European Cells and Materials Vol.50 2025 (pages 33–67) DOI: 10.22203/eCM.v050a03 ISSN 1473-2262

Review

INNOVATIVE IMMUNOMODULATORY STRATEGIES IN THE MANAGEMENT OF PERI-IMPLANTITIS: CURRENT PARADIGMS AND FUTURE DIRECTIONS

Y. Wang[1,§], Y.D. Lu[1,§], J. Kang[1], L.Y. Liu[2], X. Liu[2] and H.H. Liu[2,*]

[1]Department of Stomatology, Shanghai Huangpu District Dental Disease Prevention and Treatment Institute, 200020 Shanghai, China
[2]State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, 610041 Chengdu, Sichuan, China
[§]These authors contributed equally.

Abstract

As dental implant technology becomes increasingly widespread, peri-implantitis induced bone resorption and implant loss have garnered significant academic attention. Current clinical treatments for peri-implantitis primarily focus on plaque control, but the limitations of traditional therapies often hinder effective outcomes. Treatment strategies targeting immune responses that can eliminate inflammation, control osteolytic environments, and restore physiological bone formation are promising approaches. This article comprehensively reviews the role of the immune system in the pathogenesis and progression of peri-implantitis through a synthesis of multiple literature sources. It introduces current immunomodulatory strategies in the treatment of peri-implantitis and discusses the potential applications and challenges of novel immunotherapies, including gene therapy, cell engineering, and nanotechnology, in the management of peri-implantitis. The aim is to provide guidance for translating immunotherapies from the laboratory to clinical practice.

Keywords: Immunomodulation, peri-implantitis, inflammation, bone resorption, osteogenesis.

***Address for correspondence**: H.H. Liu, State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, 610041 Chengdu, Sichuan, China. Email: hanghangliu_hx@foxmail.com.

Introduction

In the comprehensive review conducted at the 2017 World Workshop which focused on the Classification of Periodontal and Peri-Implant Diseases and Conditions, experts collectively agreed on the characterization of peri-implantitis (PI). This condition is identified as a pathological state impacting the tissues surrounding dental implants. This is characterized by PI including inflammation and a progressive degradation of the bone tissue supporting the implant. This phenomenon is acknowledged as a major factor in the failure of dental implants [1]. The incidence of PI is relatively high, and due to varying diagnostic criteria, the reported prevalence of PI varies greatly in the literature. Krebs *et al*. [2] found that approximately 7.9 % of implants and 13.2 % of patients experienced PI within the period of 17 to 23 years following implantation, while another study has reported rates of 21 % and 34 %. While another study reported rates of 21 % and 34 % [3]. A comprehensive meta-analysis conducted in 2022 indicated that the incidence of PI is about 19 % [4]. These numbers are even higher in patients with periodontal dysfunction [5]. The main symptoms of PI include swelling of the peri-implant mucosa, bleeding gums, suppuration from peri-implant pockets, increased probing depth, and implant mobility. Severe cases can lead to extensive bone resorption and implant loss, affecting chewing function and overall health [6].

Currently, the mainstream view is that plaque accumulation on the implant surface is the initiating factor for PI. Therefore, clinical treatments for PI focus on plaque control, including mechanical debridement, antimicrobial therapy, and surgical intervention [7]. Mechanical debridement involves the use of manual scaling, ultrasonic cleaning, air polishing, and laser therapy to remove plaque and calculus from the implant surface. However, traditional instruments often find it difficult to reach the unique threaded structure of implants, making it challenging to remove deep-seated infections and toxins through mechanical debridement alone [8]. Consequently, for patients with peri-implant pockets deeper than 5 mm, thorough local de-

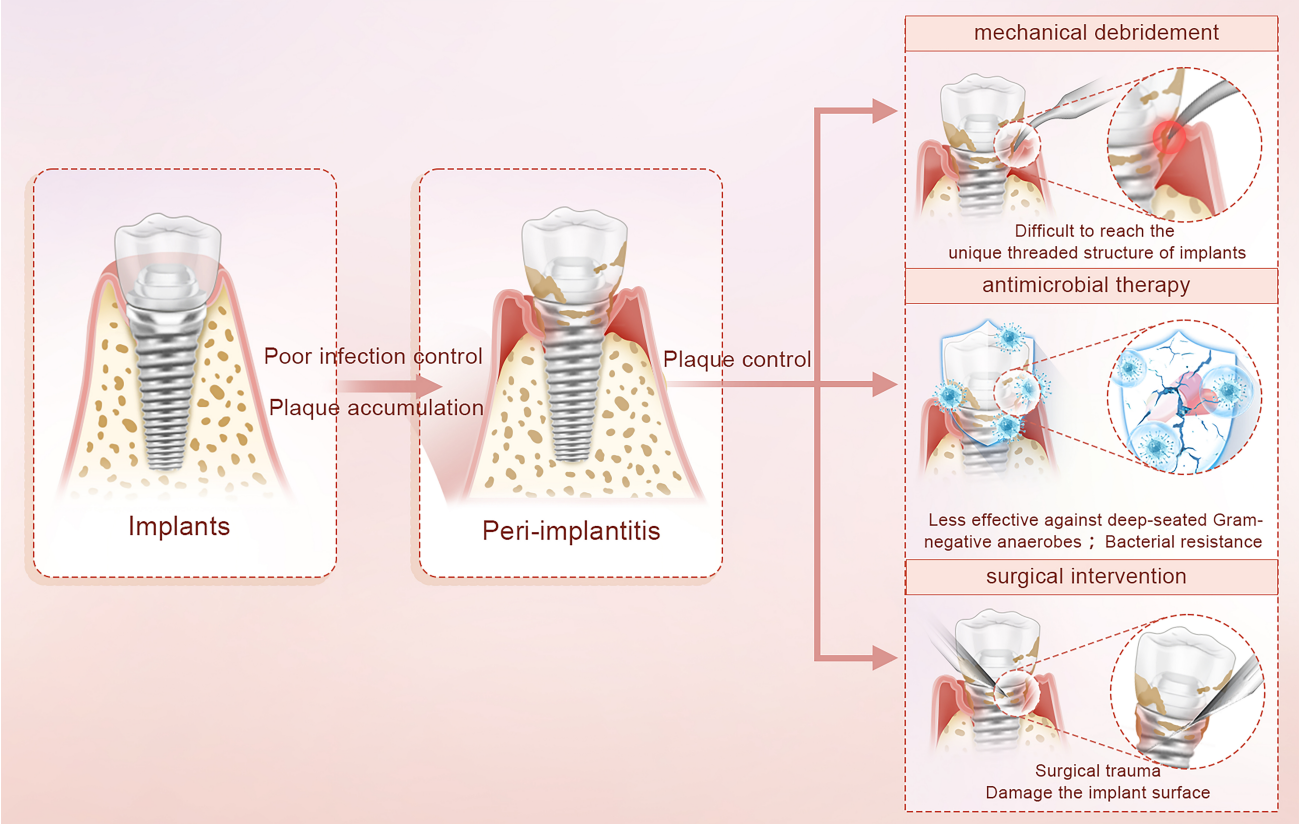

Fig. 1. PI's current treatment methods. Photoshop and Adobe Illustrator software were used for all images editing. PI, peri-implantitis.

bridement is often combined with local or systemic antimicrobial treatment. Commonly used antimicrobials include chlorhexidine, tetracycline, and metronidazole, but antimicrobial therapy is less effective against deep-seated Gram-negative anaerobes and can lead to bacterial resistance with prolonged use [9].

For severe PI with significant cup-shaped bone resorption, mechanical debridement and antimicrobial interventions may be ineffective, necessitating resective or regenerative surgical treatment options. Surgical approaches include flap surgery, debridement, resective surgery, and guided bone regeneration. Although flapless surgical access reduced surgical trauma, as reported by Carrillo de Albornoz *et al*. [10], surgical instruments can damage the implant surface, leading to re-accumulation of plaque and calculus, with a high recurrence rate postoperatively [11]. Surgical treatments may not entirely eliminate deep-seated infections or effectively control recurrences, especially in complex and severe PI cases. Furthermore, maintaining good oral hygiene and regular follow-ups require high patient compliance, which can affect treatment outcomes.

Currently, PI treatment methods are similar to those for periodontitis, and the limitations of traditional treatments, such as difficulty in removing deep-seated infections, significant trauma, high recurrence rates, and bacterial resistance, which significantly hinder effective treatment outcomes effective treatment outcomes. In recent findings, it has been observed that by manipulating the immune system's reaction to periodontal pathogens, it is possible to mitigate inflammation. This strategy also helps in managing the osteolytic conditions and facilitates the return of normal bone formation processes. Such advancements offer promising therapeutic avenues for the management of PI [12]. Research has demonstrated that the immune response is essential in both the initiation and progression of PI. By modulating the host's immune system, the inflammatory response associated with PI can be reduced, leading to an improved oral microenvironment and aiding in the healing of peri-implant tissues, particularly bone tissue [13]. Immunomodulatory therapy holds potential for PI treatment, offering a more durable and effective treatment option to better maintain oral health [14]. This article aims to review the application of immunotherapy strategies in PI, providing guidance for clinical practice and future research (Fig. 1).

Pathophysiology of PI

Role of the Immune System

PI is a multifactorial disease involving complex interactions between the immune system, microorganisms, and host-related factors [15]. After implantation, the implant acts as a foreign body, causing mesenchymal stem cells (MSCs) around it to differentiate into osteoblasts, leading to bone integration. Adequate bone volume and quality

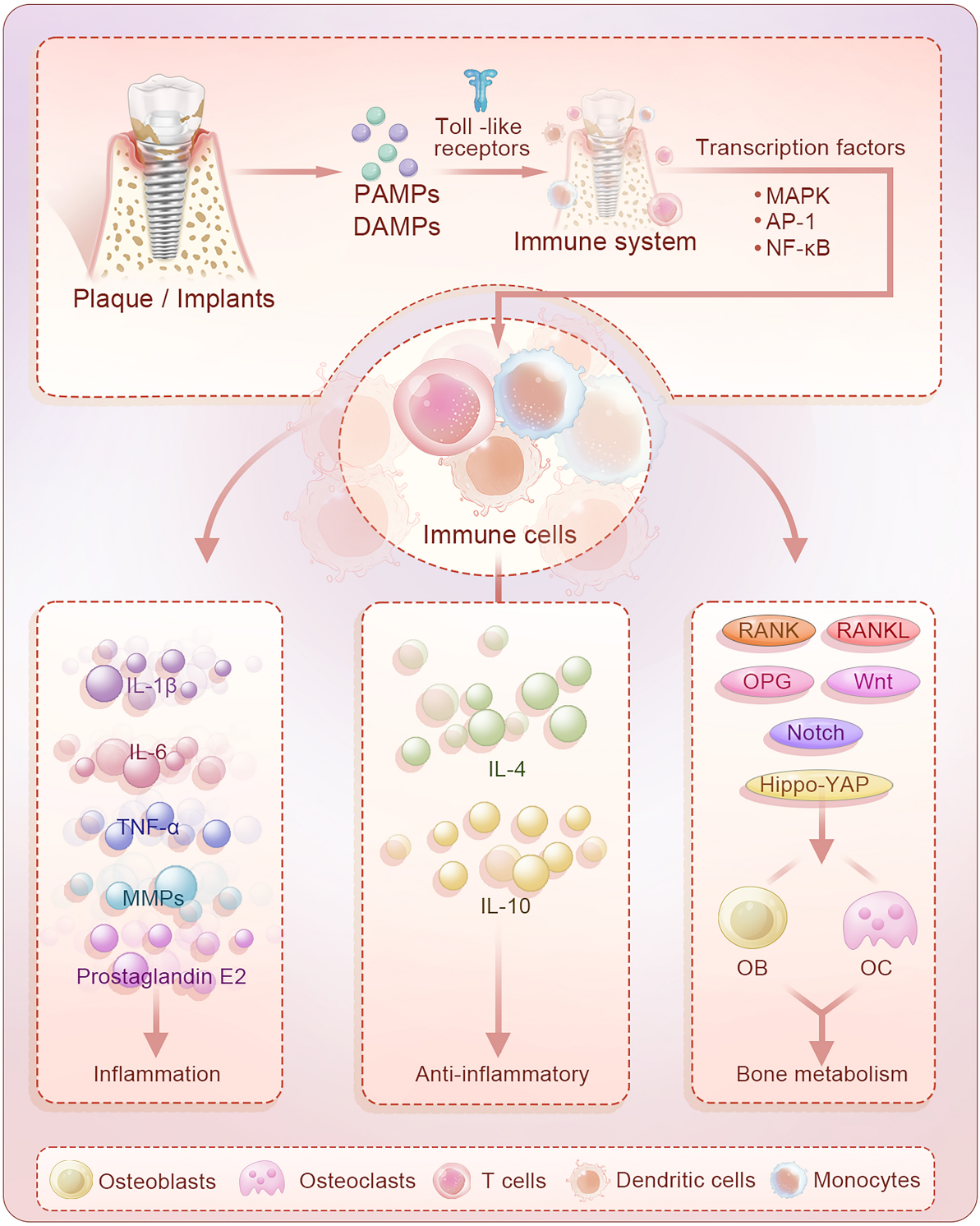

Fig. 2. The role of immune cells in PI. DAMPs, damage-associated molecular patterns; MAPK, mitogen-activated protein kinase; AP-1, activating protein-1; NF-κB, nuclear factor-kappa B; IL, interleukin; TNF, tumor necrosis factor; MMPs, matrix metalloproteinases; RANK, receptor activator of NF-κB; RANKL, receptor activator of NF-κB ligand; OPG, osteoprotegerin; OB, osteoblast; OC, osteoclast; PAMPs, pathogen-associated molecular patterns.

around the implant are crucial for ensuring initial stability and surgical success [16]. However, because implants are directly connected to the bone without a periodontal ligament, blood flow to the periosteum is reduced. This re-

sults in fewer nutrients and immune cells in the peri-implant tissues, making dental implants more susceptible to continuous bacterial infections [17]. When pathogenic bacteria invade peri-implant tissues, the immune balance is disrupted, triggering an immune response. An imbalance between osteoblasts and osteoclasts leads to bone resorption [18]. Understanding these factors is crucial for developing new treatment strategies for PI.

Immune Cell Involvement

The immune response is driven by interactions between immune cells, facilitated through direct contact and the release of cytokines and other mediators. When a dental implant is placed into the alveolar bone, the first thing that happens is the activation of our body's natural immune system. This is all about recognizing things from outside or stuff that comes from the host, which we call pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Toll-like receptors (TLRs) are like sensors that pick up on these patterns. When they do, it kicks off some important processes in our cells by activating key transcription factors like mitogen-activated protein kinase (MAPK), activating protein-1 (AP-1), and nuclear factor-kappa B (NF-κB).

The activation of these factors triggers a series of downstream kinase signaling events, which recruit immune cells to the site of infection or inflammation and promote the release of various inflammatory cytokines and immunomodulators. This results in the neutralization of harmful substances and the initiation of an inflammatory response. Simultaneously, this process is vital for activating the adaptive immune system through antigen presentation [19]. In managing PI, the immune system is essential for modulating the inflammatory response by controlling the production of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, prostaglandin E2, and matrix metalloproteinases (MMPs). Additionally, the immune system also regulates the secretion of anti-inflammatory cytokines like IL-4 and IL-10. Beyond cytokine regulation, the immune system exerts control over the expression of proteins and genes that are integral to bone resorption and destruction. This includes modulation of signaling pathways like receptor activator of NF-κB (RANK)/receptor activator of NF-κB ligand (RANKL)/osteoprotegerin (OPG), Wnt, Notch, and the Hippo-YAP pathway, which are crucial in maintaining bone health and preventing excessive bone loss [20–24] (Fig. 2).

Macrophages

Macrophages, along with neutrophils, are the first responders to infection, known for their ability to recognize, phagocytize, and clear pathogens. The immune system also facilitates antigen presentation to T cells, which is pivotal in triggering an adaptive immune response. This process involves the induction of co-stimulatory molecules on other antigen-presenting cells (APCs), thereby enhancing the activation of T cells [25]. In the context of macrophage activity, these cells can be classified into M1 and M2 phenotypes, distinguished by their functional roles. The state of these macrophages can dynamically change in response to the stimuli they encounter, allowing them to adapt their functions to the specific needs of the immune response. This flexibility is crucial for the effective management of various immune challenges.

M1 macrophages are pro-inflammatory, and their prolonged activation can lead to chronic inflammation, disrupting the balance of bone tissue. Excessive activation around implants can result in fibrosis and failure of osseointegration [26]. Research has shown a significant increase in the number and density of M1 macrophages in PI lesion tissues [27]. Their unique phagocytic function can cause alveolar bone loss in PI. Additionally, the secretion of pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8, IL-18, TNF-α, and reactive oxygen species (ROS), promotes the differentiation and maturation of osteoclasts, leading to increased bone resorption [28,29].

When the infection is brought under control and the body begins to transition toward repair, M1 macrophages can shift to M2 macrophages. These M2 macrophages possess anti-inflammatory properties and are linked to increased osteoblast activity during the bone healing process, aiding in bone reconstruction and maintaining homeostasis [30,31]. M2-type macrophages play a key role in our immune response by releasing anti-inflammatory substances like IL-4 and IL-10. These substances are super important for helping osteoprogenitor cells and mesenchymal stem cells (MSCs) grow and mineralize, which ultimately boosts bone formation. Plus, M2 macrophages also ramp up the production of vital markers for bone growth, such as bone morphogenetic protein (BMP)-2, alkaline phosphatase (ALP) and OPG. This upregulation is vital for facilitating tissue healing and promoting osteogenic differentiation, which are critical for the restoration and maintenance of bone health [32,33]. In addition to their anti-inflammatory functions, M2 macrophages also contribute to bone health by secreting pro-osteogenic factors. Oncostatin M (OSM) is one such factor that is particularly effective in promoting the differentiation and mineralization of osteoblasts. This process is essential for bone regeneration and repair, primarily facilitated by the activation of the signal transducer and activator of transcription (STAT)3 signaling pathway. The engagement of this pathway by OSM and other factors secreted by M2 macrophages significantly orchestrates the complex biological processes that drive bone remodeling and restoration [34,35]. Regulating macrophage polarization is crucial in treating bone-related diseases like osteoporosis and fracture healing, and is closely linked to the treatment of PI (Fig. 3).

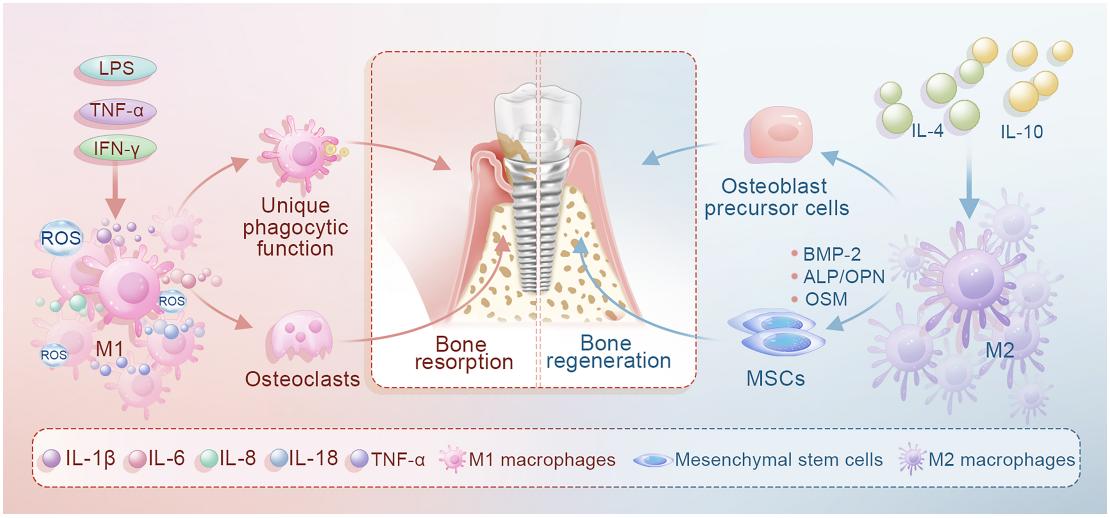

Fig. 3. Macrophages and bone metabolism. ROS, reactive oxygen species; BMP, bone morphogenetic protein; ALP, alkaline phosphatase; OPN, osteopontin; OSM, oncostatin M; MSCs, mesenchymal stem cells; IFN, interferon; LPS, lipopolysaccharides.

T Cell

T lymphocytes mediate cellular immunity and are the most predominant immune cells in the peri-implant mucosa, accounting for approximately 57.6 ± 11.2 % [36]. Among the various subsets of T cells, CD4+ T cells, also known as helper T (Th) cells, have a particularly significant role in the context of PI [37]. Th cells are vital to almost every aspect of the adaptive immune response. These cells can modulate the functions of B cells and CD8+ T cells by interacting with foreign antigens presented by APCs. Additionally, CD4+ T cells can stimulate natural killer (NK) cells and macrophages, thereby enhancing their activity. This multifaceted role of Th cells in immune regulation is crucial for orchestrating an effective immune response against pathogens and maintaining immune homeostasis [38–40].

Th cells differentiate into various effector subsets, including Th1, Th2, Th17, and regulatory T (Treg) cells [41]. Treg cells may act as a compensatory mechanism in PI, reducing tissue damage caused by excessive immune responses [42]. Research findings suggest a dynamic shift in the balance of T cell subsets as PI evolves. Specifically, there is an observed increase in the prevalence of Th1 and Th17 cells, which are typically associated with pro-inflammatory responses. Concurrently, there is a noted reduction in the proportion of Th2 cells, which are more commonly linked to anti-inflammatory and regulatory functions. Additionally, the study of Treg cells—known for their regulatory role in maintaining immune tolerance—shows an initial increase in their presence within lymph nodes. However, this increase is followed by a subsequent decrease over time. These changes in T cell subset proportions are indicative of the complex interplay between different immune responses during the progression of PI, highlighting the need for a nuanced understanding of immune dynamics in the context of implant-related diseases. Research shows that level of IL-17 is significantly lower in healthy peri-implant tissues compared to PI patients [43]. Changes in these levels, along with RANKL and Notch 1 expression, may jointly lead to increased osteoclast activity and bone resorption in PI [21].

In the PI healing phase, Th2 lymphocytes emit cytokines IL-4 and IL-13, which are crucial for the induction of M2 macrophage polarization. This polarization is essential for the resolution of inflammation and the progression of tissue repair [44]. These cytokines inhibit the activation of NF-κB and mitogen-activated protein kinase (MAPK) through the STAT6 signaling pathway, increasing OPG secretion by osteoblasts. This blocks the interaction between RANKL and RANK, inhibiting osteoclast formation and differentiation [45]. Th2 cells also regulate bone metabolism balance through interactions with other immune cells such as type 2 innate lymphoid cells (ILC2s) [46]. Th17 cells contribute to PI by secreting IL-17. Elevated levels of IL-17 inhibit autophagy in osteoblasts and promote their differentiation, calcification, and RANKL expression via the Janus kinase-2/STAT3 signaling pathway [47]. Another study indicates that IL-17 can activate the protein kinase B (AKT), STAT3, and extracellular signal-regulated kinase 1/2 (ERK1/2) pathways in an IL-6/IL-1β-dependent manner, promoting osteoblast differentiation [48]. In summary, T cell differentiation and the secretion of related cytokines play crucial roles in regulating PI inflammation and bone homeostasis and serve as potential targets for PI immunomodulation.

