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Immunomodulatory Biomaterials in Dental Pulp Regeneration: Towards Enhancing Endodontic Treatment Outcomes

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ABSTRACT

Root canal therapy, which involves removing the dental pulp and replacing it with a biomaterial, is the established treatment for damaged pulp. However, innovative methods promoting dental pulp regeneration could potentially restore original tooth anatomy and enhance long-term outcomes for previously damaged teeth. This study explores the current landscape of dental pulp tissue engineering and immunomodulatory biomaterials, aiming to merge these areas for advanced therapeutic solutions. The paper reviews the inflammation and immune responses associated with dental pulp, expanding on periapical and periodontal inflammations. It highlights recent advancements in treating infection-triggered oral issues, emphasizing materials that can modulate the immune response. These developments, derived from a decade-long literature review, involve alterations to biomaterial composition and drug integrations for immunomodulation. Such advances in biomaterials leveraging the host's immune system for targeted regeneration suggest a promising shift from traditional root canal methods to more holistic treatments.

Keywords: Biomaterials, Scaffolds, Dental pulp, Tissue regeneration, Immunomodulation

1 INTRODUCTION

Dentin, a mineralized structure that is inflexible and non-vascularized, surrounds dental pulp, a highly vascularized and innervated tissue found inside the tooth. Dental caries or trauma causes swelling, irreparable damage to the dental pulp, pulp tissue necrosis, loss of tooth vitality, and eventually apical periodontitis, which necessitates endodontic therapy or extraction. According to recent estimates from the National Health and Nutrition Examination Survey (NHANES), 37% of children (ages 2-8) and 58% of adolescents (ages 12–19) in the United States have caries in their deciduous teeth and permanent dentition, respectively. A recent thorough assessment found that apical periodontitis affects a minimum of one tooth in 50% of individuals overall [1]. Pulp and periapical problems can be successfully treated with traditional root canal therapy, which involves pulp extirpation followed by root canal sealing with inorganic materials (gutta percha and sealer cement). Conversely, teeth that have had endodontic treatment are more vulnerable to breakages, loss of sensation, loss of bio protections recurring tooth decay, and apical periodontitis.

While behavior complies with accepted standards, it has been noted that post-treatment apical periodontitis appears in 5-15% of teeth via pre-operative wounds. This is particularly concerning given that dental pulp regeneration and protection strategies are of great interest because they may lengthen the lifespan of natural teeth, thereby enhancing the standard of living [2]. Regenerative endodontic therapy is a choice to traditional root canal treatments. It is often referred to as biological procedures meant to heal damaged or diseased tooth pulp [3]. Tissue engineering is a technique that is regularly combined with regenerative medicine and has already been widely applied to dental and maxillofacial repairs. Three components are essential to traditional tissue engineering:

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bioactive growth factors (which promote and facilitate functionalities), scaffolds (which promote cell differentiation, proliferation, and biosynthesis and serve as interim extracellular matrix), and stem cells (which synthesize new tissue matrix) [4]. It is important to carefully choose each tenant depending on how effectively it will support pulp renewal [5]. An overview of the inflammatory procedure is given at the outset, with a focus on the immune responses of the tooth pulp. This is followed by an examination of the inflammation of the periapical and periodontal tissues. With a focus on biocompatible substances with immunomodulatory properties, we'll discuss recent advancements in the treatment of inflammatory oral infections. The most desirable characteristics of biomaterials for immunomodulation were then listed, followed by a discussion of current advances in the field. With an emphasis on immunomodulation, we all highlight and go through several of the most prominent surface or content/drug modifications in biomaterials in this context.

By critically summarizing recent developments in immunomodulation for pulpal, periapical, and periodontal disorders, we hope to inform readers and shed light on tissue engineering techniques for repairing and healing various tissue types.

2 PROCESS OF DENTAL PULP INFLAMMATION

Nearly half of the world's population is affected by carious lesions, which are the most prevalent non-communicable disease, and their direct and indirect expenses reached US $442 billion in 2010, according to the World Health Organization [6]. The healthy human oral environment is home to a wide variety of microbe species, and when given physical access, a sample of this diverse microbiota can contaminate the pulp chamber. Even though the teeth may appear clinically healthy, the most prevalent routes for pulpal infection are microcracks in hard tissues or breaches brought on by caries, dental surgery, trauma, or fractures . Additionally, germs from the gingival sulci or periodontal pockets can enter the pulp and infect it because of perforations in the cementum layer and revealed dental tubules at the cervical root surface [7]. Additionally, it has been established that anachoresis, a disease characterized by transient bacteremia, causes the infection to reach the pulp tissue via general distribution of blood. irrespective of how the pulp tissue became infected, pulpitis, a painful inflammation, is brought on by infected pulp tissue. The dental pulp is unique among connective tissues in that it is especially prone to damage for several reasons:

