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Review Article

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

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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.

Contents

Abbreviations: AIM2, absent in melanoma-2; CCL2, chemokine (C-C motif) ligand 2; CCR2, chemokine (C-C motif) receptor 2; DAMP, damage-associated molecular pattern; IFN, interferon; IL, interleukin; IRF, interferon regulatory factor; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; MLKL, mixed lineage kinase-like; MyD88, myeloid differentiation factor 88; NLR, nucleotide oligomerization domain-like receptor; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; RANKL, receptor activator of nuclear factor kappa-B ligand; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumor necrosis factor; TRIF, Toll/IL-1R domain-containing adapter-inducing IFN-β

* Corresponding authors.
E-mail addresses: lixinzhu880623@i.smu.edu.cn (X. Li), houjin@smu.edu.cn (J. Hou).

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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 overactivated 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-X3-C motif) ligand 1/chemokine (C-X3-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 microenvironmental factors can promote macrophage recruitment, which mediates phenotypic and functional changes in macrophages in periodontitis and leads to tissue damage and repair [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, STAT1, and IRF5 activation [54–56], whereas STAT3/STAT6, IRF4, and peroxisome 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.

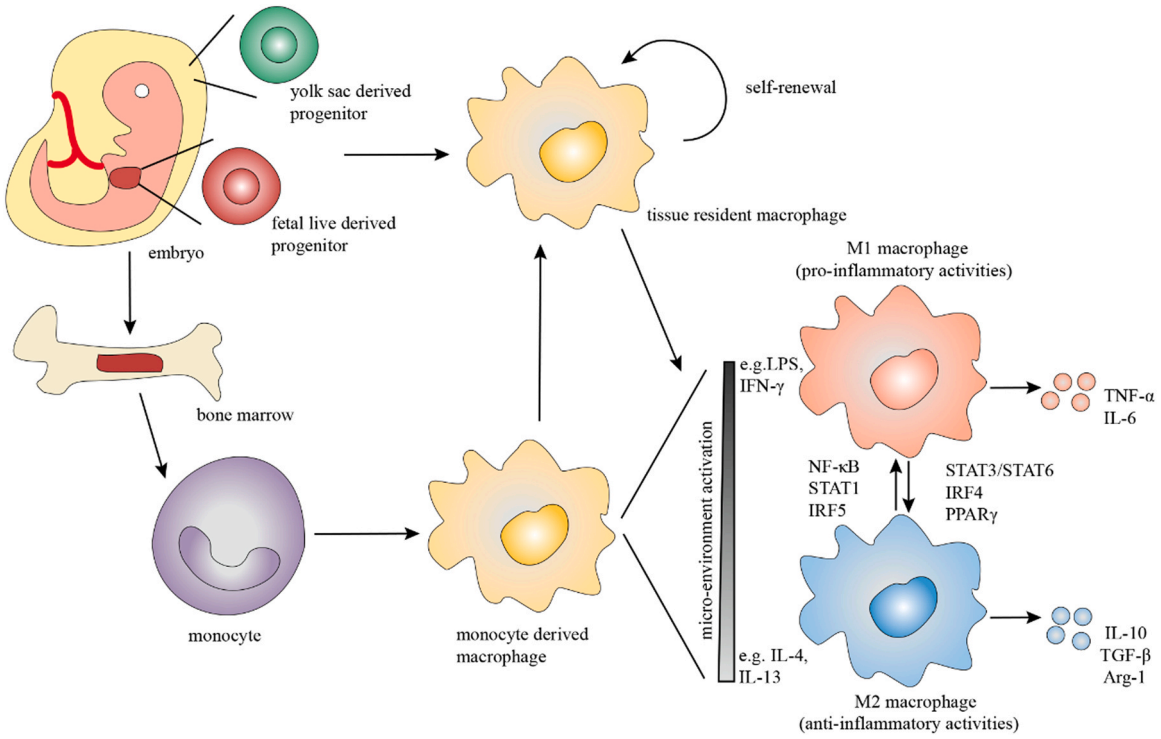

Fig. 1. Macrophage origin and plasticity. Tissue-resident macrophages arise from bone marrow-derived monocytes, yolk sac and fetal liver. These cells polarize into two major extreme states, M1 and M2, having pro-inflammatory and anti-inflammatory activities, respectively.

