REVIEW ARTICLE

Next-Generation Biomaterials for the Management of Periodontal Disease

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Abstract

Periodontal disease is a prevalent chronic inflammatory condition that leads to the destruction of tooth-supporting tissues, significantly impacting oral and systemic health. Traditional therapies, such as scaling and root planning, primarily target microbial factors but often fall short in addressing the complex host immune responses that drive disease progression and tissue destruction. Recent advances in biomaterials offer innovative approaches for periodontal therapy by integrating principles of tissue engineering, regeneration, and immunomodulation. Next-generation biomaterials – including biofunctionalized scaffolds, nanotherapeutics, and stimuli-responsive hydrogels – are designed to not only regenerate lost periodontal tissues but also modulate the local immune environment, particularly by targeting key immune cells such as neutrophils, mast cells, B-cells, and T-cells. These materials can serve as carriers for stem cells and growth factors, or directly influence immune cell behavior to promote tissue repair and limit inflammation. This review summarizes the latest developments in biomaterial-based strategies for periodontal disease management, emphasizing their potential to overcome the limitations of conventional treatments and improve long-term outcomes. By harnessing the therapeutic capabilities of next-generation biomaterials, there is promise for more effective, predictable, and personalized interventions for patients with periodontal disease.

Key words: Biomaterials, next-generation biomaterials, periodontal disease, periodontal regeneration, periodontitis, tissue engineering

INTRODUCTION

Periodontal disease is the most common chronic inflammatory disease, which causes damage to the supporting tissues of teeth, such as the periodontal ligament, alveolar bone, cementum, and gingiva.[1,2] Due to progressive tissue destruction, periodontitis is still the main reason of those who lose their teeth among the adult population.[1] The global prevalence of periodontal disease points out its significance as a health problem. Although actual data on the global prevalence of periodontal disease is highly variable depending on the population researched and diagnostic criteria used, there is an estimation that most adults worldwide are suffering from some form of periodontal disease.[3] This huge prevalence clearly indicates that effective prevention and treatment strategies are extremely necessary.

The importance of periodontal health extends beyond the oral cavity, with increasing evidence linking it to systemic health.[3] Periodontal disease is the root of several systemic conditions, just to name cardiovascular diseases, diabetes, stroke, Alzheimer's disease, and obesity.[3,4] The issues that connect two fields are convoluted and have many factors. Some scientists explain it with a theory in which they think that the journey of periodontal pathogens and of the inflammation mediators in the blood may lead to the blood becoming inflamed all over the body; thus, this inflammation can be the cause of the illness of systemic

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organs.[5] Another-further idea is about molecular mimicry, namely, to the fact that it is the immune system, which is directed against periodontal pathogens that may actually be the same one that reacts to the tissues of the body and, thus, along with systemic inflammation, could also be tissue damage.[4] Given these potential systemic effects of periodontal disease, maintaining a healthy periodontium is crucial for ensuring overall health. Figure 1 illustrates how an unbalanced microbiome in periodontal disease triggers an immune-inflammatory response, involving various immune cells such as dendritic cells (DCs), macrophages, T-cells, and neutrophils. These immune cells contribute to the upregulation of receptor activator of nuclear factor kappa-B ligand (RANKL) expression, which is involved in alveolar bone resorption.

Current periodontal treatments primarily focus on controlling the bacterial infection and reducing inflammation.[6] Traditional methods of treatment include scaling and root planning (SRP). This procedure consists of the mechanical removal of plaque and calculus from tooth surfaces.[7] SRP can certainly eliminate bacterial load and reduce inflammation; however, it is still not able to fully heal periodontitis due to reattachment of bacteria which are intractable and drug resistant.[8] In addition, SRP is mainly designed for the microbial factor of the disease; thus, it cannot be effective

