Received: 7 April 2022 | Revised: 6 August 2022 | Accepted: 18 August 2022

DOI: 10.1111/odi.14360

ORAL DISEASES Leading in Oral, Maxillofacial, Head & Neck Medicine WILEY

REVIEW ARTICLE

The homeostasis and therapeutic applications of innate and adaptive immune cells in periodontitis

Li Junxian[1] | Mojtaba Mehrabanian[2] | Hassan Mivehchi[2] | Morteza Banakar[3,4] | Enas Abdalla Etajuri[5]

[1]Department of Oral and Maxillofacial Surgery, Shanxi Provincial People's Hospital, Taiyuan, China

[2]DMD Dentist, Alumni of the Faculty of Dentistry, University of Debrecen, Debrecen, Hungary

[3]Saveetha Dental College, Chennai, India

[4]Dental Research Center, Dentistry Research Institute, Tehran University of Medical Sciences, Tehran, Iran

[5]Department of Restorative Dentistry, Faculty of Dentistry, University of Malaya, Malaya, Malaysia

Correspondence
Mojtaba Mehrabanian, Alumni of the Faculty of Dentistry, University of Debrecen, Debrecen, Hungary.
Email: m.mehrabanian@gmail.com

Abstract

Objectives: Periodontitis (PD) is one of the most common dental disorders. This chronic oral inflammation is caused by complicated interrelations between bacterial infections, dysregulated immune reactions, and environmental risk factors. A dysregulated immune response can lead to inflammatory bone resorption by allowing the recruitment of pro-inflammatory immune cells to the periodontal tissues.

Subjects: The recruitment of innate and adaptive immune cells in PD initiates the acute and following chronic inflammatory processes. The inflamed tissues, on the other hand, can be restored if the anti-inflammatory lineages are predominantly established in the periodontal tissues. Therefore, we aimed to review the published literature to provide an overview of the existing knowledge about the role of immune cells in PD, as well as their possible therapeutic applications.

Results: Experimental studies showed that drugs/systems that negatively regulate inflammatory cells in the body, as well as interventions aimed at increasing the number of anti-inflammatory cells such as Tregs and Bregs, can both help in the healing process of PD.

Conclusion: Targeting immune cells or their positive/negative manipulations has been demonstrated to be an effective therapeutic method. However, to use this sort of immunotherapy in humans, further pre-clinical investigations, as well as randomized clinical trials, are required.

KEYWORDS
cell therapy, immune cells, immunotherapy, periodontitis

1 | INTRODUCTION

Bacteria are the main cause of periodontal disease. The microbial population in the mouth cavity of a human being is enormous and is constantly evolving. The disease's intensity is determined by the host's ecological interactions with bacteria. Periodontal disorders, notwithstanding numerous other infectious illnesses, seem to be infections mediated by the proliferation of commensal organisms instead of acquiring a foreign pathogen (Cekici et al., 2014).

The inflammatory response to bacteria in the dental biofilm has a role in the etiology of periodontitis (PD). Pathological alveolar bone resorption in PD is the result of innate and adaptive immunological reactions. The initial phase in the immunological reaction to pathobionts, which are any potentially pathogenic organisms living as non-harming symbionts, is the mobilization of innate immune cells, including neutrophils and monocytes, to the infected area. Adaptive immunological cells are more easily recruited when cytokines and pro-inflammatory mediators are released by the gingival epithelium.

Primary adaptive immune cells involved in host defense against PD are $CD4^+$ T helper cells (Campbell et al., 2016). T helper (Th) 1, T helper (Th) 2, T helper (Th) 17, and T follicular helper cells (Tfh) are all subgroups of $CD4^+$ T helper cells that are distinguished by the cytokine secretion and effector function (Kim & Sadegh-Nasseri, 2015). Because of their one-of-a-kind participation in bone resorption and inflammatory responses, Th17 cells, which are a major source of the cytokine interleukin (IL)-17A, have an essential part in the evolution of the PD (Cheng et al., 2014). By enhancing the expression of pro-inflammatory cytokines, Th17 cells were demonstrated to increase the degradation of periodontal tissue (Mitani et al., 2015).

Regulatory T cells, also known as Tregs, are a specialized subset of $CD4^+$ T cells that by sustaining homeostasis and self-tolerance via the expression of immunosuppressive cytokines and contact-dependent regulation modulate the immunological reaction (Vignali et al., 2008; Zafari et al., 2018; Iranshahi et al., 2019). Additionally, Tregs inhibit the function of B cells, which successfully controls the host's humoral immunological reactions (Lukas et al., 2017; Samimi et al., 2019). Tregs are present in both normal and inflamed gingiva. On the other hand, it has been demonstrated that the frequency of these cells is higher in PD (Glowacki et al., 2013a). Anti-inflammatory cytokines produced by Tregs during PD have been shown to play an important role in the periodontal inflammatory process and skeletal homeostasis (Karthikeyan et al., 2015). In addition, a new subset of B cells has been revealed that may play an important role in the regulation of Treg/Th17 cells. An important anti-inflammatory cytokine secreted by this regulatory B-cell subgroup (Breg) is IL-10, which has substantial immunomodulatory effects (Lykken et al., 2015).

Complex disorders, such as PD, require a comprehension of how immunological processes and inflammatory reactions are controlled. It is more likely that tissue degeneration and bone resorption will occur if the pro-inflammatory subtype of cells persists for an extended period. This means that inflammation can be addressed, and tissues can be restored or regenerated if the anti-inflammatory and pro-regeneration lineages are predominantly established. Several different therapy strategies have been attempted in an effort to regulate the homeostasis of immune cells in PD patients in recent years. As a result, the purpose of this research was to conduct a literature review on previously reported works in this area to give an in-depth analysis of what is already known regarding the function of immune cells and the therapeutic roles of these cells in PD.

2 | OVERVIEW OF PD

Around 11% of the worldwide population may experience severe PD, impacting 743 million people (Richards, 2014). People with PD are two to three times more likely to have life-threatening disorders such as heart attack, stroke, or other serious heart problems (Zhang et al., 2022; Cai et al., 2022). The periodontal ligament, cementum, and alveolar bone, supporting tissues protecting the teeth, can be damaged by PD (Nazir, 2017). Dysbiosis, or an imbalance of bacteria in the dental plaque, characterizes this polymicrobial condition (Darveau, 2010). It appears that PD is caused by low-prevalence bacteria that have the potential to change the nutritional state of the community by triggering the inflammatory response. The dynamic connection shift between human immunological reactions and subgingival bacteria has also been linked to PD (Slots, 2013). It has proven difficult to identify the genuine 'pathogens' in PD. The progression of the disease is linked to the presence of particular bacteria. The existence of these bacteria in individuals with no indication of disease development, on the other hand, shows that the disease is the result of the immunological reaction and inflammation rather than the existence of the bacteria alone. Gram-negative and Gram-positive bacteria, including *Porphyromonas gingivalis (P.gingivalis)*, *F.nucleatum*, *Tannerella forsythia*, *Treponema denticola*, *Prevotella intermedia*, *Eubacterium timidu*, *Campylobacter rectus*, *Aggregatibacter actinomycetemcomitans*, *and Parvimonas micra*, are part of 800 various species of bacteria that have been found and classified in human dental plaque (Lourenço et al., 2014; Shaddox et al., 2012).

3 | IMMUNOPATHOGENESIS OF PD

PD is characterized by gingival inflammation, clinical attachment loss (CAL), radiographic signs of alveolar bone loss, pathologic bleeding, and deep pockets in gums. The gingival bleeding and erythema are prevalent and suggest a poor prognosis. The clinical transition of the gingival sulcus, a space between a tooth and the surrounding gingival tissue, to a periodontal pocket causes an increase in probing depth. In severe PD, the teeth become mobile, and tooth loss occurs. Both horizontal and vertical bone loss around the teeth is possible (Kwon et al., 2021). In addition to these clinical symptoms, intra-oral radiography is often employed in PD evaluation and disease management to identify and monitor alveolar bone loss. PD can be detected by a dental X-ray (OPG); however, there may be no radiographic signals in the early phases since a certain amount of demineralization must occur before radiologic evidence appears. Early crestal bone loss is the first radiographic alteration in PD (Corbet et al., 2009).

PD was traditionally assumed to proceed continuously until treated or tooth loss occurred, but it is now considered to proceed through recurring acute episodes, based on evidence from human and experimental studies. Most PD patients experience a cycle of progressive bone loss over tiny periods, followed by extended times of remission throughout their lives. PD patients with the fast-growing disease have an annual incidence of CAL between 0.1–1 mm, whereas those with slowly progressive PD have a loss of 0.05–0.5 mm, and those with little to no advancement had an annual attachment loss of 0.05–0.09 mm (Löe et al., 1986; Tonetti et al., 2018).

As mentioned earlier, PD is caused by complicated interrelations between particular bacterial infections and dysregulated immune reactions. Although bacterial plaque is the most common cause of PD, various additional factors might put a person at risk. The most significant environmental risk factor is smoking. Smokers had a considerably greater incidence of periodontal

bacteria in their subgingival biofilm than non-smokers (Camelo-Castillo et al., 2015). Patients with diabetes are also more likely to develop PD than healthy or well-controlled diabetic controls (Emrich et al., 1991).

Instead of a pathological response, the early periodontal inflammation should be viewed as a physiological defense mechanism against the microbe onslaught. Supragingival and subgingival plaque development, calculus production, and gingival inflammatory processes are common clinical symptoms at this phase of the disease (Cekici et al., 2014). A restoration to homeostasis occurs when plaque is eliminated, but if the lesion continues, it is recognized as pathology.

The reaction of indigenous leukocytes and endothelial cells to the bacterial biofilm is the first pathological condition. There are no clinical manifestations of inflammatory response at this point; however, histological alterations can be detected in the organs. Topical blood arteries are dilated due to the effects of bacterial metabolic products, including lipopolysaccharides (LPS), encouraging junctional epithelial cells to release cytokines and neuron cells to induce neuropeptide synthesis (Jin, Zhang, et al., 2014; Neely et al., 2005; Lotfi et al., 2021; Zafari et al., 2020; Iranshahi et al., 2016). Chemokines cause neutrophils to abandon the artery and move to the point of the inflammatory process. Immune cells are recruited to the gingival epithelium by the secretion of cytokines and pro-inflammatory mediators (Zadeh et al., 1999; Hasturk & Kantarci, 2015). In order for phagocytes to recognize bacteria, they use the pattern recognition receptors, including the Toll-like receptor (TLR). As these phagocytes fight against these pathogens, the complement system is also activated (Hasturk & Kantarci, 2015). Followed by a proliferation of neutrophils in the connective tissue and the emergence of macrophages, lymphocytes, plasma cells, and mast cells is the initial infection. Clinical indications of gingival inflammation, including hemorrhage, can be evident as the epithelium proliferates to generate rete pegs. In this condition, the flow of fluid via the gingival crevices is enhanced (Sudhakara et al., 2018).

This is followed by the development of a well-established lesion. The innate immunological response gives way to the acquired immunological response during this phase, which can be thought of as the transition period. Most immune cells are composed of macrophages, plasma cells, T lymphocytes, and B lymphocytes, including IgG1 and IgG3 subclasses of B lymphocytes. Collagenolytic activity rises as a result of reduced blood supply. Fibroblasts are also producing more collagen. A moderate to severe gingivitis with gingival hemorrhage and color and contour alterations are observed clinically at this phase. The transition to PD is the ultimate stage, and it occurs when the lesion has progressed significantly. Histologically and clinically, irreversible deterioration of adhesion and bone is documented. Alveolar bone is affected by the deep extension of the inflammatory lesion (Cekici et al., 2014; Hajishengallis, 2014).

