Macrophages in periodontitis: A dynamic shift between tissue destruction and repair

Linying Yin, Xinzhu Li*, Jin Hou*

Department of Stomatology, Nanfang Hospital, Southern Medical University, Guangzhou, China

ABSTRACT

Periodontitis is a chronic inflammatory disease associated with a dysbiotic bacterial biofilm in the subgingival environment that may disturb the balance between the oral microbiome and its host. The inability of the immune system to eliminate inflammation may result in the progressive destruction of tooth-support tissues. Macrophages are crucial cellular components of the innate immune system and play important roles in diverse physiological and pathological processes. In response to periodontitis-associated bacterial communities, macrophages contribute to inflammation and restoration of tissue homeostasis through pattern recognition receptor-induced signaling cascades; therefore, targeting macrophages can be a feasible strategy to treat patients with periodontitis. Although recent studies indicate that macrophages have a spectrum of activation states, ranging from pro-inflammatory to anti-inflammatory, the regulatory mechanism of the macrophage response to dysbiosis in a tissue-specific manner remains largely unclear. Herein, we attempt to summarize the potential role of macrophage activation in the progression of periodontitis, as well as its relevance to future approaches in the treatment of periodontitis.

© 2022 Published by Elsevier Ltd on behalf of The Japanese Association for Dental Science. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
1. Introduction

Periodontitis is a multifactorial chronic inflammatory disease in the tooth-support tissues triggered by numerous pathogenic bacteria in the subgingival plaque, resulting in the progressive destruction of the periodontal ligament and alveolar bone [1,2]. The subgingival plaque during periodontitis development has been well established by the qualitative and/or quantitative differences in the oral microbiota that transits from mainly Gram-positive to mainly obligately anaerobic Gram-negative bacteria [3,4]. Several bacterial species play a crucial role in periodontitis pathogenesis due to their abundant virulence factors, including Porphyromonas gingivalis (P.gingivalis), Tannerella forsythia, Treponema denticola, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum (F. nucleatum) [5–7]. These key drivers can impact the host immune system and destroy the microenvironment for beneficial symbionts, leading to enhanced periodontitis development [8].

Innate immune signaling is crucial for the initial response to microbial pathogens. Compromised innate immunity reportedly increases the severity of periodontitis [9,10]. However, an over-activated innate immune response results in increased inflammation and tissue injury. Damage to the periodontal ligament and alveolar bone stems from the immune system, as it attempts to destroy the microbes that disrupt the normal symbiosis between the oral tissues and the oral microbial community [11,12]. The macrophage axis is an important cellular component of the innate immune response and plays a critical role in proper immune function. Macrophages are effector cells of innate immunity that phagocytose invading pathogens and secrete both pro-inflammatory and anti-inflammatory mediators [13,14]. Additionally, macrophages can eliminate unwanted cellular material through programmed cell death, and link the innate response to adaptive immunity via antigen presentation [15–17]. Therefore, it is important to understand the mechanisms by which macrophages regulate immune homeostasis, inflammation, and pathogenesis.

Studies on macrophage activation and polarization in periodontitis have revealed their plasticity during the innate immune response. The expression of chemokine (C-X-C motif) ligand 1/chemokine (C-X-C motif) receptor 1 (CX3CL1/CX3CR1) and chemokine (C-C motif) ligand 2/chemokine (C-C motif) receptor 2 (CCL2/CCR2) signaling pathways in response to different micro-environmental factors can promote macrophage recruitment, which mediates phenotypic and functional changes in macrophages in periodontitis and leads to tissue damage and function [18–21]. Moreover, macrophage activity can be increasingly dysregulated during aging, altering their phenotype and function in periodontal inflammation and tissue homeostasis, possibly explaining the high incidence of periodontitis in aging adults [22–23]. Macrophage depletion during disease recovery in older mice can prevent increased inflammatory cytokine concentrations and bone loss [24]. Macrophages are master regulators of periodontal tissue homeostasis; they display remarkable plasticity, respond to danger signals, and adjust their phenotype and function according to the periodontal environment [25].

In this review, we describe the heterogeneity, activation, and multiple functions of macrophages in specific tissues, and their dynamic features in periodontitis. Deciphering the process of macrophage activation and polarization in periodontitis will shed some light on the development of new therapies to promote antimicrobial defense or inhibit inflammatory tissue destruction.

2. Macrophage origin, plasticity, and polarization

Over the past century, all macrophages have been considered a part of the mononuclear phagocyte system derived from committed hematopoietic stem cells located in the bone marrow [26]. Macrophage precursors are released into the peripheral blood as monocytes; they further migrate to tissues, and differentiate into macrophages or dendritic cells [27]. With the advancement of cellular and molecular technologies, several studies have demonstrated that many tissue-resident macrophage subpopulations arise from the yolk sac and fetal liver, and have the capacity for self-renewal at low levels throughout adult life to maintain themselves in the steady state independent of bone marrow-derived macrophage precursors [28,29]. Along with the heterogeneous characteristics of tissue-resident macrophage populations, these cells can undergo rapid local proliferative expansion in response to environmental factors and initiate inflammatory and immune responses [30–32] (Fig. 1).

Tissue-resident periodontal macrophages are generally present in subgingival crevices or periodontal pockets and act as the first line of host defense against microbial dysbiosis [33,34]. These cells are capable of secreting various effector molecules and can dynamically change their phenotype according to periodontal disease progression [35–37]. They also display great diversity in their morphologies, transcriptional profiles, and functional capabilities, largely dictated by their anatomical location [38]. However, the heterogeneity, functionality, and niche location of tissue-resident macrophages in the periodontium remain poorly defined.

Macrophage polarization in the periodontium has been studied using histological staining. Results revealed that these are the most plastic cells and are regulated by their surrounding microenvironment. These resident macrophages generally polarize into two major extremes upon stimulation: M1 and M2 [39,40]. On the one hand, the classically activated M1 macrophages are considered a part of the cell-mediated immune response. They are also primed in response to lipopolysaccharide (LPS) or T helper type 1 cytokines, such as interferon (IFN)-γ [41]. These macrophages usually have an enhanced ability to secrete pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-6. TNF-α and IL-6 stimulate macrophage activation and the adaptive immune response, as well as regulating host defense and countering bacterial invasion through several mechanisms. However, excessive activation of M1 macrophages may result in persistent inflammation and tissue damage [42–44]. For instance, TNF-α expression modulates the alteration of tissue macrophage M1/M2 polarization leading to increased disease severity [45]. TNF-α blockade has been shown to inhibit M1 macrophage polarization and pro-inflammatory mediators, emerged as a probable therapy for reducing disease severity [46]. On the other hand, the alternatively activated M2 macrophages are generally polarized by Th2 cytokines, such as IL-4 and IL-13. The cytokines released by M2 macrophages include IL-10, arginase-1, and transforming growth factor (TGF), which have the function of inhibiting various inflammatory responses and promoting tissue repair; therefore, M2 macrophages are associated with anti-inflammatory action and immune regulation [47–49]. Therefore, these two macrophage subpopulations exhibit varied physiological properties.