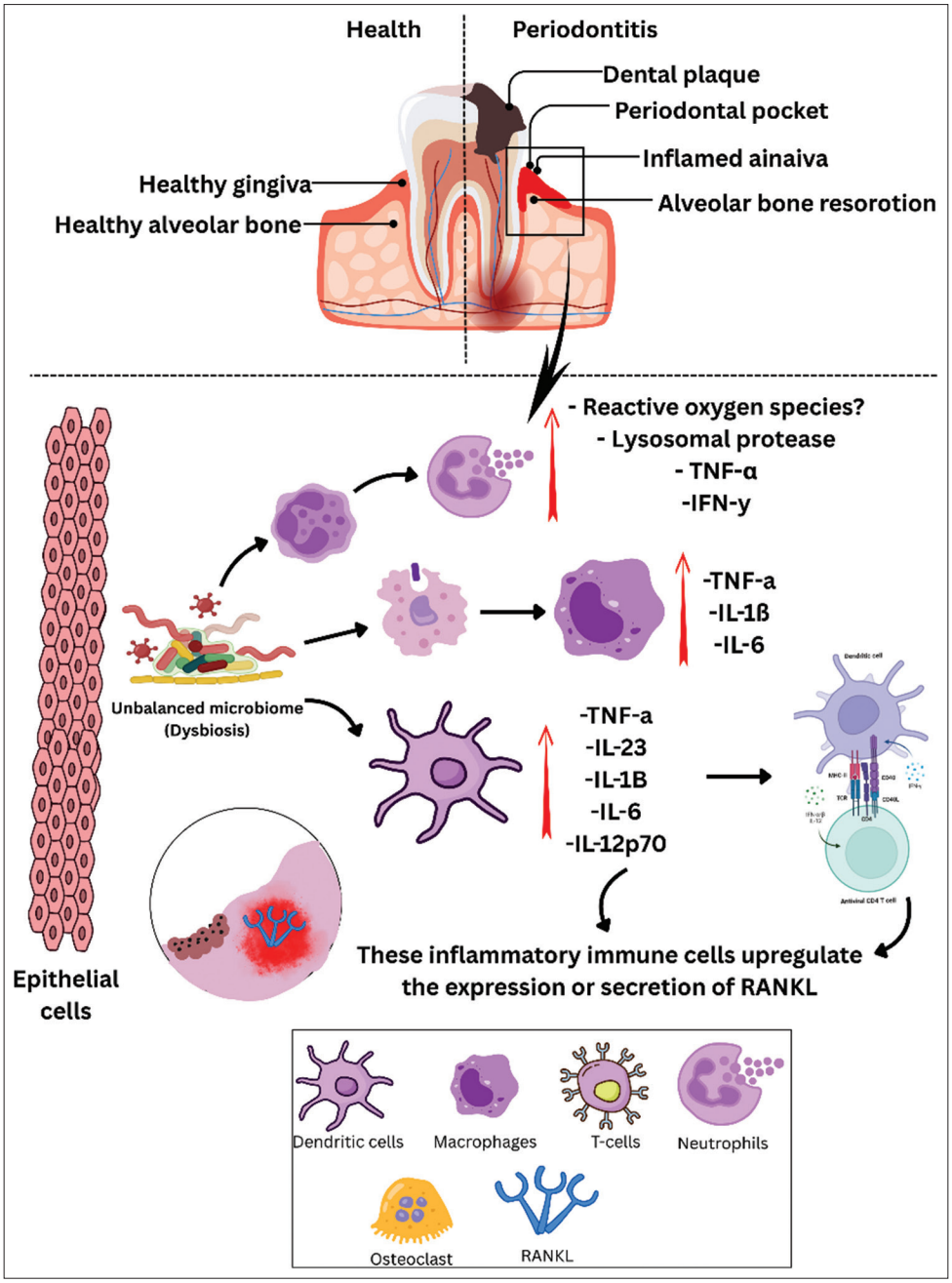

Figure 1: Periodontitis is characterized by an immune-inflammatory reaction to bacterial biofilms, leading to the destruction of cementum, periodontal ligament, and bone. Various immune cells participate in this pathological process

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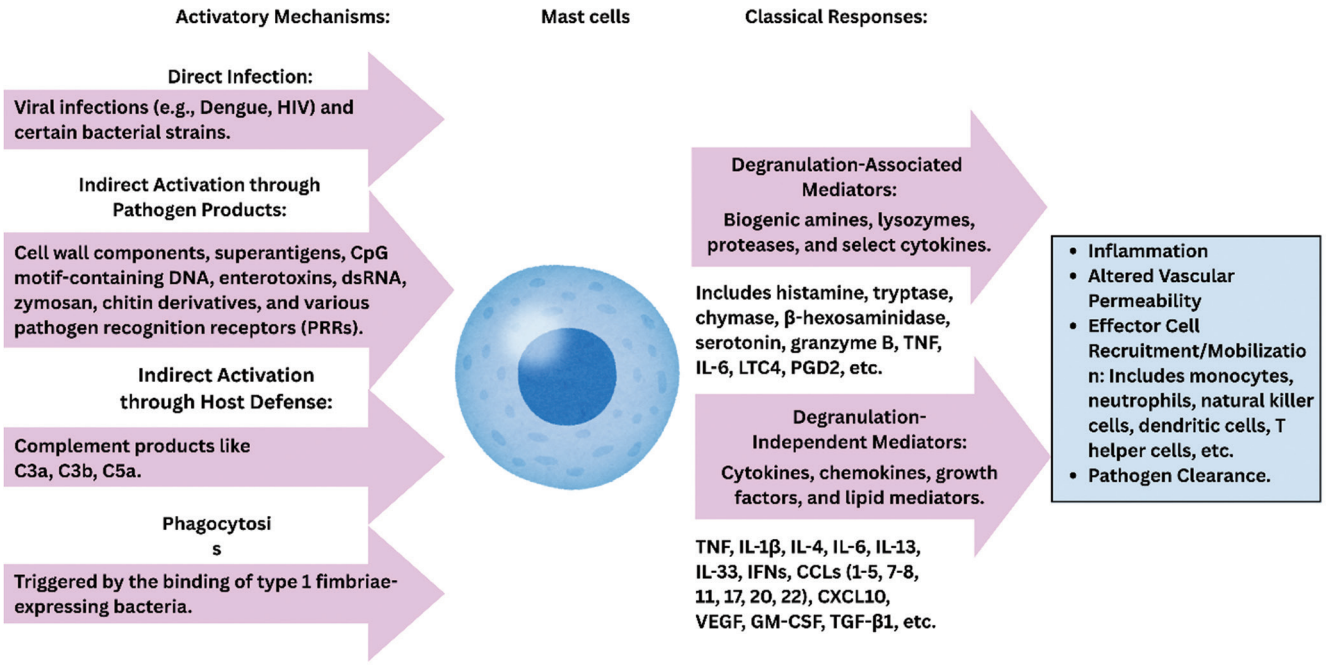

Figure 2: Mast cells play a key role in detecting and responding to pathogens, both directly via pathogen invasion and indirectly through various pathogen-derived components, host defense mechanisms, or the process of phagocytosis. On activation, mast cells release a variety of mediators, which can be classified as either degranulation-dependent or degranulation-independent. These mediators contribute to inflammation, alter the local environment at infection sites, promote the recruitment of additional immune cells, and help regulate the immune response to pathogens

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in the case of the host immune response, which is of principal importance in the development of periodontitis.[9] The shortcomings of old treatment methods have given rise to the creation of new treatments that not only focus on the microbial but also on the host responses.

The need for more effective therapies has spurred interest in biomaterials.[3] Biomaterials have made a strong comeback as a tool in periodontal therapy. Besides being the potential to scale up the regeneration of tissues, modulate the immune system, and the release of the agents of therapy directly to the place of the disease.[10] These substances can not only be intended to regenerate the injured periodontal tissues, such as bone but also those of the surrounding gum.[2] Latest progress has turned attention to the devising of biofunctionalized biomaterials which not only give off but also take up the guiding signals in order to conduct *in situ* regeneration. Such biomaterials can be filled with stem cells (e.g., mesenchymal stem cells [MSC]) or may serve as scaffolds and the carriers of growth factors.[11]

Biomaterials have a significant role in tissue engineering, regeneration, and disease management, which is one of their many faces.[12] They are capable of being scaffolds for cell attachment and growth, providing growth factors and other therapeutic agents, and influencing the local immune response.[2,13] Broadly speaking, biomaterials can be divided into ceramics and polymers.[14] The ceramic-based materials that come to mind are hydroxyapatite (HA). They are considered very important due to their biocompatibility, bioactivity, and osteoconductivity.[15] The reason why HA is widely used in bone grafting and implantation, dental materials, and drug delivery systems is the fact that it is very similar to the mineral phase of bone tissue. Another type of materials is those based on polymers like chitosan (CS). Those offer design flexibility and can be adjusted to fit the particular application. The science of biomaterials made of CS has developed enormously concerning the use in periodontal therapy, together with the fact of possessing elements such as biocompatibility, biodegradability, and the absence of pathogens.[2]

This review explores the potential of next-generation biomaterials in managing periodontal disease. By harnessing the principles of tissue engineering, regeneration, and immunomodulation, these biomaterials offer the promise of more effective and predictable treatment outcomes. The aim of this review is to provide an overview of the latest advances in biomaterials for periodontal therapy, highlighting their potential to address the limitations of traditional treatments and improve the long-term management of periodontal disease. Specifically, the review will focus on biomaterial-mediated macrophage immunotherapy, nanotherapeutics, and stimuli-responsive hydrogels. These next-generation biomaterials represent a paradigm shift in periodontal therapy, offering the potential to regenerate lost tissues, modulate the host immune response, and ultimately improve the oral and systemic health of patients with periodontal disease.

