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Immunomodulation in the Treatment of Periodontitis: Progress and Perspectives

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Periodontitis is one of the most common dental diseases. Compared with healthy periodontal tissues, the immune microenvironment plays the key role in periodontitis by allowing the invasion of pathogens. It is possible that modulating the immune microenvironment can supplement traditional treatments and may even promote periodontal regeneration by using stem cells, bacteria, etc. New anti-inflammatory therapies can enhance the generation of a viable local immune microenvironment and promote cell homing and tissue formation, thereby achieving higher levels of immune regulation and tissue repair. We screened recent studies to summarize the advances of the immunomodulatory treatments for periodontitis in the aspects of drug therapy, microbial therapy, stem cell therapy, gene therapy and other therapies. In addition, we included the changes of immune cells and cytokines in the immune microenvironment of periodontitis in the section of drug therapy so as to make it clearer how the treatments took effects accordingly. In the future, more research needs to be done to improve immunotherapy methods and understand the risks and long-term efficacy of these methods in periodontitis.

Keywords: periodontitis, immune microenvironment (IME), immunomodulation, drug therapy, microbial therapy, stem cell therapy, gene therapy

INTRODUCTION

Periodontitis, one of the most common dental diseases, is caused by an inflammatory process affecting periodontal tissues and is indicated by periodontal soft tissue inflammation and the progressive loss of periodontal ligaments and alveolar bone (1). Furthermore, severe periodontitis can lead to facial collapse, impaired mastication, and effects on the digestive system. It is also associated with various systemic and distal inflammatory diseases, including diabetes, cardiovascular disease, rheumatoid arthritis, metabolic syndrome, and Alzheimer's disease (2–5).

The etiology and mechanism of periodontitis is extremely complex. The occurrence and development of periodontitis is the result of the interaction between bacteria and the host (6). Periodontal tissue destruction begins with an inflammatory process caused by oral bacterial infection (2). Host susceptibility is a decisive factor in the development of periodontitis. The human oral cavity is a complex ecological environment, and teeth, gingival crevices and other parts are conducive to bacteria attachment and reproduction (2). Host susceptibility and the effects of oral

bacteria lead to the destruction of periodontal tissues, eventually resulting in loosening and loss of the teeth if untreated (7).

Periodontitis initiation and progression are related to multiple etiologic and risk factors. However, the most critical in periodontal disease pathogenesis is a reciprocally reinforced interplay between microbial dysbiosis and destructive inflammation (8). Pathogens induce periodontitis in susceptible patients and most of the time, the immune system is very efficient and prevents disease progression until the microbial dysbiotic environment has been established. A complex microbial community is involved in periodontitis pathogenesis (9), and *Porphyromonas gingivalis (P. gingivalis)*, *Treponema denticola*, and *Tannerella forsythia* are most often found (10–16). Pathogens can affect periodontal tissue cells by regulating the immune system (17) and leukocytes are essential players in periodontitis by control of gingival biofilm pathogenicity, activation of adaptive immunity, as well as non-resolving inflammation and collateral tissue damage (18).

Periodontitis should be treated as early as possible. Mild to moderate cases can usually be managed by nonsurgical treatments, including auxiliary antibiotics, scaling, and root planning (19, 20). For severe cases that cannot be fully controlled by nonsurgical treatments, surgical methods can reduce pocket depth and generate anatomical contours at the periodontal interface (21). However, the treatment for periodontitis is not ideal. Even in patients receiving regular professional interventions, periodontitis continues to progress and teeth are lost (22). Moreover, because the cost of treatment is high, periodontitis is still a major public health and economic burden (8).

Recently, much attention has been drawn to regulating the immune response to putative periodontal pathogens in order to resolve inflammation, control the osteolytic environment, and restore physiological bone formation (18). Drugs, stem cells, and other therapies targeting the immune microenvironment have shown promising applications. In this study, we systematically reviewed the applications of immune modulation in the treatment of periodontitis, especially those targeting the immune microenvironment changes in periodontitis **(Figure 1)**.

DRUG THERAPY

Drugs Targeting Neutrophils

As the host's first line of defense against pathogenic microorganisms (18, 23, 24), neutrophil homeostasis is key to periodontal health (1).

The periodontal lesion is initiated as acute inflammation characterized by increased numbers of neutrophils migrating into the gingival crevice through the junctional epithelium (1, 25) as a result of chemotaxis by plaque. They are activated by chemoattractants macrophage inflammatory protein-1α (MIP-1α), C-X-C motif ligand 8 (CXCL8) and constitutive higher reactive oxygen species (ROS) (26) and initiate phagocytosis with the assistance of antibodies and complement (27, 28), causing tissue damage (29) and excessive release of destructive molecules, which can be used to distinguish healthy and inflammatory periodontal tissues (30). In patients with periodontitis, recruitment, migration, and infiltration of neutrophils are increased in the early stage, while a significant reduction in phagocyte functions of neutrophils was observed in individuals with periodontitis (31). All of these changes are influenced by cytokines [e.g., granulocyte-colony stimulating factor (G-CSF)] (25), miRNAs [e.g., nod-like receptor 12 (NLRP12)] (32) and inflammasomes [e.g., nod-like receptor 12 (NLRP12)] (33). Proinflammatory cytokines [e.g., tumor necrosis factor (TNF)-α and interleukin (IL)-8], neutrophil enzymes, eosinophil cationic protein (ECP), histidine decarboxylase, histamine and neutrophil elastase (NE) secreted by neutrophils are increased (34–37) and anti-inflammatory cytokines such as IL-10 are decreased (38). All of these changes are affected by bacteria (such as *P. gingivalis*) and bacterial products [such as leukocyte toxin (LtxA)] (36, 38).

Oxidative stress is considered to be an important component in various diseases (39). Polyphenols are now attracting attention as potential sources of agents that can inhibit, reverse, or delay the progression of diseases caused by oxidative stress and inflammatory processes. The highest concentration of active polyphenols has been found in the oral mucosa (40). Resveratrol, quercetin, and N-acetylcysteine (NAC) can reduce the production of ROS by neutrophils and upregulate the synthesis of the type 1 collagen gene, therefore contributing to the integrity of gingival tissues and prevention of periodontitis. Among the three, resveratrol has the best effect as an antioxidant that slows the progression of periodontitis. However, further studies using *in vivo* models are necessary to support the clinical use of antioxidants as a supplement to reduce oxidative stress and prevent periodontitis in humans (41).

Progress have been made in the treatment of periodontitis with vitamins targeting neutrophils. Clinical studies have shown that ascorbic acid (vitamin C) can reduce inflammation in patients with periodontitis possibly because it usually acts as a reducing agent and can be used to treat periodontitis by reducing the extracellular oxidants of neutrophils (42, 43). An L-ascorbic acid derivative, L-Ascorbic acid 2-phosphate magnesium salt (APM), is effective in decreasing cell damage through the suppression of H_2O_2-induced intracellular ROS and inhibited IL-8 production through the suppression of TNF-α-induced intracellular ROS. This suggests that local application of APM can help to prevent periodontal diseases (44). In addition, 1, 25 dihydroxivitamin D3 can promote neutrophil apoptosis in type 2 diabetic periodontitis through the P38/MAPK pathway, reducing periodontitis (45) (**Figure 2**).

However, the approach of using small molecules based on the mechanism of oxidative stress using exogenous antioxidants such as vitamin C to treat other inflammation-related diseases has failed. Therefore, the prospects for these treatments are not very optimistic. Periodontitis may result from interference at the ROS level, and the future research focuses on disease-related ROS source-specific inhibition (46). In this regard, resveratrol has the greater advantage (44).