The interruption of the equilibrium between osteoblast and osteoclast operations by endotoxins and inflammatory cytokines is nowadays widely regarded as one of the primary fundamental mechanisms of inflammation-induced osteoporosis (Liu et al., 2010; Jiang et al., 2022). Once introduced to osteoclast precursor cultures, including osteoblasts and/or stromal cells, LPS induces bone resorption immediately (Iino & Hopps, 1984). Commencement of osteoporosis is associated with a TLR- and inflammation-induced osteoclastogenesis mechanism (Pihlstrom et al., 2005). There has been a lot of research conducted on how inflammation can cause osteoporosis during a reaction to periodontal infection. RANKL, tumor necrosis factor α (TNF-α), IL-1, IL-6, and prostaglandin (PG)-E2 are the mediators of the complex inflammatory pathways and cytokine networks that control osteoclastogenesis (Henderson et al., 2003).

Bone remodeling is regulated by RANKL and osteoprotegerin, which are directly engaged in the differentiation, stimulation, and persistence of osteoclasts and pre-osteocytes, respectively (Yasuda et al., 1998). Osteoblasts, stromal cells, chondrocytes, and other mesenchymal cells all express RANKL. RANKL can also be expressed by stimulated T and B cells (Kawai et al., 2006). Osteoclast progenitor cells, adult osteoclasts, chondrocytes, monocytes, and dendritic cells all express the RANK regulator. Periodontal tissue cells, such as fibroblasts and periodontal ligament cells, have been found to express the decoy receptor osteoprotegerin (Hsu et al., 1999).

Periodontal tissue degradation has been linked to the presence of collagenases and other matrix metalloproteinases (MMPs). At first, it was believed that only neutrophils were capable of producing MMPs and releasing them in a pathological context (Uitto et al., 2003). Gingival epithelial cells, fibroblasts, endothelial cells, monocytes/macrophages, and plasma cells are examples of the various cell types found in a healthy or damaged human periodontium. However, it is currently evident that these different cell types express different MMPs (Wahlgren et al., 2002; Sorsa et al., 2006). MMP-8, a collagen-degrading enzyme mostly secreted by neutrophils, is the most prevalent in PD. Gingival crevice fluid and saliva contain this enzyme, which is indicative of damaged periodontal tissue. Matrix metalloproteinase-8 is primarily responsible for the breakdown of interstitial collagens (Sorsa et al., 2006).

4 | IMMUNE CELLS AND THEIR THERAPEUTIC APPLICATIONS IN PD

Pathological alveolar bone resorption occurs in PD as a result of a cascade of innate and adaptive immunological reactions, as previously described (Figure 1). The mobilization of innate and adaptive immune cells, as well as their penetration into periodontal tissues, signals a switch to the resolution phase, or chronic inflammatory processes, once acute inflammation has been developed. Various effector cell lineages may dominate the existence in the tissue, which affects the therapeutic manifestation of the disease as a result of a sequence of environmental conditions and the interconnections of cellular and molecular components unique to the host. Innate and adaptive immune cells will be the emphasis of this section, as well as the possibility of using these cells to treat PD (Table 1).

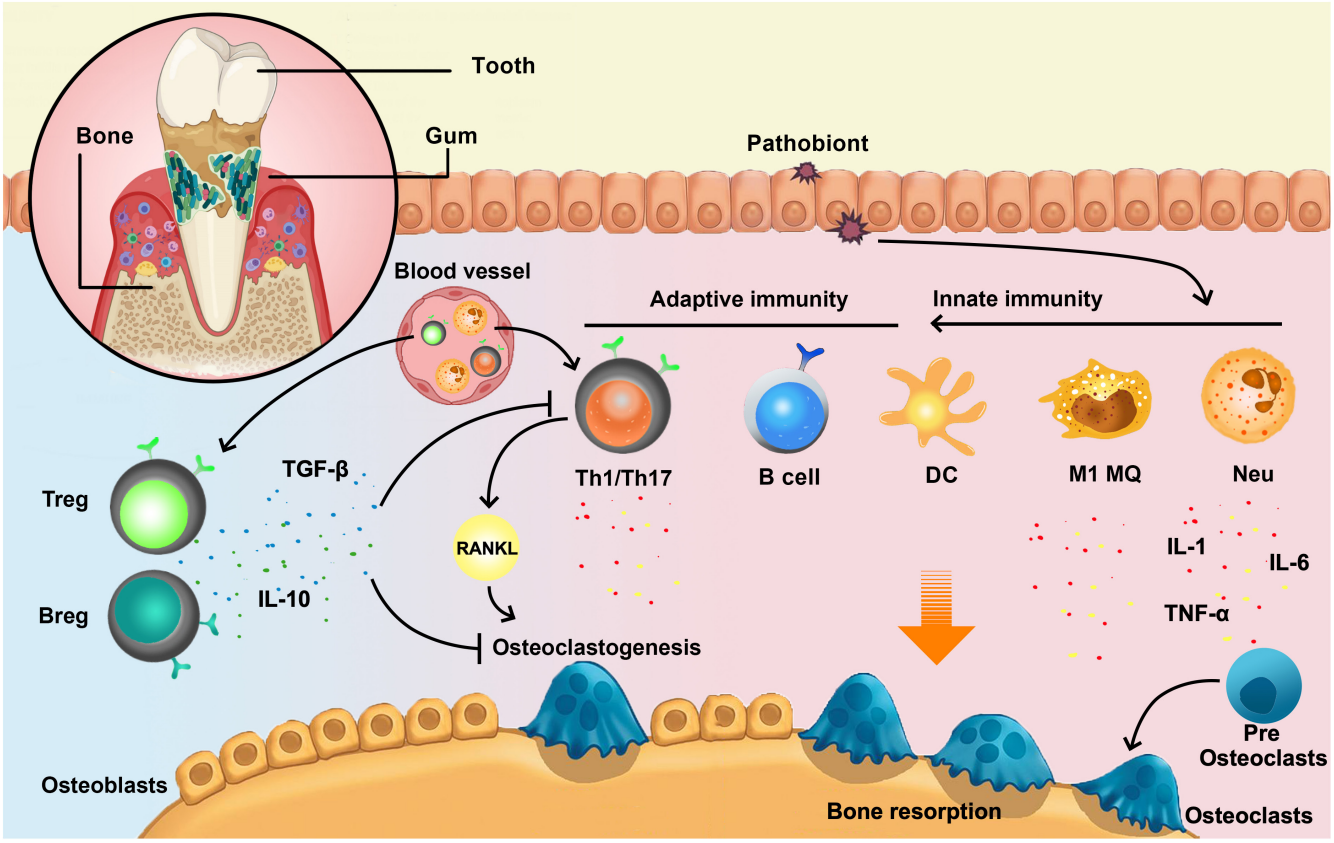

FIGURE 1 The immune-inflammatory and immune-regulatory responses in PD. Immune response in PD is complex and involves both innate and adaptive immunity. Pathobiont dysregulation can lead to the initiation of the innate immune responses and recruitment of immune cells to the inflamed tissue, including neutrophils (neu), M1 macrophages (M1 MQ), and adaptive immune cells. Th1 and Th17 cells can produce pro-inflammatory cytokines inducing osteoclastogenesis. Besides, these cytokines can activate B cells, leading to the production of autoantibodies against autoantigens and promoting tissue destruction. On the contrary, the abundance of Tregs and Bregs has the opposite effect by secreting anti-inflammatory cytokines and inhibiting osteoclastogenesis

4.1 | Innate immune cells

4.1.1 | Neutrophils

Neutrophil homeostasis is essential for periodontal health because it is the host's first line of defensive system against pathogenic bacteria (Sima et al., 2019). Because of the chemotaxis of plaque, the periodontal lesion begins as an acute inflammation with enhanced neutrophil migration into the gingival crevice via the junctional epithelium (Zhang et al., 2020). They are stimulated by chemoattractants such as macrophage inflammatory protein-1α, C-X-C motif ligand 8, and constitutive increased reactive oxygen species (ROS) and commence phagocytosis using antibodies and complement, resulting in tissue destruction and elevated secretion of harmful chemicals, which can be utilized to differentiate normal and inflamed periodontal (Rijkschroeff et al., 2018). In the initial phase of PD, there is an elevation in neutrophil mobilization, migration, and infiltration. On the other hand, a substantial decrease in the phagocyte operations of neutrophils was identified among persons experiencing PD. Pro-inflammatory cytokines (for example, TNF-α, and IL-8), neutrophil enzymes, eosinophil cationic protein, histidine decarboxylase, histamine, and neutrophil elastase affect all of these alterations (Magán-Fernández et al., 2019; Zhang et al., 2020).

Drugs targeting neutrophils

N-acetylcysteine, quercetin, and resveratrol all have the ability to lower the neutrophils' ROS generation while also increasing the expression of type 1 collagen, both of which are important in maintaining healthy gingival tissues and avoiding PD. When it comes to slowing the advancement of PD, resveratrol is the most effective antioxidant out of the three compounds mentioned above. The therapeutic application of antioxidants as a supplement to decrease oxidative stress and minimize PD in people requires more investigations utilizing in vivo prototypes (Orihuela-Campos et al., 2015).

Vitamins that specifically target neutrophils have shown promise as an effective treatment for PD in recent years. Since ascorbic acid (vitamin C) could be administered to treat PD by reducing neutrophil extracellular oxidants, clinical trials have demonstrated that it can mitigate inflammatory responses among individuals suffering from PD (Staudte et al., 2005). Cellular destruction is reduced by the suppression of H2O2-induced intracellular ROS and the inhibition of IL-8 generation via the inhibition of

TABLE 1 Immune cells modulator and their mechanism of action in PD

Drug/system	Target cells	Mechanism of action
NAC, quercetin, and resveratrol	Neutrophils	Reduced ROS generation; increased the expression of type 1 collagen.
Ascorbic acid	Neutrophils	Reduced neutrophil extracellular oxidants.
APM	Neutrophils	Suppressed the H2O2-induced intracellular ROS; inhibited IL-8 generation.
PACN and PACs	Macrophages, Leukocytes	Prevented the production of CD80 and CD86 on macrophages; inhibited IL-8 and PGE2 generated by LPS-induced fibroblasts and IL-6 released by leukocytes.
CSINCpi-2, metformin, CCL2 MPs, PMX205, CSINCpi-2, and 6-Shogaol	Macrophages	Regulated the polarization and recruitment of macrophages.
AsIV	T and B lymphocytes	Reduced CD8+ T cells, TNF-α, IL-1β, IL-2, IgA, and IgG generation; decreased inflammatory responses.
Curcumin and calcitriol	T lymphocytes	Increased the percentage of Tregs and reduced the ratio of Th17 cells
Adoptive transfer of Tregs and microparticles secreting CCL22	Regulatory T cells	Increased osteogenic and anti-inflammatory factors in the periodontium and inhibited translocation of pro-inflammatory cells.
ATRA	Regulatory T cells	Increased the ratio of $FOXP3^+$ Tregs and reduced the prevalence of Th17 cells.
Tamibarotene (Am80)	Regulatory T cells	Increased the ratio of $FOXP3^+$ Tregs and reduced the prevalence of Th17 cells; decreased the transcription of pro-inflammatory cytokines; upregulated TGF-β and IL-10.
IL-35	Regulatory T cells	Increased the ratio of Tregs, locally/systemically prevented alveolar bone resorption; elevated the osteoprotegerin.
NF-SMS	Regulatory T cells	Upregulated TGF-β; improved Treg mobilization and Treg-mediated immunomodulation.
Adoptive transfer of B10 cells	Regulatory B cells	Elevated IL-10 concentrations; reduced IL-17 and RANKL levels; enhanced alveolar bone resorption.

