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REVIEW

Roles of Pyroptosis in the Progression of Pulpitis and Apical Periodontitis

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Abstract: Pyroptosis is a type of programmed cell death that induces proinflammatory cytokine release and is closely related to inflammatory diseases. Pulpitis and apical periodontitis are common inflammatory diseases that lead to alveolar bone destruction and tooth loss. Recent studies have revealed that pyroptosis is crucial in the progression of pulpitis and apical periodontitis, which involves various cell types and leads to different results. Odontoblasts are located at the periphery of dental pulp tissue and are susceptible to various irritants, the lysates from odontoblasts act as alerts and induce immune reactions in the inner pulp after pyroptosis. The expression levels of inflammasomes in dental pulp cells (DPCs) change with the progression of pulpitis, which may serve as a diagnostic marker of pulpitis. Periodontal ligament fibroblasts (PDLFs) undergo pyroptosis when stimulated by bacterial infection or cyclic stretch and are associated with both infection-induced and trauma-induced apical periodontitis. Immune cells can undergo pyroptosis directly after infection or are influenced by the pyroptotic secretome of other cells, which changes their composition. In this review, we briefly introduce the location and function of different cell types involved in the progression of pulpitis and apical periodontitis, summarize the roles of pyroptosis in different cells, and discuss the effects of drugs targeting pyroptosis in the treatment of pulpitis and apical periodontitis.

Keywords: pyroptosis, programmed cell death, proinflammatory cytokines, pulpitis, apical periodontitis

Introduction

Pyroptosis is a type of programmed cell death. Similar to apoptosis, pyroptosis is induced in most cases by the activation of caspase, a type of aspartate-specific cysteine proteases. After activation, caspases cleave the executioner of pyroptosis, gasdermin family proteins, which contain an autoinhibitory C- terminus and an N-terminus with a pore-forming effect. However, unlike apoptosis, pyroptosis results in plasma membrane rupture and release of proinflammatory cytokines. Therefore, pyroptosis is a proinflammatory type of cell death that plays an important role in immune defense. When microbes enter the cytoplasm, they are recognized by intracellular pattern recognition receptors (PRRs), a type of receptor that directly recognize some molecules, and then pyroptosis is induced. Bacteria are subsequently released into the extracellular space after cell lysis and are eaten by phagocytes.[1] However, pyroptosis is a double-edged sword. During severe infection, many cells simultaneously undergo pyroptosis and cause a "cytokine storm", which results in elevated cytokine levels, leads to acute systemic inflammatory symptoms and is life-threatening.[2] In addition, in some cases of chronic inflammation, persistent infection sustainably induces pyroptosis and the release of proinflammatory cytokines, which ultimately results in tissue destruction. Furthermore, some molecules involved in pyroptosis are related

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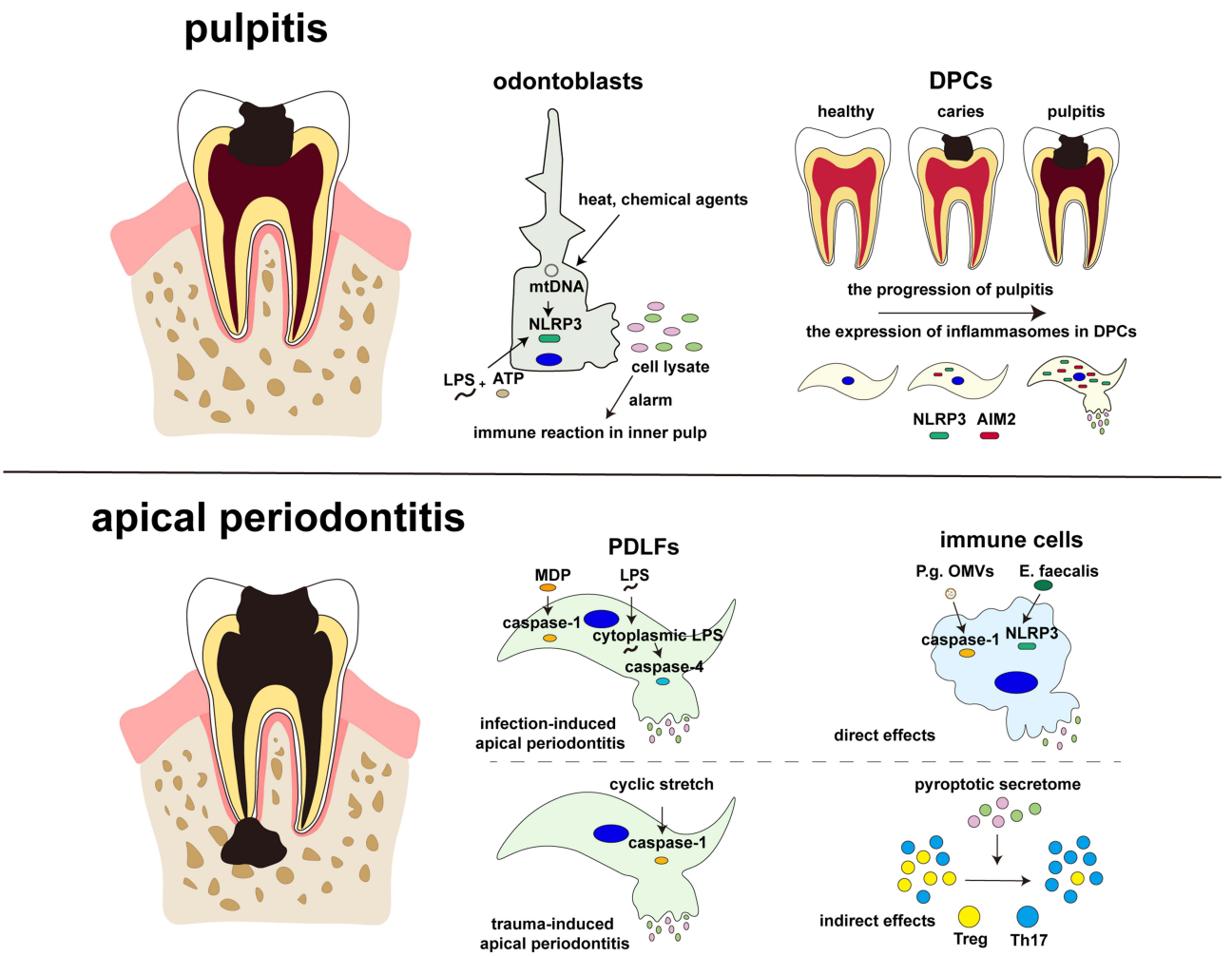
Graphical Abstract



to the initiation and progression of inflammatory diseases, such as periodontitis.[3–5] Therefore, it is important to discuss the roles of pyroptosis in inflammatory diseases.

Pulpitis and apical periodontitis are the most common oral inflammatory diseases, and are closely related to pyroptosis. The dental pulp is located in a separate space surrounded by hard tissue, and connects to the outer space through the apical foramen. Therefore, bacterial infection in the dental pulp tissue is difficult to eliminate and often leads to irreversible pulpitis. During the progression of irreversible pulpitis, proinflammatory cytokines play an important role.[6] Pyroptosis is a type of lytic cell death, which induces the release of numerous proinflammatory cytokines and is closely related to pulpitis. Apical periodontitis is typically induced by caries and pulpitis, and several environmental factors, such as stress, health status and smoking, also influence the progression of apical periodontitis.[7–9] Following pulp necrosis, intracanal pathogens invade the extraradicular space and induce inflammation in periapical tissue. During the progression of apical periodontitis, immunoreactions, such as pyroptosis, have both protective and destructive effects.[10] The immune response eliminate microbial infection and induces resorption of alveolar bone. Therefore, it is vital to elucidate the roles of pyroptosis in pulpitis and apical periodontitis.

Dental pulp tissue and periapical tissues contain various cell types. Each cell type is located in a specific niche and has unique functions. This review aims to discuss the roles of pyroptosis in different cell types and the effects of drugs that target pyroptosis in pulpitis and apical periodontitis.

Different Signaling Pathways Involved in Pyroptosis

Typically, pyroptosis can be classified into canonical pyroptosis and noncanonical pyroptosis. Canonical pyroptosis is induced by caspase-1 and noncanonical pyroptosis is mediated by mouse caspase-11 (human caspase-4/5). Recently, novel pyroptosis pathways, such as the apoptotic caspase-induced pyroptosis pathway and the caspase-independent pyroptosis pathway, have been identified (Figure 1).

Canonical Pyroptosis Pathway

The canonical pyroptosis pathway is mediated by the canonical inflammasome formation and caspase-1 activation. All types of canonical inflammasomes contain cytoplasmic PRRs and pro-caspase-1, and some inflammasomes, such as NLRP3, AIM2, and pyrin inflammasomes, also require apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) to act as an adaptor protein to link PRRs to pro-caspase-1.[11] When PRRs detect stimuli, they induce inflammasome formation. Subsequently, pro-caspase-1 is cleaved and activated caspase-1 hydrolyses pro-IL-1β and pro-IL-18 into their mature forms. Moreover, activated caspase-1 also causes the cleavage of gasdermin D (GSDMD), after which the GSDMD NT fragment, which has pore-forming activity, is liberated and forms pores in the plasma membrane.[12] Finally, mature IL-1β and IL-18, which are cleaved by caspase-1, are released from the pores formed by GSDMD NT into the extracellular space and induce inflammation.

