Roles of Immune Cells and Mechanisms of Immune Responses in Periodontitis

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Periodontitis is one of the severe oral diseases that threatens both the oral and general health of humans. It is an inflammatory disease caused by the complex interaction between the plaque microorganisms and the host immune system. The innate immune response is activated when pathogens invade the periodontium. An excessive innate immune response leads to inflammation and the destruction of periodontal tissues, which then activates the adaptive immune response. Although systemic initial therapy and guided tissue regeneration (GTR) can control periodontal inflammation to a certain extent and promote periodontal tissue regeneration, their effects are still limited. Periodontal treatment will be significantly improved if it is possible to screen the potential therapeutic targets and regulate the key molecules involved in periodontal disease; however, relevant research on the prevention and treatment of periodontitis remains limited. Thus, with the aim of assisting the immunoregulation of periodontitis, this article summarises the cells and mechanisms involved in the innate immune response and adaptive immune response caused by pathogens in the periodontium.

Key words: *adaptive immune response immune cells, inflammation, innate immune response, periodontitis*
Chin J Dent Res 2021;24(4):219–230; doi: 10.3290/j.cjdr.b2440547

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This work was supported by the Young Elite Scientist Sponsorship Program by CAST (2018QNRC001), the Natural Science Foundation of China (81970946 and 81970903), China Postdoctoral Science Foundation (2018T110259, 2016M601386, 2017M621219 and 2018T110258), Jilin Province Education Department Science and Technology Research (JJKH20190106KJ), Jilin Province Science and Technology Research (20190103088JH, 20200201611JC and 20200201527JC), Jilin Province Finance Department Science and Technology Research (JCSZ2019378-30 and JCSZ2019378-6), and Jilin Province Health Department Youth Science and Technology Research (2019Q014 and 2019Q013).

Periodontitis is an inflammatory disease caused by the complex interaction between plaque bacteria and the host immune system[1-3]. It is characterised by gingival inflammation, periodontal attachment loss and alveolar bone resorption. In the later stage of periodontitis, tooth loosening, displacement and even loss can occur, which may affect patients' physical and mental health as well as their quality of life. Studies have reported that patients with periodontitis have a significantly increased risk of suffering from atherosclerosis, pregnancy complications (premature birth, low birth weight infants, etc.), rheumatoid arthritis, aspiration pneumonia and cancer[4-6]. A recent study found that the gingival proteases released by the pathogenic bacteria in periodontitis are the keys leading to Alzheimer's disease, which indicates the severity of the connection between periodontitis and one's mental health condition[7]. Therefore, the prevention and treatment of periodontitis and the follow-up tissue repair are problems that are relevant globally. Currently, the treatment of periodontitis mainly depends on initial therapy, drug treatment and periodon-

tal surgery. The majority of existing drug treatments are only antibacterial, anti-inflammatory or regenerative, thus inhibiting the inflammation that has occurred and promoting the regeneration and repair of defective tissues. However, a deeper understanding of the pathogenesis of periodontitis has led researchers to realise that most of the tissue damage in periodontitis is caused by the host immune response to infection rather than directly by the infected microorganisms[8]. This clarified that the immune response process of periodontal disease has therefore become significant in the prevention and treatment of periodontal disease.

When the pathogens enter the body, the innate immune system is the first barrier that defends against the spread of invading microorganisms[9]. If the innate immune response fails to destroy these pathogens completely, the specific adaptive immune response will then be stimulated[10-15]. Upon continuing to protect the body, this specific immune response will generate an immune memory in order to defeat the same pathogens when encountered for the second time[16]. If the adaptive immune response does not successfully eliminate all pathogens, patients enter a state of chronic infection. Dental plaque is the initiating factor in the occurrence and development of chronic periodontitis. Dental plaque is a biofilm that contains a large number of pathogenic microorganisms and toxic products, both of which can stimulate immune cells to release various proinflammatory factors. When plaque biofilm is formed, it will attract a large number of immune cells to migrate to the periodontal tissues and locally produce sustained inflammation[17-19]. The proinflammatory factors secreted by immune cells not only play a defensive role against microorganisms, but also cause the destruction of periodontal tissue[20,21]. Thus, exploring strategies to eliminate the inflammatory response caused by plaque biofilm is particularly important.

Periodontal health requires a controlled immune–inflammatory state to maintain the homeostasis between the host and microbes[3]. In periodontitis, however, due to the destruction by microorganisms or disruptions in host immune regulation, homeostasis is destroyed and continuous pathogenicity will occur[3]. As such, from the perspective of immune regulation, suitable drug targets should be screened to regulate the interaction between plaque microorganisms and the host immune system in order to alleviate the inflammatory response caused by the excessive immune response. In this review, we will summarise the cells and mechanisms involved in the innate immune response and adaptive immune response during the development of periodontitis, which may provide new ideas and assistance for the drug treatment of periodontitis.

