Proceedings of ICBioMed 2025 Symposium: Interdisciplinary Frontiers in Pharmaceutical Sciences
DOI: 10.54254/2753-8818/2025.SH25957

Teeth Tissue Engineering: a Study on Seed Cells, Scaffold Materials, and Growth Factors

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Abstract. Tooth defects can cause severe pain, infection, and impaired daily functions, significantly affecting the quality of life for patients. Although traditional root canal treatment can prolong the lifespan of a damaged tooth, it cannot fully restore the biological activity and tissue integrity of the teeth. Dental tissue engineering, as a cutting-edge regenerative medical strategy, is of great significance for restoring the natural structure and function of teeth. It aims to achieve the regeneration and repair of dental hard and soft tissues through interdisciplinary approaches. It comprises three key elements: seed cells, scaffold materials, and growth factors. This article reviews the current developments in this field, systematically elaborating on the differentiation potential of seed cells in dental regeneration. It evaluates the performance of various scaffold materials in supporting cell adhesion, proliferation, and mineralization. It introduces the crucial role of growth factors in inducing seed cells to differentiate into cementoblasts and osteoblasts. This article aims to promote the translation of dental tissue engineering into clinical practice, providing a more effective treatment plan for patients with tooth defects.

Keywords: Teeth Tissue Engineering, Seed Cells, Scaffold Materials, Growth Factors

1. Introduction

The dental tissues mainly consist of enamel, dentin, and pulp. The coordinated action of these structures maintains the overall integrity of the teeth. In cases of tooth defects, trauma, or other pathological conditions, these tissues often suffer irreversible damage. According to the fourth national oral health epidemiological survey, the overall tooth loss rate among Chinese adults was found to be 84.4%, while the denture restoration rate was only 41.6% [1]. The pain, infection, and daily functional impairment caused by tooth defects seriously affect the quality of life of patients [1]. Currently, traditional clinical treatment methods, such as fillings, inlays, crown-bridge restorations, and implant restorations, although widely used in clinical practice, still face several limitations, including poor material biocompatibility and a limited lifespan of implants [2]. Therefore, new approaches to tooth repair are urgently needed. With the development of disciplines such as molecular biology and tissue engineering, dental tissue engineering technology has emerged as a strategy for tooth restoration.

Dental tissue engineering is a specific application of tissue engineering in the field of oral medicine. It aims to achieve the regeneration and repair of dental hard and soft tissues through

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DOI: 10.54254/2753-8818/2025.SH25957

interdisciplinary approaches. The three main components of tissue engineering include seed cells, scaffold materials, and growth factors. Among them, seed cells are highly differentiated cells with the ability of self-renewal, which can be induced to differentiate into specific cells and tissues under certain conditions. Good seed cells should exhibit characteristics such as a wide range of sources, no immune rejection reactions, and high culture efficiency [3]. Scaffold materials provide a three-dimensional framework to support cell growth into complete tissues. Appropriate scaffolds need to have specific biomechanical properties, such as interconnected pores, biocompatibility, and surface cell adhesion [4]. Growth factors are polypeptide proteins that can affect cell activities through intercellular signals, regulating cell proliferation, differentiation, and biosynthesis [5]. Obtaining suitable seed cells is a major challenge. Although embryonic stem cells and induced pluripotent stem cells can be used as seed cells, these cells may raise some serious safety and ethical concerns [6]. In addition, the selection of scaffold materials is also complex, as each material has distinct characteristics; therefore, the safety, biocompatibility, biodegradability, and mechanical properties of the scaffold materials must be comprehensively considered [7].

By reviewing previous studies, this paper systematically presents the current research status of tooth tissue engineering, with a particular focus on the research progress of seed cells, scaffold materials, and growth factors. The aim is to promote the further development of tooth restoration technology.