Noncanonical Pyroptosis Pathway

In contrast to caspase-1 in canonical pyroptosis, caspase-4/5/11 binds to cytoplasmic lipopolysaccharide (LPS) and cleaves GSDMD directly in noncanonical pyroptosis.[13,14] However, the binding process can be promoted when guanylate-binding proteins (GBPs) are present.[15,16] After binding to LPS, caspase-4 is cleaved at Asp 289 (Asp 285 of caspase-11), producing active P31 fragments, leading to noncanonical pyroptosis.[17] Like caspase-1, caspase-4/5/11 can cleave GSDMD and induce pyroptosis after activation. However, activated caspase-4/5/11 cannot cleave pro-IL-1β into the mature form, and only caspase-4 and −5, not caspase-11, have the ability to cleave pro-IL-18.[18]

Apoptotic Caspase-Induced Pyroptosis Pathways

Traditionally, members of the caspase protein family have been divided into inflammatory caspases (caspase-1/4/5/11) and apoptotic caspases (caspase-3/6/7/8/9/10).[19,20] It was previously speculated that only inflammatory caspases induce pyroptosis. However, recent studies have shown that apoptotic caspases also induce pyroptosis in some cases. Caspase-3, an apoptotic caspase, cleaves gasdermin E (GSDME) and induces pyroptosis in certain GSDME-expressing cancer cells.[21] Moreover, Yersinia outer protein J (YopJ) of *Yersinia* induces the cleavage of another apoptotic caspase, caspase-8, by inhibiting transforming growth factor-β-activated kinase 1 (TAK1) expression, leading to the release of GSDMD NT and pyroptosis.[22] Caspase-8 also cleaves gasdermin C (GSDMC) and switches the death mode of tumor cells from apoptosis to pyroptosis with the help of programmed death ligand 1 (PD-L1).[23]

Caspase-Independent Pyroptosis Pathways

In most cases, pyroptosis relies on caspase activation; however, there are also several caspase-independent pyroptosis pathways. Granzymes released from natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) are delivered to target cells by perforin, cleave gasdermin family proteins, and induce pyroptosis independent of caspases.[24,25] In addition, a recent study revealed that S-palmitoylation of intact GSDMD induces pyroptosis with the help of reactive oxygen species (ROS) rather than caspases.[26] Coincidentally, another study reported that poly(ADP-ribosyl)ation (PARylation) of full-length GSDME is sufficient to induce pyroptosis without caspase.[27]

Roles of Pyroptosis in Pulpitis

Dental pulp is the unique soft tissue in the tooth, that contains a variety of cells, such as odontoblasts, fibroblasts, stem cells, endothelial cells, and glial cells.[28] These cells are located in different niches and perform various functions. In this section, we discuss the roles of pyroptosis in different cell types during the progression of pulpitis (Figure 2).

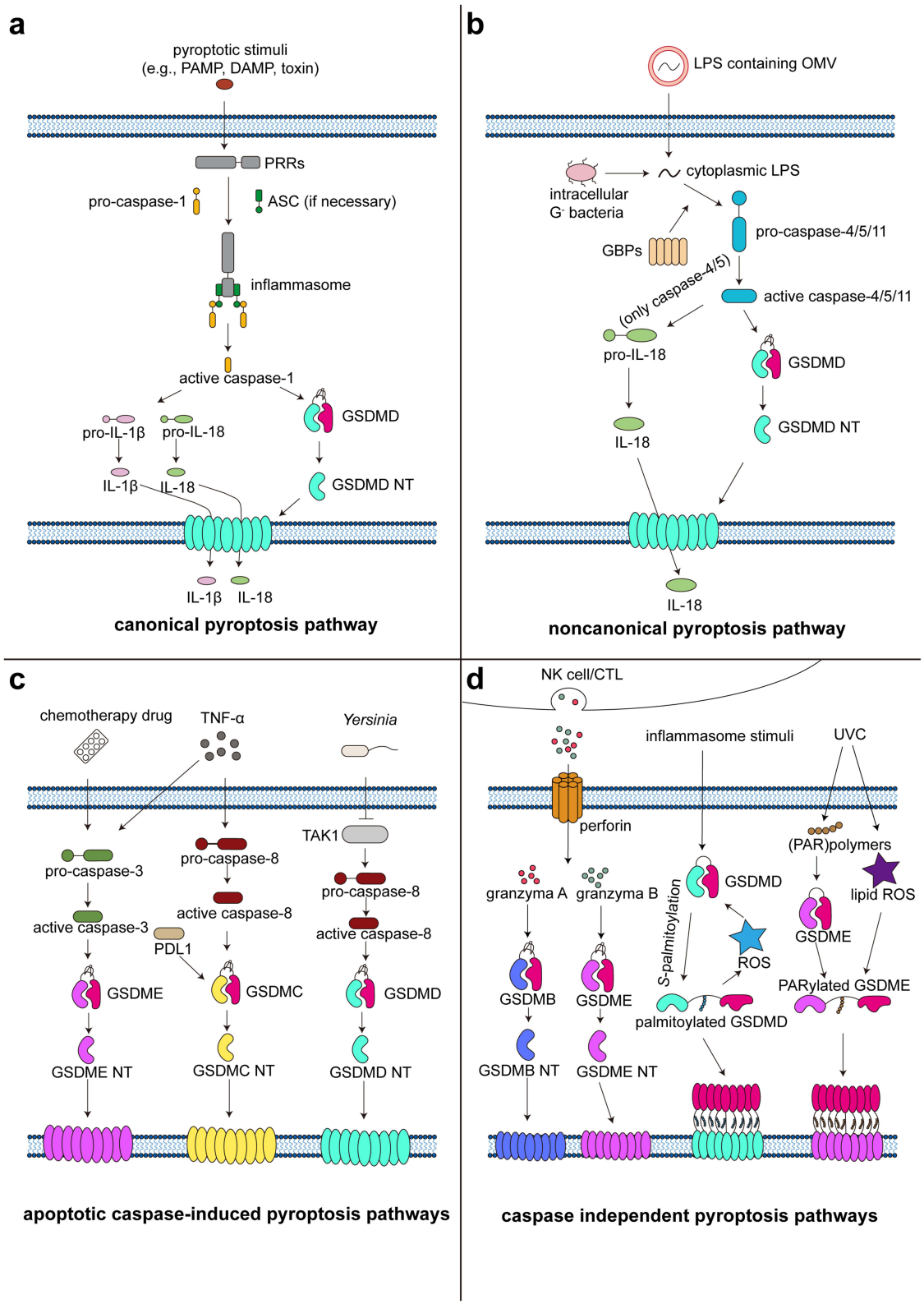


Figure 1 Schematic diagrams of different pyroptosis pathways. (**a**) In the canonical pyroptosis pathway, pyroptotic stimuli induce inflammasome formation and caspase-1 activation, leading to GSDMD cleavage and proinflammatory cytokines release. (**b**) Caspase-4/5/11 bind to cytoplasmic LPS directly and result in noncanonical pyroptosis. This process can be promoted by GBPs. (**c**) In some cases, apoptotic caspases, such as caspase-3 and caspase-8, also induce the cleavage of gasdermin family proteins and pyroptosis. (**d**) Granzymes derived from NK cells and CTLs induce caspase-independent pyroptosis in target cells. In addition, the S-palmitoylation and PARylation of gasdermin family proteins can also cause pyroptosis in the absence of caspases.