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-I-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

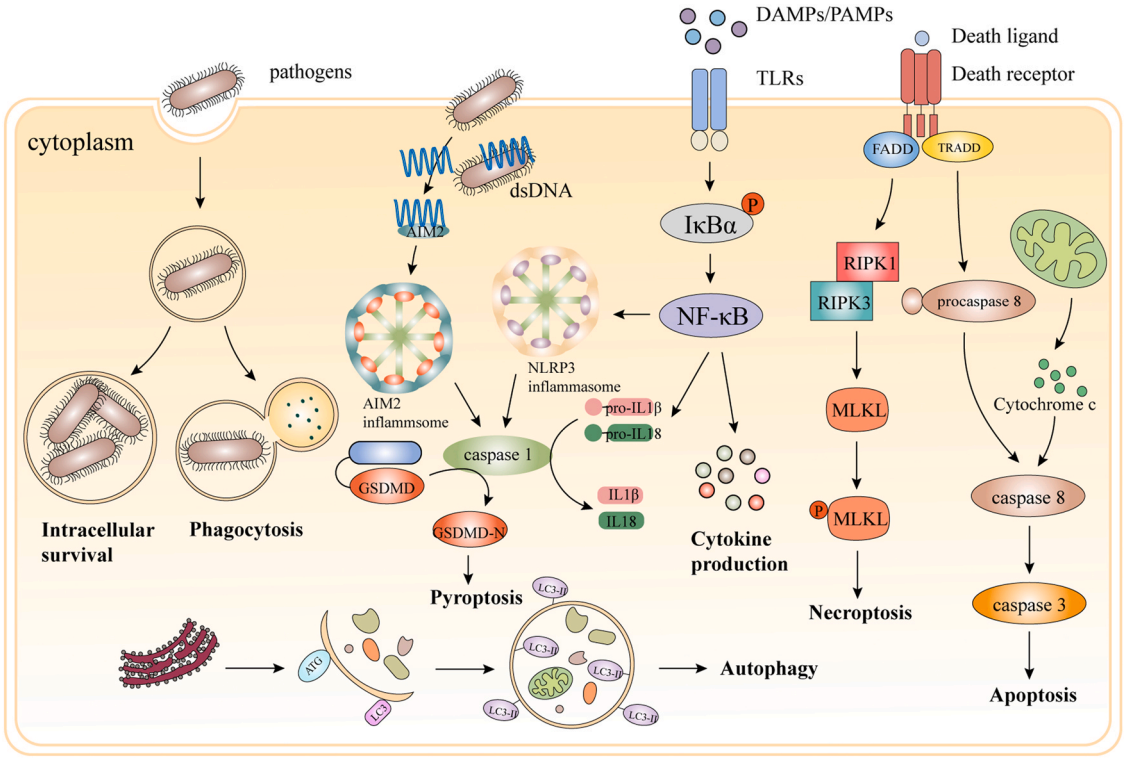

Fig. 2. Macrophage cell death and cytokine production in periodontitis. Macrophages are activated when PRRs recognize PAMPs/DAMPs. The binding stimulates multiple signal transduction pathways: (A) Binding of PRRs activates NF-κB signaling and secretes various cytokines; (B) Binding of PRRs results in 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.

signaling pathway 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 secretion, 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 signaling [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 regulates cell death. It can be initiated by the interaction of microbial components with PRRs that allows inflammasome activation, resulting in the massive release of cytosolic contents [88,100]. Further, a large number of PAMPs and DAMPs are released from necrotic

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 correlate 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. Upregulation 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

Table 1
Characteristics of macrophage-derived biomarkers in periodontitis.

