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Application and Development of Biomaterials in Dental Pulp Regeneration

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Abstract. Dental pulp regeneration aims to restore the structure and function of injured pulp tissue by using biomaterials to establish a supportive regenerative microenvironment. This review evaluates the design requirements, applications, mechanisms, and limitations of biomaterials used for dental pulp regeneration. Key requirements include biocompatibility, interconnected porosity, controlled degradation, structural integrity, and injectability. Natural polymers such as collagen; synthetic polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(lactic-co-glycolic acid) (PLGA); hydrogels; and composite materials offer distinct biological and physical properties. These materials may influence cell adhesion, proliferation, migration, odontogenic differentiation, mineralization, and vascularization. However, these outcomes alone do not establish complete functional pulp regeneration, and no single material has been shown to consistently satisfy all regenerative requirements. Multifunctional and patient-adapted materials may better accommodate the anatomical complexity of the root canal while supporting reconstruction of the pulp–dentin complex. This review aims to critically assess current biomaterial strategies and identify the principal challenges and future directions for their clinical translation.

Keywords: dental pulp regeneration, biomaterials, scaffolds, pulp–dentin complex, tissue engineering

1. Introduction

Dental pulp is the highly vascularized and innervated soft connective tissue located within the tooth. It plays essential roles in nutrient supply, sensory perception, immune defense, and dentin formation [1]. Deep untreated caries, dental trauma, repeated restorative procedures, advanced periodontitis, chronic bruxism, and inherited susceptibility may expose the pulp to mechanical irritation or bacterial invasion, leading to inflammation and, in severe cases, necrosis [2]. These conditions can impair oral function and cause pain or sensitivity to thermal stimuli. Conventional treatments primarily control disease by removing infected tissue but do not restore the original structure and physiological functions of the dental pulp. Consequently, dental pulp regeneration has become an important area of oral regenerative medicine.

Because dental pulp has limited self-repair capacity after severe injury, treatment selection generally depends on the extent of inflammation, infection, and tissue necrosis. Traditional

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approaches, including root canal therapy and tooth extraction, may compromise tooth structure or oral function. Root canal therapy removes infected or necrotic pulp tissue, disinfects the canal system, and seals the prepared canals to reduce the risk of reinfection. Tooth extraction removes the affected tooth entirely. Although these methods can control infection and alleviate symptoms [3], root canal therapy is generally preferred when the natural tooth can be retained [4]. Nevertheless, complete disinfection cannot always be guaranteed, inadequate restorations may permit reinfection, and the treated tooth may require additional reinforcement [5]. Infection control alone therefore does not restore pulp vitality, vascularization, innervation, or continued dentin formation.

In this context, regenerative approaches aim not merely to eliminate infection but to re-establish living pulp-like tissue with physiological functions. Pulp regeneration may also facilitate continued root development in immature teeth. Biomaterials play a central role because they must exhibit biocompatibility, suitable pore architecture, and controlled degradability while supporting vascular and neural regeneration [6]. Scaffold-based strategies seek to reproduce important features of the biological environment and are therefore considered important for successful dental pulp regeneration [1]. Regardless of the material selected, the core objective is to balance biocompatibility, degradation behavior, mechanical stability, and clinical handling properties [7]. Such materials can provide a three-dimensional microenvironment for cell adhesion, proliferation, and differentiation, and some can also deliver growth factors or drugs in a controlled manner.

Current biomaterials nevertheless present limitations, including inadequate mechanical properties, poorly controlled degradation, manufacturing complexity, instability, restricted root-canal space, and difficulty translating laboratory findings into clinical treatments. This review summarizes the development of biomaterials for dental pulp regeneration, explains how different materials may influence cellular responses and tissue repair, compares their advantages and limitations, and identifies priorities for future research and clinical translation.