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IMMUNE CELLS AND CELLULAR PATHWAYS INVOLVED IN PERIODONTITIS

Immune cells are crucial for maintaining alveolar bone homeostasis, particularly in the context of chronic periodontitis.[16] Both innate and adaptive immune cells, including neutrophils, mast cells, macrophages, DCs, T-cells, and B-cells, play significant roles in the immune response. In the presence of chronic microbial dysbiosis, these immune cells become chronically activated, leading to prolonged inflammatory states. This persistent inflammation accelerates the progression of periodontal disease and hinders the natural healing processes of the affected tissues.[17]

Neutrophils

Polymorphonuclear leukocytes, also called neutrophils, are the most important cells in the body's first line of defense against infections and are necessary for the innate immune system. They kill bacteria by a number of key mechanisms that involve phagocytosis (the process of engulfing and destroying pathogens), degranulation (release of antimicrobial granules), production of reactive oxygen species (ROS) (which can kill both pathogens and host cells), and the creation of neutrophil extracellular traps that not only trap and kill pathogens but also protect the area from further damage.[18]

Neutrophil homeostasis plays a crucial role in maintaining periodontal health, as imbalances – either too few or too many neutrophils – can exacerbate periodontal inflammation.[19,20] Even in the absence of overt inflammation, neutrophils continually infiltrate the periodontium in small amounts. These cells, often referred to as oral neutrophils, are commonly found in saliva and gingival crevicular fluid, with their numbers and activity being influenced by periodontitis. Pathogenic dental plaque-derived chemoattractants and proinflammatory cytokines draw more neutrophils from circulation into gingival tissues, contributing to inflammation.[21] Clinical studies have shown a link between neutrophil count and the severity of periodontitis, with patients suffering from chronic periodontitis exhibiting a 2.5-fold increase in neutrophil recruitment compared to healthy individuals.[22] In periodontitis, oral neutrophils also display functional abnormalities, including impaired chemotaxis with slower speeds, reduced accuracy, and diminished response to chemotactic signals. In addition, they show higher levels of activation and degranulation markers (e.g., CD10, CD63, CD64, CD66a) and exhibit an altered transcriptome that promotes the expression of pro-survival genes, which results in neutrophils that persist longer in the tissue.[21] The increased abundance and prolonged lifespan of these neutrophils may exacerbate inflammation and contribute to the ongoing periodontal tissue damage associated with the disease.[23] Thus, neutrophils in periodontitis are not only more numerous but also hyperactivated and functionally impaired.

Neutrophils are primarily responsible for fighting infections, but they also display plasticity by changing immune response in a way that they can even turn off T-cell activation.[24] One study shows that periodontal treatment can not only reduce the number of suppressive neutrophils but also increase the number of normal neutrophils,[25] thus indicating that the suppressive neutrophils in periodontitis could be a driving factor. However, the lack of research on suppressive neutrophils in periodontitis makes their exact position unclear, and more studies are needed to clarify their role.

Mast cells

Mast cells, key components of the innate immune system, are activated by complement proteins, damage-associated molecular patterns, and pathogen-associated molecular patterns (PAMPs).[28,29] On activation, mast cells degranulate, releasing inflammatory mediators into the local microenvironment, including tumor necrosis factor alpha (TNF-α), interleukin 1-beta (IL-1β), histamine, and monocyte chemoattractant protein-1, which recruit other inflammatory cells and promote fibrocyte migration.[30-32] Studies demonstrate that loss of mast cells reduces inflammation cytokines' production and the destruction of alveolar bone in periodontitis models.[33] Human gingival tissues from patients with periodontitis showed a mast cell density that was 1.53 times higher than those from healthy tissues. Furthermore, mast cell density and degranulation correlate with periodontitis severity.[33] Toll-like receptor 4 (TLR4) expression on mast cells is positively correlated with chronic periodontitis severity. As a sensing receptor for gram-negative bacteria, TLR4 activation induces a proinflammatory response.[34]

Mast cells are very much strategically situated in periodontal tissues that provide them with innate and adaptive immune responses because these cells release quite a number of cytokines, chemokines, and growth factors [Figure 1].[30,35] Inflammatory diseases, which are caused by non-allergic triggers as an example of neuropeptides and cytokines, have various cells in the body that take if roles beyond allergic reactions.[36] Mast cells that have been activated release histamine, proteases, and cytokines, which are the main sources of inflammation and changed vascular permeability.[29,31] Moreover, they can still produce cytokines such as TNF-α, IL-1, IL-6, IL-8, and IL-13, without the aid of degranulation.[29] TLRs are numerous on mast cells. They also include TLR2 and TLR4; thus, the mast cells are able to react to various things, such as PAMPs.[37] Proinflammatory cytokines are released upon TLR4 activation by lipopolysaccharide, which comes from Gram-negative bacteria. This TLR4-mediated response in mast cells contributes to the chronic inflammation observed in periodontitis.[38]

The precise role of mast cells in periodontitis is complex, with studies suggesting both pro-inflammatory and immunomodulatory functions.[32] Further research is needed

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to fully elucidate their contribution to the pathogenesis of periodontal disease and to explore their potential as therapeutic targets.