Innate immune response and its role in periodontitis

Innate immunity is the first line of defence against various invading pathogenic microorganisms[9]. The activation of innate immunity by pathogenic microorganisms initiates inflammatory reactions[22,23]. The response mode and intensity are not changed by repeated contact with pathogenic microorganisms, so they are non-specific. Innate immune cells are the main components of the innate immune response and include neutrophils, macrophages, dendritic cells (DCs) and many other types of cells that can bind, engulf and kill microorganisms[24-30]. Innate immune molecules are the effector molecules of the innate immune response, including various cytokines produced by immune cells, complement in tissue fluid, lysozyme and antimicrobial peptide. They can inhibit or kill bacteria and initiate and participate in the innate immune response[31-37]. In addition, the produced cytokines, such as interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α), play an important role in the destruction of the periodontium[38,39].

Cells involved in the innate immune response

Neutrophils

Neutrophils are the largest group of white blood cells in the blood and have various biological functions, such as chemotaxis, phagocytosis and sterilisation[40,41]. People with congenital deficiencies in neutrophil numbers or recruitment will develop severe periodontitis, suggesting that neutrophils are necessary for the stability of the internal environment of periodontal tissue[3,42,43]. Pathogenic microorganisms can trigger an immune response, and at the same time cause a large number of neutrophils to recruit in the periodontal pocket for a long time; however, overactive, redundant or dysregulated neutrophils can cause tissue damage by releasing inflammatory and toxic substances or tissue degrading enzymes[3,42,43]. A significant amount of clinical evidence has shown that neutrophils mediate the destruction of periodontal tissues, and their local number is positively correlated with the severity of chronic periodontal disease[3].

Neutrophils play a dual role in the process of periodontal inflammation. On one hand, as an important defensive cell, when plaque microorganisms invade the host, neutrophils are recruited to the site of the inflammation to phagocytise bacteria, and then release lysosomal enzymes or super oxygen ions to kill bacteria under the regulation of cytokines, adhesion molecules and chemokines[44,45]. On the other hand, if the response

to pathogenic stimuli is very intense, excessive super oxygen ions or lysosomal enzymes are produced, which will cause damage to the surrounding tissues and cells and aggravate the inflammatory response. In the process of phagocytosis of bacteria, the inflammatory cytokines that are produced and released by neutrophils will also aggravate inflammation. Neutrophils in peripheral blood and gingival crevicular fluid can synthesise and secrete molecules such as IL-1, TNF-α, interleukin-6 (IL-6) and interleukin-8 (IL-8)[46]. These can not only promote the degradation of connective tissue matrix but also stimulate bone resorption, which leads to the destruction of periodontal tissue. These cytokines can also stimulate the production of more IL-1, TNF-α and IL-8 through autocrine and paracrine pathways, thereby recruiting and activating more neutrophils to the site of inflammation, resulting in the aggravation and expansion of inflammation.

In summary, neutrophils are the first line of defence against periodontal pathogens and play an important role in the maintenance and regulation of periodontal tissue health.

Macrophages

Macrophages are derived from monocytes in the blood. When they pass through blood vessels and enter different tissues, they differentiate into tissue-specific macrophages and their morphology and functions also undergo major changes[47]. Macrophages are important components of innate immunity and have strong phagocytic ability. Their main biological functions include identifying and phagocytising bacteria, participating in inflammation and tissue healing, and restoring tissue homeostasis[48]. They are also an important class of antigen-presenting cells that play a key role in the induction and regulation of specific immune responses[49].

According to their different functions, macrophages are divided into two types: classically activated M1 macrophages and alternatively activated M2 macrophages. M1 macrophages are activated in the presence of interferon-gamma (IFN-γ), TNF-α or lipopolysaccharide (LPS) and secrete a large amount of pro-inflammatory factors, such as IL-6, IL-1β, TNF-α and matrix metalloproteinase-9 (MMP-9), that could promote the immune response[50]. They can effectively inhibit microorganisms and pathogens, participate in anti-tumour immunity and enhance the immune defence function; however, the metabolites produced while promoting inflammation may also indirectly cause tissue damage, leading to tissue destruction. M2 macrophages are activated in the presence of interleukin-4 (IL-4) and interleukin-13 (IL-13) and secrete a large number of anti-inflammatory factors (such as IL-10 and IL-1 receptor antagonist), which can inhibit the process of inflammation while promoting tissue healing and repair[50]. Thus, M2 macrophages can inhibit inflammation and promote tissue regeneration. The polarisation of macrophages to M1 and M2 is the two directions of the macrophage differentiation process, and differentiated M1 and M2 macrophages can be transformed into each other in certain microenvironments. There are also a variety of intermediate types between M1 and M2 macrophages.