Others

In addition, Langerhans cells, neutrophils, NK cells, and B cells are also present in PI tissues [36]. Their relationship with PI is summarized in Table 1 (Ref. [49–61]).

Table 1. Relationship of other immune cells to PI.

Immune cell	Function	Association with PI	Reference
Dendritic cells (Langerhans cells)	APCs	In PI, the number of Langerhans cells is significantly reduced. Excess titanium ions can lead to the incomplete development of Langerhans cells, causing immune dysregulation. They are directly involved in inducing osteoclast formation and bone loss. As osteoclast precursors, they can further develop into dendritic cell-derived osteoclasts under inflammatory conditions.	[49,50]
Neutrophils	Phagocytosis, secretion of various cytokines, and chemotactic factors to recruit and activate other immune cells	Neutrophils have a high detection rate in PI. They dominate the tissues around PI compared to periodontitis, and their cell size is significantly larger. Neutrophils release extracellular traps and ROS, increasing osteoclast formation through RANKL signaling, which leads to osteoblast apoptosis.	[51–55]
NK cells	Recognize and kill target cells	A higher proportion of activated NK cells is detecte in PI. They secrete cytokines such as TNF-α and interferon (IFN)-γ, regulate osteoblast apoptosis, and promote osteoclast formation.	[56–58]
B cells	Antigen presentation and antibody production	B cells may be involved in the chronic inflammatory process of PI. They express RANKL and transforming growth factor (TGF)-β to regulate bone homeostasis.	[59–61]

PI, peri-implantitis; APCs, antigen-presenting cells; ROS, reactive oxygen species; RANKL, receptor activator of NF-κB ligand; NK, natural killer; TNF, tumor necrosis factor.

Microbial Factors

Similar to periodontitis, the current mainstream view is that the initiating factor of PI is the plaque biofilm. In the early stages of implant placement, bacteria (mainly Gram-positive cocci and rods) adhere to the implant surface through nonspecific forces such as electrostatic interactions, forming an initial layer. Over time, this biofilm evolves into a more complex microbial community. The predominant bacteria around PI lesions are obligate anaerobic Gram-negative bacteria. In the context of PI, a variety of bacterial species are frequently implicated. These include asaccharolytic anaerobic Gram-positive rods and other Gram-positive bacteria. Species such as Porphyromonas gingivalis (Pg), Prevotella intermedia (Pi), Fusobacterium nucleatum (Fn), and Aggregatibacter actinomycetemcomitans (Aa), alongside Tannerella forsythia and Treponema denticola, are frequently identified strains within the oral microbiome. Additionally, various strains of Fn are also commonly recognized in this context. Additionally, rarer opportunistic pathogens, such as enterobacteria and Staphylococcus aureus (Sa), are also sometimes reported in association with PI. These diverse microbial agents contribute to the complex etiology of PI, underscoring the importance of a comprehensive approach to diagnosis and treatment [62]. The presence of Pg, Pi, Fn, and Aa is significantly associated with peri-implant disease conditions [63–66]. Moreover, the presence of Sa makes the peri-implant tissues more prone to severe purulent inflammation [67] (Table 2, Ref. [68–78]).

Host Factors

PI often tends to recur in individuals, meaning that a patient who has previously experienced PI is likely to have it again under similar risk factors. However, in some cases, exogenous factors alone cannot fully explain the occurrence of PI, and genetic susceptibility is also considered a risk factor for PI [79]. From the late 20th century onwards, research has extensively explored the link between single nucleotide polymorphisms (SNPs) and PI. This scholarly focus has been on delineating the impact of inflammatory cytokines within the realms of immune modulation, inflammatory reactions, and skeletal metabolism. Key molecules of interest include IL-1, IL-6, IL-10, IL-17, MMPs, and TNF-α. Genetic polymorphisms in these cytokines are hypothesized to modulate an individual's predisposition to periodontal inflammation PI and their therapeutic responsiveness [80–84]. Additionally, research has reported on the relationship between PI and polymorphisms in genes related to the RANK/RANKL/OPG signaling pathway, Fcγ receptor, epidermal growth factor (EGF), and CD14 [85–88]. Interestingly, some studies have produced conflicting conclusions about the association between the same susceptibility gene loci (e.g., TNFα-308 A/G) and PI, which may be due to differences in sample origin, sample size, and the con-

Table 2. Interaction between pathogens and host immune response.

Pathogens	Immunomodulatory effects	Effect on PI	Reference
Pg	Gingipains allow Pg to invade gingival epithelial cells and evade immune clearance; activates macrophages to an M1 phenotype, increasing lysosome and ROS production; induces apoptosis in CD4+ T cells; releases pro-inflammatory cytokines IL-1, IL-6, IL-17, and TNF-α; downregulates Treg-related transcription factors, inhibiting anti-inflammatory cytokines TGF-β and IL-10; disrupts host immune defense by exploiting the complement system	Triggers host immune inflammatory response; promotes osteoclast differentiation through RANKL, increasing osteoclast precursor numbers and activity, leading to bone tissue destruction around implants	[68–71]
Pi	Stimulates immune cells to secrete inflammatory mediators and MMPs	Triggers host immune inflammatory response; disrupts the OPG/RANKL/RANK pathway, causing bone resorption and destruction around implants	[72]
Fn and Aa	Induces M1 macrophage transformation; upregulates NLRP3 inflammasome and various pro-inflammatory cytokines including IL-1β and TNF-α; generates ROS; Fn damages neutrophils, lymphocytes, and macrophages	Triggers host immune inflammatory response; Fn inhibits osteogenic differentiation by reducing ALP activity, mineralized nodule formation, and the expression of osteogenic genes and proteins	[73–76]
Sa	Invades host cells and can penetrate bone trabeculae to evade immune detection; induces IL-1, IL-2, IL-6, and TNF-α secretion via NF-κB signaling; regulates T cell proliferation, differentiation, and apoptosis through the MAPK pathway	Initiates an inflammatory response; causes secondary bone degradation by inducing osteoblast apoptosis through TNF-related apoptosis-inducing ligand	[77,78]

Pg, Porphyromonas gingivalis; Pi, Prevotella intermedia; Fn, Fusobacterium nucleatum; Aa, Aggregatibacter actinomycetemcomitans; Sa, Staphylococcus aureus; MMPs, matrix metalloproteinases; NLRP3, receptor thermal protein domain associated protein 3; IL, interleukin; NF-κB, nuclear factor-kappa B; MAPK, mitogen-activated protein kinase; OPG, osteoprotegerin; RANK, receptor activator of NF-κB; ALP, alkaline phosphatase.

trol of specific stimulus factors [82,83]. Consequently, it is imperative to conduct extensive research to ascertain the correlation between PI and a spectrum of genetic propensities.

Beyond genetic variations, smoking is a significant factor influencing the immune system. It impairs neutrophil activity, diminishes the body's defense mechanisms, and disrupts the inflammatory response. Research indicates that individuals with PI who smoke exhibit elevated levels of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, MMP-1, and TNF-α, in their gingival crevicular fluid, surpassing those found in non-smokers [89,90]. Additionally, there is evidence that smoking may have a detrimental impact on the bone tissue surrounding dental implants and can intensify PI by influencing osteoblast activity and the synthesis of bone matrix proteins [91]. While the relationships between PI and autoimmune diseases [92], diabetes [6,93–95], and occlusion [96–98] have also been reported, there is currently no definitive scientific evidence, and further research with larger patient cohorts is needed in the future.

In summary, the interaction between PI and the immune system can be described as follows: During the early innate immune phase of PI, there is an increase in complement, macrophages, and neutrophils in the peri-implant tissues, with a predominance of M1 macrophages. These cells produce pro-inflammatory mediators such as IL-1β, which not only facilitate the formation of multinucleated giant cells to encapsulate and clear particulates but also influence the recruitment of other inflammatory cells in the microenvironment. Additionally, a reduction in macrophage-derived Wnt ligands decreases the recruitment of MSCs and CD4+ T cells, thereby impacting the early immune and osteogenic response around the implant [99]. Simultaneously, the implant surface is recognized by the complement

system, and the combined effect of complement proteins with IL-1β from M1 macrophages and C3a and C5a from neutrophils induces the release of IL-6 and IL-8. This upregulates the expression of RANKL/OPG through NF-κB receptor activation, regulating the osteoimmune response in the pro-inflammatory environment and promoting osteoclast development and bone remodeling [100]. With the attachment of microbial biofilm, immature dendritic cells capture microorganisms and their antigens, while mature dendritic cells stimulate T cells to respond to these captured antigens, initiating the adaptive immune response [101].

In the adaptive immune phase, when cells encounter antigens, intracellular pathogens may activate a Th1 cell-mediated immune response dominated by T lymphocytes, macrophages, and natural killer cells. In contrast, extracellular pathogens may activate a Th2 humoral immune response, primarily involving plasma cells [36]. Furthermore, when dendritic cells stimulate T cell proliferation, they also activate CD4+ T cells to express RANKL. RANKL then mediates further T cell proliferation, increasing T and B cell survival. Through the combined effects of Th cells and Treg cells, monocytes differentiate into regulatory dendritic cells, forming a positive feedback loop that enhances Treg-mediated immunoregulation. The overexpression of RANKL also increases the RANKL/OPG ratio, enabling RANKL to interact with NF-κB receptors on osteoclast precursors, promoting osteoclast maturation, differentiation, and bone resorption. The persistent elevation of Th1 and Th17 cells and a decline in Treg cells may cause bone resorption in PI [102]. In addition to IL-6 and IL-8, which are both involved in bone resorption and irritation, Th17 tissue can trigger neutrophils and macrophages [43].

The development of PI, where TLR is crucially involved in B cell-mediated inflammatory responses, is also affected by the relationship between the B and T cells. In PI, bone resorption and inflammation are promoted by research that has shown that TLR4 can upregulate the RANKL/OPG ratio and TNF expression [61]. By combining Th17/Treg cells, regulation of B cells, especially B10 cells, produces IL-10 to encourage Treg cell identification and stop native Th17 cell growth. PI-inflammatory damage is reduced by lowering IL-17 and RANKL expression [103].

Current Immunomodulatory Strategies

Currently, the main clinical immunotherapy methods for PI involve the local or systemic administration of various anti-inflammatory drugs, immunomodulators, and biological agents to help balance inflammation and immune response.

Non-Specific Immunomodulation

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs, such as ibuprofen, aspirin, and naproxen sodium, work by inhibiting cyclooxygenase, which reduces the synthesis of prostaglandins. Prostaglandins are important inflammatory mediators in PI that can stimulate osteoclasts and lead to bone resorption. NSAIDs are mainly used to treat pain and discomfort during the acute inflammatory phase of PI. Study has shown that short-term low-dose ibuprofen treatment can continuously improve the gingival condition in PI patients [104]. Short-term systemic administration of ibuprofen after implant placement can aid early wound healing without affecting marginal bone loss around the implant [105]. Naproxen sodium can significantly reduce plasma IL-6 levels six hours after implant surgery [106].

Corticosteroids

Corticosteroids, such as prednisone and dexamethasone, reduce cell-mediated immune responses by decreasing the production of prostaglandins and leukotrienes. They inhibit the expression of IL-1, IL-6, and TNF-α, and reduce T cell proliferation. Additionally, corticosteroids lower the humoral response by reducing B cell counts and antibody production, making them widely applicable due to their strong anti-inflammatory and immunosuppressive effects [107]. In the treatment of PI, corticosteroids are often used locally, such as through oral sprays, ointments, or local injections. Research has shown that covering the implant surface with dexamethasone can significantly increase the OPG/RANKL ratio and stimulate osteoblast differentiation [108].

Cytokine Inhibitors

Although the mechanisms of bone resorption in PI are complex, the activation of pro-inflammatory cytokines is a key component of the PI cascade. Cytokine inhibitors work by blocking the binding of cytokines to their receptors on target cells, thus inhibiting inflammatory signaling pathways and reducing inflammation. Therefore, cytokine inhibitors targeting pro-inflammatory cytokines can help mitigate bone loss caused by inflammation [109]. Study has shown that rats treated with TNF-α inhibitors experience milder inflammatory responses, fewer osteoclasts, and lower levels of TNF-α, RANKL, and OPG during wound healing, indicating that TNF-α inhibitors not only reduce inflammation but may also enhance bone repair in the jaw [110]. Kim *et al.* [111] reported similar findings. IL-1 receptor-associated kinase 4 inhibitors can block M1 macrophage activation and disrupt osteoclast formation, thereby promoting osteoblast differentiation and improving osseointegration [112].

Others

In addition to the drugs mentioned above, non-specific immunomodulators like resolvins, melatonin, and certain biological extracts have shown promising potential for treating PI (Table 3, Ref. [113–118]).

Table 3. Non-specific immunomodulators in PI treatment.

Immunomodulators	Immunomodulatory effects	Effect on PI	Reference
Resolvin	Reduces the number of neutrophils in tissues; reduces bone loss mediated by Th1 adaptive immune response; decreases IFN-γ expression	Anti-inflammatory; protects osteoblasts from damage by inflammatory mediators, reduces bone loss; promotes proliferation and differentiation of osteoblasts, aids in the repair and regeneration of bone tissue; decreases RANKL expression, inhibits osteoclastogenesis and activity, promotes bone matrix formation.	[113]
Melatonin	Decreases TLR4 protein levels, inhibits NF-κB signaling pathway to downregulate TNF, IL-1β, and IL-6 expression levels	Reduces inflammatory response, mitigates bone resorption, inhibits osteoclasts while promoting the differentiation and function of osteoblasts	[114]
Mangiferin	Inhibits IL-6 and TLR2 signaling	Reduces bone loss, alleviates inflammatory infiltration, has a protective effect on bone tissue	[115]
Icariin	Reduces TNF-α and IL-1β expression; promotes the differentiation and maturation of osteoblasts	Reduces inflammatory response and promotes the proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs), facilitates new bone formation	[116]
Curcumin	Inhibits the overexpression of M1 macrophages, induces M2 macrophage differentiation,and promotes osteogenic differentiation	Reduces inflammatory response and promotes the osteogenic differentiation of BMSCs; curcumin-modified surfaces can increase BMSCs migration capacity, improve osteocyte adhesion and proliferation, enhance bone regeneration ability	[117]
Asperuloside	Reduces inflammatory cell infiltration around implants; acts on NF-κB and ERK1/2 signaling pathways to inhibit osteoclastogenesis	Inhibits PI inflammation and reduces RANKL-induced osteoclast differentiation, decreases the number and size of osteoclasts, and inhibits the formation of F-actin rings and bone resorption function; downregulates nuclear factor-activated T cell 1 (NFATc1) and *c-Fos* gene and protein expression, directly inhibits osteoclastogenesis and function	[118]

IFN, interferon; TLR, Toll-like receptor; ERK1/2, extracellular signal-regulated kinase 1/2; Th, helper T.

Specific Immunomodulation

Immune Checkpoint Inhibitors

Immune checkpoints are regulatory proteins on immune cells designed to mitigate the harm from excessive T cell activity, thereby preventing inflammatory damage. Pivotal among these are cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), and its ligand (PD-L1), which are instrumental in modulating immune responses. While PD-1/PD-L1 blocking agents do not directly intervene in bone formation processes, they are capable of indirectly preserving bone integrity. This is achieved by inhibiting the differentiation of osteoclasts via the suppression of the STAT3/nuclear factor-activated T cell 1 (NFATc1) signaling pathways, thereby potentially offering a protective effect against bone loss in certain conditions [119]. Another study found that PD-1/PD-L1 inhibitors significantly reduce the expression of IL-1β, IL-6, and TNF-α. They also maintain effective immune clearance and reduce the release of inflammatory factors by increasing IL-10 expression and reducing macrophage apoptosis [120]. Additionally, in the immune response to PI, the overexpression of CTLA-4 can induce the release of anti-inflammatory cytokines, thereby reducing the proliferation of Th and cytotoxic T cells, inhibiting neutrophils, and promoting the transformation of macrophages to the M1 type. CTLA-4 inhibitors can inhibit this inflammatory response [121]. Currently, research on the application of immune checkpoint inhibitors in PI treatment is still in its early stages, and their exact mechanisms and efficacy require further investigation.

Targeted Monoclonal Antibodies

In recent years, researchers have developed monoclonal antibodies targeting toxins produced by Sa, Streptococcus pyogenes, Clostridium difficile, and Escherichia coli. For antibiotic-resistant bacteria, these antitoxin monoclonal antibodies can significantly improve the success rates of antibiotic treatments when used as adjunct therapy [122]. A human monoclonal antibody, TRL1068, which targets biofilm anchoring proteins, has demonstrated high affinity for Sa biofilms and can disrupt their three-dimensional structure, reducing bacterial aggregation [123]. While targeted monoclonal antibodies represent a promising systemic treatment strategy for implant infections, their direct application in treating PI remains limited.

Vaccine

Pg and Pi are the main pathogens associated with periodontitis. Studies have found that an arginine-gingipain A gene vaccine from Pg produces immunoglobulin (Ig)G and sIgA antibodies, effectively reducing bone loss in a canine PI model [124]. A capsule-conjugate vaccine based on Pg has also been shown to protect mice from Pg-induced oral bone loss [125]. Using a structural biology approach, Yadalam *et al*. [126] designed an immunoinformatic vaccine targeting Pg for PI, which reduces the occurrence of PI by stably interacting with the TLR2 immune receptor. Additionally, a CCL19-conjugated cleaved adhesin DNA vaccine shows promise as an innovative targeted immunotherapy strategy against Pg-induced PI [127].

Adjunctive Therapies

Probiotics and Prebiotics

The Food and Agriculture Organization of the United Nations (FAO) characterizes probiotics as "live microorganisms which, when administered in adequate amounts, confer a health advantage to the host" [128]. Such advantageous bacteria contribute to the handling of PI by competing with detrimental microbes for adhesion points, regulating the immune reaction, and generating substances with antibacterial properties. This multifaceted approach helps maintain oral health and potentially enhances the success of dental implants [129]. *In vitro* study has shown that probiotics like Lactobacillus reuteri can inhibit Pg, Pi, Streptococcus salivarius and Sa [130]. A triple-blind randomized clinical trial demonstrated that adjunctive probiotic therapy can significantly improve PI symptoms for at least 90 days [131]. Additionally, research indicates that probiotics can suppress inflammation by regulating gut microbiota, reflected in reduced serum inflammatory cytokine levels and balanced distributions of CD4, IL-17A, Th17 cells and CD4, CD25, Foxp3 Treg cells. Probiotics can significantly inhibit inflammatory alveolar bone resorption by regulating bone immune responses [132]. Their beneficial effects on the skeletal system may be closely linked to the RANKL/RANK/OPG pathway [133]. Other study has shown that probiotics promote the expression of Tfam in osteoblasts by mitigating the Tlr4-miRNA-138-H3K27me3 epigenetic cascade [134].

Prebiotics, in contrast to probiotics, are organic compounds—often non-starch polysaccharides or oligosaccharides—that the host cannot digest or absorb. They selectively foster the proliferation and activity of beneficial bacteria within the body, enhancing overall health. Unlike probiotics, which consist of live microorganisms, prebiotics do not contain such organisms. This distinction makes their effects more consistent and enduring, and potentially safer for individuals with weakened immune systems. Their primary health benefit is the enhancement of immune function through the stimulation of beneficial bacteria growth [135]. Study has shown that prebiotics can improve bone mineral density, bone mineral content, and bone biomechanical properties [136]. Supplementing with prebiotics positively affects bone mineral metabolism, and specific amounts or types of prebiotics can improve bone density and control bone resorption [137].

Nutraceuticals

Nutraceuticals are products that provide health benefits beyond their nutritional value, often used both as nutritional supplements and medicinal remedies. They have been proven effective as adjunct treatments for various inflammatory diseases. Studies indicate that nutraceuticals can significantly reduce clinical discomfort and the release of inflammatory mediators after root planning [138]. McCarty and colleagues [139] conducted an extensive review of the literature, identifying that a variety of nutraceuticals exert protective effects on bone health through distinct mechanisms. These include getting sirtuin 1 going, activating the adenosine 5'-monophosphate-activated protein kinase, firing up the nuclear factor-erythroid 2-related factor 2 (Nrf2) transcription factor, and boosting soluble guanylate cyclase. Also, some natural supplements like apigenin, curcumin, and resveratrol have been shown to boost the levels of runt-related transcription factor 2 (Runx2), small mother against decapentaplegic (Smad)5, collagen type I (COLL1), COLL4, and COLL5. This helps in healing big bone defects in the skulls of rats [140]. Genistein and lycopene, recognized as nutraceuticals, are capable of promoting bone formation and inhibiting bone resorption via distinct molecular pathways. They exert their effects through mechanisms like the Wnt/β-catenin and Nrf-2 signaling pathways, thereby playing a role in bone health [141]. These findings suggest that nutraceuticals have potential as adjunct treatments for PI.

