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REVIEW

Pyroptosis in Pulpitis

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Abstract: Pulpitis is an inflammatory disease occurs in the pulp tissues. Continuous development of pulpitis can lead to apical periodontitis and seriously damage the function of teeth, affecting the oral health and daily life of patients. Pyroptosis, alternatively termed inflammatory necrosis, is a type of programmed cell death that is characterized by the swelling of cells until the cell membrane is broken. The GSDM family of proteins can be activated by a variety of pathways, which can lead to the puncture of cell membrane, inducing the release of cellular contents and inflammatory cytokines like IL-1β and IL-18 to activate a strong inflammatory response. Pyroptosis in dental pulp may be an important direction to find new targets for pulpal inflammation prevention and treatment, which deserves further study. In this article, we reviewed the activation mechanism and potential role of pyroptosis in the progression of pulpitis, along with the interaction between pyroptosis and other regulated cell death (RCD) pathways. This review aims to enrich the mechanism under the development of dental pulp inflammation, and to uncover potential therapeutic targets for early alleviation and treatment of pulp inflammation.

Keywords: pulpitis, pyroptosis, dental pulp cells

Introduction

Dental pulp is a kind of distinct connective tissue located in the central part of teeth, which is wrapped by dental hard tissues and consists of cells, fibers, lymphatic vessels, blood vessels and nerves. The pulp and dentin are jointly known as the pulpo-dentinal complex, because of they both develop from the dental papilla, and have closely relationships in anatomy and histophysiology. As the pulpo-dentinal complex was infected or exposed to slight stimuli, dental pulp stem cells were found to differentiate into odontoblasts/odontoblast-like cells, which play a role in the formation of reparative dentin and protection of pulp tissue.

Pulpitis is a common inflammatory oral disease. Without timely intervention, pulpitis will seriously damage the function of teeth and affect the oral health of patients, thus causing time and economic losses. As a type of inflammatory cell death, pyroptosis is a key pathway in the development and progression of pulpitis. This review outlines the activation mechanism and potential role of cellular pyroptosis in the progression of pulpitis, as well as the interaction of pyroptosis with other cell death pathways, including apoptosis, autophagy, and necroptosis. This review is intended to enrich the mechanistic background of pulp inflammation and explore potential therapeutic strategies for preventing and treating pulpitis.

The Concept of Pyroptosis

In 1992, the characteristics of pyroptosis were described for the first time in Shigella flexneri infected macrophages: chromatin condensation, cytoplasmic vesiculation, cytoplasmic vacuolization, endoplasmic reticulum expansion, retention of organelle structure, and genomic DNA fragmentation. Pyroptosis had been mistaken as a kind of apoptosis for a

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time.[1] Apoptosis triggers programmed cell death by cleaving substrates through a caspase cascade reaction. In apoptosis, cells shrink and divide into apoptotic bodies, which are usually engulfed by surrounding macrophages, leading to cell death of a non-inflammatory character. Meanwhile, pyroptosis is an inflamed death that releases inflammatory factors of IL-1β and IL-18, removes intracellular pathogens and triggers an inflammatory response.[2] All these findings indicate that pyroptosis is different from apoptosis. In 2001, Brennan MA and Cookson BT formally brought out the notion of "pyroptosis", which distinguished pyroptosis from apoptosis for the first time.[3] Pyroptosis, also referred to as inflammatory necrosis, was first defined by the NCCD (The Nomenclature Committee on Cell Death) in 2018 as a specific type of regulated cell death that is dependent on the formation of plasma membrane pores by gasdermin family proteins.

Pyroptosis is classified into two distinct pathways, termed "canonical" and "non-canonical" on the basis of the underlying mechanism. The canonical pathway facilitates the recruitment and activation of caspase-1 by sensing pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs) and cytoplasmic disturbances through different inflammasomes. The currently recognized inflammasomes mainly include nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3), NLRP1, NOD-like receptor family CARD domain-containing protein (NLRC4), absent in melanoma 2 (AIM2) and pyrin. Caspase-1 cleaves and activates IL-18, IL-1β and other executive proteins of pyroptosis including cleaved GSDMD with N-terminal sequence (GSDMD-N), which binds to the membrane and generate membrane pores, resulting in pyroptosis.[4] In the non-canonical pathway, lipopolysaccharide (LPS) activates human-derived pro-caspase 4/5 or rat-derived pro-caspase 11, which then cleaves the domain of GSDMD-N, and induces pyroptosis.[5] Recent studies have shown a new activation mechanism of incomplete pyroptosis. Fas associated with death domain (FADD) was found to play a role in maintaining intestinal inflammatory homeostasis by inhibiting caspase-8/GSDMD-dependent pyroptosis-like cell death in the downstream of ZBP1 and TNFR1.[6] It has been shown that FADD was expressed in hDPSCs[7] while its role in pulpitis through the alternative pathway of NLRP3/Caspase1 activation deserves further investigation. In caspase-1/11-deficient macrophages, NLRP3 inflammasome was capable of activating caspase-8 through apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and subsequently cleaved GSDME, at last the IL-1α was released instead of the classical pyroptotic factor IL-1β.[8] Some chemotherapy drugs, such as adriamycin, actinomycin-D, bleomycin and topotecan, can switch apoptosis induced by TNF or chemotherapeutic drugs into pyroptosis by means of the activation of caspase-3 to cleave GSDME.[9] In 2020, Shao Feng's team proved that Granzyme A (GZMA) secreted by cytotoxic lymphocytes could specifically cleave GSDMB and release GSDMB-N fragments. Moreover, the liposome leakage assay confirmed that GSDMB cleaved by GZMA could cause cell perforation to induce pyroptosis.[10]