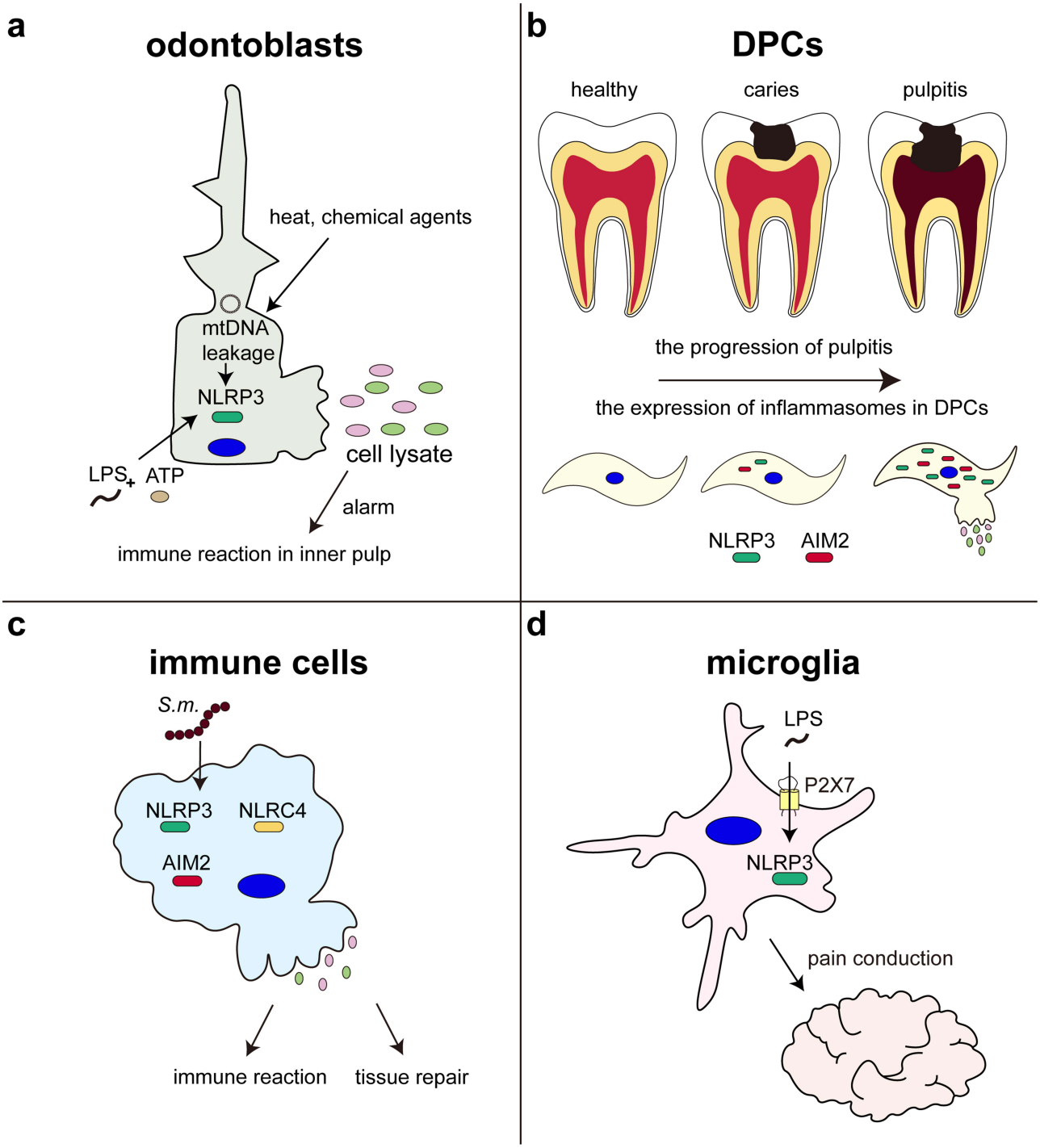


Figure 2 Roles of pyroptosis in pulpitis. (**a**) Odontoblasts are located at the periphery of the dental pulp tissue and form a barrier to protect the dental pulp from infection. Odontoblasts are susceptible to various irritants and undergo pyroptosis. After pyroptosis, the lysates from odontoblasts act as an alarm and induce immune reactions in inner pulp. (**b**) DPCs are the major cell type of dental pulp tissue and respond to various oral microbes. The expression of inflammasomes, such as NLRP3 and AIM2, are related to the progression of pulpitis. (**c**) Immune cells react to the oral microbiome and undergo pyroptosis, which depends on NLRP3, NLRC4 and AIM2. The release of proinflammatory cytokines from pyroptotic immune cells leads to immune reactions and tissue repair processes in the dental pulp. (d) Microglia play important roles in pain conduction. LPS enters microglia via the P2X7 receptor and activates the NLRP3 inflammasome, which is vital for pain conduction during pulpitis.

In Vitro Studies

Odontoblasts

Odontoblasts are located at the periphery of dental pulp tissue and constitute a barrier that protects the inner pulp. Owing to their special location, odontoblasts are the first line of defense against various irritants. Recent studies have shown that

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a variety of pyroptosis-related PRRs, including AIM2,[29,30] NLRP3,[31–33] and NLRP6,[34] are expressed in odontoblasts, suggesting that pyroptosis may play a crucial role in the immune defense of odontoblasts.

Bacterial infection is the most common cause of pulpitis, and several virulence factors, such as LPS and ATP, are involved in the progression of pulpitis. It has been showed that LPS plus ATP activates the NLRP3 inflammasome and leads to pyroptosis in odontoblasts, which subsequently induces proinflammatory cytokines release.[35] In addition to infection, pulpitis can also be induced by physical and chemical stimulation. Odontoblast, which has a process close to the tooth surface, is susceptible to external stimuli, such as heat and chemical agents, leading to the release of mitochondrial DNA (mtDNA).[36,37] A previous study revealed that mtDNA induces NLRP3-mediated canonical pyroptosis in odontoblasts.[38] Taken together, these studies showed that odontoblasts react to different stimuli and undergo NLRP3-mediated canonical pyroptosis, which results in the secretion of proinflammatory cytokines into the surrounding environment.

After pyroptosis, the cell lysates and cytokines from odontoblasts influence inner pulp cells. It has been reported that odontoblast cell lysates induce the proliferation and migration of dental pulp cells (DPCs) and lead to immune reactions in immune cells.[39] Therefore, odontoblasts, which are located at the periphery of dental pulp tissue, act as sentries to warn inner cells when facing different irritants, and the cell lysates released by odontoblasts act as signals during this process.

Dental Pulp Cells

Fibroblasts in dental pulp tissue are called DPCs. As the major cell type in the dental pulp tissue, DPCs have crucial effects on the progression of pulpitis. The DPCs react to various stimuli. *Porphyromonas gingivalis* (*P.g.)* and *Fusobacterium nucleatum* (*F.n.)* are common pathogens leading to pulpitis.[40] A previous study used *P.g*. or *F*.n. or their combination with an additional of ATP to induce pyroptosis in DPCs, showing that NLRP3, AIM2 and IL-1β were upregulated in all of the infection groups. Moreover, bacterial infection induced the dysregulation of some inflammasome regulatory proteins, such as CARD16, suggesting that the proinflammatory effects of pathogens may be due to the dysregulation of inflammasomes and IL-1β.[41] In addition, some bacterial virulence factors, such as LPS, muramyl dipeptide (MDP) and LTA, also activate NLRP3 and induce pyroptosis in DPCs.[32,42,43] After inflammasome formation and caspase activation, mature IL-1β is subsequently released, which shows proinflammatory effect. Knockdown of *NLRP3* or *AIM2* expression in DPCs significantly inhibits the secretion of IL-1β and relieves local inflammation,[43] suggesting that inflammasomes and pyroptosis in DPCs play crucial roles in the release of proinflammatory cytokines.

To further elucidate the role of DPC pyroptosis in the progression of pulpitis, several studies have investigated the level of pyroptosis in different stages of pulpitis. In healthy pulp, NLRP3 is primarily expressed in the odontoblastic layer. In moderate caries, which means that bacteria invade the dentin, NLRP3 expression is slightly increased and detected in DPCs. After pulp exposure, the expression of NLRP3 is significantly increased, especially in DPCs close to the site of bacterial infection.[32] In addition, NLRP3 expression also increases during the transformation from reversible pulpitis to irreversible pulpitis.[33] These studies suggest that the pyroptosis of DPCs may be involved in the progression from caries to reversible pulpitis and ultimately to irreversible pulpitis.

Immune Cells

Healthy dental pulp tissue acts as an immune surveillance system with only a few immune cells.[28] However, the number of immune cells increases significantly after bacterial infection.[44] The reactions of immune cells to common pathogens, such as *Shigella flexneri* and *Salmonella typhimurium*, have been extensively studied, but the oral cavity has a unique microbiome. For example, *Streptococcus mutans* (*S.m.)* is a pathogen that causes caries and is mainly detected in the oral cavity. A study investigating the reactions of immune cells after *S.m*. infection showed that the release of IL-1β by THP-1 cells increased. However, the release of IL-1β is significantly reduced when *AIM2, NLRP3* or *NLRC4* expression was knocked down, demonstrating that this process relies on canonical pyroptosis and inflammasomes.[45]

Pyroptosis and the release of proinflammatory cytokines from immune cells are double-edged swords. On the one hand, the pyroptotic secretome leads to local inflammation and tissue destruction. However, some cytokines accelerate DPC differentiation and wound healing.[44] A study showed that IL-1β released from THP-1 cells affects odontoblastic differentiation of DPCs, which depends on the NLRP3 inflammasome,[39] suggesting that proinflammatory cytokines released by pyroptotic immune cells can promote tissue repair.

Microglia

Microglia are local macrophages in the central nervous system that play important roles in pain conduction. Pulpitis causes severe inflammatory pain due to the high pressure in the pulp chamber. Pulpitis pain is transmitted along the trigeminal nerve to the trigeminal ganglion, then to the dorsal horn of the medulla, and finally to the brain.[46] However, the underlying mechanism and regulatory method of pulpitis pain conduction are unclear. A recent study revealed that the degree of pulpitis pain is positively correlated with the expression of NLRP3 and caspase-1 in the trigeminal ganglion and dorsal horn of the medulla, suggesting that canonical pyroptosis is involved in pain conduction during pulpitis. The study also revealed that the ligand-gated ion channel P2X7 plays an important role in the pyroptosis of microglia, which is crucial in pain conduction.[47] Therefore, inhibiting the activation of the NLRP3 inflammasome and canonical pyroptosis may be a promising treatment strategy for alleviating the inflammatory pain induced by pulpitis.