Drugs Targeting Monocytes

Monocytes, an important cellular defense system against pathogens, significantly increase in periodontitis tissues, especially

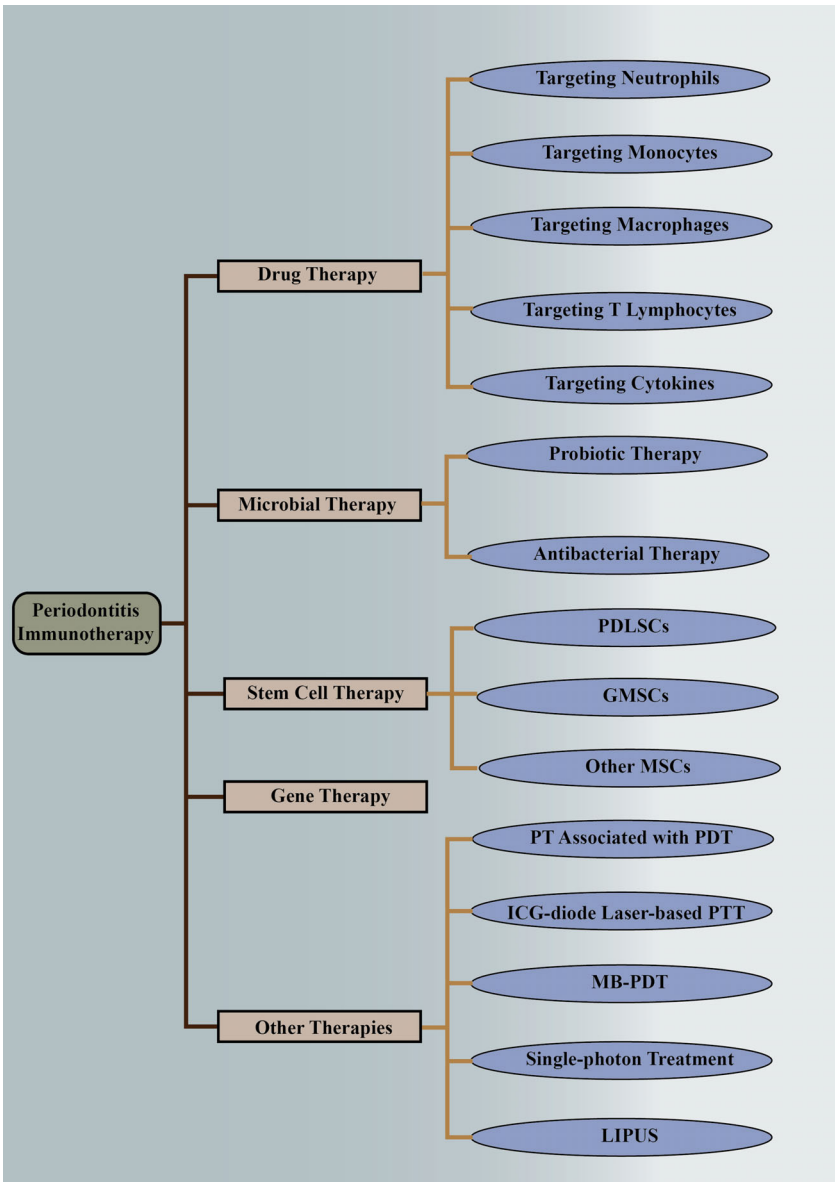

FIGURE 1 | Immunotherapies of periodontitis. The above is a detailed classification of periodontitis immunotherapy, including drug therapy, microbial therapy, stem cell therapy, gene therapy, and other therapies. They are followed by more detailed classifications. PDLSCs, periodontal ligament stem cells; GMSCs, gingival mesenchymal stem cells; MSCs, mesenchymal stem cells; PT, periodontal therapy; PDT, photodynamic therapy; ICG, indocyanine green; PTT, photothermal therapy; MB-PDT, methylene blue-mediated photodynamic therapy; LIPUS, low-intensity pulsed ultrasound.

intermediate monocytes (47). A significantly higher proportion of intermediate [Cluster of Differentiation (CD)14(+)CD16(+)] monocytes was observed in chronic periodontitis and they overexpressed human leukocyte antigen-DR (HLA-DR) and programmed cell death ligand 1 (PD-L1), indicating an activated inflammatory state (48). In addition, CD45RA(+) monocytes were increased in aggressive periodontitis (47). Depressed chemotaxis of monocyte results in increased periodontal destruction (49). There is also a reduction in the function of phagocytes of monocytes, suggesting a decrease in immune defenses in periodontitis (31). Pathogens stimulation of monocytes resulted in increased CD40 and CD54 expression, and enhanced the secretion of high levels of cytokines such as TNF-α, IL-1β, IL-6, IL-8, IL-17, IL-23, monocyte chemoattractant protein-1 (MCP-1) and interferon inducible protein-10 (50, 51).

Resveratrol can treat periodontitis by reducing *P. gingivalis*-mediated activation of the NF-κB signaling pathway. The effect on NF-κB activation likely results from the ability of resveratrol to act as a proliferator-activated receptor-γ (PPAR-γ) agonist. It can also attenuate triggering receptor expressed on myeloid cells-

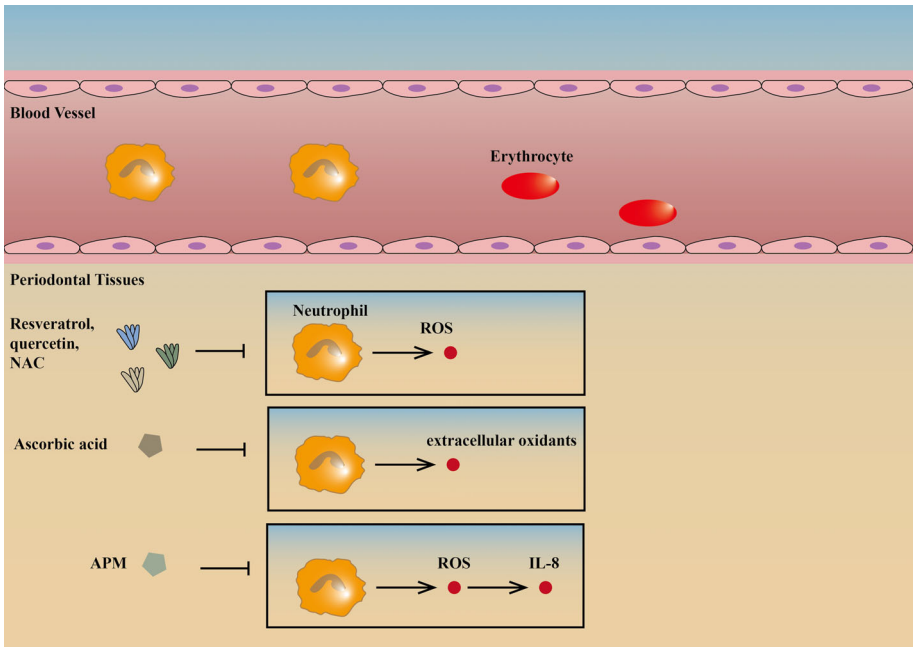

FIGURE 2 | Drugs targeting neutrophils. Resveratrol, quercetin, and NAC can reduce the production of ROS by neutrophils, therefore contributing to the integrity of gingival tissues and prevention of periodontitis (41). Ascorbic acid can reduce inflammation in patients with periodontitis possibly because it usually acts as a reducing agent and can be used to treat periodontitis by reducing the extracellular oxidants of neutrophils (42, 43). APM is effective in inhibiting IL-8 production and decreasing cell damage through the suppression of intracellular ROS (44). ↑ is a symbol for positive effects, and ↓ is a symbol for negative effects and the same goes for the figures and tables below. NAC, N-acetylcysteine; ROS, reactive oxygen species; APM, L-Ascorbic acid 2-phosphate magnesium salt.

1(TREM-1) gene expression as well as soluble TREM-1 secretion in monocytes (52).

In addition, intracanal metformin for apical periodontitis has therapeutic efficacy. It can suppress lipopolysaccharide (LPS)-induced inducible nitric oxide synthase (iNOS) and NO production by monocytes, therefore inhibiting LPS-enhanced chemokine (C-C motif) ligand 2 (CCL-2) synthesis (53). Both of these drugs can eventually reduce bone resorption and improve periodontitis.

Drugs Targeting Macrophages

Macrophages are central players in the destructive and reparative phases of periodontal disease (54). The behavior changes of macrophages are closely related to the pathogens. Pro-inflammatory macrophages increase and are activated in periodontitis (55). Increased proinflammatory responses, phagocytosis, and metabolic activity of macrophages in diseased periodontal tissue are mainly affected by various pathogenic bacteria such as *Fecal coliforms* and bacterial products such as LtxA (56, 57). Polarization is the main feature of macrophages in periodontitis that differentiates them from those in normal tissues (58). In periodontitis, macrophages tend to differentiate in the direction of M1, while M2 differentiation is inhibited significantly (48). Periodontitis is characterized by increased production of proinflammatory mediators and matrix-degrading enzymes by macrophages and increased osteoclastic activity (55). In addition, macrophages secrete increased proinflammatory cytokines such as TNF-α, interferon-γ (IFN-γ), IL-1α, IL-1β, IL-6, and IL-12; increased adhesion factors such as CXCL5 and CXCL1 (54, 59, 60); and increased inflammatory bodies such as NLRP3. In addition, the expression of other molecules such as toll-like receptors 2 (TLR2), TLR4, and nucleotide-binding oligomerization domain 2 (NOD2) is also increased (61), mainly by *in vivo* cytokines such as IL-17 and pathogenic bacteria such as *Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans)* (62, 63).