Abbreviations: APM, L-ascorbic acid 2-phosphate magnesium salt; AsIV, Astragaloside IV; ATRA, All-trans retinoic acid; NAC, N-acetylcysteine; NF-SMS, nanofibrous spongy microspheres; PACN, Proanthocyanidins; PACs, Cranberry proanthocyanidins.

TNF-α-induced intracellular ROS by an L-ascorbic acid derivative L-ascorbic acid 2-phosphate magnesium salt (APM). This shows that APM can be administered locally to assist in avoiding periodontal disease (Tsutsumi et al., 2012). Furthermore, through the P38/MAPK axis, 1, 25 dihydroxy vitamin D3 can increase neutrophil apoptosis during type 2 diabetic PD, thereby decreasing PD (Tang et al., 2018).

4.1.2 | Monocytes/macrophages

In tissues with PD, the number of monocytes, particularly intermediate monocytes, an essential cellular defense system against pathogens, greatly increases (Nagasawa et al., 2004). Chronic PD patients had a larger percentage of intermediate $CD14^+CD16^+$ monocytes. Additionally, the number of $CD45RA^+$ monocytes was elevated in patients with severe PD (Almubarak et al., 2020).

Increased and activated pro-inflammatory macrophages are seen in PD (Viniegra et al., 2018). As a result of pathogenic bacteria like Fecal coliforms and their byproducts like LtxA, macrophages in diseased periodontal tissue are more likely to elicit pro-inflammatory responses, phagocytosis, and metabolic functions (Ben Lagha et al., 2019). The primary characteristic of macrophages in PD that distinguishes them apart from regular organs is polarization (Parisi et al., 2018). Macrophages in people with PD are more likely to differentiate to the M1 pathway, whereas M2 differentiation is considerably inhibited. Enhanced generation of pro-inflammatory mediators and matrix-degrading enzymes by macrophages, as well as enhanced osteoclastic function, define PD (Almubarak et al., 2020; Viniegra et al., 2018). TNF-α, interferon-γ (IFN-γ), IL-1α, IL-1β, IL-6, and IL-12 are among the pro-inflammatory cytokines secreted by macrophages. Adhesion factors, including CXCL5 and CXCL1, are also secreted by these cells, as well as activation of inflammatory complexes like NLRP3 (Yang et al., 2018; Sun et al., 2020).

Drugs targeting monocytes/macrophages

Drugs that target monocytes and macrophages are being studied as a treatment for PD. Apical PD can be effectively treated with intracanal metformin. It is capable of minimizing LPS-enhanced CCL-2 generation via suppressing LPS-induced generation of NO and inducible nitric oxide synthase by monocytes (Wang et al., 2020).

Two of the most active compounds are proanthocyanidins (PACN) and cranberry proanthocyanidins. They are a potential option and complementary therapy for the management of PD disease in recent years. IL-8 and PGE2 generated by LPS-induced fibroblasts and IL-6 released by leukocytes can be blocked by Pelargonium sidoides dendritic cell root extract, which is high in PACN. This prevents the production of CD80 and CD86 on macrophage surfaces

as well as IL-1 and cyclooxygenase-2 in leukocytes (Jekabsone et al., 2019). CSINCpi-2, Metformin, CCL2 MPs, PMX205, CSINCpi-2, and 6-Shogaol are other medicines that impact the polarization and recruitment of macrophages (Leguizamon et al., 2019; Zhou et al., 2019; Zhuang et al., 2019; Kim et al., 2020).

4.2 | Adaptive immune cells

4.2.1 | T and B lymphocyte

Bone resorption in patients with PD is thought to be caused by T and B lymphocytes. According to previous studies, a large number of T and B cells that are antigen-specific infiltrate the gingival tissue (Cardoso & Arosa, 2017; Han et al., 2013). In addition, significant links between T lymphocytes and bone resorption have been established (Tsukasaki et al., 2018). The investigation conducted by Yoshie et al. (1987) connected stimulated T lymphocytes to the development of periodontal disease, demonstrating that T cells and their responses to oral infections like P. gingivalis aid bone remodeling in favor of osteoporosis (Baker et al., 2001).

In the periodontal disease scenario, the association of T helper 1 (Th1) cells with costimulatory compounds B7 (CD80/CD86) appears to trigger inflammatory bone resorption. This was accomplished through adoptive T-cell translocation (Kawai et al., 1998). The immunological reaction plays an active part in periodontal bone resorption, as demonstrated by the inhibition of bone resorption by a fusion antibody (CTLA-4Ig), which disrupts the CD28 and B7 link between T lymphocytes and antigen-presenting cells (APC) (Najafian & Sayegh, 2000; Gemmell et al., 2001). On the other side, Yamashita et al. conducted a research in which they introduced A. *actinomycetemcomitans*-specific Th2-cell clones to healthy rats and subsequently exposed the rats to A. *actinomycetemcomitans*. They found that osteoporosis was greatly reduced in the recipients of these clones (Yamashita et al., 1991). Th17 cells in the gingiva of patients with PD were shown to be higher in number, in addition to elevated levels of TNF-α, IL-1, and IL-6, which are the factors that cause polarization of Th17 cells (Teixeira et al., 2017). Th17 cells isolated from the local tissues of PD individuals generated a significant amount of IL-17 and receptor activator for nuclear factor (Nf)-κB ligand (RANKL), increasing the alveolar bone resorption and osteoclast differentiation (Kim et al., 2015).

Additionally, there is evidence that B lymphocytes have a role in the stimulation of bone resorption during PD (Weitzmann, 2017). A greater level of inflammatory bone resorption was found in B-cell-reconstituted SCID mice compared to B and T-cell-deficient SCID mice, showing that B cells increased bone resorption in the gingiva when numerous doses of LPS were administered in an investigation conducted by Kozuka et al. (2006). It has also been demonstrated that antigen-specific B lymphocytes transferred through adoption can lead to periodontal bone deterioration (Han et al., 2006; Harada et al., 2006). Studying the involvement of stimulated T and B cells in the resorption of periodontal bone by stimulating osteoclast precursor cells was assisted in vivo by adoptive transplantation of antigen-specific T cells and antigen-specific B lymphocytes (Kawai et al., 2000).

Drugs targeting T and B lymphocytes

The differentiation of T cells can be regulated by medications that target T lymphocytes, lowering inflammatory response and so alleviating PD and bone deterioration. In the medicinal plant Astragalus membranaceus, Astragaloside IV (AsIV), one of the active compounds, can raise the proportion of $CD4^+$ T cells in peripheral blood and the $CD4^+/CD8^+$ T-cell ratio, whereas the percentage of $CD8^+$ T cells, TNF-α, IL-1β, IL-2, IgA, and IgG can be dramatically lowered. Medications targeting $CD4^+$ T cells may reduce antibody responses dependent on T cells, which would explain the drop in IgA and IgG concentrations. PD can be slowed down by AsIV's ability to decrease inflammatory response (Zhang & Deng, 2019).

Another therapeutic function for medicines like curcumin and calcitriol is to control the differentiation of T cells. Increasing the percentage of Tregs and reducing the ratio of Th17 cells can prevent alveolar bone deterioration via altering the proportion and activity of Th cell subgroups as a result of the administration of the drugs mentioned above. As a result of calcitriol treatment, the polarization capacity of Th2 is enhanced while this parameter is decreased in the Th1 promoter (Bi et al., 2020; Bi et al., 2019).

4.2.2 | Tregs

Despite the fact that plaque bacteria constitute the first step in the progression of PD, the preponderance of tissue destruction is caused by the immune response of the host (Seymour et al., 1993). Thus, controlling the immune-inflammatory response among patients with PD is a possible medicinal strategy. As a result, the immunological system is less likely to respond to infection because of the selective accumulation of regulatory T cells (Tregs). $CD25^{high}$ $FOXP3^+CD127^{-/low}$ $GITR^+CTLA\text{-}4^+CD45RA^+$ are a subpopulation of $CD4^+$ cells (Azimi et al., 2016). One subset of Tregs is designated FOXP3-induced (iTregs), while the other is termed $FOXP3^+$ natural (nTregs). nTregs originate from thymocytes in the thymus after agonist choosing. In the availability of retinoic acid, transforming growth factor-beta (TGF-β), and IL-10, iTregs (Tr1 and Th3) differentiate from peripheral T cells in secondary lymphoid organs, particularly mucosa-associated lymphoid tissue, a complex comprising lymphoid cell aggregation in the gastrointestinal, respiratory, urinary tracts, skin, eyes, thyroid, tonsils, breasts, and salivary glands mucosal layers (Mohr et al., 2018). Peripheral tolerance is mostly due to the presence of T regulatory cells (Tregs). Through expressing co-inhibitory receptors, including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), lymphocyte-activation gene 3, programmed cell death protein 1, T-cell immunoreceptor-containing Ig and ITIM domains, and T-cell immunoglobulin and mucin domain-containing-3 (Tim-3), secreted anti-inflammatory cytokines such as TGF-β, IL-35, IL-10, and IL-4, and IL-2 absorption by CD25, these cells modulate the immunological reactions (Mohr et al., 2018).

Increased Treg cell counts have been observed in chronic PD biopsies at intermediate and progressed stages (Nakajima et al., 2005). During the ChunSheng Bi et al. study, gingival crevicular fluid (GCF) and gingival tissues were obtained from individuals with a normal periodontal region (PH group) and individuals experiencing chronic (CP group). GCF and gingival tissues from the CP group had elevated levels of IL-17, while IL-10 and IL-4 levels were significantly lower. GCF and gingival tissues from the CP group had increased concentrations of IL-17, while IL-10 and IL-4 concentrations were significantly decreased. Additionally, the PH group had a higher number of Th2 and Treg cells, while the CP group had a higher number of Th1 and Th17 cells (Bi et al., 2019). Chemokines including CCL17 and CCL22 have been reported to be more frequent in tissues that have high levels of inflammatory infiltration, which is consistent with the CCR4-dependent mobilization of Treg cells, according to the findings of further research (Cardoso et al., 2008).

On the other side, it is possible that certain $FOXP3^+$ cells will act diversely from conventional Treg cells. A modest number of $FOXP3^+IL\text{-}17A^+$ cells were seen in PD but not in gingivitis, demonstrating that Treg cells in PD may be capable of transforming into Th17 cells (Okui et al., 2012). In addition, the research conducted by Alvarez et al. demonstrated that laboratory PD was associated with the increasing elevation of Th17 and Treg-associated mediators in the gingiva, including IL-17A, IL-17F, IL-6, RANKL, IL-10, TGF-β, and GITR, in addition to the multiplication of both Treg and Th17 cells in cervical lymph nodes. Tregs derived from the cervical lymph nodes had reduced FOXP3 transcription and increased IL-17A transcription relative to Tregs derived from the spleen and normal controls (Alvarez et al., 2020a).

