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Review

Biomaterials for Dental Pulp Regeneration: Recent Advances, Mechanistic Insights, and Translational Perspectives

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Abstract: In recent years, substantial progress has been made in pulp regeneration therapy. Unlike conventional root canal therapy (RCT) and vital pulp therapy (VPT), pulp regeneration therapy not only restores the physiological structure and function of damaged teeth but also facilitates root development in immature teeth. Biomaterials play a pivotal role in this process, as they must exhibit biocompatibility, suitable pore architecture, and controlled degradability to support both vascular and neural regeneration. With advancements in biomaterial technology, the clinical application of pulp regeneration therapy has achieved remarkable success by closely mimicking the natural pulp microenvironment, offering a more biological approach for treating pulp-related diseases. This review provides a comprehensive overview of the key biological components essential for pulp regeneration and highlights recent innovations in biomaterials for this therapy. Furthermore, we examine the mechanisms through which biomaterials enhance pulp regeneration and suggest potential strategies for further improvement. Finally, we discuss emerging trends and future opportunities in this rapidly evolving field.

Keywords: pulp; tissue regeneration; biomaterials; stem cells

1. Introduction

Teeth are composed of mineralized hard tissues, including dentin and enamel, as well as internal pulp tissue. The pulp, a loose connective tissue rich in neurovascular networks, exhibits limited resistance to infection and a low regenerative capacity. Under normal physiological conditions, the pulp is well-protected by the surrounding mineralized layers [1]. However, with the rising consumption of high-sugar diets in modern society, dental caries has become increasingly prevalent worldwide [2,3]. If left untreated, caries can progress into deeper tissues, resulting in pulpitis and apical periodontitis. Acids produced by cariogenic bacteria demineralize the tooth structure and may penetrate the root canal [4]. These exogenous stimuli, including bacterial toxins, acidic metabolites, and endogenous signaling molecules such as inflammatory mediators and stress proteins released from damaged pulp tissue, ultimately activate the host's inflammatory and immune responses [1]. Persistent inflammation can compromise pulp microcirculation, leading to local ischemia, hypoxia, and metabolic disturbances. Without timely intervention, this pathological cascade progresses to irreversible pulp necrosis. Subsequently, necrotic pulp tissue may become secondarily infected, forming a periapical abscess and causing symptoms such as pain and impaired mastication, which significantly affect the patient's oral health and quality of life [5].

In the clinical management of endodontic diseases, traditional treatments primarily include root canal therapy (RCT) and vital pulp therapy (VPT). RCT involves the removal of infected or necrotic pulp tissue and its replacement with a filling material. While RCT demonstrates a high success rate, it carries certain limitations, including increased tooth fragility and the risk of microbial reinfection following root canal obturation [6,7]. VPT, on the other hand, preserves tooth vitality by maintaining healthy pulp tissue and promotes reparative dentin formation, thereby better retaining the tooth's mechanical strength and biological function. Nevertheless, its indications are limited to cases of mild pulp infection or traumatic pulp exposure [8,9]. Given these constraints of conventional therapies, the global dental community has increasingly sought biologically based alternatives, leading to the development of regenerative endodontic therapy (RET).

The emergence of RET is closely linked to the discovery of dental pulp stem cells (DPSCs) and the understanding of their microenvironmental regulatory mechanisms. In 2000, Gronthos and colleagues successfully isolated DPSCs from human dental pulp, demonstrating their multidirectional differentiation potential for the first time [10]. This landmark discovery opened new avenues in dental regenerative medicine and tissue engineering. Since then, researchers have identified a variety of mesenchymal stem cells (MSCs) with differentiation capabilities, including stem cells from human exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs), stem cells of the apical papilla (SCAP), and dental follicle progenitor cells (DFPCs) [11], providing a robust cellular foundation for pulp regeneration. In recent years, advancements in tissue engineering have shifted attention toward the strategic application of biomaterials in pulp regeneration. Biomaterials serve multiple essential functions: (1) replacing diseased dental pulp; (2) creating a microenvironment conducive to pulp regeneration, and (3) acting as a structural guide for stem cell migration and differentiation. By integrating these functions, biomaterials support the restoration of dental vitality and physiological function, establishing themselves as a critical component in modern pulp regeneration strategies [12–14].

This study employs a narrative review approach with the aim of providing a comprehensive and critical overview of multidisciplinary advances in the field of pulp regeneration. The literature search and selection strategy were designed to identify key breakthroughs and emerging trends, rather than to capture every relevant publication. Searches were primarily conducted across databases including MEDLINE/PubMed, Web of Science, and Scopus, with a focus on studies published from 2015 to the present to emphasize the rapid developments in the past decade. The main search terms comprised keywords and their combinations relevant to pulp regeneration. Literature was included based on its conceptual significance, scientific impact, and representativeness within the field. Priority was given to high-impact original research articles, authoritative review papers, milestone studies introducing key concepts or technologies, and representative works demonstrating diverse technical approaches. Studies unrelated to pulp regeneration or exhibiting non-rigorous methodologies or low-quality data were excluded. Using this approach, we systematically examine the biological factors critical for dental pulp regeneration, summarize the applications of biomaterials in this context, and explore the mechanisms through which biomaterials modulate pulp tissue regeneration. Additionally, the review discusses major challenges in clinical translation and highlights future directions for the development of materials for dental pulp regeneration.

2. Basic Biological Requirements for Dental Pulp Regeneration

Over the past decade, RET has advanced rapidly from experimental research to standardized clinical application. It is now integrated into endodontic diagnostic and therapeutic protocols, serving as a vital alternative for treating pulp tissue necrosis [15]. Unlike traditional RCT, which primarily involves filling the canal space with inert materials, the central goal of RET is to achieve comprehensive physiological restoration of damaged tooth structures, including the regeneration of dentin, root architecture, and the pulp-dentin complex. RET aims to repopulate the root canal space with the patient's own functional tissues rather than relying on biocompatible foreign materials. This biologically driven approach not only enhances the long-term survival of treated teeth but also restores their physiological function in terms of masticatory force distribution and periodontal tissue integration. It addresses the key limitation of conventional treatments, in which the loss of vascular supply leaves teeth brittle and susceptible to fracture. To further advance the study of dental pulp regeneration and support the retention of truly vital teeth, we summarize here the fundamental biological requirements for dental pulp regeneration, focusing on three core aspects: cells, growth factors, and signal regulation.

2.1. Cells

The successful regeneration of dental pulp depends on the use of appropriate cells. Stem cells, as undifferentiated cells, possess not only the ability to differentiate into multiple cell lineages but also the capacity for self-renewal, enabling effective repair of damaged tissues. Consequently, among all cell types, stem cells hold

the greatest potential in regenerative dentistry (Table 1). The sources of stem cells for dental regeneration are broadly categorized into odontogenic and non-odontogenic origins, and this diversity allows for unique approaches in repairing damaged oral tissues.

DPSCs were the first odontogenic MSCs to be isolated from dental pulp. Derived from permanent teeth, DPSCs exhibit robust self-renewal and multidirectional differentiation potential, enabling them to generate odontoblasts, osteoblasts, adipocytes, and other cell types, thereby playing a central role in dental pulp repair and regeneration [16]. Studies have shown that nucleus pulposus microspheres (NPM) loaded with DPSCs-conditioned medium can mimic the microenvironment required for dental pulp regeneration, thereby facilitating the reconstruction of the pulp-dentin complex and offering a novel research strategy in this field [17]. In another study, gelatin methacryloyl (GelMA) scaffolds with varying stiffness were employed to investigate the effect of three-dimensional (3D) matrix mechanics on DPSC differentiation, resulting in a tri-phase biomechanical structure. This structure effectively promoted crown dentin formation, regeneration of pulp tissue within the root canal, and integration with periapical tissues [18].

Another type of odontogenic MSCs is SHED, which are derived from the dental pulp of exfoliated deciduous teeth in children. Compared with DPSCs, SHED exhibit higher proliferative activity and enhanced differentiation potential [19]. Due to their low immunogenicity, non-invasive collection process, and capacity to rapidly expand *in vitro* while retaining stem cell characteristics, SHED represent a highly promising source of odontogenic MSCs. Animal studies have demonstrated that implantation of SHED into dental pulp defect models promotes angiogenesis and dental pulp tissue regeneration, resulting in the formation of functional pulp-like tissue. Furthermore, the extracellular matrix (ECM) of SHED has been utilized to fabricate biomimetic pulp scaffolds that support regeneration of the pulp-dentin complex [20]. In addition, researchers have shown that SHED can form microspheres through 3D cell culture, further enhancing their potential for dental pulp regeneration [21].

SCAP are located in the apical papilla tissue of young permanent teeth. SCAP can be isolated from apical papilla tissue when teeth are extracted due to pulp necrosis caused by trauma, caries, or other factors. These cells display high proliferative activity and possess cross-germ layer differentiation potential [22]. Notably, SCAP play a critical role in root development by regulating root elongation and apical foramen closure through the secretion of various growth factors, thereby significantly influencing the continued development of roots in young permanent teeth. However, because SCAP are derived from developing teeth that are rarely discarded in clinical practice, their clinical application is highly limited.

The three stem cell types discussed above are all odontogenic; however, non-odontogenic stem cells, such as bone marrow MSCs (BMSCs) and induced pluripotent stem cells (iPSCs), have also been shown to contribute to dental pulp regeneration. The availability of these diverse cell sources expands the options for clinical applications in pulp regeneration. In research, BMSCs can be induced *in vitro* to differentiate into odontoblast-like cells, thereby promoting pulp tissue regeneration. Gomez et al. demonstrated that transplantation of allogeneic BMSCs can stimulate the formation of dentin-pulp complex-like structures in immature teeth affected by pulp necrosis and apical periodontitis [23]. Imaging assessments of teeth treated with BMSCs reveal healing of periapical lesions, reduction of apical foramen width, and mineralization within the root canal space, highlighting the therapeutic potential of BMSCs implantation in regenerative pulpology. iPSCs, derived from reprogrammed somatic cells, offer an almost unlimited cell source, satisfying the demand for large-scale clinical applications. They possess pluripotency akin to embryonic stem cells, allowing differentiation into any cell type, and since they originate from the patient's own cells, the resulting tissues are recognized as self, minimizing immune rejection and ethical concerns. Kim et al. successfully differentiated iPSCs into dental epithelial and mesenchymal cells [24]. Encapsulation of these differentiated cells in biomaterials such as GelMA, collagen, or agarose matrices can further induce the formation of bone, cartilage, and teeth, providing new insights into iPSC-based strategies for dental restoration.