B-cells/plasma cells

B cells are antigen-presenting cells (APCs) which, on antigen exposure, become activated via T-cell interactions.[39] These cells are the source of two main effector populations: plasma cells that deliver instant humoral immunity by means of antibody secretion specific to the pathogen, and memory B-cells that provide quick anamnestic responses after antigen re-stimulation.[40]

B-cell populations undergo radical changes in the pathogenesis of periodontitis.[41] It has been reported that in both healthy gingiva and gingivitis lesions, B cells are mostly of the memory subset,[42] but periodontitis tissues are characterized by the prevalence of plasma cells – especially those accumulated at the pocket base and sparsely distributed throughout the gingiva.[43] Periodontal plasma cells are the sources of pathogen-specific immunoglobulin G antibodies that recognize major periodontopathogens like *Porphyromonas gingivalis,*[44] and at the same time, they express the RANKL, a protein that directly induces the differentiation of osteoclasts.[45]

Therapeutic SRP reverses this cellular distribution, shifting the B-cell profile back toward memory phenotypes. This demonstrates that sustained plaque biofilm exposure drives terminal B-cell differentiation into plasma. Notably, circulating B-cells in periodontitis patients exhibit upregulated RANKL expression compared to healthy controls.[46]

Periodontal plasma cells display functional heterogeneity. Subpopulations specifically produce interleukin-37 (IL-37) or co-produce IL-35 and IL-37.[43] These cytokines demonstrate dose-dependent inhibition of osteoclast formation *in vitro*,[46] suggesting certain plasma cell subsets may attenuate alveolar bone resorption by suppressing osteoclastogenesis.[45]

These findings collectively indicate that distinct subsets of B-cells have their specific regulatory roles in the alveolar bone homeostasis in periodontitis: plasma cells are responsible for both the pathogenic (RANKL-mediated) and the protective (IL-35/IL-37-mediated) bone remodeling pathways,[43,45] while memory B-cells give the adaptive immunological memory.[40] The equilibrium between these populations seems.

T-cells

T cell-targeted periodontal therapy faces significant scientific and translational challenges despite its immunomodulatory promise. Mechanistically, the delicate balance between Th17-driven inflammation and Treg-mediated suppression remains difficult to harness therapeutically. In periodontitis lesions, Th17 cells dominate with IL-17 overproduction, triggering RANKL-mediated osteoclastogenesis and irreversible bone loss.[47] While Tregs naturally counter this destruction, their dysfunction in chronic inflammation limits endogenous repair.[47] Notably, advanced periodontitis exhibits reduced $FOXP3^+$ Treg density in gingival tissues, particularly in Stage IV/Grade C disease, where Tregs were diminished by ~40% compared to healthy controls.[47] Therapeutic approaches that are aimed at the reversal of this imbalance – such as adoptive Treg transfer and biomaterial-driven immunomodulation – are still in early stages and encountering difficulties in cell source, stability, and delivery accuracy. Nanoparticle systems (e.g., CeO_2 NPs, ZIF-8 NPs) show potential by skewing macrophage polarization toward M2 phenotypes and enhancing local Treg recruitment.[10] However, their inability to sustain long-term immunomodulation risks rebound inflammation, as evidenced by persistent Th17 reactivation in preclinical models.

Clinical translation is further complicated by heterogeneous patient responses. The specific regulation of T cell populations through age and sex has also a significant role to play in the course of treatment, as demonstrated by the gradual transition to an immunosenescent state that presently affects older adults, in which there are few regulatory T cells whose functional capabilities have become impaired.[48] Technical limitations plague cell-based approaches: MSC therapies attempting to modulate T cells encounter inconsistent survival post-transplantation, with <15% of administered cells remaining viable at defect sites after 4 weeks.[49] Biomaterials like CS scaffolds offer cytokine-controlled release (e.g., TGF-β for Treg induction) but suffer from suboptimal spatiotemporal precision, often provoking unintended Th17 activation in adjacent tissues.[2,8] Key knowledge gaps persist regarding tissue-resident memory T cells (Trm), which may drive periodontitis recurrence despite therapy, yet their role remains underexplored.[50] Future solutions may lie in combinatorial approaches: Engineered "smart" biomaterials with dual cytokine release (IL-10 + TGF-β) coupled with CAR-Treg technologies could achieve site-specific immunomodulation, but rigorous safety studies are paramount before clinical adoption.

DCs

DCs represent a core type of APCs, whose functional dynamics have a wasting impact on the periodontal disease pathogenesis, that is, chronic inflammatory disease that affects tissues through destruction.[51] Their capacity to recognize and capture antigens from bacterial biofilms initiates and regulates immune responses, promoting inflammation and tissue destruction.[51,52] Dysregulation of DC function can lead to excessive inflammation and tissue destruction.

DCs, as sentinels in the oral mucosa, capture oral microbes and migrate to lymph nodes, orchestrating the differentiation

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of CD4+ T cells.[53] In the development and suppression of periodontal disease, T cells and T CD4 + cells are principal. The DCs regulate the activation and control of these cells. The gingival epithelium and connective tissue of periodontal pockets have DCs that are Factor XIIIa+ as well as S-100 protein +Langerhans cells. Following non-surgical periodontal treatment, these cells can be checked to learn how immune responses are achieved in periodontal pockets.[54]

While standard periodontal therapy is not the best treatment for the local cellular mechanisms that are responsible for the chronic inflammation, it can still be utilizing the properties of the biomaterials that are locally recruiting and programming DCs as a result they can direct the T-cell effector responses (Sands *et al*., 2020).[5] Nanomaterials that alter a local cytokine environment in periodontal tissues may modulate DCs and regulatory T cells (Tregs) in the periodontium. It is vital, as periodontitis is a chronic inflammatory disease that arises from the interactions of the tissue, the immune system, and microbiota.[55] By using T cell phenotypes, the application of polylysine-derived carbon quantum dots (PLL-CQDs) can realize the recovery of periodontal bone loss through amelioration. Recent studies have pointed out that PLL-CQDs (with particle size of 2.31 ± 0.70 nm), having fluorescence characteristics and maintaining positive charges, which are essential for their binding to immune cells, are thus able to modulate the response of T lymphocytes.[56]

Innovative approaches using MSC-derived apoptotic bodies have shown promise in alleviating alveolar bone destruction by regulating osteoclast differentiation and function.[57] Furthermore, human periodontal ligament stem cells (PDLSCs) can suppress T-cell proliferation by down-regulating the non-classical major histocompatibility complex-like glycoprotein CD1b on DCs.[58]