2. Seed cells

In the field of dental tissue engineering, seed cells have long been a key area of research. Under certain conditions, they can regenerate damaged dental tissues, including dentin, dental pulp, cementum, and periodontal ligament [8]. Their presence is not only crucial for initiating tissue formation, but also for maintaining cell signaling, regulating immune responses, and integrating the newly formed tissue with the host environment [9]. Ideal seed cells should have high proliferation capacity, multi-potent differentiation potential, low immunogenicity, and compatibility with biomaterials. Various types of seed cells, such as dental pulp stem cells (DPSCs), dental follicle stem cells (DFSC), stem cells from the apical papilla (SCAP), stem cells from human exfoliated deciduous teeth (SHED), and periodontal ligament stem cells (PDLSC), have been widely studied for their potential in dental regeneration [10] (Table 1).

2.1. Dental Pulp Stem Cells（DPSCs）

DPSCs, isolated from adult dental pulp, are the first type of stem cells discovered in dental pulp tissue. DPSCs possess strong proliferation and self-renewal capabilities, and can express neural markers as well as differentiate into adipocytes. DPSCs are typically derived from the third molar and eventually differentiate into odontoblast-like cells and osteoblasts, thereby forming dentin and bone [11]. In a study conducted in Spain, researchers inoculated human DPSCs onto decellularized tooth scaffolds. After six weeks of inoculation, characteristic reticular connective tissue was observed, and the DPSCs successfully adhered, proliferated, and differentiated into cementoblast-like cells, indicating the potential of DPSCs to regenerate cementum and support periodontal tissue regeneration [12]. In another study, human DPSCs were inoculated onto decellularized human tooth scaffolds and transplanted into immunocompromised mice. After nine weeks, the DPSCs differentiated into pulp-like tissue, exhibiting gene expression associated with vascular regeneration and hard tissue formation, which demonstrated the potential of DPSCs to form dental tissue [13].

DOI: 10.54254/2753-8818/2025.SH25957

2.2. Dental Follicle Stem Cells (DFSC)

DFSC, derived from extracted wisdom teeth, exhibits a strong ability to proliferate in vitro and has the potential to differentiate into periodontal ligament stem cells (PDL), osteoblasts, and odontoblasts, making it highly suitable for application in dental tissue engineering [14]. In one study, researchers co-implanted DFSC and Treated Dentin Matrix (TDM) under the skin of the backs of nude mice; after four weeks of culture, root-like tissue was formed, and the tissue expressed markers of dental pulp and periodontal tissue, such as dentin-specific protein (DSP), neural crest protein (Nestin), and collagen type I (COLI), indicating successful regeneration of root tissue [14]. In another study, human DFSC was xenotransplanted into periodontal defects in rats, where it induced the N2 phenotype in neutrophils, thereby reducing inflammation and promoting the regeneration of periodontal ligament-like tissue with a well-organized, mineralized structure similar to natural periodontal tissue [15]. These research results indicate that DFSC has significant application value in dental tissue engineering, especially in the regeneration of tooth roots and their attached tissues.

2.3. Stem Cells from Apical Papilla (SCAP)

SCAP is a multipotent mesenchymal stem cell derived from the root tip papilla of developing teeth, with the ability to differentiate into various types of dental and non-dental cells. It has high proliferation capacity, strong mineralization potential, immunomodulatory properties, and the ability to regenerate dental tissues, making it an ideal source of stem cells for dental and periodontal tissue engineering [16]. Sonoyama et al. isolated SCAP from human root tip papillae and demonstrated that combining SCAP with PDLSC resulted in higher proliferation capacity, mineralization capacity, migration ability, telomere activity, and multipotent differentiation ability. Subsequently, they implanted SCAP into a small pig model, and after 4 weeks, a bioengineered dental root with dentin-pulp-like components was formed [17]. Yang et al. combined SCAP with HA/TCP ceramic particles. Then, they transplanted them onto subcutaneously nude mice. Eight weeks after transplantation, SCAP formed bone- and dentin-like mineralized tissues [18, 19]. These studies demonstrated the ability of SCAP to differentiate into dental tissue.