In Vivo Studies

To date, in vivo studies regarding the effects of pyroptosis in pulpitis are limited. Wang et al established an experimental pulpitis model through pulp exposure in rats and reported that AIM2, a type of inflammasome related to canonical pyroptosis, is detected only in the odontoblast layer in healthy pulp. In contrast, the expression of AIM2 is significantly upregulated in inflammatory cells and DPCs after pulp exposure.[29] Another study used a rat experimental pulpitis model to investigate the role of canonical pyroptosis in pain conduction, suggesting that pulpitis pain is related to the expression of NLRP3 and caspase-1 in the trigeminal ganglion and medullary dorsal horn.[47]

Drugs That Target Pyroptosis in Pulpitis

Although pyroptosis is an important process in immune defense, it also causes local inflammation. Bacterial infection in dental pulp is difficult to eliminate, resulting in persistent infection and extensive pyroptosis. Therefore, several studies have investigated the effects of some drugs that target pyroptosis in the treatment of pulpitis. Considering that NLRP3 and caspase-1 are key molecules in pyroptosis, some inhibitors of NLRP3 and caspase-1 have been investigated for their ability to treat inflammatory diseases. The use of NLRP3 inhibitor MCC950 and caspase-1 inhibitor Ac-YVAD-CHO has been shown to reduce the release of proinflammatory cytokines, such as IL-1β, in pulpitis.[32,39] In addition, the expression of some noncoding RNAs, such as microRNA-223 and microRNA-22, also regulates the formation of inflammasomes during the progression of pulpitis.[31,33] Dimethyl fumarate (DMF) is an FDA-approved drug that is typically used for the treatment of multiple sclerosis. Previous studies have shown that DMF treatment blocks pyroptosis in DPCs and macrophages, suggesting that this drug might be used in the treatment of pulpitis.[48,49]

An unavoidable problem in the treatment of pulpitis is that the dental pulp is surrounded by hard tissue and communicates to the outside space only through the apical foramen. Therefore, local drug delivery is almost inaccessible when hard tissue is intact. However, blocking pyroptosis may be a treatment strategy in cases where the pulp is exposed. For example, local administration of drugs that inhibit pyroptosis might relieve local inflammation and prevent irreversible pulpitis during vital pulp therapy (VPT). Considering that the initiation and progression of pulpitis is a prolonged process, controlled release of drugs may be needed. A recent study showed that composite hydrogels are ideal delivery materials that have desirable biological properties for VPT.[50] Therefore, we expect that drugs that target pyroptosis together with hydrogels may be used as potential pulp capping agents in VPT.

Roles of Pyroptosis in Apical Periodontitis

Apical periodontitis usually results from caries and pulp necrosis. Various cell types are involved in the progression of apical periodontitis. For example, periodontal ligament fibroblasts (PDLFs) constitute the periapical ligament, immune cells contribute to immune defense against pathogens, and osteoblasts and osteoclasts participate in the regulation of alveolar bone homeostasis (Figure 3).

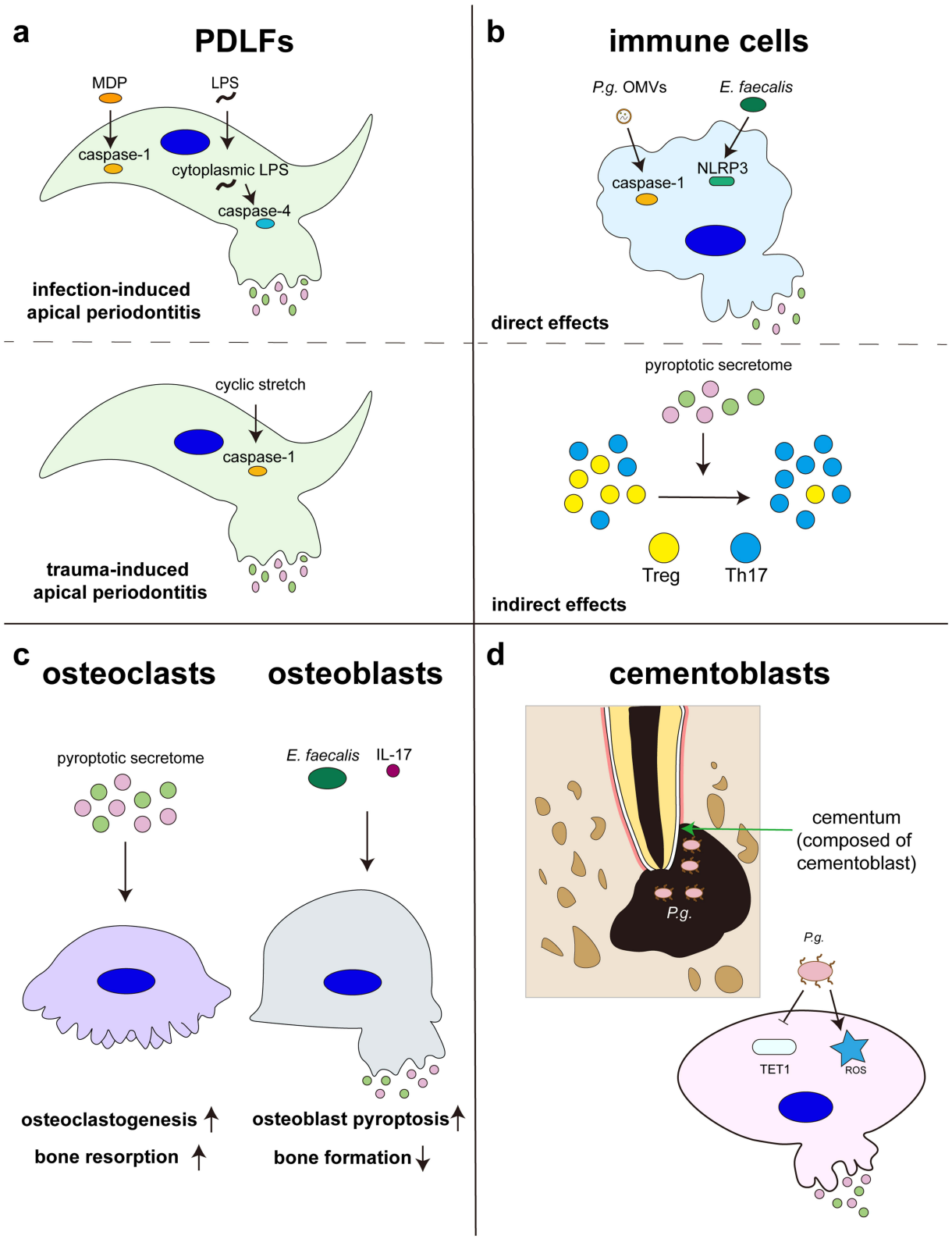

Figure 3 Roles of pyroptosis in apical periodontitis. (**a**) PDLFs undergo pyroptosis when stimulated by bacterial infection or cyclic stretch and are associated with both infection-induced and trauma-induced apical periodontitis. (**b**) Some intracanal bacteria, such as *E. faecalis* and *P. gingivalis*, induce pyroptosis and proinflammatory cytokines release in immune cells. Immune cells are also influenced by the pyroptotic secretome of other cells. Then, the composition and proportions of immune cells may be changed. (**c**) Bone metabolism is mediated by osteoblasts and osteoclasts. The pyroptotic secretome, which includes IL-1β and HMGB1, promotes osteoclastogenesis and bone resorption. In refractory apical periodontitis, the pyroptosis of osteoblasts might account for delayed healing. (**d**) Cementoblasts are located on the root surface and respond actively to microbial infection. After invading extra-radicular space, *(**P**)g*. infection induces pyroptosis and the release of proinflammatory cytokines in cementoblasts.

In Vitro Studies

Periodontal Ligament Fibroblasts

PDLFs are the major cell type in the periodontal ligament (PDL). In a healthy state, the PDL forms a barrier between the intracanal space and periapical tissue, preventing bacteria from invading the outside space. Therefore, the immune response of PDLFs is crucial in the progression of infection-induced apical periodontitis. *P. gingivalis* is commonly detected in contaminated root canals.[51] *P.g*. LPS has been shown to induce pyroptosis in PDLFs.[52] Moreover, another virulence factor, MDP, also induces NLRP3-mediated canonical pyroptosis in PDLFs.[53] In addition to being involved in canonical pyroptosis, PDLFs also respond to stimuli of noncanonical pyroptosis, such as cytoplasmic LPS.[48,52] These studies suggested that both canonical and noncanonical pyroptosis are crucial in apical periodontitis.

In addition to bacterial infection, acute and chronic dental trauma also leads to apical periodontitis. The PDL is sensitive to mechanical stimulation, and PDLFs are crucial in the sensing of biting force applied to the tooth. A previous study revealed that cyclic stretch activates GSDMD and induces pyroptosis in PDLFs, resulting in maturation and secretion of IL-1β and IL-18. In addition, inhibition of caspase-1 blocks cyclic stretch-induced pyroptosis,[54] suggesting that canonical pyroptosis in PDLFs is also related to trauma-induced apical periodontitis.