Emerging Immunomodulatory Therapies

The immune system is a very well-regulated and steady system that maintains a particular degree of stability even though regular treatment techniques are now being

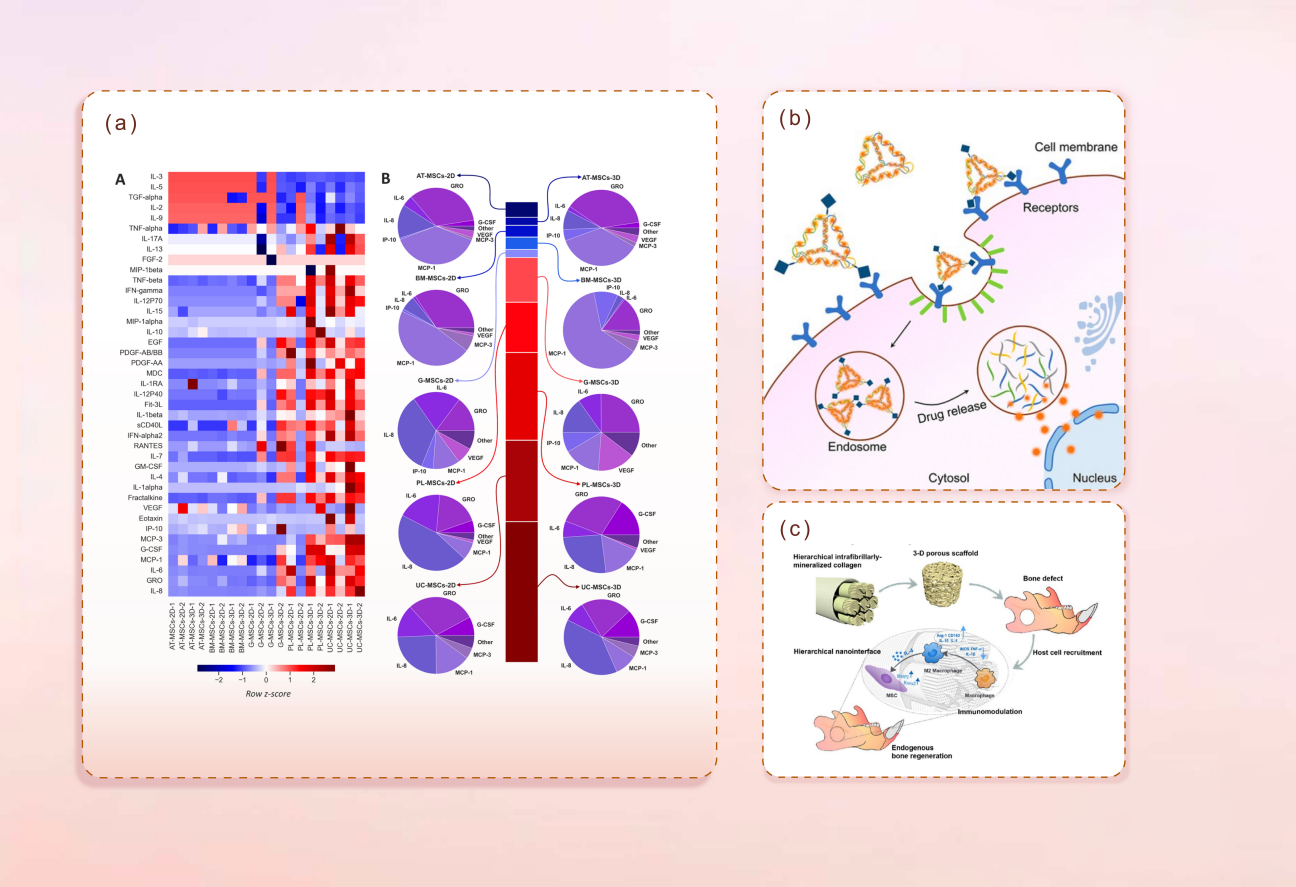

Fig. 4. Recent advances in immunotherapy. (a) Cytokine profiles of AT-MSCs-CM, BM-MSCs-CM, G-MSCs-CM, PL-MSCs-CM, and UC-MSCs-CM from 2D and 3D cultures. (A) Heatmap of 41 cytokines in CM from five sources scaled to row z-score; (B) stacked bar chart showing the ratio between the volumes of secretomes of different CM and corresponding pie charts with cytokine profile structure [178] Copyright ©2023, The Author(s). (b) DNA nanotechnology-enabled drug delivery systems [249] Copyright ©2019, American Chemical Society. (c) Potential molecular mechanism of how M2 macrophage polarization activated by a biomimetic hierarchical nanointerface contributes to endogenous bone regeneration [235] Copyright ©2019, American Chemical Society. TGF, transforming growth factor; IFN, interferon; EGF, epidermal growth factor; 2D, two dimensional; 3D, three dimensional; FGF, fibroblast growth factor; MIP, macrophage inflammatory protein; PDGF, platelet-derived growth factor; MDC, macrophage-derived chemokine; RANTES, regulated on activation normal T cell expressed and secreted; GM-CSF, granulocyte-macrophage colony-stimulating factor; sCD40L, soluble CD40 ligand; VEGF, vascular endothelial growth factor; MCP, monocyte chemoattractant protein; G-CSF, granulocyte colony-stimulating factor; GRO, growth-related oncogene; IP-10, interferon-γ inducible protein-10.

used quite frequently in medical settings. Traditional treatments have anti-inflammatory effects, but they also have the potential to exaggerate the host immune response, causing pro-inflammatory cells to multiply and cause adverse reactions [142]. However, long-term use of non-steroidal NSAIDs may increase the risk of PI, possibly as a result of their inhibitory effects on platelet and bone formation [143]. Additionally, high glucocorticoid concentrations and prolonged use may have an impact on how well cells and tissues function, leading to dental tissue damage, infection risk, and impaired immune function [143,144]. Furthermore, long-term cytokine inhibitor recipients have reported severe infections and lost peri-implant bone tissue [145]. The prevalence of these thoughts in cancer therapy ranges from 54 to 76 % despite the unusual cases of immune checkpoint antagonists in PI treatment. The timing, severity, and affected organs are frequently uncertain due to serious reactions that could cause life-threatening events [146]. There are now uncountable numbers of specific bioproducts, targeted stereo antibodies, vaccines, nutraceuticals, bacteria, and germs that are used as adjunctive therapies for PI. The primary objective of the current research is to increase immunotherapy's performance while reducing expected part effects. With the development of technology, learning PI women's DNA to create more specific treatment plans has become a hot topic of study. Additionally, stem cells, with their unique abilities for self-renewal and multi-lineage differentiation, are considered a powerful tool for the repair of PI-affected tissues. Nanomaterials, due to their unique physical and chemical properties, can target specific im-

mune cells and modulate inflammatory and regenerative processes, presenting limitless potential in the application of immunotherapy for PI [147].

Gene Therapy

Mechanisms and Potential Applications

Gene therapy, an emerging immunotherapy method, aims to repair or replace disease-causing genes. It works through three main mechanisms: (1) Replacement: Replacing the faulty gene with a normal one to achieve stable, controllable, and targeted expression, thereby protecting and repairing damaged tissues; (2) Silencing: Silencing the expression of malfunctioning genes; (3) Insertion: Introducing a new or modified gene [148]. Gene therapy can use gene delivery, gene editing, and gene regulation methods to reduce local inflammation around implants, inhibit bone resorption, and promote new bone formation, thereby alleviating PI symptoms and offering a novel treatment approach [149,150]. Zhang and colleagues [151] utilized bioinformatics to scrutinize publicly accessible data, pinpointing IL-6, TLR4, Fibronectin, IL-1β, IL-8, MMP-9, and macrophage-derived osteopontin as promising candidates for gene therapy interventions in the context of PI. This approach suggests a targeted strategy for managing PI by modulating these key genetic factors.

Current Research and Clinical Trials

Gene Delivery. At present, viral vectors are the predominant choice for gene delivery in the treatment of PI. Researchers, such as Hou and colleagues [152], have leveraged adenoviral vectors to specifically target the *A20* gene. Through inducing *A20* knockdown and overexpression in mice, they have shown that *A20* can suppress bone resorption and prevent the polarization of M1 macrophages mediated by nucleotide-binding oligomer-zation domain (NOD) like receptor thermal protein domain associated protein 3 (NLRP3). This approach highlights the potential of gene therapy in modulating the immune response and bone metabolism in PI. Adenoviral vectors containing semaphorin 3A (Sema3A) have been shown to have positive effects on early bone integration [153]. In diabetic PI, reduced expression of macrophage Alk B homologue 5 (ALKBH5) is associated with abnormal cell polarization and inhibited osteoblast differentiation. Weng *et al*. [154] achieved ALKBH5 overexpression through a lentiviral vector and demonstrated that it can enhance osteoblast differentiation and reduce inflammation in PI patients. Another lentiviral vector based on autophagy protein Beclin1 has also been shown to reverse cell apoptosis caused by high levels of IL-17A [155]. These results indicate that gene delivery has broad application prospects in PI treatment.

Gene Editing. The Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and CRISPR-associated protein 9 (Cas9) technology is a highly efficient and precise gene editing tool. Its core components are the CRISPR sequence and the Cas9 protein. The CRISPR sequence, derived from the immune system of bacteria and archaea, can recognize and record the sequence information of exogenous genomes, while the Cas9 protein has the ability to cut DNA. In the fascinating field of gene editing, a single-guide RNA that is complementary to the target DNA sequence is carefully synthesized. This RNA then forms a complex with the Cas9 protein. Together, this complex has the remarkable ability to recognize and bind to specific sites within the target gene, allowing for exciting possibilities such as gene knockout, insertion, or replacement [156,157]. Currently, CRISPR/Cas9 technology is used for the treatment of various diseases. Ponta *et al*. [158] used CRISPR/Cas9 technology to knock out the NF-κB *p65* gene in target cells, demonstrating resistance to the pro-inflammatory environment when co-cultured with IL-1β. Farhang *et al*. [159] demonstrated the feasibility of CRISPR/Cas9 technology in inhibiting the expression of inflammatory cytokines TNF-α and IL-1β. Kinane *et al*. [150], after reviewing numerous studies, suggested that using CRISPR to replace genetic haplotypes that cause IL-8 response deficiencies to reduce inflammation or to modify the epigenome, particularly by reducing TLR2-associated DNA methylation to improve receptor function in biofilm-related innate immune responses, is a feasible strategy for PI treatment.

Gene Regulation. MicroRNA (miRNA) is a small non-coding RNA. Dysregulated expression of miRNAs around PI is considered a biological marker for early diagnosis compared to successfully implanted patients [160]. Additionally, miRNAs can pair with complementary messenger RNA in different animal branches to regulate gene expression post-transcriptionally. An experiment in a canine PI model showed that miR-27a can positively regulate osteogenesis and angiogenesis by inhibiting TNF-α, promoting new bone formation and bone integration *in vivo* [161]. Another study demonstrated that anti-inflammatory miR-146a can inhibit RANKL-mediated PI bone resorption by regulating TLR2/4 signaling and inhibiting TNF-α expression [162]. Moreover, miR-128 can promote osteogenic differentiation of stem cells, providing a promising approach for PI treatment [163].

Cell-Based Therapies

MSCs. Stem cells have a wonderful ability to self-renew and hold the exciting potential to differentiate into various cell lineages. This dual capability makes them a cornerstone in regenerative medicine and a subject of extensive research for their therapeutic applications. This versatility positions them as potent agents for tissue and organ repair. Beyond their regenerative capabilities, stem cells also engage in intricate interactions with immune cells, contributing to the maintenance of systemic homeostasis. These in-

teractions are vital for both sustaining health and facilitating therapeutic interventions in various diseases [164]. Stem cells regulate the immune system mainly through direct cell contact and the release of soluble factors. However, they also respond to inflammatory environments, which can control and modulate their activity. Pro-inflammatory cytokines like TNF-α, interferon (IFN)-γ, IL-1, and IL-17 can activate stem cells, prompting them to release cytokines such as prostaglandin E2 (PGE2), IL-6, and IL-10, which in turn influence the functions of immune cells [165–167].

Non-Odontogenic Stem Cells. The primary sources of stem cells utilized in clinical settings include those derived from bone marrow, adipose tissue, and peripheral blood. These stem cells have demonstrated impressive potential in facilitating new bone formation and integrating with implants, particularly in the management of PI. Their regenerative and immunomodulatory properties make them valuable tools in enhancing the outcomes of dental and periodontal treatments influence the functions of immune cells [168–170]. Research indicates that bone marrow mesenchymal stem cells (BMSCs) can significantly enhance the osseointegration rates of dental implants in both normal and diabetic rabbits [171]. BMSCs are pivotal in immune modulation, promoting the M2 macrophage phenotype to reduce inflammation and inhibiting monocyte and T cell activation. They secrete cytokines like IL-6 and Monocyte chemoattractant protein-1, which are essential for immune regulation and inflammation control, highlighting BMSCs' value in immune-related therapies. Compared to other stem cells, BMSCs offer unique advantages in multipotent differentiation and immunomodulation, making them a key player in regenerative medicine [172]. Exosomes derived from adipose-derived mesenchymal stem cells can regulate macrophage polarization by increasing the expression of M2 macrophage markers [173]. Peripheral blood mesenchymal stem cells not only promote the M2 transformation of macrophages but also exhibit anti-inflammatory effects through the Th17/Treg system [174]. Moreover, umbilical cord mesenchymal stem cells have been shown to upregulate IL-10 expression in a rat PI model, helping to reduce inflammation. They can also regulate bone resorption by increasing the expression of TGF-β, BMP-2, OPG, and osterix, further enhancing osteogenic activity and implant integration in PI rats through endogenous bone formation [175].

Odontogenic Stem Cells. Recently, odontogenic stem cells have gained attention for their potential in immunomodulatory therapy due to their minimal invasiveness and ease of acquisition. Periodontal ligament mesenchymal stem cells (PDL-MSCs), dental pulp stem cells (DP-MSCs), and gingival mesenchymal stem cells are under exploration for their therapeutic potential in PI [176–179]. Research suggests that these oral-derived stem cells share immunomodulatory properties with BMSCs [180]. They can curb the proliferation of activated CD4 and CD8 T cells, reduce the secretion of IFN-γ and TNF-α, and upregulate the expression of PD-L1, CTLA-4, IL-10, and prostaglandin E2, thereby contributing to a balanced immune response. Additionally, MSCs from supracrestal gingival connective tissue have shown promise in immunomodulation by increasing IL-10 and TGF-β while inhibiting TNF-α expression [181]. Additionally, an *in vitro* experiment demonstrated that IL-37 can activate autophagy in DP-MSCs, promoting their osteogenic differentiation [182].

Stem Cell Combined with Gene Therapy. Combining stem cell therapy with gene therapy has shown great promise in treating PI. Gene therapy can significantly enhance the effects of stem cell treatments [183]. In a specific study, the use of lentiviral vectors to engineer canine BMSCs with the TLR2 gene led to a marked increase in the expression of hypoxia-inducible factor-1α and BMP-2. This upregulation fostered the expression of osteogenic and angiogenic genes, indicating a capacity to bolster alveolar bone regeneration even in inflammatory settings. This approach underscores the potential of gene-modified BMSCs in advancing bone healing and tissue repair in challenging conditions such as periodontal disease [184]. *BMP-2* gene therapy using PDL-MSCs demonstrated the ability to promote new bone formation in two different PI models [177]. Additionally, miR-758-5p plays a crucial role in the osteogenic differentiation of PDL-MSCs [185].

Immune Cell Engineering. Immune cell engineering involves modifying immune cells to recognize and respond to disease states, functioning as "living drugs" when introduced into the body. The most common techniques include T cell receptor-engineered T cell therapy and chimeric antigen receptor T cell technology [186]. Treg cell therapy is a promising strategy for treating inflammatory diseases. Bittner *et al*. [187] equipped mouse and human Treg cells with inflammation-sensing mechanisms using artificial immune receptors. These engineered Treg cells showed superior protective effects compared to regular Treg cells, indicating their potential for treating inflammation-driven diseases. Tartrate-resistant acid phosphatase (TRAP)+ cells from the macrophage lineage play a critical role in periosteal homeostasis and regeneration by secreting periosteum-inducing proteins and recruiting periosteum-derived cells to the periosteal surface [188]. Eaton *et al*. [189] designed macrophages-cTLR4 cells that specifically regulate inflammatory responses and promote wound healing. Although the use of immune cell engineering in PI treatment is still limited, further research could confirm its efficacy.

Nanotechnology in Immunomodulation. Nanomaterials, with their unique physical and chemical properties, have

distinctive applications in immunomodulation. The characteristics of nanomaterials, such as size, shape, surface charge, and surface chemistry, can significantly influence their function in the body. By carefully designing the components and surface modifications of nanomaterials, specific immune cells can be targeted, and inflammatory and regenerative processes can be regulated, providing immense potential for nanotechnology in PI immunotherapy [147]. Immunomodulation in PI primarily involves implant surface modification, metal nanoparticles, and using nanocarriers to deliver various drugs and biological agents targeting immune cells [190].

Implant Surface Modification. Implant surface modification involves altering the physicochemical properties and structure of biomaterial surfaces to enhance immune function. With advancements in nanotechnology, nanotube-modified implant surfaces and various nanomaterial coatings are used to modulate the immune response, improving bone and soft tissue integration of dental implants.

Titanium Dioxide Nanotubes (TNTs). TNTs prepared using electrochemical anodization technology can selectively reduce macrophage proliferation (immunomodulation) while enhancing the activity of osteoblasts (bone integration) and fibroblasts (soft tissue integration) compared to traditional pure titanium implants [191]. The surface morphology of TNTs significantly affects immune cell behavior. Study shows that adjusting the diameter of TNTs can promote filopodia formation in macrophages and enhance M2 polarization by activating the RhoA/Rho-associated protein kinase signaling pathway [192]. Additionally, 30 nm diameter TNTs can spontaneously induce M2 macrophage polarization [193]. TNTs also serve as a controllable drug release system in nanodrug delivery. Shen *et al*. [194] used 70 nm TNTs to load dexamethasone, encapsulated in chitosan, and co-cultured them with primary osteoblasts and macrophages. This combination showed excellent osteogenic potential and reduced inflammatory response in macrophages. Another experiment achieved sequential release of IFN-γ and IL-4 by loading IL-4 at the bottom of nanotubes and encapsulating IFN-γ at the top with sodium hyaluronate. This sequential release caused macrophages to undergo phenotype changes at specific times, regulating inflammation and promoting osteogenic repair [195]. Ma *et al*. [196] applied an aspirin/polylactic-co-glycolic acid (PLGA) coating over icariin-loaded TiO_2 nanotubes and found that this combination promotes M2 macrophage polarization, enhances cell proliferation and adhesion, and improves the expression of osteogenic genes and proteins, thereby promoting bone integration.

Graphene Family Nanomaterials (GFNs). GFNs are popular in implants due to their high surface area and ease of surface modification. They have antibacterial and immunomodulatory effects by causing mechanical damage to bacterial cell membranes, inhibiting bacterial adhesion, inducing oxidative stress, and suppressing bacterial metabolism. Additionally, they promote osteoblast differentiation and bone formation [197]. Study shows that graphene-coated titanium implants can induce M2 macrophage polarization in inflammatory conditions, demonstrating strong immunomodulatory capabilities [198]. Graphene oxide also restores and enhances the osteogenic potential of BMSCs around implants [199]. The unique structure and high surface area of GFNs make them effective slow-release carriers for drugs within tissues [200].

Nano-Hydroxyapatite (nHA). nHA has excellent osteogenic properties and is widely used for implant surface modifications [201]. It reduces inflammatory factor levels after root planning [202] and decreases the adhesion of Streptococcus sanguinis around implants [203]. Thin sputter-coated HA on implant surfaces shows excellent bone integration and less bone loss [204], possibly due to nHA's effect on T cell proliferation [205].

Metal Nanoparticles. Metal ions are crucial for transmitting cellular signals and driving cell differentiation, and they have good immunomodulatory properties. Metal nanoparticles can manage PI through antibacterial actions, immunomodulation, oxidative stress induction, and promotion of osteogenesis. Chen *et al*. [206] developed TNTs loaded with silver nanoparticles that control the release of low-dose Ag ions, which inhibit inflammation and promote bone healing by inducing M2 macrophage polarization. Another study synthesized an AuAg nanocomposite from two types of metal ions. This nanocomposite effectively suppresses ROS accumulation in cells and mitochondria when exposed to bacterial biofilms and inhibits ROS-triggered inflammatory protein expression via the MAPK and AKT pathways [207]. Another experiment using the peroxidase activity of cerium oxide combined cerium oxide with gold nanorods to develop a Gold core@CeO_2, which triggers a potent ROS storm to disrupt pathogenic biofilms, providing anti-inflammatory and bone-preserving effects [208] (Table 4, Ref. [206,209–222]).

Nanocarriers for Targeted Drug Delivery and Immunomodulatory Agents. Traditional anti-inflammatory drugs face challenges such as low tissue specificity, poor water solubility, and inefficient crossing of biological barriers. Systemic administration of small molecules with immunomodulatory activity often causes adverse effects. However, with the advancement of nanotechnology, nanocarriers have been widely applied in targeted drug delivery due to their high surface area and high reactivity. Drug delivery systems, particularly nanocarriers, offer a sophisticated ap-

Table 4. Immunomodulatory effects of metal nanoparticles.

Nanoparticles	Immunomodulatory effects	Reference
Ag	Induces apoptosis and M2 polarization of macrophages; downregulates the expression of inhibitor of NF-κB; inhibits the secretion of TNF-α, IL-6, and IL-1β; scavenges ROS; promotes new bone formation	[206,209–211]
Au	Reduces the expression of TNF-α, IL-1β, IL-6, Cyclooxygenase-2, and NF-κB; inhibits RANKL-mediated osteoclastogenesis	[212,213]
Cu	Modulates TLR4/NF-κB and MAPK signaling; promotes M1 polarization of macrophages, enhances bacterial phagocytosis; reduces NF-κB, TNF-α, and IL-6 expression, and enhances cellular antioxidants; increases BMP-6, osteocalcin, and Runx2 expression, promotes osteogenesis	[214,215]
Zn	Inhibits M1 polarization of macrophages; inhibits NF-κB expression; increases OPG and osteocalcin expression to promote osteogenesis	[216,217]
Mg	Inhibits macrophage activation; reduces nuclear translocation and phosphorylation of NF-κB; decreases the expression of IL-1β, IL-6, and IL-10; has antioxidant activity; promotes osteogenesis	[218–220]
Ce	Reduces bacterial adhesion; scavenges ROS; inhibits the expression of TNF-α, IL-6, and IL-1β	[221,222]

BMP, bone morphogenetic protein; Runx2, runt-related transcription factor 2.

proach to managing peri-implantitis. These systems enable the controlled and sustained release of therapeutic agents at implant sites, optimizing treatment efficacy and reducing adverse effects. Furthermore, nanocarriers capable of delivering small interfering RNA (siRNA) can selectively suppress the synthesis of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. They can also be equipped with chemokines or chemokine inhibitors to regulate the migration and targeting of immune cells, providing a targeted strategy for immune modulation in the treatment of PI [223,224].

Inorganic Nanocarriers. Inorganic nanocarriers include metal and metal oxide nanoparticles, as well as inorganic non-metal nanoparticles synthesized through methods such as chemical vapor deposition, physical vapor deposition, mechanical alloying, liquid-phase chemical synthesis, and ultrasonic irradiation. These nanoparticles are diverse in shape, easy to synthesize, and can be easily modified. Various modification methods can enhance their controlled release properties and targeting ability, improving drug bioavailability [225].

Inorganic nanocarriers have gained attention in the immunotherapy of PI. Researchers like Moses *et al.* [226] have developed mesoporous Silk-Bioactive Glass Nanocomposites. These nanocomposites are capable of encapsulating antibiotics such as gentamicin and doxycycline, facilitating their rapid release at the implant site. This approach not only ensures the delivery of the drugs but also preserves their bioactivity, enhancing the therapeutic outcomes in PI treatment. Mesoporous nanocomposites' modifiability enhances their ability to carry hydrophobic drugs like dexamethasone, allowing for a controlled and sustained release. This property is particularly beneficial in applications requiring prolonged drug action. Furthermore, dexamethasone-coated nanocomposites have been shown to support MSCs adhesion, osteoinduction, and immunomodulation, which are crucial for bone repair and immune regulation. In addition, bioactive glass nanocomposites loaded with antibiotics such as tetracycline hydrochloride and dexamethasone have demonstrated antibacterial effects against Sa, while also promoting the growth of osteoblast-like cells (MG-63). This dual action makes them promising tools in the treatment of PI and in enhancing bone tissue integration around dental implants [227]. Irisin, recognized for its capacity to aid bone regeneration, also exerts anti-inflammatory effects by influencing macrophage differentiation. A study involving irisin-loaded bioactive glass nanoparticles developed a nanocomposite that demonstrated enhanced anti-inflammatory characteristics. Importantly, this material has been shown to induce osteogenic differentiation in human periodontal ligament cells through the p38 signaling pathway. This induction leads to higher expression of osteogenic markers, increased ALP activity, and improved mineralization potential compared to controls. These findings suggest the potential of this composite in facilitating bone repair and tissue restoration [228].

Polymeric Nanocarriers. Polymeric nanoparticles are delightful nanoscale carriers crafted from natural polymers, such as chitosan, or synthetic polymers like PLGA. These nanoparticles are designed with specific compositions, structures, and functions. They include self-assembled polymeric nanoparticles, star-shaped polymeric nanoparticles, and inorganic-polymer hybrid nanoparticles. These carriers are highly stable and easily modified, allowing

for drug adsorption or encapsulation for targeted delivery [229].