In summary, stem cells play a central role in dental pulp regeneration, with their proliferative, differentiative, and microenvironment-interacting capacities critically influencing the success of tissue repair. They not only directly differentiate into odontogenic cells to replace damaged tissues but also secrete bioactive factors via paracrine signaling, coordinating angiogenesis, innervation, and immune modulation to create a regenerative microenvironment from multiple dimensions. Moreover, integrating stem cells with biomaterials to construct functional scaffolds represents a highly promising strategy in pulp regeneration research. The key advantage of this approach lies in the complementary functions of its components: biomaterials provide 3D structural support and a conducive microenvironment for stem cell colonization, proliferation, and differentiation, while enabling controlled growth factor release; concurrently, stem cells confer biological activity to the scaffold, allowing it to execute complex regenerative processes. This bioactive composite system holds substantial potential to overcome major challenges associated with standalone cell therapies, including low cell survival, poor localization, and

difficulty in controlling tissue morphology. Consequently, it opens new avenues for achieving both structural and functional dental pulp regeneration and significantly advances the clinical translation of this technology.

Table 1. Sources and applications of stem cells in dental pulp regeneration.

Stem Cells	Sources	Applications	Reference
DPSCs	Isolated from the dental pulp of permanent teeth	Promote the regeneration of pulp-dentin complex and angiogenic differentiation	[17,18,25]
SHED	Derived from the dental pulp tissue of exfoliated deciduous teeth in children	Differentiate into dentin and secretes dentin matrix, promote pulp nerve regeneration and regulate the immune microenvironment	[20,21,26]
SCAP	Derived from the apical papilla tissue of young permanent teeth	Promote root development, directly participate in the reconstruction of the pulp-dentin complex, and repair immature tooth injuries	[27–29]
BMSCs	Isolated from bone marrow tissue	Differentiate into odontoblast-like cells, and promote the regeneration of dental pulp tissue, accompanied by angiogenesis and the formation of dentin bridge	[23,30,31]
iPSCs	Derived from differentiated somatic cells through *in vitro* reprogramming technology	Differentiate into multiple tissue types such as dental pulp, dentin, and enamel, and can also reshape the dental pulp microenvironment	[24,32,33]

2.2. Growth Factors

Growth factors, as key regulatory agents within the dental pulp regenerative microenvironment, play critical roles in angiogenesis, odontoblast differentiation, and nerve growth. These cell-secreted proteins or polypeptides bind to receptors on cell surfaces, thereby regulating a wide array of physiological processes [12]. In recent years, growth factor-based therapies for dental pulp regeneration have attracted considerable attention. Such therapies can stimulate the proliferation, migration, and differentiation of cells in damaged pulp regions, and when combined with cell-based treatments, they effectively enhance dental pulp regeneration.

Regarding dentin regeneration, transforming growth factor-β (TGF-β) and fibroblast growth factor (FGF) are particularly influential [34,35]. FGF serves as a critical regulator of odontoblast differentiation, promoting the formation of odontoblasts and regulating dentin matrix (DM) synthesis and mineralization to facilitate dentin regeneration. Research has shown that FGF modulates cell proliferation, stemness maintenance, migration, and differentiation in vascular and mineralized tissues through selective activation of FGF receptors (FGFRs) and downstream signaling pathways, thereby supporting the repair and regeneration of the pulp-dentin complex [36]. TGF-β similarly regulates odontoblast differentiation and dentin mineralization and can act synergistically to promote dentin-pulp regeneration or reparative dentin formation. Studies have demonstrated that chitosan nanoparticles activated by sonic, ultrasonic, or laser stimulation can enhance the release of TGF-β1 from dentin, subsequently promoting pulp regeneration [37]. In addition to these dentin-associated growth factors, epidermal growth factor (EGF) and insulin-like growth factor (IGF) can stimulate the proliferation and differentiation of dental pulp cells, contributing further to the formation of functional dental pulp tissue [38].

In dental pulp regeneration, a well-developed vascular network is essential for delivering oxygen and nutrients to cells, supporting the survival and functional restoration of dental pulp tissue. Key growth factors involved in vascular regeneration include vascular EGF (VEGF), platelet-derived growth factor (PDGF), and basic FGF (bFGF) [39]. VEGF, a principal regulator of angiogenesis, specifically targets vascular endothelial cells (ECs), promoting their proliferation and migration to accelerate new blood vessel formation. Its expression level is directly correlated with the extent of vascularization during dental pulp regeneration. PDGF, released upon platelet degranulation, mediates chemotaxis and proliferation of MSCs through PDGFRα/β receptors and also stimulates vascular EC migration and lumen formation. Additionally, PDGF recruits smooth muscle cells to surround nascent vessels, enhancing vascular stability and regulating DPSC-mediated vasculogenesis [40]. bFGF, widely present in dental pulp, periodontal ligaments, and bone tissue, possesses strong proliferative and differentiation-promoting abilities and can induce vascular EC proliferation and angiogenesis. Divband et al. demonstrated that a highly porous Poly(ε-caprolactone)/chitosan scaffold loaded with bFGF increased angiogenic marker expression in DPSCs and supported vitality in the dentin-pulp complex [41].

Nerve regeneration is a critical component of dental pulp regeneration, relying on the synergistic regulation of multiple growth factors, including nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and various dental pulp-derived growth factors [42]. NGF binds to the high-affinity receptor TrkA on sensory neurons, activating downstream signaling pathways that inhibit neuronal apoptosis and promote axonal growth. Studies have demonstrated that the complement C5a receptor (C5aR) negatively regulates NGF secretion, thereby affecting neurite outgrowth in pulp fibroblasts. In caries models, C5aR activation suppresses NGF release,

impairing nerve regeneration, whereas blocking C5aR restores NGF secretion and promotes axonal extension, offering a potential therapeutic target for nerve repair in inflammatory microenvironments [43]. GDNF enhances both proliferation and migration of glial cells while supporting the survival of sensory neurons and is particularly important for facilitating remyelination of injured nerves. Notably, GDNF produced by dental pulp cell sheets has been employed to promote facial nerve regeneration via localized delivery, demonstrating its potential in nerve tissue engineering [44].

In addition to the previously mentioned growth factors, members of the bone morphogenetic protein (BMP) family also play important roles in odontoblast differentiation and dentin formation during dental pulp regeneration [45]. For example, BMP2 and BMP7 can induce DPSCs to differentiate into odontoblasts, upregulate odontoblast-specific markers, and promote DM secretion and mineralization. Liang et al. investigated the potential of BMP7 in dental pulp regeneration using ectopic nude mouse models and in-situ beagle dog models, implanting collagen gels loaded with BMP7. Their study demonstrated that BMP7 enhances DPSCs migration, odontogenic differentiation, and angiogenesis [46]. Additionally, Lee et al. developed a biomimetic composite scaffold capable of sustained BMP2 release, which effectively promoted bone formation. This work illustrates that BMP2 can function efficiently in scaffold-based sustained-release systems, with mechanisms directly applicable to dental pulp regeneration. Consequently, composite scaffolds incorporating BMPs can continuously induce DPSCs differentiation into odontoblasts, enhance hard tissue formation, and provide robust support for dental pulp tissue repair [47].

The successful regeneration of dental pulp tissue requires stem cells with differentiation potential, and effective stem cell homing is a critical prerequisite for this process. In this context, stromal cell-derived factor-1 (SDF-1), which promotes cell homing, plays a particularly important role [48]. SDF-1 is a small cytokine belonging to the CXC chemokine subfamily, exhibiting strong chemotactic activity that guides stem cells toward sites of dental pulp injury. By binding to the CXCR4 receptor on stem cells, SDF-1 activates intracellular signaling pathways that direct their migration to the damaged area, ensuring an adequate cellular supply for dental pulp regeneration. Researchers have incorporated SDF-1 into biological scaffolds, enabling the continuous recruitment of endogenous DPSCs into the root canal and thereby facilitating in situ regeneration of dental pulp tissue [49].

The primary mechanism by which growth factors facilitate dental pulp repair lies in their ability to replicate and accelerate the endogenous signaling environment that occurs during natural healing. By precisely regulating cellular behaviors, growth factors can steer tissue repair from unpredictable scar formation toward functional regeneration. Despite their considerable clinical potential, a major challenge in translating growth factors into practice is achieving accurate spatiotemporal control of their activity. The effects of growth factors are highly dependent on concentration and timing: excessive doses or prolonged exposure may cause adverse outcomes, such as ectopic mineralization, whereas insufficient levels or brief exposure fail to elicit the desired regenerative response. Moreover, dental pulp regeneration relies on the coordinated action of multiple signaling molecules in a defined sequence, limiting the efficacy of single-factor therapies. Accurately simulating this natural synergistic sequence remains a significant technical hurdle. Importantly, advances in biomaterial technology have enabled carrier-based delivery systems to address these challenges. By integrating growth factors with intelligent biomaterials, researchers are moving beyond single-factor release toward multi-factor, sequential controlled-release systems. This approach is expected to enhance the fidelity and effectiveness of the regenerative process, advancing dental pulp regeneration therapy to a new stage of clinical applicability.

2.3. Signal Regulation

During dental pulp regeneration, multiple signaling pathways interact to form a complex regulatory network that orchestrates orderly cellular behaviors. The self-renewal and differentiation of DPSCs are largely regulated by the Wnt/β-catenin signaling pathway [50]. Activation of Wnt signaling leads to the accumulation and nuclear translocation of β-catenin, which binds to TCF/LEF transcription factors in the nucleus and activates downstream genes that promote odontoblastic differentiation. The Notch signaling pathway is also critical for maintaining DPSCs stemness and self-renewal. When Notch receptors engage with ligands such as Jagged1 or Delta1, the intracellular domain is released and binds transcription factors to activate target genes. Notably, activation by Jagged1 suppresses odontogenic differentiation while preserving the undifferentiated state of DPSCs [51], whereas Delta1 promotes differentiation by upregulating Dentin sialophosphoprotein expression and enhancing mineralized nodule formation [52]. Beyond these roles, Notch signaling has been applied in innovative tissue engineering approaches; for example, a Notch-responsive hydrogel was developed to support vascular and neural regeneration in dental pulp. Co-culturing DPSCs and ECs on this hydrogel significantly increased the expression of Notch target genes and pro-angiogenic markers [53].

Additionally, the mitogen-activated protein kinase (MAPK) pathway regulates DPSCs proliferation, apoptosis, and differentiation [54]. The MAPK pathway transmits extracellular cues, such as growth factors and stress signals, through its subfamilies ERK1/2, p38, and JNK, which activate specific transcription factors to control key cellular processes. EGF-like domain protein 6 (EGFL6) has been shown to enhance DPSCs migration, angiogenesis, and odontogenic differentiation via MAPK activation [55], while melatonin protects preodontoblasts from TEGDMA-induced apoptosis, partially through the JNK/MAPK pathway [56]. Furthermore, Wu et al. demonstrated that a zirconia/DPSCs composite scaffold effectively activated p-ERK1/2 and p-p38 MAPK, promoting osteogenic repair and modulating immune responses [57].