There is much research on drugs targeting macrophages to treat periodontitis. Proanthocyanidins (PACN) and cranberry proanthocyanidins (PACs) are two of the most active substances with positive effects on both cell behavior and molecular expression. Because of a lower risk of development of resistance and side effects, PACN, a multicomponent plant-derived antibacterial substance, has become a promising alternative and adjunctive therapy candidate for the treatment of periodontitis. Pelargonium sidoides dendritic cell root extract (PSRE), as one of the most PACN-enriched plants, can inhibit IL-8 and prostaglandin E2 (PGE2) produced by LPS-induced fibroblasts and IL-6 by leukocytes, blocking the expression of CD80 and CD86 on the surface of macrophages and IL-1 and cyclooxygenase-2 (COX-2) in leukocytes. Thus, PACN could be an effective drug for periodontitis (64).

PACs can neutralize the cytolytic and proinflammatory responses in human macrophages treated with LtxA. It can protect macrophages against the cytotoxic effect of purified LtxA, inhibiting caspase-1 activation, and consequently

decreasing the secretion of IL-1β and IL-18. Apart from the above therapeutic effects, highbush blueberry PACs can also inhibit the release of TNF-α, IL-6, CXCL8, matrix metalloproteinase-3 (MMP-3), MMP-9, and TREM-1 in a dose-dependent manner. PACs have been a potential candidate for the treatment and prevention of periodontal disease because of the combination of strong pathogen-selective antibacterial, anti-inflammatory, and gingival tissue protection properties (57, 65) **(Figure 3)**.

By summarizing the drugs studied in recent years, we found that most of the drugs can affect the polarization and infiltration behaviors of macrophages [such as CSINCpi-2 (66), Metformin (67), and CCL2 MPs (68)] and inhibit the production of a variety of pro-inflammatory cytokines by macrophages [such as PMX205 (69), CSINCpi-2 (66), 6-Shogaol (70)], a few drugs can promote the production of anti-inflammatory cytokines [e.g. PMX205 (69)]. In addition, they still have some other effects, such as promoting bone regeneration [Dioscin (71)], antibacterial (Perillyl alcohol [POH) (72)] and so on. The effects of other drugs targeting macrophages with positive effects either on cell behavior or molecular expression are shown in **Table 1**.

Drugs Targeting T Lymphocytes

T lymphocytes in tissues can maintain balanced in the gingival environment (83). The number of T cells is significantly higher and they play an important role in alveolar bone resorption (84–86). The differentiation of T cells is caused by ongoing microbial challenges and the ensuing inflammation (87). The activation of different T cell subtypes controls chronic inflammation through secretion of cytokines and regulation of osteoclast production, and they play an important role in determining whether the inflammatory lesion will lead to tissue-destructive periodontitis (83). Overall, Th1 and Th17 responses increase while Th2 and Treg responses decrease in periodontitis, which can independently or interactively increase the receptor activator of NF-κB ligand (RANKL)/osteoprotegerin (OPG) ratio (88, 89). The early oral infection response is mainly attributed to pathogenic Th17 up regulation or protective Treg downregulation, and this imbalance determines the resorption of alveolar bone (90). Persistent oral *P. gingivalis* infection stimulates an initial IL-17A-based response changing into a later *de novo* Th1 response with only sporadic transdifferentiation of Th17 cells (87). As for the memory T cell subsets, a significant increase in the proportion of CD4(+)CD69(+) CD103(-) memory T cells was observed in periodontitis tissues compared with healthy gingiva (91). CD4(+) memory T cells from periodontitis tissues produced either IL-17 or IFN-γ whereas CD8 (+) memory T cells produced only IFN-γ (91). In addition, during the development of periodontitis, the expression levels of IFN-γ (linked to Th cell polarization toward the Th1 cells), IL-17A, IL-17F, IL-1β, IL-6, IL-23 (linked to Th cell polarization toward the Th17 cells), TNF-α, RANKL, glucocorticoid-induced TNFR-related gene (GITR), T-bet, and GATA-3 are all highly increased

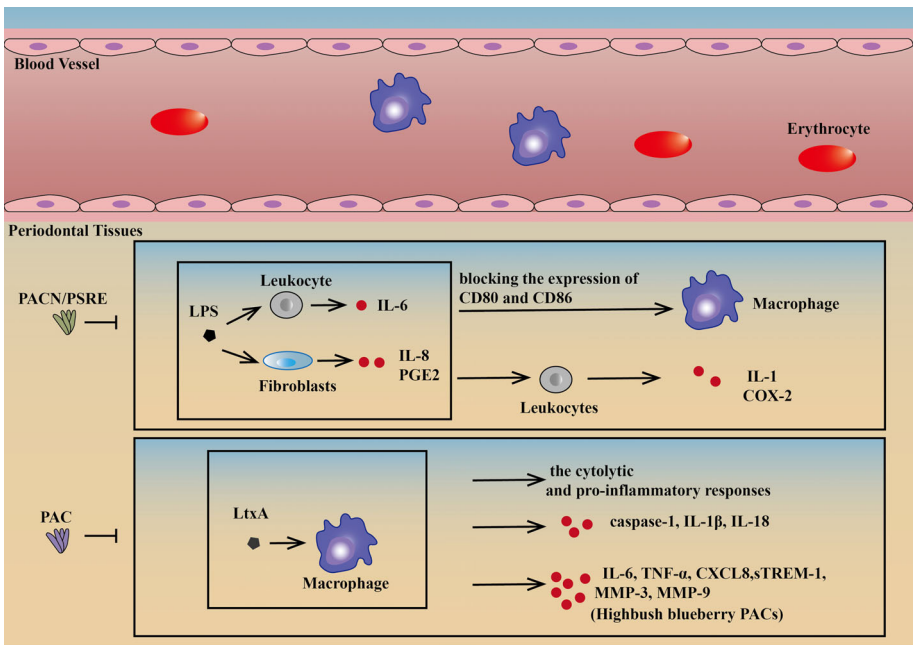

FIGURE 3 | Drugs targeting macrophages. PSRE and PACN can decrease IL-8 and PGE2 by lipopolysaccharide-induced fibroblasts and IL-6 by leukocytes, blocking the expression of CD80 and CD86 on the surface of macrophages and IL-1 and COX-2 in leukocytes (64). PAC can protect macrophages against the cytotoxic effect of purified LtxA, reducing caspase-1 activation in LtxA-treated macrophages, consequently decreasing the release of IL-1β and IL-18. PACs can also neutralize the cytolytic and pro-inflammatory responses of human macrophages treated with LtxA. In addition, highbush blueberry PACs can also inhibit the secretion of IL-6, CXCL8, TNF-α, MMP-3, MMP-9, and sTREM-1in a dose-dependent manner (57, 65). PSRE, Pelargonium sidoides DC root extract; PACN, Proanthocyanidins; PAC, Proanthocyanidins.

TABLE 1 | Effects of drugs targeting macrophages.