1. It includes an immense amount of tissue of a small volume of blood supply;

2. It is a terminal circulation center with almost no collateral circulation;

3. It is enclosed inside calcified tissue walls, creating a low compliance environment [8].

When a carious lesion results in a bacterial invasion, the pulpdentin complex activates innate and adaptive immune responses [9]. Innate immunity plays a critical role in the development of superficial caries after the early tooth lesions reach the dentin-enamel juncture (DEJ). The proximity of the pulp-dentin complex and the migration of bacterial toxins towards dental tubules results in a mild chronic inflammatory response. This reversible pulpitis scenario develops when bacterial invasion, toxin concentration, and inflammation are all mild [10].

The dentin pulp complex can respond to injuries in a dose-dependent way thanks to the dental pulp stem cells (DPSCs), which develop toward multiple generations, include dentin-forming odontoblasts that secrete reactionary dentin. As a result, connective tissue that has been moderately injured or insulted undergoes self-repair. When the pulp tissue becomes permanently inflamed, primarily as a result of bacterial invasion (such as untreated caries), the transition from innate to adaptive immunity takes place. This permanent collapse of the pulp and subsequent necrosis may result in periradicular lesions in the nearby alveolar bone. Newly developed odontoblasts from the DPSCs population secrete reparative dentin slowly in the severed inflamed-infected pulp tissue after the original primary odontoblasts die [11]. It is essential to concentrate on these precursor cells since they play a significant role when developing substances to encourage the renewal of pulp tissue. Neutrophils, T lymphocytes, monocytes, dendritic cells, natural killer (NK) cells, B cells, and regulatory T cells (Tregs) are among the numerous immune cells present in the pulp tissue [9].

These immune cells coexist in harmony with the surrounding odontoblasts, fibroblasts, and pulpal stem cells and are essential for the immunological response to infections. Host immune cells are assisted in identifying potential dangers by recognizing pattern receptors (PRRs), which recognize pathogen-associated molecular patterns (PAMPs) [12]. Toll-like receptors (TLRs) are transmembrane receptors that are the main PRRs. Once they are near to the pulp, the odontoblasts, which are immune competent cells that produce PRRs, act as the first line of defense. Although coordinating an inflammatory response is not their major purpose, their cellular activities extend into the dentinal tubules [13]. TLR-2 is primarily activated by peptididoglycan, lipoteichoic acid (LTA), or lipoproteins produced by gram-positive bacteria when there is a carious lesion present. Gram-positive bacteria often outweigh gram-negative bacteria in pulp tissue. TLR2 expression therefore first stands out more than TLR4 expression in dental pulp that has been exposed to the oral environment [14]. Inflammation can be brought on by PAMP lipopolysaccharide, or LPS, the main byproduct produced by bacteria during infections with gram-negative bacteria [15]. It binds to the TLR-4 and activates the inflammatory molecular

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cascade through the nuclear factor kappa B pathway (NF-Kb), which in turn mediates innate immune responses by regulating phagocytosis and inducing antimicrobial activity. Two proinflammatory cytokines, tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), are released as a result [9]. Blood-borne immune/inflammatory cells and tissue-resident immune/inflammatory cells are attracted to the area by chemokines. The TLRs cause the adjacent pulp fibroblasts to be activated to take part in the host response, just like odontoblasts do, as long as microorganisms continue to invade the pulp and cause destruction of the odontoblast layer. The macrophage is one of the most significant immune cells drawn to the area. In response to the proper immunologic stimuli, they arise from monocytes and polarize irreversibly into an M1 or M2 phenotype [16]. Future pulpitis treatments may be made possible by this reversible macrophage shift. When an inflammatory response is triggered by an expanding carious lesion, there are numerous M1 macrophages and their byproducts present [9]. Their continued and intensified activity prevents the resolution of inflammatory reached by a transformed M2 resolving phenotype once they have established an environment that is favorable for tissue regeneration [17]. In order to treat reversible pulpitis clinically, it would be crucial to halt the pro-inflammatory processes by producing anti-inflammatory macrophages as soon as it was practical. Factors that encourage this macrophage polarity change are extremely relevant when considering bioactive materials.