When periodontal pathogens invade the gingival tissue, the macrophages in the tissue, together with gingival epithelial cells and dendritic cells, will secrete cytokines, chemokines and neuropeptides, which cause local vasodilation and recruitment of neutrophils. When *Porphyromonas gingivalis* (*P. gingivalis*) invades the periodontium, toll-like receptors (TLRs) on the surfaces of the macrophages can recognise the LPS of *P. gingivalis*. The activated M1 macrophages produce IL-1β, IL-6, TNF-α and other proinflammatory cytokines and chemokines, thus initiating the immune defence response[51]. At the same time, M2 macrophages secrete IL-10 and other factors to promote the regeneration of periodontal tissue, and ultimately eliminate the inflammatory response in periodontal tissue[52]. Macrophages, as the main regulatory cells of the inflammatory response, can limit the above process as well as stimulate the following defence response, namely acquired immunity. Researchers have found that compared with chronic gingivitis, the ratio of M1–M2 in the gingival tissue of patients with chronic periodontitis is significantly increased, and it is also associated with the expression of IL-1β and MMP-9 in the gingival tissue[53]. These results imply that macrophage polarisation may be closely related to chronic periodontitis.

DCs

DCs originate from pluripotent haematopoietic stem cells in the bone marrow. TLRs, Fc receptors and complement receptors on the surface of DCs play a role in antigen uptake[54]. In addition, DCs express major histocompatibility complex (MHC) class II molecules, costimulatory molecules and adhesion molecules, which play a role in antigen presentation[55]. DCs can effectively stimulate the activation of T cells and B cells, and link innate immunity and adaptive immunity. In this process, DCs secrete IL-1, IL-6, interleukin-12 (IL-12), IFN-γ and various chemokines to participate in immune regulation[56,57]. As DCs mature, their antigen presentation ability gradually

increases and their uptake ability weakens. Compared with normal periodontal tissues, the number of immature DCs in the periodontal tissues of patients with chronic periodontitis is increased. The number of immature DCs is positively correlated with probing depth, indicating that in the development of chronic periodontitis, the maturation of DCs is impaired[58]. Other innate immune cells, such as mast cells, eosinophils and natural killer cells, also participate in the innate immune response in periodontitis.

Mechanisms of the innate immune response in periodontitis

Barrier function

In the innate immune response, the antibacterial substances and normal bacterial flora in the skin and mucous membranes act as physical, chemical and microbial barriers. They can protect the body from the invasion of external pathogens and have an immediate immune defence effect. In the oral environment, the gingival epithelium is an extremely important physical barrier. The gingival tissue is connected to the surface of the tooth by the junctional epithelium, sealing the soft and hard tissues. The junctional epithelium renews quickly, which causes the senescent cells on the surface layer to fall off into the gingival sulcus at a rapid rate. As a result, the bacteria attached to the junctional epithelium will also fall off with the senescent cells; this is one of the important defence mechanisms of the junctional epithelium. In addition to the epithelial barrier function, junctional epithelial cells can produce effective antibacterial substances such as lysosomal enzymes and defensins, which play an important role in resisting the invasion of pathogenic microorganisms[59,60].

Recognition by pattern recognition receptors

Pattern recognition receptors (PRRs) are molecules that are mainly expressed on the surface of innate immune cells, as well as the endosomes, lysosomes and cytoplasm, and that can recognise one or more pathogen associated molecule patterns (PAMPs)/damage associated molecule patterns (DAMPs). PRRs mainly include the TLR, retinoic acid-inducible gene I–like receptor (RLR) and nucleotide oligomerisation domain (NOD)–like receptor (NLR) families, which could recognise intracellular and extracellular pathogens, viral ribonucleic acid (RNA) in the cytoplasm and pathogens in the cytoplasm, respectively[61]. In periodontitis, the immune response may be triggered due to the simultaneous activation of multiple cell signalling pathways by PRRs[14].