Pyroptotic Proteins Expressed in Inflamed Dental Pulp Tissues

Studies have confirmed that the expressions of NLRP3,[11] AIM2[12] and NLRP6[13] inflammasome are upregulated in inflamed pulp tissues. However, the expressions of NLRP1 and NLRC4 have no significant differences between healthy and inflamed pulp tissues.[14] NLRP3 was highly expressed in pulp tissues with irreversible pulpitis compared to normal pulp or tissues with reversible pulpitis. In inflamed pulp tissues, the gene expression of caspase-1 and IL-1β were also upregulated comparing with normal pulp.[11] Normally, AIM2 protein was expressed only in the cytoplasm of odontoblast, while it was significantly expressed in both inflamed odontoblasts and fibroblasts. Studies have shown that interferon γ and cytoplasmic DNA activated AIM2 inflammasome in HDPCs, and the inhibition of AIM2 downregulated the expression of cleaved caspase-1 and suppressed the release of IL-1β.[12] Persistent development of pulpitis may lead to periapical inflammation. The levels of NLRP3, AIM2 and ASC were significantly upregulated in apical lesions compared to healthy tissues. Also, NLRP3 and AIM2 were significantly overexpressed in inflammatory cells of periapical lesions, including neutrophils, monocytes, macrophages, and plasma cells.[15]

Immunohistochemical staining analysis of human samples confirmed that NLRP6 was expressed in both normal and inflamed pulp tissues. Meanwhile, in LPS-pretreated DPSCs, the expression of NLRP6 was found to increase in a time-dependent manner and IL-1β was significantly decreased after NLRP6 was silenced.[16] ELISA assay also revealed that the level of NLRP6/caspase-4 inflammasome was up-regulated in inflamed human pulp tissues.[13] These results indicate that NLRP6 is significantly involved in the LPS-induced inflammatory immune response of DPSCs, yet the specific mechanism needs to be further investigated.

The Activation of Pyroptosis in Dental Pulp Cells

A variety of pathogen recognition receptors (PRRs) that detect PAMPs and DAMPs are expressed in odontoblasts, fibroblasts, and DPSCs, especially Toll-like (TLR) and NOD-like receptorsin (NLR).[17–19] These PRRs regulate the immune defense and pathological processes of dental pulp tissues by inducing the inflammasome, mitochondrial dysfunction, and other mechanisms upon activation.

The Bacteria and Their Metabolites

Porphyromonas gingivalis (*Pg*) and *Fusobacterium nucleatum* (*Fn*) have significant roles in the progression of dental pulp infection[20,21] and apical abscesses.[22] In HDPCs, LPS from *Pg* upregulates the levels of *NLRP6, CASP4* and *CASP1* in a type I interferon-dependent way.[13] It has also been shown that with ATP induction, *Pg* remarkably enhances the level of IL-1β in HDPCs by NLRP3 upregulation and CARD16 downregulation. *Fn* could increase the expression of precursor and mature IL-1β in HDPCs without upregulating the levels of AIM2 and NLRP3 inflammasomes. Therefore, it was deduced that *Fn* may not regulate the inflammatory reactions of HDPCs via inflammasomes. Notably, simultaneous stimulation of *Pg* and *Fn* may also upregulate AIM2 and lead to a dysregulation of IL-1β.[23]