3 INFLAMED PERIODONTAL AND PERIAPICAL TISSUE

If the pulpal inflammation is not treated, it spreads to the nearby periodontal and periapical tissues [18]. The pulp response's mechanisms are followed by the inflammatory process in these tissues, but with the addition of the immune and skeletal systems' interaction. In the apical region of the tooth root, the necrotic endodontic environment offers a habitat for the development of a mixed, primarily anaerobic microbial community. These bacteria interact with TLR-4 to release LPS into the periapex region through the apical foramen, where it causes and maintains apical periodontitis [19]. As soon as they become active, these receptors imitate a number of proinflammatory cytokines, including IL-1, TNF-a, and IL-6. They also boost the production of RANKL (receptor activator of nuclear factor-kB ligand), a cytokine that is comparable to TNF-a [18]. Pre-osteoclasts go from the periradicular tissue to the bone's surface with the blood as monocytes. Osteoclast growth and activation are regulated by the communication between RANK (receptor activator of nuclear factor kB) and RANKL, its ligand [20]. A member of the tumor necrosis factor receptor family, RANK is a transmembrane protein that is expressed by macrophages, pre-osteoclasts, dendritic cells, and fibroblasts [21]. Along with RANK and RANKL, OPG (osteoprotegerin), an osteoclast-produced RANKL decoy receptor, is also present. OPG blocks RANK-RANKL interaction by attaching to RANKL. This RANK/RANKL/OPG ratio is essential for regulating osteoclastogenesis and bone resorption in the periodontal and periapical areas [22]. Normal balance between RANKL and OPG leads in minimal osteoclastogenesis and bone resorption throughout bone turnover. Following a microorganism's pollution and subsequent inflammatory reaction, the RANKL/OPG ratio rises in periodontal and periapical tissues as a result of an increase in RANKL release and a decrease in OPG. This encourages osteoclast activity and results in pathologic bone resorption [22]. The LPS that left the apical foramen attracted neutrophils via chemotaxis as well [18].

Leukotrienes and prostaglandins are released by these cells as they battle the microorganisms, luring additional neutrophils and macrophages to the area [9]. Direct short-term bone resorption is the cause of prostaglandins' (particularly PGE2's) release via the cyclooxygenase pathway. A short while later, active M1 macrophages also develop in the periapical area and start to generate a variety of cytokines, which are intercellular messengers that promote inflammation [23]. The cytokines in question boost endothelial cell adhesion to leukocytes, osteoclastic activity, local vascular response, and neutrophil potency, all of which encourage bone resorption and inhibit bone formation [23]. Contrarily, proinflammatory cytokine production is suppressed by cytokines generated from M2 macrophages, such as IL-4 and IL-10, which stimulate the synthesis of tissue inhibitors of matrix metalloproteinases (TIMPs) and OPG. A feature of apical periodontitis, a chronic inflammatory condition, is the imbalance of M1/M2 [24]. By doing this, the desired immunomodulatory substance should cause the M1 pro-inflammatory phenotypes of the macrophage population to change to the M2 anti-inflammatory morphologies, resulting in a setting that is both anti-inflammatory and pro-regenerative. The microbial biofilm that has colonized the apical end of a necrotic root canal is resistant to both host defenses and antibiotic therapy since there isn't enough blood flow to it. As a result, the periapical region is constantly invaded by bacterial toxins and metabolites, irritating the periapical tissues and resulting in continual periradicular tissue degeneration. Damaged periradicular tissues also have a hard time healing [19]. If the root canal is cleared of the bacteria that cause apical periodontitis and this empty canal space is sealed by normal endodontic therapy, a lesion will regress. Additionally, systemic diseases like diabetes mellitus (DM), high blood pressure, osteoporosis, chronic liver condition, etc. have been related to a decline in innate immune responses and cause significant changes in how rapidly wounds heal [25].