Several in vivo investigations have connected the progression of PD to a decrease in Treg cell activity. In A. actinomycetemcomitans-induced PD in mice, anti-GITR decreased the function of Treg cells, which led to alveolar bone resorption and an increase in inflammatory cytokines, in addition to downregulation of TGF-β, IL-10, and CTLA-4 (Garlet et al., 2010). Similar to the IDO-deficient mouse model, Treg cell function is influenced by the activity of Indoleamine pyrrole 2,3-dioxygenase (IDO) (Qin et al., 2017). In an empirical PD prototype, the role of Tregs was altered in a similar way. Foxp3 downregulation and lower suppression of osteoclast formation aggravated Th17-driven bone deterioration, which was related to the PD-induced hypermethylation of CpG sites in the Foxp3 locus (Alvarez et al., 2020b).

Therapeutic applications of Tregs

In recent years, a variety of immunotherapy methods based on Tregs' immunosuppressive properties have been established (Lotfi et al., 2021; Singer et al., 2014). Clinical effectiveness of Treg infusion in autoimmunity, liver transplantation, graft versus host disease (GVHD), and type 1 diabetes mellitus (T1DM) have been demonstrated thus far in several clinical studies, particularly those in phases I and II (Bluestone et al., 2015; Hartemann et al., 2013; Safinia et al., 2015; Rezaiemanesh et al., 2022; Rajabinejad et al., 2022). Ex vivo alteration of Tregs for adoptive translocation, like Bregs, is one of these techniques. This is where the host or donor's peripheral blood or banked umbilical cord blood is used to isolate Tregs (Fan et al., 2012). Various particular techniques, such as anti-CD3/CD28, donor APCs or artificial APCs, can be used to effectively culture and proliferate Tregs. These techniques are all capable of expanding a particular Treg population in an effective manner. Eventually, the patient receives the purified Tregs (Kasahara et al., 2017).

Another form of immunotherapy is the manipulation of the Treg population in vivo by employing a range of systemically or topically delivered drugs boosting Treg multiplication, half-life, and function (Figure 2). One of these approaches involves the employment of microparticles secreting CCL22 with the intention of specifically recruiting Tregs to a particular inflamed periodontal lesion (Garlet et al., 2014). By upregulating osteogenic and anti-inflammatory factors in the periodontium and inhibiting translocation of pro-inflammatory cells, this method substantially reduced bone resorption in PD murine and canine models (Glowacki et al., 2013b). Another strategy employed in a PD model in mice was the oral administration of All-trans retinoic acid (ATRA). It has been established that this treatment can effectively manage the Th17/Treg equilibrium. This is accomplished by increasing the ratio of $FOXP3^+CD4^+$ Tregs while simultaneously reducing the prevalence of $RORt^+CD4^+$ Th17 cells (Wang et al., 2014). Likewise, oral administration of a retinoic acid receptors (RARs) agonist, tamibarotene (Am80), decreased $RORt^+CD4^+$ Th17 cell polarization and raised $FOXP3^+CD4^+$ Tregs in murine PD gingival tissues, cervical lymph nodes, and spleen. While decreasing the transcription of pro-inflammatory cytokines, including L-17A, RANKL, MCP-1, IL-6, and IL-1, Am80 also upregulated TGF-β and IL-10 (Jin et al., 2014). The Th17/Treg balance was altered by P. gingivalis vaccination to safeguard mice against inflammatory response and alveolar bone resorption. Vaccinated mice had fewer overall $CD4^+$ T cells and $RORt^+CD4^+$ cells; however, their spleen and cervical lymph nodes had higher proportions of Tregs (Wang et al., 2015).

Treg cell-positive modulation has also yielded encouraging outcomes. PD patients in a clinical study conducted by Rajendran et al. (2019) were randomly assigned to receive either 7 days of oral metronidazole/amoxicillin antibiotic therapy or no antibiotic intervention. The results demonstrated that antibiotics could be employed to alter the advancement of inflamed blood myeloid dendritic cells (mDCs) and the transition of Tregs to Th17 cells among individuals experiencing PD. Administration of IL-35 either locally or systemically prevents alveolar bone resorption in PD mice. This is accomplished by changing the equilibrium between Th17 and Treg cells, elevating concentrations of osteoprotegerin (OPG), and RANKL downregulation (Cafferata et al., 2020a). Cafferata et al. treated mice with PD triggered by ligation by administering IL-35 either locally or systemically. IL-35 inhibited alveolar bone resorption in PD mice. In addition, while simultaneously elevating the number of Tregs and the generation of Treg-related mediators, treatment with IL-35 decreased the number of Th17 cells and the synthesis of Th17-related mediators in PD-affected tissue (Cafferata et al., 2020b).

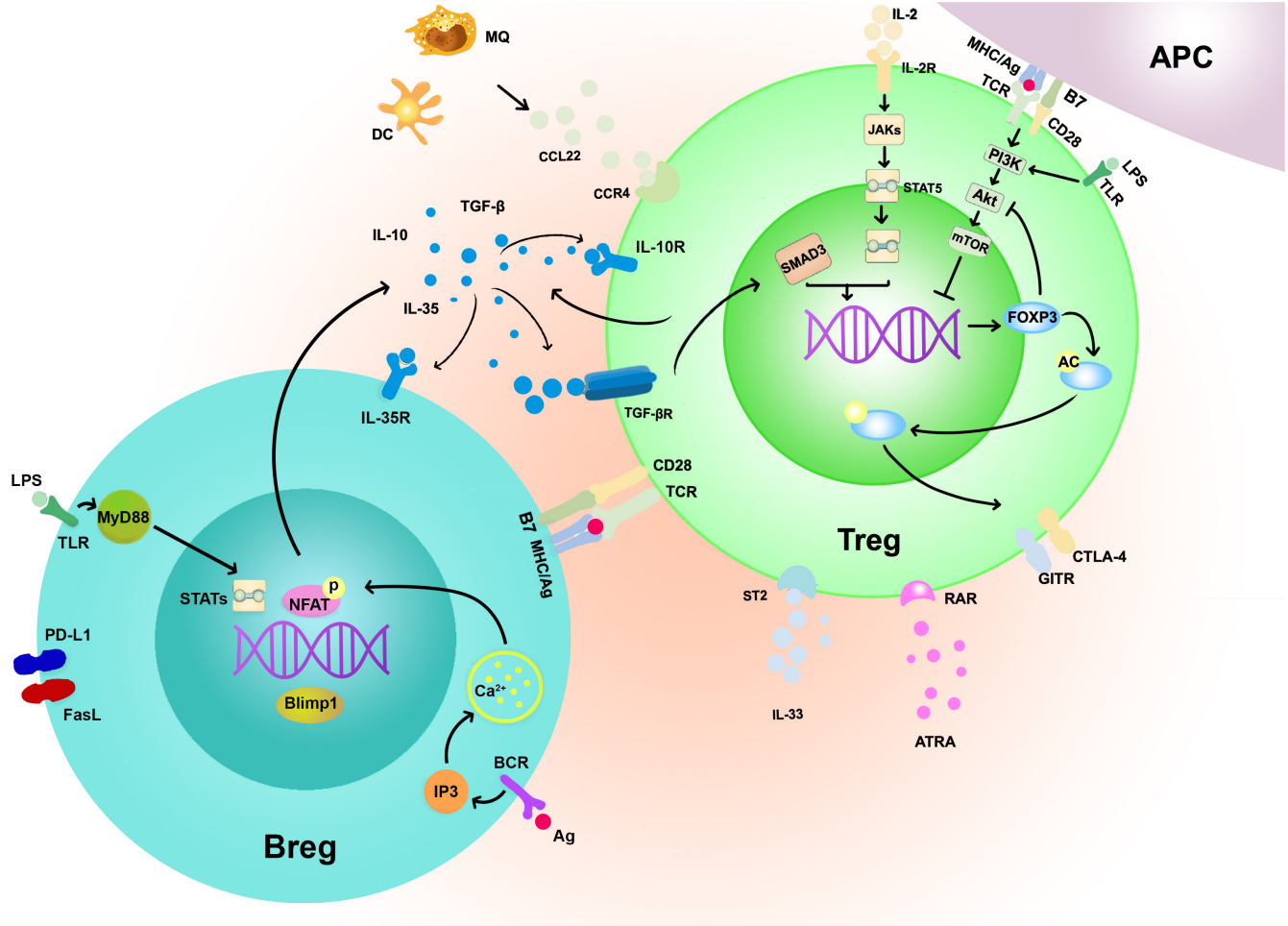

FIGURE 2 Schematic illustration of possible therapeutic approaches of Treg and Breg in PD. IL-2 is an important cytokine for Treg expansion. IL-2 interaction with IL-2R can induce the expression of FOXP3, resulting in the expression of co-inhibitory receptors such as CTLA-4, GITR, and the secretion of anti-inflammatory cytokines. IL-33 and all-trans retinoic acid (ATRA) has also been reported to be important for the immunosuppressive functions of Tregs. Bregs can reinforce the activation of Tregs through MHC-TCR immune synapse and anti-inflammatory cytokines such as IL-10 and TGF-β. Pathogenic structures like lipopolysaccharide. (LPS) can activate B-cell receptor (BCR) and Toll-like receptors (TLRs), resulting in the activation of the downstream pathways in Bregs, such as MyD88, STATs, Blimp1, IP3, calcium–calcineurin–nuclear factor of activated T cells (NFAT) signaling pathway. Activation of these transcription factors can increase the transcription and secretion of IL-10, IL-35, and TGF-β. Breg surface receptors, such as PD-L1 and FasL, can also inhibit the inflammatory responses through the inhibition of effector T cells

The release of regulatory miRNA and TGF-β by nanofibrous spongy microspheres (NF-SMS) administration improved Treg mobilization and Treg-mediated immunomodulation against osteoporosis in a mouse model of PD (Liu et al., 2018). By transporting Sirtuin-1 (SIRT1) protein into $CD4^+$ T cells, P. gingivalis-induced PD environment exosomes also had a role in the regulation of Treg cell location, resulting in enhanced expression of Th17 and decreased expression of Treg (Zheng et al., 2019). By regulating the Th17/Treg cell equilibrium in inflammatory periodontal tissues and compared to mesenchymal stem cell-derived exosomes generated via 2D culture (2D-exos), 3D-exos (MSC exosomes produced by 3D culture) showed greater anti-inflammatory effects in the ligature-induced prototype of PD (Zhang et al., 2021). The proportion of Treg/Th17 cells was increased in laboratory PD by oral therapy using all-trans retinoic acid (ATRA), leading to the prevention of PD (Wang et al., 2014).

4.2.3 | Bregs

TGF-β, IL-35, and IL-10 production, formation of autoantibodies against autoantigens, and activation of Tregs are the primary functions of regulatory B cells (Breg), which are also known as inhibitory B-cell subgroups (Zou et al., 2018). $CD4^+$ effector T cells may decrease, and $CD8^+$ effector T cells may become anergic as a result of LPS-stimulated B cell production of TGF-β1 (Tian et al., 2001; Parekh et al., 2003). Bregs have heterogeneity of phenotypes (Yoshie et al., 1987); however, the vast majority are IL-10-competent B cells. These cells were initially discovered as $CD19^+CD1d^{high}$ $CD5^+IL10^+$ cells and were given the name B10 cells due to the fact that they produce the vast majority of IL-10 released by B cells (Yanaba et al., 2008). Numerous different varieties of B10 cells have been identified since then, each with its own set of transcription factors and cell surface indicators. As a direct

consequence of this, IL-10-producing B cells that also possess IL-10-dependent regulatory characteristics are now known as B10 cells. In addition to IL-10 and CD19, B10 cell markers include CD9 (which is expressed in 90% of mice B10 cells) (Sun et al., 2015).