Comparing with LPS, lipoteichoic acid (LTA) treated HDPCs not only significantly up-regulated the expression of NLRP3 and IL-1β, but also provoked more ASC specks formation, suggesting LTA may be the first signal of inflammasome activation.[24] For HDPCs pre-treated with LPS of *Pg*, LTA can promote caspase-1 maturation as well as the release of IL-18 and IL-1β via activating NLRP6/caspase-4 inflammasome. NLRP6 or caspase-4 knockdown effectively inhibited the inflammasome activation triggered by cytoplasmic LTA, suggesting that NLRP6/caspase-4 inflammasome may involve in inflammation and immune defense of pulp.[13] Enterococcus faecalis-derived lipoteichoic acid (Ef. LTA) and short-chain fatty acids consist of acetate, propionate, and butyrate had been found in inflammatory apical lesions. Furthermore, the combination of butyrate and Ef. LTA were confirmed to significantly activate pyroptosis via K^+ efflux and NF-κB pathway without LDH releasing in human acute monocytic leukemia cell line (THP-1). In addition, caspase-4 and caspase-1 inhibitors reduced the maturation and release of IL-1β, suggesting that both canonical and non-canonical activation contributed to the secretion of IL-1β. In rat model of periapical periodontitis treated with butyrate and Ef. LTA, the levels of IL-1β and cleaved caspase-1 were substantially increased around the apical tissues, moreover, the pulp was severely necrosis comparing with other groups.[25] It has also been shown that THP-1 treated with LPS from Porphyromonas gingivalis, resulting in an increased expression of IL-1β and caspase-1 and activation of NLRP3 and AIM2 in the cells.[15] LPS combines with Nigerian bacteriocin, poly (dA: dT) or LPS transfection by lipofectamine 2000 were separately used to induce pyroptosis of periodontal ligament fibroblasts (PDLFs) and dental pulp cells (DPCs). The results suggested that agonists of AIM2 and NLRP3 inflammasome cannot induce typical pyroptosis in PDLFs and DPCs. In contrast, after the LPS was transfected into cells by Lipofectamine 2000, cytoplasmic LPS induced significant pyroptosis and expression of cleaved-gasdermin D in PDLFs and DPCs.[26] Above results led to the conclusion that PDLFs and DPCs may be much more sensitive to non-canonical pyroptosis elicited by cytoplasmic LPS compared to the canonical pathway.

In dermal fibroblasts stimulated with LPS or pre-treated with TNF-α/IL-1β, the expression of AIM2 inflammasome and caspase-1 was synergistically upregulated, and this effect was further amplified by co-culture with DPSCs. Notably, co-cultured fibroblasts exhibited an augmented inflammatory response, characterized by increased release of IL-1β, IL-6, and fibronectin. These findings suggest that DPSCs may influence the fibrosis by modulating the AIM2 inflammasome pathway to regulate caspase-1 activation and inflammatory cytokine secretion, while balancing fibrotic progression by suppressing collagen deposition and promoting extracellular matrix degradation. Thus, AIM2 may be a key target for DPSCs to mediate the balance between inflammation and fibrosis.[27]

NLRP6 was functionally expressed in inflamed periapical tissues and human periodontal membrane cells (HPDLCs). Meanwhile, NLRP6 has been shown to exert anti-inflammatory effects in apical periodontitis tissues and the LPS-induced inflammatory response of HPDLCs, which significantly reduced IL-6 and TNF-α by inhibiting the NF-κB and ERK signaling pathways.[28] NLRP6 may be a potential target for future apical periodontitis therapy in the future.

Pulp Metabolic Pathways and Its by Products

The studies on NLRP3/caspase-1 inflammasome showed that ATP triggers K^+ efflux and induces the formation of pannexin-1 channels by activating P2X7 receptors on cell membrane in human dental pulp fibroblasts (HDPFs). As a result, the extracellular LPS transfers into the cytoplasm and then activates NLRP3 inflammasome. Moreover, the intracellular microenvironment with low K^+ concentration induces the release of reactive oxygen species (ROS), which can also activate NLRP3.[11] In a word, the priming signal is LPS upregulates the expression of NLRP3 and IL-1β by TLR4/MyD88/NF-κB pathway, while the activation signal is ATP induced ROS production, which can regulate IL-1β secretion and activation of caspase-1 and NLRP3 inflammasomes by LPS and ATP.[29]

Dimethyl fumarate (DMF) is a cyto-permeable fumaric acid derivative. Studies have confirmed that DMF attenuates pyroptotic cell death in LPS-transfected PDLFs and DPCs by inhibiting GSDMD-N expression and cell localization. As DMF can prevent LPS-induced non-canonical pyroptosis of PDLFs and DPCs, the therapy strategies of pulpitis based on DMF may be potential research interests.[26]

Lu Zhang et al showed that LPS induced mitochondrial damage in mDPC6T cells, and promoted the translocation of BAX from cytoplasm to mitochondrial membrane. Subsequently, the mitochondrial DNA (mtDNA) triggered the pyroptosis of mDPC6T cells and increased the release of CXCL10 and IFN-β. After overexpression of mtDNA in cells with GSDMD knockdown, the STING pathway was substantially activated, the levels of cleaved-GSDMD, CXCL10 and IFN-β were upregulated, resulting in severe inflammation of odontoblasts.[30] These results suggest that cytoplasmic mtDNA may be implicated in regulating odontoblast inflammation in vitro through GSDMD mediated pyroptosis (Figure 1).