The NF-κB pathway is activated following dental pulp injury and plays a pivotal role in regulating inflammatory factors, such as TNF-α and IL-6, to remove necrotic tissue and indirectly promote stem cell recruitment [58]. BRCA1/BRCA2 complex subunit 3 (BRCC3) has been identified as a key mediator of pro-inflammatory responses in various inflammatory conditions through multiple mechanisms [59]. In the context of pulpitis, BRCC3 intensifies inflammation by activating the NF-κB signaling pathway in dental pulp cells. Elevated BRCC3 expression has been observed in human and mouse pulpitis samples, as well as in lipopolysaccharide-treated human dental pulp cells (hDPCs), suggesting its role in enhancing pro-inflammatory cytokine production and inducing apoptosis in hDPCs. Conversely, mice with conditional BRCC3 knockout exhibited reduced p-p65 levels compared to control mice, indicating suppression of the NF-κB pathway. These findings confirm that BRCC3 exacerbates pulpitis by activating NF-κB signaling in dental pulp cells [59]. Additionally, Wnt4 has been shown to inhibit the NF-κB pathway, thereby suppressing apoptosis and inflammatory responses in dental pulp cells and enabling DPSCs to maintain their odontogenic differentiation potential under inflammatory conditions [60].

Moreover, signaling pathways do not operate in isolation but often engage in complex crosstalk. For instance, the fate determination of DPSCs during pulp regeneration, which involves whether they retain stemness to preserve the cellular reservoir or differentiate into odontoblasts, is regulated through the coordinated interaction of the Wnt and Notch pathways. These pathways establish a dynamic balance via direct molecular interactions and functional antagonism, collectively determining DPSCs fate. Studies have demonstrated that the biomaterial Biodentine significantly enhances proliferation in aged hDPSCs and suppresses senescence markers p53 and p21 through activation of the Wnt/β-catenin pathway. Biodentine promotes nuclear translocation of β-catenin while downregulating Axin1, an inhibitor of Wnt signaling, and concurrently inhibits NF-κB-mediated inflammatory signals, thereby achieving dual effects of odontoblastic differentiation and anti-aging [61]. Conversely, when DPSCs transfer mitochondria to Schwann cells via tunneling nanotubes (TNTs), the Notch pathway is activated to maintain DPSCs stemness. TNFα secreted by Schwann cells can stimulate NF-κB signaling in DPSCs, inducing expression of the Notch ligand Jagged1. Jagged1 subsequently binds to the Notch1 receptor on DPSCs, mitigating excessive p38 MAPK activation and ultimately balancing oxidative stress responses and cell survival during mitochondrial transfer [62]. These findings highlight the intricate interplay among signaling pathways, demonstrating that pulp regeneration is not a linear process but a highly regulated signaling network. Consequently, research should extend beyond individual pathways to encompass a comprehensive understanding of the entire biological process.

3. Types of Biomaterials and Their Applications in Pulp Regeneration

3.1. Bioceramics

Bioceramics are inorganic, non-metallic materials with excellent biocompatibility, capable of promoting tissue repair. In endodontics, they are primarily utilized as restorative materials in procedures such as root filling, pulp capping, perforation repair, and apical surgery, demonstrating significant potential for pulp regeneration [63,64].

Calcium silicate cement (CSC) has emerged as a widely used bioactive material for pulp regeneration due to its bioactivity, sealing ability, biocompatibility, and osteoinductive properties [65,66]. Numerous studies have highlighted the effectiveness of mineral trioxide aggregate (MTA) in facilitating the formation of continuous and complete dentin bridges, while preserving the morphology and function of exposed pulp tissue and promoting reparative dentin formation [67,68]. Biodentine, a recently developed bioactive dentin substitute, exhibits mechanical properties comparable to natural dentin and offers several advantages over MTA, including superior mechanical strength, shorter setting time, and reduced risk of tooth discoloration [69]. Its high density, low porosity, and favorable biocompatibility support the proliferation of key pulp cells and the deposition of reparative dentin. Additionally, Abuarqoub et al. reported that Biodentine modulates complement activation by regulating macrophage polarization, thereby eliciting an anti-inflammatory response to maintain tissue homeostasis and enhancing the migratory capacity of DPSCs, making it a critical factor in dentin–pulp regeneration [70]. iRoot BP Plus is recognized as an alternative to MTA, providing faster setting, improved cell viability and adhesion, enhanced

tissue regeneration, and a tighter seal, along with greater acid resistance [66]. These attributes have facilitated its widespread use in various pulp treatments, including direct and indirect pulp capping as well as VPT [69]. *In vitro* and *in vivo* evaluations by Ning et al. demonstrated that iRoot BP Plus, when used as a coronal sealing material in regenerative pulp surgery, exhibited excellent sealing ability, promoted SCAP migration, and induced dentin–pulp complex formation (Figure 1A) [71]. Similarly, Zeng et al. investigated the combined effects of concentrated growth factor (CGF) and iRoot BP Plus on hDPSCs and inflamed rat dental pulp tissue, finding that by day 28, the CGF–iRoot BP Plus group showed extensive hard tissue deposition, effective sealing of the injury site, and minimal inflammatory cell infiltration (Figure 1B) [72]. These results indicate that CGF and iRoot BP Plus act synergistically to suppress inflammation and accelerate pulp repair, highlighting iRoot BP Plus as a promising coronal sealing material.

Calcium phosphate (CaP) materials can mimic the mineralization processes of skeletal and dental tissues while exhibiting excellent biological activity, making them highly suitable as bioactive materials for regenerative pulp therapy [73]. Among these, hydroxyapatite (HAP), tricalcium phosphate (TCP), and biphasic calcium phosphate (HAP/TCP) are commonly employed as synthetic CaP materials for bone transplantation [74]. HAP, due to its similarity to the inorganic components of dentin, has been widely applied in pulp regeneration [75,76]. Chi et al. developed an inorganic submicron calcium sulfate hemihydrate/porous HAP pulp capping material (sCSHA-GFs) that demonstrated excellent biodegradability and solubility, enabling sustained release of calcium ions and growth factors. This property promoted the adhesion, proliferation, differentiation, and migration of hDPSCs, indicating that sCSHA-GFs cement is suitable for dentin and pulp regeneration in VPT [77]. β-TCP is another widely used and effective bone graft substitute, possessing both osteoconductive and osteoinductive properties. Liu et al. constructed antibiotic-loaded CM (GM)-β-TCP/gelatin composite scaffolds based on β-TCP [78]. These scaffolds replicated bone architecture, provided mechanical strength, and featured interconnected porous structures to support cell migration and proliferation (Figure 1C). Additionally, the scaffolds enabled sustained gentamicin release to eliminate bacteria. After four weeks, the scaffolds integrated with the surrounding bone, achieving infection-free regeneration and new tissue formation (Figure 1D). This study highlights β-TCP's capability for hard tissue repair and its potential application in dental pulp regeneration. However, β-TCP is prone to collapse due to its excessively rapid degradation, which can impair tissue repair. In vivo studies on polycaprolactone/β-TCP (PT) composites conducted by Wu et al. demonstrated that the fast degradation of PT scaffolds disrupts macrophage responses and leads to bone healing failure [79]. Macrophage co-culture experiments and subcutaneous implantation models revealed that scaffold degradation dynamically influences macrophage behavior, particularly polarization. RNA-Seq analysis further indicated that phagocytosis of degradation products from PT37 scaffolds induces oxidative stress and promotes pro-inflammatory M1 macrophage polarization, thereby compromising bone regeneration. To address these limitations, HAP/TCP was developed to combine the advantages of HAP and TCP at the submicron level: HAP provides higher stability, while TCP enhances resorption. Gu et al. engineered a novel biphasic CaP cement (CPC) [80]. Compared to traditional CPC, the CPC+20%TCP formulation exhibited excellent cell compatibility, appropriate injectability, higher compressive strength, enhanced dentin expression, and increased mineral deposition, while avoiding pro-inflammatory effects.

Bioactive glass (BG) is composed of components from the Na_2O-CaO-SiO_2-P_2O_5 system in defined ratios. When implanted near bone defects, BG releases Si, Ca, P, and certain doped ions, such as Zn, Mg, and Cu, which trigger beneficial intracellular and extracellular responses, thereby accelerating new bone formation [81]. BG-based wound dressings and peripheral nerve regeneration products have already been developed, demonstrating that BG is suitable not only for hard tissues but also for soft tissues, highlighting its broad applicability [82]. Zhu et al. prepared a silver-doped BG/chitosan hydrogel (Ag-BG/CS) as a pulp capping material [83]. In a rat pulpitis model, the Ag-BG/CS group preserved the dentin–pulp tissue structure more effectively than the MTA group (Figure 1E), demonstrating superior pulp repair capabilities. This effect was attributed to Ag-BG/CS enhancing DPSCs differentiation through activation of the MAPK pathway (Figure 1F). Similarly, Li et al. developed zinc-doped BG (BGz) nanoparticles as a pulp capping agent (Figure 1G) [84]. *In vitro* stimulation of macrophages with BGz showed that BGz microspheres were internalized by RAW cells, leading to significant downregulation of inflammation-related gene expression (Figure 1H). These results indicate that BGz functions as an immunomodulatory biomaterial capable of releasing zinc ions to regulate macrophage phenotype, restore a regenerative microenvironment, and promote pulp cell proliferation and dentin regeneration.