When *P. gingivalis* invades the body as PAMPs by breaking through the barrier, the surface LPS can be recognised by the PRRs on the innate immune cell surface. In response, innate immune cells are directly stimulated, and a large number of inflammatory factors (such as IL-1, IL-6, IL-8, TNF-α, etc.) are released to initiate the innate immune response and cause periodontitis[62]. Among all the PRRs, TLRs are currently considered the most important and are being studied thoroughly[63,64]. Based on the different types of PAMPs, TLRs can be divided into three categories: the first mainly includes lipid PAMPs, such as TLR1, TLR2, TLR4 and TLR6; the second usually activates protein PAMPs such as TLR5; and the third generally interacts with nucleic acid PAMPs, e.g., TLR3, TLR7, TLR8 and TLR9 (Fig 1)[61]. Studies have confirmed that both healthy gingival tissue and gingival tissue of patients with periodontal disease can express TLR1-TLR9[65], with TLR4 highly expressed in the gingival tissue of patients with periodontitis[66,67]. TLR4 can be activated by recognising LPS, then recruitment of myeloid differentiation primary response protein 88 (MyD88) and activating transcription factors nuclear factor kappa-B (NF-κB) and activator protein-1 (AP-1) through a mitogen-activated protein kinase (MAPK) pathway[68]. As a result, the proinflammatory factors IL-8, TNF-α, IL-12 and IFN-γ are released and give rise to the destruction of periodontal tissue.

As an intracytoplasmic receptor, NLR can recognise different PAMPs and endogenous DAMPs in the cytoplasm. NLR is composed of three domains: the C-terminal is leucine-rich repeat (LRR), which is mainly responsible for identifying and binding specific PAMPs and DAMPs; the middle is a characteristic domain (i.e., NOD domain) shared by NLR family members; and the N-terminal is the effector domain for sending the downstream signals[69]. According to the types and structural characteristics of the effector domains, the NLR family can be divided into multiple subfamilies, including NLRA, NLRB, NLRC and NLRP[70]. NLRP is the largest subfamily of NLRs, and researchers have found that the expression of NLRP3 in patients with chronic periodontitis is significantly increased[71,72]. NLRP3 inflammasome is a group of protein complexes consisting of NLRP3, apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain (CARD) (ASC) and pro-caspase-1[73]. When the inflammasome is stimulated by pathogens, pro-caspase-1 is activated to cleave pro-IL-1β and pro-IL-18, and finally produce inflammatory cytokines IL-1β and IL-18[73].

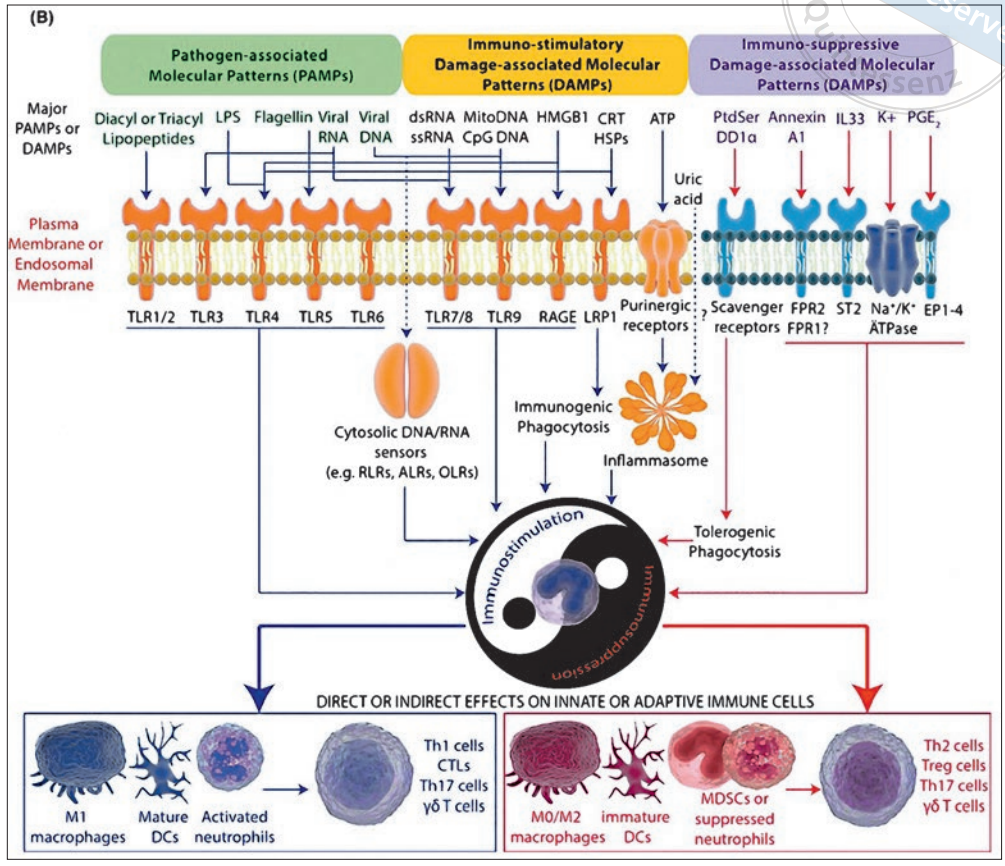

Fig 1 PAMPs and DAMPs can be recognised by TLRs in the innate immune response, having direct or indirect effects on innate or adaptive immune cells. (Reprinted from Garg and Agostinis[61] with permission.)