Immune Cells

When bacteria invade the periapical tissue, immune cells begin to gather around the periapical lesion and react actively to the bacterial infection. *Enterococcus faecalis* (*E. faecalis*) is a common intracanal bacterium. Recently, it was reported that *E. faecalis* infection can induce pyroptosis in both human and mouse macrophages.[55,56] However, this process is blocked by the inhibition of either NLRP3 or caspase-1 activity, suggesting that the canonical pyroptosis pathway plays important roles in this process.[55] In addition to *E. faecalis, P. gingivalis*, another common intracanal microbe, is also related to pyroptosis. *P.g*. OMVs induce pyroptotic cell death and the release of proinflammatory cytokines in immune cells, which also depends on caspase-1.[57]

Immune cells not only respond directly to bacterial infection but are also influenced by the pyroptotic secretome released by other cells. The pyroptotic secretome, which includes cytokines and chemokines, can influence immune cell composition and proportions to exert proinflammatory or anti-inflammatory effects. Thus, immune cells indirectly participate in apical periodontitis. For example, the NLRP3 inflammasome in dendritic cells (DCs) is activated under *P. gingivalis* stimulation, after which activated DCs affect the balance between regulatory T cells (Tregs) and T helper 17 cells, thus determining the direction of the inflammatory response.[58] Moreover, stem cells from the apical papilla (SCAPs) undergo NLRP3-mediated canonical pyroptosis when stimulated with LPS in addition to ATP, and the inflammatory cytokines released from SCAPs affect the stability of Treg cells in periapical lesions.[59]

Osteoclasts

Apical periodontitis can induce alveolar bone resorption and osteoclasts play an important role in bone destruction. Both canonical and noncanonical pyroptosis pathways induce the release of proinflammatory cytokines into the extracellular space. Some cytokines, such as IL-1β and HMGB1, promote the differentiation and maturation of osteoclasts.[60,61] In this way, pyroptosis is related to osteoclasts and bone resorption. Moreover, several pyroptosis-related genes participate in the regulation of osteoclastogenesis. Compared with those from wild-type (WT) mice, monocytes from *Nlrp3*$^{-/-}$ mice exhibit impaired osteoclastogenesis ability.[59] Similarly, osteoclasts from *Gsdmd*$^{-/-}$ mice presented increased lysosome numbers and enhanced bone resorption activity compared to those from WT mice.[62]

Osteoblasts

Root canal treatment reduces the amount of intracanal bacteria and leads to the healing of bone defects. However, persistent bacterial infection may delay alveolar bone healing. Osteoblasts mediate the healing process of bone destruction; therefore, investigating the function of osteoblasts in refractory apical periodontitis is crucial. *E. faecalis* is commonly associated with persistent root canal infection and treatment failure. Ran et al reported that *E. faecalis* infection activated the NLRP3 inflammasome and induced canonical pyroptosis in osteoblasts.[63] This study provides a possible explanation for *E. faecalis*-induced persistent periapical lesions. IL-17 is a proinflammatory cytokine that plays an important role in the progression of apical periodontitis.[64,65] Recently, IL-17 stimulation was shown to induce the activation of NLRP3 inflammasome and

canonical pyroptosis in osteoblasts,[66] which may account for the delayed healing of bone defects. Taken together, these studies revealed that pyroptosis of osteoblasts may be a reason for refractory apical periodontitis.

Cementoblasts

The cementum is the hard tissue that covers the root surface. Cementoblasts, the major cells in the cementum, can secrete collagen and promote cementum formation. When intracanal bacteria invade periapical tissue, they induce immunoreactions in adjacent cells, such as cementoblasts.[67] It has been reported that *P. gingivalis* infection induces caspase-11 activation and noncanonical pyroptosis of cementoblasts and the release of proinflammatory cytokines, including IL-1β and IL-18. The underlying mechanism is associated with decreased expression of tet methylcytosine dioxygenase 1 (TET1) and increased mitochondrial ROS.[68,69] Considering that proinflammatory cytokines released by pyroptotic cells promote local inflammation, extraradicular bacteria, such as *P.g*., may facilitate the process of apical periodontitis by inducing pyroptosis in cementoblasts.

In Vivo Studies

During the progression of apical periodontitis, different cell types cooperate with one another and work in concert; therefore, some studies have investigated the roles of pyroptosis in apical periodontitis through animal models. Pulp exposure is commonly used to establish an experimental apical periodontitis model. In a rat pulp exposure model, the expression of NLRP3, caspase-1, and caspase-11 was upregulated in periapical lesions, and the level of pyroptosis was positively correlated with the level of inflammatory infiltration.[70,71] Moreover, compared with WT mice, *Nlrp3*$^{-/-}$ mice showed reduced periapical bone destruction after pulp exposure, suggesting an important role of pyroptosis in apical periodontitis.[59]

Estrogen influences bone metabolism and plays a crucial role in apical periodontitis, but the underlying mechanisms remain unclear. One study revealed that the expression of NLRP3 and caspase-1 is elevated in the periapical lesions of postmenopausal patients compared to that in premenopausal patients. In addition, the levels of NLRP3 and caspase-1 are significantly higher in ovariectomized (OVX) rats than in sham-surgery rats after pulp exposure,[72] indicating that pyroptosis also plays an important role in estrogen-mediated apical periodontitis.

Drugs That Target Pyroptosis in Apical Periodontitis

Considering that pyroptosis plays an important role in apical periodontitis, whether some drugs that target pyroptosis can be a treatment method for apical periodontitis has received widespread attention. MicroRNAs can regulate gene expression profile. Some microRNA mimics and inhibitors are promising drugs for the treatment of inflammatory diseases. Previous studies have reported that microRNA-590-3p and microRNA-155 can regulate pyroptosis in apical periodontitis, demonstrating that these drugs might be potential treatment options.[73,74] Furthermore, some caspase inhibitors, such as VX765 and dioscin, are also used to treat apical periodontitis and have positive effects.[75,76] DMF is a methyl ester of fumaric acid, and our previous study revealed that DMF attenuates pyroptosis in PDLFs by targeting GSDMD.[48] DMF also inhibits osteoclastogenesis by blocking ROS signaling.[77] Therefore, this drug may be a potential intracanal medication agent that alleviates inflammation by inhibiting pyroptosis and reducing bone destruction by blocking ROS signaling.

Limitations and Future Perspectives

Effects of Noncanonical Pyroptosis in Pulpitis and Apical Periodontitis

Canonical and noncanonical pyroptosis pathways are the two most extensively studied pathways and are widely related to various diseases. To date, studies on the effects of pyroptosis on pulpitis and apical periodontitis models have focused mainly on the canonical pyroptosis pathway, and few studies have investigated the roles of noncanonical pyroptosis (Table 1 and Table 2). However, noncanonical pyroptosis is crucial for the progression of many inflammatory diseases.[78–80] Moreover, fibroblasts are the main cell components in dental pulp tissue and periapical lesions. Previous studies have shown that different types of dental fibroblasts, such as DPCs, PDLFs and periodontal ligament stem cells, are more sensitive to noncanonical pyroptosis than to canonical pyroptosis,[48,81] suggesting that noncanonical pyroptosis is important in the development of pulpitis and apical periodontitis. However, their effects have been neglected in previous studies.

Table 1 Studies Regarding Pyroptosis in Pulpitis

In vitro/in vivo	Pyroptosis Pathway	Inflammasomes Involved	Study Materials	Stimuli	References
In vitro	Canonical	AIM2	Clinical pulpitis samples, human DPCs	IFN-γ, poly(dA:dT)	[30]
In vitro	Canonical	AIM2	Human DPCs	IFN-γ, poly(dA:dT)	[87]
In vitro	Canonical	NLRP3	Human DPCs	LPS, ATP	[43]
In vitro	Canonical	NLRP3	Human DPCs	LPS	[88]
In vitro	Canonical	NLRP3	Human DPCs	MDP	[42]
In vitro	Canonical	NLRP3	Clinical pulpitis samples, human DPCs	LPS plus ATP, hypoxia	[33]
In vitro	Canonical	NLRP3	Clinical pulpitis Samples, human DPCs	LPS plus ATP	[31]
In vitro	Canonical	NLRP3	Clinical pulpitis samples, human DPCs	LPS plus ATP	[89]
In vitro	Canonical	NLRP3	Clinical pulpitis samples, human DPCs, THP-1 cell line	LPS, LTA	[32]
In vitro	Canonical	NLRP3	Clinical pulpitis samples, human DPCs	n/a*	[90]
In vitro	Canonical	NLRP3	THP-1 cells	Odontoblast cell lysate	[39]
In vitro	Canonical	NLRP3	mDPC6T (mouse dental pulp papilla) cells	mtDNA	[38]
In vitro	Canonical	NLRP3	Clinical pulpitis samples, mDPC6T cells	LPS plus ATP	[35]
In vitro	Canonical	NLRP3, AIM2	Human DPCs	*P.g., F.n.*, ATP	[41]
In vitro	Canonical	NLRP3, AIM2, NLRC4	THP-1 cells	*S.m.*	[45]
In vitro	Canonical	NLRP6	Clinical pulpitis samples, human DPCs	LPS	[34]
In vitro	Noncanonical	Caspase-4	Human DPCs	LPS	[48]
In vitro + in vivo	Canonical	AIM2	Rat DPCs, rat experimental pulpitis model	LPS, IFN-γ	[29]
In vitro + in vivo	Canonical	NLRP3	BV2 (mouse microglial) cells, rat experimental pulpitis model	LPS	[47]

Notes: *n/a: The data were not mentioned in the study.