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4 THERAPEUTIC APPROACHES FOR PULP INFLAMMATION CAUSED BY INFECTIONS

To address the etiology of the disease and stimulate regeneration, innovative therapies adapted to the pulpal and periapical inflammatory processes are required. Creating biomaterial solutions for pulpal wound healing is a logical course of action given the substantial body of biomaterials science that has arisen from the field of tissue engineering and the clinical translation of regenerative biomaterials to date. Important therapeutic properties of the ideal biomaterial include antimicrobial properties to get rid of pulp contamination and immunomodulatory properties to control the host proinflammatory response and induce inflammation resolution by inducing the production of anti-inflammatory mediators to stimulate repair response. The optimal biomaterial ought to maintain its immunomodulatory effects for extended periods of time without repeated dosing given the isolated pulpal milieu within the tooth root. There are two well-documented methods in the literature for treating pulpal inflammation, which are cell homing and cell transplantation. However, the outcomes of these approaches have been varied. The procedure of inserting donor cells, such as DPSCs, into a recipient is referred to as cell transplantation. In preclinical animal models, it has been shown that it aids in the regeneration of pulp by creating a layer of odontoblasts, promoting the growth of blood vessels in the pulp, and providing proof of neuronal regeneration [26]. To enhance the amount of the transplanted cells, they may be processed (removed from tissues) or created in vitro. Both the host and a donor can provide them (autologous and allogeneic, respectively). Although there has been enthusiasm about it in preclinical investigations, few human clinical trials have had good results, and these procedures are not yet a practical substitute for endodontic root canal treatment as it is now practiced [27]. Cell homing is the effective chemotactic recruitment of stem/progenitor endogenous cells into a particular anatomical compartment without the need for cell transplantation, immunogenicity, or complex in vitro cell manipulation. Cell homing may be a more effective, reasonably priced, and clinically useful therapy plan. One illustration is the way that induced bleeding draws periapical/peridontal cells from the tooth apex and can promote the development of pulp-like tissue in the root canals and pulp chamber [28]. This technique involves first cleaning the root canal system with an antibiotic or calcium hydroxide solution, followed by the application of a blood clot that serves as a scaffold and attracts stem cells from the periapical area. However, histological investigations in animals and people consistently demonstrate that the majority of regenerated tissues inside the root canal are periodontal-related tissues, other than pulpal tissue, because of the existence of cellular cementum on the dentin wall, bone tissue, and periodontal ligament [29]. Despite the potential of these techniques, significant advancements are needed to promote biomimetic pulpal wound repair and regeneration. Furthermore, it would be wise to have a better understanding of how the host immune system and the implanted biomaterial interact.

5 IMMUNE SYSTEM INTERACTIONS WITH BIOMATERIALS

The implantation of biomaterials results in tissue damage, which is followed by an inflammatory response and wound healing [30]. The features of the biomaterial play a crucial role in determining the biocompatibility and immunomodulatory capabilities because they affect the intensity, length, and duration of physiologic responses as well as their resolution. Immune-mediated reactions to foreign body implants typically produce fibrosis with a collagenous encapsulation. The breakdown of biomaterials and possibly future failure are caused by adhering macrophages and foreign body giant cells [31]. This unfavorable immune response can reduce the device's functionality, efficacy, and durability since the biomaterial and surrounding tissues interact poorly. The immune system may be activated or affected by a biomaterial's breakdown products and the ensuing surface alterations [32]. Reid and others [33] showed that poly (ethylene glycol) (PEG) scaffolds placed in the abdominal cavity revealed a stronger inflammatory response than subcutaneous implants. The local environment may be crucial in influencing how much inflammation develops or occurs [33]. Reactive oxygen species (ROS), which are produced as a result of the inflammatory process, may cause the biomaterial to deteriorate [33]. After the implantation of a biomaterial, a process known as biofouling takes place in which fibrinogen and other proteins from blood and interstitial liquids cling to the surface of the device [34].

These proteins' receptors serve as adhesion substrates and can bind to cause platelets to erupt. In addition, macrophages join together with these proteins to form multinucleated large cells. These cells subsequently release growth factors and inflammatory cytokines. This results in the formation of fibrin-rich clots, which serve as a temporary framework for cell attachment and motility. They also contain growth factors and cytokines that trigger inflammation and aid in the healing of wounds [34]. The device's characteristics can change how blood and biomaterials interact. The fundamental aspects of the biomaterial that directly affect the makeup of the proteins adsorbed on the surface of the implanted material are its composition, shape, topography, surface characteristics, volume, and dimensions [35]. Protein composition and structure, in turn, can influence how immune cells are recognized and activated [36]. In order to prevent the development of the collagen capsule, which can lead to biomaterial failure, it is thought that a biomaterial's qualities can minimize or even completely prohibit the adsorption of general proteins on the surface of the implanted device [37]. This is because the initial stage of the foreign body reaction is the adsorption of non-specific proteins on the surface of the implanted device. However, these characteristics,

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such as wettability and charge/polarity, can be altered by altering the surface. From a few minutes to days, inflammation's acute phase lasts [30]. In reaction to cytokines and growth factors, this phase starts. It is distinguished by the infiltration of leukocytes, primarily polynuclear neutrophils, followed by monocytes, and eventually lymphocytes, at the site of injury [38]. Leukocytes then initiate processes such as phagocytosis and discharge extracellular chemicals including cytokines and chemokines.