Studies showed that mitochondrial oxidative stress can activate NLRP3 inflammasome and promote pyroptosis in an odontoblast-like cell line named mDPC6T cells. After co-cultured with mDPC6T, mouse bone marrow mesenchymal stem cells (mBMSCs) were able to inhibit mitochondrial oxidative stress and pyroptosis by selectively transferring mitochondria to mDPC6T that pre-treated with LPS and ATP. Further studies revealed that tunnelling nanotubes (TNT) played a role in mitochondrial transferring between mBMSCs and mDPC6T. Furthermore, the pyroptotic mDPC6T

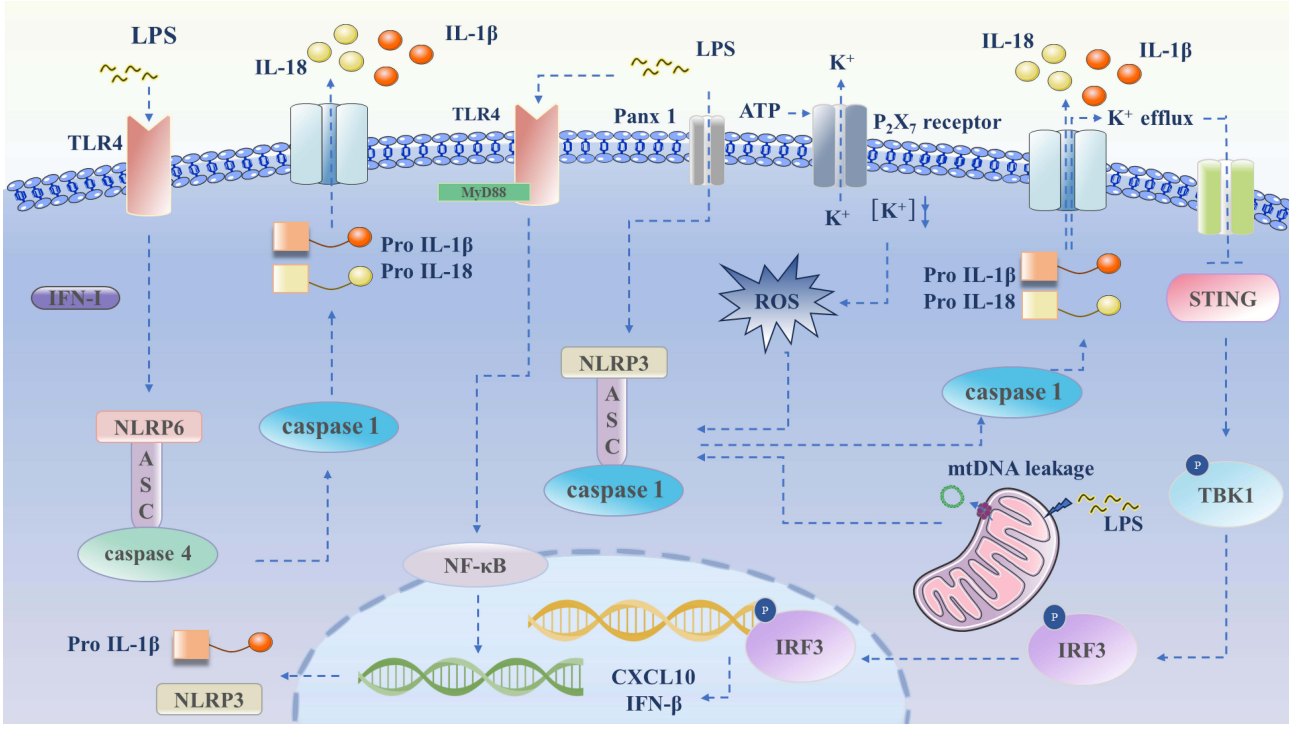

Figure 1 Pyroptosis in dental pulp tissues. Pyroptosis has been demonstrated to occur in HDPCs, HDPFs and mDPC6T. Early and moderate pyroptosis in favor of rapid response to bacterial infection, whereas dysregulation of the inflammatory response induced by hyperactivated pyroptosis may be associated with the irreversible pulpitis. Figure 1 was independently designed by the authors using Microsoft PowerPoint 2019, with all elements created using native software features.

secreted TNF-α and promoted the formation of TNT in mBMSCs via NF-κB signaling. This positive feedback leaded to increased mitochondrial translocation, thereby reducing the pyroptosis initiated by mitochondrial dysfunction and NLRP3 inflammasome in mDPC6T cells[31] (Figure 2).

Other Small Molecules and Exogenous Compounds

In 2021, Wenkai Jiang's team identified NLRP3 as a straight target of miR-223 in HDPFs by dual-luciferase reporter assay. In HDPFs pre-treated with ATP and LPS, the overexpression of NLRP3 promoted the expression of caspase-1 p20 and the secretion of mature IL-18 and IL-1β. Otherwise, knockdown or inhibitors of miR-223 facilitated the activation of NLRP3/caspase-1 pathway.[32] Furthermore, as a co-negative regulatory factor, miR-22 was also found to be correlated with the regulation of the secretion of pro-inflammatory cytokines IL-18 and IL-1β by targeting HIF-1α and NLRP3/caspase-1 inflammasome pathway.[33]

Odontoblast necrotic cell lysat (ONCL) produced by freezing-thawing cycles of odontoblast-like cells can induce migration and proliferation of HDPCs. NLRP3 inflammasome was significantly found to be activated in THP-1 cells previously treated with ONCL, as well as leading to the inflammatory cytokine release including IL-8, IL-6, IL-1β, TNF-α, CCL2, and IFN-γ. These results proved that direct damage to odontoblasts triggered a severe inflammatory response. Notably, NLRP3 inflammasome activation products, especially IL-1β, were observed to effectively stimulate the mineralization and odontogenic differentiation of HDPCs. This was demonstrated by the upregulation of osteogenic/odontogenic-related genes, including DSP, RUNX-2, DMP-1, and Secreted Phosphoprotein 1 (SPP1), as well as an increase in alkaline phosphatase activity.[34] The shortcoming of this study is that the ONCL-induced inflammatory responses were verified only in THP-1 cells but not in HDPCs.