Table 2 Studies Regarding Pyroptosis in Apical Periodontitis

In vitro/in vivo	Pyroptosis Pathway	Inflammasomes Involved	Study Materials	Stimuli	References
IN vitro	Canonical	NLRP3	THP-1 cells	*E. faecalis*	[55]
In vitro	Canonical	NLRP3	RAW264.7 cells	LTA	[75]
IN vitro	Canonical	NLRP3	Clinical periapical lesion samples, human PDLFs	LPS, MDP	[53]
In vitro	Canonical	NLRP3	MG63 (human osteosarcoma) cells	*E. faecalis*	[63]
In vitro	Canonical	NLRP3, AIM2	Clinical periapical lesion samples, THP-1 cells	LPS	[91]
In vitro	Canonical	NLRP6	Clinical periapical lesion samples, human PDLFs	LPS	[92]
In vitro	Canonical	n/a*	Human PDLFs	Cyclic stretch	[54]
In vitro	Noncanonical	Caspase-4	Human PDLFs	LPS	[48]
In vivo	Canonical	NLRP3	Rat experimental apical periodontitis model	Oral microbes (pulp exposure)	[71]
In vitro + in vivo	Canonical	NLRP3	Clinical periapical lesion samples, human PDLFs, rat experimental apical periodontitis model	LPS	[76]
In vitro + In vivo	Canonical	NLRP3	Clinical periapical lesion samples, rat experimental apical periodontitis model	Oral microbes (pulp exposure)	[72]
In vitro + in vivo	Canonical	NLRP3	RAW264.7 cells, rat experimental apical periodontitis model	*E. faecalis*, LTA	[56]

(*Continued*)

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Table 2 (Continued).

In vitro/in vivo	Pyroptosis Pathway	Inflammasomes Involved	Study Materials	Stimuli	References
In vitro + in vivo	Canonical	NLRP3	Clinical periapical lesion samples, mDPC6T cells, mouse experimental apical periodontitis model (WT mice and *Nlrp3*$^{-/-}$ mice)	LPS plus ATP	[59]
In vitro + in vivo	Canonical	NLRP3	Clinical periapical lesion samples, mouse dendritic cells, mouse experimental apical periodontitis model	Heat-killed *P.g.*	[58]
In vitro + in vivo	Noncanonical	Caspase-11	OCCM-30 (mouse cementoblast) cells, mouse experimental apical periodontitis model	*P.g.*	[68]
In vitro + in vivo	Canonical + noncanonical	Caspase-1/4/5/11	Clinical periapical lesion samples, THP-1 cells, rat experimental apical periodontitis model	LPS	[70]

Notes: *n/a: The data were not mentioned in the study.

Cleavage of Gasdermin Family Proteins in Pulpitis and Apical Periodontitis

Currently, it is believed that the cleaved N terminals of gasdermin family proteins are the final executors of pyroptosis in most cases. However, some studies regarding pyroptosis in pulpitis and apical periodontitis have verified only the expression of PRRs and the activation of caspases without confirming the cleavage of gasdermin family proteins. Notably, inflammasome formation and caspase activation do not guarantee the occurrence of pyroptosis.[82,83] The widely accepted hallmark of pyroptosis is the cleavage of gasdermin family proteins.[84–86] Therefore, the cleavage of gasdermin family proteins in pulpitis and apical periodontitis needs further research.

Conclusion

Studies on pyroptosis in pulpitis (Table 1) and apical periodontitis (Table 2) have focused on various cell types. The effects of pyroptosis are distinct and related to cell type and function. For example, the pyroptosis of odontoblasts serves as alerts and induces immune reactions in the inner pulp after pyroptosis, and the expression levels of some pyroptotic markers in DPCs may reflect the progression of pulpitis. In addition, studies on pyroptosis have revealed several potential drug targets, such as NLRP3 and caspase-1, which might be used for the treatment of pulpitis and apical periodontitis.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors have no relevant financial or non-financial interests to disclose.

References

1. Aachoui Y, Sagulenko V, Miao EA, et al. Inflammasome-mediated pyroptotic and apoptotic cell death, and defense against infection. *Curr Opin Microbiol*. 2013;16(3):319–326. doi:10.1016/j.mib.2013.04.004
2. Fajgenbaum DC, June CH. Cytokine storm. *N Engl J Med*. 2020;383(23):2255–2273. doi:10.1056/NEJMra2026131
3. Mahmood AA, Abbas RF. Assessment of NLRP3 gene polymorphisms with periodontitis as compared with healthy periodontium in Iraqi Arabs patients. *Eur J Dent*. 2023;17(4):1338–1348. doi:10.1055/s-0043-1761185
4. Ali DZ, Al-Ghurabi BH, Al-Qarakhli A, et al. Association between AIM2 and pycard genes polymorphisms and susceptibility to periodontitis with coronary heart disease. *Clin Cosmet Investig Dent*. 2023;15:307–320. doi:10.2147/CCIDE.S440577
5. Mousa AO, Al HA, Hussein HM. The potential role of reactive oxygen species produced by low-density neutrophils in Periodontitis. *Eur J Dent*. 2024;18(4):1142–1148. doi:10.1055/s-0044-1782211
6. Zanini M, Meyer E, Simon S. Pulp inflammation diagnosis from clinical to inflammatory mediators: a systematic review. *J Endod*. 2017;43 (7):1033–1051. doi:10.1016/j.joen.2017.02.009
7. Mahmood AA, AbdulAzeez AR, Hussein HM. The effect of smoking habit on apical status of adequate endodontically treated teeth with and without periodontal involvement. *Clin Cosmet Investig Dent*. 2019;11:419–428. doi:10.2147/CCIDE.S236747
8. Hussein HM, AlAnsari SAS, Baldawi MKH, et al. Association between health risk factors and apical periodontitis in fitted endodontically and non-endodontically treated teeth. *J Emerg Med Trauma Acute Care*. 2023;2023. doi:10.5339/jemtac.2023.midc.7
9. Amory Z, Hussein H, Nashwan A, et al. Effect of academic-environmental stress on apical periodontitis of non-endodontic teeth. *Med J Babylon*. 2024;21:65–70. doi:10.4103/MJBL.MJBL_103_23
10. Márton IJML, Kiss CMPD. Overlapping protective and destructive regulatory pathways in apical periodontitis. *J Endod*. 2014;40(2):155–163. doi:10.1016/j.joen.2013.10.036
11. Barnett KC, Li S, Liang K, et al. A 360 degrees view of the inflammasome: mechanisms of activation, cell death, and diseases. *Cell*. 2023;186 (11):2288–2312. doi:10.1016/j.cell.2023.04.025
12. Ding J, Wang K, Liu W, et al. Pore-forming activity and structural autoinhibition of the gasdermin family. *Nature*. 2016;535(7610):111–116. doi:10.1038/nature18590
13. Kayagaki N, Warming S, Lamkanfi M, et al. Non-canonical inflammasome activation targets caspase-11. *Nature*. 2011;479(7371):117–121. doi:10.1038/nature10558
14. Kayagaki N, Wong MT, Stowe IB, et al. Noncanonical inflammasome activation by intracellular LPS independent of TLR4. *Science*. 2013;341 (6151):1246–1249. doi:10.1126/science.1240248
15. Liu BC, Sarhan J, Panda A, et al. constitutive interferon maintains GBP expression required for release of bacterial components upstream of pyroptosis and anti-DNA responses. *Cell Rep*. 2018;24(1):155–168. doi:10.1016/j.celrep.2018.06.012
16. Wandel MP, Kim BH, Park ES, et al. Guanylate-binding proteins convert cytosolic bacteria into caspase-4 signaling platforms. *Nat Immunol*. 2020;21(8):880–891. doi:10.1038/s41590-020-0697-2
17. Wang K, Sun Q, Zhong X, et al. Structural mechanism for GSDMD targeting by autoprocessed caspases in pyroptosis. *Cell*. 2020;180(5):941–955. doi:10.1016/j.cell.2020.02.002
18. Shi X, Sun Q, Hou Y, et al. Recognition and maturation of IL-18 by caspase-4 noncanonical inflammasome. *Nature*. 2023;624(7991):442–450. doi:10.1038/s41586-023-06742-w
19. Van Opdenbosch N, Lamkanfi M. Caspases in cell death, inflammation, and disease. *Immunity*. 2019;50(6):1352–1364. doi:10.1016/j.immuni.2019.05.020
20. Mahmood AA, Abbas RF. Association between caspase-1, TNF-alpha salivary level and their diagnostic potential to discriminate periodontitis from healthy control. *Oral Health Prev Dent*. 2023;21:61–68. doi:10.3290/j.ohpd.b3904349
21. Wang Y, Gao W, Shi X, et al. Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin. *Nature*. 2017;547(7661):99–103. doi:10.1038/nature22393
22. Orning P, Weng D, Starheim K, et al. Pathogen blockade of TAK1 triggers caspase-8-dependent cleavage of gasdermin D and cell death. *Science*. 2018;362(6418):1064–1069. doi:10.1126/science.aau2818
23. Hou J, Zhao R, Xia W, et al. PD-L1-mediated gasdermin C expression switches apoptosis to pyroptosis in cancer cells and facilitates tumour necrosis. *Nat Cell Biol*. 2020;22(10):1264–1275. doi:10.1038/s41556-020-0575-z
24. Zhou Z, He H, Wang K, et al. Granzyme A from cytotoxic lymphocytes cleaves GSDMB to trigger pyroptosis in target cells. *Science*. 2020;368 (6494). doi:10.1126/science.aaz7548
25. Zhang Z, Zhang Y, Xia S, et al. Gasdermin E suppresses tumour growth by activating anti-tumour immunity. *Nature*. 2020;579(7799):415–420. doi:10.1038/s41586-020-2071-9
26. Du G, Healy LB, David L, et al. ROS-dependent S-palmitoylation activates cleaved and intact gasdermin D. *Nature*. 2024;630(8016):437–446. doi:10.1038/s41586-024-07373-5
27. Zhou B, Jiang ZH, Dai MR, et al. Full-length GSDME mediates pyroptosis independent from cleavage. *Nat Cell Biol*. 2024;26:1545–1557. doi:10.1038/s41556-024-01463-2
28. Yin W, Liu G, Li J, et al. Landscape of cell communication in human dental pulp. *Small Methods*. 2021;5(9):e2100747. doi:10.1002/smtd.202100747
29. Wang Y, Zhai S, Wang H, et al. Absent in melanoma 2 (AIM2) in rat dental pulp mediates the inflammatory response during Pulpitis. *J Endod*. 2013;39(11):1390–1394. doi:10.1016/j.joen.2013.07.003
30. Huang S, Song Z, Jiang L, et al. Absent in melanoma 2 (AIM2) expressed in human dental pulp mediates IL-1β secretion in response to cytoplasmic DNA. *Inflammation*. 2015;38(2):566–575. doi:10.1007/s10753-014-9963-5
31. Wang D, Sun S, Xue Y, et al. MicroRNA-223 negatively regulates LPS-induced inflammatory responses by targeting NLRP3 in human dental pulp fibroblasts. *Int Endod J*. 2021;54(2):241–254. doi:10.1111/iej.13413
32. Al Natour B, Lundy FT, About I, et al. Regulation of caries-induced pulp inflammation by NLRP3 inflammasome: a laboratory-based investigation. *Int Endod J*. 2022;56:193–202. doi:10.1111/iej.13855