Macrophages

Macrophages are pivotal mediators in the immune system of periodontal disease, as they can be both helpful and harmful to the tissue depending on their phenotypic polarization.[59] These cells have been generally described as the pro-inflammatory M1 (classically activated) and the anti-inflammatory M2 (alternatively activated) subtypes; however, of late, it has been established that they exist at a continuous range of activation states. This flexibility of macrophages is an asset as well as a problem in periodontal treatment.[60] M1 macrophages, induced by PAMPs and inflammatory cytokines, produce mediators like IL-1β, TNF-α, and IL-6 that not only result in local inflammation but also lead to alveolar bone resorption.[61] On the other hand, M2 macrophages generate cytokines such as IL-10 and TGF-β, which are anti-inflammatory, and hence, they can help heal the damaged tissues.[62]

In healthy gums, M2-type macrophages, which are the majority in the population, are responsible for the maintenance of tissue homeostasis, while periodontitis is generally characterized by a disturbed M1/M2 ratio, mostly dominated by chronic inflammation. It has been shown that this ratio can be adjusted to the good side by either stimulating M2 polarization or inhibiting M1 activation, which will result in the reduction of periodontitis symptoms.[63] Biodegradable materials, including hydrogels or nanoparticles (NPs), have been utilized for the purpose of carrying anti-inflammatory drugs or M2-generating cytokines, such as IL-4, when going to the periodontal areas directly. These treatments showed to be very efficient in decreasing bone loss and the markers of inflammation in studies on animals.

Moreover, cellular therapies involving the transplantation of *ex vivo* polarized M2 macrophages have demonstrated notable anti-inflammatory effects in experimental periodontitis. However, conflicting findings complicate this narrative. Some studies report elevated M1 and M2 populations even in early gingival inflammation, with little differentiation between disease states, suggesting macrophage behavior may be context-dependent and temporally regulated. Variability in sampling, surface marker expression, and disease progression stages likely contribute to these inconsistencies.[64] Furthermore, macrophage heterogeneity and the existence of hybrid phenotypes blur the binary classification, necessitating a more nuanced understanding of their functional roles. Despite these challenges, targeting macrophage polarization remains a promising therapeutic strategy. Ongoing advancements in immunomodulatory biomaterials offer a controlled and site-specific approach to harness the regenerative potential of M2 macrophages while mitigating the harmful effects of persistent M1-driven inflammation in periodontal therapy.[59]

NEXT-GENERATION BIOMATERIALS IN PERIODONTAL THERAPY

Periodontal disease is a condition that requires surgical treatment as it completely destroys supporting structures of teeth caused by a chronic bacterial infection and inflammation. The conventional periodontal surgical techniques are largely based on mechanical debridement and removal of the diseased tissue, and although they achieve adequate healing, they do not fully regenerate periodontal tissues. With the increase in knowledge in terms of tissue engineering, a strong focus is placed on the incorporation of biomaterials into it that provide antibacterial, anti-inflammatory, and regenerative properties. Graft substitutes, guided tissue regeneration (GTR)/guided bone regeneration (GBR) membranes, injectable hydrogels as well as scaffolds are being investigated as biomaterials that help promote wound healing and bone regeneration. Specifically, recent advances such as nanoparticle, formulations, and bioactive molecule-loaded gels appear as interesting forms of modulating the local microenvironment, tissue repair, as well as reinfection prevention. These strategies can be seen as a paradigm shift

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of traditional surgery to biologically-guided periodontal regeneration strategies [Figure 3].

Immunomodulation with biomaterials

Periodontitis is an inflammatory chronic disease that is initiated and modulated by an imbalanced microbial biofilm and host immune response, and leads to the progressive damage of the periodontal tissues. Conventional treatments such as SRP are aimed at removing bacteria but are generally unable to eliminate inflammation completely or regenerate lost tissues. Immunomodulation – the modulation of the host response in addition to, or as opposed to, the pathogens – is a new perspective in periodontal treatment. Biomaterial platforms allow for delivery of immune-modulating agents with much less off-target effect, control over spatiotemporal release, and improved regenerative performance.[65]

Mechanisms of immunomodulation

Biomaterials modulate immune responses primarily through

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Macrophage Polarization Proinflammatory M1 macrophages to anti-inflammatory, pro-healing M2 phenotypes. NPs such as cerium oxide (CeO_2) or gold (Au) NPs can scavenge ROS, protecting from oxidative stress and driving towards M2 conversion. For instance, CeO_2 NPs decrease TNF-α and IL-6 while increasing IL-10, fostering tissue repair.[10,66]

Cytokine and Chemokine Regulation: CS-based hydrogels release anti-inflammatory cytokines (e.g., IL-4, IL-10) or siRNA targeting proinflammatory mediators like TNF-α and IL-1β. CS's inherent bioactivity promotes neutrophil apoptosis and reduces IL-8 secretion.[2,67]

T-Cell Modulation: Biomaterials laden with TGF-β or regulatory T-cell (Treg)-inducing agents (e.g., rapamycin) suppress Th17 responses, which drive bone resorption.[68]

Biomaterial platforms for immunomodulation

- NPs: Polymeric, lipid-based, or metallic NPs deliver immunomodulators (e.g., resolvins, cytokines, siRNA). PLGA NPs encapsulating curcumin significantly reduce gingival crevicular fluid IL-1β and MMP-8 levels, enhancing clinical attachment gain.[69]
- Hydrogels: Self-assembling peptide hydrogels or thermosensitive polymers (e.g., poloxamers) provide sustained release. Adhesive hydrogels functionalized with M2 macrophage-targeting peptides (M2pep) localize anti-inflammatory effects to periodontal pockets.[67]
- Scaffolds: 3D-printed bioceramic scaffolds (e.g., HA) combined with MSCs secrete paracrine factors (e.g., PGE2, TSG-6) that suppress T-cell proliferation and promote osteogenesis.[70]

Antibacterial and anti-biofilm biomaterials

The use of antibacterial and anti-biofilm biomaterials is a paradigm shift in periodontal treatment that addresses two objectives: destruction of microbes and regeneration of the tissue. The traditional therapy, such as mechanical debridement and systemic antibiotics, has their limitations due to biofilm resistance and the short residence time of the medications in the periodontal pockets. New developments, including multifunctional polymer vesicles and dual corona nanocarriers, not only directly promote delivery of antibiotics but also provide inherent antibacterial effects to enable biofilm destruction with a much lower dose of a drug.[71] Similar effects are noted with functional hydrogel and NPs that may deliver localized antimicrobial activity while promoting healing.[72,73] Materials like zinc-doped bioactive glass outperform traditional counterparts by significantly inhibiting key periodontal pathogens *in vitro*,[74] while chalcone-based compounds and dietary polyphenols demonstrate effective inhibition of both planktonic and biofilm-forming bacterial strains (Satokata *et al*., 2022),