Polymeric nanocarriers present a promising strategy for the treatment of PI through targeted drug delivery systems. Research has shown that ibuprofen-loaded nanoparticles made from synthetic copolymers can sustain drug release for over seven hours *in vitro* [230]. Another study demonstrated that aspirin-loaded chitosan nanoparticles could successfully maintain drug release and enhance osteogenesis in rat cranial defects [231]. Chen *et al*. [232] devised a novel therapeutic intervention for PI by encapsulating ibuprofen and basic fibroblast growth factor within amphiphilic copolymer nanoparticles. These nanoparticles are stable and dispersible in water, providing a controlled release of the drugs. The formulation has demonstrated the ability to boost the proliferation and adhesion of human gingival fibroblasts, as well as to increase the expression of adhesion-related proteins such as vinculin. This approach supports tissue repair and possesses anti-inflammatory properties, positioning it as a promising option for the targeted and early treatment of PI. Lima *et al*. [233] immobilized antibodies on the surface of chitosan-hyaluronic acid nanoparticles to neutralize the inflammatory and bone-destructive effects of IL-6. This polymer showed compatibility with human macrophages and demonstrated longer-lasting and more potent effects compared to free antibodies. Additionally, polymer citraconic anhydride grafted poly-L-lysine combined with helical peptides for IL-4 and miR-21 delivery exhibited complementary functions in reducing inflammation and promoting resolution. This approach mitigated inflammation by inhibiting NF-κB and promoted macrophage polarization to the M2a/M2c phenotype [234]. A biomimetic collagen interface loaded with IL-4 promotes M2 macrophage polarization and bone regeneration in mandibular defects [235]. Ji *et al*. [236] created an electrospun PLGA/gelatin nanofiber system with a dual-drug delivery mechanism for substance P (SP) and alendronate (ALN). This system enables timed release of SP to promote BMSCs migration and osteogenic differentiation, and sustained ALN release to curb bone resorption. It fosters an environment that supports osteogenesis and inhibits osteoclastogenesis, offering potential for immunotherapy in PI.

Metal organic frameworks (MOFs), exemplified by University of Oslo (UiO)-66, are versatile coordination polymers. A UiO-66-based nanocomposite with the antimicrobial peptide UBI29-41 leverages photodynamic therapy to target periodontal biofilms and reduce inflammation, showing promise in gingival tissue protection [237]. Zhang *et al*. [238] have engineered nanomembranes of MOF-agomir capable of loading and delivering miR-27a agomir in a sustained manner. *In vitro* study has shown that L-MOF-agomir can alter the mitochondrial function and metabolic pathways of macrophages, facilitating a shift from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype. This reprogramming also promotes the osteogenic differentiation of BMSCs. When applied in a rat model of ligature-induced PI, L-MOF-agomir demonstrated robust immunomodulatory effects on macrophage polarization and mitigated bone resorption caused by the ligature. This highlights the potential of L-MOF-agomir as a therapeutic nanomaterial for modulating the immune response and enhancing bone health in PI.

Zeolitic imidazolate frameworks (ZIFs) are a class of porous materials that integrate the robustness of inorganic zeolites with the high porosity and organic characteristics of MOFs. They consist of transition metal ions, typically zinc or cobalt, coordinated in a tetrahedral geometry with imidazole-based organic ligands, forming a crystalline structure. This unique combination endows ZIFs with exceptional properties such as high thermal and chemical stability, tunable porosity, and the ability to incorporate a variety of functional groups, making them versatile for applications in catalysis, gas storage, and drug delivery, among others. Yan *et al*. [239] utilized ZIF-8 loaded with cerium (Ce) to prepare Ce@ZIF-8, which corrected mitochondrial function by catalyzing oxygen production from hydrogen peroxide while inhibiting hypoxia-inducible factor-1α. Through this metabolic reprogramming pathway, macrophages were repolarized from M1 to M2, promoting soft tissue integration by regulating the fibrogenesis, adhesion, and contraction of gingival fibroblasts. In another experiment, ZIF-8 loaded with hematoporphyrin monomethyl ether, PLGA loaded with BMP-2, and metformin were incorporated into gelatin methacrylate hydrogel. This composite material demonstrated efficient ROS production and antibacterial efficacy under ultrasound stimulation, reduced the release of inflammatory factors IL-6 and TNF-α, and decreased bone loss around implants in a rat model of bacterial-induced PI [20].

Liposome-Based Nanocarriers. Liposomes have gained widespread application in nanodrug delivery due to their low immunogenicity, good biocompatibility, ease of preparation, ability to encapsulate both hydrophilic and hydrophobic drugs, and strong targeting ability. They enter cells via endocytosis and can be surface-modified to increase targeting, effectively enhancing drug therapeutic effects [240]. A nanocomposite using liposomal carriers and chitosan to load quercetin and ciprofloxacin demonstrated excellent antioxidant capability and inhibition of biofilm formation [241]. A therapeutic system featuring resveratrol encapsulated within liposomes has demonstrated favorable biocompatibility and the capacity to induce a phenotypic switch in macrophages from inflammatory M1 to anti-inflammatory M2 by activating p-STAT3 and reducing p-STAT1 levels. This system also neutralizes ROS, curbs NF-κB signaling and inflammasome activation, and decreases the secretion of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α [242]. The research of Li

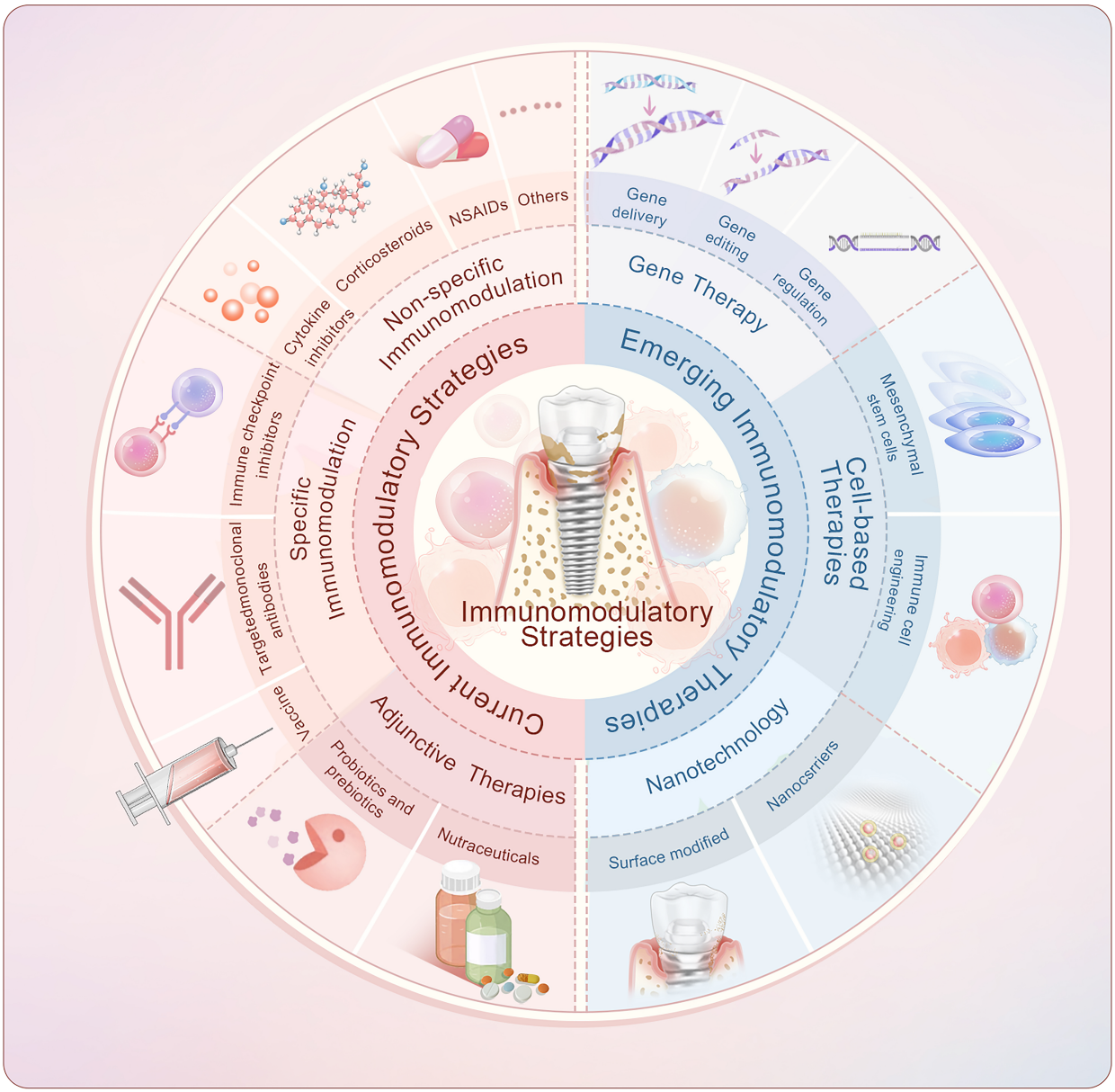

Fig. 5. Immunomodulatory strategies of PI.

et al. [243] indicated that a nano-liposome formulation loaded with docosahexaenoic acid (DHA) can effectively neutralize ROS, suppress NF-κB activation, and exert anti-inflammatory actions on macrophages. When compared to free DHA, the DHA-loaded nanoliposomes displayed enhanced efficacy in curbing bone resorption within a rat model of PI. This suggests that nanoliposomal delivery systems could be instrumental in the localized and controlled release of therapeutic agents, offering a promising avenue for the treatment of inflammatory bone diseases. Additionally, liposomes can be combined with inorganic carriers like calcium phosphate to achieve dual loading of dexamethasone and its water-soluble salt dexamethasone phosphate. This combination effectively encourages the polarization of macrophages towards the M2 phenotype while also helping to reduce the production of pro-inflammatory cytokines. It achieves this by inhibiting the activation and function of NF-κB [244].

Biological-Derived Nanocarriers. Biological-derived nanomaterials, extracted and purified from organisms, though non-living, possess special biological functions and good biocompatibility. With natural cell receptors on their surface, they provide biomimetic camouflage for drugs, avoiding rapid degradation and immune rejection. Examples include exosomes and DNA tetrahedral nanostructures. Exosomes, important mediators of intercellular communication, carry various proteins, nucleic acids, and

lipids, mediating tissue metabolism through paracrine transmission, playing a crucial role in immunoregulation and bone formation [245]. Study has shown that natural nanoparticles exosomes isolated from dendritic cells can inhibit the expression of bone-resorptive cytokines and reduce osteoclast-mediated bone loss [246]. Exosomes with inserted Golgi glycoprotein 1 can carry Wnt-1 agonists to reduce bone loss, promote bone formation, and accelerate fracture healing. Fetal bovine serum exosomes loaded with icariin can effectively promote osteoblast proliferation and bone regeneration [247]. In another study, hybrid nanoparticles produced by merging chemokine receptor (CXCR)4 exosomes with antagomir-188 carrying liposomes could promote osteogenic differentiation of BMSCs and inhibit adipogenesis, reducing bone loss [248].

DNA tetrahedral nanostructures are three-dimensional DNA nanostructures with tetrahedral shapes formed by four single strands automatically hybridizing, designed based on the principle of base complementary pairing. They possess good biocompatibility and excellent cell membrane permeability [249]. Tetrahedral DNA nanomaterials modified with TLR4-siRNA can reduce the percentage of M1 RAW264.7 macrophages by regulating mitochondrial homeostasis of polarized macrophages, reverse the imbalance of macrophage polarization phenotypes, accelerate wound healing, and inhibit bone resorption [250]. Using DNA as a template to prepare Sr-doped CaP nanoparticles can optimize targeted gene transfer, regulate osteocyte functions, and play a role in immunotherapy [251] (Fig. 4, Ref. [178,235,249]; Fig. 5) (Table 5, Ref. [20,85,152–155,158,159,161–163,171,172,174,175,180–182,187–189,192–196,198–208,226–228,232,238,241–243,246,248,250,252,253]).

Discussion

For emerging therapies, ongoing comprehensive and critical reviews are essential for advancing PI treatment. In this discussion, we will examine the key limitations in three major areas: gene editing, stem cell therapy, and nanotechnology, while proposing potential strategies to overcome these challenges.

Enhancing the Precision and Safety of Gene Editing. Technologies like CRISPR/Cas9 have created new opportunities for targeted therapies against PI by altering genes related to inflammation and bone resorption. However, off-target effects may lead to unintended genetic modifications, potentially resulting in adverse consequences. Research must focus on improving the specificity of gene editing tools to address this issue. Approaches to consider include optimizing guide RNA design, utilizing high-fidelity Cas9 variants, and employing advanced bioinformatics algorithms to predict and minimize off-target risks. Furthermore, the development of innovative delivery methods that precisely target gene editing components to tissues surrounding the implantation site—such as nanoparticle-based carriers or hydrogels—can further enhance safety and efficacy. Rigorous preclinical models and long-term studies are necessary to comprehensively understand and mitigate the risks associated with gene editing in clinical settings.

Establishing Ethical and Regulatory Guidelines for Stem Cell Therapy. Stem cell-based therapies hold significant potential in the regeneration of periodontal bone and soft tissues. However, this field faces substantial ethical and regulatory challenges, particularly concerning the sources and utilization of stem cells. It is crucial to develop comprehensive ethical guidelines that address issues such as informed consent from donors and equitable access to treatments. Furthermore, there should be coordination of international regulatory frameworks to promote advancements in global stem cell research while ensuring patient safety. To enhance moral transparency, researchers must collaborate with ethicists, regulatory bodies, and patient advocacy organizations throughout the research and development process. Another critical aspect is ensuring the functional stability and long-term efficacy of transplanted stem cells. This necessitates a deeper understanding of how stem cells interact with the immune microenvironment surrounding implants, which can be achieved through strategies such as developing more biocompatible scaffolds to integrate their functions effectively.

Assessment of the Toxicity and Biocompatibility of Nanomaterials. Nanotechnology offers new solutions for targeted drug delivery and enhanced bone regeneration in the treatment of PI. However, the potential toxicity, long-term biocompatibility, and environmental impact of nanomaterials cannot be overlooked. Comprehensive toxicological evaluations using both *in vitro* and *in vivo* models are necessary. Researchers should investigate how various properties of different nanomaterials—such as size, shape, and surface charge—affect their interactions with cells and tissues. Furthermore, the development of novel nanomaterials that can safely degrade *in vivo* or be efficiently cleared is essential to minimize potential adverse effects. Collaborative efforts among stakeholders are required to establish standardized procedures for assessing the safety of nanomaterials. Additionally, regulatory agencies must provide clear guidelines for the application of nanotechnology in clinical settings to ensure that benefits outweigh risks.

By addressing key issues, future research can more effectively tackle the complexities of personalized treatment for PI, paving the way for safer and more effective therapeutic approaches, ultimately enhancing treatment outcomes for each individual patient.

Future Directions

While current PI treatment methodologies have shown some degree of effectiveness, there remains a pressing need

European Cells and Materials Vol.50 2025 (pages 33–67) DOI: 10.22203/eCM.v050a03

Table 5. Immunomodulatory strategies of PI.

Emerging immunomodulatory therapies	Mechanism of action	Research progress	Advantages	Limitations	Reference
Gene therapy					
Gene delivery	The introduction of target gene into recipient cells using gene vectors	(1) The use of adenoviral vectors to achieve knockout and overexpression of *A20* in mice has been shown to inhibit bone resorption and NLRP3-mediated M1 macrophage polarization; (2) Adenoviral vectors carrying Sema3A have demonstrated positive effects on early bone integration in an *in vivo* rabbit model; (3) Overexpression of ALKBH5 was achieved using lentiviral vectors, which confirmed its ability to enhance osteoblast differentiation and reduce inflammation in diabetic mouse models; (4) Lentiviral vectors based on the autophagy protein Beclin1 have also been shown to reverse osteoclast apoptosis induced by elevated levels of IL-17A.	Gene therapy can facilitate long-term and tissue-specific expression of therapeutic proteins without the need for pharmacological intervention or surgical treatment.	Considerations regarding the immunogenicity of the vectors, the risk of gene mutations due to random insertion, low transfection efficiency, and ethical safety issues must be addressed.	[152–155,158,159], [161–163,252]
Gene editing	Utilization of CRISPR/Cas9 technology for gene knockout, insertion, or replacement	(1) The CRISPR/Cas9 technique was employed to knock out the NF-κB *p65* gene in chondrocytes, demonstrating resistance to the pro-inflammatory environment when co-cultured with IL-1β; (2) Successful inhibition of the expression of inflammatory cytokines TNF-α and IL-1β in intervertebral disc cells was achieved using CRISPR/Cas9 technology.			
Gene regulation	Utilization of miRNA complementary to messenger RNA for post-transcriptional regulation of gene expression	(1) miR-27a can inhibit TNF-α in dogs, positively regulating osteogenesis and angiogenesis, promoting new bone formation and bone integration; (2) miR-146a can suppress RANKL-mediated bone resorption in a mouse model by modulating TLR2/4 signaling and inhibiting the expression of TNF-α; (3) miR-128 promotes osteogenic differentiation of stem cells.			

Table 5. Continued.

Emerging immunomodulatory therapies	Mechanism of action		Research progress	Advantages	Limitations	Reference
Cell-based therapies						
Mesenchymal stem cells	Non-odontogenic stem cells	Exhibiting self-renewal and multi-directional differentiation capabilities, primarily mediating immunoregulation through cell-to-cell contact and/or the release of soluble factors	(1) Bone marrow-derived mesenchymal stem cells (BMSCs) can significantly enhance the bone integration rates of dental implants in both normal and diabetic rabbits; (2) BMSCs promote the M2 differentiation of macrophages through direct or indirect mechanisms while inhibiting the activation of monocytes and T cells; (3) Exosomes derived from adipose-derived mesenchymal stem cells can also promote M2 polarization of macrophages; (4) Peripheral blood mesenchymal stem cells not only facilitate the M2 conversion of macrophages but also exert anti-inflammatory properties through the Th17/Treg system; (5) Umbilical cord mesenchymal stem cells can inhibit inflammatory responses and modulate bone resorption in a rat PI model	These cells demonstrate excellent new bone formation and integration capabilities in the treatment of PI	Efficacy may be unstable, with individual differences, ethical considerations, and safety in clinical applications needing to be addressed.	[171,172,174,175]
	Odontogenic stem cells	Immunoregulatory properties similar to non-dental-derived stem cells	(1) An *in vitro* study demonstrated that PDL-MSCs, DP-MSCs, and G-MSCs can suppress the production of IFN-γ and TNF-α while increasing the expression of PD-L1, CTLA-4, IL-10, and prostaglandin E; (2) Gingival connective tissue-derived mesenchymal stem cells exhibit immunoregulatory properties by upregulating IL-10 and TGF-β expression while inhibiting TNF-α expression, thereby displaying anti-inflammatory characteristics; (3) *In vitro* experiments indicated that IL-37 can activate autophagy in DP-MSCs, promoting their osteogenic differentiation	These cells are relatively easy to obtain	There is a certain degree of trauma involved. Their proliferation and differentiation capabilities require further research, and the efficiency and extent of regeneration are currently difficult to control precisely.	[180–182]
Immune cell engineering	Designing and modifying immune cells that can recognize and respond to disease states to function as “living drugs” for therapeutic purposes		(1) Engineered Treg cells with inflammatory ligands can be used to treat inflammation-driven diseases; (2) TRAP+ macrophage lineage cells play an important role in regulating the homeostasis and regeneration of the periosteum by secreting transcriptionally expressed periosteum-inducing proteins and recruiting periosteum-derived cells to the surface of the periosteum; (3) Macrophage-cTLR4 cells can specifically modulate inflammatory responses and promote wound healing.	These therapies exhibit rapid responses, significant effects, and minimal side effects	Challenges such as antigen escape, immunosuppressive microenvironments, and the need for further research on efficacy and safety remain.	[187–189]

Table 5. Continued.

Emerging immunomodulatory therapies	Mechanism of action	Research progress	Advantages	Limitations	Reference
Nanotechnology in immunomodulation					
Implant surface modification	TNTs	TNTs can selectively reduce macrophage proliferation (immunoregulation) while simultaneously enhancing the activity of osteoblasts (bone integration) and fibroblasts (soft tissue integration)	(1) The diameter of TNTs promotes the formation of filopodia in macrophages and enhances their M2 polarization by activating the RhoA/Rho-associated protein kinase signaling pathway; (2) TNTs with a diameter of 30 nm can spontaneously induce M2 polarization of macrophages; (3) The use of 70 nm TNTs loaded with dexamethasone, encapsulated with chitosan, demonstrates excellent osteogenic potential when co-cultured with primary osteoblasts and macrophages *in vitro*, while reducing inflammatory responses in macrophages; (4) Combining various nanocarriers allows for the programmed release of multiple drugs, thereby specifically regulating inflammation and promoting osteogenic repair.	The surface morphology can influence the behavior of immune cells, establishing a controllable drug release system based on a nanomedicine delivery system.	Mechanical stress post-implantation may lead to delamination and shedding of the TNT coating, provoking an immune response.	[192–196,253]
	GFNs	Exhibiting antibacterial and immunoregulatory effects through mechanisms such as mechanical damage to cell membranes, inhibition of bacterial adhesion, oxidative stress, and suppression of bacterial metabolism, while simultaneously promoting osteoblast differentiation and bone formation	(1) Graphene-coated titanium implants can induce the M2 polarization of macrophages, demonstrating excellent immunomodulatory capabilities; (2) Graphene oxide can restore or even enhance the osteogenic potential of BMSCs surrounding the implants; (3) Serving as a sustained-release carrier, it achieves efficient drug delivery within tissues.	These materials are easy to modify on the surface and possess a high specific surface area	Cytotoxicity and biosafety are critical for further clinical applications.	[198–200]
	Nha	Reducing the levels of inflammatory factors within tissues and decreasing the adhesion of Streptococcus sanguinis around implants	(1) Surface modifications for implants have demonstrated excellent bone integration and reduced bone loss; (2) There is a certain regulatory effect on T cell proliferation.	These modifications exhibit excellent osteogenic potential	Lack antibacterial properties.	[201–205]

European Cells and Materials Vol.50 2025 (pages 33–67) DOI: 10.22203/eCM.v050a03

Table 5. Continued.

Emerging immunomodulatory therapies	Mechanism of action		Research progress	Advantages	Limitations	Reference
Implant surface modification	Metal nanoparticles	Metal ions play a crucial role in transmitting cell signals and driving directed cell differentiation within the body, exhibiting good immunomodulatory properties	(1) Silver nanoparticles can not only inhibit inflammatory processes but also promote bone healing by inducing M2 polarization associated with healing; (2) AuAg nanocomposites synthesized from two types of metal ions effectively suppress the accumulation of ROS in cells and mitochondria while inhibiting the expression of ROS-triggered inflammatory proteins through the MAPK and AKT pathways; (3) The development of semi-encapsulated Gold core@CeO_2 by combining cerium oxide with gold nanorods can trigger a potent ROS storm, disrupting pathogenic biofilms, thereby exerting anti-inflammatory and bone-preserving effects.	These materials exhibit antibacterial properties, immunoregulation, oxidative stress induction, and promotion of osteogenesis	Exhibit some cytotoxicity.	[206–208]
Nanocarriers for targeted drug delivery and immunomodulatory agents						
Inorganic nanocarriers	Enhancing drug release performance and targeting through various methods, thereby improving drug bioavailability		(1) Mesoporous nanocomposites loaded with antibiotics (gentamicin and doxycycline) and dexamethasone facilitate slow and sustained drug release, promoting mesenchymal stem cell adhesion, bone induction, and exerting immunomodulatory effects; (2) Bioglass nanocomposites loaded with tetracycline hydrochloride and dexamethasone exhibit growth inhibition against Staphylococcus aureus and promote deep proliferation of osteoblast-like cells (MG-63); (3) Nanocomposites prepared from bioactive glass nanoparticles loaded with irisin demonstrate enhanced anti-inflammatory properties and stimulate osteogenic differentiation of human periodontal ligament cells (hPDLCs).	These materials feature diverse shapes, are easy to synthesize, and are readily modifiable	Their biodegradability still needs improvement.	[226–228]

Table 5. Continued.