Despite the differences between the two macrophage subpopulations, both exogenous and endogenous danger signals can alter macrophage polarization. Inflammation may alter macrophage phenotypes, which may contribute to disease progression and resolution [50]. Significantly, macrophage phenotype, both in vitro and in vivo, can be converted by the signal transducer and activator of transcription (STAT) family and interferon regulatory factor (IRF) [51–53]. Accumulating evidence has shown that M1 macrophage polarization can be regulated by nuclear factor kappa-B (NFκB), STAT1, and IRF5 activation [54–56], whereas STAT3/STAT6, IRF4, and peryxosime proliferator-activated receptor-γ activation promote M2 macrophage polarization [52,57–61]. Therefore, these findings provide a rationale for the treatment of inflammation by regulating macrophage polarization.
3. Macrophages as contributory factors in periodontal tissue destruction and repair

Macrophages are activated when pathogens are detected through recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). The binding of these factors to pattern recognition receptors (PRRs) stimulates multiple signal transduction pathways, which ultimately alert the host to cell death and orchestrate the synthesis of various effector molecules [62]. Ideally, PRR responses, death signaling, and effector outputs coordinate immune responses against invading pathogens, which can ultimately contribute to periodontal tissue destruction and repair. Recent findings, as presented in this review, have highlighted that contradictory regulation of macrophages and their interactions with other cell types are responsible for both periodontal tissue damage and repair. The delicate balance between the oral microbial community and the host might be disrupted by either host immunoregulatory defects or an increase in the microbial challenge. Therefore, inflammation and dysbiosis can positively reinforce each other in a self-sustained feedforward loop [63,64]. Alternatively, macrophages express various effector molecules required for tissue regeneration, such as TGF-β and IL-10, suggesting that the secretory actions of macrophages play important pro-reparative roles [65,66]. Although macrophage-mediated tissue destruction and healing may occur simultaneously in human periodontitis, the inability to resolve inflammation drives extracellular matrix degradation and bone resorption [25,67]. Herein, we integrated the current knowledge on immune sensing of macrophages contributing to periodontal tissue destruction and repair (Fig. 2).

3.1. Macrophage PRRs

Macrophages are considered sentinels of the immune system because they ubiquitously express a multitude of PRRs that are in contact with the external environment and can thus recognize PAMPs from pathogens as well as DAMPs from apoptotic host cells and damaged senescent cells when present, and subsequently activate various intracellular signaling pathways [68,69]. Currently, based on protein domain homology, these receptors can be divided into the following five types: toll-like receptors (TLRs), absent in melanoma-2 (AIM2)-like receptors, nucleotide oligomerization domain-like receptors (NLRs), retinoic acid-inducible gene-1-like receptors, and C-type lectin receptors. These five types of PRRs are widely present within the plasma membrane, intracellular compartment membranes, and macrophage cytoplasm [70,71]. We focused on three types of PRRs identified in macrophages associated with periodontitis.

Activation of TLR2/TLR4/TLR9 signaling in macrophages plays a crucial role in triggering intracellular signaling cascades, mediated by the adaptor proteins namely, myeloid differentiation factor 88 (MyD88) and/or Toll/IL-1R domain-containing adapter-inducing IFN-β (TRIF), and subsequent activation of inflammatory responses [72–74]. TLR2 specifically recognizes fimbriae in combination with CD14 on the cell membrane of macrophages to activate two distinct signaling pathways, thereby mediating pro-inflammatory and pro-adhesive effects [75]. Activated TLR2 leads to nuclear factor kappa-B activation through the Toll-interleukin-1 receptor domain-containing adaptor protein/MyD88-dependent signaling pathway, thereby increasing the secretion of pro-inflammatory molecules [73,75]. Induction of TLR2 inside-out signaling proceeds through Rac1, phosphoinositide-3-kinase, and cytohesin-1 upregulation of the high-affinity conformation of complement receptor 3, which is associated with increased intracellular persistence [76,77]. In addition to binding to fimbriae, TLR2 is involved in the recognition of lipoprotein and P. gingivalis LPS [78,79]. The recognition of LPS by TLR4 triggers the activation of two different signaling pathways. First, the MyD88-dependent pathway, resulting in the activation of C and c-Jun N-terminal kinase, required for the expression of CCL2 and macrophage inflammatory protein 1. Second, the MyD88-independent pathway, leading to the activation of the IFN-β/STAT1
NLRP3, adapt or protein apopt osis-associate d speck -like pr ot ein

the key molecules for the integ rity of tissue homeostasis and bac

conv ersion of pro-IL-1

procaspase-1

containing a caspase re cruitment domain (ASC), and effector pr ot ein

characterized component that consists of the cytopl asmic sensor

may initiate a cascade of signals through inter action with o ther in

nitric o xide is reporte dl y due to the destruction of periodontal health

IP -1 0) production

1 , IL-1

loss in periodontitis, follow ed by significant upr egulation of caspase-

opt osis thr ough the formation of plasma membrane pores and

development of periodontitis. The NLRP3 inflammasome is the best-

located in the cytoplasm that are associated with the occurrenc e and

nate sensors, including TLR2 and TLR4. How ever , the underl ying

treated macrophag es

synthase e xpression and nitric o xide secretion in

kappa-B ligand (RANKL)

lating levels of IL-6, TNF , and recep tor activ ator of nuclear fact or

duction of TNF and the decreased secretion of IL-1

Jun N-terminal kinase, essential for IFN-

. Notably , it has been report ed that TLR9

signaling pathw ay via P38 mitogen-activated protein kinase and c-

Jun N-terminal kinase, essential for IFN-γ-inducible 10 kDa protein
(IP-10) production [80,81]. Interestingly, macrophages of differential states may respond distinctively to virulence factors, such as LPS-tolerant macrophages, which respond through the excessive production of TNF and the decreased secretion of IL-1β [82]. TLR9 binding periodontitis-associated bacterial DNA initiates inflammation. TLR9 signaling can mediate periodontal bone loss by upregulating levels of IL-6, TNF, and receptor activator of nuclear factor kappa-B ligand (RANKL) [74]. Furthermore, the overproduction of nitric oxide is reportedly due to the destruction of periodontal health [83]. TLR9 is involved in the regulation of inducible nitric oxide synthase expression and nitric oxide secretion in P. gingivalis LPS-treated macrophages [84]. Notably, it has been reported that TLR9 may initiate a cascade of signals through interaction with other innate sensors, including TLR2 and TLR4. However, the underlying mechanism remains unknown [74].

In addition to TLRs, NLR inflammasomes are a subset of PRRs located in the cytoplasm that are associated with the occurrence and development of periodontitis. The NLRP3 inflammasome is the best-characterized component that consists of the cytoplasmic sensor NLRP3, adaptor protein apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and effector protein procaspase-1 [85,86]. NLRP3 signaling is crucial for orchestrating microbial crosstalk with macrophages, because it can induce pyroptosis through the formation of plasma membrane pores and conversion of pro-IL-1β and pro-IL-18 into mature ligands, which are the key molecules for the integrity of tissue homeostasis and bacterial colonization [85,87,88]. NLRP3 also regulates alveolar bone loss in periodontitis, followed by significant upregulation of caspase-1, IL-1β and IL-18, resulting in a large number of inflammatory cell recruitment and promoting osteoclastic differentiation [89,90]. Ablation of NLRP3 can result in a switch in the polarization of microglia toward an anti-inflammatory and M2 phenotype, displaying enhanced tissue remodeling [91]. Together, the regulation of the NLRP3 inflammasome might emerge as an effective strategy to modify periodontal inflammatory changes [92].