The common feature of inflammasomes is the final activation of caspase-1, which activates the involved cytokines in the inflammatory response.

Activation of complement

The complement system is a group of proteins that exist in human and animal serum or tissue fluid. Once activated, their enzymatic activity can mediate the immune and inflammatory response[74]. The main activation pathways of complement are the classical, alternative and mannan-binding lectin (MBL) pathways (Fig 2)[75]. The activator of the classical pathway is the immune complex formed by the antigen and antibody; it therefore works in the middle and late stages of infection. The activators of the alternative pathway are pathogenic microorganisms, such as bacteria, fungi and viruses, and that of the MBL pathway is the glycan structure on the surface of pathogenic microorganisms. Both the alternative and MBL pathways play an important role in anti-infection in the early stage of innate immunity.

Although the activators of these three pathways are different, a common terminal effect is achieved. The C5 convertase formed by the three pathways can cleave C5 into small fragments, C5a and C5b. C5b can bind to the cell surface and sequentially bind to C6, C7 and C8 to form a C5b678 complex and insert into the membrane. This complex will then interact with 12-15 C9 molecules to form the C5b6789n membrane attack complex (MAC) (Fig 2)[75]. MAC forms small pores in the cell membrane that allow small and soluble molecules (such as ions and water) to pass through the cell membrane freely, while still preventing larger molecules such as intracellular proteins from escaping from the cytoplasm. The consequence of these small pores formed by the MAC is the reduction of internal osmotic pressure and thus the dissolution of cells, bacteria and viruses[76]. On the other hand, complement can also play an important role in opsonisation. C3b, C4b and iC3b produced during the complement activation process can be fixed on the surface of bacteria or other particulate substances and can promote phagocytosis by binding to complement receptor 1 (CR1), complement receptor 3 (CR3) or complement receptor 4 (CR4) on the surface of phagocytes[33]. In addition, a variety of active fragments with inflammatory mediator effects are produced in the process of complement activation, such as C3a and C5a, which can bind to C3aR and C5aR

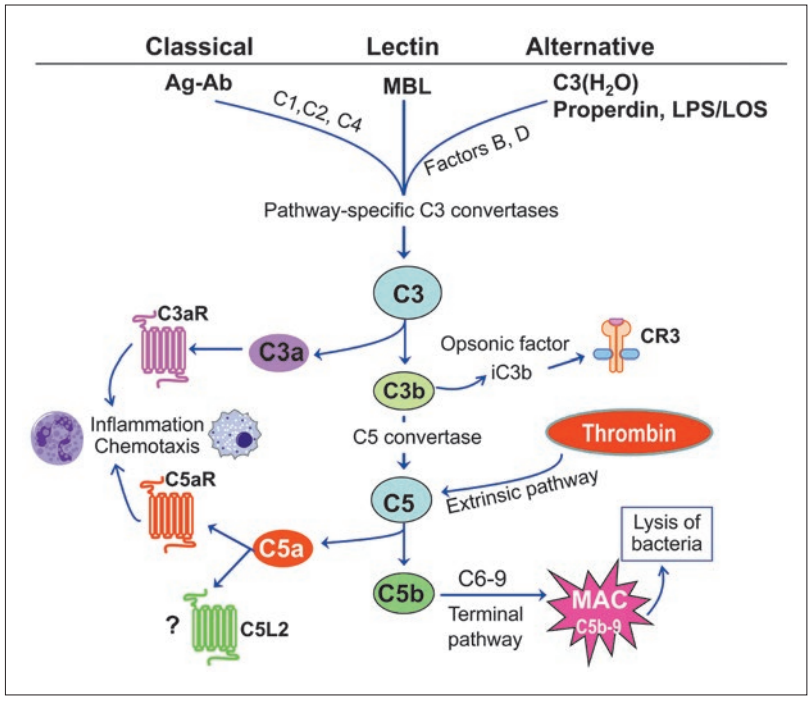

Fig 2 Three activation pathways of the complement system. (Reprinted from Krauss et al[75] with permission.)

respectively on the surface of mast cells or basophils to trigger cell degranulation and release histamine and other biologically active substances[77]. These substances can cause vasodilatation and increase capillary permeability, thereby mediating inflammation. C5a also has a strong chemotactic activity on neutrophils[78].