Marker	Inflammation	Mechanism & notes	References
IFN-γ	Pro-	Activates M1 macrophages to promote periodontal bone loss	[39,181]
IL-6	Pro-	Promotes periodontal tissue damage	[39,181]
IL-4	Anti-	Activates M2 macrophages to regulate inflammation	[49]
IL-10	Anti-	Inhibits osteoclastogenesis and stimulates osteoblastic differentiation	[66]
RANKL	Pro-	Promotes periodontal bone loss	[74]
TNF-α	Pro-	Promotes periodontal bone loss	[139–141]
MMP-9	Pro-	Promotes extracellular matrix degradation and alveolar bone resorption	[149]
MMP-13	Pro-	Promotes periodontal bone loss	[150]
CCL2	Pro-	Recruits macrophages to the site of infection and induces alveolar bone loss and epithelial lesions	[131,160]
CX3CR1	Anti- /pro-	Regulates inflammation and induces bacterial survival and bone resorption	[160,170]
TGF-β	Anti-	Enhances the production and deposition of extracellular matrix and suppresses the expression of pro-inflammatory cytokines	[162–164]
Cystatin C	Anti-	Promotes bone regeneration by regulating osteoblasts and osteoclasts	[180]

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 [131–133]. CCL2 downregulation can alleviate alveolar bone loss and rescue epithelial lesions by suppressing periodontal inflammation [21,134]. 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 [135,136].

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 [73,75]. 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 [137]. 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 [138]. 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 [139–141]. Moreover, patients with periodontitis exhibit significantly higher RANKL levels than healthy individuals and an increased ratio of RANKL to its inhibitor, osteoprotegerin [142,143]. 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[144]. Furthermore, TNF shares many biologic properties with IL-1 family. Blockade of IL-1 and TNF activities in mouse models could suppress inflammatory cell infiltration and inhibit osteoclast formation during periodontal bone resorption [145]. Therefore, the TNF superfamily has direct damaging effects on the periodontal tissues of patients with periodontitis.

Matrix metalloproteinases (MMPs) are pro-inflammatory mediators that belong to the most prominent and widely studied proteinase family associated with periodontal diseases. They may play a significant role as drivers of destructive inflammation, causing periodontal destruction by degrading the extracellular matrix and regulating tissue remodeling [146]. In vitro experiments showed that *F. nucleatum* and *Treponema denticola*, which are leading pathogens in chronic periodontitis, can upregulate the secretion of MMP-9 in macrophages [147,148]. These increased levels of MMP-9 have pro-inflammatory effects in destructive periodontal diseases, including degradation of the extracellular matrix and basement membrane components and resorption of alveolar bone [149]. MMP-13 immunoreactivity was identified in macrophage-like cells of patients with periodontitis, which may also potentiate bone resorption [150]. MMP-13 has been implicated in the generation of collagen fragments that activate osteoclasts and proMMP-9 in vitro [151,152]. In turn, active MMP-9 released by osteoclasts further digests denatured collagen derived from MMP-13 activity, leading to pre-osteoclast recruitment to sites for osteoclast differentiation and bone loss [151,153]. Accordingly, it appears that MMP-13 and -9 form a positive feedback loop to perpetuate periodontal soft- and hard-tissue destruction in vivo. These results may be useful for macrophage-targeted drug development in future [153]. Furthermore, tissue fibrosis observed in periodontitis contributes to dysregulation of periodontal homeostasis [154]. Recent studies based on liver fibrosis models have suggested that hepatic macrophages can express several MMPs, including MMP-9, MMP-12, and MMP-13, which function in matrix degradation and thus favor the resolution of liver injury and fibrosis [155–157]. However, the mechanisms by which macrophage-derived MMPs act as key regulators of periodontal fibrosis are not yet fully understood.

Recent studies have shown that tissue repair in inflammation not only depends on the clearance of virulence factors but also on the capacity of the remaining cells to boost tissue regeneration and remodeling [158,159]. Macrophages perform timely removal of cell debris and pathogens, and participate in extracellular matrix deposition and bone formation in periodontitis [50,160]. Macrophage depletion during distinct phases of mouse skin repair demonstrates that macrophages exert specific functions at different stages and facilitate tissue homeostasis [161]. Therefore, alterations in the secretion 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 [162]. Recent studies have identified that TGF-β can suppress the expression of pro-inflammatory cytokines and contribute to the induction of LPS tolerance [163–165]. Impairment of TGF-β signaling in macrophages results in increased severity of intestinal inflammation during the resolution phase [166]. Moreover, TGF-β regulates various cellular processes, such as cell proliferation, differentiation, and migration, and affects the production and deposition of extracellular matrix [162]. 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 [167–169]. 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 leucocytes 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 macrophage 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 osteoblastic 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 [177,178].