Triethyleneglycol dimethacrylate (TEGDMA) is a commonly used dental copolymer monomer,[35] which can diffuse into the dental pulp through dentinal tubules under high concentration environment. In human peripheral blood mononuclear cells, TEGDMA was shown to upregulate the pyroptotic factors IL-18 and IL-1β by promoting the formation of NLRP3 inflammasome.[36] Human primary dental pulp stem cells (hpDPSCs) and human immortalized dental pulp stem

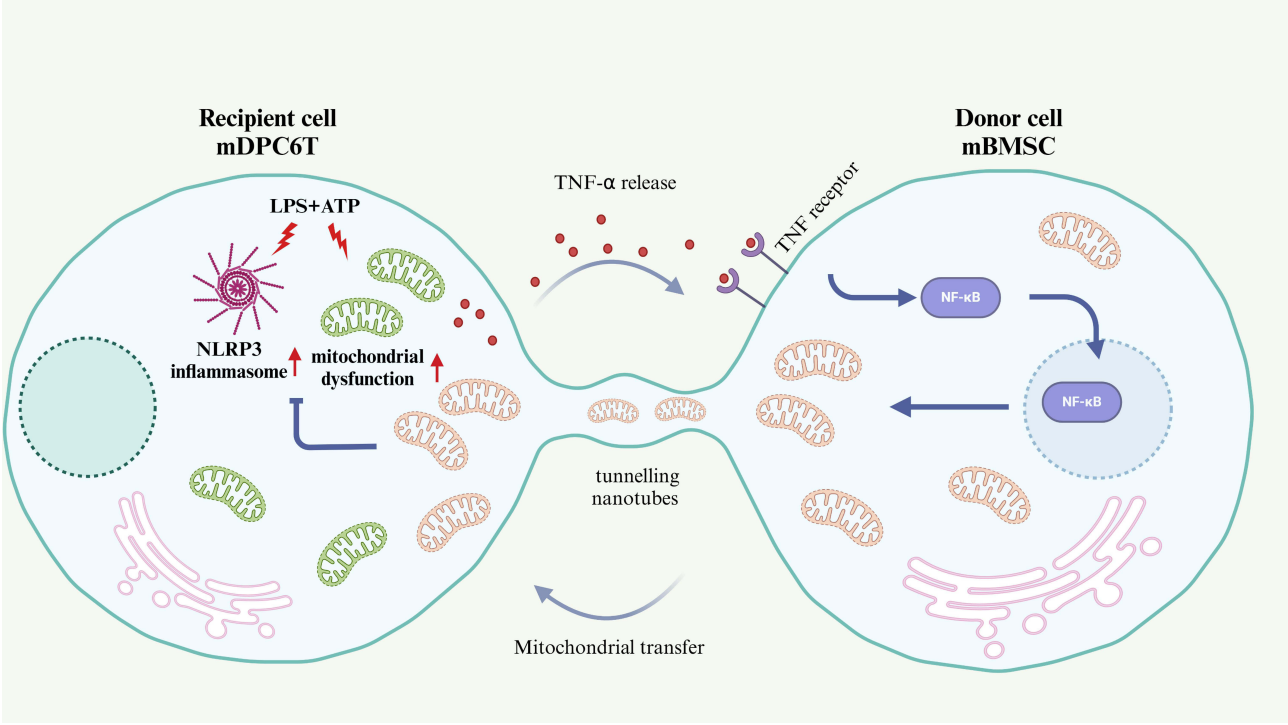

Figure 2 Intercellular mitochondrial transfer alleviates pyroptosis in dental pulp. The pyroptotic mDPC6T secreted TNF-α and promoted the formation of tunnelling nanotubes (TNT) in mBMSCs via NF-κB signaling, thereby reducing the pyroptosis initiated by mitochondrial dysfunction and NLRP3 inflammasome in mDPC6T cells. Created in BioRender. Zhang, X. (2025) https://BioRender.com/0dn3cjf.

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cells (hiDPSCs) were cultured with TEGDMA monomers and concurrently treated with N-acetyl cysteine (NAC). As a result, NAC rescued the damage on viability and proliferation of hpDPSCs and hiDPSCs induced by TEGDMA. Besides, NAC also decreased the expression level of NLRP3 inflammasome, COX2, and IL-8 in hpDPSCs and hiDPSCs.[37] All these suggest that NAC could be used to alleviate the toxic damage of TEGDMA on dental pulp cells.