AIM2-like receptors are intracellular PRRs that recognize and bind to cytosolic double-stranded DNA [93]. The N-terminal pyrin domain of AIM2 binds to the ASC, which recruits caspase-1 through its caspase recruitment domain, thereby stimulating inflammasome formation and inducing the maturation and release of IL-1β and IL-18 [94]. Patients with periodontitis display upregulated AIM2 inflammasome, which releases IL-1β, promotes bone resorption, and induces tissue-degrading proteinase production [95–97].

3.2. Macrophage cell death

Upon stimulation with PAMPs/DAMPs, PRR-induced signal transduction pathways ultimately result in immune activation of the host to increase phagocytosis and pro-inflammatory cytokine se-
cretion, and induce cell death. Regulated cell death is a genetically encoded process that can be activated not only in the context of physiological states but also as a consequence of microenvironmental disruption, and plays a role in key processes that might lead to the initiation, amplification, or chronicity of inflammatory sig-
naling [98,99]. Here, we briefly discuss the mechanisms that govern PRR-induced regulation of cell death in macrophages and their participation in the development of periodontitis.

Pyroptosis is a highly inflammatory form of cell lysis that reg-
ulates cell death. It can be initiated by the interaction of microbial components with PRRs that allows inflammasome activation, re-
sulting in the massive release of cytosolic contents [88,100]. Further, a large number of PAMPs and DAMPs are released from necrotic

Fig. 2. Macrophage cell death and cytokine production in periodontitis. Macrophages are activated when PRRs recognize PAMPs/DAMPs. The binding stimulates multiple signal transduction pathways: (A) Binding of PRRs activates NF-κB signaling and secretes various cytokines; (B) Binding of PRRs results in various forms of cell death, including pyroptosis, necroptosis, apoptosis and autophagy; ultimately leading to periodontal tissue destruction and repair. NF-κB: nuclear factor kappa-B; IκBα: NF-κB inhibitor α; dsDNA: double-stranded DNA; FADD: Fas-associated protein with death domain; TRADD: tumor necrosis factor receptor type 1-associated death domain; RIPK: receptor interacting protein kinase; GSDMD: gasdermin D; ATG: autophagy-related; LC3: microtubule-associated protein 1A/1B-light chain 3.
cells. These PAMPs and DAMPs can trigger a cascade of inflammatory responses from the neighboring cells (such as immune cells, epithelial cells and fibroblasts). Pyroptosis in macrophages infected with periodontal pathogens is dependent on the cleavage of gasdermin D by inflammatory caspases, including caspase-1 or caspase-11, -4, and -5, resulting in subsequent activation of the inflammatory response [85,87,88]. A recent report on *Salmonella typhimurium*-infected mice demonstrated that macrophages mediate crucial innate immune responses to intracellular bacteria via caspase-1-induced pyroptosis. With the lytic death of macrophages, pathogens are released into the extracellular space and become exposed to uptake and efficient killing by neutrophils through the activity of reactive oxygen species [101]. In addition, increased staining of gasdermin D was observed in human periodontitis tissues, implying that the pyroptotic cell death correlates with periodontitis severity [102]. In a mouse model of diabetes-associated periodontitis, NLRP3-mediated pyroptosis in macrophages plays a pivotal role in further impairing macrophage function and aggravating periodontal tissue injury [103]. One study shows that miR-155 expression can influence macrophage pyroptosis and the ability to engulf pathogens through regulating the NLRP3 inflammasome. Excessive uncontrolled pyroptosis in macrophage may contribute to the severe inflammatory response and tissue damage via the generation of multiple proinflammatory cytokines in vivo, including TNF-α and IL-6, which can promote osteoclast differentiation and activation, resulting in alveolar bone resorption [104]. Furthermore, there is a bidirectional crosstalk between apoptosis and pyroptosis. In gasdermin D low/null cell types, caspase-1 induces apoptotic cell death by activating caspase-3/7 [105]. Together, these studies contribute to the view that macrophage pyroptosis can eliminate intracellular microbes and increase pro-inflammatory molecules that appear to coordinate cellular repair, although the regulatory mechanism of macrophage pyroptosis in periodontitis warrants further investigation.

Necroptosis is another form of inflammatory cell death that can be triggered by different PRRs, such as TLR3, TLR4, and retinoic acid-inducible gene-I [69]. Activation of necroptosis induces the release of DAMPs, which is dependent on the activation of receptor-interacting protein kinase-3 and the phosphorylation of its substrate, mixed lineage kinase-like (MLKL), which drives the amplification and chronicity of inflammation and contributes to inflammation-induced tissue damage [106–108]. Moreover, positive staining was detected for phosphorylated MLKL in the periodontal supporting structure. Phosphorylated MLKL has been identified as a biomarker of necroptosis, suggesting that necroptosis contributes to *P. gingivalis*-induced periodontitis [109,110]. However, evidence that macrophage necroptosis has detrimental effects on human periodontitis remains limited. A recent report based on a mouse model suggested that MLKL-mediated necroptosis accelerates periodontitis progression induced by *P. gingivalis* LPS. Uregulation of inflammatory cytokines at the mRNA level was detected in bone marrow-derived macrophages, and MLKL deficiency led to decreased bone resorption and attenuated osteoclast activation, indicating that MLKL-induced necroptosis in macrophages is a critical event that amplifies inflammation and contributes to disease pathology [111]. Although these studies indicate that macrophage necroptosis may be involved in tissue destruction in periodontitis, more studies using definite molecular markers of necroptosis and macrophages are required to establish the potential role of macrophage necroptosis in the pathogenesis of periodontitis.

Apoptosis is a genetically encoded death process in multicellular organisms that may have an anti-inflammatory effect on host defenses against pathogens [112,113]. Apoptosis induction consists of two major pathways: an extrinsic pathway initiated by death receptors and an intrinsic pathway involving mitochondria [114]. Not surprisingly, PRR stimulation (TLR2 and TLR4) promotes apoptosis in macrophages through a MyD88/TRIF downstream signaling pathway that converges on effector caspase-3 activation. The clearance of apoptotic cells resolves inflammation, and is dependent on the formation of apoptotic bodies before the contents spill out of the dying cells, which would cause inflammation in the surrounding tissue [98,114–116]. Several periodontal bacteria, such as *Aggregatibacter actinomycetemcomitans* and *F. nucleatum*, have been shown to cause apoptosis in macrophages. Intracellular *F. nucleatum* can inhibit macrophage apoptosis through activation of the phosphoinositide-3-kinase/Akt and extracellular-signal-regulated kinase signaling pathways, implying that macrophage apoptosis participates in the dissemination of bacterial infection during periodontitis [117–119]. Although the main function of macrophage apoptosis in periodontitis is often less defined, apoptosis of infected macrophages plays an essential role in the elimination of many intracellular bacteria, including *Mycobacterium tuberculosis*, which enters macrophages with the aid of major virulence factors [120]. Studies indicate that the success of the initial infection by *M. tuberculosis* relies on the ability of the pathogen to inhibit activation of the extrinsic apoptotic pathway in host macrophages. If apoptosis is dominant, the infection may cease and potentially be cleared. In contrast, if virulent bacteria successfully inhibit caspase-mediated apoptosis of their host cells, their increased number contributes to the rapid development of macrophage necrosis [121,122]. It is unclear whether similar mechanisms exist in macrophages infected with periodontal pathogens. Infected macrophages also undergo autophagy, a major intracellular degradation process that forms double-membrane vesicles termed autophagosomes and drives the sequestration and degradation of cytoplasmic material in the lysosome [123]. Recently, many studies have broadened autophagy to include an antibacterial outcome of TLR responses to PAMPs [124,125]. TLR4 can induce autophagy in RAW264.7 macrophages upon stimulation with bacterial LPS, dependent on TRIF, receptor-interacting protein 1, and p38 mitogen-activated protein kinase signaling [126]. Moreover, the levels of Beclin-1, autophagy-related protein 5, and microtubule-associated protein 1A/1B-light chain 3-II, which are the specific markers of autophagy, increased in macrophages infected with *P. gingivalis* or *Aggregatibacter actinomycetemcomitans*, suggesting that macrophage autophagy contributes to the pathology of periodontitis. Activation of autophagy not only promotes bacterial clearance, but also limits NLRP3 and AIM2 inflammasome activity, thereby inhibiting IL-1β production [127]. Conversely, deletion of autophagic proteins promotes the activation of caspase-1 and secretion of IL-1β and IL-18, demonstrating that inflammasome-autophagy crosstalk in macrophages is critically linked to the severity of inflammation. Autophagic protein-depleted macrophages may enhance mitochondrial reactive oxygen species production by destroying mitochondrial integrity [128,129]. Hence, impaired autophagy has been proposed to be responsible for poor outcomes in periodontitis, and the regulation of autophagy can function as an effective way to alleviate inflammation by eliminating active inflammasomes [130].