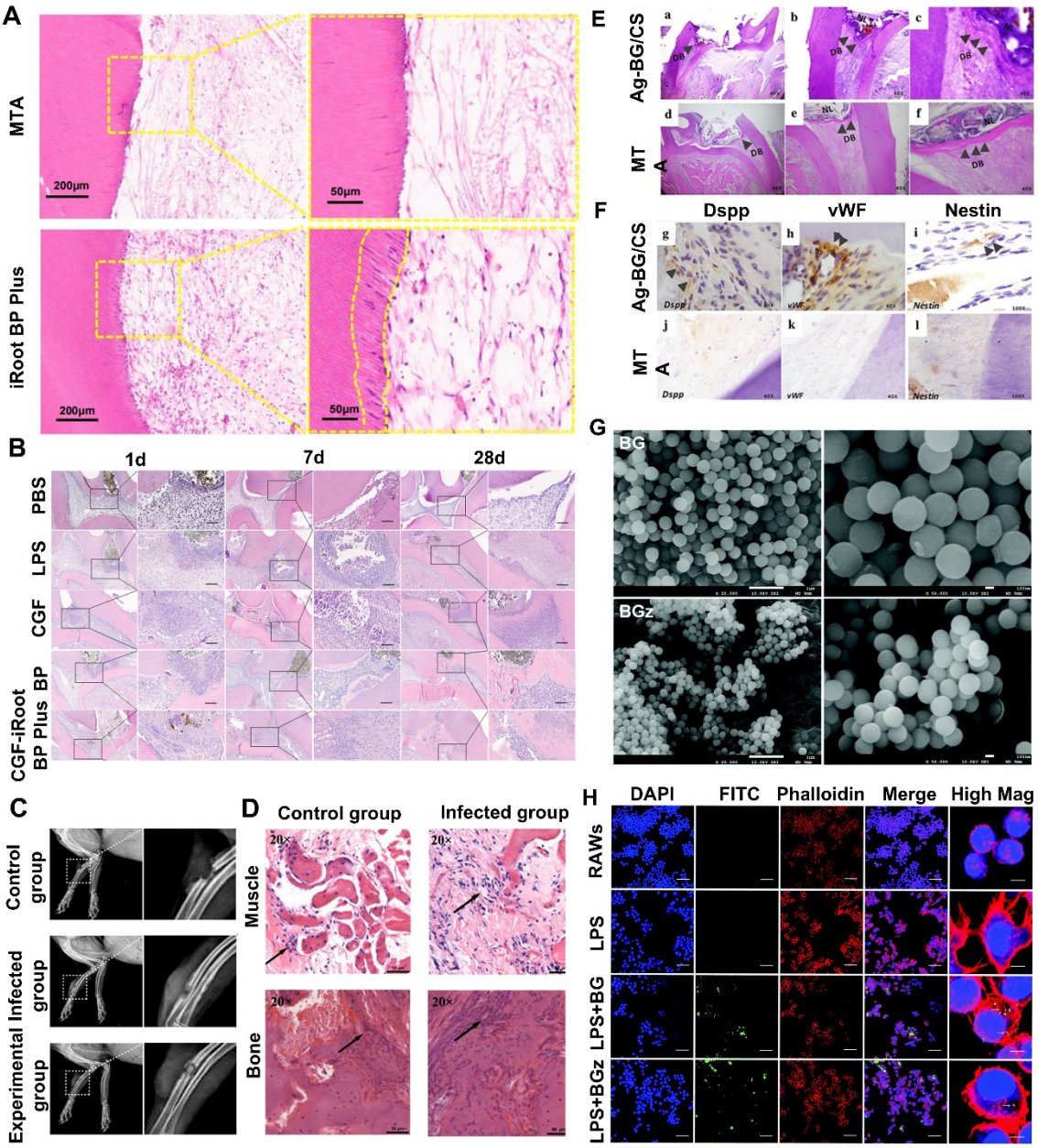

Figure 1. Bioceramics promoting dental pulp repair. (**A**). HE staining shows that iRoot BP Plus loaded with SCAP promotes regeneration of the pulp-dentin complex [71]. Copyright 2024, Springer Nature. (**B**). HE staining of rat pulpitis models after direct pulp capping with CGF, iRoot BP Plus, and CGF-iRoot BP Plus [72]. Copyright 2023, Springer Nature. (**C**). X-ray results of the control group, infection group, and experimental group in the rabbit radius segment bone defect model. (**D**). HE staining results of muscle and bone tissue in the control group and infected group after model establishment. Black arrows indicate inflammatory cells [78]. Copyright 2022, Public Library of Science. (**E**). HE staining shows regenerated dentin tissue after pulp capping with Ag-BG/CS and MTA. (**F**). Expression of cell markers Dspp, vWF, and Nestin in tissue sections [83]. Copyright 2019, American Chemical Society. (**G**). Representative SEM images of BG and BGz nanospheres. (**H**). Confocal images of RAWs internalizing nanospheres. DAPI staining of cell nuclei, FITC staining of BG/BGz, and phalloidin staining of cell cytoplasm [84]. Copyright 2021, Royal Society of Chemistry.

3.2. Hydrogels

Hydrogels are 3D, cross-linked hydrophilic polymer networks that closely mimic the ECM. They possess high water absorption capacity and flexible mechanical properties, which contribute to their excellent biocompatibility [85]. These features make hydrogels highly promising for the regeneration of complex tissues, including periodontal structures and osteochondral lesions [86,87]. Table 2 shows the hydrogels with various biological functions, most of which are composed of natural polymers.

Table 2. The function and application of hydrogels.

Classification	Hydrogel modification	Mechanism	Reference
Mineralisation	HPCH/TA	Promote reparative dentin formation	[88]
	C-NZ/GelMA antioxidative system	Form reparative dentin with regularly arranged dentinal tubules	[89]
	Alginate-fibrin fibers encapsulating hPDLSCs and metformin	Upregulate The Shh/Gli1 signaling pathway and affecte the metformin-induced osteogenesis of hPDLSCs	[90]
	PAA-CMC-TDM	Promote the odontogenesis or osteogenic differentiation of MSCs, adapt to irregular hard tissue defects, and promote in situ regeneration of defective tooth and bone tissues	[91]
Angiogenesis	PRFe-loaded ChitMA/ColMA hydrogel	Facilitate angiogenesis by enhancing VEGFA gene expression.	[92]
	SF/SA/ApoVs	Improve angiogenesis by enhancing paracrine functions of DPSCs, and promote capillary lumen formation of human umbilical vein endothelial cells (HUVECs) via the focal adhesion signaling pathway	[93]
	AZI-laden	Heighten the expression of endothelial cell surface markers like CD31	[94]
	SC/Gel	Enhance the odontogenesis of DPSCs and angiogenesis of HUVECs	[95]
Immunomodulatory	AS/Ns-gel	Downregulate the mRNA expression of IL-6 and IL-8 while upregulate the mRNA expression of IL-10 expression	[96]
	CHI–OCS–PDLSC/GMSC composite	Increase the number of IL-10 regulatory T cells, reduce the secretion of pro-inflammatory cytokines, and increase the production of anti-inflammatory cytokines.	[97]
	L-(CaP-ZnP)/SA nanocomposite hydrogel	Reduce the expression of TNF-α and IL-1β	[98]
	TGH/DM	Facilitate macrophage polarization	[99]
Antibacterial	Amoxicillin-loaded	Broad-spectrum antibacterial activity against *B. subtilis* and *E. coli*.	[100]
	Dentin ECM-chitosan hydrogels	Control the growth of *E. faecalis* bacteria and inhibit its biofilm formation	[101]
	low molecular weight chitosan	Be capable of reducing the number of CFUs of E. faecalis	[102]
	CHX/GelMA	Inhibit the activity of E. faecalis and A. naeslundii	[103]

Abbreviations: HPCH/TA: tannin-containing hydroxypropyl chitin hydrogel, C-NZ: carbon dot nanozymes, PAA-CMC-TDM: a composite mineral matrix hydrogel containing amorphous calcium phosphates, polyacrylic acid, carboxymethyl chitosan and dentin matrix, PRF: platelet-rich fibrin, SF/SA/ApoVs: ApoVs-laden silk fibroin/sodium alginate hydrogel, AZI: azithromycin, SC/Gel: $SrCuSi_4O_{10}$/gelatin methacrylate, AS/Ns-gel: asiaticoside-loaded nanosponges hydrogel, CHI–OCS–PDLSC/GMSC composite: an aligned porous hydrogel scaffold combined with PDLSCs and GMSCs, L-(CaP-ZnP): L-Arginine modified calcium phosphate/zinc phosphate nanoparticles, SA: sodium alginate, TGH/DM: GelMA/HAMA composite hydrogel mixed with peptide Tet213 and demineralized dentin matrix, ECM: demineralized dentin extracellular matrix, CHX: photocrosslinkable chlorhexidine.

Currently, researchers have developed various hydrogels with broad applications in pulp regeneration. GelMA retains the natural RGD sequence of gelatin, allowing it to closely mimic the ECM of dental pulp. Its excellent biocompatibility has made it one of the most widely used hydrogel materials. Khayat et al. demonstrated that GelMA supports the adhesion and proliferation of hDPSCs and HUVECs, while also providing attachment sites for infiltrating host cells, thereby promoting the formation of a well-organized vascular network [104]. This highlights GelMA as a promising clinically relevant material for dental pulp vascularization and human pulp tissue regeneration. However, GelMA lacks inherent antibacterial properties and exhibits limited mechanical strength, which restricts its broader application. To address these limitations, Li et al. enhanced GelMA by incorporating antibacterial nanoparticles [105]. They prepared hollow-structured nanoscale silver bromide-doped mesoporous silica ($AgBr@SiO_2$) microspheres using a modified Stöber method, incorporated them into GelMA, and cross-linked the mixture with UV light. The resulting hydrogel exhibited improved mechanical properties and effective antibacterial activity against both *Staphylococcus aureus* and *Escherichia coli*. Chitosan is valued for its intrinsic antimicrobial properties and its ability to support fibroblast and odontoblast activity, thereby contributing to pulp regeneration [12]. Nguyen et al. investigated injectable hydrogels (HACM) formulated from hyaluronic acid (HA) and carboxymethyl chitosan (CMC) [100]. HACM loaded with erythropoietin (EPO) significantly enhanced bioactivity and reduced reactive oxygen species (ROS) levels (Figure 2A). Additionally, HACM could be combined with amoxicillin (HACM/AX) to provide strong antimicrobial effects (Figure 2B), demonstrating its therapeutic potential for treating bacterial pulpitis. Methacrylated collagen (ColMA), owing to its native cell-binding sites and low immunogenicity, promotes DPSCs attachment, proliferation, and odontogenic differentiation [106]. Its

photopolymerizable properties make it suitable for 3D-printed scaffolds that reconstruct the pulp–dentin microenvironment. Noohi et al. developed a PRFe-loaded methacrylated chitosan/ColMA hydrogel, which enhanced biomineralization and upregulated the expression of ALP, COL I, DSPP, and DMP1, supporting SCAP odontogenic differentiation while also promoting angiogenesis via increased VEGFA expression [92]. Methacrylated alginate (AlgMA) can form a unique dual-network structure through photopolymerization and Ca^{2+}-mediated physical cross-linking. By adjusting the degree of methacrylation and Ca^{2+} concentration, the hydrogel's stiffness and degradation rate can be precisely tuned, enabling controlled release of loaded therapeutics. Fei et al. prepared a silk fibroin/sodium alginate (SF/SA) hydrogel with tunable release kinetics, capable of slowly releasing apoptotic vesicles (ApoVs) to amplify DPSCs paracrine signaling and induce vascular lumen formation in HUVECs (Figure 2C,D), thereby establishing a microenvironment conducive to both dentin and nerve regeneration [93].