	Macrophage activity	Molecular expression	Inflammatory response	Other effects
PSRE and PACN (64)	CD80, CD86 ↓	IL-8, PGE2, IL-6, IL-1, COX-2 ↓	/	/
PAC (57, 65)	Pro-inflammatory responses ↓	IL-1β, IL-18 ↓; IL-6, CXCL8, TNF-α, MMP-3, MMP-9, sTREM-1 (highbush blueberry PACs) ↓	↓	Pathogen-selective antibacterial Gingival tissue protecting properties
Chemically-Modified Curcumin 2.24 (CMC2.24) (73, 74)	Phagocytic activity↓	TNF-α, IL-1β, IL-10, MMP-9, MMP-2 ↓; ROS ↑	/	Bone resorption↓
PMX205 (69)	Macrophage phagocytosis function ↑	NO, IL-23, TGF-β1, IL-10, Arg-1↑; Macrophage TNF-α, IL-6↓	↓	C5a receptor antagonist
CsinCPI-2 (66)	M1 Polarization↓ (Regulation of endogenous M2 macrophages)	Cathepsin K, Cathepsin B, IL-1β, TNF-α↓	↓	Caspase inhibitor
Perillyl alcohol (POH) (72)	Proliferation -	Macrophage ROS, arginase-1↓	/	Antibacterial effect
Metformin (67)	Infiltration ↓	IL-1β ↓	↓	Reduce NLRP3 inflammatory response activity by inhibiting Nek7 expression
Glyburide (75)	Infiltration ↓	Macrophage IL-1β ↓	↓	Osteoclast number ↓
Gliclazide (76)	Migration ↓	Myeloperoxidase activity, malondialdehyde, IL-1β, TNF-α, COX-2, cathepsin k, MMP-2, RANK, RANKL, SOD-1, GPx-1, MIF, Pl3k, NF-kaP50, Pl3k, AKT, F4/80 ↓; OPG↑	↓	Bone loss ↓
6-Shogaol (70)	Number ↓	TNF-α, IL-1β ↓	/	Active ingredients of ginger Neutrophil count↓
Tea polyphenols (77)	/	/	↓	Protect gingival keratinocytes from TNF-α-induced tight junction barrier dysfunction
Dioscin (71)	/	IL-1β, NLRP3, Caspase-1 (macrophages- derived) ↓	↓	Osteo-genesis↑
Ursodeoxycholic acid (UDCA) (78)	/	Macrophage pro-inflammatory cytokines ↓	/	/
Catechin (79)	/	Pro-IL-1β, IL-1β ↓	↓	/
An ethanol extract of paracasei NTU 101 (NTU101FM) (80)	/	Macrophage pro-inflammatory cytokines ↓	/	Antibacterial activity Osteoclast differentiation ↓
Hinokatil (81)	/	Macrophage inflammatory cytokine related gene mRNA levels ↓	/	Local treatment Alveolar bone loss, osteoclast differentiation ↓
CCL2 MPs (68)	M1 Polarization ↓ (Regulation of endogenous M2 macrophages)	/	↓	/
Triclosan (82)	/	*In vitro* protein citrullination and carbamylation of macrophages ↓; post-translational protein modification↓	/	As an adjuvant treatment for inflammatory periodontal disease

(92–94). While less IL-4 (linked to Th cell polarization toward the Th2 cells), IL-10 (linked to Th cell polarization toward the Treg) and transforming growth factor-β (TGF-β) are detected in the patients with periodontitis (95). The more detail of changes of various T cell subtypes in periodontitis is summarized in **Supplementary Table 1**.

Some drugs targeting T lymphocytes can regulate the differentiation of T cells to reduce inflammation, thereby reducing bone loss and improving periodontitis. Astragaloside IV (AsIV), as one of the active ingredients in the medicinal plant *Astragalus membranaceus*, can increase peripheral blood CD4(+)T cell percentages and the CD4(+)/CD8(+) T cell ratio, while the percentage of CD8(+) T cells can be significantly reduced, as well as TNF-α, IL-1β, IL-2, IgA, and IgG. The reduction in IgA and IgG may be because the drugs target CD4(+) T cells, reducing T cell-dependent antibody responses. By this mechanism, AsIV can slow the progress of periodontitis by suppressing inflammation (96).

Other drugs, for example, curcumin and calcitriol, can regulate the differentiation of Th cells, thus playing a therapeutic role. Both of them can inhibit the loss of alveolar bone by changing the proportion and function of Th cell subsets, which is manifested by the increase of Tregs and the decrease of Th17 cells. Calcitriol intervention can also increase Th2 polarization potential and decrease the Th1 promoter (97, 98). In addition, curcumin also exerts antibacterial and antioxidant effects (99, 100) (**Figure 4**).

For periodontitis in patients with Parkinson's disease, vitamin D can reduce peripheral blood CD3, CTL counts, proinflammatory cytokines in saliva, and autophagy-related

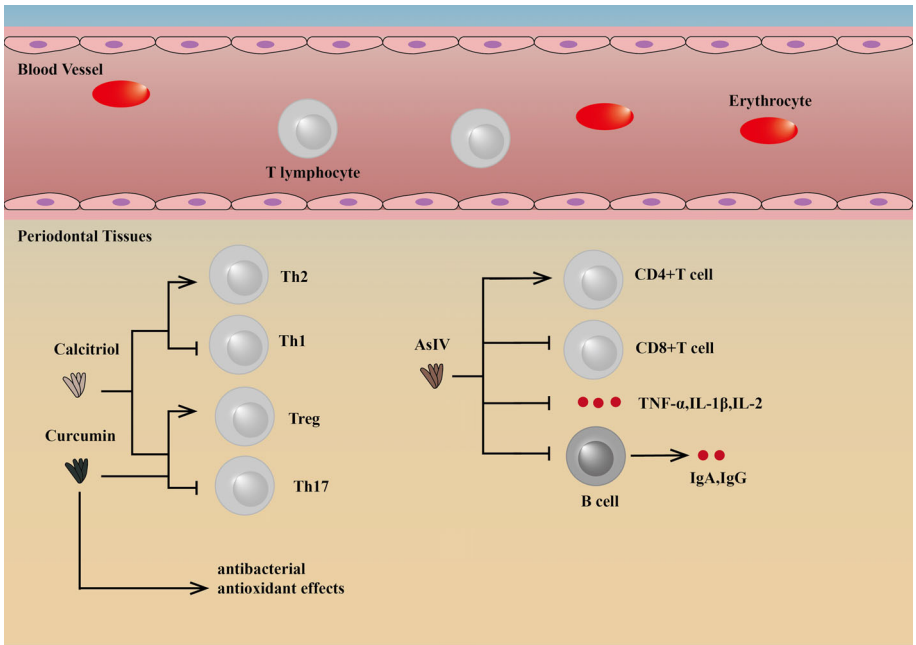

FIGURE 4 | Drugs targeting T lymphocytes and their mechanisms. Curcumin and calcitriol can regulate the differentiation of Th cells, thus playing a therapeutic role. Both of them can inhibit the loss of alveolar bone by changing the proportion and function of Th cell subsets, which is manifested by the increase of Treg cells and the decrease of Th17 cells. Calcitriol intervention can also increase Th2 polarization potential and decrease Th1 promoter (97, 98). In addition, curcumin also exerts antibacterial and antioxidanteffects (99, 100). AsIV can increase peripheral blood CD4(+)T cell percentages and the CD4(+)CD8/CD8(+) T-cell ratio, while the percentage of CD8(+) T cells can be significantly reduced, as well as TNF-α, IL-1β, IL-2, IgA and IgG (96). AsIV, Astragaloside IV.

proteins in whole peripheral blood mononuclear cells. Vitamin D had varied effects on reducing systemic inflammation and promoting the induction of autophagy-related proteins related to antibacterial function. This study has entered the clinical trial stage (101).

Drugs Targeting Cytokines

Imbalance in the inflammatory cytokine network is involved in the periodontal disease process. The interactions between the pathogens and host cells, including leukocytes, can lead to a cytokine cascade. Pro-inflammatory cytokines (such as IL-1 and TNF) lead to periodontitis while anti-inflammatory cytokines ameliorate the disease (102). At the site of periodontitis, the levels of proinflammatory cytokines such as TNF-α, IFN-γ, IL-1, IL-6, IL-12 and G-CSF are significantly increased (25, 54, 103) while anti-inflammatory cytokines are decreased (IL-4 and IL-10) (104). Cytokines and other molecules can be used to diagnose periodontitis, in which the combination of IL-6 and MMP-8 shows the best diagnostic performance (105).

Drugs that target cytokines have been mostly studied *in vitro*. They can inhibit inflammation and reduce bone resorption by inhibiting the production and action of pro-inflammatory factors. Among them, most drugs can inhibit the expression of TNF-α, such as trans-cinnamic aldehyde (106), kawa-205ME (107), β-carotene (108), calcitonin gene-related peptide (CGRP) (109), *Platycarya strobilacea* leaf extract (PLE) (110), and bismuth drugs (111). In addition, trans-cinnamic aldehyde (106), psoralen and angelicin (112), bismuth drugs (111), SIM-PPI (113), and benzydamine (114) can inhibit the expression of IL-1β. On the contrary, drugs that target cytokines have no effect on anti-inflammatory factors. This may be because some studies have shown that there is little change in anti-inflammatory cytokines in gingival crevicular fluid in patients with periodontitis (115). More detailed effects of these drugs are shown in **Table 2**.

OTHER IMMUNE CELLS PARTICIPATING IN PERIODONTITIS

In addition to the immune system components aforementioned, other components such as DCs, mast cells (MCs) and B lymphocytes also play a role in the development of periodontitis.

DCs act as a bridge for innate and adaptive immune responses (122). The presence of DCs in periodontitis may be a sign of the severity of the lesion (123). Activated in periodontitis by the protein kinase B (AKT)/Forkhead box O1 (FoxO1) axis, DCs play both protective and destructive roles through activation of the acquired immune response (124, 125). DCs can promote Th17-specific differentiation (126) and Treg and Th17 responses (127), thereby alleviating periodontitis. However, *P. gingivalis* upregulated its short mfa1 fimbriae, leading to increased invasion of DCs, which may have negative consequences for the host (128).