### 3.3. Macrophage-derived effector molecules

The relationship between effector molecules and periodontitis is complicated, but several key factors require attention because they always coexist with periodontitis. Various effector molecules are released by macrophages and involved in the host defense against infection. To understand the destruction and repair mechanisms underlying periodontitis, it is important to understand the role of effector molecules, including chemokines, pro-inflammatory cytokines, and anti-inflammatory cytokines.

The pro-inflammatory mediators predominantly derived from activated macrophages accumulate and probably contribute to chronic inflammation. Evidence shows a correlation between macrophage-derived effector molecules and tissue destruction during
periodontitis (Table 1). For instance, major chemokines, including CCL2, macrophage inflammatory protein 1α, and macrophage migration inhibitory factor, are characterized by pro-inflammatory and chemotactic responses, and their expression is increased in periodontitis, leading to periodontal tissue damage. CCL2 downregulation can alleviate alveolar bone loss and rescue epithelial lesions by suppressing periodontal inflammation. Additionally, the production of prostaglandin E2, which contributes to the destruction of the extracellular matrix in periodontal lesions, is generally upregulated in macrophages and is associated with increased cyclooxygenase 2 activity.

Production of TNF superfamily members, especially TNF-α and RANKL, is intricately involved in the pathology of periodontitis. TLRs induce the production of TNF-α from macrophages, which not only activates macrophages but also triggers stronger activation of the nuclear factor kappa-B pathway. Furthermore, TNF-α can form an autocrine loop that sustains the expression of inflammatory genes and induces delayed expression of interferon-response genes, as well as enhances macrophage responses to subsequent stimulation of cytokines and TLRs. This TNF-dependent feedforward loop plays an important role in sustaining inflammation. Recent clinical study demonstrates that elevated serum levels of TNF-α in patients with periodontitis may also contribute to B-cell response and associate with periodontitis disease severity. Besides its immunoregulatory functions, the proinflammatory cytokine TNF-α may also exhibit an important role in bone metabolism and inflammatory bone diseases. TNF-α appears to contribute to inflammatory bone loss by promoting osteoclast differentiation with RANKL and mediating osteoblast apoptosis. Moreover, patients with periodontitis exhibit significantly higher RANKL levels than healthy individuals and an increased ratio of RANKL to its inhibitor, osteoprotegerin. Systemic administration of osteoprotegerin can suppress osteoclast formation by inhibiting the RANKL/RANK interaction, thereby alleviating alveolar bone resorption in an experimental ligature-induced periodontitis in rats. Furthermore, TNF shares many biologic properties with IL-1 family, TNF shares many biologic properties with IL-1 family. Further upregulation of anti-inflammatory factors by macrophages may significantly contribute to modulating and defining the process of periodontal tissue repair.

The production of TGF-β, a member of a family of dimeric polypeptide growth factors, has been associated with inflammation resolution. Recent studies have identified that TGF-β can suppress the expression of pro-inflammatory cytokines and contribute to the induction of LPS tolerance. Impairment of TGF-β signaling in macrophages results in increased severity of intestinal inflammation during the resolution phase. Moreover, TGF-β regulates various cellular processes, such as cell proliferation, differentiation, and migration, and affects the production and deposition of extracellular matrix. In a model of pulmonary inflammation and fibrosis, upregulation of TGF-β derived from alveolar macrophages was detected, which may be associated with inflammation suppression and stimulation of collagen production to resolve lesions. Although these studies indicate that TGF-β...
is indispensable for tissue regeneration and remodeling in human diseases, further studies are required to establish the involvement of macrophage-derived TGF-β in the pathogenesis of human periodontitis.

The chemokine receptor CX3CR1 acts as a critical regulator of tissue homeostasis and periodontitis pathogenesis by modulating the inflammatory response of macrophages. The upregulated level of CX3CR1, binding to the chemokine CX3CL1, correlates with leukocyte migration into the inflamed periodontal tissue [19]. While some studies have revealed that CX3CR1 accounts for bacterial survival and bone resorption, most studies corroborate that CX3CR1 is required for the resolution of inflammation in periodontitis [160,170]. Decreased CX3CR1 expression in macrophages has been linked to elevated and persistent inflammation [171]. By using a DSS-induced colitis model in mice, the CX3CR1/CX3CL1 axis has been demonstrated that contributes to macrophage anti-inflammatory activities for maintaining intestinal homeostasis and induces the production of anti-inflammatory cytokines such as IL-10 [172]. However, how CX3CR1-expressing macrophages regulate the process of periodontal tissue repair remains to be confirmed. Interestingly, the production of the anti-inflammatory cytokine IL-10 is significantly increased in macrophages infected with periodontal pathogens that could inhibit osteoclastogenesis and stimulate osteoelastic differentiation [66]. Recent research based on mice models suggests that induction of IL-10 may negatively regulate IL-17-mediated periodontitis. IL-10 deficient mice develop an elevated level of IL-17 in the ligation model and stimulate macrophage into M1 phenotype in the gingival tissue, which contributes to alveolar bone loss [173]. IL-10 also prevents the metabolic switch to glycolysis in LPS-stimulated macrophages and suppresses the accumulation of dysfunctional mitochondria, which are usually cleared by autophagy [174].

4. Macrophages as therapeutic targets in periodontitis

Currently, strategies have been developed to target tissue-resident macrophages and improve disease pathology, including tumors, liver diseases, and central nervous system diseases [175]. However, to date no agent designed to manipulate macrophage reprogramming in the inflammatory microenvironment has been tested to treat periodontitis. Despite these cellular dynamics and plasticity, given the consensus that macrophages play an important role in tissue damage and repair, the mechanisms described above may provide possible macrophage-targeting therapies. Herein, we discuss several potential therapeutic methods targeting macrophages to inhibit their inflammatory response and promote tissue repair in periodontitis.