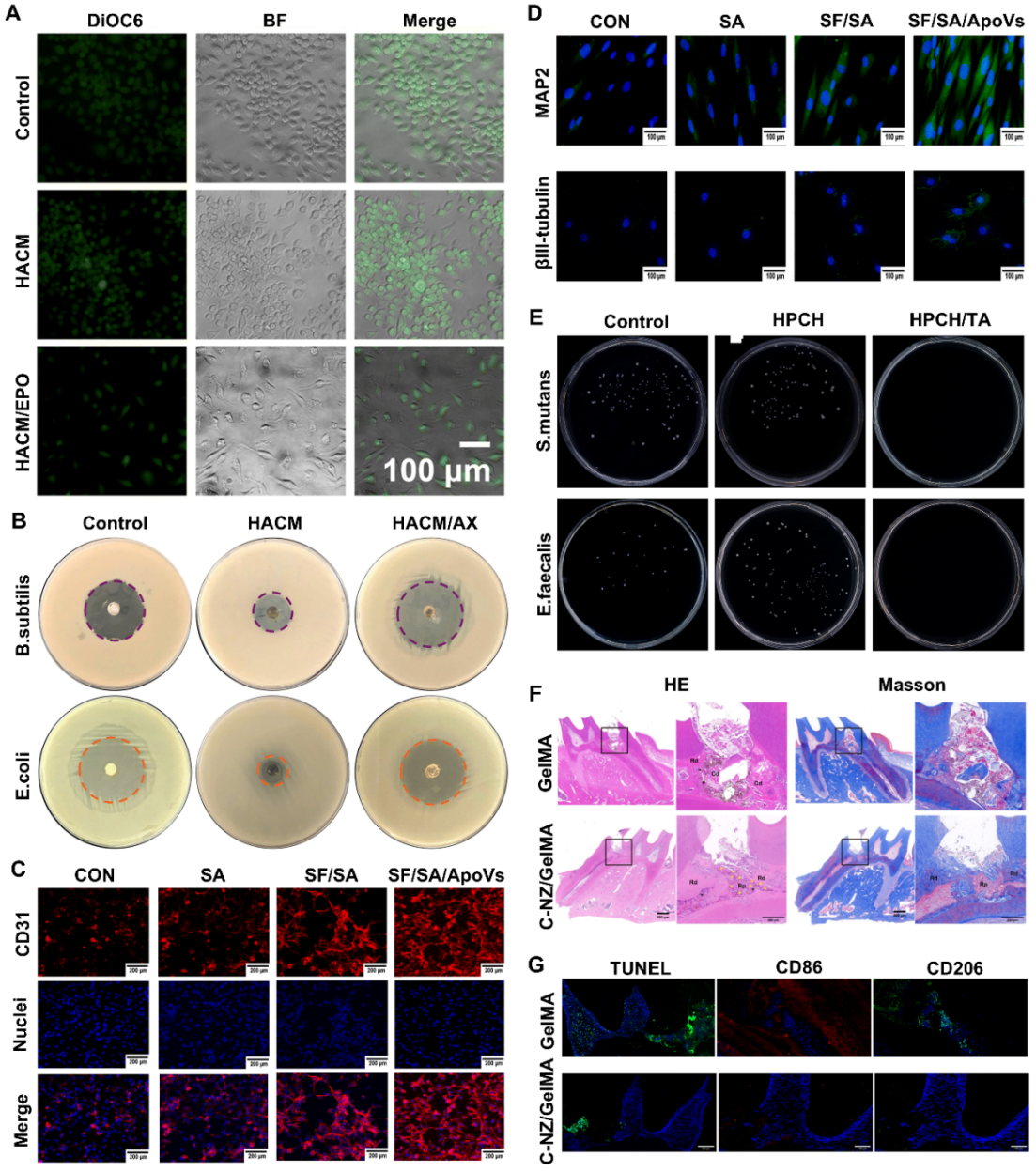

Figure 2. Hydrogel materials promoting dental pulp repair. (**A**). ROS production in RAW 264.7 macrophages after incubation with HACM and HACM/EPO. (**B**). Evaluation of the antimicrobial activity by the disk diffusion method [100]. Copyright 2025, Royal Society of Chemistry. (**C**). Immunofluorescence staining of CD31 in HUVECs after co-culture with hydrogel for 3 days. (**D**). Immunofluorescence staining images of MAP2 and βIII-tubulin after co-culturing DPSCs with hydrogel for 14 days [93]. Copyright 2025, Elsevier. (**E**). The bacterial plate test showed the antibacterial properties of different groups [88]. Copyright 2024, Multidisciplinary Digital Publishing Institute. (**F**). HE staining images and Masson staining images of rat pulpitis treated with GelMA or C-NZ/GelMA hydrogel. (**G**). Immunofluorescence images of TUNEL, CD86 and CD206 in dental pulp tissue [89]. Copyright 2024, Springer Nature.

The incorporation of immunomodulatory factors into hydrogels is increasingly employed in pulp regeneration. The interplay between inflammatory cells, cytokines, and the oxidative stress microenvironment plays a critical role in the repair process. Zhou et al. developed a hydroxypropyl chitosan hydrogel containing tannic acid (HPCH/TA) [88]. This hydrogel demonstrated strong antibacterial activity (Figure 2E), inhibited cytokine release in inflamed human pulp cells by blocking the NF-κB pathway, alleviated pulp inflammation in a rat pulpitis model, and promoted dentin repair. Similarly, Zhang et al. designed an antioxidant system (C-NZ/GelMA) composed of carbon dot nanoenzymes (C-NZ) and GelMA [89]. The C-NZ/GelMA system effectively scavenged ROS, restored intracellular redox homeostasis, reduced oxidative stress damage, and facilitated pulp regeneration and dentin repair (Figure 2F,G). These findings highlight the potential of immunomodulatory and antioxidant hydrogels as effective biomaterials for treating pulpitis.

Hydrogels can exhibit antimicrobial properties due to their polymeric composition. Their 3D network allows direct contact with bacteria in narrow dental tissue gaps, facilitating effective disinfection, while also serving as a barrier to prevent bacterial colonization [107]. Osman et al. developed a biomimetic, smart dentin ECM–chitosan hydrogel that reduced bacterial colony-forming unit (CFU) activity by 96–98% through inhibition of *Escherichia coli* biofilm formation, demonstrating strong antimicrobial efficacy and potential for regenerative endodontic applications [101]. While some hydrogels possess intrinsic antimicrobial activity, this property can be further enhanced through chemical modification. For instance, Lee et al. showed that alginate hydrogels inherently inhibit pathogens such as *Streptococcus viridans* and *Candida albicans*, and that the introduction of alkyl groups onto alginate molecules further amplifies this effect [108]. Additionally, hydrogels can be engineered to deliver antimicrobial agents, providing controlled and sustained antibacterial activity [109]. Ribeiro et al. developed a chlorhexidine-loaded methacrylic acid gelatin hydrogel (CHX/GelMA), which demonstrated a low degradation rate, enabling sustained drug delivery to the target site and exhibiting strong antimicrobial potential.

In summary, hydrogels, owing to their unique biocompatibility and structural properties, effectively support DPSCs attachment, proliferation, and lineage differentiation. Moreover, they can be combined with bioactive factors to promote dental pulp regeneration, dentin mineralization, and vascularization, offering versatile scaffold design strategies for regenerative endodontic therapies.

3.3. Synthetic Polymer

Polymers can be categorized into natural and synthetic types. Natural polymers, including gelatin, chitosan, and alginate, have been discussed in the hydrogel section; this section focuses on synthetic polymers. Synthetic polymers, such as polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), PT (PCL), and polyethylene glycol (PEG), are widely used in dental pulp tissue regeneration due to their excellent mechanical properties, controllable degradation rates, non-toxicity, and the ability to precisely regulate porosity and microstructure. However, their hydrophobic surfaces and lack of cell adhesion sites limit cellular attachment, proliferation, and differentiation, reducing bioactivity. Chemical modifications, such as incorporation of RGD peptides, growth factors, or HAP, can significantly enhance cytocompatibility and functionality [110,111].

PLA degrades into soluble lactic acid via hydrolysis and offers biocompatibility, degradability, low inflammatory response, and cost-effectiveness. Dawood et al. co-coated 3D-printed PLA scaffolds with nano-HAP (nHA) and naringin (NAR), which improved mechanical strength, antibacterial properties, and bioactivity [112]. PLGA, a copolymer of lactic and glycolic acids, can be fabricated into biodegradable, biocompatible composites and polymer scaffolds for drug delivery. Chen et al. developed PLGA/gelatin electrospun sheets (APES) loaded with treated TDM and natural dental pulp ECM (DPEM). In animal experiments, APES with aligned fiber orientation guided cell proliferation, while TDM and DPEM retained their native structures and proteins, promoting the formation of root-like tissues in porcine jawbones 12 weeks post-implantation [113]. PEG also exhibits excellent biomaterial properties, though its surface characteristics depend on the synthesis process, and it can be fabricated as hydrogels, microspheres, blocks, or fibers [110]. Han et al. created an injectable dual-drug programmed-release chitosan nanofiber microsphere/PLGA-PEG-PLGA hydrogel system loaded with VEGF and DPSC-derived exosomes (DPSCs-Exo), which enhanced angiogenesis in human umbilical vein ECs and promoted osteogenic differentiation of pre-osteoblasts [114]. PCL offers good processability, low melting point, high mechanical strength, and excellent biocompatibility, making it suitable for scaffolds in bone and periodontal tissue engineering. Anselmi et al. incorporated quercetin (QU) and calcium hydroxide (CH) into PCL/polyethylene oxide (PEO) scaffolds, which inhibited LPS-induced inflammatory responses and upregulated genes associated with mineralized matrix formation, thereby promoting DPSCs differentiation in an inflammatory environment [115].

In general, synthetic polymers possess limited intrinsic biological functionality in dental pulp regeneration and primarily serve as carriers or scaffolds. Compared with natural polymers, they exhibit notable shortcomings in terms of bioactivity, cell adhesion, and the ability to actively support tissue regeneration.

3.4. Nanomaterials

In recent years, the use of nanomaterials in medicine, particularly in dentistry, has expanded significantly. Researchers have explored their precise application in pulp therapy to overcome the longstanding challenge of limited therapeutic efficacy through nanoscale regulation of materials. Studies indicate that nanoparticles outperform traditional materials due to their superior surface chemistry and adhesion properties [116,117].

Graphene family nanomaterials (GFNs) have garnered considerable attention in biomedical applications because of their unique physicochemical characteristics, including high surface area, mechanical strength, and hydrophilicity [118]. Their two-dimensional layered structure provides abundant active sites while conferring excellent mechanical flexibility and conductivity. Moreover, GFNs can inhibit inflammation, resist bacterial colonization, and enhance cell adhesion, making them promising candidates for pulp revitalization, periodontal reconstruction, and implant-surface engineering [119]. For instance, Rosa et al. treated DPSCs with graphene oxide (GO), resulting in increased mRNA expression of odontoblast- and osteoblast-related genes, suggesting that GO can induce DPSCs differentiation toward odontogenic and osteogenic lineages [120].

Similarly, HAP nanoparticles (nHAP) are increasingly utilized in bone tissue engineering and dental restoration due to their strong remineralization capacity for early enamel lesions and their ability to enhance the performance of dental materials [121]. Dawood et al. co-coated nHAP with NAR on 3D-printed PLA scaffolds and conducted osteogenic induction experiments using hDPSCs. The nHAP/NAR combination significantly promoted cell adhesion, ALP expression, and mineralized matrix deposition, confirming that nHAP effectively enhances both proliferation and differentiation of stem cells [122]. By leveraging the unique properties of nanomaterials, dental tissue regeneration can overcome the limitations of conventional therapies, offering a novel paradigm for regeneration of the pulp–dentin complex.

3.5. Smart Responsive Materials

Smart responsive materials are capable of detecting endogenous cues or external stimuli and adapting their behavior in real time [123–125].This responsiveness can be harnessed to regulate various biochemical functions, providing significant advantages in drug delivery by enabling precise control over spatial, temporal, and dosage parameters [126,127].