The expression of GSDME in normal tissues of OSCC patients is significantly higher than that in carcinoma tissues, and cisplatin could cause chemotherapy-associated toxicities by inducing caspase-3 maturation and GSDME cleavage, which triggered the pyroptosis and the release of IL-1β and TNF-α.[38] Also, GSDMB is one of the key differentially expressed genes related to tumor mutational load in OSCC and may be a reliable biomarker for predicting the prognosis of OSCC patients.[39] However, the functions of GSDME and GSDMB in dental pulp inflammation and their interactions with other gasdermin family members still need to be further studied.

Crosstalk Between Pyroptosis with Other RCD in Pulpitis

As we learn more about RCD, it has been found that different RCD signaling pathways are interconnected. Thus, crosstalk between pyroptosis and other RCDs like apoptosis, autophagy and necroptosis are of great importance for cell death and the progression of dental pulp inflammation.

Apart from caspase-8 has crucial impacts on apoptosis,[40] it has also been proved to activate inflammasome and regulate pyroptosis.[41,42] In mouse macrophage infected by Yersinia outer protein J, TAK1 inhibition activated caspase-8, which subsequently cleaved GSDME and GSDMD, resulting in pyroptosis.[42] Besides, the metabolite α-ketoglutaric acid (α-KG) was also able to trigger pyroptosis through mediating the caspase-8-dependent cleavage of GSDMC.[43]

It has been found that Caspase-3 triggered the molecular transition from apoptosis to pyroptosis by specifically cleaving the Asp270 site of GSDME. In the GSDME-deficient model, apoptotic stimuli induced only apoptotic body formation, whereas wild-type cells shifted to secondary necrosis or pyroptosis via the caspase-3/GSDME axis.[44] In the presence of GSDMD, caspase-1 triggered pyroptosis by cleavage of GSDMD. Whereas in GSDMD-deficient cells, caspase-1 could induce apoptosis by directly cleavage and activation of Caspase-3/7,[45] or by activation of the Bid-caspase-9-caspase-3 signaling axis.[46] Activated caspase-3/7 during apoptosis specifically cleaved the Asp87 site of GSDMD, generating an inactive p43 fragment, thus blocking GSDMD-mediated pyroptosis signaling.[45]

Rapamycin and 3-methyladenine (3-MA) can be utilized for activation and inhibition of autophagy, respectively. Among dental pulp cells, LPS activated pyroptosis via the pNF-κB/IκBα signaling pathway, which could be inhibited through the autophagy induced by rapamycin. In contrast, 3-MA promoted LPS-induced activation of caspase-1 and IL-1β.[47]

Recent years, the interactive connection that existed between relationship between NLRP3 inflammasome and autophagy have been extensively proved. Autophagy was able to exert a negative effect on the NLRP3 inflammasome by eliminating related components, cytokines, and endogenous activators, including damaged mitochondria.[48] Autophagic mechanisms also contributed to the unconventional release of IL-1β, thereby modulating the inflammatory response.[49,50] Excessive inflammation can lead to tissue damage and the onset of inflammatory diseases. Conversely, autophagy may attenuate the inflammatory response by removing NLRP3 inflammasome activators and other inflammatory elements.

Meanwhile, crosstalk seemed to exist between the NLRP3 inflammasome and necroptosis. Phosphorylated mixed lineage kinase-domain like (MLKL) oligomers generated by necroptosis in small intestinal epithelial cells translocated and which caused the secretion of ATP into the extracellular matrix. In neighboring cells, such as immune and epithelial cells, ATP triggered the formation of the NLRP3 inflammasome, facilitating the maturation of IL-1β.[51] Mitochondrial damage triggered by the MLKL/p-MLKL translocation in necroptosis of epithelial cells promoted ROS production, which subsequently promoted NLRP3 inflammasome and IL-1β, ultimately promoted *Pseudomonas aeruginosa*-mediated inflammatory responses in the lungs[52] (Figure 3).

Recent studies have provided substantial evidences supporting the interaction between the different regulated cell death pathways. However, the crosstalk of pyroptosis and NLRP3 inflammasome with other regulated cell deaths have not been directly demonstrated in pulpitis or dental pulp cells, which still need to be investigated in depth.