Emerging immunomodulatory therapies	Mechanism of action	Research progress	Advantages	Limitations	Reference
Polymer nanocarriers	These carriers can encapsulate drugs through adsorption or dispersion	(1) Amphiphilic copolymer nanoparticles loaded with ibuprofen and basic fibroblast growth factor can provide sustained drug release and promote the proliferation and adhesion of human gingival fibroblasts by upregulating the expression of adhesion factors such as vinculin, exhibiting anti-inflammatory properties that may offer early local treatment for periodontitis (PI); (2) In a ligature-induced peri-implantitis model in rats, L-MOF-agomir implants demonstrated strong immunomodulatory activity through macrophage polarization and alleviated ligature-induced bone resorption; (3) ZIF-8 composites loaded with blood porphyrin methyl ether showed good ROS production efficiency and antibacterial efficacy under ultrasound stimulation, reducing bone loss around implants induced by bacteria in a peri-implantitis rat model.	These materials exhibit high stability and ease of surface modification	There is a lack of sufficient methods for in-depth evaluation of the safety, biocompatibility, and biodegradability of novel polymer materials. Additionally, the complexity of structural design and the tediousness of material synthesis limit their applications.	[20,232,238]
Lipid-based nanocarriers	These carriers enter cells via endocytosis and can enhance targeting through surface modification, effectively improving the therapeutic efficacy of drugs	(1) Nanocomposites made from lipid carriers and chitosan loaded with quercetin and ciprofloxacin exhibit excellent antioxidant capacity and the ability to inhibit biofilm formation; (2) Therapeutic liposomal systems loaded with resveratrol can convert inflammatory macrophages to the M2 phenotype, scavenge ROS, and inhibit NF-κB signaling and inflammasomes, thereby reducing the release of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α; (3) Nanolipid carriers loaded with DHA can scavenge ROS, inhibit NF-κB activation, exert anti-inflammatory effects on macrophages, and more effectively prevent bone resorption in a rat peri-implantitis model.	These materials have low immunogenicity, good biocompatibility, ease of preparation, and the ability to encapsulate both hydrophilic and hydrophobic drugs with strong targeting capabilities	For certain water-soluble drugs, the encapsulation efficiency may be low, and stability can be poor.	[241–243]

Table 5. Continued.

Emerging immunomodulatory therapies	Mechanism of action	Research progress	Advantages	Limitations	Reference
Bio-derived nanocarriers	These carriers can provide biomimetic camouflage for drugs, thereby avoiding rapid degradation and immune rejection	(1) Natural nanoparticle exosomes isolated from dendritic cells, when purified and loaded with TGF-β1 and IL-10, can suppress the expression of bone-resorptive cytokines and reduce bone loss caused by osteoclasts; (2) Hybrid nanoparticles generated by fusing CXCR4 exosomes with lipid carriers loaded with antagomir-188 can promote the osteogenic differentiation of BMSCs and inhibit adipogenesis, thereby reducing bone loss; (3) TLR4-siRNA modified tetrahedral DNA nanomaterials can reduce the percentage of M1 RAW264.7 macrophages by regulating mitochondrial homeostasis in polarized macrophages, reversing the imbalance of macrophage polarization phenotypes, and accelerating wound healing while inhibiting bone resorption.	These materials exhibit good biocompatibility and possess natural cell receptors on their surfaces	They face challenges such as low intracellular delivery efficiency and low yield.	[85,246,248,250]

CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; Cas9, CRISPR-associated protein 9; Sema3A, semaphorin 3A; ALKBH5, Alk B homologue 5; miRNA, microRNA; PDL-MSCs, periodontal ligament mesenchymal stem cells; DP-MSCs, dental pulp stem cells; PD-L1, programmed death-1 ligand; CTLA-4, cytotoxic T-lymphocyte antigen-4; TGF, transforming growth factor; TRAP, tartrate-resistant acid phosphatase; TNTs, titanium dioxide nanotubes; BMSCs, bone marrow mesenchymal stem cells; MOF, metal organic framework; ZIF, zeolitic imidazolate framework; DHA, docosahexaenoic acid; CXCR, chemokine receptor; GFNs, graphene family nanomaterials; siRNA, small interfering RNA.

to develop more advanced and integrative strategies. The future of PI research should focus on well-defined and innovative pathways that address both the complexity of the disease and the limitations of existing treatments. Two particularly promising areas for advancement include optimizing combination therapeutic regimens and developing precision medicine through robust biomarker identification and immune profiling.

Optimizing Combination Therapeutic Regimens. Future PI research should focus on combining immune-boosting therapies with mechanical cleaning and antimicrobial treatments. This mix could work better together than separately, like using a treatment that ramps up the immune system along with cleaning out the infection to calm down inflammation and make the area around the implant healthier. We need to find the best way to give these treatments, like when and how much, to get the most benefit and fewest side effects. Also, we have to test new ways to give drugs right where they're needed, which could make the treatment work better. The end game is to create treatments that change based on how each person's body reacts and how bad their PI is.

Development and Application of Predictive Biomarkers. Treating PI better in the future means using precision medicine, which means finding biomarkers that can tell us early if PI is starting, how well treatments will work, and help us customize treatments for each person. Scientists need to find markers in genes, proteins, and immune responses that can sort patients by their risk and how their PI might progress. Things like signs of inflammation, certain immune cells, or gene differences could be good for predicting PI and how well treatments work. These markers would help doctors keep an eye on the implant area and change treatments as needed. Also, finding easier ways to check these markers, maybe with saliva tests, could make check-ups easier and help patients stick with their treatment plans.

Harnessing Emerging Technologies. Merging cutting-edge tech like nanomedicine and gene editing could really change how we treat PI. Nanoparticles can be tailored to carry drugs straight to where they're needed, curbing side effects and boosting tissue healing. Meanwhile, gene-editing tools like CRISPR could be used to tweak genes linked to PI or to tweak immune responses that cause inflammation and bone loss. But, we need to thoroughly test these methods in preclinical studies and carefully design clinical trials to make sure they're safe, accurate, and long-lasting. Plus, we have to think about the ethics and rules for using these new technologies to make sure they're used responsibly.

Fostering a Systems Biology Approach. To really get PI, we need to look at how the immune system, germs, and gums all work together. Future studies should use fancy computer models and AI to understand these complex interactions and how treatments might affect them. This could help us create treatments that change in real-time to fit each person's needs, making care more precise.

Establishing Standardized Guidelines and Frameworks. Because PI can be different from person to person and treatments are always improving, we need clear rules for how to diagnose and treat PI. Scientists need to work together to agree on standards for diagnosing PI, figuring out if treatments work, and running tests. We also need clear rules for new treatments like using stem cells or changing genes to make sure they're safe and work well in real life.

The theoretical basis of immunotherapy is to treat diseases by regulating/repairing the body's immune response. The development of immunotherapy depends on advances in foundational disciplines such as immunology, human microbiome genomics, and genetic engineering. Immunotherapy is characterized by strong individuality, and future mainstream approaches will involve analyzing patients' genomes and immune compositions to design personalized immunotherapy plans. The immune system is a complex network, and disrupting its balance can cause severe side effects. Therefore, it is crucial to detect and assess immune levels in patients before immunotherapy to ensure precision and minimize unintended side effects. Current research in this field is still in its early stages and requires further technological support. Furthermore, immunotherapy must function through the body's own immune system, and the immune response takes time to develop. The efficacy of immunotherapy may appear relatively slowly, and the extent of immune system damage significantly impacts its effectiveness. Combining immunotherapy with conventional treatments for synergistic effects can enhance treatment outcomes. Lastly, immunotherapy is an emerging technology. Standardization of different immunotherapy products, determination of treatment courses, exploration of application dosages, and establishing efficacy assessment criteria are needed. The safety, ethical, and legal issues arising from new treatment strategies such as gene editing and stem cell therapy have sparked extensive academic discussions, making it essential to establish reasonable norms and guidelines for the healthy development of this field.

In conclusion, a forward-thinking, multidisciplinary approach that integrates personalized medicine, cutting-edge technology, and robust scientific inquiry will be key to advancing PI treatment. By focusing on these strategic research pathways, we can move toward more precise, effective, and patient-centered care, ultimately improving long-term outcomes for those affected by peri-implantitis.

Conclusions

This review summarizes recent advancements in immunomodulatory strategies for managing PI, a common complication in oral implantology. PI progresses rapidly, has a high incidence, and causes significant harm by continuously destroying the surrounding soft and hard tissues of implants. Thus, its prevention and treatment are crucial global health issues. Traditional treatments, such as mechanical debridement, antimicrobial therapy, and surgical interventions, have notable limitations, particularly due to the rise of bacterial resistance, highlighting the urgent need for new therapeutic strategies.

Recent advancements in immunological theories and technologies have deepened the understanding of the relationship between PI and the immune system, making immunotherapy a research focus. PI is a complex disease involving interactions among the immune system, microorganisms, and the host. There are three main immunomodulatory strategies for PI:

Active immunity: Enhancing the body's natural defenses through therapeutic vaccines, probiotics, and nutraceuticals.

Passive immunity: Supplementing the immune system with engineered cells or antibodies that the body cannot produce on its own.

Immune regulation: Blocking negative regulatory factors with cells, cytokines, and micro-RNAs.

As immune technologies continue to evolve, new approaches such as nanotechnology and gene editing show promising applications in PI immunotherapy. However, due to individual variations in immune responses, extensive research, particularly clinical studies, is required to ensure the precision and minimize the unintended side effects of these new technologies. Establishing reasonable standards and guidelines remains a key focus for future research in this field.

List of Abbreviations

PI, peri-implantitis; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; TLRs, Toll-like receptors; MAPK, mitogen-activated protein kinase; AP-1, activating protein-1; NF-κB, nuclear factor-kappa B; IL, interleukin; TNF, tumor necrosis factor; MMPs, matrix metalloproteinases; RANK, receptor activator of NF-κB; RANKL, receptor activator of NF-κB ligand; APCs, antigen-presenting cells; MSCs, mesenchymal stem cells; BMP, bone morphogenetic protein; ALP, alkaline phosphatase; OSM, oncostatin M; STAT, signal transducer and activator of transcription; Th, helper T; NK, natural killer; Treg, regulatory T; Pg, Porphyromonas gingivalis; Pi, Prevotella intermedia; Fn, Fusobacterium nucleatum; Aa, Aggregatibacter actinomycetemcomitans; Sa, Staphylococcus aureus; SNPs, single nucleotide polymorphisms; EGF, epidermal growth factor; BMSCs, bone marrow mesenchymal stem cells; CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed death-1; PD-L1, programmed death-1 ligand; NSAIDs, non-steroidal anti-inflammatory drugs; NLRP3, receptor thermal protein domain associated protein 3; miRNA, microRNA; PDL-MSCs, periodontal ligament mesenchymal stem cells; DP-MSCs, dental pulp stem cells; TNTs, titanium dioxide nanotubes; GFNs, graphene family nanomaterials; PLGA, polylactic-co-glycolic acid; ZIFs, zeolitic imidazolate frameworks; OPG, osteoprotegerin; ERK1/2, extracellular signal-regulated kinase 1/2; NFATc1, nuclear factor-activated T cell 1; Ig, immunoglobulin; Runx2, runt-related transcription factor 2; Smad, small mother against decapentaplegic; ALKBH5, Alk B homologue 5; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; Cas9, CRISPR-associated protein 9; TGF, transforming growth factor; IFN, interferon; TRAP, tartrate-resistant acid phosphatase; nHA, nanohydroxyapatite; ROS, reactive oxygen species; siRNA, small interfering RNA; MOFs, metal organic frameworks; CXCR, chemokine receptor; UiO, University of Oslo; Ce, cerium; Sema3A, semaphorin 3A; ALN, alendronate; DHA, docosahexaenoic acid; OB, osteoblast; OC, osteoclast; OPN, osteopontin; COLL1, collagen type I.

Availability of Data and Materials

Data availability is not applicable to this article as no new data were created or analyzed in this study.

Author Contributions

HHL contributed to the design of this work and took on oversight and leadership responsibilities for the planning and execution of the research activities. YW and YDL contributed to the interpretation and analysis of the data. YW, YDL, and JK drafted the work. LYL and XL critically revised the work for important intellectual content and the presentation of the published work by those from the original research group, including during pre- or post-publication stages. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgments

Not applicable.

Funding

This research is supported by the Huangpu District Young Physician Training Program (Second Batch) (2021QN27), National Nature Science Foundation of China 82401072, the Natural Science Foundation of Sichuan

Province 2023NSFSC1512, and the Natural Science Foundation of Sichuan Province 2024NSFSC0536.

Conflict of Interest

The author(s) declare no conflict of interest.

References

[1] Berglundh T, Armitage G, Araujo MG, Avila-Ortiz G, Blanco J, Camargo PM, *et al*. Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. Journal of Periodontology. 2018; 89: S313–S318. https://doi.org/10.1002/jper.17-0739.

[2] Krebs M, Kesar N, Begić A, von Krockow N, Nentwig GH, Weigl P. Incidence and prevalence of peri-implantitis and peri-implant mucositis 17 to 23 (18.9) years postimplant placement. Clinical Implant Dentistry and Related Research. 2019; 21: 1116–1123. https://doi.org/10.1111/cid.12848.

[3] Kordbacheh Changi K, Finkelstein J, Papapanou PN. Peri-implantitis prevalence, incidence rate, and risk factors: A study of electronic health records at a U.S. dental school. Clinical Oral Implants Research. 2019; 30: 306–314. https://doi.org/10.1111/clr.13416.

[4] Ramanauskaite A, Schwarz F, Sader R. Influence of width of keratinized tissue on the prevalence of peri-implant diseases: A systematic review and meta-analysis. Clinical Oral Implants Research. 2022; 33: 8–31. https://doi.org/10.1111/clr.13766.

[5] Lv PX, Zhong JS, Ouyang XY, Iao S, Liu J, Xie Y. Investigation of peri-implant diseases prevalence and related risk indicators in patients with treated severe periodontitis over 4 years after restoration. Journal of Dental Sciences. 2024; 19: 894–899. https://doi.org/10.1016/j.jds.2023.08.010.

[6] Weinstein T, Clauser T, Del Fabbro M, Deflorian M, Parenti A, Taschieri S, *et al*. Prevalence of Peri-Implantitis: A Multi-Centered Cross-Sectional Study on 248 Patients. Dentistry Journal. 2020; 8: 80. https://doi.org/10.3390/dj8030080.

[7] West N, Chapple I, Culshaw S, Donos N, Needleman I, Suvan J, *et al*. BSP Implementation of prevention and treatment of peri-implant diseases—The EFP S3 level clinical practice guideline. Journal of Dentistry. 2024; 149: 104980. https://doi.org/10.1016/j.jdent.2024.104980.

[8] da Silva RVC, Almeida AB, de Assis RIF, Dos Santos EJ, Rozendo DMM, Sallum AW. Treatment of peri-implantitis using nonsurgical debridement combined with bioresorbable doxycycline nanospheres: a case report with 3-year follow-up. General Dentistry. 2024; 72: 70–73.

[9] Riben Grundström C, Lund B, Kämpe J, Belibasakis GN, Hultin M. Systemic antibiotics in the surgical treatment of peri-implantitis: A randomized placebo-controlled trial. Journal of Clinical Periodontology. 2024; 51: 981–996. https://doi.org/10.1111/jcpe.13994.

[10] Carrillo de Albornoz A, Montero E, Alonso-Español A, Sanz M, Sanz-Sánchez I. Treatment of peri-implantitis with a flapless surgical access combined with implant surface decontamination and adjunctive systemic antibiotics: A retrospective case series study. Journal of Clinical Periodontology. 2024; 51: 968–980. https://doi.org/10.1111/jcpe.13993.

[11] Roccuzzo A, Stähli A, Monje A, Sculean A, Salvi GE. Peri-Implantitis: A Clinical Update on Prevalence and Surgical Treatment Outcomes. Journal of Clinical Medicine. 2021; 10: 1107. https://doi.org/10.3390/jcm10051107.

[12] Yang B, Pang X, Li Z, Chen Z, Wang Y. Immunomodulation in the Treatment of Periodontitis: Progress and Perspectives. Frontiers in Immunology. 2021; 12: 781378. https://doi.org/10.3389/fimmu.2021.781378.

[13] López-Valverde N, López-Valverde A, Blanco Rueda JA. The role of probiotic therapy on clinical parameters and human immune response in peri-implant diseases: a systematic review and meta-analysis of randomized clinical studies. Frontiers in Immunology. 2024; 15: 1371072. https://doi.org/10.3389/fimmu.2024.1371072.

[14] Wei X, Qian S, Yang Y, Mo J. Microbiome-based therapies for periodontitis and peri-implantitis. Oral Diseases. 2024; 30: 2838–2857. https://doi.org/10.1111/odi.14782.

[15] Ng E, Tay JRH, Mattheos N, Bostanci N, Belibasakis GN, Seneviratne CJ. A Mapping Review of the Pathogenesis of Peri-Implantitis: The Biofilm-Mediated Inflammation and Bone Dysregulation (BIND) Hypothesis. Cells. 2024; 13: 315. https://doi.org/10.3390/cells13040315.

[16] He Z, Liu Y, Liu X, Sun Y, Zhao Q, Liu L, *et al*. Smart Porous Scaffold Promotes Peri-Implant Osteogenesis under the Periosteum. ACS Biomaterials Science & Engineering. 2020; 6: 6321–6330. https://doi.org/10.1021/acsbiomaterials.0c00956.

[17] Butera A, Pascadopoli M, Pellegrini M, Gallo S, Zampetti P, Scribante A. Oral Microbiota in Patients with Peri-Implant Disease: A Narrative Review. Applied Sciences. 2022; 12: 3250. https://doi.org/10.3390/app12073250.

[18] Fragkioudakis I, Tseleki G, Doufexi AE, Sakellari D. Current Concepts on the Pathogenesis of Peri-implantitis: A Narrative Review. European Journal of Dentistry. 2021; 15: 379–387. https://doi.org/10.1055/s-0040-1721903.

[19] Alves CH, Russi KL, Rocha NC, Bastos F, Darrieux M, Parisotto TM, *et al*. Host-microbiome interactions regarding peri-implantitis and dental implant loss. Journal of Translational Medicine. 2022; 20: 425. https://doi.org/10.1186/s12967-022-03636-9.

[20] Hu B, Qiao W, Cao Y, Fu X, Song J. A sono-responsive antibacterial nanosystem co-loaded with metformin and bone morphogenetic protein-2 for mitigation of inflammation and bone loss in experimental peri-implantitis. Frontiers in Bioengineering and Biotechnology. 2024; 12: 1410230. https://doi.org/10.3389/fbioe.2024.1410230.

[21] Milinkovic I, Djinic Krasavcevic A, Nikolic N, Aleksic Z, Carkic J, Jezdic M, *et al*. Notch down-regulation and inflammatory cytokines and RANKL overexpression involvement in peri-implant mucositis and peri-implantitis: A cross-sectional study. Clinical Oral Implants Research. 2021; 32: 1496–1505. https://doi.org/10.1111/clr.13850.

[22] Oliveira JA, de Oliveira Alves R, Nascimento IM, Hidalgo MAR, Scarel-Caminaga RM, Cristina Pigossi S. Pro- and anti-inflammatory cytokines and osteoclastogenesis-related factors in peri-implant diseases: systematic review and meta-analysis. BMC Oral Health. 2023; 23: 420. https://doi.org/10.1186/s12903-023-03072-1.

[23] Rakic M, Radunovic M, Petkovic-Curcin A, Tatic Z, Basta-Jovanovic G, Sanz M. Study on the immunopathological effect of titanium particles in peri-implantitis granulation tissue: A case-control study. Clinical Oral Implants Research. 2022; 33: 656–666. https://doi.org/10.1111/clr.13928.

[24] Zhang Q, Liu J, Ma L, Bai N, Xu H. Wnt5a is involved in LOX-1 and TLR4 induced host inflammatory response in peri-implantitis. Journal of Periodontal Research. 2020; 55: 199–208. https://doi.org/10.1111/jre.12702.

[25] Menini M, Delucchi F, Baldi D, Pera F, Bagnasco F, Pesce P. Macrophagic Inflammatory Response Next to Dental Implants with Different Macro- and Micro-Structure: An *In Vitro* Study. Applied Sciences. 2021; 11: 5324. https://doi.org/10.3390/app11125324.

[26] Kheder W, Bouzid A, Venkatachalam T, Talaat IM, Elemam NM, Raju TK, *et al*. Titanium Particles Modulate Lymphocyte and Macrophage Polarization in Peri-Implant Gingival Tissues. International Journal of Molecular Sciences. 2023; 24: 11644. https://doi.org/10.3390/ijms241411644.

[27] Fretwurst T, Garaicoa-Pazmino C, Nelson K, Giannobile WV, Squarize CH, Larsson L, *et al*. Characterization of macrophages infiltrating peri-implantitis lesions. Clinical Oral Implants Research.

2020; 31: 274–281. https://doi.org/10.1111/clr.13568.

[28] Dionigi C, Larsson L, Carcuac O, Berglundh T. Cellular expression of DNA damage/repair and reactive oxygen/nitrogen species in human periodontitis and peri-implantitis lesions. Journal of Clinical Periodontology. 2020; 47: 1466–1475. https://doi.org/10.1111/jcpe.13370.

[29] Yuan S, Wang C, Jiang W, Wei Y, Li Q, Song Z, *et al*. Comparative Transcriptome Analysis of Gingival Immune-Mediated Inflammation in Peri-Implantitis and Periodontitis Within the Same Host Environment. Journal of Inflammation Research. 2022; 15: 3119–3133. https://doi.org/10.2147/jir.S363538.

[30] Galarraga-Vinueza ME, Dohle E, Ramanauskaite A, Al-Maawi S, Obreja K, Magini R, *et al*. Anti-inflammatory and macrophage polarization effects of Cranberry Proanthocyanidins (PACs) for periodontal and peri-implant disease therapy. Journal of Periodontal Research. 2020; 55: 821–829. https://doi.org/10.1111/jre.12773.

[31] Schlundt C, Fischer H, Bucher CH, Rendenbach C, Duda GN, Schmidt-Bleek K. The multifaceted roles of macrophages in bone regeneration: A story of polarization, activation and time. Acta Biomaterialia. 2021; 133: 46–57. https://doi.org/10.1016/j.actbio.2021.04.052.

[32] Hamlet SM, Lee RSB, Moon HJ, Alfarsi MA, Ivanovski S. Hydrophilic titanium surface-induced macrophage modulation promotes pro-osteogenic signalling. Clinical Oral Implants Research. 2019; 30: 1085–1096. https://doi.org/10.1111/clr.13522.

[33] Li Y, Li X, Guo D, Meng L, Feng X, Zhang Y, *et al*. Immune dysregulation and macrophage polarization in peri-implantitis. Frontiers in Bioengineering and Biotechnology. 2024; 12: 1291880. https://doi.org/10.3389/fbioe.2024.1291880.