Dysregulation of the Bregs has also been found in PD patients. More $CD25^+$ B cells and increased production of TGF-β, IL-35, and IL-10 were seen in patients with PD after induction of the disease, according to Han et al. TLR agonists enhanced Breg growth and function. $CD25^+$ B cells differentiation induced by LPS and CpG and the production of TGF-β, IL-35, and IL-10 were enhanced in this study. In addition, the adoptive transfer of $CD25^+$ B cells was shown to reduce alveolar bone deterioration and concentrations of both IFN-γ and IL-17. Adoptive transplantation of $CD25^+$ B cells restores the pathogenic variation in the fraction of IL-1 and Th1/Th17 in local lesions (Han et al., 2021).

Therapeutic applications of Bregs

Elevated IL-10 concentrations, reduced IL-17 and RANKL levels, enhanced alveolar bone resorption, and diminished periodontal osteoclastogenesis and Th17 cells in local lesions were observed following administration of pathogen-specific B10 cells to mice experiencing laboratory PD (Shi et al., 2020). According to a study conducted by Yu et al., periodontal bone resorption and pro-inflammatory cytokines, including TNF-α, IL-1, and RANKL, were reduced among mice transplanted with $CD5^+CD1d^{high}$ B cells, whereas the expression of IL-10 gene was increased. This was in comparison to animals transplanted with CD5-CD1dlow B cells (Yu et al., 2017). The frequencies of $CD19^+$ IL-10-producing cells, $CD5^+CD19^+CD1d^{high}$ cells, and P.gingivalis-specific $CD19^+$ cells increased in the inflammatory periodontal tissues of mice transplanted with $CD5^+$CD1dhigh B cells (Shi et al., 2020), demonstrating that B10 cell mobilization could decrease periodontal inflammatory response and bone deterioration in vivo. Considering the positive effects of adoptive B10 cell transmission in PD, it may be able to reduce alveolar bone degeneration by triggering a local up-regulation of B10 cells. A significant increase in IL-10 mRNA expression decreased alveolar bone loss, and alleviation of alveolar bone resorption was seen following the gingival injection of CpG and CD40L. $IL\text{-}10^+CD45^+$ cells were also significantly increased (Yu et al., 2017; Wang et al., 2017). In B cells, production of IL-10 and decreased alveolar resorption might be reported by a mixture of IL-21, CD40L, and an antibody targeting Tim-1 (Hu et al., 2017).

5 | CONCLUSION

Pathological alveolar bone resorption occurred in PD is a result of dysregulated immune responses. The recruitment of innate and adaptive immune cells, including T cells, B cells, DCs, macrophages, and neutrophils, signals a switch to the resolution phase or chronic inflammation in the inflamed periodontal tissue. Immunoregulatory cells, particularly Tregs and Bregs, play a vital role in preventing tooth damage and inflammation. These cells become dysregulated or develop plasticity in PD, which can contribute to chronic inflammation. As a result, in experimental research, the use of these cells or their positive manipulation has been demonstrated to be an effective therapeutic method. However, to use this sort of immunotherapy in humans, further preclinical investigations, as well as randomized clinical trials, are required.

AUTHOR CONTRIBUTIONS

Li Junxian: Investigation; methodology; project administration; writing – original draft. **Mojtaba mehrabanian:** Supervision; validation. **Hassan Mivehchi:** Methodology; project administration. **Morteza banakar:** Investigation; validation. **Enas Abdalla Etajuri:** Investigation; validation.

ACKNOWLWDGEMENTS

None.

FUNDING INFORMATION

The authors received no financial support for the research, authorship, and/or publication of this article.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

N/A

INFORMED CONSENT

It is not applicable.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/odi.14360.

ORCID

Mojtaba Mehrabanian https://orcid.org/0000-0002-3095-9111
Morteza Banakar https://orcid.org/0000-0003-1715-0198

REFERENCES

Almubarak, A., Tanagala, K. K. K., Papapanou, P. N., Lalla, E., & Momen-Heravi, F. (2020). Disruption of monocyte and macrophage homeostasis in periodontitis. *Frontiers in Immunology*, *11*, 330.

Alvarez, C., Suliman, S., Almarhoumi, R., Vega, M. E., Rojas, C., Monasterio, G., Galindo, M., Vernal, R., & Kantarci, A. (2020a). Regulatory T cell phenotype and anti-osteoclastogenic function in experimental periodontitis. *Scientific Reports*, *10*(1), 1–12.

Alvarez, C., Suliman, S., Almarhoumi, R., Vega, M. E., Rojas, C., Monasterio, G., Galindo, M., Vernal, R., & Kantarci, A. (2020b). Regulatory T cell phenotype and anti-osteoclastogenic function in experimental periodontitis. *Scientific Reports*, *10*(1), 19018. https://doi.org/10.1038/s41598-020-76038-w

Azimi, M., Aslani, S., Mortezagholi, S., Salek, A., Javan, M. R., Rezaiemanesh, A., Ghaedi, M., Gholamzad, M., & Salehi, E. (2016). Identification, isolation, and functional assay of regulatory T cells. *Immunological Investigations*, *45*(7), 584–602. https://doi.org/10.1080/08820139.2016.1193869

Baker, P. J., Garneau, J., Howe, L., & Roopenian, D. C. (2001). T-cell contributions to alveolar bone loss in response to oral infection with

Porphyromonas gingivalis. *Acta Odontologica Scandinavica*, *59*(4), 222–225. https://doi.org/10.1080/00016350152509247

Ben Lagha, A., Howell, A., & Grenier, D. (2019). Cranberry Proanthocyanidins neutralize the effects of Aggregatibacter actinomycetemcomitans leukotoxin. *Toxins*, *11*(11), 662.

Bi, C. S., Li, X., Qu, H. L., Sun, L. J., An, Y., Hong, Y. L., Tian, B. M., & Chen, F. M. (2020). Calcitriol inhibits osteoclastogenesis in an inflammatory environment by changing the proportion and function of T helper cell subsets (Th2/Th17). *Cell Proliferation*, *53*(6), e12827.

Bi, C. S., Sun, L. J., Qu, H. L., Chen, F., Tian, B. M., & Chen, F. M. (2019). The relationship between T-helper cell polarization and the RANKL/OPG ratio in gingival tissues from chronic periodontitis patients. *Clinical and Experimental Dental Research*, *5*(4), 377–388.

Bi, C. S., Wang, J., Qu, H. L., Li, X., Tian, B. M., Ge, S., & Chen, F. M. (2019). Calcitriol suppresses lipopolysaccharide-induced alveolar bone damage in rats by regulating T helper cell subset polarization. *Journal of Periodontal Research*, *54*(6), 612–623.

Bluestone, J. A., Buckner, J. H., Fitch, M., Gitelman, S. E., Gupta, S., Hellerstein, M. K., Herold, K. C., Lares, A., Lee, M. R., Li, K., Liu, W., Long, S. A., Masiello, L. M., Nguyen, V., Putnam, A. L., Rieck, M., Sayre, P. H., & Tang, Q. (2015). Type 1 diabetes immunotherapy using polyclonal regulatory T cells. *Science Translational Medicine*, *7*(315), 315ra189. https://doi.org/10.1126/scitranslmed.aad4134

Cafferata, E. A., Terraza-Aguirre, C., Barrera, R., Faúndez, N., González, N., Rojas, C., Melgar-Rodríguez, S., Hernández, M., Carvajal, P., Cortez, C., González, F. E., Covarrubias, C., & Vernal, R. (2020a). Interleukin-35 inhibits alveolar bone resorption by modulating the Th17/Treg imbalance during periodontitis. *Journal of Clinical Periodontology*, *47*(6), 676–688. https://doi.org/10.1111/jcpe.13282

Cafferata, E. A., Terraza-Aguirre, C., Barrera, R., Faúndez, N., González, N., Rojas, C., Melgar-Rodríguez, S., Hernández, M., Carvajal, P., Cortez, C., González, F. E., Covarrubias, C., & Vernal, R. (2020b). Interleukin-35 inhibits alveolar bone resorption by modulating the Th17/Treg imbalance during periodontitis. *Journal of Clinical Periodontology*, *47*(6), 676–688.

Cai, K., Wang, F., Lu, J.-Q., Shen, A. N., Zhao, S. M., Zang, W. D., Gui, Y. H., & Zhao, J. Y. (2022). Nicotinamide mononucleotide alleviates cardiomyopathy phenotypes caused by short-chain enoyl-CoA hydratase 1 deficiency. *Basic to Translational Science*, *7*(4), 348–362.

Camelo-Castillo, A. J., Mira, A., Pico, A., Nibali, L., Henderson, B., Donos, N., & TomÃ¡s, I. (2015). Subgingival microbiota in health compared to periodontitis and the influence of smoking. *Frontiers in Microbiology*, *6*, 119. https://doi.org/10.3389/fmicb.2015.00119

Campbell, L., Millhouse, E., Malcolm, J., & Culshaw, S. (2016). T cells, teeth and tissue destruction–what do T cells do in periodontal disease? *Molecular Oral Microbiology.*, *31*(6), 445–456.

Cardoso, C. R., Garlet, G. P., Moreira, A. P., Júnior, W. M., Rossi, M. A., & Silva, J. S. (2008). Characterization of CD4+CD25+ natural regulatory T cells in the inflammatory infiltrate of human chronic periodontitis. *Journal of Leukocyte Biology*, *84*(1), 311–318. https://doi.org/10.1189/jlb.0108014

Cardoso, E. M., & Arosa, F. A. (2017). CD8(+) T cells in chronic periodontitis: Roles and rules. *Frontiers in Immunology*, *8*, 145. https://doi.org/10.3389/fimmu.2017.00145

Cekici, A., Kantarci, A., Hasturk, H., & Van Dyke, T. E. (2014). Inflammatory and immune pathways in the pathogenesis of periodontal disease. *Periodontology 2000*, *64*(1), 57–80. https://doi.org/10.1111/prd.12002

Cheng, W. C., Hughes, F. J., & Taams, L. S. (2014). The presence, function and regulation of IL-17 and Th17 cells in periodontitis. *Journal of Clinical Periodontology*, *41*(6), 541–549.