TABLE 2 | Effects of drugs targeting cytokines.

	Pro-inflammatory cytokines	Other molecules	For bone	Other effects
Trans-cinnamic aldehyde (106)	TNF-α, IL-1β ↓	/	Bone loss↓	Anti-inflammatory effects
Kava-205Me (107)	TNF-α ↓	/	/	Reduce the secretion of other cytokines involved in early inflammation, including IL-12, eotaxin, RANTES, IL-10 and IFN-γ
Carnosic Acid (116)	CXCL9, CXCL10, CXCL11 (IL-27 stimulation) ↓	/	/	By inhibiting the activation of STAT1, STAT3 and Akt
β- carotene (108)	TNF-α, IL-6, MCP-1 ↓	/	/	/
Psoralen and Angelicin (112)	IL-1β, IL-8 ↓	/	Alveolar bone loss↓	Anti-inflammatory effects
Calcitonin generelated peptide (CGRP) (109)	TNF-α (Osteoblast-derived) ↓	cCaspase3, cCaspase8 activation ↓	Osteoblast apoptosis↓	An important neuropeptide for bone remodeling
Platycarya strobilacea leaf extract (PLE) (110)	TNF-α(Macrophage-derived) ↓	MMP-9, Cathepsin K ↓	Bone resorption↓	Block NFATc1, osteoclast fusion DC-STAMP and osteoclast active cathepsin K gene expression levels
Bismuth drugs (111)	IL-6, IL-1β, TNF-α (Macrophage-derived) ↓	/	/	Anti-inflammatory effects
The Amyl-1-18 peptide (A peptide derived from rice) (117)	IL-6(Macrophage-derived)↓	/	/	Neutralize lipopolysaccharides and inhibit NF-κB signal transduction and IL-1R-related signal transduction Anti-inflammatory effects
SIM-PPi (113) Local Application of Pyrophosphorylated Simvastatin Prevents Experimental Periodontitis	IL-1β, IL-6 ↓	/	/	Synthesized by directly conjugating a SIM trimer to a pyrophosphate (PPi), greatly improving water-solubility of SIM and shows strong binding to hydroxyapatite (HA)
Benzydamine (114)	Pro-inflammatory cytokines (IL-1β) ↓	Prostaglandin↓	Bone resorption, Osteoclast differentiation↓ Osteoblast differentiation↑	Used as a cytokine inhibitor or non-steroidal anti-inflammatory drug
Flavan-3-ols and proanthocyanidins from Limonium brasiliense (118)	↓	/	/	/
Simvastatin(SIM) (113)	/	/	Osteogenesis↑	Widely used in the treatment of hypercholesterolemia HMG CoA reductase inhibitors Anti-inflammatory effects
Resolvins (119, 120)	/	/	/	Cannot suppress acute inflammation; prevent the prolongation of inflammation
Rice peptides REP9 and REP11 (121)	/	/	/	Transcriptional activity of inflammatory and osteoclast-related molecules↓

MCs participate in immune regulation. In the evolution of periodontal disease there are significant dynamic alterations in migration and localization of MCs (129). There is a correlation between the number of MCs and depth of the gingival pocket (130). The significantly increased number of tryptase- T cell immunoglobulin mucin domain 1 (TIM-1) double-positive MCs had the similar tendency as the severity of periodontitis inflammation (131), especially in invasive periodontitis (132). Pro-inflammatory cytokines in MCs increase, including TNF-α (133), IL-31 (134), and TLR4 (135). Through releasing different proinflammatory cytokines, MCs can also promote leukocyte infiltration under various inflammatory states in the oral tissues (136).

B cells can aggravate the RANKL-dependent osteoclast differentiation in alveolar bone loss, leading the periodontitis (83) to a more severe extent compared with T cells (137). The proportion of memory B cells decreases in periodontitis, which shows the highest tendency to support osteoclast differentiation (137). However, there is also a class of B cells that produce IL-10, which can downregulate adaptive and innate immunity, inflammation, and autoimmunity (138). Migration of B10 cells in periodontitis resulted in increased IL-10, decreased IL-17 and RANKL, regulating local host immune response by reducing the expression of pro-inflammatory cytokines and inhibiting the local proliferation of Th17 cells (139).

It's worth noting that a lot of drug research has focused on natural molecules like resveratrol and PACN. These natural molecules are a more promising alternative and adjunct to traditional antibiotic treatment strategies because they reduce the risk of developing resistance, short-term and long-term toxicity, adverse and side effects (64). However, many related researches failed to enter clinical application, one of the important reasons is that the biological activity, toxicity and other characteristics of natural molecules have not been

scientifically and effectively explored. We don't know yet how effective or safe they are. On the other hand, most of the relevant studies lacked the actual pathophysiological aspects of the disease (140). Nevertheless, the potential value of natural molecules in the development of periodontitis therapeutics requires a multidisciplinary research and development team to comprehensively address the actual disease challenges and patient treatment needs (141).

All in all, drug therapy, as a traditional method, has made faster progress compared with the emerging treatment methods. Most drugs target macrophages, T cells, and/or cytokines. Most of the drug studies are still *in vitro*, but there are still some drugs (such as ascorbic acid) that can be used in human periodontitis. At present, drug therapies targeting components of the immune system are still lacking and more laboratory and clinical studies are needed.

MICROBIAL THERAPY

Probiotic Therapy

Oral probiotics are a relatively safe and effective adjunctive treatment for periodontitis. Their complementary use has the potential to improve disease indicators and reduce the need for antibiotics (142). In order to make better use of adjuvant therapy of probiotics, we believe that it is necessary to find more correct probiotics strains, gain more recognition from patients, and focus on developing more individualized treatment plans (143).

Probiotic-assisted routine treatment of periodontitis treatment (144) may have a positive impact on the immune prognosis of patients. It has been found that GCF/MMP-8 levels were significantly reduced in patients treated with scraping and root planning (SRP) and probiotics combined (145). Significantly reduced levels of pro-inflammatory cytokines IL-1ß and IL-8 were observed in patients with generalized chronic periodontitis treated with a probiotic buccal adjuvant containing *Bifidobacterium animalis* subsp. *lactis (B. lactis)* HN019 for SRP (146), while the levels of β-defensin-3, TLR4, CD57 and CD4 were significantly increased (147). Supplementation with probiotics containing *Lactobacillus reuteri* during periodontal therapy was associated with a significant decrease in MMP-8 levels and a significant increase in matrix metalloproteinase-tissue inhibitor (TIMP-1) levels. This suggests that lozenges reduce inflammatory markers in the short term (148). Using the intestinal symbiotic *Akkermansia Muciniphila* in an experimental periodontitis model induced by *P. gingivalis*, alveolar bone loss was improved. *In vitro*, bone marrow macrophages increased IL-10 and decreased IL-12, and expressions of connective integrity markers such as integrin -β1, e-cadherin, and ZO-1 in gingival epithelial cells were also increased. This proves that *Akkermansia muciniphila* can be considered as an adjunct to periodontal therapy (149).

As an independent means of treatment, the therapeutic effect of probiotics has also been positive. Gastric administration of *Lactobacillus gasseri* SBT2055 in mice enhanced immune regulation and prevented periodontitis through intestinal immune system. The expression and secretion of TNF-α and IL-6 decreased significantly. The mRNA and peptide products of β-defensin-14 were significantly increased in the distal mucosa and intestinal tract of mice (150).

In addition, probiotics have also been found to have a preventive effect. Prophylactic administration of a combination of omega-3 and probiotics reduced alveolar bone loss and improved serum IL-1β, IL-6, and IL-10 levels (151).

Existing meta-analyses have shown that probiotics have a positive therapeutic effect on periodontitis (152). Many probiotic strains have strong aggregation ability, strong adhesion ability to oral tissue, and high antagonistic activity against oral pathogens. And they were largely free of antibiotic resistance (153). However, this treatment does not seem to be a permanent solution, as most of these probiotics originate from the external oral microenvironment and may not succeed in permanently colonizing the oral cavity. For them to continue to play an active therapeutic role, we need to develop a more appropriate frequency of administration (154). Therefore, the extraction of probiotics from the mouth of healthy people may promote the permanent colonization of probiotics and may be a more ideal treatment method (155).

Antibacterial Therapy

There have been many achievements in antibacterial treatment of periodontitis, but there is still no clinical treatment available. As for antibacterial therapy, the main method is to induce immunity to pathogens through vaccination.