[34] Horwood NJ. Macrophage Polarization and Bone Formation: A review. Clinical Reviews in Allergy & Immunology. 2016; 51: 79–86. https://doi.org/10.1007/s12016-015-8519-2.

[35] Hu K, Shang Z, Yang X, Zhang Y, Cao L. Macrophage Polarization and the Regulation of Bone Immunity in Bone Homeostasis. Journal of Inflammation Research. 2023; 16: 3563–3580. https://doi.org/10.2147/jir.S423819.

[36] Malmqvist S, Clark R, Johannsen G, Johannsen A, Boström EA, Lira-Junior R. Immune cell composition and inflammatory profile of human peri-implantitis and periodontitis lesions. Clinical and Experimental Immunology. 2024; 217: 173–182. https://doi.org/10.1093/cei/uxae033.

[37] Chen Z, Yan Q, Zhang R, Li Y, Huang S. Identification of novel candidate biomarkers related to immune cell infiltration in peri-implantitis. Oral Diseases. 2024; 30: 3982–3992. https://doi.org/10.1111/odi.14828.

[38] Künzli M, Masopust D. $CD4^+$ T cell memory. Nature Immunology. 2023; 24: 903–914. https://doi.org/10.1038/s41590-023-01510-4.

[39] Tait Wojno ED, Hunter CA, Stumhofer JS. The Immunobiology of the Interleukin-12 Family: Room for Discovery. Immunity. 2019; 50: 851–870. https://doi.org/10.1016/j.immuni.2019.03.011.

[40] Wu L, Deng H, Feng X, Xie D, Li Z, Chen J, *et al*. Interferon-γ^+ Th1 activates intrahepatic resident memory T cells to promote HBsAg loss by inducing M1 macrophage polarization. Journal of Medical Virology. 2024; 96: e29627. https://doi.org/10.1002/jmv.29627.

[41] Lim Y, Kim HY, An SJ, Choi BK. Activation of bone marrow-derived dendritic cells and $CD4^+$ T cell differentiation by outer membrane vesicles of periodontal pathogens. Journal of Oral Microbiology. 2022; 14: 2123550. https://doi.org/10.1080/20002297.2022.2123550.

[42] Giro G, Tebar A, Franco L, Racy D, Bastos MF, Shibli JA. Treg and TH17 link to immune response in individuals with peri-implantitis: a preliminary report. Clinical Oral Investigations. 2021; 25: 1291–1297. https://doi.org/10.1007/s00784-020-03435-w.

[43] Farhad SZ, Rezazadeh F, Mohammadi M. Interleukin-17 and Interleukin-10 as Inflammatory and Prevention Biomarkers in Peri-implant Diseases. International Journal of Preventive Medicine. 2019; 10: 137. https://doi.org/10.4103/ijpvm.IJPVM_27_19.

[44] Zhang J, Shi H, Zhang N, Hu L, Jing W, Pan J. Interleukin-4-loaded hydrogel scaffold regulates macrophages polarization to promote bone mesenchymal stem cells osteogenic differentiation via TGF-β1/Smad pathway for repair of bone defect. Cell Proliferation. 2020; 53: e12907. https://doi.org/10.1111/cpr.12907.

[45] Iwaszko M, Biały S, Bogunia-Kubik K. Significance of Interleukin (IL)-4 and IL-13 in Inflammatory Arthritis. Cells. 2021; 10: 3000. https://doi.org/10.3390/cells10113000.

[46] Omata Y, Frech M, Saito T, Schett G, Zaiss MM, Tanaka S. Inflammatory Arthritis and Bone Metabolism Regulated by Type 2 Innate and Adaptive Immunity. International Journal of Molecular Sciences. 2022; 23: 1104. https://doi.org/10.3390/ijms23031104.

[47] Wang Z, Wei Y, Lei L, Zhong J, Shen Y, Tan J, *et al*. RANKL expression of primary osteoblasts is enhanced by an IL-17-mediated JAK2/STAT3 pathway through autophagy suppression. Connective Tissue Research. 2021; 62: 411–426. https://doi.org/10.1080/03008207.2020.1759562.

[48] Liao C, Zhang C, Jin L, Yang Y. IL-17 alters the mesenchymal stem cell niche towards osteogenesis in cooperation with osteocytes. Journal of Cellular Physiology. 2020; 235: 4466–4480. https://doi.org/10.1002/jcp.29323.

[49] Heyman O, Koren N, Mizraji G, Capucha T, Wald S, Nassar M, *et al*. Impaired Differentiation of Langerhans Cells in the Murine Oral Epithelium Adjacent to Titanium Dental Implants. Frontiers in Immunology. 2018; 9: 1712. https://doi.org/10.3389/fimmu.2018.01712.

[50] Wang B, Dong Y, Tian Z, Chen Y, Dong S. The role of dendritic cells derived osteoclasts in bone destruction diseases. Genes & Diseases. 2021; 8: 401–411. https://doi.org/10.1016/j.gendis.2020.03.009.

[51] Al-Bakri SMR, Magan-Fernandez A, Galindo-Moreno P, O'Valle F, Martin-Morales N, Padial-Molina M, *et al*. Detection and comparison of neutrophil extracellular traps in tissue samples of peri-implantitis, periodontitis, and healthy patients: A pilot study. Clinical Implant Dentistry and Related Research. 2024; 26: 631–641. https://doi.org/10.1111/cid.13325.

[52] Amara N, Cooper MP, Voronkova MA, Webb BA, Lynch EM, Kollman JM, *et al*. Selective activation of PFKL suppresses the phagocytic oxidative burst. Cell. 2021; 184: 4480–4494.e15. https://doi.org/10.1016/j.cell.2021.07.004.

[53] Chapple ILC, Hirschfeld J, Kantarci A, Wilensky A, Shapira L. The role of the host—Neutrophil biology. Periodontology 2000. 2023. (online ahead of print) https://doi.org/10.1111/prd.12490.

[54] Fischer V, Haffner-Luntzer M. Interaction between bone and immune cells: Implications for postmenopausal osteoporosis. Seminars in Cell & Developmental Biology. 2022; 123: 14–21. https://doi.org/10.1016/j.semcdb.2021.05.014.

[55] Radaelli K, Alberti A, Corbella S, Francetti L. The Impact of Peri-Implantitis on Systemic Diseases and Conditions: A Review of the Literature. International Journal of Dentistry. 2021; 2021: 5536566. https://doi.org/10.1155/2021/5536566.

[56] Fan W, Tang J, Xu H, Huang X, Wu D, Zhang Z. Early diagnosis for the onset of peri-implantitis based on artificial neural network. Open Life Sciences. 2023; 18: 20220691. https://doi.org/10.1515/biol-2022-0691.

[57] Seidel A, Seidel CL, Weider M, Junker R, Gölz L, Schmetzer H. Influence of Natural Killer Cells and Natural Killer T Cells on Periodontal Disease: A Systematic Review of the Current Literature. International Journal of Molecular Sciences. 2020; 21: 9766. https://doi.org/10.3390/ijms21249766.

[58] Villalobos V, Silva I, Morales D, Canelo J, Garrido M, Carreño LJ, *et al*. Topological insight of immune-vascular distribution in peri-implantitis lesions. Oral Diseases. 2024; 30: 5305–5314. https://doi.org/10.1111/odi.14935.

[59] Chaparro A, Sanz A, Wolnitzky A, Realini O, Bendek MJ, Betancur D, *et al*. Lymphocyte B and Th17 chemotactic cytokine levels in peri-

implant crevicular fluid of patients with healthy, peri-mucositis, and peri-implantitis implants. Journal of Oral Research. 2020; S1: 20–25. https://doi.org/10.17126/joralres.2020.029.

[60] Chen D, Wu X, Liu Q, Cai H, Huang B, Chen Z. Memory B Cell as an Indicator of Peri-implantitis Status: A Pilot Study. The International Journal of Oral & Maxillofacial Implants. 2021; 36: 86–93. https://doi.org/10.11607/jomi.8641.

[61] Han Y, Jin Y, Miao Y, Shi T, Lin X. Improved RANKL expression and osteoclastogenesis induction of CD27+CD38-memory B cells: A link between B cells and alveolar bone damage in periodontitis. Journal of Periodontal Research. 2019; 54: 73–80. https://doi.org/10.1111/jre.12606.

[62] Murakami H, Tsuzukibashi O, Fukatsu A, Takahashi Y, Idei K, Usuda K, *et al*. Investigation of Bacteria Species Most Involved in Peri-Implantitis. Open Journal of Stomatology. 2023; 13: 353–366. https://doi.org/10.4236/ojst.2023.1310029.

[63] Canullo L, Peñarrocha-Oltra D, Covani U, Botticelli D, Serino G, Penarrocha M. Clinical and microbiological findings in patients with peri-implantitis: a cross-sectional study. Clinical Oral Implants Research. 2016; 27: 376–382. https://doi.org/10.1111/clr.12557.

[64] de Waal YC, Eijsbouts HV, Winkel EG, van Winkelhoff AJ. Microbial Characteristics of Peri-Implantitis: A Case-Control Study. Journal of Periodontology. 2017; 88: 209–217. https://doi.org/10.1902/jop.2016.160231.

[65] Lafaurie GI, Sabogal MA, Castillo DM, Rincón MV, Gómez LA, Lesmes YA, *et al*. Microbiome and Microbial Biofilm Profiles of Peri-Implantitis: A Systematic Review. Journal of Periodontology. 2017; 88: 1066–1089. https://doi.org/10.1902/jop.2017.170123.

[66] Wang HL, Garaicoa-Pazmino C, Collins A, Ong HS, Chudri R, Giannobile WV. Protein biomarkers and microbial profiles in peri-implantitis. Clinical Oral Implants Research. 2016; 27: 1129–1136. https://doi.org/10.1111/clr.12708.

[67] Wang Q, Lu H, Zhang L, Yan X, Zhu B, Meng H. Peri-implant mucositis sites with suppuration have higher microbial risk than sites without suppuration. Journal of Periodontology. 2020; 91: 1284–1294. https://doi.org/10.1002/jper.19-0634.

[68] Cai X, Li Z, Zhao Y, Katz J, Michalek SM, Feng X, *et al*. Enhanced dual function of osteoclast precursors following calvarial Porphyromonas gingivalis infection. Journal of Periodontal Research. 2020; 55: 410–425. https://doi.org/10.1111/jre.12725.

[69] Jia L, Wu R, Han N, Fu J, Luo Z, Guo L, *et al*. *Porphyromonas gingivalis* and *Lactobacillus rhamnosus* GG regulate the Th17/Treg balance in colitis via TLR4 and TLR2. Clinical & Translational Immunology. 2020; 9: e1213. https://doi.org/10.1002/cti2.1213.

[70] Xu W, Zhou W, Wang H, Liang S. Roles of Porphyromonas gingivalis and its virulence factors in periodontitis. Advances in Protein Chemistry and Structural Biology. 2020; 120: 45–84. https://doi.org/10.1016/bs.apcsb.2019.12.001.

[71] Zheng S, Yu S, Fan X, Zhang Y, Sun Y, Lin L, *et al*. Porphyromonas gingivalis survival skills: Immune evasion. Journal of Periodontal Research. 2021; 56: 1007–1018. https://doi.org/10.1111/jre.12915.

[72] Rajasekar A, Varghese SS. Microbiological Profile in Periodontitis and Peri-Implantitis: A Systematic Review. Journal of Long-Term Effects of Medical Implants. 2022; 32: 83–94. https://doi.org/10.1615/JLongTermEffMedImplants.2022043121.

[73] Ando-Suguimoto ES, Benakanakere MR, Mayer MPA, Kinane DF. Distinct Signaling Pathways Between Human Macrophages and Primary Gingival Epithelial Cells by *Aggregatibacter actinomycetemcomitans*. Pathogens. 2020; 9: 248. https://doi.org/10.3390/pathogens9040248.

[74] Chen Y, Shi T, Li Y, Huang L, Yin D. *Fusobacterium nucleatum*: The Opportunistic Pathogen of Periodontal and Peri-Implant Diseases. Frontiers in Microbiology. 2022; 13: 860149. https://doi.org/10.3389/fmicb.2022.860149.

[75] Groeger S, Zhou Y, Ruf S, Meyle J. Pathogenic Mechanisms of *Fusobacterium nucleatum* on Oral Epithelial Cells. Frontiers in Oral Health. 2022; 3: 831607. https://doi.org/10.3389/froh.2022.831607.

[76] Kang W, Ji X, Zhang X, Tang D, Feng Q. Persistent Exposure to *Fusobacterium nucleatum* Triggers Chemokine/Cytokine Release and Inhibits the Proliferation and Osteogenic Differentiation Capabilities of Human Gingiva-Derived Mesenchymal Stem Cells. Frontiers in Cellular and Infection Microbiology. 2019; 9: 429. https://doi.org/10.3389/fcimb.2019.00429.

[77] de Jong NWM, van Kessel KPM, van Strijp JAG. Immune Evasion by *Staphylococcus aureus*. Microbiology Spectrum. 2019; 7: GPP3-0061-2019. https://doi.org/10.1128/microbiolspec.GPP3-0061-2019.

[78] Li Y, Stewart CA, Finer Y. Advanced Antimicrobial and Anti-Infective Strategies to Manage Peri-Implant Infection: A Narrative Review. Dentistry Journal. 2024; 12: 125. https://doi.org/10.3390/dj12050125.

[79] Lafuente-Ibáñez de Mendoza I, Setien-Olarra A, García-De la Fuente AM, Aguirre-Urizar JM, Marichalar-Mendia X. Role of proinflammatory mutations in peri-implantitis: systematic review and meta-analysis. International Journal of Implant Dentistry. 2022; 8: 2. https://doi.org/10.1186/s40729-022-00400-y.

[80] Ghassib I, Chen Z, Zhu J, Wang HL. Use of IL-1 β, IL-6, TNF-α, and MMP-8 biomarkers to distinguish peri-implant diseases: A systematic review and meta-analysis. Clinical Implant Dentistry and Related Research. 2019; 21: 190–207. https://doi.org/10.1111/cid.12694.

[81] He K, Jian F, He T, Tang H, Huang B, Wei N. Analysis of the association of TNF-α, IL-1A, and IL-1B polymorphisms with peri-implantitis in a Chinese non-smoking population. Clinical Oral Investigations. 2020; 24: 693–699. https://doi.org/10.1007/s00784-019-02968-z.

[82] Rakic M, Petkovic-Curcin A, Struillou X, Matic S, Stamatovic N, Vojvodic D. CD14 and TNFα single nucleotide polymorphisms are candidates for genetic biomarkers of peri-implantitis. Clinical Oral Investigations. 2015; 19: 791–801. https://doi.org/10.1007/s00784-014-1313-3.

[83] Saremi L, Shafizadeh M, Esmaeilzadeh E, Ghaffari ME, Mahdavi MH, Amid R, *et al*. Assessment of IL-10, IL-1ß and TNF-α gene polymorphisms in patients with peri-implantitis and healthy controls. Molecular Biology Reports. 2021; 48: 2285–2290. https://doi.org/10.1007/s11033-021-06253-9.

[84] Talib EQ, Taha GI. Involvement of interlukin-17A (IL-17A) gene polymorphism and interlukin-23 (IL-23) level in the development of peri-implantitis. BDJ Open. 2024; 10: 12. https://doi.org/10.1038/s41405-024-00193-9.

[85] Kadkhodazadeh M, Baghani Z, Ebadian AR, Kaghazchi Z, Amid R. Receptor activator of nuclear factor kappa-B gene polymorphisms in Iranian periodontitis and peri-implantitis patients. Journal of Periodontal & Implant Science. 2014; 44: 141–146. https://doi.org/10.5051/jpis.2014.44.3.141.

[86] Li J, Qiao X, Shang J. Association analysis between CD14 gene polymorphisms and peri-implantitis susceptibility in a Chinese population. Immunity, Inflammation and Disease. 2024; 12: e1230. https://doi.org/10.1002/iid3.1230.

[87] Motahari P, Rasi A. The relationship between polymorphism of interleukin-6 and osteoprotgerin genes with dental peri-implant disease: A meta-analysis. Gene Reports. 2021; 23: 101133. https://doi.org/10.1016/j.genrep.2021.101133.

[88] Saremi L, Esmaeilzadeh E, Ghorashi T, Sohrabi M, Ekhlasmand Kermani M, Kadkhodazadeh M. Association of Fc gamma-receptor genes polymorphisms with chronic periodontitis and Peri-Implantitis. Journal of Cellular Biochemistry. 2019; 120: 12010–12017. https://doi.org/10.1002/jcb.28486.

[89] Abduljabbar T, Akram Z, Vohra F, Warnakulasuriya S, Javed F. Assessment of interleukin-1β, interleukin-6, and tumor necrosis factor-A levels in the peri-implant sulcular fluid among waterpipe (narghile) smokers and never-smokers with peri-implantitis. Clin-

ical Implant Dentistry and Related Research. 2018; 20: 144–150. https://doi.org/10.1111/cid.12557.

[90] Alshahrani FA, Alqarawi FK, Alqutub MN, AlMubarak AM, Al-Hamdan EM, Al-Saleh S, *et al*. Association of Self-Rated Pain with Clinical Peri-Implant Parameters and Cytokine Profile in Smokers and Never Smokers with and without Peri-Implantitis. Applied Sciences. 2021; 11: 5559. https://doi.org/10.3390/app11125559.

[91] Reis INRD, do Amaral GCLS, Hassan MA, Villar CC, Romito GA, Spin-Neto R, *et al*. The influence of smoking on the incidence of peri-implantitis: A systematic review and meta-analysis. Clinical Oral Implants Research. 2023; 34: 543–554. https://doi.org/10.1111/clr.14066.

[92] Hyldahl E, Gotfredsen K, Lynge Pedersen AM, Storgård Jensen S. Survival and Success of Dental Implants in Patients with Autoimmune Diseases: a Systematic Review. Journal of Oral & Maxillofacial Research. 2024; 15: e1. https://doi.org/10.5037/jomr.2024.15101.

[93] Al-Askar M, Ajlan S, Alomar N, Al-Daghri NM. Clinical and Radiographic Peri-Implant Parameters and Whole Salivary Interleukin-1β and Interleukin-6 Levels among Type-2 Diabetic and Nondiabetic Patients with and without Peri-Implantitis. Medical Principles and Practice: International Journal of the Kuwait University, Health Science Centre. 2018; 27: 133–138. https://doi.org/10.1159/000488032.

[94] Lv X, Zou L, Zhang X, Zhang X, Lai H, Shi J. Effects of diabetes/hyperglycemia on peri-implant biomarkers and clinical and radiographic outcomes in patients with dental implant restorations: A systematic review and meta-analysis. Clinical Oral Implants Research. 2022; 33: 1183–1198. https://doi.org/10.1111/clr.14010.

[95] Romero-Díaz C, Duarte-Montero D, Gutiérrez-Romero SA, Mendivil CO. Diabetes and Bone Fragility. Diabetes Therapy: Research, Treatment and Education of Diabetes and Related Disorders. 2021; 12: 71–86. https://doi.org/10.1007/s13300-020-00964-1.

[96] Lee SJ, Alamri O, Cao H, Wang Y, Gallucci GO, Lee JD. Occlusion as a predisposing factor for peri-implant disease: A review article. Clinical Implant Dentistry and Related Research. 2023; 25: 734–742. https://doi.org/10.1111/cid.13152.

[97] Viña-Almunia J, Pellicer-Chover H, García-Mira B, Romero-Millán J, Peñarrocha-Oltra D, Peñarrocha-Diago M. Influence of occlusal loading on peri-implant inflammatory cytokines in crevicular fluid: a prospective longitudinal study. International Journal of Implant Dentistry. 2020; 6: 71. https://doi.org/10.1186/s40729-020-00262-2.

[98] Xu W, Lu Y, Yue J, Lu W, Zhou W, Zhou X, *et al*. Occlusal trauma inhibits osteoblast differentiation and bone formation through IKK-NF-κB signaling. Journal of Periodontology. 2020; 91: 683–692. https://doi.org/10.1002/jper.18-0710.

[99] Abaricia JO, Shah AH, Chaubal M, Hotchkiss KM, Olivares-Navarrete R. Wnt signaling modulates macrophage polarization and is regulated by biomaterial surface properties. Biomaterials. 2020; 243: 119920. https://doi.org/10.1016/j.biomaterials.2020.119920.

[100] Takamori Y, Atsuta I, Nakamura H, Sawase T, Koyano K, Hara Y. Histopathological comparison of the onset of peri-implantitis and periodontitis in rats. Clinical Oral Implants Research. 2017; 28: 163–170. https://doi.org/10.1111/clr.12777.

[101] Corrêa MG, Pimentel SP, Ribeiro FV, Cirano FR, Casati MZ. Host response and peri-implantitis. Brazilian Oral Research. 2019; 33: e066. https://doi.org/10.1590/1807-3107bor-2019.vol33.0066.

[102] Zhang H, Sun M, Xu H, Huang H. Th-Cell Subsets of Submandibular Lymph Nodes in Peri-Implantitis. The Journal of Craniofacial Surgery. 2024; 35: 692–698. https://doi.org/10.1097/scs.0000000000009927.

[103] Shi T, Jin Y, Miao Y, Wang Y, Zhou Y, Lin X. IL-10 secreting B cells regulate periodontal immune response during periodontitis. Odontology/the Society of the Nippon Dental University. 2020; 108: 350–357. https://doi.org/10.1007/s10266-019-00470-2.

[104] Pârvu AE, Tălu S, Taulescu MA, Bota A, Cătoi F, Crăciun C, *et al*. Fractal analysis of ibuprofen effect on experimental dog peri-implantitis. Implant Dentistry. 2014; 23: 295–304. https://doi.org/10.1097/id.0000000000000065.

[105] Sakka S, Hanouneh SI. Investigation of the effect of ibuprofen on the healing of osseointegrated oral implants. Journal of Investigative and Clinical Dentistry. 2013; 4: 113–119. https://doi.org/10.1111/j.2041-1626.2012.00164.x

[106] Theken KN, Chen M, Wall DL, Pham T, Secreto SA, Yoo TH, *et al*. A randomized, double-blind pilot study of analgesic and anti-inflammatory effects of naproxen sodium and acetaminophen following dental implant placement surgery. Frontiers in Pharmacology. 2023; 14: 1199580. https://doi.org/10.3389/fphar.2023.1199580.

[107] Zhou Z, Zhang Q, Wang Y. Preparation and characterization of antibacterial and anti-inflammatory hyaluronic acid-chitosan-dexamethasone hydrogels for peri-implantitis repair. Journal of Biomaterials Applications. 2022; 36: 1141–1150. https://doi.org/10.1177/08853282211047939.

[108] Toledano-Osorio M, de Luna-Bertos E, Toledano M, Manzano-Moreno FJ, Costela-Ruiz V, Ruiz C, *et al*. Dexamethasone and doxycycline functionalized nanoparticles enhance osteogenic properties of titanium surfaces. Dental Materials: Official Publication of the Academy of Dental Materials. 2023; 39: 616–623. https://doi.org/10.1016/j.dental.2023.05.004.

[109] Maruyama M, Rhee C, Utsunomiya T, Zhang N, Ueno M, Yao Z, *et al*. Modulation of the Inflammatory Response and Bone Healing. Frontiers in Endocrinology. 2020; 11: 386. https://doi.org/10.3389/fendo.2020.00386.