2.4. Periodontal Ligament Stem Cells (PDLSC)

PDLSC originates from the periodontal ligament tissue that connects the tooth root and the alveolar bone, and can be isolated from human teeth (including the third molars and deciduous teeth). These cells possess the ability of self-renewal and multipotent differentiation, including the ability to differentiate into osteoblasts, odontoblasts, adipocytes, and chondrocytes, and they also exhibit immunomodulatory characteristics that support tissue regeneration [3]. Kim et al. inoculated PDLSC onto decellularized human tooth scaffolds and implanted them into immunocompromised mice. The results showed that PDLSC successfully differentiated into dentin and periodontal ligament (PDL)-like tissues, forming tooth-like structures [13]. Calabrese et al. combined PDLSC with DPSCs to form tooth-root-like organoids. PDLSC formed peripheral mineralized tissues and dentin-like structures, while DPSCs formed a central unmineralized core surrounded by dentin-like tissues. The successful regeneration of this tooth-like structure demonstrated the potential of PDLSC in dental restoration [20].

DOI: 10.54254/2753-8818/2025.SH25957

Table 1. Comparison of the advantages and disadvantages of various seed cells

Name	Advantage	Disadvantage	Citation
DPSCs	High proliferation Self-renewal ability Expression of neural markers Support for vascular and neural regeneration Can form mineralized tissue Paracrine effect Multidirectional differentiation ability in vivo and in vitro	The mineralized tissue structure is immature. The regenerative structure is irregular. The nerve and blood vessel regenerative capacity is limited.	[11-13]
DFSC	Strong in vitro proliferation ability Multidirectional differentiation Rich sources Immune regulatory effect	Cell heterogeneity Lack of immunogenicity Short-term survival limitation	[14, 15]
SCAP	High proliferation, migration, and regeneration ability Strong mineralization potential Immune regulatory characteristics Capable of forming dentin in the body	Limited source (absent in adult teeth) Lack of immunogenicity	[16-19]
PDLSC	Self-renewal ability Extracellular multi-potential differentiation ability Immune regulation ability Intracellular mediation of periodontal cell regeneration	Limited regenerative capacity Lack of immunogenicity	[3, 13, 20]

3. Scaffold materials

In dental tissue engineering, the choice of scaffold material is a key factor in achieving successful tissue regeneration. Scaffolds not only serve as a three-dimensional structural basis for cell adhesion, growth, and differentiation, but also play an irreplaceable role in simulating the microenvironment of natural tooth tissue, guiding the formation of new tissue, and regulating the regeneration process [21]. Scaffolds should not only possess good biocompatibility, biodegradability, and suitable mechanical properties, but also exhibit a well-organized three-dimensional structure and porosity to support cell adhesion, proliferation, and differentiation [22]. According to the source, structure, and function of the materials, scaffold materials can be roughly divided into three categories: natural scaffold materials, composite scaffold materials, and nanoscaffold materials (Table 2).

3.1. Natural scaffold materials

3.1.1. Collagen protein

As a natural biomaterial derived from the human body and the main component of dental tissue, collagen exhibits good biocompatibility, low antigenicity, supports the proliferation and differentiation of DPSCs into odontoblasts, and promotes the synthesis of hard tissues. At the same time, it exhibits good degradability and can be processed into various forms [4]. Prescott et al. inoculated DPSCs onto collagen scaffolds and successfully induced the generation of new tissue

DOI: 10.54254/2753-8818/2025.SH25957

with vascular distribution and morphology similar to dental pulp cells under specific conditions in mice subcutaneously. This suggests that collagen scaffolds offer a suitable 3D structure and microenvironment for DPSC adhesion, proliferation, and differentiation [4, 23]. The application of engineered bovine dentin collagen scaffold alone achieved effective root regeneration in nude mice and piglets, indicating that collagen has great potential as a scaffold material in the field of dental tissue engineering [24].