Corbet, E., Ho, D., & Lai, S. (2009). Radiographs in periodontal disease diagnosis and management. *Australian Dental Journal*, *54*(s1), S27–S43. https://doi.org/10.1111/j.1834-7819.2009.01141.x

Darveau, R. P. (2010). Periodontitis: A polymicrobial disruption of host homeostasis. *Nature Reviews Microbiology*, *8*(7), 481–490. https://doi.org/10.1038/nrmicro2337

Emrich, L. J., Shlossman, M., & Genco, R. J. (1991). Periodontal disease in non-insulin-dependent diabetes mellitus. *Journal of Periodontology*, *62*(2), 123–131. https://doi.org/10.1902/jop.1991.62.2.123

Fan, H., Yang, J., Hao, J., Ren, Y., Chen, L., Li, G., Xie, R., Yang, Y., Gao, F., & Liu, M. (2012). Comparative study of regulatory T cells expanded ex vivo from cord blood and adult peripheral blood. *Immunology*, *136*(2), 218–230. https://doi.org/10.1111/j.1365-2567.2012.03573.x

Garlet, G. P., Cardoso, C. R., Mariano, F. S., Claudino, M., de Assis, G. F., Campanelli, A. P., Ávila-Campos, M. J., & Silva, J. S. (2010). Regulatory T cells attenuate experimental periodontitis progression in mice. *Journal of Clinical Periodontology*, *37*(7), 591–600. https://doi.org/10.1111/j.1600-051X.2010.01586.x

Garlet, G. P., Sfeir, C. S., & Little, S. R. (2014). Restoring host-microbe homeostasis via selective chemoattraction of Tregs. *Journal of Dental Research*, *93*(9), 834–839. https://doi.org/10.1177/0022034514544300

Gemmell, E., McHugh, G. B., Grieco, D. A., & Seymour, G. J. (2001). Costimulatory molecules in human periodontal disease tissues. *Journal of Periodontal Research*, *36*(2), 92–100. https://doi.org/10.1034/j.1600-0765.2001.360205.x

Glowacki, A. J., Yoshizawa, S., Jhunjhunwala, S., Vieira, A. E., Garlet, G. P., Sfeir, C., & Little, S. R. (2013a). Prevention of inflammation-mediated bone loss in murine and canine periodontal disease via recruitment of regulatory lymphocytes. *Proceedings of the National Academy of Sciences*, *110*(46), 18525–18530.

Glowacki, A. J., Yoshizawa, S., Jhunjhunwala, S., Vieira, A. E., Garlet, G. P., Sfeir, C., & Little, S. R. (2013b). Prevention of inflammation-mediated bone loss in murine and canine periodontal disease via recruitment of regulatory lymphocytes. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(46), 18525–18530. https://doi.org/10.1073/pnas.1302829110

Hajishengallis, G. (2014). Immunomicrobial pathogenesis of periodontitis: Keystones, pathobionts, and host response. *Trends in Immunology*, *35*(1), 3–11. https://doi.org/10.1016/j.it.2013.09.001

Han, X., Kawai, T., Eastcott, J. W., & Taubman, M. A. (2006). Bacterial-responsive B lymphocytes induce periodontal bone resorption. *The Journal of Immunology : Official Journal of The American Association of Immunologists*, *176*(1), 625–631. https://doi.org/10.4049/jimmunol.176.1.625

Han, X., Lin, X., Yu, X., Lin, J., Kawai, T., LaRosa, K. B., & Taubman, M. A. (2013). Porphyromonas gingivalis infection-associated periodontal bone resorption is dependent on receptor activator of NF-κB ligand. *Infection and Immunity*, *81*(5), 1502–1509. https://doi.org/10.1128/iai.00043-13

Han, Y., Yu, C., Yu, Y., & Bi, L. (2021). CD25+ B cells produced IL-35 and alleviated local inflammation during experimental periodontitis. *Oral Diseases*.

Harada, Y., Han, X., Yamashita, K., Kawai, T., Eastcott, J. W., Smith, D. J., & Taubman, M. A. (2006). Effect of adoptive transfer of antigen-specific B cells on periodontal bone resorption. *Journal of Periodontal Research*, *41*(2), 101–107. https://doi.org/10.1111/j.1600-0765.2005.00839.x

Hartemann, A., Bensimon, G., Payan, C. A., Jacqueminet, S., Bourron, O., Nicolas, N., Fonfrede, M., Rosenzwajg, M., Bernard, C., & Klatzmann, D. (2013). Low-dose interleukin 2 in patients with type 1 diabetes: A phase 1/2 randomised, double-blind, placebo-controlled trial. *The Lancet Diabetes and Endocrinology*, *1*(4), 295–305. https://doi.org/10.1016/s2213-8587(13)70113-x

Hasturk, H., & Kantarci, A. (2015). Activation and resolution of periodontal inflammation and its systemic impact. *Periodontology 2000*, *69*(1), 255–273. https://doi.org/10.1111/prd.12105

Henderson, B., Nair, S. P., Ward, J. M., & Wilson, M. (2003). Molecular pathogenicity of the oral opportunistic pathogen Actinobacillus actinomycetemcomitans. *Annual Reviews in Microbiology*, *57*(1), 29–55.

Hsu, H., Lacey, D. L., Dunstan, C. R., Solovyev, I., Colombero, A., Timms, E., Tan, H. L., Elliott, G., Kelley, M. J., Sarosi, I., Wang, L., Xia, X. Z.,

Elliott, R., Chiu, L., Black, T., Scully, S., Capparelli, C., Morony, S., Shimamoto, G., … Boyle, W. J. (1999). Tumor necrosis factor receptor family member RANK mediates osteoclast differentiation and activation induced by osteoprotegerin ligand. *Proceedings of the National Academy of Sciences*, *96*(7), 3540–3545.

Hu, Y., Yu, P., Yu, X., Hu, X., Kawai, T., & Han, X. (2017). IL-21/anti-Tim1/CD40 ligand promotes B10 activity in vitro and alleviates bone loss in experimental periodontitis in vivo. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1863*(9), 2149–2157.

Iino, Y., & Hopps, R. M. (1984). The bone-resorbing activities in tissue culture of lipopolysaccharides from the bacteria Actinobacillus actinomycetemcomitans, Bacteroides gingivalis and Capnocytophaga ochracea isolated from human mouths. *Archives of Oral Biology*, *29*(1), 59–63.

Iranshahi, N., Assar, S., Amiri, S. M., Zafari, P., Fekri, A., & Taghadosi, M. (2019). Decreased gene expression of Epstein–Barr virus-induced gene 3 (EBI-3) may contribute to the pathogenesis of rheumatoid arthritis. *Immunological Investigations*, *48*(4), 367–377. https://doi.org/10.1080/08820139.2018.1549066

Iranshahi, N., Zafari, P., Yari, K., & Alizadeh, E. (2016). The most common genes involved in epigenetics modifications among Iranian patients with breast cancer: A systematic review. *Cellular and Molecular Biology*, *62*(12), 116–122.

Jekabsone, A., Sile, I., Cochis, A., Makrecka-Kuka, M., Laucaityte, G., Makarova, E., Rimondini, L., Bernotiene, R., Raudone, L., Vedlugaite, E., Baniene, R., Smalinskiene, A., Savickiene, N., & Dambrova, M. (2019). Investigation of antibacterial and antiinflammatory activities of proanthocyanidins from pelargonium sidoides DC root extract. *Nutrients*, *11*(11), 2829.

Jiang, J., Guo, Y., Huang, Z., Zhang, Y., Wu, D., & Liu, Y. (2022). Adjacent surface trajectory planning of robot-assisted tooth preparation based on augmented reality. *Engineering Science and Technology, an International Journal*, *27*, 101001.

Jin, J., Zhang, X., Lu, Z., Li, Y., Lopes-Virella, M. F., Yu, H., Haycraft, C. J., Li, Q., Kirkwood, K. L., & Huang, Y. (2014). Simvastatin inhibits lipopolysaccharide-induced osteoclastogenesis and reduces alveolar bone loss in experimental periodontal disease. *Journal of Periodontal Research*, *49*(4), 518–526. https://doi.org/10.1111/jre.12132

Jin, Y., Wang, L., Liu, D., & Lin, X. (2014). Tamibarotene modulates the local immune response in experimental periodontitis. *International Immunopharmacology*, *23*(2), 537–545. https://doi.org/10.1016/j.intimp.2014.10.003

Karthikeyan, B., Talwar, K., & Kalaivani, S. (2015). Evaluation of transcription factor that regulates T helper 17 and regulatory T cells function in periodontal health and disease. *Journal of Pharmacy & Bioallied Sciences*, *7*(Suppl. 2), S672–S676.

Kasahara, H., Kondo, T., Nakatsukasa, H., Chikuma, S., Ito, M., Ando, M., Kurebayashi, Y., Sekiya, T., Yamada, T., Okamoto, S., & Yoshimura, A. (2017). Generation of Allo-antigen-specific induced Treg stabilized by vitamin C treatment and its application for prevention of acute graft versus host disease model. *International Immunology*, *29*(10), 457–469. https://doi.org/10.1093/intimm/dxx060

Kawai, T., Eisen-Lev, R., Seki, M., Eastcott, J. W., Wilson, M. E., & Taubman, M. A. (2000). Requirement of B7 costimulation for Th1-mediated inflammatory bone resorption in experimental periodontal disease. *The Journal of Immunology : Official Journal of the American Association of Immunologists*, *164*(4), 2102–2109. https://doi.org/10.4049/jimmunol.164.4.2102

Kawai, T., Matsuyama, T., Hosokawa, Y., Makihira, S., Seki, M., Karimbux, N. Y., Goncalves, R. B., Valverde, P., Dibart, S., Li, Y. P., Miranda, L. A., Ernst, C. W. O., Izumi, Y., & Taubman, M. A. (2006). B and T lymphocytes are the primary sources of RANKL in the bone resorptive lesion of periodontal disease. *The American Journal of Pathology*, *169*(3), 987–998.

Kawai, T., Shimauchi, H., Eastcott, J. W., Smith, D. J., & Taubman, M. A. (1998). Antigen direction of specific T-cell clones into gingival tissues. *Immunology*, *93*(1), 11–19. https://doi.org/10.1046/j.1365-2567.1998.00408.x

Kim, A., & Sadegh-Nasseri, S. (2015). Determinants of immunodominance for CD4 T cells. *Current Opinion in Immunology.*, *34*, 9–15.

Kim, K.-W., Kim, H.-R., Kim, B.-M., Cho, M.-L., & Lee, S.-H. (2015). Th17 cytokines regulate osteoclastogenesis in rheumatoid arthritis. *The American Journal of Pathology*, *185*(11), 3011–3024.

Kim, Y. G., Kim, M. O., Kim, S. H., Kim, H. J., Pokhrel, N. K., Lee, J. H., Lee, H. J., Kim, J. Y., & Lee, Y. (2020). 6-shogaol, an active ingredient of ginger, inhibits osteoclastogenesis and alveolar bone resorption in ligature-induced periodontitis in mice. *Journal of Periodontology*, *91*(6), 809–818.

Kozuka, Y., Ozaki, Y., Ukai, T., Kaneko, T., & Hara, Y. (2006). B cells play an important role in lipopolysaccharide-induced bone resorption. *Calcified Tissue International*, *78*(3), 125–132. https://doi.org/10.1007/s00223-005-0149-x

Kwon, T., Lamster, I. B., & Levin, L. (2021). Current concepts in the management of periodontitis. *International Dental Journal*, *71*(6), 462–476. https://doi.org/10.1111/idj.12630

Leguizamon, N. D. P., Rodrigues, E. M., de Campos, M. L., Nogueira, A. V. B., Viola, K. S., Schneider, V. K., Neo-Justino, D. M., Tanomaru-Filho, M., Zambuzzi, W. F., Henrique-Silva, F., Soares-Costa, A., Faria, G., & Cirelli, J. A. (2019). In vivo and in vitro anti-inflammatory and pro-osteogenic effects of citrus cystatin CsinCPI-2. *Cytokine*, *123*, 154760.