In pulp regeneration, common stimulation signals include heat, light, and pH, among others [128]. Thermoresponsive materials are those whose properties vary with temperature, allowing controlled drug release or morphological changes in response to thermal variations [129]. The primary advantage of thermoresponsive materials lies in their ability to conform perfectly to defect sites upon implantation. Under the influence of body temperature, the material solidifies, thereby immobilizing the drug in situ at the target location. This process effectively prevents drug diffusion and ensures both the continuity and efficacy of early-stage treatment. Reis-Prado et al. investigated the incorporation of azithromycin (AZI) into thermosensitive chitosan for use as an intracanal drug in regenerative endodontic procedures. The resulting hydrogels exhibited thermal gelation at 37 °C and rapidly reformed a gel state upon injection at the treatment site, preventing undesired diffusion. Mechanical and rheological analyses demonstrated that AZI incorporation did not compromise hydrogel strength or injectability, while simultaneously enhancing antibacterial activity against pulp pathogens [94].

Light-responsive materials are characterized by their ability to undergo reversible or irreversible changes in physical or chemical properties upon exposure to specific wavelengths of light. The light-induced switching occurs almost instantaneously and can be precisely localized to the micrometer or even nanometer scale, enabling micropatterning or targeted actuation. This precision control underscores the unique advantages of light-responsive systems. Qiu et al. developed a $SrCuSi_4O_{10}$/GelMA (SC/Gel) composite hydrogel, using GelMA as a matrix to embed SC particles. This composite exhibited exceptional near-infrared photothermal conversion and multiple bioactivities. The photothermal activation of the SC/Gel hydrogel during the early phase of pulp repair effectively eliminated bacteria and suppressed biofilm formation. At later stages, the controlled release of bioactive ions could be precisely triggered by applying external near-infrared light at predetermined time points. This on-demand release mechanism ensures that signals inducing odontogenic differentiation and angiogenesis emerge within the optimal therapeutic window [95].

pH-responsive materials typically contain acidic or basic functional groups, allowing their properties to change in response to variations in pH. These materials find extensive applications in drug delivery, environmental

sensing, and tissue engineering [129]. Wang et al. developed a pH responsive peptide microsphere/carboxymethyl chitosan complex (PM/CS) loaded with TVH-19 (an amelogenin derived peptide). PM/CS achieved antibacterial and mineralization stimulating effects through the sequential release of ions and peptides. In the acidic environment of dental caries, the degradation of PM/CS resulted in the cumulative release of 60% TVH-19 within 48 h, demonstrating strong bactericidal efficacy against Streptococcus mutans. At physiological pH, TVH-19 slowly released about 80% within 9 days. This maintained the stability of the microenvironment of the dentin pulp complex, and promoted the migration of hDPCs and driving biomineralization, demonstrating significant mineralization induction ability [130].

4. Mechanism of Biomaterials Regulating Pulp Tissue Regeneration

4.1. Stem Cell Recruitment and Homing

Stem cell recruitment and homing are central objectives in endogenous pulp regeneration therapy. The efficient execution of this process relies on the multidimensional synergy among signaling molecules, stem cell phenotypes, and biomaterial scaffolds. Among these factors, the SDF-1/CXCR4 pathway serves as a pivotal driver, regulating stem cell homing and recruitment. SDF-1 binds specifically to the CXCR4 receptor on the stem cell surface, establishing a concentration gradient at the site of pulpal injury. This interaction triggers a signaling cascade involving intracellular Ca^{2+} mobilization, actin reorganization, and other cellular responses, thereby precisely directing the migration of stem cells [131,132].

In the context of pulp regeneration, the role of SDF-1 is highly targeted. For example, in a canine root canal graft model, SDF-1 selectively enhanced the activity of CD31/CD146 side-population cells, which function as a primary source of vascular endothelial progenitor cells. The recruitment of these cells ultimately supported the regeneration of pulp-like tissues containing capillaries and nerves, establishing the structural basis for restored pulpal function [133,134]. Moreover, SDF-1 modulates the local microenvironment through paracrine signaling, suppresses excessive inflammation, and thereby creates a favorable niche for the survival of homing stem cells. This property allows SDF-1 to maintain efficient recruitment even under inflammatory conditions, such as chronic periapical periodontitis [135].

Beyond the SDF-1/CXCR4 pathway, additional signaling molecules act in complementary or synergistic manners to form a complex regulatory network for stem cell homing. PDGF mediates MSCs chemotaxis and proliferation via PDGFRα/β receptors and facilitates the vascular pathway for stem cell migration by promoting EC migration and lumen formation [136,137]. FGF 2 enhances pulp cell migration by binding to cell surface acetylheparin sulfate. Transwell migration assays demonstrated that FGF2 treatment nearly doubled the number of migrating cells compared to controls, and this pro-migratory effect occurred independently of early differentiation, enabling rapid accumulation of stem cells at injury sites [138]. TGF-β1 promotes cytoskeletal reorganization through ERK/MAPK pathway activation and downregulation of Rho GTPase-activating protein, thereby increasing stem cell migration rates [139]. Additionally, TGF-β1 stimulates ECM production, including collagen and laminin, which serve as adhesion sites for homing cells.

Biomaterial scaffolds serve as carriers for signaling molecules and provide platforms for stem cell colonization, thereby enhancing the efficiency of homing regulation. In pulp regeneration experiments using canine incisors, collagen scaffolds incorporating SDF-1 and $CD105^{+}$ pulp stem cells demonstrated excellent outcomes. The regenerated tissue exhibited a nearly 40% increase in nerve fiber density and blood vessel number compared to scaffolds containing SDF-1 alone, highlighting the synergistic effect of signaling molecules and stem cells [140]. Conversely, synthetic scaffolds functionalized with growth factors can extend the duration of signaling through controlled release mechanisms. Bordini et al. developed chitosan-calcium aluminate scaffolds loaded with PDGF, which sustained effective concentrations for up to seven days, thereby enhancing MSCs migration and increasing the deposition of mineralized substrate [141]. The coordinated action of signaling molecules, stem cells, and scaffolds ultimately facilitates the efficient recruitment of stem cells within periapical tissues.

4.2. Angiogenesis

The dental pulp vascular system exhibits a distinctive anatomical configuration. Its blood vessels communicate with the surrounding periapical tissues solely through a narrow apical foramen and lack functional collateral circulation. This unique structure limits the pulp's ability to self-repair via its vascular network following injury [142]. Due to the absence of sufficient collateral circulation, pulp tissue is highly vulnerable to necrosis during episodes of ischemia, inflammation, or infection. While conventional RCT effectively eliminates infection, it cannot restore the pulp's inherent physiological functions. Consequently, strategies to reconstruct the vascular

system of the dental pulp have emerged as a critical focus in pulp tissue regeneration. Research indicates that successful pulp regeneration relies on the timely establishment of a functional circulatory system, which provides essential oxygen and nutrients to the developing tissue [143]. Vascular formation involves a sequence of cellular processes, including initiation, proliferation, migration, and tubular structure formation. In the context of pulp regeneration, early vascular network formation not only sustains cell viability but also promotes stem cell recruitment and differentiation, establishing the foundational conditions for functional restoration. Furthermore, the nascent vascular system secretes a range of bioactive factors that regulate the local microenvironment, enhance nerve regeneration, and support matrix deposition, collectively contributing to the physiological recovery of the pulp-dentin complex [144].

DPSCs constitute the primary cellular population driving vascular reconstruction in pulp tissues. These cells exhibit two principal functional mechanisms. First, they influence ECs through the secretion of pro-angiogenic factors such as VEGF, bFGF, and PDGF. Second, DPSCs can differentiate directly into endothelial-like cells, contributing to neovascularization [145]. Li et al. reported that hypoxia-preconditioned DPSCs-Exo (Hypo-Exos) contained elevated levels of pro-angiogenic proteins compared with exosomes derived under normoxic conditions, significantly enhancing proliferation, migration, and capillary-like network formation in HUVECs [146]. Liu et al. developed self-assembled spherical dental pulp-like organoids via co-culture of DPSCs and ECs. Under hypoxic conditions, DPSCs underwent endothelial lineage commitment and formed a perfusable circulatory architecture, markedly improving organoid survival and functional integration. This model offers a promising pre-vascularization approach for clinical pulp regeneration [147]. Notably, DPSCs cultured under low oxygen tension demonstrated superior vascularization potential, primarily mediated through activation of the hypoxia-inducible factor-1α (HIF-1α) pathway, which upregulates the production of multiple pro-angiogenic factors [16]. Kim et al. used $CoCl_2$ to simulate hypoxia and observed that the vascularization capacity of SHED significantly surpassed that of adipose-derived stem cells (ADSCs) and BMSCs under low-oxygen conditions [148], accompanied by elevated HIF-1α and VEGF expression.

Vascular-related cytokines, including VEGF, FGF, PDGF, TNF-α, and IGF, function as critical regulators during neovascularization, supporting tissue repair by stimulating EC proliferation, motility, vascular plexus assembly, and maintenance of vascular homeostasis. Among these factors, VEGF plays a central role in promoting EC growth and migration by binding specifically to vascular endothelial receptors (VEGFR-1 and VEGFR-2) and activating downstream signaling pathways such as PI3K/Akt and MAPK/ERK [149]. Additionally, VEGF increases vascular permeability, facilitating plasma protein extravasation and the formation of a provisional ECM that supports subsequent cell migration and neovascular development.

4.3. Nerve Regeneration

The pulp tissue contains an extensive neural network that serves dual functions: transmitting nociceptive signals to the central nervous system and simultaneously maintaining local tissue homeostasis and facilitating repair through neuropeptide release. A close interplay exists between nerve regeneration and angiogenesis, as newly formed nerve fibers secrete pro-angiogenic factors, while nascent blood vessels provide essential nutrients and chemotactic cues to support nerve growth [150]. Calcitonin gene-related peptide (CGRP) promotes VEGF expression and angiogenesis by activating specific receptors on ECs, acting as a key signaling molecule. At the molecular level, CGRP activates the cyclic adenosine monophosphate–protein kinase A (cAMP-PKA) signaling pathway via the CLR/RAMP1 receptor complex on EC surfaces. This activation not only enhances VEGF expression but also strengthens vascular EC adhesion through phosphorylation of focal adhesion kinase (FAK), thereby improving the stability of newly formed vessels. Moreover, CGRP-mediated PKA signaling regulates matrix metalloproteinase (MMP) activity and facilitates ECM remodeling, establishing a structural framework conducive to both neural and vascular regeneration [151]. In addition to its pro-regenerative functions, CGRP exhibits significant anti-inflammatory effects, fostering a microenvironment favorable for tissue repair. Ning et al. demonstrated that CGRP markedly attenuates sepsis-induced intestinal injury by inhibiting NLR-family pyrin domain protein 3 (NLRP3) inflammasome activation and reducing ROS accumulation [152]. Evidence further indicates that CGRP decreases the secretion of pro-inflammatory mediators, including TNF-α and IL-6, while enhancing IL-10 production through suppression of the NF-κB signaling pathway.

