evident that there was scanty literature available on cell homing treatment strategy. There are no long-term clinical trials consisting of larger sample size showing the comparative effectiveness of cell homing and validate its long-term success in regenerative endodontic treatment (Table 3). Most of the publications either case reports or comprehensive and narrative review articles.[9-31]Therefore, in this article, authors made an effort to construct a structured overview of different research papers published on cell homing approach which is elaborately tabulated in Table 3. In a recent study, Kim et al[9]investigators published an article showing regeneration of dental-pulp-like tissue using cell homing approach. This is the remarkable pioneer research work done under the domain of tissue engineering pertaining to regenerative endodontics.

In their experiment following in vivo implantation of endodontically treated real-size, native human teeth in mouse dorsum which was tested almost for 3 weeks.[9] The results showed delivery of some essential vital growth factors like vascular endothelial growth factor and fibroblast growth factor. These growth factors developed revascularizedconnective tissue with rich cells appeared to incorporate with the original dentin wall of the root canal. Additionally, following delivery of some combination of vital growth factors, more vascularized and cellularized pulp like tissue was formed. The newly formed tissue showed positive to VEGF antibody staining procedure. Histological examination demonstrated a newly formed dental pulp tissue which was dense with manycells surrounded by extracellular matrix.[9]In addition to this, erythrocyte-filled blood vessels were also evident containing endothelial-like cells. Scanning electronic images illustrated full of dental-pulp-like tissue in root canal starting from pulp chamber to root apex. As a result, this experiment can be highlighted in the endodontic history as these factors represent the first demonstration of regenerated dental-pulp-like tissue in endodontically treated root canals of real-size, native human teeth. [9] Apart from few studies, there are no randomized controlled clinical trials demonstrating the outcome of dental pulp-dentin regeneration using either cell transplantation or cell homing approaches (Table 3).[9-31]Hence regeneration of pulp tissue cannot be standardized as ultimate alternative to traditional root canal treatment. In order to meet the clinical demand as well as to make all dental practitioners to adopt this transformative treatment approach as a routine protocol in their clinical practice, the American Association of Endodontists (AAE) Foundation has enthusiastically opened huge gateway of proposals for clinical research work about regenerative endodontic treatment strategy consisting of $2.5 million grants.[10-12]

CONCLUSION

Cell homing in regenerative endodontic procedure can be definitely considered a ‘dream come true to tangible reality’ as it transforms from passive root canal filling procedure to active new tissue formation by harnessing the body’s innate healing potential. However, there are challenges that need to be overlooked before concluding it as the future in the panorama endodontic therapy and could be translated to regular clinical practice. Fortunately, ongoing tremendous research work along with technological advancements in biomaterials and growth factory delivery methods are paving the way for more predictable, biologically driven pulp tissue repair with functionality and vitality. Following upon standardized clinical protocols and rapid revolution in biomaterials, regenerative endodontic treatment modality may soon replace conventional root canal treatment as the ‘gold standard’ for preserving tooth vitality. Therefore, it is not too far from the transition to happen from "damaged tissue to healing tissue" phenomenon utilising cell homing treatment strategy. Moreover, cell homing in regenerative endodontic procedure is not just a possibility, it is the inevitable futuristic technology of regenerative endodontics.

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