Liu, Y. C. G., Lerner, U. H., & Teng, Y. T. A. (2010). Cytokine responses against periodontal infection: Protective and destructive roles. *Periodontology 2000*, *52*, 163–206.

Liu, Z., Chen, X., Zhang, Z., Zhang, X., Saunders, L., Zhou, Y., & Ma, P. X. (2018). Nanofibrous spongy microspheres to distinctly release miRNA and growth factors to enrich regulatory T cells and rescue periodontal bone loss. *ACS Nano*, *12*(10), 9785–9799. https://doi.org/10.1021/acsnano.7b08976

Löe, H., Anerud, A., Boysen, H., & Morrison, E. (1986). Natural history of periodontal disease in man. Rapid, moderate and no loss of attachment in Sri Lankan laborers 14 to 46 years of age. *Journal of Clinical Periodontology*, *13*(5), 431–445. https://doi.org/10.1111/j.1600-051x.1986.tb01487.x

Lotfi, R., Nasiri Kalmarzi, R., Rajabinejad, M., Hasani, S., & Zamani, F. (2021). The role of immune semaphorins in the pathogenesis of multiple sclerosis: Potential therapeutic targets. *International Immunopharmacology*, *95*, 107556. https://doi.org/10.1016/j.intimp.2021.107556

Lourenço, T. G., Heller, D., Silva-Boghossian, C. M., Cotton, S. L., Paster, B. J., & Colombo, A. P. (2014). Microbial signature profiles of periodontally healthy and diseased patients. *Journal of Clinical Periodontology*, *41*(11), 1027–1036. https://doi.org/10.1111/jcpe.12302

Lukas, D., Yogev, N., Kel, J. M., Regen, T., Mufazalov, I. A., Tang, Y., Wanke, F., Reizis, B., Müller, W., Kurschus, F. C., Prinz, M., Kleiter, I., Clausen, B. E., & Waisman, A. (2017). TGF-β inhibitor Smad7 regulates dendritic cell-induced autoimmunity. *Proceedings of the National Academy of Sciences*, *114*(8), E1480–E1489.

Lykken, J. M., Candando, K. M., & Tedder, T. F. (2015). Regulatory B10 cell development and function. *International Immunology*, *27*(10), 471–477.

Magán-Fernández, A., O'Valle, F., Abadía-Molina, F., Muñoz, R., Puga-Guil, P., & Mesa, F. (2019). Characterization and comparison of neutrophil extracellular traps in gingival samples of periodontitis and gingivitis: A pilot study. *Journal of Periodontal Research*, *54*(3), 218–224.

Mitani, A., Niedbala, W., Fujimura, T., Mogi, M., Miyamae, S., Higuchi, N., Abe, A., Hishikawa, T., Mizutani, M., Ishihara, Y., Nakamura, H., Kurita, K., Ohno, N., Tanaka, Y., Hattori, M., & Noguchi, T. (2015). Increased expression of interleukin (IL)-35 and IL-17, but not IL-27, in

gingival tissues with chronic periodontitis. *Journal of Periodontology*, *86*(2), 301–309.

Mohr, A., Malhotra, R., Mayer, G., Gorochov, G., & Miyara, M. (2018). Human FOXP 3+ T regulatory cell heterogeneity. *Clinical & Translational Immunology*, *7*(1), e1005.

Nagasawa, T., Kobayashi, H., Aramaki, M., Kiji, M., Oda, S., & Izumi, Y. (2004). Expression of CD14, CD16 and CD45RA on monocytes from periodontitis patients. *Journal of Periodontal Research*, *39*(1), 72–78.

Najafian, N., & Sayegh, M. H. (2000). CTLA4-Ig: a novel immunosuppressive agent. *Expert Opinion on Investigational Drugs*, *9*(9), 2147–2157. https://doi.org/10.1517/13543784.9.9.2147

Nakajima, T., Ueki-Maruyama, K., Oda, T., Ohsawa, Y., Ito, H., Seymour, G. J., & Yamazaki, K. (2005). Regulatory T-cells infiltrate periodontal disease tissues. *Journal of Dental Research*, *84*(7), 639–643. https://doi.org/10.1177/154405910508400711

Nazir, M. A. (2017). Prevalence of periodontal disease, its association with systemic diseases and prevention. *International Journal of Health Sciences (Qassim)*, *11*(2), 72–80.

Neely, A. L., Holford, T. R., Löe, H., Anerud, A., & Boysen, H. (2005). The natural history of periodontal disease in humans: Risk factors for tooth loss in caries-free subjects receiving no oral health care. *Journal of Clinical Periodontology*, *32*(9), 984–993. https://doi.org/10.1111/j.1600-051X.2005.00797.x

Okui, T., Aoki, Y., Ito, H., Honda, T., & Yamazaki, K. (2012). The presence of IL-17+/FOXP3+ double-positive cells in periodontitis. *Journal of Dental Research*, *91*(6), 574–579. https://doi.org/10.1177/0022034512446341

Orihuela-Campos, R. C., Tamaki, N., Mukai, R., Fukui, M., Miki, K., Terao, J., & Ito, H. O. (2015). Biological impacts of resveratrol, quercetin, and N-acetylcysteine on oxidative stress in human gingival fibroblasts. *Journal of clinicAl Biochemistry and Nutrition*, *56*, 14–129.

Parekh, V. V., Prasad, D. V., Banerjee, P. P., Joshi, B. N., Kumar, A., & Mishra, G. C. (2003). B cells activated by lipopolysaccharide, but not by anti-Ig and anti-CD40 antibody, induce anergy in CD8+ T cells: Role of TGF-β1. *The Journal of Immunology*, *170*(12), 5897–5911.

Parisi, L., Gini, E., Baci, D., Tremolati, M., Fanuli, M., Bassani, B., Farronato, G., Bruno, A., & Mortara, L. (2018). Macrophage polarization in chronic inflammatory diseases: Killers or builders? *Journal of Immunology Research*, *2018*, 1–25.

Pihlstrom, B. L., Michalowicz, B. S., & Johnson, N. W. (2005). Periodontal diseases. *The lancet*, *366*(9499), 1809–1820.

Qin, X., Liu, J. Y., Wang, T., Pashley, D. H., al-Hashim, A. H., Abdelsayed, R., C Yu, J., Mozaffari, M. S., & Baban, B. (2017). Role of indoleamine 2,3-dioxygenase in an inflammatory model of murine gingiva. *Journal of Periodontal Research*, *52*(1), 107–113. https://doi.org/10.1111/jre.12374

Rajabinejad, M., Asadi, G., Ranjbar, S., Varmaziar, F. R., Karimi, M., Salari, F., Karaji, A. G., Rezaiemanesh, A., & Hezarkhani, L. A. (2022). The MALAT1-H19/miR-19b-3p axis can be a fingerprint for diabetic neuropathy. *Immunology Letters*, *245*, 69–78. https://doi.org/10.1016/j.imlet.2022.03.004

Rajendran, M., Looney, S., Singh, N., Elashiry, M., Meghil, M. M., el-Awady, A. R., Tawfik, O., Susin, C., Arce, R. M., & Cutler, C. W. (2019). Systemic antibiotic therapy reduces circulating inflammatory dendritic cells and Treg–Th17 plasticity in periodontitis. *The Journal of Immunology*, *202*(9), 2690–2699.

Rezaiemanesh, A., Mahmoudi, M., Amirzargar, A. A., Vojdanian, M., Babaie, F., Mahdavi, J., Rajabinejad, M., Jamshidi, A. R., & Nicknam, M. H. (2022). Upregulation of unfolded protein response and ER stress–related IL-23 production in M1 macrophages from ankylosing spondylitis patients. *Inflammation*, *45*(2), 665–676. https://doi.org/10.1007/s10753-021-01575-z

Richards, D. (2014). Review finds that severe periodontitis affects 11% of the world population. *Evidence-Based Dentistry*, *15*(3), 70–71. https://doi.org/10.1038/sj.ebd.6401037

Rijkschroeff, P., Loos, B. G., & Nicu, E. A. (2018). Oral polymorphonuclear neutrophil contributes to oral health. *Current Oral Health Reports*, *5*(4), 211–220.

Safinia, N., Scotta, C., Vaikunthanathan, T., Lechler, R. I., & Lombardi, G. (2015). Regulatory T cells: Serious contenders in the promise for immunological tolerance in transplantation. *Frontiers in Immunology*, *6*, 438. https://doi.org/10.3389/fimmu.2015.00438

Samimi, Z., Kardideh, B., Zafari, P., Bahrehmand, F., Roghani, S. A., & Taghadosi, M. (2019). The impaired gene expression of adenosine monophosphate-activated kinase (AMPK), a key metabolic enzyme in leukocytes of newly diagnosed rheumatoid arthritis patients. *Molecular Biology Reports*, *46*(6), 6353–6360.

Seymour, G. J., Gemmell, E., Reinhardt, R. A., Eastcott, J., & Taubman, M. A. (1993). Immunopathogenesis of chronic inflammatory periodontal disease: Cellular and molecular mechanisms. *Journal of Periodontal Research*, *28*(6 Pt 2), 478–486. https://doi.org/10.1111/j.1600-0765.1993.tb02108.x

Shaddox, L. M., Huang, H., Lin, T., Hou, W., Harrison, P. L., Aukhil, I., Walker, C. B., Klepac-Ceraj, V., & Paster, B. J. (2012). Microbiological characterization in children with aggressive periodontitis. *Journal of Dental Research*, *91*(10), 927–933. https://doi.org/10.1177/0022034512456039

Shi, T., Jin, Y., Miao, Y., Wang, Y., Zhou, Y., & Lin, X. (2020). IL-10 secreting B cells regulate periodontal immune response during periodontitis. *Odontology*, *108*(3), 350–357.

Sima, C., Viniegra, A., & Glogauer, M. (2019). Macrophage immunomodulation in chronic osteolytic diseases—The case of periodontitis. *Journal of Leukocyte Biology*, *105*(3), 473–487.

Singer, B. D., King, L. S., & D'Alessio, F. R. (2014). Regulatory T cells as immunotherapy. *Frontiers in Immunology*, *5*, 46. https://doi.org/10.3389/fimmu.2014.00046

Slots, J. (2013). Periodontology: Past, present, perspectives. *Periodontology 2000*, *62*(1), 7–19. https://doi.org/10.1111/prd.12011

Sorsa, T., Tjäderhane, L., Konttinen, Y. T., Lauhio, A., Salo, T., Lee, H. M., Golub, L. M., Brown, D. L., & Mäntylä, P. (2006). Matrix metalloproteinases: Contribution to pathogenesis, diagnosis and treatment of periodontal inflammation. *Annals of Medicine*, *38*(5), 306–321.

Staudte, H., Sigusch, B., & Glockmann, E. (2005). Grapefruit consumption improves vitamin C status in periodontitis patients. *British Dental Journal*, *199*(4), 213–217.

Sudhakara, P., Gupta, A., Bhardwaj, A., & Wilson, A. (2018). Oral Dysbiotic communities and their implications in systemic diseases. *Dentistry Journal*, *6*(2), 10. https://doi.org/10.3390/dj6020010

Sun, J., Wang, J., Pefanis, E., Chao, J., Rothschild, G., Tachibana, I., Chen, J. K., Ivanov, I. I., Rabadan, R., Takeda, Y., & Basu, U. (2015). Transcriptomics identify CD9 as a marker of murine IL-10-competent regulatory B cells. *Cell Reports*, *13*(6), 1110–1117.