4.4. Immunomodulatory Function

During pulpal inflammatory pathology, the inflammatory microenvironment exhibits a characteristic biphasic pattern: transient, moderate inflammation enhances the proliferative and differentiation capacities of DPSCs, whereas chronic or severe inflammation results in stem cell dysfunction and irreversible tissue damage [153]. This biphasic

effect is closely associated with both the concentration and duration of inflammatory factor exposure [154]. As key immune regulators, macrophages display remarkable plasticity during tissue injury and regeneration, dynamically shifting between classically activated (M1) and alternatively activated (M2) states in response to local microenvironmental cues [155,156]. Consequently, promoting macrophage polarization toward the M2 phenotype has emerged as a pivotal strategy in the design of endodontic regenerative biomaterials. For instance, Li et al. synthesized a polydopamine-coated BG (BG-PDA) capable of inducing macrophage polarization toward the M2 phenotype (Figure 3A). BG-PDA was found to modulate macrophage phenotype by enhancing mitochondrial function, thereby reducing intracellular ROS levels, suppressing pro-inflammatory factors (TNF-α, IL-6), and increasing anti-inflammatory factors (IL-10, Arg-1) [157]. The unique advantage of this material lies in its synergistic combination of inflammation control and tissue regeneration, integrating the dentin-inducing potential of BG with the immunomodulatory properties of polydopamine (Figure 3B).

The principal challenge for endodontic regenerative biomaterials is to precisely modulate the inflammatory microenvironment—mitigating excessive inflammatory damage while preserving essential restorative signals. Accordingly, ideal regenerative materials must exhibit both anti-inflammatory and pro-regenerative properties. Dadgar et al. developed a gelatin nanofiber scaffold loaded with rutin nanoparticles for endodontic regeneration [158]. This scaffold effectively inhibited the growth of *Enterococcus faecalis* and *Pseudomonas aeruginosa*, while significantly reducing the expression of inflammatory factors in LPS-induced pulp stem cells. Simultaneously, it promoted DPSCs proliferation and differentiation via suppression of the NF-κB pathway, achieving a dual function of inflammation control and regeneration. Additionally, Xie et al. designed a temperature-sensitive hydrogel (TGH/DM) composite incorporating an antimicrobial peptide (AMP) and demineralized DM to enhance the immune microenvironment in infected pulpitis [99]. TGH/DM was shown to facilitate odontoblastic differentiation of hDPSCs through activation of the peroxisome proliferator-activated receptor γ (PPARγ) pathway and to promote macrophage polarization toward the M2 phenotype, markedly improving dentin-pulp tissue regeneration compared with conventional direct pulp capping agents. This innovative approach addresses both infection control and functional tissue regeneration through immunometabolic modulation.

DPSCs not only serve as seed cells for pulp regeneration but also actively participate in shaping the immune microenvironment. Evidence suggests that DPSCs regulate various immune cell functions via paracrine mechanisms [159], and biomaterials can further amplify or direct these effects. Shen et al. engineered a chitosan hydrogel incorporating DPSCs-Exo/CS, which significantly promoted the transition of macrophages from M1 to M2 phenotypes, increasing M2 macrophages by 130% in murine periodontitis models (Figure 3C) [160]. This study demonstrated that DPSCs-Exo/CS alleviates periodontitis through immunomodulatory and anti-inflammatory effects, offering a novel strategy for periodontal regeneration. Yang et al. developed a miR-146a nanodelivery system that maintained the inflammatory microenvironment at the injury site by precisely regulating the NF-κB signaling pathway [58]. This system prevented stem cell dysfunction due to excessive inflammation while ensuring sufficient inflammatory signaling to initiate repair. The results showed that MSN+miR-146a promoted early osteogenesis in infected mice with mandibular defects and exerted macrophage immune-regulatory effects (Figure 3D,E). Similarly, dental follicle stem cells (DFSCs), another type of dental MSCs, exhibit enhanced immunometabolic regulation through their small extracellular vesicles (DFSC-sEVs). Tian et al. demonstrated that DFSC-sEVs alleviate LPS-induced pulpitis in rats [161]. Heat shock protein 70 (HSP70) within DFSC-sEVs is incorporated into lysosomes of macrophages in the inflammatory microenvironment, inducing mitochondrial autophagy and promoting degradation of depolarized mitochondria (Figure 3F). This process ultimately drives M2 macrophage polarization, enhancing dental pulp repair, and offering a new perspective for immune-metabolic interventions.

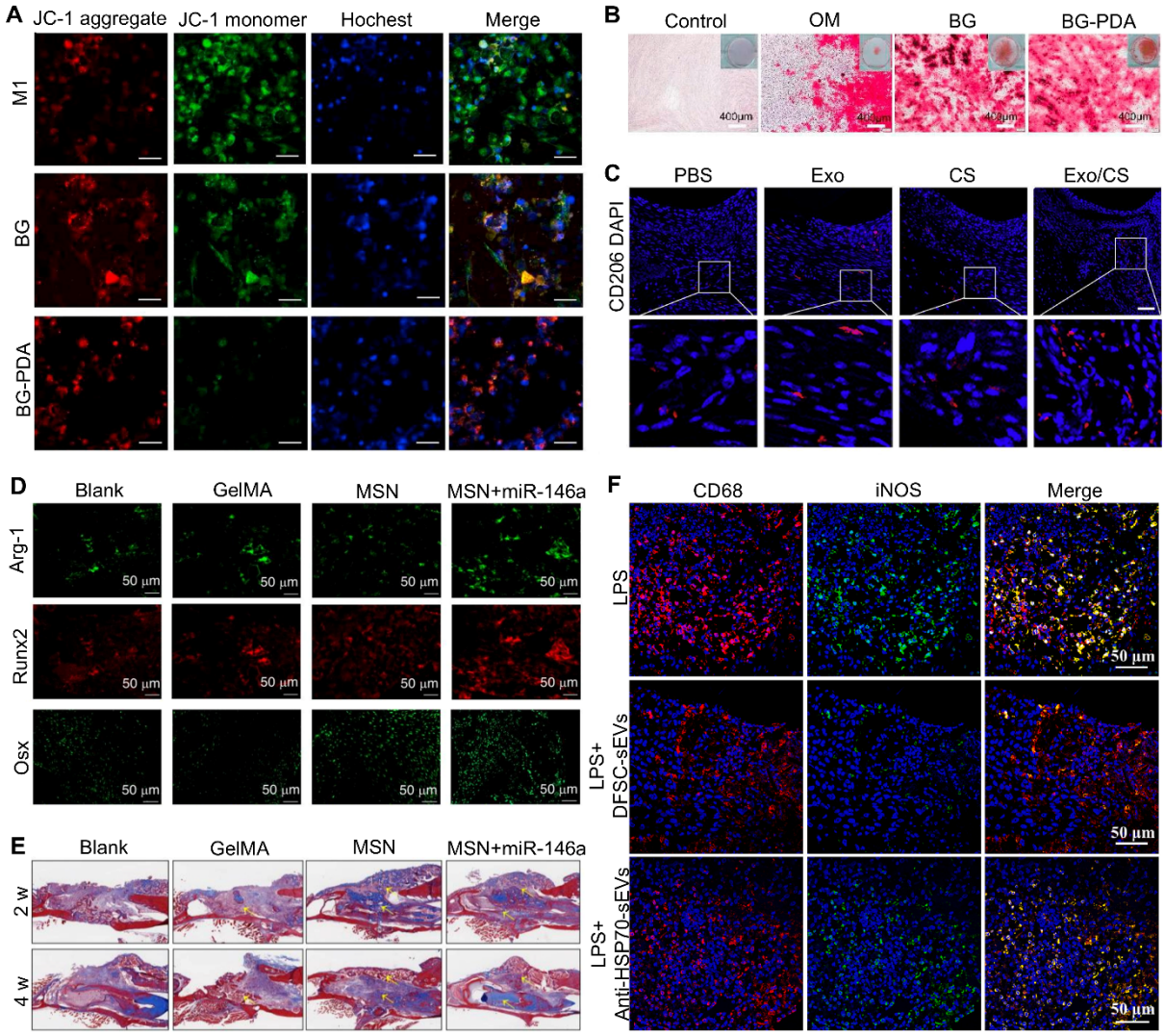

Figure 3. Biomaterials regulating the immune microenvironment of dental pulp. A. BG-PDA could enhance mitochondrial function in inflammatory macrophages by preserving MMP. B. Alizarin red staining showed that BG-PDA promoted mineralization of hDPC [157]. Copyright 2024, Elsevier. C. $CD206^+$ cells were significantly more abundant in the periodontal tissues of mice in the Exo/CS group than in other groups [160]. Copyright 2020, KeAi Communications Co. D. The expression of Arg-1, Runx2, and OSX was significantly increased in the MSN+miR-146a group after two weeks. E. Masson staining results showed that the MSN group and MSN+miR-146a group had more bone tissue observed in the defect area than the blank group and GelMA group [58]. Copyright 2024, Springer Nature. F. The LPS+Anti-HSP70-sEVs group had more CD68iNOS macrophages in the pulp tissue. The results showed that HSP70 in DFSC-sEVs could protect lysosomes, thereby inhibiting M1 inflammatory macrophages [161]. Copyright 2025, KeAi Communications Co.

5. Current Status of Clinical Research and Translational Applications

The clinical application of endodontic biomaterials is crucial for addressing challenges in the treatment of endodontic and periapical diseases. Multiple clinical trials have highlighted the potential of stem cells and biomaterials in regenerating the pulp-dentin complex. For example, combining BMSCs with bioactive ceramics significantly enhanced alveolar bone healing and improved implant stability, with therapeutic outcomes of bone regeneration reaching up to 85% in localized bone defects [162]. However, success rates were lower in patients with compromised systemic health or extensive bone loss. Additionally, the use of SCAP composite bioactive scaffolds has been preliminarily validated in clinical settings, demonstrating partial regeneration of pulpal tissues and improvement of pulpal function [163]. These findings indicate that endodontic tissue engineering techniques hold substantial promise for treating conditions such as pulpitis and traumatic dental avulsion. However, various types of stem cells exhibit distinct characteristics in treating various dental pulp diseases. MSCs tend to differentiate towards osteogenesis and adipogenesis, aiming to promote alveolar bone healing and periapical tissue

repair. For pure pulp necrosis, its ability to promote pulp-like tissue regeneration may not be optimal [164,165]. DPSCs and SCAP have excellent odontogenic and neurogenic differentiation abilities, as well as strong proliferative capacity. They can secrete more chemokines, neurotrophic factors, and proteins involved in metabolic processes and transcription, especially suitable for treating pulp necrosis and young permanent teeth with unclosed apical foramen [166,167].

Despite considerable advances, achieving complete regeneration of physiologically functional pulp tissue remains a significant challenge. While various endodontic regenerative biomaterials targeting angiogenesis, nerve regeneration, and immunomodulation have been developed in laboratory settings, their application is largely limited to *in vitro* studies and animal models. Clinical trials have predominantly focused on evaluating dental function restoration, with limited investigation into the physiological functionality of regenerated teeth. Consequently, regenerative approaches in endodontics have primarily aimed at improving clinical outcomes in cases involving periapical tissue damage [6,86]. Studies indicate that combining stem cells with bioscaffold materials supplemented with platelet-rich plasma (PRP) or exogenous growth factors can achieve partial tissue regeneration within the root canal system [168]. Clinical evidence shows that this strategy significantly enhances patient recovery and reduces the risk of reinfection [169]. For instance, in a clinical case involving severe periodontal attachment loss and alveolar bone and periodontal membrane resorption, DPSCs and platelet-rich fibrin (PRF) were incorporated into a clot to promote tissue regeneration. Six-month follow-up revealed functional regeneration of the periodontium, increased bone density, improved periodontal probing depth, and other key indicators, confirming that the DPSCs-PRF scaffold effectively supports both structural and functional periodontal regeneration.