3.1.2. Chitosan

Chitosan is a natural polysaccharide that holds great significance in the field of dental tissue engineering due to its excellent biocompatibility, biodegradability, controllable absorption rate, and dissolution rate [25]. 3D porous chitosan scaffolds have been successfully applied to the culture of DPSCs. This scaffold not only provided an excellent three-dimensional structure to promote cell attachment and survival but also significantly enhanced the proliferation ability and neural differentiation potential of DPSCs [26]. Yang et al. seeded a plasmid carrying the bone morphogenetic protein-7 (BMP-7) gene onto a porous chitosan/collagen composite scaffold and seeded DPSCs onto this scaffold. During in vitro culture, the cells were found to exhibit enhanced proliferative capacity and significant odontoblast differentiation characteristics [27]. These results demonstrated the potential of Chitosan as a scaffold material for dental tissue engineering.

3.1.3. Hyaluronic acid

As a natural polymer, hyaluronic acid exhibits excellent biocompatibility, low immunogenicity, and minimal biological toxicity. It can effectively maintain the extracellular matrix space and promote cell adhesion and differentiation. Felszeghy et al. found that hyaluronic acid provides a favorable microenvironment for cells by regulating the composition and function of extracellular matrix, thereby contributing to the differentiation of odontoblasts and ameloblasts, and thus supporting the formation of tooth-like structures [4, 28]. One study found that hyaluronic acid hydrogels provide a favorable environment for DPSCs attachment and growth by mimicking the 3D structure of the natural extracellular matrix. This scaffold not only promotes the proliferation of DPSCs but also effectively induces their differentiation into odontoblasts by regulating signal transduction in the microenvironment [29]. These findings suggest that hyaluronic acid has the potential to promote the generation of tooth-like structures by stem cells.

3.2. Composite scaffold material

3.2.1. Hydroxyapatite and Tricalcium Phosphorus-β (HA/TCP-β)

HA/TCP-β composites not only provide a good microenvironment for seed cells to promote attachment and differentiation, but also enhance the structural stability and mineralization ability of the scaffolds [21, 30]. Gu et al. developed a novel gelatin-HA-β-TCP composite scaffold. The scaffold exhibits good structural homogeneity, an interconnected porous structure, and strong mechanical properties, which significantly promote the proliferation and alkaline phosphatase (ALP) activity of DPSCs, thereby enhancing the formation of a mineralized matrix. These results show that HA-TCP composite scaffolds have great potential in inducing osteogenic differentiation of DPSCs [31].

DOI: 10.54254/2753-8818/2025.SH25957

3.2.2. Polylactic acid and Polyglycolic Acid Polymer (PLGA)

PLGA exhibits excellent biocompatibility, controllable degradation, low cost, high manufacturing reproducibility, and flexible processing. At the same time, PLGA exhibits adjustable mechanical properties, porosity, and biomolecular release rates, and induces only a mild inflammatory reaction, making it an ideal scaffold for dental tissue regeneration [22]. Tooth germ tissue from a porcine third molar was seeded on a PLGA scaffold, which was subsequently implanted into the rat peritoneum. After 20 to 30 weeks of in vivo culture, dentin, dental pulp, and cementum were successfully cultivated, and periodontal ligaments and crowns covered with intact enamel were formed, fully demonstrating the great potential of PLGA scaffolds in the field of dental tissue engineering [2, 32].

3.3. Nano-scaffold materials

Nano-scaffold materials can effectively simulate the tooth microenvironment, promote cell behavior, and improve the scaffold performance due to their size advantages. At the same time, their high specific surface area and controllable drug release characteristics, combined with good biocompatibility and similarity to dental minerals, make it an ideal scaffold and carrier in dental tissue engineering [33]. Yang et al. showed that a scaffold composed of polycaprolactone (PCL), gelatin, and nano-hydroxyapatite (nHA) not only facilitated the adhesion and proliferation of human DPSCs but also effectively induced their differentiation into odontoblasts. This scaffold can promote the formation of dentin-like mineralized tissue [34, 35]. A 30- and 90-day observational study in canine immature teeth showed that mesoporous silica nanoparticle (MSN) scaffolds significantly promoted increasing root length and thickness, viable tissue regeneration, and new hard tissue formation. Studies have also found that the regenerative effect of MSNs is further enhanced when combined with bone morphogenetic protein-2 (BMP-2) [36]. These studies demonstrate the promising application of nano-scaffolds in dental tissue engineering.