A large number of studies have shown that complement is closely related to periodontitis[79,80]. The study of a mouse periodontitis model induced by *P. gingivalis* found that the C5ar -/- mice exhibited milder periodontitis as well as certain resistance effects on periodontitis compared with wild-type mice, indicating that C5aR has a certain relationship with the occurrence of periodontitis[81,82]. In the gingivitis model, the progress of gingival inflammation was found to be related to C3 in the gingival crevicular fluid[83].

As an important part of innate immunity, the complement system not only plays a role in immune defence, but also cooperates with other PRRs of the host, such as interacting with TLRs[84]. As reported in previous literature, the fimbriae of *P. gingivalis* can activate TLR2, causing the release of downstream cyclic adenosine monophosphate (cAMP). In addition, *P. gingivalis* can secrete gingipains to convert C5 to C5a, which can activate the complement system by binding to C5aR and release cAMP. As a result, increased release of cAMP can activate the cAMP-dependent protein kinase A (PKA) in macrophages, which can inhibit glycogen synthase kinase 3β (GSK3β) to destroy the antibacterial effect of inducible nitric oxide synthase (iNOS) and allow periodontal pathogens to escape the host immune defence and avoid elimination. In the process of activating the C5aR-TLR2 signal pathway, IL-1β, IL-17, IL-6 and TNF-α will be produced[85]. These inflammatory factors aggravate the inflammation of the periodontal tissue and alveolar bone resorption. It is also reported that CR3, as a β2 integrin receptor, plays an important role in iC3b mediated phagocytosis, which could promote the migration of leukocytes to inflammatory sites and induce cytokine responses[86]. The fimbriae of *P. gingivalis* can interact with TLR2, while the activation of CR3 is promoted by the binding of CR3 with CD14 and TLR2, and the activated CR3 can directly interact with bacteria[87]. During this process, IL-1β, IL-6 and TNF-α can be released and cause the resorption and destruction of alveolar bone.

In summary, the complement system is involved in the occurrence of periodontal inflammation. *P. gingivalis* can induce periodontal microenvironment disorders through the complement system, regulate the interaction between complement and TLRs, undermine the host immunoregulatory capability and cause periodontal tissue damage.

Initiation of specific immune response

The role of innate immune cells is to detect pathogenic microorganisms, maintain the immune homeostasis of

host microorganisms and induce antibacterial defence mechanisms. Innate immune cells such as epithelial cells, fibroblasts, dendritic cells, macrophages and neutrophils are the first line of defence against the invasion of pathogens. Like antigen-presenting cells, if pathogenic microorganisms are not eliminated, activated macrophages and dendritic cells could process exogenous antigens or endogenous antigens into small polypeptides with immunogenicity, which can initiate an adaptive immune response[49,55].

Adaptive immune response and its role in periodontitis

Innate immune cells play a role in the protection of the periodontal tissues, but when acute infections occur and destruction of the periodontium is aggravated, these innate immune cells cannot effectively remove the pathogenic bacteria that constantly colonise and invade the periodontium. On one hand, innate immune cells can be used as antigen-presenting cells to participate in the induction of corresponding cellular and humoral immune responses by presenting antigens to initial T cells and B cells, respectively[14,88]. On the other hand, cytokines secreted by innate immune cells could participate in inducing an adaptive immune response. The synergistic effect of the innate immune response enhances the immune response against periodontal microorganisms[14,88]. Although an excessive immune response can eliminate periodontal pathogenic bacteria, damage to the periodontal tissues is also aggravated. The adaptive immune response therefore plays an important role in destruction of the periodontium.

Cells involved in the adaptive immune response

B cells

B lymphocytes are derived from the bone marrow and matured in the bone marrow. Studies have found that the infiltration of B lymphocytes increased in the diseased gingival tissue of patients with chronic periodontitis, suggesting that B cells are involved in the occurrence of periodontitis[89]. The main function of B cells is to differentiate into plasma cells and produce antibodies. Antibodies can bind to pathogens to prevent the infection of target cells. They can also carry out an opsonisation function when their Fc segment binds with Fc receptors on the surface of phagocytes, so that they can be recognised and phagocytised by phagocytes[90]. In addition, antibodies bind to pathogens to activate complement, and form an antigen-antibody-complement complex. The complement components can then bind to the corresponding complement receptors on the surface of phagocytes. As a result, the pathogen is swallowed by phagocytes and holes are punched in the membrane to lyse the microorganisms.