P. gingivalis capsular defect mutant strains cause reduced loss of alveolar bone because of non-expression of RANKL and a decrease in Th1/Th17 cytokines, Th1/Th17 lymphocytes, and osteoclasts (156). Subcutaneously vaccination with formalin-killed *P. gingivalis* can result in upregulation of Tregs through the production of IL-10 and TGF-β, downregulation of Th17 cells and IL-17A production and inhibition of lymphocyte proliferation (157). *P. gingivalis*-specific inflammatory immune response can be protected by therapeutic vaccination with a chimera (KAS2-A1) (parenteral or intraoral administration) immunogen targeting the major virulence factors of the bacterium, the gingipain proteinases. In addition, this protection is characterized by an antigen-specific IgG1 isotype antibody and Th2 response, which produced an effective therapeutic intervention that protected against *P. gingivalis*-induced periodontitis (158).

To date, however, *P. gingivalis* vaccination has been studied only in animals, and no effective prophylactic human periodontal vaccine has been developed, with the reason for the failure of prophylactic human periodontal vaccines unknown (157). We consider patients with *P. gingivalis*-associated periodontitis have higher threshold levels of pathogens in the subgingival plaque and exhibit an inflammatory immune response. Therefore, therapeutic vaccination may exacerbate inflammation and bone resorption in these patients **(Figure 5)**.

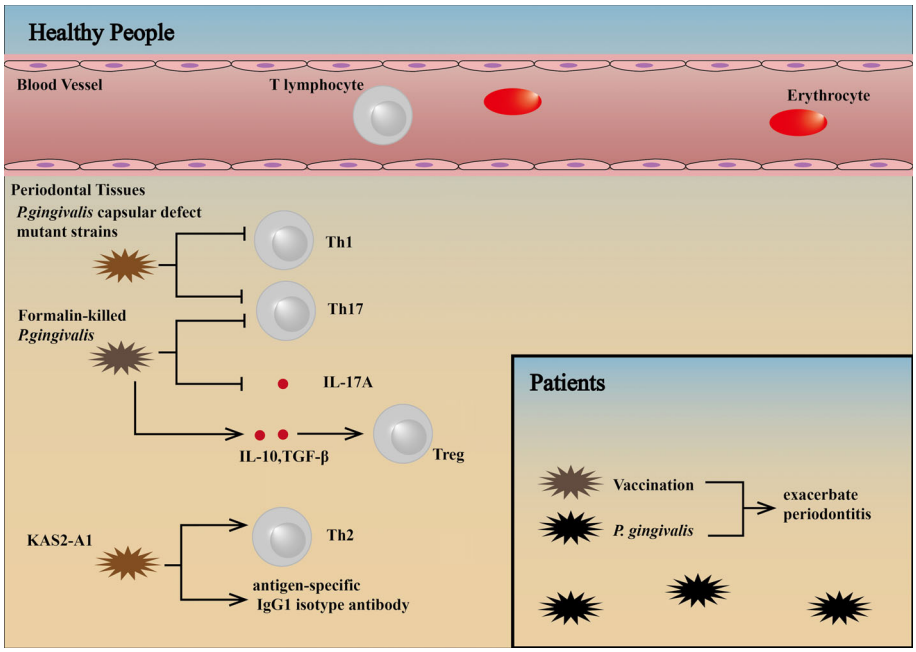

FIGURE 5 | Influence of vaccination against pathogens in patients and healthy people. *P. gingivalis* capsular defect mutant strains cause reduced loss of alveolar bone because of non-expression of RANKL and a decrease in Th1/Th17 cytokines, Th1/Th17 lymphocytes, and osteoclasts (156). Subcutaneously vaccination with formalin-killed *P. gingivalis* can result in upregulation of Tregs through the production of IL-10 and TGF-β, downregulation of Th17 cells and IL-17A production and inhibition of lymphocyte proliferation (157). *P. gingivalis*-specific inflammatory immune responses can be protected by therapeutic vaccination with a chimera (KAS2-A1) immunogen targeting the major virulence factors of the bacterium, the gingipain proteinases. This protection is characterized by an antigen-specific IgG1 isotype antibody and Th2 cell response (158). Patients with *P. gingivalis*-associated periodontitis have higher threshold levels of pathogens in the subgingival plaque and exhibit an inflammatory immune response. Therefore, therapeutic vaccination may exacerbate inflammation and bone resorption in these patients (89, 94).

STEM CELL THERAPY

Mesenchymal stem cells (MSCs), including oral mesenchymal stem cells, have significant regenerative potential and immunological roles of interacting with the inflammatory microenvironment, while inflammation can also affect the properties of oral MSCs (159, 160). These cells encompass the periodontal ligament stem cells (PDLSCs), the gingival mesenchymal stem cells (GMSCs), the stem cells from human exfoliated deciduous teeth (SHED), the dental pulp stem cells (DPSCs), the dental follicle stem cells (DFSCs), the bone marrow mesenchymal stem cells (BMMSCs) and so on. With the emergence of bioengineered therapies, some studies have investigated the potential use of cell therapies, in which the main ones include undifferentiated mesenchymal cells together with different scaffolds (161). Additionally, genetic modulation may enhance the therapeutic potential of MSCs (159).

Inflamed tooth tissue, including pulp and gums, can serve as a source of MSCs with full stem cell properties. The osteogenic capability of DPSCs and GMSCs is not only preserved but increased by the overexpression of several proinflammatory cytokine-dependent chaperones and stress response proteins (162). Similarly, infected DFSCs maintain their stem cell functionality, reduce polymorphonuclear leukocyte (PMN)-induced tissue and bone degradation *via* suppression of PMN-activity, but allowed for the survival of the oral pathogens (163). However, PDLSCs from periodontitis patients are less capable of forming cell aggregates, and show impaired osteogenesis and regeneration. The decline in function can be attributed in part to TNF-α (164), which can be improved by osthole (165), tetramethylpyrazine (166) and resveratrol (167).

The immunoregulative capacity of MSCs is largely governed by the surrounding inflammatory intensity (168). Under low inflammatory condition, MSCs promote the inflammatory response through the secretion of cytokines that recruit immune cells to the local area, while if the inflammatory cytokines exceed a certain threshold, MSCs shift from pro- to anti-inflammatory cells, preventing an overexpression of immunoreaction (169–171). This means that mesenchymal stem cells can adjust their role as inflammation progresses, maintaining tissue integrity and homeostasis, which could pave the way for ameliorating periodontitis.

PDLSCs

PDLSCs in periodontitis tissues have impaired immune regulatory function due to changes in their inflammatory microenvironment, resulting in immune response imbalance and inflammation-related bone loss. PDLSCs provide new prospects and potential therapeutic cells for tooth regeneration

and reconstruction of periodontal ligament tissue damaged by periodontal disease (172, 173).

PDLSCs possess low immunogenicity and marked immunosuppression *via* PGE2-induced T-cell anergy (174). PDLSCs can induce polarization of macrophages to the M2 phenotype, which contributes to enhanced periodontal regeneration after stem cell transplantation (175). In addition, PDLSCs significantly decrease the level of non-classical major histocompatibility complex glycoprotein CD1b on DCs, resulting in defective T cell proliferation, demonstrating their potential to be utilized in promising new stem cell therapies (176). The use of allogeneic PDLSCs in a miniature pig model led to a reduction in humoral immunity. This may be because PDLSCs inhibit B cell activation through intercellular contact, mainly mediated by programmed cell death protein 1 (PD-1) and PD-L1. In addition, PDLSCs can inhibit the proliferation, differentiation and migration of B cells. But interestingly, PDLSCs enhanced B cell viability by secreting IL-6 (177).

Approaches based on extracellular vesicles (EVs) appear to provide a new paradigm for cell-free therapies that overcomes many of the clinical limitations of current cell transplantation. As an ideal vector, EVs have been shown to display anti-inflammatory and immunosuppressive actions in different tissues and could represent a potent therapeutic tools against chronic inflammation during periodontitis (178).

EVs from PDLSCs grown on gelatin-coated alginate microcarriers may be used to target chronic inflammation during periodontitis in bioreactors. EVs permanently suppressed basal and LPS-induced activity of NF-κB in PDLSCs and partially suppressed inhibitory effect of anti-TLR4 blocking Ab, without affection to osteogenic mineralization (178). MicroRNA-155-5p in PDLSC-derived EVs can upregulate sirtuin-1 in CD4(+) T cells, thereby alleviating Th17/Treg imbalance (90). Furthermore, the conditioned medium of PDLSCs reduced mRNA levels of TNF-α in periodontal healing tissue (179).