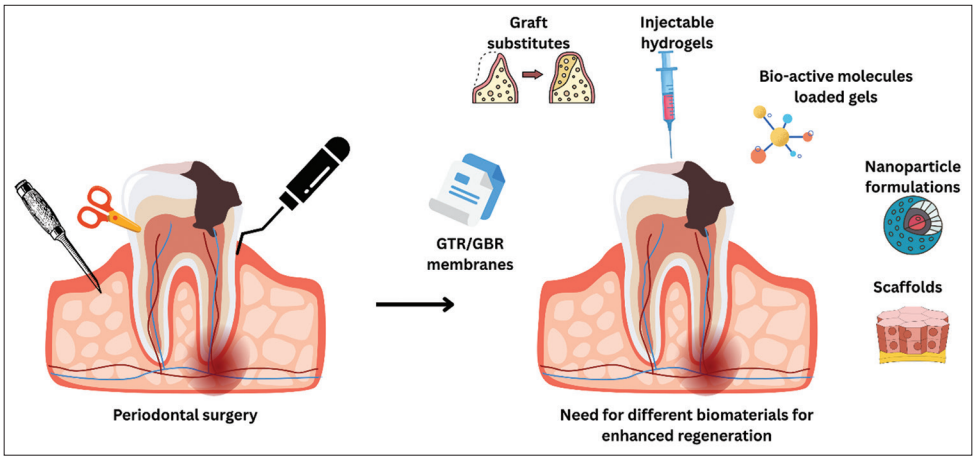

Figure 3: Schematic illustration showing the transition from conventional periodontal surgery toward the use of regenerative biomaterials

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(Shahzad *et al*., 2015).[75,76] However, there are still its critical gaps, including the necessity of standardizing clinical validation, the possible cytotoxicity of materials, and long-term efficacy. Moreover, biofilms are structurally complex with host immune responses complicating the outcomes of treatment, making it necessary to use materials that kill bacteria in addition to reducing inflammation and damaged tissue and promoting regeneration, simultaneously.[77,78]

Antibacterial and anti-biofilm biomaterials are revolutionizing the management of periodontitis by directly targeting the microbial etiology while simultaneously supporting tissue healing. Xi *et al*. (2019) introduced a dual-corona vesicle system co-assembled from poly(ε-caprolactone)-block-poly(lysine-stat-phenylalanine) and poly (ethylene oxide)-block-poly(ε-caprolactone), which showed intrinsic antibacterial activity and enhanced antibiotic delivery capabilities. Their vesicles exhibited "stealth" features enabling them to penetrate biofilm matrices while delivering antibiotics at half the typical dose required, significantly reducing plaque and inflammation in a rat periodontitis model.[71] Wu *et al*. (2025) emphasized the extreme importance of multifunctional properties, that is, antibacterial, anti-inflammatory, and regenerative, that should be introduced into periodontal biomaterials. They contended an ineffective number of prevailing therapies to treat the multifaceted microenvironment of periodontitis and suggested how a combination of bioactive agents to scaffolds can be used to modulate the immune response and enhance the regeneration of soft/hard tissue.[78] Similarly, Luan *et al*. (2022) provided a comprehensive review of how functional biomaterials such as hydrogels, NPs, and responsive delivery systems can enhance outcomes by maintaining drug concentrations locally and minimizing resistance. They outlined how these biomaterials could regulate inflammation, suppress pathogens, and promote regenerative healing, thereby addressing the limitations of SRP and systemic antibiotics.[77]

Graft substitutes

Alloplasts, xenografts, and allografts are emerging as next-generation biomaterials in the field of periodontal treatment providing a variety of options in the arena of bone repair and bone regeneration.[79] Alloplasts can be defined as a group of osteoconductive materials, which are themselves synthetic, biocompatible (e.g., HA or beta-tricalcium phosphate), and which, as such, serve as scaffolds, supporting new bone formation, with no chance of disease or complication to the donor site, but without osteoinductive capabilities.[80] Xenografts (bovine or porcine bone) have a structure similar to human bone and are very osteoconductive, allowing cell infiltration and vascularization; they are cheap and plentiful, but their resorption may be slow, although, even with stringent processing, they have a very slight chance of producing an immune reaction.[81] Grafts derived by human donors (allografts) have osteoconductive as well as some osteoinductive capability, particularly in demineralized form, and show far better bone fill and clinical attachment gain than alloplasts, with the benefit of not requiring a second surgical site, although they must be painstakingly screened to reduce the risk of disease transmission. In sum, these graft alternatives are core to current periodontal regenerative measures most commonly combined with barrier membrane(s) or biologically active component(s) to improve clinical outcomes and predictability in the management of periodontal defects.[82]

Recent advancements in periodontal regenerative therapy have placed significant emphasis on optimizing graft substitutes such as alloplasts, xenografts, and allografts to enhance clinical outcomes and biological integration. Esfahanian *et al*. (2022) provided one of the most comprehensive experimental comparisons of these three classes of grafts by analyzing their effects on PDLSCs behavior. Their *in vitro* study revealed that xenografts exhibited the highest initial cell attachment, whereas allografts promoted superior long-term cell proliferation. Osteogenic potential was most strongly induced by xenografts, while alloplasts lagged in both proliferation and osteogenesis, reinforcing the differential biological responsiveness elicited by each material type.[83]

Deploying a histological component, Zampara *et al*. (2022) carried out a randomized clinical trial to assess graft integration and new bone formation, through a core biopsy technique. Their findings showed that allografts produced the best percentage of viable bone, and the lesser particle grafts remained after 3 months, thus no weak regenerative performance. Conversely, the bone formation as measured through xenografts is significantly reduced, and it was found that it contains large amounts of residual particles, which may fetter the ability to remodel. Interestingly, alloplasts provided regenerative results that equally matched with allografts, getting its greatest potential as an alternative form of synthetic material less appreciated.[84]

Miron *et al*. (2024) introduced a novel perspective by describing the development of non-resorbable bone allografts, processed using sintering techniques traditionally used for xenografts. These modified allografts demonstrated minimal resorption in a 52-week monkey model, combining the volume stability of xenografts with the osteogenic advantages of allografts. This hybrid approach may represent a new generation of biomaterials capable of achieving long-term structural integrity without the need for multiple products.[85]