33. Jiang W, Sun S, Wang D, et al. MicroRNA-22 suppresses NLRP3/CASP1 inflammasome pathway-mediated proinflammatory cytokine production by targeting theHIF-1α and NLRP3 in human dental pulp fibroblasts. *Int Endod J*. 2022;55(11):1225–1240. doi:10.1111/iej.13814
34. Zhao Y, Chen L, Shen Z, et al. Expression of nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 6 in human dental pulp tissues and cells. *Arch Oral Biol*. 2020;117:104794. doi:10.1016/j.archoralbio.2020.104794
35. Wang K, Zhou L, Mao H, et al. Intercellular mitochondrial transfer alleviates pyroptosis in dental pulp damage. *Cell Prolif*. 2023;56(9):e13442. doi:10.1111/cpr.13442
36. Zhou L, Zhang YF, Yang FH, et al. Mitochondrial DNA leakage induces odontoblast inflammation via the cGAS-STING pathway. *Cell Commun Signal*. 2021;19(1):58. doi:10.1186/s12964-021-00738-7
37. Harapas CR, Idiiatullina E, Al-Azab M, et al. Organellar homeostasis and innate immune sensing. *Nat Rev Immunol*. 2022;22(9):535–549. doi:10.1038/s41577-022-00682-8
38. Zhang Y, Zhou L, Mao H, et al. Mitochondrial DNA leakage exacerbates odontoblast inflammation through gasdermin D-mediated pyroptosis. *Cell Death Discov*. 2021;7(1):381. doi:10.1038/s41420-021-00770-z
39. Al Natour B, Lundy FT, Moynah PN, et al. Odontoblast cell death induces NLRP3 inflammasome-dependent sterile inflammation and regulates dental pulp cell migration, proliferation and differentiation. *Int Endod J*. 2021;54(6):941–950. doi:10.1111/iej.13483
40. Zargar N, Ashraf H, Marashi S, et al. Identification of microorganisms in irreversible pulpitis and primary endodontic infections with respect to clinical and radiographic findings. *Clin Oral Invest*. 2020;24(6):2099–2108. doi:10.1007/s00784-019-03075-9
41. Aral K, Milward MR, Cooper PR. Dysregulation of inflammasomes in human dental pulp cells exposed to porphyromonas gingivalis and fusobacterium nucleatum. *J Endod*. 2020;46(9):1265–1272. doi:10.1016/j.joen.2020.06.008
42. Lee S, Kang S, Jung H, et al. Muramyl dipeptide activates human beta defensin 2 and pro-inflammatory mediators through toll-like receptors and NLRP3 inflammasomes in human dental pulp cells. *Clin Oral Invest*. 2015;19(6):1419–1428. doi:10.1007/s00784-014-1361-8
43. Zhang A, Wang P, Ma X, et al. Mechanisms that lead to the regulation of NLRP3 inflammasome expression and activation in human dental pulp fibroblasts. *mol Immunol*. 2015;66(2):253–262. doi:10.1016/j.molimm.2015.03.009
44. Galler KM, Weber M, Korkmaz Y, et al. Inflammatory response mechanisms of the dentine-pulp complex and the periapical tissues. *Int J mol Sci*. 2021;22(3):1480. doi:10.3390/ijms22031480
45. Song Y, Na HS, Park E, et al. Streptococcus mutans activates the AIM2, NLRP3 and NLRC4 inflammasomes in human THP-1 macrophages. *Int J Oral Sci*. 2018;10(3):23. doi:10.1038/s41368-018-0024-z
46. Edvinsson J, Vigano A, Alekseeva A, et al. The fifth cranial nerve in headaches. *J Headache Pain*. 2020;21(1):65. doi:10.1186/s10194-020-01134-1
47. Sun S, Jiang W, Yan X, et al. Ligand-gated ion channel P2X7 regulates NLRP3/Caspase-1-mediated inflammatory pain caused by pulpitis in the trigeminal ganglion and medullary dorsal horn. *Brain Res Bull*. 2023;192:1–10. doi:10.1016/j.brainresbull.2022.10.020
48. Gu F, Wu H, Huang Z, et al. The effects of dimethyl fumarate on cytoplasmic LPS-induced noncanonical pyroptosis in periodontal ligament fibroblasts and dental pulp cells. *Int Endod J*. 2023;56(7):869–880. doi:10.1111/iej.13926
49. Humphries F, Shmuel-Galia L, Ketelut-Carneiro N, et al. Succination inactivates gasdermin D and blocks pyroptosis. *Science*. 2020;369 (6511):1633–1637. doi:10.1126/science.abb9818
50. Xie Z, Jiang W, Liu H, et al. Antimicrobial peptide- and dentin matrix-functionalized hydrogel for vital pulp therapy via synergistic bacteriostasis, immunomodulation, and dentinogenesis. *Adv Healthc Mater*. 2024;13(18):e2303709. doi:10.1002/adhm.202303709
51. Barbosa-Ribeiro M, Arruda-Vasconcelos R, Louzada LM, et al. Microbiological analysis of endodontically treated teeth with apical periodontitis before and after endodontic retreatment. *Clin Oral Invest*. 2021;25(4):2017–2027. doi:10.1007/s00784-020-03510-2
52. Oka S, Li X, Sato F, et al. A deficiency of Dec2 triggers periodontal inflammation and pyroptosis. *J Periodont Res*. 2021;56(3):492–500. doi:10.1111/jre.12849
53. Lu WL, Song DZ, Yue JL, et al. NLRP3 inflammasome may regulate inflammatory response of human periodontal ligament fibroblasts in an apoptosis-associated speck-like protein containing a CARD (ASC)-dependent manner. *Int Endod J*. 2017;50(10):967–975. doi:10.1111/iej.12722
54. Zhuang J, Wang Y, Qu F, et al. Gasdermin-d played a critical role in the cyclic stretch–induced inflammatory reaction in human periodontal ligament cells. *Inflammation*. 2019;42(2):548–558. doi:10.1007/s10753-018-0912-6
55. Ran S, Huang J, Liu B, et al. Enterococcus Faecalis activates NLRP3 inflammasomes leading to increased interleukin-1 beta secretion and pyroptosis of THP-1 macrophages. *Microb Pathogenesis*. 2021;154:104761. doi:10.1016/j.micpath.2021.104761
56. Wang L, Jin H, Ye D, et al. Enterococcus faecalis lipoteichoic acid–induced NLRP3 inflammasome via the activation of the nuclear factor kappa B pathway. *J Endod*. 2016;42(7):1093–1100. doi:10.1016/j.joen.2016.04.018
57. Fleetwood AJ, Lee MKS, Singleton W, et al. Metabolic remodeling, inflammasome activation, and pyroptosis in macrophages stimulated by porphyromonas gingivalis and its outer membrane vesicles. *Front Cell Infect Mi*. 2017;7.
58. Leng S, Xu W, Wu L, et al. NLRP3 disturbs treg/Th17 cell balance to aggravate apical periodontitis. *J Dent Res*. 2023;102(6):656–666. doi:10.1177/00220345231151692
59. Wang K, Liu J, Yue J, et al. Nlrp3 inflammasome drives regulatory T cell depletion to accelerate periapical bone erosion. *Int Endod J*. 2024;57 (8):1110–1123. doi:10.1111/iej.14062
60. Lin YC, Zheng G, Liu HT, et al. USP7 promotes the osteoclast differentiation of CD14+ human peripheral blood monocytes in osteoporosis via HMGB1 deubiquitination. *J Orthop Transl*. 2023;40:80–91.
61. Levescot A, Chang MH, Schnell J, et al. IL-1β–driven osteoclastogenic Tregs accelerate bone erosion in arthritis. *J Clin Invest*. 2021;131(18). doi:10.1172/JCI141008
62. Li M, Yang D, Yan H, et al. Gasdermin D maintains bone mass by rewiring the endo-lysosomal pathway of osteoclastic bone resorption. *Dev Cell*. 2022;57(20):2365–2380. doi:10.1016/j.devcel.2022.09.013
63. Ran S, Chu M, Gu S, et al. Enterococcus faecalis induces apoptosis and pyroptosis of human osteoblastic MG 63 cells via the NLRP 3 inflammasome. *Int Endod J*. 2019;52(1):44–53. doi:10.1111/iej.12965
64. Ajuz NC, Antunes H, Mendonca TA, et al. Immunoexpression of interleukin 17 in apical periodontitis lesions. *J Endod*. 2014;40(9):1400–1403. doi:10.1016/j.joen.2014.03.024
65. Xiong H, Wei L, Peng B. The presence and involvement of interleukin-17 in apical periodontitis. *Int Endod J*. 2019;52(8):1128–1137. doi:10.1111/iej.13112
66. Lei L, Sun J, Han J, et al. Interleukin-17 induces pyroptosis in osteoblasts through the NLRP3 inflammasome pathway in vitro. *Int Immunopharmacol*. 2021;96:107781. doi:10.1016/j.intimp.2021.107781