2. Basic requirements of biomaterials for dental pulp regeneration

2.1. Biological basis of dental pulp regeneration

Dental pulp regeneration imposes substantial demands on scaffold materials. In addition to providing physical stability, a scaffold must support the survival, proliferation, and differentiation of dental cells and create an appropriate environment for bioactive molecules. Biocompatibility is therefore a central consideration in material selection. A review of biomaterials for tooth regeneration states that scaffolds should be biocompatible and nontoxic, undergo biologically safe degradation, and support cell adhesion, proliferation, and differentiation [8]. These requirements are particularly relevant because dental pulp contains interacting cell populations, including odontoblasts, fibroblasts, vascular cells, and neural cells. Together, these cells maintain pulp structure, nutrition, sensation, and repair. A material that merely maintains cell survival may therefore be insufficient to restore normal pulp function or reconstruct a functional pulp–dentin complex.

Kim et al. examined how scaffold composition influences dental pulp cell behavior. Human dental pulp cells were cultured on type I collagen, type III collagen, gelatin, and chitosan scaffolds, and cell attachment, proliferation, alkaline phosphatase (ALP) activity, differentiation-related gene expression, and mineralization were evaluated. Cells attached and proliferated rapidly on collagen and gelatin, whereas chitosan did not adequately support cell growth [9]. These findings show that natural polymers can produce different cellular responses under the tested conditions. Collagen appeared more favorable than the other evaluated materials for supporting odontogenic activity,

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although this result does not establish its universal superiority across all scaffold designs and experimental settings.

Overall, biocompatibility should be evaluated together with the ability of a material to regulate cell proliferation and odontogenic differentiation. The favorable response to collagen and the weaker performance of some other natural polymers indicate that material composition should be optimized rather than selected solely on the basis of natural origin.

2.2. Porosity, degradation, and clinical requirements

Materials for dental pulp regeneration must meet biological requirements while retaining sufficient structural stability. Their architecture should permit cells to migrate into the scaffold and obtain nutrients and oxygen. An effective scaffold therefore requires interconnected pores that support cell infiltration and mass transport, while its degradation rate should remain broadly coordinated with new tissue formation. An ideal scaffold should be porous and permeable, degrade into nontoxic products, and permit the diffusion of growth factors, nutrients, and waste products [1]. Zhang et al. fabricated three-dimensional collagen scaffolds with mean pore sizes of approximately 20, 65, and 145 μm and cultured human dental pulp cells on them. The 65 and 145 μm scaffolds improved cell ingrowth and proliferation, while the 65 μm scaffold yielded the highest expression of dentin sialophosphoprotein (DSPP) and dentin matrix protein 1 (DMP-1), as well as the largest mineralized area and greatest vascular pulp-like tissue formation [10].

These results suggest that scaffold architecture can influence cell adhesion, migration, proliferation, and differentiation, with downstream effects on vascularization and pulp-like tissue formation. However, they do not demonstrate a simple linear relationship between pore size and regenerative performance. The favorable outcomes observed with the 65 μm scaffold indicate that an intermediate pore architecture may provide a useful balance under the conditions examined. The objective should therefore be to identify an optimal pore structure rather than maximize porosity. Root-canal anatomy creates an additional clinical challenge because the available space is narrow and irregular. Injectable scaffolds can be delivered into narrow and tortuous locations and can conform to complex pulp-cavity geometry [11]. This property makes hydrogels and other injectable systems attractive for clinical application. As shown in Figure 1, a gelatin methacryloyl (GelMA) hydrogel containing dental pulp stem cells has been proposed to promote endothelial cell activity and angiogenesis through extracellular matrix–integrin signaling [12]. An ideal scaffold should therefore balance porosity, degradation, structural stability, and injectability rather than maximize any single property.

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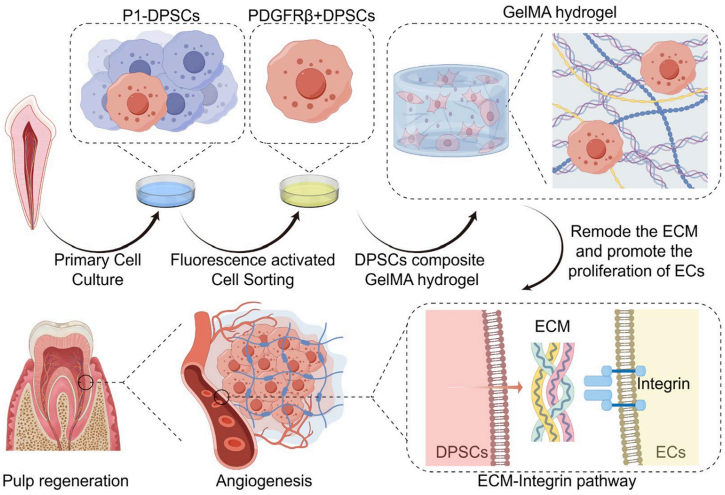