Sun, L., Girnary, M., Wang, L., Jiao, Y., Zeng, E., Mercer, K., Zhang, J., Marchesan, J. T., Yu, N., Moss, K., Lei, Y. L., Offenbacher, S., & Zhang, S. (2020). IL-10 dampens an IL-17–mediated periodontitis-associated inflammatory network. *The Journal of Immunology*, *204*(8), 2177–2191.

Tang, Y., Liu, J., Yan, Y., Fang, H., Guo, C., Xie, R., & Liu, Q. (2018). 1, 25-dihydroxyvitamin-D3 promotes neutrophil apoptosis in periodontitis with type 2 diabetes mellitus patients via the p38/MAPK pathway. *Medicine*, *97*(52), e13903.

Teixeira, M. K. S., Lira-Junior, R., Telles, D. M., Lourenço, E. J. V., & Figueredo, C. M. (2017). Th17-related cytokines in mucositis: Is there any difference between peri-implantitis and periodontitis patients? *Clinical Oral Implants Research*, *28*(7), 816–822.

Tian, J., Zekzer, D., Hanssen, L., Lu, Y., Olcott, A., & Kaufman, D. L. (2001). Lipopolysaccharide-activated B cells down-regulate Th1 immunity and prevent autoimmune diabetes in nonobese diabetic mice. *The Journal of Immunology.*, *167*(2), 1081–1089.

Tonetti, M. S., Greenwell, H., & Kornman, K. S. (2018). Staging and grading of periodontitis: Framework and proposal of a new classification

and case definition. *Journal of Periodontology*, *89*(Suppl. 1), S159–S172. https://doi.org/10.1002/jper.18-0006

Tsukasaki, M., Komatsu, N., Nagashima, K., Nitta, T., Pluemsakunthai, W., Shukunami, C., Iwakura, Y., Nakashima, T., Okamoto, K., & Takayanagi, H. (2018). Host defense against oral microbiota by bone-damaging T cells. *Nature Communications*, *9*(1), 701. https://doi.org/10.1038/s41467-018-03147-6

Tsutsumi, K., Fujikawa, H., Kajikawa, T., Takedachi, M., Yamamoto, T., & Murakami, S. (2012). Effects of L-ascorbic acid 2-phosphate magnesium salt on the properties of human gingival fibroblasts. *Journal of Periodontal Research*, *47*(2), 263–271.

Uitto, V. J., Overall, C. M., & McCulloch, C. (2003). Proteolytic host cell enzymes in gingival crevice fluid. *Periodontology 2000*, *31*(1), 77–104.

Vignali, D. A. A., Collison, L. W., & Workman, C. J. (2008). How regulatory T cells work. *Nature Reviews Immunology*, *8*(7), 523–532. https://doi.org/10.1038/nri2343

Viniegra, A., Goldberg, H., Çil, Ç., Fine, N., Sheikh, Z., Galli, M., Freire, M., Wang, Y., van Dyke, T. E., Glogauer, M., & Sima, C. (2018). Resolving macrophages counter osteolysis by anabolic actions on bone cells. *Journal of Dental Research*, *97*(10), 1160–1169.

Wahlgren, J., Salo, T., Teronen, O., Luoto, H., Sorsa, T., & Tjäderhane, L. (2002). Matrix metalloproteinase-8 (MMP-8) in pulpal and periapical inflammation and periapical root-canal exudates. *International Endodontic Journal*, *35*(11), 897–904.

Wang, H.-W., Lai, E. H.-H., Yang, C.-N., Lin, S. K., Hong, C. Y., Yang, H., Chang, J. Z. C., & Kok, S. H. (2020). Intracanal metformin promotes healing of apical periodontitis via suppressing inducible nitric oxide synthase expression and monocyte recruitment. *Journal of Endodontics*, *46*(1), 65–73.

Wang, L., Guan, N., Jin, Y., Lin, X., & Gao, H. (2015). Subcutaneous vaccination with Porphyromonas gingivalis ameliorates periodontitis by modulating Th17/Treg imbalance in a murine model. *International Immunopharmacology*, *25*(1), 65–73. https://doi.org/10.1016/j.intimp.2015.01.007

Wang, L., Wang, J., Jin, Y., Gao, H., & Lin, X. (2014). Oral administration of all-trans retinoic acid suppresses experimental periodontitis by modulating the Th17/Treg imbalance. *Journal of Periodontology*, *85*(5), 740–750. https://doi.org/10.1902/jop.2013.130132

Wang, Y., Yu, X., Lin, J., Hu, Y., Zhao, Q., Kawai, T., Taubman, M. A., & Han, X. (2017). B10 cells alleviate periodontal bone loss in experimental periodontitis. *Infection and Immunity*, *85*(9), e00335–e00317.

Weitzmann, M. N. (2017). Bone and the immune system. *Toxicologic Pathology*, *45*(7), 911–924. https://doi.org/10.1177/0192623317735316

Yamashita, K., Eastcott, J. W., Taubman, M. A., Smith, D. J., & Cox, D. S. (1991). Effect of adoptive transfer of cloned Actinobacillus actinomycetemcomitans-specific T helper cells on periodontal disease. *Infection and Immunity*, *59*(4), 1529–1534. https://doi.org/10.1128/iai.59.4.1529-1534.1991

Yanaba, K., Bouaziz, J.-D., Haas, K. M., Poe, J. C., Fujimoto, M., & Tedder, T. F. (2008). A regulatory B cell subset with a unique CD1dhiCD5+ phenotype controls T cell-dependent inflammatory responses. *Immunity*, *28*(5), 639–650.

Yang, J., Zhu, Y., Duan, D., Wang, P., Xin, Y., Bai, L., Liu, Y., & Xu, Y. (2018). Enhanced activity of macrophage M1/M2 phenotypes in periodontitis. *Archives of Oral Biology*, *96*, 234–242.

Yasuda, H., Shima, N., Nakagawa, N., Mochizuki, S. I., Yano, K., Fujise, N., Sato, Y., Goto, M., Yamaguchi, K., Kuriyama, M., Kanno, T., Murakami, A., Tsuda, E., Morinaga, T., & Higashio, K. (1998). Identity of osteoclastogenesis inhibitory factor (OCIF) and osteoprotegerin (OPG): A mechanism by which OPG/OCIF inhibits osteoclastogenesis in vitro. *Endocrinology*, *139*(3), 1329–1337.

Yoshie, H., Taubman, M. A., Olson, C. L., Ebersole, J. L., & Smith, D. J. (1987). Periodontal bone loss and immune characteristics after adoptive transfer of Actinobacillus-sensitized T cells to rats. *Journal of Periodontal Research*, *22*(6), 499–505. https://doi.org/10.1111/j.1600-0765.1987.tb02061.x

Yu, P., Hu, Y., Liu, Z., et al. (2017). Local induction of B cell interleukin-10 competency alleviates inflammation and bone loss in ligature-induced experimental periodontitis in mice. *Infection and Immunity*, *85*(1), e00645–e00616.

Zadeh, H. H., Nichols, F. C., & Miyasaki, K. T. (1999). The role of the cell-mediated immune response to Actinobacillus actinomycetemcomitans and Porphyromonas gingivalis in periodontitis. *Periodontology 2000*, *20*, 239–288. https://doi.org/10.1111/j.1600-0757.1999.tb00163.x

Zafari, P., Yari, K., Mostafaei, S., Iranshahi, N., Assar, S., Fekri, A., & Taghadosi, M. (2018). Analysis of Helios gene expression and Foxp3 TSDR methylation in the newly diagnosed rheumatoid arthritis patients. *Immunological Investigations*, *47*(6), 632–642.

Zafari, P., Zarifian, A., Alizadeh-Navaei, R., Taghadosi, M., & Rafiei, A. (2020). Association between polymorphisms of cytokine genes and brucellosis: A comprehensive systematic review and meta-analysis. *Cytokine*, *127*, 154949.

Zhang, F., Yang, X.-M., & Jia, S.-Y. (2020). Characteristics of neutrophil extracellular traps in patients with periodontitis and gingivitis. *Brazilian Oral Research*, *34*, e015.

Zhang, L., & Deng, S. (2019). Effects of astragaloside IV on inflammation and immunity in rats with experimental periodontitis. *Brazilian Oral Research*, *33*, e032.

Zhang, X., Liu, L., Chen, W. C., Wang, F., Cheng, Y. R., Liu, Y. M., Lai, Y. F., Zhang, R. J., Qiao, Y. N., Yuan, Y. Y., Lin, Y., Xu, W., Cao, J., Gui, Y. H., & Zhao, J. Y. (2022). Gestational Leucylation suppresses embryonic T-box transcription factor 5 signal and causes congenital heart disease. *Advanced Science*, *9*(15), e2201034.

Zhang, Y., Chen, J., Fu, H., Kuang, S., He, F., Zhang, M., Shen, Z., Qin, W., Lin, Z., & Huang, S. (2021). Exosomes derived from 3D-cultured MSCs improve therapeutic effects in periodontitis and experimental colitis and restore the Th17 cell/Treg balance in inflamed periodontium. *International Journal of Oral Science*, *13*(1), 1–15.

Zhang, Z., Yuan, W., Deng, J., Wang, D., Zhang, T., Peng, L., Tian, H., Wang, Z., & Ma, J. (2020). Granulocyte colony stimulating factor (G-CSF) regulates neutrophils infiltration and periodontal tissue destruction in an experimental periodontitis. *Molecular Immunology*, *117*, 110–121.

Zheng, Y., Dong, C., Yang, J., Jin, Y., Zheng, W., Zhou, Q., Liang, Y., Bao, L., Feng, G., Ji, J., Feng, X., & Gu, Z. (2019). Exosomal microRNA-155-5p from PDLSCs regulated Th17/Treg balance by targeting sirtuin-1 in chronic periodontitis. *Journal of Cellular Physiology*, *234*(11), 20662–20674. https://doi.org/10.1002/jcp.28671

Zhou, X., Zhang, P., Wang, Q., Ji, N., Xia, S., Ding, Y., & Wang, Q. (2019). Metformin ameliorates experimental diabetic periodontitis independently of mammalian target of rapamycin (mTOR) inhibition by reducing NIMA-related kinase 7 (Nek7) expression. *Journal of Periodontology*, *90*(9), 1032–1042.

Zhuang, Z., Yoshizawa-Smith, S., Glowacki, A., Maltos, K., Pacheco, C., Shehabeldin, M., Mulkeen, M., Myers, N., Chong, R., Verdelis, K., Garlet, G. P., Little, S., & Sfeir, C. (2019). Induction of M2 macrophages prevents bone loss in murine periodontitis models. *Journal of Dental Research*, *98*(2), 200–208.

Zou, F., Wang, X., Han, X., Rothschild, G., Zheng, S. G., Basu, U., & Sun, J. (2018). Expression and function of tetraspanins and their interacting partners in B cells. *Frontiers in Immunology*, *9*, 1606.

How to cite this article: Junxian, L., Mehrabanian, M., Mivehchi, H., Banakar, M., & Etajuri, E. A. (2022). The homeostasis and therapeutic applications of innate and adaptive immune cells in periodontitis. *Oral Diseases*, *00*, 1–13. https://doi.org/10.1111/odi.14360