GMSCs

GMSCs, a unique group of MSCs with the characteristic of inflammatory resistance, have been the focus of extensive research due to their easy accessibility, numerous distinct properties, including their homing to injury sites, their contribution to tissue regeneration and prominent immunomodulatory properties (160, 180).

It has been reported when transplanting GMSCs *via* the tail vein of mice, these cells were able to enter the site of periodontal injury (181). The delivery of GMSCs led to a significant decrease in TNF-α, IL-1β and IL-6 (M1 markers), a significant increase in IL-10 (M2 markers), thus inhibiting the activation of M1 macrophages (182, 183). GMSCs can also decrease the infiltration of DCs, MCs, CD8(+) T cells and Th17 cells, and increase the infiltration of Tregs (184). Hypoxic stimulation promoted the immunomodulatory properties of human GMSCs by enhancing the suppressive effects of human GMSCs on peripheral blood mononuclear cells (PBMCs) (185). In addition, GMSC-derived EVs can promote the conversion of M1 to M2 and reduce the proinflammatory cytokines produced by M1 macrophages (such as TNF-α, IL-1β and IL-12) (186).

However, many issues need to be resolved, such as costs, time-consuming culture procedures, insufficient stem cell sources, and other safety issues (187, 188).

Other MSCs

In an induced rat model of periodontitis, SHED survived in periodontal tissue for about 7 days with minimal tissue diffusion. Then, the treatment of periodontitis with multi-dose SHED every 7 days can change the expression profile of cytokines in gingival crevicular fluid, with a reduction in the pro-inflammatory cytokines TNF-α, IFN-γ and IL-2, and an increase in the anti-inflammatory molecule IL-10. SHED can also promote the differentiation of macrophage M2 (189) and induce an immune regulatory phenotype in monocyte derived DC (moDCs) cells, thus increasing CD4(+)Foxp3(+)IL-10(+) T cells (190).

IFN-γ stimulated DFSCs by inducing immunomodulated effects of healthy donor PBMC, promoting the proliferation and differentiation of DFSCs, thereby inhibiting IL-4 and IFN-γ levels, increasing IL-10 levels, and increasing the number of CD4(+) FoxP3(+) cells (191). Dental follicle progenitor cells (DFPCs) can also sense and respond to LPS, resulting in the down-regulation of TLR4 mRNA expression and significantly increasing the migration of DFPCs. But IL-6 levels remained the same. Based on the role of DFPCs in the immune microenvironment of periodontitis, the potential of DFPCs as biological grafts for periodontal regeneration has been further confirmed (192).

Using BMMSCs in a rat model of periodontitis, significant reverse of alveolar bone lesion was observed after BMMSC transplantation. The expression of TNF-α, IFN-γ and IL-1β was down-regulated by BMMSC transplantation (193, 194). When combined with acetylsalicylic acid, the levels of TNF-α and IL-17 decreased, while the levels of IL-10 increased, and the inflammatory microenvironment was improved more (195). Injection of BMMSCs in a mouse model of periodontitis was also shown to reduce periodontitis inflammation (196). Meanwhile, BMMSCs-derived apoptotic extracellular vesicles (ApoEVs) could also regulate the polarization of macrophages (197).

DPSCs are capable of self-renewal and multidirectional differentiation, which provides a broad prospect for tooth regeneration. DPSCs have low immunogenicity and can inhibit lymphocyte proliferation and regulate cytokine production *in vitro*. DPSCs can inhibit T cell proliferation, B cell proliferation and mixed lymphocyte response. The number of Th17 cells in peripheral blood mononuclear cells co-cultured with DPSCs was significantly increased, while the number of Treg was significantly decreased. DPSCs significantly inhibited the secretion of TNF-α, IFN-γ, IL-2 and IL-17 and promoted IL-10 secretion without affecting IL-1β and IL-6 production (198, 199). These results have shed light on the therapeutic mechanism of DPSCs. In addition, DPSC-derived exosomes-incorporated chitosan hydrogel (DPSC-Exo/CS) can also facilitate macrophages to convert from a pro-inflammatory phenotype to an anti-inflammatory phenotype, thus ameliorating periodontal lesion (200).

The more detailed role of MSCs in the immune microenvironment of periodontitis is summarized in **Table 3**.

Oral MSCs have the unique clinical advantage of availability in large numbers, controlling proliferation, migration and

TABLE 3 | Role of MSCs in anti-inflammation.

	PDLSCs	GMSCs	SHEDs	DFSCs	BMMSCs	DPSCs
cytokines	IL-6, IL-10 ↑; TNF-α, CD1b ↓	IL-10↑; TNF-α, IL-1β, IL-6, IL-12 ↓	TNF-α, IFN-γ ↓	IL-10 ↑; IFN-γ, IL-4↓	IL-10 ↑; TNF-α, IL-1α, IL-1β, IL-17, IFN-γ ↓	IL-10 ↑; TNF-α, IFN-γ, IL-2, IL-17 ↓
T lymphocytes	Anergy of T cells Imbalance of Tregs↓	Infiltration of Tregs ↑; Infiltration of CD8(+) T cells and Th17 cells↓;	TNF-α(+)IFN-γ(+)CD4 (+)cells ↓	Tregs ↑	/	Tregs ↑; Th17 cells↓
B lymphocytes	Proliferation, migration, differentiation, activation of B cells ↓	/	/	/	/	/
Macrophages	M1 macrophages ↓; M2 macrophages↑	M1 macrophages ↓; M2 macrophages↑	M1 macrophages ↓; M2 macrophages↑	/	M1 macrophages ↓; M2 macrophages↑	M1 macrophages ↓; M2 macrophages↑
References	(160, 173, 175–177)	(160, 183–186)	(160, 189, 190)	(191, 192)	(194–197)	(160, 198–200)

homing, multidirectional differentiation, and inflammatory responses. However, in order to convert laboratory periodontal regeneration methods to clinical application, the mechanisms of cell-based immunomodulatory and regeneration processes need to be understood (187).

GENE THERAPY

Gene therapy was defined as therapy "that mediates their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms" by the U.S. Food and Drug Administration (FDA) (201). Gene therapy has been developed to expose multiple factors to damaged surfaces for long periods of time and maintain constant protein levels, promoting recovery (202). Many studies have found that gene expression of cells in periodontitis tissues changes (203, 204). And genotypes are also important for susceptibility to periodontitis (205). These both provide the possibility of gene therapy to improve immune microenvironment, alleviating periodontitis.

Some studies have focused on immune-related genes. Through gene delivery or gene modification, it can play a good role in improving inflammation or periodontal regeneration. However, the number of studies is still inadequate and further research is needed to determine the exact effect.

It has been found that the gene modification of the P2X7 receptor (P2X7R) can promote the repair of inflammatory lesions in PDLSCs. In addition to maintaining their robust functionality under inflammatory conditions, P2X7R gene-modified stem cells may have positive influences on their neighbors through paracrine mechanism, suggesting a novel strategy to modify the harsh local microenvironment of periodontitis to accommodate stem cells and promote improved tissue regeneration (206).

Follicular dendritic cell secreted protein (FDC-SP) is considered as an immune molecule that regulates the interaction between Follicular DCs and B cells (207). FDC-SP was also found to inhibit osteogenic differentiation of human periodontal ligament cells (hPDLCs). Therefore, a stable and effective recombinant lentiviral vector expressing FDC-SP was constructed to study its effect on the phenotypic expression of hPDLCs. The results showed that in FDC-SP transfected cells, the expressions of type 1 collagen α 1, type 1 collagen α 2, and type 3 collagen were up-regulated, while the expressions of osteocalcin, osteopontin, and sialoprotein were down-regulated. In addition to the insignificant adverse effect of transfection FDC-SP on the proliferation of hPDLCs, FDC-SP can inhibit the differentiation of hPDLCs into the mineralization tissue forming cells, which can regulate the regeneration of periodontal tissue engineering (208).

Functional studies *in vitro* and *in vivo* have indicated that an isoform of Atp6i, T-cell immune response cDNA7 (TIRC7), has a significant association with the regulation of T cell and B cell activation (209). The possibility of adeno-associated virus (AAV)-mediated RNAi knockdown for the treatment of periodontal disease was first explored. AAV-small hairpin (sh) RNA-Atp6i/TIRC7 was locally injected into periodontal tissue *in vivo*, and the number of T cells in the periodontal ligament in the treatment group was significantly reduced. Meanwhile, the expression of IL-6, IL-17A, RANKL, Cathepsin K (Ctsk), acid phosphatase 5 (Acp5) and CD115 in gingival tissue was also decreased (210).