4.1. Targeting macrophage polarization

The M1/M2 concept is well known for its opposing effects in periodontitis, mediating dynamic changes between pro-inflammatory and anti-inflammatory responses (Fig. 3). Depending on the periodontal microenvironment, while unactivated macrophages can initially drive the polarization of pro-inflammatory M1 macrophages under the stimulation of periodontal microbes and their products, M1 macrophages can reprogram their phenotypes toward anti-inflammatory M2 macrophages in the presence of IL-4, resulting in conversion of the overall environment [176]. Additionally, given the complex functioning of macrophages, there is an increasing concern that phenotypic switching from M1 to M2 macrophages during the transition from acute to chronic inflammatory conditions would protect an overwhelming and uncontrolled immune response [172,178].

The specific inhibition M1 pro-inflammatory effect is a possible therapeutic strategy. Several studies have indicated that a higher ratio of M1 macrophages plays an important role in the initiation and maintenance of the inflammatory state during chronic periodontitis, which may cause or reflect tissue damage, and is positively correlated with clinical probing depth [25,40,179]. Notably, many M1-related cytokines and proteinases, such as IFN-γ, IL-6, and MMP-9, have been shown to promote alveolar bone loss and aggravate periodontitis [39,180–182]. Therefore, this strategy can be potentially implemented for targeting M1 macrophages in periodontitis immunotherapy, limiting the catabolic and pro-inflammatory activities of these cells. One example is the use of binder, a CCL2 synthesis inhibitor, which can suppress the infiltration of pro-inflammatory monocytes and alter the inflammatory properties of macrophages, leading to decreased production of inflammatory cytokines and MMPs by macrophages in the inflamed periodontium under diabetic conditions, thus improving the periodontal microenvironment [21]. Together, these findings emphasize the need for future research to determine whether M1 macrophages can promote inflammation and destroy tissues while simultaneously maintaining innate immune function.

Another approach is to repolarize M1 macrophages to M2 macrophages, in which the interactions between macrophages and T cells are central not only for suppressing osteolytic activity but also for triggering the repair process. M2 macrophages are responsible for enhanced anti-inflammatory activity mediated by the production of anti-inflammatory molecules, migration of aged neutrophils, and phagocytosis by macrophages. However, M2 macrophages also secrete cystatin C, which promotes bone regeneration through osteoblast and osteoclast regulation [176,180]. In general, M2 macrophages are crucial for bridging the gap between inflammatory regression and tissue repair. It has been demonstrated that injecting M2 macrophages into murine periodontal tissues increases the ratio of regulatory T cells, resulting in the inhibition of osteoclast activity [183]. Using a mouse model of stem cell transplantation, macrophage polarization toward the M2 phenotype has been demonstrated to enhance periodontal tissue regeneration in the early stages of tissue repair [184]. Notably, exosomes derived from gingival mesenchymal stem cells seem to promote M1 macrophage transformation into M2 macrophages, preventing the production of pro-inflammatory factors [185]. These results indicate that M2 macrophages may be crucial to decrease inflammatory injury or stimulate tissue repair. Despite the anabolic and anti-inflammatory functions of M2 macrophages, the mechanisms by which M1 macrophages convert their phenotype to M2 in periodontitis require further investigation.

4.2. Modulating macrophage PRRs

The mechanisms outlined above suggest that the highly sensitive recognition of PRRs by PAMPs/DAMPs acts as a double-edged sword. On the one hand, it activates many intracellular signaling pathways to effectively clear pathogens and danger signals. On the other hand, it promotes the production of inflammatory molecules and produces an inflammatory microenvironment, thereby causing tissue damage [186,187]. Given the important role of PRRs in stimulating both innate and acquired immunity in periodontitis, we propose that PRRs could serve as drug targets for inflammatory diseases and as important immune checkpoints for immunotherapy.

Modulation of PRRs may be another way to regulate macrophage function in periodontitis. TLRs and NLRs have been the most studied and characterized in the pathophysiology of some inflammatory diseases. Studies have revealed that TLR2 and TLR4 signaling are both predominantly required for the effective clearance of pathogens, and thus play crucial roles in infection-induced inflammation. Polymicrobe-infected TLR2−/− and TLR4−/− mice demonstrated that TLR deficiency could inhibit accelerated alveolar bone resorption, indicating the important role of TLR2 and TLR4 in periodontitis
To date, several therapeutic strategies for targeting TLR signaling pathways have been recognized for modulating the host response [189]. In periodontitis, macrophages can be targeted with specific CXC-chemokine receptor 4 antagonists that promote the clearance of *P. gingivalis* by interfering with TLR2 activation [190]. Furthermore, the NLR family and the NLRP3 inflammasome are reportedly involved in various inflammatory diseases. Inhibition of NLRP3 inflammasome activation regulates inflammasome-mediated inflammation [191,192]. MCC950, a selective inhibitor of the NLRP3 inflammasome, has been developed to treat periodontitis and can reduce alveolar bone loss by inhibiting osteoclast differentiation in ligature-induced periodontitis [89]. MCC950 also suppressed the inflammatory response in THP-1 cell line macrophage-like cells induced by periodontal bacteria [193]. Taken together, the effects of macrophage PRRs on periodontitis appear to be complex and remain to be demonstrated.

5. Conclusions and perspectives

In this review, we outlined the relationship between macrophage activation and periodontitis progression. Macrophages have high plasticity that allows them to respond efficiently to various environmental stimuli and shift their phenotypes. The physiological characterization of macrophages may contribute to homeostatic processes and host defense in a tissue-specific manner. Macrophages perform important functions in periodontitis during the innate immune response to dysbiotic bacterial biofilms and initiation of inflammation. In addition to their tissue destructive effects, macrophages can act as key regulators of tissue homeostasis and repair. Consequently, it is important to appreciate macrophage heterogeneity and evolution during periodontal tissue damage and repair. It is also pertinent to recognize that most studies on macrophage activation have been performed in vitro using microbial agonists or cytokines to stimulate cells and measure the effector cytokine production and changes in gene expression. Therefore, harnessing the host’s immune system to control and prevent periodontitis requires a more comprehensive characterization of macrophage activation in human patients.

Macrophage activation is a multidimensional occurrence in response to integrated signals from a specific microenvironment [194]. However, many aspects of macrophage biology in inflammation remain unresolved, as the M1/M2 paradigm does not fully represent the situation in vivo. For example, the M1/M2 paradigm does not pay sufficient attention to cell origins, tissue microenvironment, and time. When tissue-resident macrophages coexist with monocyte-derived macrophages during infection and tissue injury, they are
influenced by a combination of ontogenic and dynamic tissue microenvironments [195,196]. Furthermore, identifying macrophage functions based on stimuli does not adequately reflect immune conditions. Since there is a nearly infinite combination of stimuli, each of the combination can develop different population of macrophages [195]. Finally, the transcription of human monocyte-derived macrophages activated by different in vitro stimuli or combinations of stimuli associated with chronic inflammation revealed a spectrum model of macrophage activation rather than M1/ M2 polarization [197]. Therefore, it is necessary to realize that the M1 or M2 phenotype is an oversimplification that insufficiently describes macrophage activation during disease progression. The ability to define a standard naming convention for macrophages based on their morphology and function is becoming one of the most important tasks. In addition, the extension of macrophage activation from M1/M2 polarization to a spectrum model brings a new perspective to explore their functions in chronic inflammation and contributes to improving therapeutic strategies targeting specific macrophage subsets. Therefore, a deeper understanding of macrophage tissue-specific functions will help elucidate the signaling pathways and mechanisms driving periodontal tissue destruction and repair, provide potential therapeutic strategies for the treatment of periodontitis. Besides, this information will enhance our overall understanding of inflammation and immune system.