DOI: 10.54254/2753-8818/2025.SH25957

Table 2. Comparison of different scaffold materials

Scaffold material		Advantage	Disadvantage	Citation
Natural scaffold materials	Collagen protein	Good biocompatibility Low antigenicity Promote hard tissue synthesis Good degradability	Weak mechanical properties The degradation rate is too fast Poor shape retention	[4, 23, 24]
	Chitosan	Controlled absorption and dissolution rate Good biocompatibility To simulate the extracellular matrix Promoting neural differentiation Strong drug/gene loading capacity	Low mechanical strength The induction of odontogenic differentiation was weak Surface charge may inhibit some cell adhesion	[25-27]
	Hyaluronic acid	Regulates cell migration and proliferation Promoting angiogenesis Low immunogenicity Good biocompatibility	Weak mechanical properties The degradation rate is too fast Poor structural stability	[4, 28, 29]
	HA/TCP-β	Good biocompatibility and bioactivity The structural stability and mineralization ability are strong	Mechanical strength is weak Lack of resilience	[21, 30, 31]
Composite scaffold material	PLGA	Good biocompatibility Controlled degradability Low cost Flexible processing Mechanical properties can be adjusted The porosity can be adjusted	The mechanical properties were weak There was limited cytocompatibility Insufficient surface properties	[2, 22, 32]
Nano-scaffold materials		High surface area Mimics the natural extracellular matrix Improve mechanical properties and structural stability Flexible processing Promotes cell-directed growth	Potential toxicity and immune response Limited structural strength Slow production rate Complex preparation High cost	[33-36]

4. Growth factors

Growth factors are peptide signaling molecules that influence cellular activity via intercellular signaling pathways. They regulate essential biological processes, such as cell proliferation, differentiation, migration, and morphogenesis, and play a crucial role in dental tissue engineering [5]. An ideal growth factor should be characterized by high specificity, pleiotropic effects, synergistic/antagonistic effects, low concentration, high efficacy, and local effects [37]. Previous studies have also found that some growth factors can effectively promote the repair and regeneration of dental pulp and periodontal tissues. For example, transforming growth factor-β (TGF-β), bone morphogenetic proteins (BMPs), and platelet-derived growth factors (PDGFs) have been widely studied for their ability to induce seed cells to differentiate into odontoblasts or tooth-like structures, thereby promoting tooth repair or regeneration [38].

4.1. Bone Morphogenetic Proteins (BMPs)

BMPs belong to the transforming growth factor-β superfamily and have the ability to promote stem cells to differentiate into osteoblasts and odontoblasts. BMPs play pleiotropic and highly specific roles in bone regeneration, tooth development, and periodontal tissue repair. Its isoforms, BMP-2, BMP-4, and BMP-7, play a crucial role in tooth development, inducing the proliferation of mesenchymal cells during the early stage of tooth germ development, and participate in the

DOI: 10.54254/2753-8818/2025.SH25957

formation of developmental signal centers [37]. Researchers loaded BMP-2 onto biomaterial scaffolds, such as collagen, hydrogels, or calcium phosphate ceramics, and found that these scaffolds were able to induce DPSCs to form macroscopic mineralized nodules [39]. In one study, BMP-4 was combined with a decellularized dental pulp matrix scaffold to successfully induce the differentiation of human DPSCs and the formation of tissue with a structure and function similar to that of natural dental pulp [40]. In some in vitro studies, PDLSC isolated from the periodontal ligament were cultured in medium containing BMP-7. After 21 days, PDLSCs differentiated into both cementoblasts and osteoblasts, forming mineralized nodules [41]. These experiments demonstrated the ability of BMPs to promote dentin formation and mineralization.