The protracted stage of the inflammatory response starts a few days after the biomaterial is implanted and can extend for weeks [38]. During this stage, macrophages, monocytes, and lymphocytes are present, along with the formation of a blood vascular network and intermingled tissue to reorganize the damaged region [39]. The presence of macrophages, fibroblast infiltration, and the growth of new blood vessels in the recently created scar tissue suggest the existence of granulation tissue once the acute and chronic inflammatory responses have subsided [32]. Granulation tissue acts as a transitional tissue substrate for the development of fibrous capsules, which may later result in scarring or fibrosis [39]. Monocytes, macrophages, and foreign body giant cells form a layer that the cellular components of the foreign body response (FBR) use to form a barrier between the implanted biomaterial and the granulation tissue [32]. Various strategies have been experimentally tested to reduce FBR and fibrosis. In order to enhance the qualities of biomaterials, these techniques entail surface modifications (geometrical and biochemical) or molecular routes (such as topical immunosuppression, moderation of leukocyte and fibroblast activation, or promotion of vascular expansion) [40].

Infrared-excited nonlinear microscopy was recently created and proven to address issues with three-dimensional (3D) organization, implanted biomaterial failure, and the analysis of cause-and-effect relationships in the FBR [40]. The goal of the first biomaterials was to "achieve a suitable combination of physical properties to match those of the replaced tissue with a minimal toxic response in the host" [41]. The initial generation of biomaterials' biological inertness was created with the goal of reducing the immune system's reaction to the foreign body [42]. The desirable and necessary properties for biomaterials to enhance biological integration and influence cell adhesion, penetration, and proliferation include texture and porosity. Positive cellular responses at the tissue-biomaterial interface may lead to organogenesis and speedier repair . The rough and porous characteristics of prosperous implanted devices in the 1940s were early examples of characteristics for creating biomaterials. The surface of the device functions as a crucial contact between the host and the implant, coordinating subsequent biological processes.

Porous materials' capacity to permit bone to grow into their pores strengthens the bond between the device and the bone/tissue [43]. Second-generation biomaterials evolved from first-generation biomaterials with an emphasis on inducing a controlled reaction with the surrounding tissues to achieve the targeted therapeutic effect [42]. Some of the greatest examples of this generation are the bioglasses and bioceramics used in orthopedics, heart valves, ventricular assist devices, and stents (used in catheterization procedures). Resorbable biomaterials with therapeutically useful controlled chemical decomposition and resorption were also developed in the second generation. Long-term, there are no noticeable differences between the implant site and the host tissue because the foreign material is replaced by regenerating tissues, which enables the resolution of a discrete interface between the biomaterial and tissue [41]. The third generation of biomaterials sought to restore functional tissue by molecularly activating particular biological responses [42].

Biomaterials with the ability to stimulate cells, regulate the release of bioactive molecules, and modify the host's innate immune response are now more important than ever [44]. As a result, procedures for synthesis and modification of the materials have been developed. Resorbable materials have been made bioactive, and vice versa, bringing together the notions of bioactive and resorbable materials [42]. With the progress made in tissue engineering and regenerative medicine, along with a deeper comprehension of the immune system's pathophysiology, it is crucial to develop innovative manufacturing strategies for biomaterial design and architecture. This is necessary to ensure excellent biological compatibility while maintaining the necessary therapeutic properties [43].

6 IMMUNOMODULATORY BIOMATERIALS

The design of the biomaterials is essential for controlling macrophage phenotype. In order to repair and regenerate wounded tissue, as well as to prevent infection and remove necrotic tissue, the transition from the M1 to M2 phenotype at the right stage of the inflammatory response is crucial. These macrophage-based therapies have a lot of potential for regenerative medicine since they concentrate on the design of biomaterials and eventually molecular delivery. In order to do this, the design of nanoparticles, hydrogels, and scaffolds is discussed along with the characteristics of tunable biomaterials to enable tissue immune system regulation in the subsequent domains.