Declaration of Competing Interest
None.

Acknowledgment
This work was supported by the National Natural Science Foundation of China (Grant NO. 81971902).

References
[1] Belström D, Grande MA, Sembler-Moller ML, Kirby N, Cotton SL, Paster BJ, et al. Influence of periodontal treatment on subgingival and salivary microorganisms. J Periodontol 2018;89:531–9.
[2] Caton JG, Armitage G, Berglundh T, Chapelle IJC, Jepsen S, Kornman KS, et al. A new classification scheme for periodontal and peri-implant diseases and conditions — introduction and key changes from the 1999 classification. J Clin Periodontol 2017;44(Suppl 20):1–8.
[3] Mersic V, Le Gail-David S, Boyer Y, Acuta-Amador I, Martin B, Fong SB, et al. Signature of microbial dysbiosis in periodontitis. Appl Environ Microbiol 2017;83.
[4] Marsh PD. Microbial ecology of dental plaque and its significance in health and disease. Adv Dent Res 1994;8:263–71.
[5] Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent JR. Microbial complexes in subgingival plaque. J Clin Periodontol 1998;25:134–44.
[6] Deng ZL, Szafranski SP, Jarek M, Bhuj S, Wagn Dehler I. Dysbiosis in chronic periodontitis: key microbial players and interactions with the human host. Sci Rep 2017;7:3703.
[7] Ng HM, Kin LX, Dasgupta SG, Slakesni K, Butler CA, Reynolds EC. Bacterial interactions in pathogenic subgingival plaque. Microb Pathog 2016;94:60–8.
[8] Sima C, Glogauer M. Macrophage subsets and osteoimmunology: tuning of the immune pathway. Sci Adv 2020;6.
[9] cameo and CD86 on alveolar macrophages in the presentation of allergen to T lymphocytes in asthma. Clin Exp Allergy 2001;31:625–36.
[10] Zaid A, Thamarajah K, Mostafavi H, Freitas JS, Shin KC, Foo SS, et al. Modulation of monocyte-driven myeloperoxidase in alveolar infection reveals a role for C3(3)CR1(+)(+) macrophages in tissue repair. mBio 2020;11.
[11] Hinojosa R, Nakamura M, Takeuchi N, Nakae K, Matsuo T. Expression of fractalkine (CX3C1) and its receptor, CX3CR1, in periodontal diseased tissue. Clin Exp Immunol 2005;139:506–12.
[12] Bonakowska AE, Kimball AS, Joshi A, Schaller M, Davis FM, dEngDekker A, et al. Murine macrophage chemokine receptor CCR2 plays a crucial role in macrophage recruitment and regulated inflammation in wound healing. Eur J Immunol 2018;48:1454–55.
[13] Shen Z, Huang S, Zhang M, Huang X, Chen J, Guan M, et al. Inhibition of CCL2 by bindand alleviates diabetes-associated periodontitis by suppressing inflammatory monocyte infiltration and altering macrophage properties. Cell Mol Med 2021;18:2224–35.
[14] Zhang Z, Schlamp F, Huang L, Clark H, Braboy L. Inflammaging is associated with shifted macrophage polarization and aging in the mouse aging mouse. Reproduction 2020;199:325–37.
[15] Gonzalez OA, Novak MJ, Kirakodi S, Stromberg A, Nagarajan R, Huang CB, et al. Differential gene expression profiles reflecting macrophage polarization in aging and periodontal diseased tissues. Immunol Invest 2015;44:643–658.
[16] Clark D, Halpenn B, McIoul T, Nakamura M, Kapila Y, Marcuccio R. The contribution of macrophages in old mice to periodontal disease. J Dent Res 2021;100:1397–404.
[17] Almubarak A, Tangala KKK, Papapanou PN, Laila E, Momem-Heravi F. Disruption of monocyte and macrophage homeostasis in periodontitis. Front Immunol 2020;11:330.
[18] van Furth R, Cohn ZA. The origin and kinetics of mononuclear phagocytes. J Exp Med 1968;128:415–35.
[19] Auffray C, Fogg D, Garfa M, Elain G, Join-Lambert O, Kayal S, et al. Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior. Science 2007;317:666–70.
[20] Hoelzel G, Chen J, Lain W, Low D, Almeida FF, See P, et al. C-Myc(+) erythromyeloid progenitor-derived fetal monocytes give rise to adult tissue-resident macrophages. Immunology 2015;142:665–78.
[21] Biau Z, Gong Y, Huang T, Lee CZW, Biau L, Bao Z, et al. Deciphering human macrophage development at single-cell resolution. Nature 2020;582:571–6.
[22] Jenkins SJ, Rucker D, Cook PC, Jones LH, Finkelman FD, van Roonen J, et al. Local macrophage proliferation, rather than recruitment from the blood, is a signature of TH2 inflammation. Science 2011;332:1284–8.
[23] Davies LC, Rosas M, Jenkins SJ, Liao CT, Lelieveld D, Brombach F, et al. Distinct bone marrow-derived and tissue-resident macrophage lineages proliferate at key stages during infection. Nat Commun 2013;4:1886.
[24] Ginhoux F, Jung S. Monocytes and macrophages: developmental pathways and immune homeostasis. Nat Rev Immunol 2014;14:397–404.
[25] Hassell TM. Tissues and cells of the periodontium. Periodontol 2000 1993;3.
[26] Wyna TA, Chawla A, Pollard JW. Macrophage biology in development, homeostasis and disease. Nat Rev Immunol 2016;16:496–505.
[27] Char J, Toto PD, Gargulo AW. Activated macrophages in human periodontitis. J Periodontol 1981;52:328–35.
[28] Davies P, Page RC, Allison AC. Changes in cellular enzyme levels and extracellular release of lysosomal acid hydrolases in macrophages exposed to group A streptococcal cell wall substance. J Exp Med 1974;139:1262–82.
[29] Huang CB, Alimova Y, Ebersole JL. Macrophage polarization in response to oral commensals and pathogens. Pathog Dis 2016;74.
[30] Mass E, Ballesteros I, Farik M, Hallbacker F, Günther P, Crozet L, et al. Specification of tissue-resident macrophages during organogenesis. Science 2016;353.
[31] Zhou LN, Bi CS, Gao LN, An Y, Chen F, Chen FM. Macrophage polarization in human gingival tissue in response to periodontal disease. Oral Dis 2019;25:265–73.
[32] Zhang B, Yang Y, Yi J, Zhao Z, Ye Y. Hyperglycemia modulates M1/M2 macrophage polarization via reactive oxygen species overproduction in ligature-induced periodontitis. J Periodontal Res 2015;50:543–51.
[33] Martinez FO, Gordon S, Locati M, Mantovani A. Transcriptional profiling of the human monocyte-to-macrophage differentiation and polarization: new molecules and patterns of gene expression. J Immunol 2006;177:3703–11.
[34] Steen M, Keshav S, Hansen C. Interleukin-14 potently enhances murine macrophage mannose receptor activity: a marker of alternative immunologic macrophage activation. J Exp Med 1992;176:287–92.
[35] Maseeh L, Hartliva A, Isaksen S, Sundin J, Mavrikos G, Savolainen O, et al. Immunolocalization of chemokines in murine macrophage maturation in patients with ulcerative colitis during remission. Cell Mol Gastroenterol Hepatol 2021;12:1415–32.
[36] Nathan CF. Secretory products of macrophages. J Clin Invest 1987;79:319–26.
[45] Ait-Louis A, Laraba-Djebari F. TNF-alpha modulates adipose macrophage polarization to M1 phenotype in response to scorpion venom. Inflamm Res 2012;61:929–36.