Lastly, Nurcahyanti and Amalia (2023) tested the efficacy of alloplast and xenograft in crater defect. In their literature review, they arrived at a conclusion that the potential of achieving equally successful graft clinical outcomes was equal between the two types of grafts, but the local factors, such as oral hygiene and the systemic disease control, were more significant in terms of determining the outcome of treatment

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rather than the type of material used. Strengths in this solidify the idea that effectiveness of grafts is considerably contextual and that the abilities of clinicians and the patient compliance are essential necessities of success.[86]

GTR/GBR membranes

The GTR and the GBR membranes can be regarded as the next generation of artificial materials in treating periodontal and bone defects and are able to revolutionize periodontal and bones lesion treatments. The membranes serve as physical barriers that inhibit rapid movement of epithelial and connective tissue cells into the periodontal defects thus enabling the slower-growing bone and periodontal ligament cells to proliferate and repopulate the defect and restore the lost tissue.[87] Recent forms of GTR/GBR membranes are designed such that the membranes are cell-occlusive, but nutrients and small molecules can flow freely improving a favorable environment in which the tissue regenerates. They are available as resorbable (biodegradable) or non-resorbable (requiring surgical removal) types, with current trends favoring resorbable membranes to eliminate the need of a second surgery and minimize morbidity of the patient.[88] Advances in membrane design involve the utilisation of natural or synthetic polymers such as collagen, synthetic polymers, or hybrid materials that could be coupled with bioactive agents in order to stimulate osteogenesis, angiogenesis, and antibacterial effects. It has the potential to be used as the ideal membrane that is biocompatible, mechano-stable, with selective permeability and a degradation rate that allows tissue remodeling and space preservation, and permits adsorption of the wound tissue. Despite significant progress, challenges remain in optimizing mechanical strength, degradation rates, and functional integration, driving ongoing research into advanced materials and smart delivery systems for growth factors and biomolecules tailored to clinical needs. Thus, GTR/GBR membranes are at the forefront of regenerative periodontal therapy, offering promising solutions for predictable and effective tissue and bone regeneration [Figure 4].[89,90]

Bottino *et al*. (2012) proposed a transformative vision for GTR/GBR membranes by introducing the concept of functionally graded nanofibrous biomaterials that mimic the native extracellular matrix. Their review argued that conventional membranes, whether resorbable or non-resorbable, are mechanically and biologically inadequate for complete periodontal regeneration. They emphasized the need for spatially organized structures that not only block epithelial migration but also actively support cellular differentiation, angiogenesis, and antibacterial activity. Notably, they advocated for combining hydrogels with scaffolds to form next-generation bioactive membranes capable of dynamic interaction with the wound microenvironment.[91]

Building on these ideas, Bee and Hamid (2025) explored the potential of CS-based membranes in their comprehensive

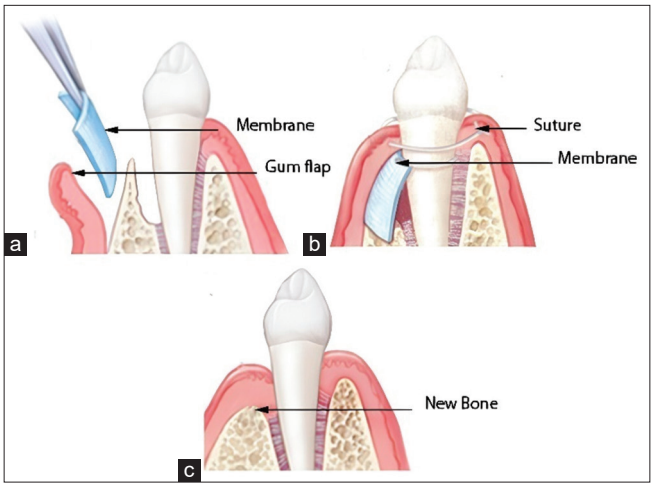

Figure 4: Guided tissue regeneration is an advanced periodontal technique used to restore bone and tissue defects. (a) The procedure begins with a surgical flap to expose the affected area, followed by placement of a protective membrane – sometimes combined with bone graft material – over the defect. (b) The gum is then repositioned and sutured to secure the site. (c) During healing, the stitches either dissolve naturally or are professionally removed, allowing tissue regeneration beneath the membrane. (Adapted from[87] under the terms and conditions of the creative commons attribution [CC-BY] license [CC-BY 4.0])

review. They highlighted CS's biocompatibility, antimicrobial activity, and film-forming properties as ideal characteristics for GTR/GBR applications. Moreover, they detailed how composite CS-based membranes reinforced with bioactive fillers and therapeutic agents – such as calcium phosphates or antibiotics – can significantly improve regenerative outcomes. Their discussion of functionally graded CS membranes particularly echoed Bottino's approach, pointing to advances where each membrane layer is tailored for different biological functions, from tissue exclusion to bone stimulation.[92]

Similarly, Bajpai (2022) highlighted that an ideal membrane as used in GTR/GBR was never created based on the drawbacks recorded in mechanical stability, embedding, and degradation control in current products. Their review reinforced the shift toward bioinspired designs, particularly graded biomaterials that replicate the mechanical and cellular cues found in native tissues. They referred to spatially differentiated experimental scaffolds, including, for example, stiffness or porosity gradients, which increase the bone as well as soft-tissue attachment levels (integration) at the boundary sites.[93]

Further pushing the envelope, Bee and Hamid (2022) also explored asymmetric resorbable-based membranes, where each side of the membrane is engineered for a distinct purpose. One side is designed to inhibit soft-tissue invasion, while the other supports bone-forming cells. They noted that asymmetric membrane architecture significantly improves tissue selectivity and regeneration outcomes in periodontal

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applications. Their findings supported the idea that membrane architecture – not just composition – is critical in achieving full functional regeneration. They also emphasized the potential of combining these membranes with graft materials for more predictable clinical outcomes.[94]

CHALLENGES AND FUTURE DIRECTIONS

Challenges

Next-generation biomaterials hold great promise for the management of periodontal disease, but their successful clinical translation faces multiple challenges. One of the major issues is the complexity of the periodontium itself – a heterogeneous structure composed of cementum, periodontal ligament, alveolar bone, and gingiva – making full regeneration a multifaceted task.[95] Despite advances, current biomaterials struggle to simultaneously promote regeneration of all periodontal tissues due to insufficient spatial and temporal coordination in healing processes.[96] Furthermore, the immunomodulatory properties of biomaterials remain poorly understood and inconsistently controlled, which can lead to unpredictable inflammatory responses and limit tissue integration.[97] There is also a lack of standardization in preclinical and clinical studies, making it difficult to compare outcomes and develop universally accepted treatment protocols.[98] Manufacturing reproducibility, scalability, and long-term biocompatibility of biomaterials also remain unresolved concerns.[99] Finally, while the incorporation of nanotechnology and bioactive agents enhances the regenerative potential, it introduces new complexities in terms of regulatory approval and clinical adoption.[100] These multifactorial challenges are summarized in Figure 5.