In addition to producing antibodies, B cells can play an antigen-presenting role[91]. B-cell receptor (BCR) on the surface of B cells can bind to soluble antigens, and after internalisation and processing, the antigens are presented to T cells. B cells can also participate in immunoregulation and the inflammatory response by contacting with other cells and producing cytokines.

T cells

T lymphocytes are derived from bone marrow and matured in the thymus. Depending on whether they express CD4 or CD8 molecules, matured T cells can be divided into CD4+ and CD8+ T cells. According to the different phenotypes and functions in the immune response, they can also be classified into helper T (Th) lymphocytes and regulatory T cells (Tregs) that are derived from CD4+ T cells, and cytotoxic T lymphocytes (CTLs) that are derived from CD8+ T cells.

Th cells can selectively differentiate into Th1 and Th2 cells in different microenvironments. Th1 cells can synthesise proinflammatory cytokines, such as IFN-γ, IL-2 and TNF-α, that can activate macrophages and induce inflammation. Th2 cells can synthesise IL-4, IL-5, IL-10, IL-13 and other anti-inflammatory factors to exert anti-inflammatory effects, which could inhibit the activation of macrophages. Studies have found that the expression of INF-γ and IL-2 increased in the early period of periodontal tissue infection, while the expression of IL-4 and IL-5 decreased[92]. Some studies believe that the differences in cytokines are related to the preferential activation of Th1 cells by local antigen-presenting cells, and have shown that Th1 cells preferentially express chemokine receptor 3 (CXCR3) and chemokine receptor 5 (CCR5) in order to recruit to the periodontium and exert their function[93,94]. Thus, the proinflammatory cytokines produced by Th1 cells participate in the destruction of periodontal tissue, while the anti-inflammatory cytokines secreted by Th2 cells aim to maintain the homeostasis and repair of the tissue during the inflammatory process. The imbalance between the proinflammatory cytokines produced by Th1 cells and the anti-inflammatory cytokines produced by Th2 cells leads to the occurrence of periodontitis. In addition, Th17 cells infiltrate the periodontal tissues of chronic periodontitis, which can secrete proinflamma-

tory cytokines such as IL-17 and IL-23. Th17 cells can produce antimicrobial peptides and recruit neutrophils to promote local inflammation[95]. They can also act on osteoblasts to promote the expression of receptor activator of nuclear factor-κB ligand (RANKL), thus inducing the maturation and differentiation of osteoclasts. After treatment, IL-17 expression decreased, suggesting that Th17 cells are the main participants secreting proinflammatory factor IL-17 in the pathological process of periodontitis[96]. Th17 cells can cause long-term inflammation, tissue damage and the pathogenesis of various autoimmune diseases[95].

Regulatory T cells have immunosuppressive functions and participate in the pathological process of the occurrence and development of various immune diseases. In the destruction period of chronic periodontitis, the Tregs in the damaged periodontal tissue decrease, as do the corresponding cytokines (TGF-β, IL-10). However, in the period of periodontium repair, the Tregs in the diseased gingiva increase and the corresponding cytokines are upregulated. The binding of glucocorticoid induced tumour necrosis factor receptor (GITR) ligand to the surface of Th1 and Th2 cells can provide costimulatory signals and promote the proliferation of Tregs. Using GITR antibody to block the inhibitory function of Tregs in vivo can aggravate the inflammation of periodontitis, suggesting that Tregs have an inhibitory effect on the pathogenesis of periodontitis[97].

After being stimulated by specific antigens, CD8+ T cells differentiate into cytotoxic T lymphocytes (CTLs) with the help of Th cells. The main function of CTLs is to specifically and directly kill the target cells by exerting cytotoxic effects through two mechanisms: secreting perforin, granzyme and lymphotoxin to directly kill target cells[98], and inducing apoptosis of target cells through the Fas/FasL pathway[99].

Mechanism of the adaptive immune response in periodontitis

Humoral immunity

B cells mediate the humoral immune response by synthesising and secreting antibodies. The response process of B cells can be divided into thymus-dependent antigen (TD-Ag) response and thymus-independent antigen (TI-Ag) response depending on the types of antigens. Bacterial polysaccharides, polysaccharide proteins and lipopolysaccharides are thymus-independent antigens that can activate B cells to produce antibodies without the assistance of Th cells and do not cause T cell responses.