67. Ma L, Wang X, Liu H, et al. CXXC5 mediates P. gingivalis-suppressed cementoblast functions partially via MAPK signaling network. *Int J Biol Sci*. 2019;15(8):1685–1695. doi:10.7150/ijbs.35419
68. Peng Y, Wang H, Huang X, et al. Tet methylcytosine dioxygenase 1 modulates porphyromonas gingivalis-triggered pyroptosis by regulating glycolysis in cementoblasts. *Ann Ny Acad Sci*. 2023;1523(1):119–134. doi:10.1111/nyas.14979
69. Sun W, Yang T, Wang C, et al. Mitochondrial ROS participates in Porphyromonas gingivalis-induced pyroptosis in cementoblasts. *Heliyon*. 2024;10 (9):e30814. doi:10.1016/j.heliyon.2024.e30814
70. Wu Z, Li M, Ren X, et al. Double-edged sword effect of pyroptosis: the role of caspase-1/-4/-5/-11 in different levels of apical periodontitis. *Biomolecules*. 2022;12(11):1660. doi:10.3390/biom12111660
71. Liu S, Li Q, Liu Y. Immunohistochemical localization of NALP3 inflammasome in experimental periapical lesions. *Int Endod J*. 2014;47 (10):949–957. doi:10.1111/iej.12240
72. Guan X, Guan Y, Shi C, et al. Estrogen deficiency aggravates apical periodontitis by regulating NLRP3/caspase-1/IL-1β axis. *Am J Transl Res*. 2020;12(2):660–671.
73. Han X, Chen H, Li C. Effect of human periodontal ligament stem cell-derived extracellular vesicles on macrophage pyroptosis and periodontal inflammatory injury in periodontitis. *Cells Tissues Organs*. 2022;211(1):57–72. doi:10.1159/000519569
74. Li C, Yin W, Yu N, et al. miR-155 promotes macrophage pyroptosis induced byPorphyromonas gingivalis through regulating the NLRP3 inflammasome. *Oral Dis*. 2019;25(8):2030–2039. doi:10.1111/odi.13198
75. Yin W, Liu S, Dong M, et al. A new NLRP3 inflammasome inhibitor, dioscin, promotes osteogenesis. *Small*. 2020;16(1):e1905977. doi:10.1002/ smll.201905977
76. Cheng R, Feng Y, Zhang R, et al. The extent of pyroptosis varies in different stages of apical periodontitis. *Biochim Biophys Acta mol Basis Dis*. 2018;1864(1):226–237. doi:10.1016/j.bbadis.2017.10.025
77. Yamaguchi Y, Kanzaki H, Katsumata Y, et al. Dimethyl fumarate inhibits osteoclasts via attenuation of reactive oxygen species signalling by augmented antioxidation. *J Cell mol Med*. 2017;22(2):1138–1147. doi:10.1111/jcmm.13367
78. Hagar JA, Powell DA, Aachoui Y, et al. Cytoplasmic LPS activates caspase-11: implications in TLR4-independent endotoxic shock. *Science*. 2013;341(6151):1250–1253. doi:10.1126/science.1240988
79. Demon D, Kuchmiy A, Fossoul A, et al. Caspase-11 is expressed in the colonic mucosa and protects against dextran sodium sulfate-induced colitis. *Mucosal Immunol*. 2014;7(6):1480–1491. doi:10.1038/mi.2014.36
80. Zaslona Z, Flis E, Wilk MM, et al. Caspase-11 promotes allergic airway inflammation. *Nat Commun*. 2020;11(1):1055. doi:10.1038/s41467-020-14945-2
81. Chen Q, Liu X, Wang D, et al. Periodontal inflammation-triggered by periodontal ligament stem cell pyroptosis exacerbates periodontitis. *Front Cell Dev Biol*. 2021;9.
82. Hara H, Seregin SS, Yang D, et al. The NLRP6 inflammasome recognizes lipoteichoic acid and regulates gram-positive pathogen infection. *Cell*. 2018;175(6):1651–1664. doi:10.1016/j.cell.2018.09.047
83. Zhang P, Liu Y, Hu L, et al. NLRC4 inflammasome-dependent cell death occurs by a complementary series of three death pathways and determines lethality in mice. *Sci Adv*. 2021;7(43):eabi9471. doi:10.1126/sciadv.abi9471
84. Broz P, Pelegrin P, Shao F. The gasdermins, a protein family executing cell death and inflammation. *Nat Rev Immunol*. 2020;20(3):143–157. doi:10.1038/s41577-019-0228-2
85. Devant P, Kagan JC. Molecular mechanisms of gasdermin D pore-forming activity. *Nat Immunol*. 2023;24(7):1064–1075. doi:10.1038/s41590-023-01526-w
86. Lawlor KE, Murphy JM, Vince JE. Gasdermin and MLKL necrotic cell death effectors: signaling and diseases. *Immunity*. 2024;57(3):429–445. doi:10.1016/j.immuni.2024.02.011
87. Huang S, Song Z, Huang Q, et al. AIM2 inflammasome is critical for dsDNA-induced IL-1beta secretion in human dental pulp cells. *Inflammation*. 2018;41(2):409–417. doi:10.1007/s10753-017-0697-z
88. Gao Y, You X, Liu Y, et al. Induction of autophagy protects human dental pulp cells from lipopolysaccharide-induced pyroptotic cell death. *Exp Ther Med*. 2020;19(3):2202–2210. doi:10.3892/etm.2020.8475
89. Jiang W, Lv H, Wang H, et al. Activation of the NLRP3/caspase-1 inflammasome in human dental pulp tissue and human dental pulp fibroblasts. *Cell Tissue Res*. 2015;361(2):541–555. doi:10.1007/s00441-015-2118-7
90. Song Z, Lin Z, He F, et al. NLRP3 is expressed in human dental pulp cells and tissues. *J Endod*. 2012;38(12):1592–1597. doi:10.1016/j. joen.2012.09.023
91. Ran S, Liu B, Gu S, et al. Analysis of the expression of NLRP3 and AIM2 in periapical lesions with apical periodontitis and microbial analysis outside the apical segment of teeth. *Arch Oral Biol*. 2017;78:39–47. doi:10.1016/j.archoralbio.2017.02.006
92. Lu WL, Zhang L, Song DZ, et al. NLRP6 suppresses the inflammatory response of human periodontal ligament cells by inhibiting NF-κB and ERK signal pathways. *Int Endod J*. 2019;52(7):999–1009. doi:10.1111/iej.13091