4.2. Transforming Growth Factor-β (TGF-β)

TGF-β is a key class of multifunctional cytokines with high specificity, pleiotropic effects, high efficiency at low concentrations, and local release. It can produce synergistic or antagonistic effects with other growth factors and plays a crucial role in regulating cell proliferation and differentiation. Studies have shown that TGF-β can promote the differentiation of odontogenic stem cells into dentin-like cells and activate the mineralization process mediated by DPSCs [39]. Widbiller et al. did this by extracting endogenous TGFβ1 from the root canal system and loading it in a hydrogel carrier. After the composite carrier was implanted into the dental pulp cavity, it successfully induced the directional migration and aggregation of exogenous DPSCs, resulting in the formation of a pulp-like tissue with a vascularized structure and an odontoblast-like cell arrangement in vivo [42]. Further studies in vitro and in vivo models demonstrated that TGFβ1 at a low concentration (0.1-1 ng/mL) could significantly induce DPSCs and increase alkaline phosphatase (ALP) activity, indicating that it effectively induces DPSCs to differentiate into early odontoblasts [43]. These experiments fully demonstrated that TGF-β has significant potential as a growth factor in dental tissue engineering.

4.3. Platelet-Derived Growth Factor (PDGF)

PDGF is a pleiotropic regulator that can significantly promote cell proliferation, induce angiogenesis, and promote the differentiation of dentin cells [44]. This factor has the characteristics of high specificity, low dose, and high efficiency. It often acts in coordination with TGF-β, VEGF, and other growth factors, and can achieve precise targeted release and regulation through a locally controlled release system. Researchers inoculated DPSCs overexpressing PDGF-BB into calcium phosphate cement scaffolds and subcutaneously implanted the complex in mice. The results successfully induced the formation of dentin-like mineralized tissue, which was surrounded by pulp-like connective tissue with a dense vascular network of blood vessels, confirming the key regulatory role of PDGF-BB in the regeneration of tooth-like structures [45]. Researchers co-loaded PDGF-BB with nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) on type I collagen and applied it to rat bone marrow mesenchymal stem cells (BMSCs). The results significantly promoted cell proliferation and migration, as well as induced angiogenesis and nerve regeneration. Finally, a tissue structure with rich blood vessels and a morphology similar to that of natural dental pulp was regenerated in vivo. These findings indicate that PDGF-BB has a broad application prospect in dental tissue engineering [46].

DOI: 10.54254/2753-8818/2025.SH25957

5. Discussion and conclusion

As an emerging technology in stomatology, dental tissue engineering offers a novel solution to the limitations of traditional dental restoration, and it is currently in its basic research stage. By integrating seed cells, scaffold materials, and growth factors, this technology aims to regenerate tooth tissues, including enamel, dentin, and pulp, and restore the complete function of teeth. Despite the challenges, dental tissue engineering has some clinical applications. The research team has successfully constructed a complete tooth germ in vitro and implanted it into the jawbones of mouse and dog models, causing it to erupt and function. These regenerated teeth possess complete dentin, enamel, pulp, and periodontal tissues, laying a solid foundation for future human tooth regeneration [47]. Additionally, in clinical trials on dental pulp necrosis, DPSCs have been successfully applied to regenerate dental pulp tissue, yielding promising results that demonstrate favorable safety and efficacy profiles [48].

In terms of seed cells, odontogenic stem cells such as DPSCs, DFSC, SCAP, and PDLSC have shown great potential. First, the heterogeneity of different seed cells needs to be further studied to develop safer and efficient cell acquisition and expansion methods. Second, there are still challenges in obtaining suitable seed cells, including potential safety and ethical concerns associated with embryonic stem cells and induced pluripotent stem cells. Scaffold materials provide a three-dimensional framework for cell adhesion, growth, and differentiation. Composite and nanomaterials have proven promising applications in dental tissue engineering. Obtaining structurally stable and biocompatible scaffold materials remains a significant challenge. The research and development of scaffold materials should focus on simulating the complex microenvironment of natural tooth tissue to achieve more accurate biomechanical matching and controlled degradation. In addition, finding novel growth factor combinations and their precise dosing and release strategies to maximize tissue regeneration will be the focus of future research. Ultimately, these basic research findings will be translated into clinical applications, and through multidisciplinary collaboration, it is anticipated that they will provide more effective, durable, and biocompatible treatment options for patients with tooth defects.

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