[46] Lin SH, Chung HY, Ho JC, Lee CH, Hisao CC. Treatment with TNF-a inhibitors rectifies M1 macrophage polarization from blood CD14+ monocytes in patients with piaiosis independent of STAT1 and IRF1 activation. J Dermatol Sci 2010;60:276–8.

[47] Doyle AG, Herbein G, Montaner LJ, Minty AJ, Caput D, Ferrara P, et al. Interleukin-13 alters the activation state of murine macrophages in vitro: comparison with interleukin-4 and interferon-gamma. Eur J Immunol 1994;24:1441–5.

[48] Luke F, Gallagher I, Nair MG, Zang X, Frombacher F, Mohrs M, et al. Alternative activation is an innate injury to response that requires CD4+ T cells to be sustained during chronic infection. J Immunol 2007;179:3296–32.

[49] Gordon S. Alternative activation of macrophages. Nat Rev Immunol 2003;3:23–35.

[50] Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol 2008;8:958–69.

[51] Li CC, Chen SY, Lien HY, Lin SZ, Lee TM. Targeting the PI3K/STAT3 axis modulates age-related differences in macrophage phenotype in rats with myocardial infarction. J Cell Mol Med 2019;23:6788–92.

[52] Satoh T, Takeuchi O, Vendembon A, Vasuda K, Tanaka Y, Kagamai Y, et al. The Tmj33–slf4 axis regulates M2 macrophage polarization and host responses against helminth infection. Nat Immunol 2010;11:936–44.

[53] Lacey DC, Achurhan A, Fleetwood AJ, Dinh H, Roiniotis J, Scholz GM, et al. Defining GM-CSF- and macrophage-CSF dependent macrophage responses by Ctrl, Hex and Hex2 models. J Immunol 2012;188:5790–2.

[54] Liao X, Sharma N, Kapadia F, Zhou G, Yu L, Hong H, et al. Kruppel-like factor 4 inhibits IFN-gamma-induced NO production in macrophages infected with Trypanosoma brucei. Infect Immun 2013;81:4513–27.

[55] Krausgruber T, Blazek K, Smallle T, Alizahn S, Lockstone H, Sahlg ̈n N, et al. IRF5 promotes inflammatory macrophage polarization and TH1-TIIH1 responses. Nat Immunol 2011;12:231–2.

[56] O‘Shea JJ, Pesu M, Borie DC, Changelian PS. A new modality for immunomodulation: targeting the JAK/STAT pathway. Nat Rev Drug Discov 2004;3:555–60.

[57] Gory M, Zhao X, Ma A. STAT6 upregulation promotes M2 macrophage polarization to suppress atherosclerosis. Med Sci Monit Basic Res 2017;23:240–9.

[58] Szanto A, Balint BL, Nagy ZS, Barta E, Dezso B, Pap A, et al. St A T6 transcription blockers promote macrophage polarization to CD169+ M2a phenotype. J Periodontol 2012;83:3772–3.

[59] Hussain QA, McKay JG, Gonzales-Marin C, Allarker RP. Detection of adrenomedullin and nitric oxide in different forms of periodontal disease. J Periodontal Res 2016;51:16–25.

[60] Park OJ, Cho MK, Yun CH, Han SH. Lipopolysaccharide of Aggregatibacter actinomycetemcomitans cytolethal distending toxin A activates toll-like receptor 4 (TLR4) in human monocytes. Infect Immun 2014;82:4127–34.

[61] Malireddi RKS, Gurung P, Kesavardhana S, Samir P, Burton A, Mummareddy H, et al. NLRP3 inflammasome in Alzheimer’s disease. Translational Target Ther 2021;6:291.

[62] Kim PD, Xia-Juan X, Crump KE, Abe T, Hajsinghallas G, Sahingur SE. Toll-Like Receptor 9-Mediated Inflammation Triggers Alveolar Bone Loss in Experimental Murine Periodontitis. Infect Immun 2015;83:2992–2002.

[63] Hajsinghallas G, Wang M, Liang S. Induction of distinct TLR2-mediated proinflammatory and proadhesive signaling pathways in response to Aggregatibacter actinomycetemcomitans. J Immunol 2003;170:2499–50.

[64] Wang M, Shakharthek MA, James D, Liang S, Nishiyama S, Yoshimura F, et al. Fimbrial proteins of Porphyromonas gingivalis mediate in vivo virulence and exploit TLR2 and complement receptor 3 to persist in macrophages. J Immunol 2013;190:2349–58.

[65] Hajsinghallas G, Shakharthek MA, Wang M, Liang S. Complement receptor 3 blockade promotes IL-12-mediated clearance of Porphyromonas gingivalis and negates its virulence in vivo. J Immunol 2007;179:2359–67.

[66] Shamsada E, Katahira Y, Miyazawa Y, Yamamoto M, Igarashi T. Lipoproteins of Actinobacillus actinomycetemcomitans cytolethal distending toxin induces IL-6, IL-8, IL-12, and IL-18 production in human epithelial cells. J Periodontal Res 2009;44:175–82.

[67] Park OJ, Cho MK, Yun CH, Han SH. Lipopolysaccharide of Aggregatibacter actinomycetemcomitans lipopolysaccharide antisense oligonucleotide, or its FimA protein. Infect Immun 2005;73:935–43.

[68] Nussbaum G, Ben-Adi S, Genzler T, Sela M, Rosen G. Involvement of Toll-like receptors 2 and 4 in the innate immune response to Treponema denticola and its outer sheath components. Infect Immun 2009;77:3939–47.

[69] Papadopoulos G, Weinberg EO, Massari F, Gibson 3rd FC, Wetzler LM, Morgan EF. Macrophage-specific TLR2 signaling induces TLR4-dependent TNF-dependent inflammatory oral bone loss. J Immunol 2013;190:1148–57.