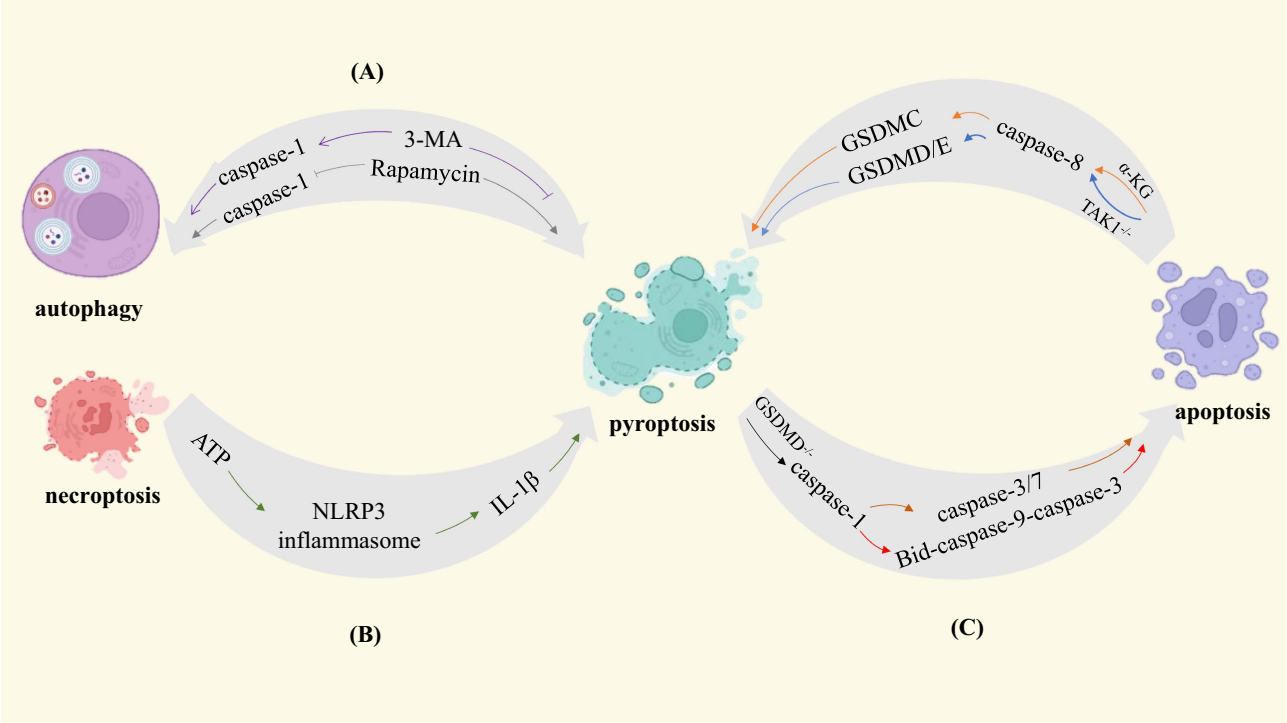


Figure 3 Functional overlap of apoptotic, autophagic, and necroptotic proteins with pyroptotic proteins. (**A**) Autophagy and pyroptosis. (**B**) Necroptosis and pyroptosis. (**C**) Apoptosis and pyroptosis. Created in BioRender. Tu, D. (2025) https://BioRender.com/gmxfo36.

Prospects of Pyroptosis in the Treatment of Pulpitis

Currently, therapeutic strategies against pyroptosis primarily involve inhibiting inflammasome formation, preventing the activation of cysteine proteases, and antagonizing the function of gasdermin proteins.

Pyroptosis causes perforation of cell membrane, leading to the release of cell contents and inflammatory cytokines especially IL-1β and IL-18, thereby activating a severe inflammatory response. There is evidence that that activation of the NLRP3 inflammasome promoted inflammation and neuropathic pain. By establishing an experimental pulpitis model in rats, a study found that the decrease in pain threshold after pulp exposure was linked to the elevated expression of P2X7, caspase-1, NLRP3, IL-1β, and IL-18 in the trigeminal ganglion and dorsal horn of the medulla. Additionally, injection of P2X7 inhibitor in rats with pulpitis intraperitoneally elevated the pain threshold and suppressed the expression of NLRP3, IL-18 and IL-1β. Treating microglial cell lines to model the in vitro inflammatory microenvironment, the P2X7 inhibitor markedly diminished the expression of NLRP3, IL-1β, IL-18, and caspase-1 in microglial cells exposed to 10 μg/mL LPS.[53] This finding indicated that targeting the P2X7/NLRP3/caspase-1 pathway could be a promising therapeutic strategy for relieving pulp inflammatory pain.

There are many NLRP3 inhibitors had been reported, such as MCC950,[24,54,55] CY-09,[56,57] and OLT1177.[58,59] As an alternative inhibitor of NLRP3 inflammasome, MCC950 was studied extensively. Among diabetic SD rats with periodontitis, a large number of pyroptotic macrophages were found in periodontal tissues, accompanying by a high expression of IL-1β. Local injection of MCC950 into gingiva inhibited the levels of GSDMD and IL-1β in periodontal tissues, which effectively attenuated alveolar bone resorption.[54] Meanwhile, other studies showed that MCC950 reduced LPS-induced pyroptosis of human gingival fibroblasts (HGFs) along with the level of caspase-1 p20 and IL-1β.[55] After DPCs along with THP-1 cells were co-cultured and subsequently exposed to LTA, MCC950 markedly downregulated the levels of IL-1β and IL-6, whereas it failed to affect IL-8 or MMP-9[24].