6.1 Nanoparticles

Due to the fact that macrophages are specialized phagocytic cells, the administration of nanoparticles represents a significant potential to modify macrophage phenotype. Because of surface opsonization, once these particles enter the host, macrophages recognize them as foreign objects and engulf them through endocytosis or phagocytosis [46]. The dosage, size, distribution mechanism, substance, and surface properties can all have an impact on the macrophage's outcome. For instance, iron oxide-loaded li-

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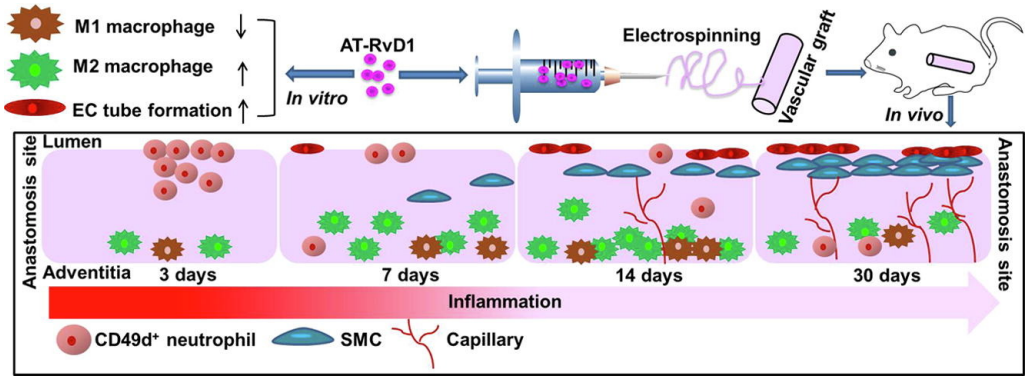

Fig. 1. The immune-altering properties of specially designed chitosan-based nanoparticles (CSnp) used as treatments against biofilm, particularly when introduced to macrophages (MQ) co-cultured with periodontal ligament fibroblasts (PdLF). This was assessed through both protein and cytokine analysis. These nanoparticles entered cells through various endocytic routes. Interactions with CSnp led to expanded MQ activity and enhanced PdLF movement. The MQ response to a CSnp-treated biofilm was weighed against a biofilm that wasn't treated. To study the MQ's protein composition, tandem mass tag (TMT)-mass spectrometry (MS) was utilized. After a comprehensive bioinformatics review of the protein data, select proteins were further verified using parallel reaction monitoring (PRM)-targeted MS. Notably, CSnp raised the levels of proteins linked with immune regulation and antioxidant functions. MQs, when introduced to a CSnp-treated biofilm, generated more anti-inflammatory substances and fewer inflammation-promoting ones. This suggests that CSnp may help in managing inflammation caused by biofilms, aiding in the healing process for apical periodontitis [45].

posomes and phosphatidylserine (PS), a cell surface ligand found on apoptotic cells, caused murine macrophages to change into an M2-like phenotype [47]. lately Hussein and Kishen [45] studied how macrophages co-cultured with the antibiofilm medication PdLF responded to a bioactive nanoparticle (CSnp) produced from modified chitosan in terms of immunomodulatory effects Fig.1.

Chitosan is particularly attractive in this application because of its antibacterial capabilities; chitosan nanoparticles (CSnp) show an affinity for bacterial cell membranes and diffuse into biofilm formations, providing a potential antimicrobial agent for root canal cleaning. The proteomics analysis performed by the authors, which revealed that CSnp administration upregulated proteins involved in immunoregulation, antioxidant activities, and proteins related to the ferroptosis route, which contributes to bacterial nourishment, and downregulated proteins related to this pathway, highlighted the ability of CSnp administration to regulate the healing process in the management of apical periodontitis. A nanoparticle's ability to polarize macrophages can be diminished by making it smaller and boosting its surface charge in order to decrease macrophage absorption. The macrophage polarization power, however, can be increased by coating the particle with a chemical that targets macrophages [48]. The primary factor in applying immunomodulatory nanoparticles is safety. The immunotoxicity brought on by nanoparticles emitted from biomaterials has to be carefully investigated and evaluated before to usage in clinical settings. The size, makeup, and charge of the particles have a big impact on it.

6.2 *Hydrogels*

An injectable hydrogel comprising quercetin and bioactive glass was previously used to regenerate articular cartilage. Quercetin, a common flavonoid present in a variety of fruits and vegetables, has the capacity to significantly decrease the amount of inflammatory mediators generated by macrophages, as well as the expression and secretion of cytokines like IL-1, IL-6, and TNF-, and to activate macrophages toward the M2 phenotype [49]. Bioglass could therefore encourage macrophages to take on the anti-inflammatory M2 phenotype [50]. Due to the absence of blood arteries, lymphatic cells, and neurons in articular cartilage, self-repair following injury can be challenging. The necrotic pulp tissue has the same traits; oral tissues could benefit from this method. It can be utilized to fill complicated anatomies like the root canal system because of its injectability.