Future directions

- Immunomodulatory biomaterials: Future materials will focus on fine-tuning the immune response to control

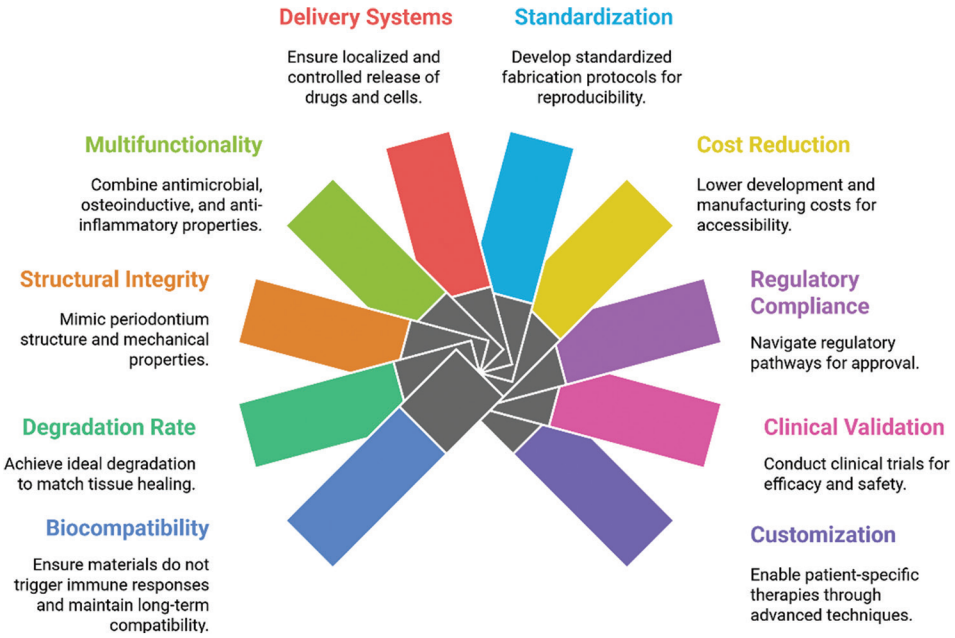

Figure 5: Key challenges in the clinical translation of next-generation biomaterials for periodontal disease management. These include issues related to drug/cell delivery systems, standardization, cost reduction, regulatory compliance, clinical validation, customization, biocompatibility, degradation rate, structural integrity, and multifunctionality

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Table 1: Key advances in neutrophil-targeting biomaterials

Biomaterial type	Mechanism of action	Key outcomes	References
CeO_2/polymer NPs	ROS scavenging, NETosis inhibition	60% ROS reduction; 30% less tissue damage *in vivo*	[10]
Mg^{2+}-loaded hydrogels	MMP-9 downregulation, neutrophil apoptosis	40% lower MMP-9; ×2 faster inflammation resolution	[26]
Resolvin D1-releasing NPs	Neutrophil phenotype reprogramming	45–50% ↓ TNF-α/IL-1β; enhanced M2 macrophage shift	[27]
Anti-ICAM-1 membranes	Block neutrophil adhesion	35% reduced infiltration; improved scaffold integrity	[26]

NPs: Nanoparticles, ROS: Reactive oxygen species, TNF-α: Tumor necrosis factor alpha, IL-1β: Interleukin 1-beta

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inflammation while promoting tissue repair. Materials that interact directly with immune cells to modulate inflammation locally (without systemic side effects) are especially promising.[97]

- Integration with stem cell therapy combining biomaterials with stem cells – like PDLSCs and MSCs – could enable more effective, multi-tissue regeneration of bone, ligament, and cementum.[98]
- Hierarchical and biomimetic scaffolds future scaffolds will better replicate the complex structure of periodontal tissues, using layered or compartmentalized designs that support coordinated regeneration across different tissue types.[101]
- Nanotechnology and smart delivery systems, nanoengineered materials and systems, will enhance localized drug or gene delivery with improved control over release timing, targeting, and bioavailability. These approaches also aim to reduce side effects and improve healing outcomes.[102]

CONCLUSION

The management of periodontal disease remains a significant challenge due to its multifactorial etiology and complex interplay between microbial biofilms and host immune responses. Traditional therapies, while effective in controlling infection and reducing inflammation, often fail to address the underlying tissue destruction and immune dysregulation that characterize chronic periodontitis. Recent advances in biomaterials science have opened new avenues for periodontal therapy, offering innovative solutions that extend beyond conventional approaches.

Next-generation biomaterials – including biofunctionalized scaffolds, nanotherapeutics, and stimuli-responsive hydrogels – demonstrate remarkable potential to promote periodontal regeneration, modulate local immune responses, and deliver targeted therapeutics directly to affected sites. These materials can interact with key immune cells such as neutrophils, mast cells, B-cells, and T-cells, thereby influencing the inflammatory milieu and supporting tissue repair. Furthermore, the integration of stem cells and growth factors into biomaterial platforms holds promise for true periodontal tissue regeneration. Despite these promising developments, several challenges remain. The precise mechanisms by which biomaterials interact with immune cells require further elucidation, and long-term clinical studies are needed to confirm their safety, efficacy, and predictability in diverse patient populations. In addition, the translation of these advanced materials from bench to bedside will require multidisciplinary collaboration and rigorous regulatory evaluation. In summary, next-generation biomaterials represent a paradigm shift in the management of periodontal disease. By combining principles of tissue engineering, immunomodulation, and targeted therapy, these materials offer the potential for more effective, personalized, and durable treatment outcomes. Continued research and innovation in this field are essential to fully realize the benefits of biomaterial-based therapies and to improve the oral and systemic health of patients affected by periodontal disease.

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