[110] Ferreira-Junior AEC, Barros-Silva PG, Oliveira CC, Lima Verde MEQ, Sousa FB, Mota MRL, *et al*. Influence of infliximab therapy on bone healing post-dental extraction in rats. Archives of Oral Biology. 2020; 112: 104680. https://doi.org/10.1016/j.archoralbio.2020.104680.

[111] Kim JH, Kim AR, Choi YH, Jang S, Woo GH, Cha JH, *et al*. Tumor necrosis factor-α antagonist diminishes osteocytic RANKL and sclerostin expression in diabetes rats with periodontitis. PLoS One. 2017; 12: e0189702. https://doi.org/10.1371/journal.pone.0189702.

[112] Zhao J, Li J, Xu A, Xu Y, He F, Mao Y. IRAK4 inhibition: an effective strategy for immunomodulating peri-implant osseointegration via reciprocally-shifted polarization in the monocyte-macrophage lineage cells. BMC Oral Health. 2023; 23: 265. https://doi.org/10.1186/s12903-023-03011-0.

[113] Heyman O, Horev Y, Mizraji G, Haviv Y, Shapira L, Wilensky A. Excessive inflammatory response to infection in experimental peri-implantitis: Resolution by Resolvin D2. Journal of Clinical Periodontology. 2022; 49: 1217–1228. https://doi.org/10.1111/jcpe.13631.

[114] Wu X, Qiao S, Wang W, Zhang Y, Shi J, Zhang X, *et al*. Melatonin prevents peri-implantitis via suppression of TLR4/NF-κB. Acta Biomaterialia. 2021; 134: 325–336. https://doi.org/10.1016/j.actbio.2021.07.017.

[115] Li H, Chen Z, Zhong X, Li J, Li W. Mangiferin alleviates experimental peri-implantitis via suppressing interleukin-6 production and Toll-like receptor 2 signaling pathway. Journal of Orthopaedic Surgery and Research. 2019; 14: 325. https://doi.org/10.1186/s13018-019-1387-3.

[116] Liu N, Huang S, Guo F, Zhai S, Wang D, Li F, *et al*. Calcium phosphate cement with icariin-loaded gelatin microspheres as a local drug delivery system for bone regeneration. Biomedical Engineering Online. 2022; 21: 89. https://doi.org/10.1186/s12938-022-01052-0.

[117] Chen D, Yu C, Ying Y, Luo Y, Ren L, Zhu C, *et al*. Study of the Osteoimmunomodulatory Properties of Curcumin-Modified Copper-Bearing Titanium. Molecules: a Journal of Synthetic Chemistry and Natural Product Chemistry. 2022; 27: 3205. https://doi.org/10.3390/molecules27103205.

[118] Wang X, Chen X, Zhang Z, Chen J, Ge Z, Huang S, *et al*. As-

peruloside Prevents Peri-Implantitis via Suppression of NF-κB and ERK1/2 on Rats. Pharmaceuticals. 2022; 15: 1027. https://doi.org/10.3390/ph15081027.

[119] Gassner T, Chittilappilly C, Pirich T, Neuditschko B, Hackner K, Lind J, *et al*. Favorable impact of PD1/PD-L1 antagonists on bone remodeling: an exploratory prospective clinical study and *ex vivo* validation. Journal for Immunotherapy of Cancer. 2024; 12: e008669. https://doi.org/10.1136/jitc-2023-008669.

[120] Bailly C. The implication of the PD-1/PD-L1 checkpoint in chronic periodontitis suggests novel therapeutic opportunities with natural products. The Japanese Dental Science Review. 2020; 56: 90–96. https://doi.org/10.1016/j.jdsr.2020.04.002.

[121] Hossen MM, Ma Y, Yin Z, Xia Y, Du J, Huang JY, *et al*. Current understanding of CTLA-4: from mechanism to autoimmune diseases. Frontiers in Immunology. 2023; 14: 1198365. https://doi.org/10.3389/fimmu.2023.1198365.

[122] Motley MP, Banerjee K, Fries BC. Monoclonal antibody-based therapies for bacterial infections. Current Opinion in Infectious Diseases. 2019; 32: 210–216. https://doi.org/10.1097/QCO.0000000000000539.

[123] Burke ZDC, Hart CM, Kelley BV, Mamouei Z, Blumstein GW, Hamad C, *et al*. Monoclonal Antibody Disrupts Biofilm Structure and Restores Antibiotic Susceptibility in an Orthopedic Implant Infection Model. Antibiotics. 2023; 12: 1490. https://doi.org/10.3390/antibiotics12101490.

[124] Li C, Wang Z, Zhu L, Fan X, Lan J. Experimental research on Arginine-gingipain A gene vaccine from Porphyromonas gingivalis that prevents peri-implantitis in Beagle dogs. Hua Xi Kou Qiang Yi Xue Za Zhi = Huaxi Kouqiang Yixue Zazhi = West China Journal of Stomatology. 2018; 36: 76–81. https://doi.org/10.7518/hxkq.2018.01.015.

[125] Rocha FG, Berges A, Sedra A, Ghods S, Kapoor N, Pill L, *et al*. A *Porphyromonas gingivalis* Capsule-Conjugate Vaccine Protects From Experimental Oral Bone Loss. Frontiers in Oral Health. 2021; 2: 686402. https://doi.org/10.3389/froh.2021.686402.

[126] Yadalam PK, Rengaraj S, Mugri MH, Sayed M, Porwal A, Alahmari NM, *et al*. Designing an immunoinformatic vaccine for *peri*-implantitis using a structural biology approach. Saudi Journal of Biological Sciences. 2022; 29: 622–629. https://doi.org/10.1016/j.sjbs.2021.09.041.

[127] Fan X, Qu PY, Luan KF, Sun CY, Ren HP, Sun XH, *et al*. A cleaved adhesin DNA vaccine targeting dendritic cell against Porphyromonas gingivalis-induced periodontal disease. Molecular Oral Microbiology. 2024; 39: 433–445. https://doi.org/10.1111/omi.12465.

[128] Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, *et al*. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Reviews. Gastroenterology & Hepatology. 2014; 11: 506–514. https://doi.org/10.1038/nrgastro.2014.66.

[129] Ambili R, Nazimudeen NB. Adjunctive benefit of probiotic supplementation along with nonsurgical therapy for peri-implant diseases—A systematic review and meta-analysis. Journal of Indian Society of Periodontology. 2023; 27: 352–361. https://doi.org/10.4103/jisp.jisp_308_22.

[130] Mulla M, Mulla M, Hegde S, Koshy AV. *In vitro* assessment of the effect of probiotic lactobacillus reuteri on peri-implantitis microflora. BMC Oral Health. 2021; 21: 408. https://doi.org/10.1186/s12903-021-01762-2.

[131] Galofré M, Palao D, Vicario M, Nart J, Violant D. Clinical and microbiological evaluation of the effect of Lactobacillus reuteri in the treatment of mucositis and peri-implantitis: A triple-blind randomized clinical trial. Journal of Periodontal Research. 2018; 53: 378–390. https://doi.org/10.1111/jre.12523.

[132] Jia L, Tu Y, Jia X, Du Q, Zheng X, Yuan Q, *et al*. Probiotics ameliorate alveolar bone loss by regulating gut microbiota. Cell Proliferation. 2021; 54: e13075. https://doi.org/10.1111/cpr.13075.

[133] Amin N, Boccardi V, Taghizadeh M, Jafarnejad S. Probiotics and bone disorders: the role of RANKL/RANK/OPG pathway. Aging Clinical and Experimental Research. 2020; 32: 363–371. https://doi.org/10.1007/s40520-019-01223-5.

[134] Behera J, Ison J, Voor MJ, Tyagi N. Probiotics Stimulate Bone Formation in Obese Mice via Histone Methylations. Theranostics. 2021; 11: 8605–8623. https://doi.org/10.7150/thno.63749.

[135] Davani-Davari D, Negahdaripour M, Karimzadeh I, Seifan M, Mohkam M, Masoumi SJ, *et al*. Prebiotics: Definition, Types, Sources, Mechanisms, and Clinical Applications. Foods. 2019; 8: 92. https://doi.org/10.3390/foods8030092.

[136] Artoni de Carvalho JA, Magalhães LR, Polastri LM, Batista IET, de Castro Bremer S, Caetano HRDS, *et al*. Prebiotics improve osteoporosis indicators in a preclinical model: systematic review with meta-analysis. Nutrition Reviews. 2023. (online ahead of print) https://doi.org/10.1093/nutrit/nuac097.

[137] Whisner CM, Castillo LF. Prebiotics, Bone and Mineral Metabolism. Calcified Tissue International. 2018; 102: 443–479. https://doi.org/10.1007/s00223-017-0339-3.

[138] Isola G, Polizzi A, Iorio-Siciliano V, Alibrandi A, Ramaglia L, Leonardi R. Effectiveness of a nutraceutical agent in the non-surgical periodontal therapy: a randomized, controlled clinical trial. Clinical Oral Investigations. 2021; 25: 1035–1045. https://doi.org/10.1007/s00784-020-03397-z.

[139] McCarty MF, Lewis Lujan L, Iloki Assanga S. Targeting Sirt1, AMPK, Nrf2, CK2, and Soluble Guanylate Cyclase with Nutraceuticals: A Practical Strategy for Preserving Bone Mass. International Journal of Molecular Sciences. 2022; 23: 4776. https://doi.org/10.3390/ijms23094776.

[140] Lorusso F, Scarano A, Fulle S, Valbonetti L, Mancinelli R, Di Filippo ES. Effectiveness of Apigenin, Resveratrol, and Curcumin as Adjuvant Nutraceuticals for Calvarial Bone Defect Healing: An *In Vitro* and Histological Study on Rats. Nutrients. 2023; 15: 1235. https://doi.org/10.3390/nu15051235.

[141] Mannino F, D'Angelo T, Pallio G, Ieni A, Pirrotta I, Giorgi DA, *et al*. The Nutraceutical Genistein-Lycopene Combination Improves Bone Damage Induced by Glucocorticoids by Stimulating the Osteoblast Formation Process. Nutrients. 2022; 14: 4296. https://doi.org/10.3390/nu14204296.

[142] Jamilloux Y, El Jammal T, Vuitton L, Gerfaud-Valentin M, Kerever S, Sève P. JAK inhibitors for the treatment of autoimmune and inflammatory diseases. Autoimmunity Reviews. 2019; 18: 102390. https://doi.org/10.1016/j.autrev.2019.102390.

[143] Etikala A, Tattan M, Askar H, Wang HL. Effects of NSAIDs on Periodontal and Dental Implant Therapy. Compendium of Continuing Education in Dentistry. 2019; 40: e1–e9.

[144] Kim JY, Choi H, Park JH, Jung HD, Jung YS. Effects of antiresorptive drugs on implant survival and peri-implantitis in patients with existing osseointegrated dental implants: a retrospective cohort study. Osteoporosis International: a Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2020; 31: 1749–1758. https://doi.org/10.1007/s00198-019-05257-3.

[145] Cillo JE Jr, Barbosa N. Adalimumab-Related Dental Implant Infection. Journal of Oral and Maxillofacial Surgery: Official Journal of the American Association of Oral and Maxillofacial Surgeons. 2019; 77: 1165–1169. https://doi.org/10.1016/j.joms.2019.01.033.

[146] Xu C, Chen YP, Du XJ, Liu JQ, Huang CL, Chen L, *et al*. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. BMJ: British Medical Journal/British Medical Association. 2018; 363: k4226. https://doi.org/10.1136/bmj.k4226.

[147] Zhang Y, Gulati K, Li Z, Di P, Liu Y. Dental Implant Nano-Engineering: Advances, Limitations and Future Directions. Nano-

materials. 2021; 11: 2489. https://doi.org/10.3390/nano11102489.
[148] Weber EW, Maus MV, Mackall CL. The Emerging Landscape of Immune Cell Therapies. Cell. 2020; 181: 46–62. https://doi.org/10.1016/j.cell.2020.03.001.
[149] Goker F, Larsson L, Del Fabbro M, Asa'ad F. Gene Delivery Therapeutics in the Treatment of Periodontitis and Peri-Implantitis: A State of the Art Review. International Journal of Molecular Sciences. 2019; 20: 3551. https://doi.org/10.3390/ijms20143551.
[150] Kinane DF. Epigenetic and Gene Modification Precision Medicine Approaches for the "Chronic Destructive Perio-Diseases": Periodontitis and Peri-implantitis. In Sahingur, S. (ed.) Emerging Therapies in Periodontics (pp. 87–96). Springer, Cham: Switzerland. 2020. https://doi.org/10.1007/978-3-030-42990-4_7.
[151] Zhang X, Wang Z, Hu L, Shen X, Liu C. Identification of Potential Genetic Biomarkers and Target Genes of Peri-Implantitis Using Bioinformatics Tools. BioMed Research International. 2021; 2021: 1759214. https://doi.org/10.1155/2021/1759214.
[152] Hou L, Ye Y, Gou H, Tang H, Zhou Y, Xu X, *et al*. A20 inhibits periodontal bone resorption and NLRP3-mediated M1 macrophage polarization. Experimental Cell Research. 2022; 418: 113264. https://doi.org/10.1016/j.yexcr.2022.113264.
[153] Song A, Jiang F, Wang Y, Wang M, Wu Y, Zheng Y, *et al*. Semaphorin3A promotes osseointegration of titanium implants in osteoporotic rabbits. Clinical Oral Investigations. 2022; 26: 969–979. https://doi.org/10.1007/s00784-021-04081-6.
[154] Weng J, Fan H, Liu H, Tang S, Zheng Y. Abnormal Decrease of Macrophage ALKBH5 Expression Causes Abnormal Polarization and Inhibits Osteoblast Differentiation. Stem Cells International. 2023; 2023: 9974098. https://doi.org/10.1155/2023/9974098.
[155] Xue Y, Liang Z, Fu X, Wang T, Xie Q, Ke D. IL-17A modulates osteoclast precursors' apoptosis through autophagy-TRAF3 signaling during osteoclastogenesis. Biochemical and Biophysical Research Communications. 2019; 508: 1088–1092. https://doi.org/10.1016/j.bbrc.2018.12.029.
[156] Huang X, Wang M, Wu X, Zou Y, Xu J, Cao C, *et al*. Screening DNA aptamers that control the DNA cleavage, homology-directed repair, and transcriptional regulation of the CRISPR-(d)Cas9 system. Molecular Therapy: the Journal of the American Society of Gene Therapy. 2023; 31: 260–268. https://doi.org/10.1016/j.ymthe.2022.10.009.
[157] Kedlaya MN, Puzhankara L, Prasad R, Raj A. Periodontal Disease Pathogens, Pathogenesis, and Therapeutics: The CRISPR-Cas Effect. The CRISPR Journal. 2023; 6: 90–98. https://doi.org/10.1089/crispr.2022.0094.
[158] Ponta S, Bonato A, Neidenbach P, Bruhin VF, Laurent A, Applegate LA, *et al*. Streamlined, single-step non-viral CRISPR-Cas9 knockout strategy enhances gene editing efficiency in primary human chondrocyte populations. Arthritis Research & Therapy. 2024; 26: 66. https://doi.org/10.1186/s13075-024-03294-w.
[159] Farhang N, Ginley-Hidinger M, Berrett KC, Gertz J, Lawrence B, Bowles RD. Lentiviral CRISPR Epigenome Editing of Inflammatory Receptors as a Gene Therapy Strategy for Disc Degeneration. Human Gene Therapy. 2019; 30: 1161–1175. https://doi.org/10.1089/hum.2019.005.
[160] Urvasizoglu G, Kilic A, Barlak N, Gundogdu M, Karatas OF. MiR-4484 Acts as a Potential Saliva Biomarker for Early Detection of Peri-implantitis. The International Journal of Oral & Maxillofacial Implants. 2021; 36: 115–121. https://doi.org/10.11607/jomi.8470.
[161] Wu X, Gu Q, Chen X, Mi W, Wu T, Huang H. MiR-27a targets DKK2 and SFRP1 to promote reosseointegration in the regenerative treatment of peri-implantitis. Journal of Bone and Mineral Research: the Official Journal of the American Society for Bone and Mineral Research. 2019; 34: 123–134. https://doi.org/10.1002/jbmr.3575.
[162] Pan K, Hu Y, Wang Y, Li H, Patel M, Wang D, *et al*. RANKL blockade alleviates peri-implant bone loss and is enhanced by anti-inflammatory microRNA-146a through TLR2/4 signaling. International Journal of Implant Dentistry. 2020; 6: 15. https://doi.org/10.1186/s40729-020-00210-0.
[163] Wang C, Qiao X, Zhang Z, Li C. MiR-128 promotes osteogenic differentiation of bone marrow mesenchymal stem cells in rat by targeting DKK2. Bioscience Reports. 2020; 40: BSR20182121. https://doi.org/10.1042/bsr20182121.
[164] Naik S, Larsen SB, Cowley CJ, Fuchs E. Two to Tango: Dialog between Immunity and Stem Cells in Health and Disease. Cell. 2018; 175: 908–920. https://doi.org/10.1016/j.cell.2018.08.071.
[165] Shang V, Li J, Little CB, Li JJ. Understanding the effects of mesenchymal stromal cell therapy for treating osteoarthritis using an *in vitro* co-culture model. European Cells & Materials. 2023; 45: 143–157. https://doi.org/10.22203/eCM.v045a10.
[166] López-García L, Castro-Manrreza ME. TNF-α and IFN-γ Participate in Improving the Immunoregulatory Capacity of Mesenchymal Stem/Stromal Cells: Importance of Cell-Cell Contact and Extracellular Vesicles. International Journal of Molecular Sciences. 2021; 22: 9531. https://doi.org/10.3390/ijms22179531.
[167] Najar M, Rahmani S, Faour WH, Alsabri SG, Lombard CA, Fayyad-Kazan H, *et al*. Umbilical Cord Mesenchymal Stromal/Stem Cells and Their Interplay with Th-17 Cell Response Pathway. Cells. 2024; 13: 169. https://doi.org/10.3390/cells13020169.
[168] Ding L, Tang S, Liang P, Wang C, Zhou PF, Zheng L. Bone Regeneration of Canine Peri-implant Defects Using Cell Sheets of Adipose-Derived Mesenchymal Stem Cells and Platelet-Rich Fibrin Membranes. Journal of Oral and Maxillofacial Surgery: Official Journal of the American Association of Oral and Maxillofacial Surgeons. 2019; 77: 499–514. https://doi.org/10.1016/j.joms.2018.10.018.
[169] Egido-Moreno S, Valls-Roca-Umbert J, Céspedes-Sánchez JM, López-López J, Velasco-Ortega E. Clinical Efficacy of Mesenchymal Stem Cells in Bone Regeneration in Oral Implantology. Systematic Review and Meta-Analysis. International Journal of Environmental Research and Public Health. 2021; 18: 894. https://doi.org/10.3390/ijerph18030894.
[170] Singhal L, Belludi SA, Pradhan N, Manvi S. A comparative evaluation of the effect of platelet rich fibrin matrix with and without peripheral blood mesenchymal stem cells on dental implant stability: A randomized controlled clinical trial. Journal of Tissue Engineering and Regenerative Medicine. 2022; 16: 422–430. https://doi.org/10.1002/term.3290.
[171] Abdullah Alqahtani N, Chandramoorthy HC, Shaik S, Syed J, Chowdhary R, Antony L. Bone Marrow Mesenchymal Stromal Cells (BMMSCs) Augment Osteointegration of Dental Implants in Type 1 Diabetic Rabbits: An X-Ray Micro-Computed Tomographic Evaluation. Medicina. 2020; 56: 148. https://doi.org/10.3390/medicina56040148.
[172] Cao C, Tarlé S, Kaigler D. Characterization of the immunomodulatory properties of alveolar bone-derived mesenchymal stem cells. Stem Cell Research & Therapy. 2020; 11: 102. https://doi.org/10.1186/s13287-020-01605-x.
[173] Heo JS, Choi Y, Kim HO. Adipose-Derived Mesenchymal Stem Cells Promote M2 Macrophage Phenotype through Exosomes. Stem Cells International. 2019; 2019: 7921760. https://doi.org/10.1155/2019/7921760.
[174] Yang R, Gao H, Chen L, Fang N, Chen H, Song G, *et al*. Effect of peripheral blood-derived mesenchymal stem cells on macrophage polarization and Th17/Treg balance *in vitro*. Regenerative Therapy. 2020; 14: 275–283. https://doi.org/10.1016/j.reth.2020.03.008.
[175] Hendrijantini N, Kuntjoro M, Agustono B, Maya Sitalaksmi R, Dimas Aditya Ari M, Theodora M, *et al*. Human umbilical cord mesenchymal stem cells induction in peri-implantitis Rattus norvegicus accelerates and enhances osteogenesis activity and implant osseointegration. The Saudi Dental Journal. 2023; 35: 147–153. https://doi.org/10.1016/j.sdentj.2023.01.003.
[176] Diniz IMA, Chen C, Ansari S, Zadeh HH, Moshaverinia M, Chee

D, *et al*. Gingival Mesenchymal Stem Cell (GMSC) Delivery System Based on RGD-Coupled Alginate Hydrogel with Antimicrobial Properties: A Novel Treatment Modality for Peri-Implantitis. Journal of Prosthodontics: Official Journal of the American College of Prosthodontists. 2016; 25: 105–115. https://doi.org/10.1111/jopr.12316.

[177] Park SY, Kim KH, Kim S, Rhee SH, Yeo IS, Heo SJ, *et al*. Comparison of experimental peri-implantitis models after application of *ex vivo* BMP2 gene therapy using periodontal ligament stem cells. Scientific Reports. 2020; 10: 3590. https://doi.org/10.1038/s41598-020-60341-7.

[178] Peshkova M, Korneev A, Suleimanov S, Vlasova II, Svistunov A, Kosheleva N, *et al*. MSCs' conditioned media cytokine and growth factor profiles and their impact on macrophage polarization. Stem Cell Research & Therapy. 2023; 14: 142. https://doi.org/10.1186/s13287-023-03381-w.

[179] Sánchez N, Fierravanti L, Núñez J, Vignoletti F, González-Zamora M, Santamaría S, *et al*. Periodontal regeneration using a xenogeneic bone substitute seeded with autologous periodontal ligament-derived mesenchymal stem cells: A 12-month quasi-randomized controlled pilot clinical trial. Journal of Clinical Periodontology. 2020; 47: 1391–1402. https://doi.org/10.1111/jcpe.13368.

[180] De la Rosa-Ruiz MDP, Álvarez-Pérez MA, Cortés-Morales VA, Monroy-García A, Mayani H, Fragoso-González G, *et al*. Mesenchymal Stem/Stromal Cells Derived from Dental Tissues: A Comparative *In Vitro* Evaluation of Their Immunoregulatory Properties Against T cells. Cells. 2019; 8: 1491. https://doi.org/10.3390/cells8121491.

[181] Inthayat J. The immunomodulatory roles of supracrestal gingival connective tissue-derived human mesenchymal stromal cells in the polarization of macrophages [master's thesis]. Chulalongkorn University. 2020. https://digital.car.chula.ac.th/chulaetd/68/.

[182] Li N, Yan M, Chen Y, Wang Y, Wu J, Fu L, *et al*. Extracellular IL-37 promotes osteogenic and odontogenic differentiation of human dental pulp stem cells via autophagy. Experimental Cell Research. 2021; 407: 112780. https://doi.org/10.1016/j.yexcr.2021.112780.

[183] Mordini L, Sun N, Chang N, De Guzman JP, Generali L, Consolo U. Peri-Implantitis Regenerative Therapy: A Review. Biology. 2021; 10: 773. https://doi.org/10.3390/biology10080773.