Figure 1: Schematic illustration of a gelatin methacryloyl hydrogel incorporating platelet-derived growth factor receptor beta-positive (PDGFRβ+) dental pulp stem cells and its proposed role in promoting endothelial cell activity and angiogenesis through extracellular matrix–integrin signaling [12]

3. Applications of biomaterials in dental pulp regeneration

Natural polymers used in dental pulp regeneration include collagen, gelatin, chitosan, and hyaluronic acid. These materials have been widely investigated because they can reproduce selected biological features of the extracellular matrix. Collagen is especially promising: Kim et al. reported greater proliferation and differentiation of human dental pulp cells on collagen than on gelatin or chitosan, with an intensely mineralized extracellular matrix in the collagen group [9]. Within that experimental system, collagen provided both structural support and biochemical cues conducive to odontogenic differentiation. Natural polymers may nevertheless have limited mechanical strength and variable degradation behavior. Soares et al. compared a chitosan–collagen scaffold with and without a calcium aluminate mineral phase to combine the biological interactions of organic polymers with the mineralization-related properties of an inorganic component [13]. This comparison illustrates how complementary components may address specific shortcomings, although one material system cannot establish that composites universally overcome the limitations of natural polymers.

Synthetic polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(lactic-co-glycolic acid) (PLGA) permit greater control over mechanical properties and biodegradation than some natural polymers. Synthetic scaffolds can also be customized in size, shape, and mechanical behavior, and their manufacture can be standardized [1]. These properties favor reproducible fabrication, but synthetic polymers generally provide fewer intrinsic biological cues than extracellular matrix-derived materials.

Hydrogels represent another important material class because they can be injected into irregular root canals together with cells or bioactive agents. Injectable hydrogels undergo a sol–gel transition and can therefore conform to narrow and nonuniform pulp spaces [11]. This feature is clinically relevant because a prefabricated scaffold may not fit the geometry of each root canal precisely.

Composite biomaterials may integrate complementary properties. An organic polymer can provide biocompatibility and flexibility, whereas an inorganic phase may supply mineral ions and

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structural stability. Composite performance, however, depends on component selection, interfacial compatibility, degradation behavior, and fabrication method; combining materials does not necessarily produce additive benefits.

4. Mechanisms by which biomaterials promote dental pulp regeneration

4.1. Cell differentiation and mineralized tissue formation

A major mechanism by which biomaterials may contribute to pulp regeneration is the regulation of dental pulp stem/progenitor cells (DPSCs). Rather than functioning only as mechanical supports, scaffolds can affect cell attachment, proliferation, migration, and differentiation through their surface chemistry, porosity, stiffness, and bioactivity. Biological signals delivered by a scaffold may also promote the differentiation of DPSCs into odontoblast-like cells capable of producing and mineralizing dentin matrix.

In the study by Kim et al., cells cultured on collagen exhibited increased expression of osteocalcin (OCN), DSPP, and DMP-1, together with mineralized extracellular matrix formation [9]. These findings associate collagen culture with enhanced expression of markers related to mineralization and odontogenic differentiation. However, marker expression and mineral deposition should be interpreted as indicators of odontogenic activity rather than definitive evidence of complete functional dentin regeneration.

Similarly, Soares et al. described an organic–inorganic scaffold containing calcium aluminate. The enriched scaffold exhibited odontogenic properties when cultured with human dental pulp cells, suggesting that an inorganic mineral phase can modify the behavior of an organic scaffold [13]. Calcium-based materials may create an ion-rich environment favorable to mineral deposition, while chitosan and collagen provide additional structural and biochemical properties. The findings support the potential complementarity of composite components, although studies that isolate individual physicochemical mechanisms are needed to determine their respective contributions.