This composite hydrogel promoted macrophage M2 polarization, reduced inflammation, and delayed the degradation of the ECM by inhibiting the generation of inducible nitric oxide synthase (iNOS) [52]. Hu, et al. [53] In order to create a pro-healing microenvironment under the DM scenario, another injectable biomaterial was recently studied. In an injectable microsphere that self-assembled utilizing gelatin nanofibers, interleukin 4 (IL-4), a high heparin-affinity interleukin that polarizes proinflammatory M1 into an anti-inflammatory M2 phenotype, was used [54]. The substance was used in a diabetic rat model of a mandibular periodontal fenestration defect, and it improved osteoblast differentiation and brought back bone regeneration to levels that were nearly normal. This effectively resolved inflammation by changing proinflam-

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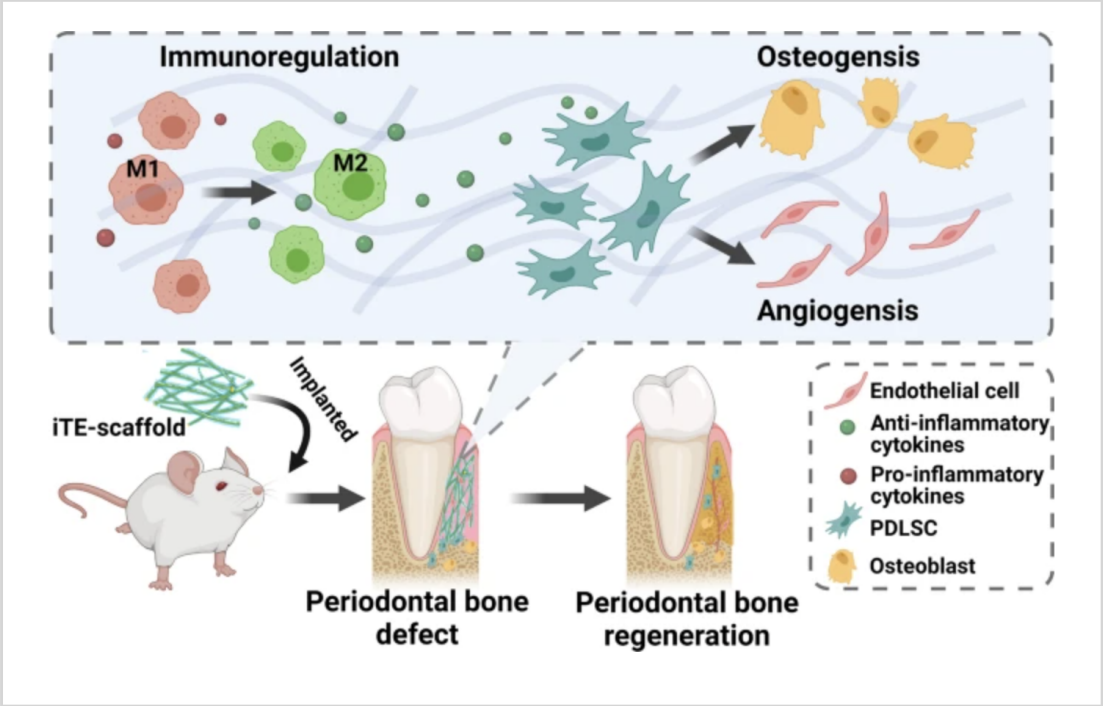

Fig. 2. A scematic view of a core/shell fibrous scaffold releasing bFGF and bone BMP-2 in a sequential manner to modulate the osteoimmune environment and angiogenic activity during periodontal bone defect restoration [51].

matory M1 macrophages into pro-healing M2 phenotypes. The advantages of using this injectable microsphere include minimally invasive administration and fast adaptation to complicated abnormalities, including periodontal and inside the root canal system, deformities.