[70] Kim PD, Xia-Juan X, Crump KE, Abe T, Hajsinghallas G, Sahingur SE. Toll-Like Receptor 9-Mediated Inflammation Triggers Alveolar Bone Loss in Experimental Murine Periodontitis. Infect Immun 2015;83:2992–2002.
Yarilina A, Park M-K, Hwang T, Antoniades T, Hu X, Ivashkiv LB. TNF activates an IRF1-Schroder K, Tschopp J. The inflammasomes. Cell 2010;140:821–32.
He D, Li X, Zhang F, Wang C, Liu Y, Bhawal UK, et al. Dec2 inhibits macrophage
Murakami Y, Yuhara K, Takada N, Arai T, Tsuda S, Takamatsu S, et al. Effect of
Kato S, Muro M, Akifusa S, Hanada N, Semba I, Fujii T, et al. Evidence for
Knittel T, Mehde M, Kobold D, Saile B, Dinter C, Ramadori G. Expression pat-
Rath-Deschner B, Memmert S, Damanaki A, Nokhbehsaim M, Eick S, Cirelli JA,
Victor DJ, Subramanian S, Gnana PP, Kolagani SP. Assessment of matrix me-
Bostanci N, Ilgenli T, Emingil G, Afacan B, Han B, Töz H, et al. Differential e
Gawrisch K. Mycobacterium tuberculosis enters macrophages with aid from a
Fine DH, Markowitz K, Ferlandiz J, Godbolley D, Zhuang Z, Yoshizawa-Smith S, Glowacki A, Maltos K, Pacheco C, Shehabeldin M,
Yang Y, Wang L, Zhang H, Luo L. Mixed lineage kinase domain-like pseudokinase-mediated necroptosis aggravates periodontitis progression. J Mol Med 2020;100:77–86.
Yamaguchi H, Maruyama T, Urade Y, Nagata S. Immunosuppression via adeno-
rice-activated TRF signaling to promote yersinia-induced apoptosis. J Immunol 2016;197:4110–70.
Kato S, Muro M, Akifusa S, Hanada N, Sembu I, Fujii T, et al. Evidence for apoptosis of murine macrophages by Actinobacillus actinomycetemcomitans. In Vivo 2015;29:1313–22.
Aliprantis AO, Yang RB, Weiss DS, Godowski P, Zychlinsky A. The apoptotic signaling pathway activated by Toll-like receptor-2. EMBO J 2000;19:3325–36.
Pellicoro A, Auclott RL, Ramachandran P, Robson AJ, Goldfield JA, Snowdon VK,



Inhibition of bone resorbtion in vitro by selective inhibitors of gelatinase and
Gawrisch K. Mycobacterium tuberculosis enters macrophages with aid from a
Fine DH, Markowitz K, Ferlandiz J, Godbolley D, Zhuang Z, Yoshizawa-Smith S, Glowacki A, Maltos K, Pacheco C, Shehabeldin M,
Yang Y, Wang L, Zhang H, Luo L. Mixed lineage kinase domain-like pseudokinase-mediated necroptosis aggravates periodontitis progression. J Mol Med 2020;100:77–86.
Yamaguchi H, Maruyama T, Urade Y, Nagata S. Immunosuppression via adeno-
rice-activated TRF signaling to promote yersinia-induced apoptosis. J Immunol 2016;197:4110–70.
Kato S, Muro M, Akifusa S, Hanada N, Sembu I, Fujii T, et al. Evidence for apoptosis of murine macrophages by Actinobacillus actinomycetemcomitans. In Vivo 2015;29:1313–22.
Aliprantis AO, Yang RB, Weiss DS, Godowski P, Zychlinsky A. The apoptotic signaling pathway activated by Toll-like receptor-2. EMBO J 2000;19:3325–36.
Pellicoro A, Auclott RL, Ramachandran P, Robson AJ, Goldfield JA, Snowdon VK,
Rani R, Smulian A G, Grevess DR, Hogan SP, Herbert DBR, Yang J, Zhu Y, Duan D, Wang P, Xin Y, Bai L, et al. Enhanced activity of macrophages: the bridge between inflammation and tissue repair. J Dent Res 2018;97:1079–81.

Kim H, Wang SY, Kwek G, Yang Y, Rwon SC, Kim SH. Exosome-guided Phenotypic Switch of M1 to M2 macrophages for cutaneous wound healing. Adv Sci 2019;6:1900513.

O’Brien EM, Spiller KL. Pro-inflammatory polarization primes Macrophages to transition into a distinct M2-like phenotype in response to IL-4. J Leukoc Biol.; 2021.

Yu T, Zhao L, Huang X, Ma C, Wang Y, Zhang J, et al. Enhanced activity of the macrophage M1/M2 phenotypes and phenotypic switch to M1 in Periodontitis. J Peridontol 2016;87:1092–102.

Vinerega A, Goldberg H, Cil C, Fine N, Sheikh Z, Galli M, et al. Resolving macrophages counter oestrogen by anabolic actions on bone cells. J Dent Res 2018;97:1160–9.

Yang J, Zhu Y, Duan D, Wang P, Xin Y, Bai L, et al. Enhanced activity of macrophage M1/M2 phenotypes in periodontitis. Arch Oral Biol 2018;96:234–42.

Matusiewicz M, Neubauer K, Mierzchala-Pasierb M, Gamian A, Krzyztek-Korpacka M. Matrix metalloproteinase-9: its interplay with angiogenic factors in inflammatory bowel diseases. Dis Markers 2014;2014:643645.

Miao Y, He L, Qi X, Lin X. Injecting immunosuppressive M2 macrophages alleviates the symptoms of periodontitis in mice. Front Mol Biosci 2020;7:603817.

Liu J, Chen B, Bao J, Zhang Y, Lei L, Yan F. Macrophage polarization in periodontal ligament stem cells enhanced periodontal regeneration. Stem Cell Res Ther 2019;10:320.

Wang R, Ji Q, Meng C, Liu H, Fan C, Lipkind S, et al. Role of gingival mesenchymal stem cell exosomes in macrophage polarization under inflammatory conditions. Int Immunopharmacol 2020;81:106030.

Maekawa T, Krauss JL, Abe T, Jotwani R, Triantafilou M, Triantafilou K, et al. Mechanism of endotoxin desensitization: involvement of interleukin 10 and transforming growth factor beta. J Exp Med 1995;181:1887–92.

Rani R, Smulian AG, Greaves DR, Hogan SP, Herbert DBR, TGF-β limits IL-33 production and promotes the resolution of colitis through regulation of macrophage function. Eur J Immunol 2011;41:2000–9.

Khalil N, Whitman C, Zuo L, Danielpour D, Greenberg A. Regulation of alveolar macrophage transforming growth factor-beta secretion by corticosteroids in bleomycin-induced pulmonary inflammation in the rat. J Clin Invest 1993;92:1812–8.

Tabas I. Macrophage death and defective inflammation resolution in atherosclerosis. Nat Rev Immunol 2010;10:36–46.

Frutkin AD, Otsuka G, Stemperski A, Sesti C, Du L, Jaffe M, et al. TGF-[beta] limits plaque growth, stabilizes plaque structure, and prevents aortic dilation in apolipoprotein E-null mice. Arterioscler Thromb Vasc Biol 2009;29:1251–7.

Steinmetz O, Hoch S, Anvil-Polak S, Krawczuk K, Garlet GP, Giannobile WV. Macrophage M1/M2 phenotypes and phenotypic switch to M1 in Periodontal disease. J Periodontol 2018;89:1453–65.

Chukkapalli SS, Velsko IM, Rivera-Kweh MF, Larjava H, Lucas AR, Kivisaal L. Kaewharan Y, Kaneko T, Yoshihaga Y, Arita Y, Nakamura K, Koga C, et al. Effects of HDAC8 on periodontal disease progression. J Periodontol 2017;88:2177–91.

Ip WKE, Hoshu N, Shouval DS, Snapper S, Medzhitov R. Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages. Science 2017;356:513–9.

Hu G, Su Y, Kang BH, Fan Z, Dong T, Brown DR, et al. High-throughput phenotypic screen and transcriptional analysis identify new compounds and targets for macrophage reprogramming. Nat Commun 2021;12:772.

Garlet GP, Giannobile WV. Macrophages: the bridge between inflammation resolution and tissue repair? J Dent Res 2018;97:1079–81.

Kim H, Wang SY, Kwek G, Yang Y, Rwon SC, Kim SH. Exosome-guided Phenotypic Switch of M1 to M2 macrophages for cutaneous wound healing. Adv Sci 2019;6:1900513.