Collectively, these studies indicate that scaffolds should not be regarded solely as inert structures. Their composition and architecture may influence cell behavior and odontogenic differentiation. Successful pulp regeneration requires not only occupation of the pulp space by cells but also appropriate differentiation and dentin formation. Suitable biomaterials should therefore combine mechanical stability, biocompatibility, appropriate porosity, and biochemical cues that support cell attachment, proliferation, odontogenic differentiation, and subsequent matrix mineralization.

4.2. Vascularization, neuralization, and the microenvironment

Functional dental pulp requires vascular and neural elements in addition to odontoblast-like cells. Blood vessels supply nutrients and oxygen, whereas nerves contribute to sensory function. Regeneration should therefore be evaluated in terms of functional tissue reconstruction rather than mineralization alone.

Zhang et al. observed increased odontogenic marker expression and mineralization, together with vascular pulp-like tissue formation after six weeks of subcutaneous implantation [10]. The findings suggest that scaffold architecture may influence several regenerative outcomes. However, subcutaneous implantation is an indirect model that does not fully reproduce the anatomical, microbial, and vascular conditions of the human root canal.

Evidence of vascularized pulp-like tissue alone is insufficient to demonstrate complete pulp regeneration. The broader objective is to regenerate the pulp–dentin complex and restore lost

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functions rather than merely fill the root canal with new tissue [1]. Future biomaterials should therefore regulate multiple aspects of the regenerative microenvironment. Scaffold performance will ultimately depend on how well the material supports coordinated pulp–dentin regeneration rather than any single outcome, such as proliferation or mineralization.

5. Current challenges and future directions

No currently available biomaterial possesses all the characteristics desired for dental pulp regeneration. Natural polymers generally offer favorable biological interactions but may have limited mechanical strength, whereas synthetic polymers permit greater control but may lack intrinsic biological activity. Available evidence is insufficient to identify a single optimal scaffold composition for the complex demands of dental pulp tissue engineering [1]. Experimental findings show that collagen can support odontogenic differentiation, while composite materials have been developed to add mineralization-related or structural properties.

Similar tradeoffs occur in scaffold architecture. Greater porosity may improve cell penetration and nutrient distribution but reduce mechanical strength, while rapid degradation may create space for new tissue yet prematurely impair scaffold function. Future research should therefore optimize combinations of properties for defined regenerative purposes rather than seek a universally superior material. Composite scaffolds offer one possible strategy by assigning distinct biological and mechanical roles to different components.

An additional challenge is the gap between experimental testing and clinical practice. Many studies report favorable findings *in vitro* using isolated cells or animal models, whereas the human root canal presents complex anatomy, residual microorganisms, immune responses, and restricted vascular access. Materials must be processable, biodegradable, sufficiently porous, mechanically appropriate, and capable of supporting vascularization while conforming to the dimensions of the pulp cavity [1].

These requirements support further investigation of injectable and patient-adapted materials. Injectable hydrogels may conform to irregular root-canal spaces, while three-dimensional modeling may assist in designing scaffolds adapted to individual anatomy. Their clinical advantages, however, must be established using standardized preclinical models and well-designed human studies. Future research should therefore move beyond single-function materials toward multifunctional and potentially personalized systems while addressing reproducibility, sterilization, manufacturing, long-term safety, and clinically meaningful functional outcomes.

6. Conclusion

Dental pulp regeneration requires biomaterials that support reconstruction of a functional pulp–dentin complex rather than merely filling the root-canal space. Cell survival alone is insufficient; successful regeneration also requires conditions that support cell proliferation, odontogenic differentiation, nutrient supply, vascularization, neural integration, and dentin formation. Natural polymers, synthetic polymers, hydrogels, and composite materials each offer distinct advantages and limitations, and no single class has been established as meeting all regenerative requirements.

Future research should balance biocompatibility, structural stability, porosity, degradation, and injectability while determining whether promising experimental outcomes translate into durable functional regeneration. Multifunctional and patient-adapted materials warrant further investigation, but their clinical value will depend on standardized evaluation, reproducible manufacturing, long-term safety, and evidence from clinically representative studies.

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