6.3 Scaffolds

Ding, et al. [51] evaluated the effects of an in-situ tissue engineering scaffold (iTE- scaffold) expressing basic fibroblast growth factor (bFGF) and bone morphogenic protein-2 (BMP-2) on osteoimmunomodulation and angiogenesis Fig.2. Due to its tunable and relatively rapid rate of deterioration, poly (lactide-co-glycolide) was utilized to construct the scaffold, whereas poly (L-lactic acid) (PLGA/PLLA) was employed for the inside structure due to its slower rate of deterioration. The same loaded scaffold has been shown to promote cell homing, proliferation, and osteogenic differentiation [55]. Sharpey's fiber development, osteoblast differentiation by MSCs, and bone tissue healing and regeneration are all facilitated by the potent osteoinductive growth factor BMP-2 [56]. The advantages of bFGF, the first member of the fibroblast growth factor family to be identified, as a potent inducer of vascularization, proliferation, and migration are essential for the healing of wounds. Additionally, it reduces the synthesis of pro-inflammatory proteins and polarizes LPS-stimulated macrophages toward an anti-inflammatory M2 phenotype via AKT/P38/NF-B signaling pathways [57]. In vitro, a vestigated scaffold was effective at directing macrophages toward the prohealing M2 phenotype and promoting vascularization. When implanted in vivo, it demonstrated an anti-inflammatory response, supplied enough blood flow, and produced the necessary bone healing result [51]. Recent research by Liu et al. [58] successfully electrospun poly (lacticco-glycolic acid) PLGA with dimethyloxalylglycine (DMOG) and nanosilicate (nSi) to examine its potential for periodontal bone regeneration. It has been demonstrated that DMGO decreases the LPS-induced inflammatory response in human gingival fibroblasts and helps with bone regeneration in vivo by increasing vascularization and directing macrophages toward an anti-inflammatory M2 phenotype [59]. The nSi also induces macrophage M2 phenotypic shift and has osteo-immunomodulatory activities when bone marrow (BM) mesenchymal stem cells (BMSCs) are present. When used in the Wistar mouse periodontal deficient model, the DMOG/nSi-PLGA fibrous membrane shifted macrophages towards the M2 phenotype at the start of tissue repair, lowering inflammation and promoting tissue regeneration [58]. He, et al. [60] In order to evaluate its immunomodulatory properties, a novel hierarchically structured mineralized nanofiber (HMF) scaffold enriched with calcium phosphate (CaP) was subcutaneously implanted into the rat dorsum and placed inside a periodontal bone defect (width: 1.5 mm, length: 2 mm, depth: 2 mm) [60]. The CaP covering can, as previously mentioned, enhance the osteoinductive and osteoimmunomodulatory properties of the nanofibers [61]. This study's mineralized nanofibers produced CD206 + M2 macrophages, which

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in turn produced the anti-inflammatory cytokines IL-10 and IL-4, as well as enhanced bone density and volume in the periodontal defect, which led to excellent bone regeneration. A analogous substance is beta-tricalcium phosphate (bTCP), a well-known osteoconductive biomaterial with excellent osteoimmunomodulatory properties that is currently being employed in clinical settings for bone regeneration [62]. Chen and co. In order to control the adverse osteoimmunomodulatory effects of Mg scaffolds when they break down quickly in vivo and cause a transient, unfavorable inflammatory response, [63] coated Mg scaffolds with b-TCP. When used as a coating layer, CaP materials like bTCP result in a slower deterioration rate since they deteriorate much more slowly than Mg. The enhanced production of the CD163 surface marker and the interleukin-1 receptor antagonist is proof that the macrophage phenotype has been shifted to the M2 side (IL-1RA). This results in a positive osteoimmunomodulatory response. Therefore, Mg-b-TCP scaffolds may be a promising bioactive material for bone tissue regeneration. These materials' innate physical (dimensionality, stiffness, porosity, and topography) or chemical (wettability, electric property, and molecular presentation) properties are responsible for triggering an immune response and hindering the loaded compound's intended immunomodulation, in addition to the hydrogel's (6.2) and scaffold-carrying abilities. The impact of changes to these traits on the activity and responsiveness of immune cells will then be thoroughly explained.

7 CONCLUSION

To sustain the dentition for the rest of a person's life, the dental pulp complex poses a difficult yet compelling specific regeneration necessity. Significant progress has been achieved in creating and analyzing biomaterials that use the immune system of the host to direct a certain regeneration result. In this paper, we first give a detailed analysis of the inflammatory process in the mouth. In light of this, we present a number of research that modify the phenotypic polarization of macrophages, promote tissue growth, and increase wound healing. When compared to endodontic root canal treatment, biomaterials that modify dental pulp complex cells effectively and reliably show substantial clinical potential for improving quality of care.

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Ethical consideration: The study was approved by University of Al-Qadisiyah, Al-Qadisiyah, Iraq.
Data Availability: No data was used for the research described in the article.

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