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 bindarit, 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

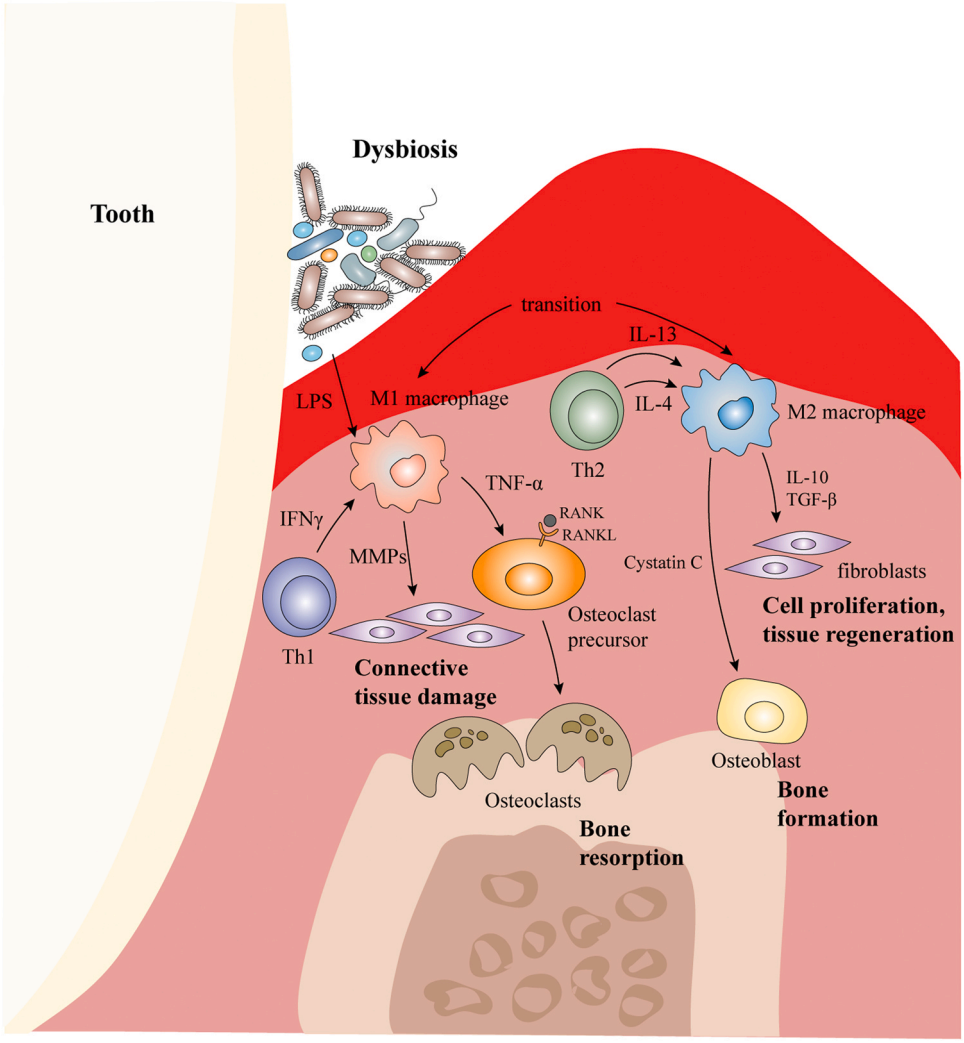

Fig. 3. The dynamic changes in macrophage polarization and functions in tissue damage and repair during periodontitis progression. Depending on the periodontal microenvironment: non-activated macrophages can initially drive the polarization of pro-inflammatory M1 macrophages under the stimulation of periodontal microbes and their products; M1 macrophages release TNF-α and MMPs leading to tissue damage; M1 macrophages can reprogram their phenotypes toward anti-inflammatory M2 macrophages in the presence of IL-4 or IL-13; M2 macrophages secrete IL-10 and TGF-β leading to tissue regeneration and conversion of the overall environment. Th: T helper cells.

[188]. 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 ligation-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 ontogeny 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 transcriptome 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.

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