According to the different ways of activating B cells and their structural characteristics, TI antigens can be divided into TI-1 and TI-2[100]. TI-1 antigens are mainly composed of bacterial cell wall with mitogen components. At high concentrations, the mitogen in the TI-1 antigens can bind to the mitogen receptor on the surface of B cells and activate polyclonal B cells non-specifically. Low dose TI-1 antigens only activate B cells that express specific BCR. B cells respond to low concentrations of TI-1 antigens, so that the body can produce specific antibodies before the thymus-dependent immune response occurs[101]. TI-2 antigens are mainly bacterial capsular polysaccharides and polymeric flagellins with many repetitive epitopes. TI-2 antigens stimulate CD5+ B cells by crosslinking BCR through its repetitive epitopes, and it is the density of TI-2 epitopes that determines the activation of B cells. If the density is too low, the crosslinking of BCR is not sufficient to activate B cells, but if it is too high, BCR will be over-crosslinked and the B cells will become resistant. Antibodies produced by CD5+ B cells against TI-2 antigens can play an opsonising role and promote the phagocytosis of pathogens by macrophages[102]. Additionally, the produced antibodies can neutralise bacterial exotoxins or form antigen–antibody complexes to activate the complement system through classical pathways, thereby initiating an immune response.

Cellular immunity

The immune response mediated by T lymphocytes is called the cellular immune response, which includes T cells that specifically recognise antigens, and then differentiate into effector T cells to exert effects.

The specific binding of T cell receptor (TCR) with the antigen-MHC complexes on the surface of the antigen presenting cells (APCs) is the first step in the specific activation of T cells[103]. According to their sources, the antigens are divided into exogenous and endogenous antigens. Exogenous antigens can be absorbed and processed by APCs, and expressed on the surface of APCs in the form of MHC-antigen complexes in order to be effectively presented to CD4+ Th cells for recognition. In the process of specific recognition, TCR must recognise the MHC molecules that form complexes with the antigens due to the limitation of MHC. The CD4 and CD8 molecules are helper receptors for T cells to recognise antigens. CD4 recognises and binds to MHC class II molecules on the surface of APCs, while CD8 recognises and binds to MHC class I molecules on the surface of APCs.

TCR and CD3 molecules can form a TCR-CD3 complex. TCR is responsible for recognising antigens, and CD3 is responsible for transmitting TCR-mediated extracellular signals into the cells[104]. The activation of initial T cells requires two different extracellular costimulation signals. The first comes from the antigens, and is transmitted into the cells by CD3 after the MHC-antigen complexes interact with the TCR, and the second is composed of the microbial products or costimulatory molecules provided by the APCs[105].

Cytokines can also play an important role in the interaction between T cells and APCs, and the process of T cell differentiation. APCs present exogenous antigens through the MHC class II pathway to stimulate the activation of CD4+ T cells and differentiate into Th cells. Th0 cells differentiate into Th1 cells with the involvement of IL-12, and after activation, IL-2 and IFN-γ are secreted to promote Th1-type cellular immune response[106]. IFN-γ can activate and recruit macrophages and enhance the anti-infection function, while IL-2 (T cell growth factor) can activate T cells, promote the activation and proliferation of CTLs and Th1 cells, and thus amplify the immune effect. Th0 cells differentiate into Th2 cells with the involvement of IL-4, and secrete cytokines such as IL-4, IL-5, IL-10 and IL-13 after activation[107]. These cytokines not only promote B cell proliferation and activation, but also promote the humoral immune response. APCs present exogenous antigens to stimulate the activation of CD8+ T cells through the MHC I pathway and differentiate into CTLs. T cell differentiation enables activated T cells to exert their functions of secreting cytokines or killing cells.

Conclusion

When pathogens invade the periodontium, it enters the stage of innate immune response. An excessive innate immune response causes inflammation, which in turn will lead to the destruction of the periodontium and the initiation of the adaptive immune response stage. The clinical medication currently used to treat periodontitis cannot regulate the interaction between the plaque microorganisms and the host immune system. Furthermore, long-term use of antibiotics risks the development of drug-resistant strains. Therefore, from an immunological point of view, screening potential therapeutic targets based on the key molecules in the innate and adaptive immunity of periodontal disease is of great significance for the prevention and treatment of periodontitis, and is also one of the future research directions. The present study summarised the cells and mechanisms that are involved in the innate and adaptive immune responses during the development of periodontitis. Nevertheless, there are still several issues to be addressed, including how to screen and regulate the key molecules precisely and how to prevent the destruction of the periodontium in patients who are susceptible to periodontitis by immunoregulation. These issues indicate the urgent need for further studies of the immunoregulation of periodontitis treatment.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

All authors contributed to the writing of the manuscript. Drs Xiao Wei XU and Xia LIU collected the literature and prepared the manuscript; Prof Hong Chen SUN and Dr Ce SHI designed and revised the manuscript.

(Received Oct 31, 2020; accepted Dec 22, 2020)

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