Given its crucial role and specific expression in osteoclasts, Ctsk is often considered as an important therapeutic target for targeting bone loss in periodontal disease (211). Using a known mouse model of periodontitis, AAV Expressing Ctsk shRNA (AAV-shRNA-Ctsk) was locally injected into periodontal tissues *in vivo*. AAV-shRNA-Ctsk inhibited the expression of pro-inflammatory cytokines TNF-α, INF-γ IL-1α, IL-1β, IL-12 and IL-17, but increased the expression of IL-6 in infected mice. In addition, T cells and DCs in the periodontal ligament were significantly reduced in the AAV-shRNA-Ctsk group, which significantly reduced inflammation. This suggests that AAV-mediated Ctsk silencing can significantly protect mice from *P. gingivalis* osteoclast bone resorption (212).

Injection of naked plasmid DNA encoding miR-200c into the gingiva effectively rescued miR-200c downregulation, prevented periodontal and systemic inflammation, and reduced the transcription of IL-6 and IL-8, which explained the mechanisms of gingival application of miR-200c in attenuating systemic inflammation in periodontitis (213).

Soluble protein delivery of a TNF-α antagonist inhibits alveolar bone resorption induced by periodontitis. The delivery of the TNF receptor-immunoglobulin Fc (TNFR : Fc) fusion gene to rats led to sustained therapeutic levels of serum TNFR protein and can reduce local inflammatory cell infiltration and the levels of several pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6 and IL-10, protecting bone volume and density (214).

To date, most gene therapy for periodontitis has focused on bone regeneration (215–217). There is still little research on the immune microenvironment, but some of the existing studies show good application prospects (214). Gene therapy targeting the immune microenvironment can not only change the environment for cell survival but also indirectly promote bone regeneration. Transient gene expression is easier to achieve in periodontitis than in some genetic diseases that require lifelong expression of certain genes (218). At present, relatively high transfection efficiency and relatively low mutation rates can be achieved in gene therapy (219). However, the disadvantage of gene therapy is that some viral vectors themselves may induce an immune response, which may worsen the immune microenvironment of periodontitis (220). Some newly developed nonviral vectors can solve these problems to some extent (221).

OTHER THERAPIES

The periodontal therapy (PT) associated with photodynamic therapy (PDT) reduced the expression of TNF-α in gingiva (222). Indocyanine green (ICG)-diode laser-based photothermal therapy (PTT) decreased the expression of IL-1β and MMP-8 (223). Methylene blue-mediated photodynamic therapy (MB-PDT) reduced the level of TNF-α and IL-1β and induced macrophage apoptosis through ROS and mitochondria-dependent apoptosis pathways (224). In addition, singlet phototherapy can lead to the development of reactive inflammation in periodontitis and significant vascularization of periodontal tissue, contributing to rapid tissue regeneration and stable remission (225). The above treatment methods can effectively slow down the development of periodontitis.

Low-intensity pulsed ultrasound (LIPUS) treatment inhibits the secretion of cytokines such as IL-1α, IL-1β, IL-6, IL-8, CCL2, CXCL1, and CXCL10 by periodontal ligament fibroblasts (PDLFs) and reduces the inflammatory response induced by IL-1β and TNF-α. It can also inhibit the development of periodontitis (226) **(Table 4)**.

CONCLUSION

The change in the immune microenvironment in periodontitis is enormous. Activity of leukocytes and inflammatory molecules increases, which can eliminate inflammation, but this excessive activity can cause great damage to the periodontal tissues, including alveolar bone. The treatment of periodontitis by modulating the immune microenvironment is a promising strategy. New anti-inflammatory and periodontal regeneration therapies can enhance the immune microenvironment and promote cell homing and tissue formation, thus achieving higher levels of immune regulation and tissue repair. In the future, more work will be needed to refine immunotherapy approaches, understand the risks and long-term efficacy of these approaches, and further develop treatment techniques to reduce the pain and social burden for patients with periodontal diseases.

TABLE 4 | A summary of immunotherapies and their target.

	Drug therapy	Microbial therapy	Stem cell therapy	Gene therapy	Other therapy
Neutrophil	Vitamin C, 1, 25 dihydroxivitamin D3, resveratrol, quercetin, NAC	/	DFSCs, GMSCs	/	/
Monocyte	Resveratrol, metformin	/	/	/	/
Macrophage	PACN, PSRE, PACs, CMC2.24, Dioscin, Tea polyphenols, POH, 6-Shogaol, UDCA, Catechin, Metformin, Glyburide, Gliclazide, NTU101FM, Hinokatil, CCL2 MPs, CsinCPI-2, Triclosan, PMX205	/	PDLSCs, GMSCs, DPSCs, SHED, EV-GMSCs	/	MB-PDT
Lymphocyte	AsIV, Curcumin, Calcitriol, Vitamin D, antibiotic therapy	*P. gingivalis* capsular defect mutant strains, formalin-killed *P. gingivalis*, KAS2-A1	PDLSCs, GMSCs, DPSCs, SHED, DFSCs, EV-PDLSCs	TIRC7, Ctsk	/
Cytokines	Trans-cinnamic aldehyde, Resolvins, Flavan-3-ols and proanthocyanidins from Limonium Brasiliense, Benzydamine, Rice peptides REP9 and REP11, the Amyl-1-18 peptide, SIM, SIM-PPi, Kava-205Me, Carnosic Acid, β- carotene, Psoralen and Angelicin, CGRP, PLE, Bismuth drugs	*B. lactis* HN019, *Lactobacillus reuteri*, *Akkermansia muciniphila, Lactobacillus gasseri* SBT2055, *P. gingivalis* capsular defect mutant strains, formalin-killed *P. gingivalis*	PDLSCs, GMSCs, DPSCs, SHED, DFSCs, BMMSCs	P2X7R, miR-200c, TIRC7, Ctsk, TNFR: Fc	PT-PDT, ICG-PTT, MB-PDT, LIPUS

PERSPECTIVES

Great progress has been made in studying changes in the immune microenvironment of periodontitis through research on various leukocytes and cytokines that play key roles. However, as with immunotherapy for other diseases, it is necessary to research in more detail the effects of different types of immune regulation on the periodontal microenvironment and periodontal tissue regeneration, including immune response patterns and cytokine networks in periodontal tissue in both healthy and inflammatory conditions.

Pathogens induce periodontitis in susceptible patients and in most of the time the immune system is very efficient and prevents disease progression until a microbial dysbiotic environment has been established. Abundant experimental evidence shows that immunotherapy is effective in the repair and regeneration of periodontal tissue and can be used as a treatment for periodontitis. Standard therapies fail to completely solve the pathogenesis of periodontitis, but we believe that mature immune-targeted therapies will play an irreplaceable role if the immune microenvironment of periodontitis can be studied in depth. A conceptually reasonable treatment strategy for periodontitis may be the transformation of macrophages from the M1 to the M2 phenotype, increasing anti-inflammatory subtypes of T cells and anti-inflammatory cytokines and decreasing pro-inflammatory cytokines.

Previous studies have shown that it is possible to manipulate the changes in the immune microenvironment. There are many drugs that target the immune microenvironment in treating periodontitis, and they are relatively well established. The use of new therapies for anti-inflammatory and periodontal regeneration or the combination of these new approaches with existing therapeutic drugs and cytokines can enhance the generation of a viable local immune microenvironment, promote cell homing and tissue formation and thereby achieve higher levels of immune regulation and tissue repair. It is undeniable that new treatment methods have great prospects. However, they always have other defects and inappropriate places, which may be the problem of safety, the uncertainty of treatment effect, or technical and economic problems. These uncertain problems that need to be improved urgently need further research to draw scientific conclusions in order to benefit patients.

It is important to note that most of the treatments mentioned in this review have not yet been used in the clinic and cannot be used as a reference for clinical decisions. In the future, more research needs to be done to improve immunotherapy methods and understand the risks and long-term efficacy of these methods.

AUTHOR CONTRIBUTIONS

BY summarized the literature, provided critical comments, and wrote the manuscript. XP summarized the literature, prepared figures and wrote part of the manuscript. ZL and ZC summarized the literature and oversaw preparation of the tables and figures. YW provided critical comments and supervised all the work. All authors have made contributions to this article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.781378/full#supplementary-material

Supplementary Table 1 | Changes of various T cell subtypes in periodontitis. MDSCs: myeloid dendritic suppressor cells; FOXO1, Forkhead box protein O1; RvD2, docosahexaenoic acid (DHA) metabolite resolvin D2; T-bet, T-cell-specific T-box transcription factor; TBX21-1993T/C (RS4794067), Tbx21 genetic polymorphism, facilitates the occurrence of Th1 immune response.

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