[184] Zhou Q, Gu X, Dong J, Zhu C, Cai Z, He D, *et al*. The use of TLR2 modified BMSCs for enhanced bone regeneration in the inflammatory micro-environment. Artificial Cells, Nanomedicine, and Biotechnology. 2019; 47: 3329–3337. https://doi.org/10.1080/21691401.2019.1626867.

[185] Yan C, Li N, Xiao T, Ye X, Fu L, Ye Y, *et al*. Extracellular vesicles from the inflammatory microenvironment regulate the osteogenic and odontogenic differentiation of periodontal ligament stem cells by miR-758-5p/LMBR1/BMP2/4 axis. Journal of Translational Medicine. 2022; 20: 208. https://doi.org/10.1186/s12967-022-03412-9.

[186] Irvine DJ, Maus MV, Mooney DJ, Wong WW. The future of engineered immune cell therapies. Science. 2022; 378: 853–858. https://doi.org/10.1126/science.abq6990.

[187] Bittner S, Ruhland B, Hofmann V, Schmidleithner L, Schambeck K, Pant A, *et al*. Biosensors for inflammation as a strategy to engineer regulatory T cells for cell therapy. Proceedings of the National Academy of Sciences of the United States of America. 2022; 119: e2208436119. https://doi.org/10.1073/pnas.2208436119.

[188] Gao B, Deng R, Chai Y, Chen H, Hu B, Wang X, *et al*. Macrophage-lineage TRAP+ cells recruit periosteum-derived cells for periosteal osteogenesis and regeneration. The Journal of Clinical Investigation. 2019; 129: 2578–2594. https://doi.org/10.1172/jci98857.

[189] Eaton KV, Yang HL, Giachelli CM, Scatena M. Engineering macrophages to control the inflammatory response and angiogenesis. Experimental Cell Research. 2015; 339: 300–309. https://doi.org/10.1016/j.yexcr.2015.11.021.

[190] Dong J, Wang W, Zhou W, Zhang S, Li M, Li N, *et al*. Immunomodulatory biomaterials for implant-associated infections: from conventional to advanced therapeutic strategies. Biomaterials Research. 2022; 26: 72. https://doi.org/10.1186/s40824-022-00326-x.

[191] Gulati K, Moon HJ, Li T, Sudheesh Kumar PT, Ivanovski S. Titania nanopores with dual micro-/nano-topography for selective cellular bioactivity. Materials Science & Engineering. C, Materials for Biological Applications. 2018; 91: 624–630. https://doi.org/10.1016/j.msec.2018.05.075.

[192] Zhu Y, Liang H, Liu X, Wu J, Yang C, Wong TM, *et al*. Regulation of macrophage polarization through surface topography design to facilitate implant-to-bone osteointegration. Science Advances. 2021; 7: eabf6654. https://doi.org/10.1126/sciadv.abf6654.

[193] Luo J, He Y, Meng F, Yan N, Zhang Y, Song W. The Role of Autophagy in M2 Polarization of Macrophages Induced by Micro/Nano Topography. International Journal of Nanomedicine. 2020; 15: 7763–7774. https://doi.org/10.2147/ijn.S270100.

[194] Shen K, Tang Q, Fang X, Zhang C, Zhu Z, Hou Y, *et al*. The sustained release of dexamethasone from TiO_2 nanotubes reinforced by chitosan to enhance osteoblast function and anti-inflammation activity. Materials Science & Engineering. C, Materials for Biological Applications. 2020; 116: 111241. https://doi.org/10.1016/j.msec.2020.111241.

[195] Yang PM, Mu HZ, Zhang YS, Wang WC, Liu C, Zhang SY. Sequential release of immunomodulatory cytokines binding on nano-hydroxyapatite coated titanium surface for regulating macrophage polarization and bone regeneration. Medical Hypotheses. 2020; 144: 110241. https://doi.org/10.1016/j.mehy.2020.110241.

[196] Ma A, You Y, Chen B, Wang W, Liu J, Qi H, *et al*. Icariin/Aspirin Composite Coating on TiO_2 Nanotubes Surface Induce Immunomodulatory Effect of Macrophage and Improve Osteoblast Activity. Coatings. 2020; 10: 427. https://doi.org/10.3390/coatings10040427.

[197] Bahrami S, Baheiraei N, Shahrezaee M. Biomimetic reduced graphene oxide coated collagen scaffold for *in situ* bone regeneration. Scientific Reports. 2021; 11: 16783. https://doi.org/10.1038/s41598-021-96271-1.

[198] Lei J, Luo B, Sun X, Zhang Y, Hu X, Lan F, *et al*. Preparation of Graphene Mediated Macrophage Membrane Coating and Its Effects on the Anti-fouling and Immunomodulatory Properties of Tianium Implants. Chemical Journal of Chinese Universities. 2024; 45: 20230451. http://www.cjcu.jlu.edu.cn/EN/10.7503/cjcu20230451.

[199] Qin W, Wang C, Jiang C, Sun J, Yu C, Jiao T. Graphene Oxide Enables the Reosteogenesis of Previously Contaminated Titanium *In Vitro*. Journal of Dental Research. 2020; 99: 922–929. https://doi.org/10.1177/0022034520913873.

[200] Srimaneepong V, Skallevold HE, Khurshid Z, Zafar MS, Rokaya D, Sapkota J. Graphene for Antimicrobial and Coating Application. International Journal of Molecular Sciences. 2022; 23: 499. https://doi.org/10.3390/ijms23010499.

[201] Ko YC, Lee D, Koo KT, Seol YJ, Lee YM, Lee J. A randomized controlled trial of immediate implant placement comparing hydroxyapatite nano-coated and uncoated sandblasted/acid-etched implants using a digital surgical guide. International Journal of Implant Dentistry. 2024; 10: 29. https://doi.org/10.1186/s40729-024-00549-8.

[202] Song L, Yan P, Dong Z, Wang L, Ma J. Application of Nano-Hydroxyapatite Implantation for Periodontitis Treatment and Oral Tissue Regeneration. Journal of Biomedical Nanotechnology. 2024; 20: 1358–1363. https://doi.org/10.1166/jbn.2024.3841.

[203] Reis-Neta GRD, Ricomini-Filho AP, Martorano-Fernandes L, Vargas-Moreno VF, Cury AADB, Marcello-Machado RM. Effect of hydroxyapatite nanoparticles coating of titanium surface on biofilm adhesion: An *in vitro* study. Archives of Oral Biology. 2024; 164: 105986. https://doi.org/10.1016/j.archoralbio.2024.105986.

[204] Madi M, Zakaria O, Ichinose S, Kasugai S. Effect of Induced Peri-implantitis on Dental Implants With and Without Ultrathin Hydrox-

yapatite Coating. Implant Dentistry. 2016; 25: 39–46. https://doi.org/10.1097/id.0000000000000331.

[205] Guo F, Yuan C, Huang H, Deng X, Bian Z, Wang D, *et al*. Regulation of T Cell Responses by Nano-Hydroxyapatite to Mediate the Osteogenesis. Frontiers in Bioengineering and Biotechnology. 2022; 10: 884291. https://doi.org/10.3389/fbioe.2022.884291.

[206] Chen Y, Guan M, Ren R, Gao C, Cheng H, Li Y, *et al*. Improved Immunoregulation of Ultra-Low-Dose Silver Nanoparticle-Loaded TiO_2 Nanotubes via M2 Macrophage Polarization by Regulating GLUT1 and Autophagy. International Journal of Nanomedicine. 2020; 15: 2011–2026. https://doi.org/10.2147/ijn.S242919.

[207] Lee CW, Lin ZC, Chiang YC, Li SY, Ciou JJ, Liu KW, *et al*. AuAg nanocomposites suppress biofilm-induced inflammation in human osteoblasts. Nanotechnology. 2023; 34: 165101. https://doi.org/10.1088/1361-6528/acb4a1.

[208] Li S, Ding Q, Zhang L, Shi F, Liu C, Li T, *et al*. Gold core@CeO_2 halfshell Janus nanocomposites catalyze targeted sulfate radical for periodontitis therapy. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2024; 370: 600–613. https://doi.org/10.1016/j.jconrel.2024.05.016.

[209] Li Y, Yang C, Yin X, Sun Y, Weng J, Zhou J, *et al*. Inflammatory responses to micro/nano-structured titanium surfaces with silver nanoparticles *in vitro*. Journal of Materials Chemistry B. 2019; 7: 3546–3559. https://doi.org/10.1039/C8TB03245A.

[210] Park HS, Kim KH, Jang S, Park JW, Cha HR, Lee JE, *et al*. Attenuation of allergic airway inflammation and hyperresponsiveness in a murine model of asthma by silver nanoparticles. International Journal of Nanomedicine. 2010; 5: 505–515. https://doi.org/10.2147/ijn.s11664.

[211] Tyavambiza C, Elbagory AM, Madiehe AM, Meyer M, Meyer S. The Antimicrobial and Anti-Inflammatory Effects of Silver Nanoparticles Synthesised from *Cotyledon orbiculata* Aqueous Extract. Nanomaterials. 2021; 11: 1343. https://doi.org/10.3390/nano11051343.

[212] Khan MA, Khan MJ. Nano-gold displayed anti-inflammatory property via NF-kB pathways by suppressing COX-2 activity. Artificial Cells, Nanomedicine, and Biotechnology. 2018; 46: 1149–1158. https://doi.org/10.1080/21691401.2018.1446968.

[213] Yuan Q, Gao F, Yao Y, Cai P, Zhang X, Yuan J, *et al*. Gold Clusters Prevent Inflammation-Induced Bone Erosion through Inhibiting the Activation of NF-κB Pathway. Theranostics. 2019; 9: 1825–1836. https://doi.org/10.7150/thno.31893.

[214] Huang Q, Ouyang Z, Tan Y, Wu H, Liu Y. Activating macrophages for enhanced osteogenic and bactericidal performance by Cu ion release from micro/nano-topographical coating on a titanium substrate. Acta Biomaterialiaialia. 2019; 100: 415–426. https://doi.org/10.1016/j.actbio.2019.09.030.

[215] Sarawi WS, Alhusaini AM, Fadda LM, Alomar HA, Albaker AB, Aljrboa AS, *et al*. Nano-Curcumin Prevents Cardiac Injury, Oxidative Stress and Inflammation, and Modulates TLR4/NF-κB and MAPK Signaling in Copper Sulfate-Intoxicated Rats. Antioxidants. 2021; 10: 1414. https://doi.org/10.3390/antiox10091414.

[216] Elghareeb MM, Elshopakey GE, Elkhooly TA, Salama B, Samy A, Bazer FW, *et al*. Estradiol and zinc-doped nano hydroxyapatite as therapeutic agents in the prevention of osteoporosis; oxidative stress status, inflammation, bone turnover, bone mineral density, and histological alterations in ovariectomized rats. Frontiers in Physiology. 2022; 13: 989487. https://doi.org/10.3389/fphys.2022.989487.

[217] Li Z, Xie K, Yang S, Yu T, Xiao Y, Zhou Y. Multifunctional Ca-Zn-Si-based micro-nano spheres with anti-infective, anti-inflammatory, and dentin regenerative properties for pulp capping application. Journal of Materials Chemistry. B. 2021; 9: 8289–8299. https://doi.org/10.1039/d1tb01517f.

[218] Hu T, Xu H, Wang C, Qin H, An Z. Magnesium enhances the chondrogenic differentiation of mesenchymal stem cells by inhibiting activated macrophage-induced inflammation. Scientific Reports. 2018; 8: 3406. https://doi.org/10.1038/s41598-018-21783-2.

[219] Shahid S, Ejaz A, Javed M, Mansoor S, Iqbal S, Elkaeed EB, *et al*. The Anti-Inflammatory and Free Radical Scavenging Activities of Bio-Inspired Nano Magnesium Oxide. Frontiers in Materials. 2022; 9: 875163. https://doi.org/10.3389/fmats.2022.875163.

[220] Zhang X, Chen Q, Mao X. Magnesium Enhances Osteogenesis of BMSCs by Tuning Osteoimmunomodulation. BioMed Research International. 2019; 2019: 7908205. https://doi.org/10.1155/2019/7908205.

[221] Li D, Tan X, Zheng L, Tang H, Hu S, Zhai Q, *et al*. A Dual-Antioxidative Coating on Transmucosal Component of Implant to Repair Connective Tissue Barrier for Treatment of Peri-Implantitis. Advanced Healthcare Materials. 2023; 12: e2301733. https://doi.org/10.1002/adhm.202301733.

[222] Li X, Qi M, Sun X, Weir MD, Tay FR, Oates TW, *et al*. Surface treatments on titanium implants via nanostructured ceria for antibacterial and anti-inflammatory capabilities. Acta Biomaterialia. 2019; 94: 627–643. https://doi.org/10.1016/j.actbio.2019.06.023.

[223] Hakim LK, Yari A, Nikparto N, Mehraban SH, Cheperli S, Asadi A, *et al*. The current applications of nano and biomaterials in drug delivery of dental implant. BMC Oral Health. 2024; 24: 126. https://doi.org/10.1186/s12903-024-03911-9.

[224] Seoane-Viaño I, Seoane-Gigirey M, Bendicho-Lavilla C, Gigirey LM, Otero-Espinar FJ, Seoane-Trigo S. The Integration of Advanced Drug Delivery Systems into Conventional Adjuvant Therapies for Peri-Implantitis Treatment. Pharmaceutics. 2024; 16: 769. https://doi.org/10.3390/pharmaceutics16060769.

[225] Zou Y, Huang B, Cao L, Deng Y, Su J. Tailored Mesoporous Inorganic Biomaterials: Assembly, Functionalization, and Drug Delivery Engineering. Advanced Materials. 2021; 33: e2005215. https://doi.org/10.1002/adma.202005215.

[226] Moses JC, Mandal BB. Mesoporous Silk-Bioactive Glass Nanocomposites as Drug Eluting Multifunctional Conformal Coatings for Improving Osseointegration and Bactericidal Properties of Metal Implants. ACS Applied Materials & Interfaces. 2022; 14: 14961–14980. https://doi.org/10.1021/acsami.2c00093.

[227] Bargavi P, Chandran RR, Durgalakshmi D, Rajashree P, Ramya R, Balakumar S. Drug infused Al_2O_3-bioactive glass coatings toward the cure of orthopedic infection. Progress in Biomaterials. 2022; 11: 79–94. https://doi.org/10.1007/s40204-022-00181-y.

[228] Hu W, Lu Y, Duan Y, Yang Y, Wang M, Guo J, *et al*. Regulation of Immune Inflammation and Promotion of Periodontal Bone Regeneration by Irisin-Loaded Bioactive Glass Nanoparticles. Langmuir: the ACS Journal of Surfaces and Colloids. 2024; 40: 3440–3452. https://doi.org/10.1021/acs.langmuir.3c02894.

[229] Weng J, Tong HHY, Chow SF. *In Vitro* Release Study of the Polymeric Drug Nanoparticles: Development and Validation of a Novel Method. Pharmaceutics. 2020; 12: 732. https://doi.org/10.3390/pharmaceutics12080732.

[230] Eroglu I, Gultekinoglu M, Bayram C, Erikci A, Ciftci SY, Ayse Aksoy E, *et al*. Gel network comprising UV crosslinked PLGA-b-PEG-MA nanoparticles for ibuprofen topical delivery. Pharmaceutical Development and Technology. 2019; 24: 1144–1154. https://doi.org/10.1080/10837450.2019.1643880.

[231] Zhang J, Ma S, Liu Z, Geng H, Lu X, Zhang X, *et al*. Guided bone regeneration with asymmetric collagen-chitosan membranes containing aspirin-loaded chitosan nanoparticles. International Journal of Nanomedicine. 2017; 12: 8855–8866. https://doi.org/10.2147/ijn.S148179.

[232] Chen W, Zhi M, Feng Z, Gao P, Yuan Y, Zhang C, *et al*. Sustained co-delivery of ibuprofen and basic fibroblast growth factor by thermosensitive nanoparticle hydrogel as early local treatment of peri-implantitis. International Journal of Nanomedicine. 2019; 14: 1347–1358. https://doi.org/10.2147/ijn.S190781.

[233] Lima AC, Cunha C, Carvalho A, Ferreira H, Neves NM. Interleukin-6 Neutralization by Antibodies Immobilized at the Sur-

face of Polymeric Nanoparticles as a Therapeutic Strategy for Arthritic Diseases. ACS Applied Materials & Interfaces. 2018; 10: 13839–13850. https://doi.org/10.1021/acsami.8b01432.

[234] Deng Y, Zhou Y, Liang Q, Ge C, Yang J, Shan B, *et al*. Inflammation-Instructed Hierarchical Delivery of IL-4/miR-21 Orchestrates Osteoimmune Microenvironment toward the Treatment of Rheumatoid Arthritis. Advanced Functional Materials. 2021; 31: 2101033. https://doi.org/10.1002/adfm.202101033.

[235] Jin SS, He DQ, Luo D, Wang Y, Yu M, Guan B, *et al*. A Biomimetic Hierarchical Nanointerface Orchestrates Macrophage Polarization and Mesenchymal Stem Cell Recruitment to Promote Endogenous Bone Regeneration. ACS Nano. 2019; 13: 6581–6595. https://doi.org/10.1021/acsnano.9b00489.

[236] Ji H, Wang Y, Liu H, Liu Y, Zhang X, Xu J, *et al*. Programmed core-shell electrospun nanofibers to sequentially regulate osteogenesis-osteoclastogenesis balance for promoting immediate implant osseointegration. Acta Biomaterialiaialia. 2021; 135: 274–288. https://doi.org/10.1016/j.actbio.2021.08.050.

[237] Li W, You F, Bao H, Yang J, Gu D, Li Y, *et al*. UBI29-41-targeted, NIR-triggered nanoparticles for enhanced PDT against periodontal plaque biofilm formation and immunomodulation. Research Square. 2024. (preprint) https://doi.org/10.21203/rs.3.rs-4020511/v1.

[238] Zhang H, Yuan Y, Xue H, Yu R, Jin X, Wu X, *et al*. Reprogramming mitochondrial metabolism of macrophages by miRNA-released microporous coatings to prevent peri-implantitis. Journal of Nanobiotechnology. 2023; 21: 485. https://doi.org/10.1186/s12951-023-02244-z.

[239] Yan Q, Shi S, Ge Y, Wan S, Li M, Li M. Nanoparticles of Cerium-Doped Zeolitic Imidazolate Framework-8 Promote Soft Tissue Integration by Reprogramming the Metabolic Pathways of Macrophages. ACS Biomaterials Science & Engineering. 2023; 9: 4241–4254. https://doi.org/10.1021/acsbiomaterials.3c00508.

[240] Rommasi F, Esfandiari N. Liposomal Nanomedicine: Applications for Drug Delivery in Cancer Therapy. Nanoscale Research Letters. 2021; 16: 95. https://doi.org/10.1186/s11671-021-03553-8.

[241] Angellotti G, Presentato A, Murgia D, Di Prima G, D'Agostino F, Scarpaci AG, *et al*. Lipid Nanocarriers-Loaded Nanocomposite as a Suitable Platform to Release Antibacterial and Antioxidant Agents for Immediate Dental Implant Placement Restorative Treatment. Pharmaceutics. 2021; 13: 2072. https://doi.org/10.3390/pharmaceutics13122072.

[242] Shi J, Zhang Y, Zhang X, Chen R, Wei J, Hou J, *et al*. Remodeling immune microenvironment in periodontitis using resveratrol liposomes as an antibiotic-free therapeutic strategy. Journal of Nanobiotechnology. 2021; 19: 429. https://doi.org/10.1186/s12951-021-01175-x.

[243] Li Z, Yin Z, Li B, He J, Liu Y, Zhang N, *et al*. Docosahexaenoic Acid-Loaded Nanostructured Lipid Carriers for the Treatment of Peri-Implantitis in Rats. International Journal of Molecular Sciences. 2023; 24: 1872. https://doi.org/10.3390/ijms24031872.

[244] Dong K, Zhang Y, Ji HR, Guan ZL, Wang DY, Guo ZY, *et al*. Dexamethasone-Loaded Lipid Calcium Phosphate Nanoparticles Treat Experimental Colitis by Regulating Macrophage Polarization in Inflammatory Sites. International Journal of Nanomedicine. 2024; 19: 993–1016. https://doi.org/10.2147/ijn.S442369.

[245] Meng F, Xue X, Yin Z, Gao F, Wang X, Geng Z. Research Progress of Exosomes in Bone Diseases: Mechanism, Diagnosis and Therapy. Frontiers in Bioengineering and Biotechnology. 2022; 10: 866627. https://doi.org/10.3389/fbioe.2022.866627.

[246] Elashiry M, Elashiry MM, Elsayed R, Rajendran M, Auersvald C, Zeitoun R, *et al*. Dendritic cell derived exosomes loaded with immunoregulatory cargo reprogram local immune responses and inhibit degenerative bone disease *in vivo*. Journal of Extracellular Vesicle. 2020; 9: 1795362. https://doi.org/10.1080/20013078.2020.1795362.

[247] Dong M, Wu S, Xu H, Yu X, Wang L, Bai H, *et al*. FBS-Derived Exosomes as a Natural Nano-Scale Carrier for Icariin Promote Osteoblast Proliferation. Frontiers in Bioengineering and Biotechnology. 2021; 9: 615920. https://doi.org/10.3389/fbioe.2021.615920.

[248] Hu Y, Li X, Zhang Q, Gu Z, Luo Y, Guo J, *et al*. Exosome-guided bone targeted delivery of Antagomir-188 as an anabolic therapy for bone loss. Bioactive Materials. 2021; 6: 2905–2913. https://doi.org/10.1016/j.bioactmat.2021.02.014.

[249] Hu Q, Li H, Wang L, Gu H, Fan C. DNA Nanotechnology-Enabled Drug Delivery Systems. Chemical Reviews. 2019; 119: 6459–6506. https://doi.org/10.1021/acs.chemrev.7b00663.

[250] Zhang T, Ma H, Zhang X, Shi S, Lin Y. Functionalized DNA Nanomaterials Targeting Toll-Like Receptor 4 Prevent Bisphosphonate-Related Osteonecrosis of the Jaw via Regulating Mitochondrial Homeostasis in Macrophages. Advanced Functional Materials. 2023; 33: 2213401. https://doi.org/10.1002/adfm.202213401.

[251] Khalifehzadeh R, Arami H. DNA-Templated Strontium-Doped Calcium Phosphate Nanoparticles for Gene Delivery in Bone Cells. ACS Biomaterials Science & Engineering. 2019; 5: 3201–3211. https://doi.org/10.1021/acsbiomaterials.8b01587.

[252] Tang R, Xu Z. Gene therapy: a double-edged sword with great powers. Molecular and Cellular Biochemistry. 2020; 474: 73–81. https://doi.org/10.1007/s11010-020-03834-3.

[253] Ribeiro B, Offoiach R, Rahimi E, Salatin E, Lekka M, Fedrizzi L. On Growth and Morphology of TiO_2 Nanotubes on Ti6Al4V by Anodic Oxidation in Ethylene Glycol Electrolyte: Influence of Microstructure and Anodization Parameters. Materials. 2021; 14: 2540. https://doi.org/10.3390/ma14102540.

Editor's note: The Scientific Editor responsible for this paper was Matteo D' Este.

Received: 29th July 2024; **Accepted**: 26th November 2024; **Published**: 8th April 2025