Although pulp regeneration remains challenging, notable clinical progress has been achieved, offering promising strategies for pulp tissue repair. A randomized controlled trial compared PRP with traditional blood clots (BC) for pulp regeneration in 20 necrotic teeth over an 18-month follow-up [170]. The PRP group achieved complete root tip closure on average within 8 months, compared with 9 months for the BC group, although the difference was not statistically significant. Similarly, a 2018 randomized trial demonstrated the efficacy of hDPSC clusters in regenerating immature necrotic pulp tissue, with treated patients exhibiting normal blood markers, root elongation, and apical foramen closure, indicating functional pulp regeneration [171]. Additionally, a randomized controlled trial explored the use of a hydrogel matrix containing umbilical cord MSCs (UC-MSCs) as an allograft in mature permanent teeth with apical lesions, showing promising preliminary results. However, the study's safety assessment was limited by a 12-month follow-up and small cohort size. To validate these findings, future randomized controlled trials with larger sample sizes and appropriate control groups without stem cell transplantation are required [172].

Although biomaterial-based therapies hold transformative potential for dental pulp regeneration, their translation into routine clinical practice faces multiple challenges. From a stability standpoint, the long-term survival, controlled differentiation, and sustained functional performance of these biomaterials require further optimization to ensure durable efficacy within the complex endodontic environment. Safety considerations are equally critical, as allogeneic DPSCs used for pulp repair may elicit immune rejection or pose potential tumorigenic risks after transplantation. Iohara et al. conducted a safety study on clinical-grade DPSCs [173], performing xenotransplantation of canine pulp stem cells into immunodeficient mice and normal beagle dogs. Within 28 days, serum and urine biochemical parameters remained within normal ranges, and autopsy with histopathological evaluation revealed no abnormalities or tumor formation in any organs or tissues. To enable the widespread clinical application of cell-material combination therapies, a rigorous safety evaluation framework is essential. Preclinical studies should employ techniques such as radioactive or fluorescent labeling to track biodistribution, homing, and clearance kinetics of cell-material complexes. Furthermore, considering the long-term and delayed risks associated with tissue regeneration, clinical trials should incorporate follow-up periods of 3–5 years, using imaging to monitor root development and changes in the root canal wall, in addition to long-term carcinogenicity assessments. Beyond acute tumorigenicity, regulatory evaluations should also address potential long-term effects of cytokine secretion or immunomodulatory activity on subclinical lesions. Ethical considerations in dental pulp regeneration primarily revolve around the sources of stem cells and the limits of gene-editing applications, encompassing not only scientific concerns but also societal acceptance and legal constraints. Strengthening international collaboration is crucial to establish unified regulatory standards and ethical guidelines, including clear compliance requirements for stem cell sourcing, standardized boundaries for gene-editing applications, and development of clinical translation pathways suitable for different regions. Furthermore, fostering interdisciplinary dialogue that integrates perspectives from scientists, clinicians, ethicists, and policymakers is essential to ensure that technological innovations are applied safely and effectively in clinical practice. Adherence to ethical and legal frameworks will ultimately support the standardization and broader adoption of pulp regeneration therapies.

Table 3. Summary of key clinical studies/case series on pulp regeneration.

Design	Study Model	Intervention	Sample	Follow-Up Duration	Examinations	Outcomes	Reference
Case report	Pulpitis	Implanted the patient's own DPSC and L-PRF into the dental pulp.	Patient (n = 1)	3 years	Periapical radiographs, Cone-beam computed tomographic, Sensitivity, Vitality tests	The response of teeth to cold after treatment was delayed, and imaging examination showed that the periapical area remained normal. The vitality test conducted showed a low blood perfusion unit.	[169]
Clinical research	Pulp necrosis	Used platelet rich plasma or traditional blood clots to fabricate tissue scaffolds, and covered them with white mineral trioxide aggregates.	Patients (n = 20)	18 months	Clinical and imaging follow-up	Platelet rich plasma scaffolds could effectively regenerate dental pulp, but there was no significant difference in treatment efficacy between them and traditional blood clot scaffolds.	[170]
Clinical research	Pulp necrosis	30 patients were randomly assigned to the hDPSCs implantation group, and 10 patients were assigned to the group receiving traditional periapical treatment.	Patients (n = 40)	24 months	Clinical examination, Radioactive Ventricle Graphy examination, Laser Doppler flowmetry, Electric pulp testing	Compared with the apical group, hDPSCs implantation increased root length ($p < 0.0001$) and reduced apical foramen width ($p < 0.0001$). In addition, hDPSCs implantation leads to regeneration of dental pulp tissue containing sensory nerves.	[171]
Clinical research	Mature teeth with apical lesions	The patients were randomly and evenly assigned to either the experimental group or the traditional root canal treatment group. The patients in the experimental group received treatment with plasma derived biomaterials encapsulated with allogeneic UC-MSCs.	Patients (n = 36)	12 months	Clinical examination, Sensitivity, Vitality tests	The plasma derived biomaterial encapsulated human UC-MSCs for pulp regeneration surgery is safe and effective in mature permanent tooth apical lesions.	[172]

6. Future Development Directions and Challenges

With rapid technological advancements, endodontic treatment is undergoing a paradigm shift. Beyond achieving the mechanical sealing characteristic of traditional RCT, the ultimate objective is now to reconstruct a vital pulp-dentin complex with sensory function, vascularization, and self-repair capacity. However, the root canal system presents significant challenges due to its anatomical complexity, hypoxic microenvironment, and resident bacterial flora, which can lead to secondary infections. No single technology can independently accomplish the three critical tasks of sterilization, anti-inflammation, and regeneration within such a demanding environment. Therefore, the key challenge for future therapies lies not merely in developing new materials but in ensuring that these materials perform the right functions at the appropriate time, location, and dosage within a confined cavity that is constantly at risk of infection.

Multifunctional composite biomaterials have emerged as a promising solution to this challenge. Their design goes beyond simply incorporating antimicrobial agents, growth factors, or stem cells into a scaffold; instead, they aim to construct a spatiotemporal "command chain" synchronized with the pathological progression of pulp injury repair. Specifically, the material must initially release high concentrations of broad-spectrum antimicrobial agents during the acute infection phase to rapidly reduce bacterial load by several orders of magnitude. During the intermediate phase, it transitions to an anti-inflammatory mode, controlling the release of immune modulators such as IL-10 and TGF-β3 and promoting polarization of M1 macrophages into the M2 repair phenotype. In the regeneration-dominant stage, the material continuously releases regenerative factors to induce DPSCs differentiation into odontoblasts, vascular ECs, and neurons, thereby achieving synergistic regeneration of nerves, vasculature, and dentin. In this design, the material functions not as a passive carrier but as an intelligent, programmatic regenerative system.

Nevertheless, if drug release follows a traditional rapid-release pattern, even the most sophisticated design becomes ineffective within 72 h due to precipitous concentration decline. Consequently, a sustained-release system is essential. This can be achieved either by encapsulating drugs within a sustained-release shell, extending their half-life from hours to several weeks, or by embedding smart triggers within the scaffold that respond to stimuli such as light, electricity, magnetic fields, temperature, or ultrasound. Such systems enable secondary release or dose adjustment, allowing drug delivery to adapt dynamically to specific scenarios and meet the temporal demands of pulp regeneration.

Currently, the development of intelligent multifunctional pulp repair materials remains largely limited to laboratory studies and animal model validation. Although pulp regenerative medicine shows considerable potential, most repair materials that have entered clinical use or trials rely on single components, such as stem cells or bioactive factors, targeting narrowly defined repair objectives [174]. The transition from "single-function" to intelligent multifunctional strategies has been delayed by several critical bottlenecks. First, therapeutic efficacy is often unstable, and the mechanisms of action remain insufficiently understood. Pulp regeneration is a highly complex process involving cell homing, angiogenesis, innervation, and odontogenic differentiation. The synergistic effects, spatiotemporal release kinetics, and molecular mechanisms of the multiple components within multifunctional materials are not yet fully elucidated, resulting in poor reproducibility of experimental outcomes. Second, significant concerns persist regarding long-term biosafety and risk control. As combination products, these materials face more stringent and complex requirements for quality control, standardized manufacturing, and clinical evaluation than single-component products. Consequently, despite researchers' extensive efforts spanning material design, mechanistic studies, and safety assessments, every step toward clinical translation requires meticulous and prolonged validation.

These scientific uncertainties and complexities manifest as three major practical bottlenecks: production, regulation, and clinical application. In terms of production, the synthesis and processing of multifunctional composite biomaterials often exceed conventional pharmaceutical or medical device manufacturing capabilities and lack standardized operating procedures. Quality management norms and regulatory considerations should be integrated early in the development process. For example, closed automated production systems should be prioritized to minimize challenges related to sterile manufacturing and reduce human error. Critical quality attributes should be identified during the design phase, with rigorous quality control strategies established to ensure batch-to-batch consistency. Regarding regulation, multifunctional composite biomaterials often qualify as combination products (e.g., drug-device), resulting in ambiguous classification within regulatory frameworks, unclear clinical evaluation pathways, and increased registration challenges. In clinical practice, as novel therapeutic modalities, intelligent multifunctional pulp repair materials necessitate adaptation of existing treatment paradigms. Uniform operating procedures and safety training must be provided to clinicians to facilitate rapid and safe adoption, thereby minimizing the risk of adverse events.

7. Conclusions

Biomaterials for pulp regeneration are rapidly emerging as one of the most transformative frontiers in dentistry. Unlike traditional fillings, these materials aim to restore living pulp rather than simply fill cavities, seeking to fully revive endangered teeth in terms of function, sensation, and anatomical integrity. In the future, such materials are expected to redefine the paradigm of RCT, shifting from passive closure to programmatic regeneration and enabling the pulp–dentin complex to regain vascularization, neural function, and self-repair capacity. This approach emphasizes patient-centered tissue restoration rather than tissue removal, substantially reducing the need for extractions and preventing irreversible damage. With further advances in sequential release systems, microenvironment-responsive biomaterials, and interdisciplinary integration, regenerative strategies are poised to transform clinical pulp repair, establishing pulp regeneration as a guiding principle in modern dental practice. Ultimately, the focus of treatment will center entirely on the patient, promoting long-term, authentic dental health with minimal invasiveness and maximal physiological benefit, ushering the dental profession into a true era of regeneration.

Author Contributions

S.G. (Shijie Gao), J.W., and Y.J.: contributed to conceptualization, original draft writing, review, and editing; B.C., Y.L., S.G. (Shengyuan Gao), and Y.Z.: assisted with data curation and visualization; B.L. and S.C.: contributed to reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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Data will be made available on request.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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