GSDMD inhibitors include necrosulfonamide (NSA),[60] disulfiram (DSF),[61] GI-Y1,[62] LDC7559,[63] fumarate[64] and Bay.11−7082[65] High concentrations of palmitic acid (PA) activated caspase-4 and GSDMD through NF-κB pathway in vitro, causing the pyroptosis of periodontal ligament cells (PDLCs). The NF-κB inhibitor SC75741 could reduce the level

of IL-1β and partially inhibit the pyroptosis in PA-treated cells. Although the GSDMD inhibitors, neither NSA nor DSF had effects on the secretion of IL-1β, these two drugs significantly inhibited pyroptosis indeed.[66] GI-Y1 could bind to GSDMD-N and inhibit the oligomerization and membrane perforation activity of GSDMD-N by directly binding to Arg7 residues. Meanwhile, GI-Y1 prevented the binding of GSDMD-N to mitochondria and mitigated mitochondrial damage under hypoxia/reoxygenation (H/R) or ischemia/reperfusion (I/R) conditions.[62] LDC7559 reduced the expression and cleavage of GSDMD in subarachnoid hemorrhage (SAH), but had no major effects on the expression of NLRP3.[63] In patients with periodontitis, the level of Synoviolin produced by peripheral blood mononuclear cells was downregulated, which resulted in less ubiquitination and higher levels of GSDMD proteins, increasing the activation of inflammasome.[67]

VX-765,[68,69] Z-YVAD-FMK,[70] Ac-yvad-cmk,[71] Boc-D-FMK[72] and Ac-yvad-cmk[73] have been proved to be inhibitors of caspase-1. VX765 suppressed IL-1β, MCP-1, IL-6, and IL-8 through inhibiting caspase-1 in hPDLFs. In an experimental periapical inflammation on rat, VX765 was shown to increase the thickness of trabecular bone without altering the magnitude of periapical lesions. This suggests that caspase-1 inhibition could partially reduce bone loss.[68] In inflammatory gingival tissues from human and rat, the expressions of NLRP3, caspase-1, caspase-4/11, and IL-18 were increased, while the levels of E-cadherin were reduced. In comparison to the LPS-treated sample, the mRNA expression of E-cadherin was upregulated among oral mucosal epithelial cells treated with LPS and Z-YVAD-FMKGA, while the caspase-1, IL-18, and IL-1β were decreased. Therefore, Z-YVAD-FMKGA partly attenuated LPS-induced pyroptosis and reversed the changes in E-cadherin, which may influence epithelial junctions.[70]

In addition, AR-A014418,[74,75] enamel matrix derivative (EMD),[76] curcumin[77] have been shown to inhibit pyroptosis. AR-A014418, was shown to increase the migration and osteogenic differentiation of rat dental pulp stem cells (rDPSCs).[74] Besides, AR-A014418 effectively inhibited the NLRP3 inflammasome, cleaved caspase-1 as well as pro-inflammatory factors of TNF-α, IL-6, CXCL1, and IL-1β within a dose-dependent response on rDPSCs.[75] EMD have been proved to be used to facilitate periodontal regeneration. Primary macrophages extracted from mouse bone marrow along with RAW 264.7 were pre-treated with EMD before LPS stimulation, which resulted in a notable reduction in NLRP3. Simultaneously, the levels of caspase-1 and IL-1β were downregulated among RAW 264.7.[76] Curcumin exhibited anti-inflammatory properties by inhibiting the phosphorylation of NF-κB p65 and inactivating NLRP3 inflammasome in human dental pulp stem cells (hDPSCs). In inflammatory hDPSCs induced by LPS and ATP, curcumin not only markedly reduced the activation of NLRP3, ASC, caspase-1, and IL-1β, but also suppressed phosphorylation of p65. Meanwhile, downregulated pro-inflammatory factors of IL-6, IL-8, TNF-α and COX-2 associated with NF-κB pathway.[77]

Also, the therapies targeting pyroptosis show equal potential in the treatment of apical periodontitis, a more severe progression of pulpitis. In an in vivo model of periapical inflammation induced with Enterococcus faecalis, the expression of NLRP3, caspase-1, and IL-1β proteins was significantly elevated in inflamed tissues. Whereas the NF-κB inhibitor BAY 11–7082 effectively blocked Enterococcus faecalis LTA-induced NLRP3 inflammasome activation and IL-1β release by inhibiting the NF-κB pathway, suggesting that this drug might be used in the treatment of apical periodontitis.[78] In mouse experimental apical periodontitis demonstrated that NLRP3 was significantly overexpressed in apical periodontitis tissues, and NLRP3 inhibitor MCC950 could significantly decrease the proportion of Th17 cells, increase the proportion of Treg cells, and decrease the serum levels of IL-1β, IL-6, and IL-17, which resulted in attenuation of periapical inflammation and bone resorption. However, the NLRP3 activator nigericin showed the opposite effect.[79]

The pyroptosis inhibitor exhibits the potential to reduce pulp and periodontal tissue inflammation, inhibit bone resorption, alleviate pain, and promote restoration via the key processes such as interfering NLRP3 inflammasome activation, blocking GSDMD-mediated membrane perforation, inhibiting caspase-1 activity, and decreasing the release of inflammatory factors. Further validation of pyroptosis inhibitors' safety and efficacy in humans is necessary for clinical translation in future.

Conclusion

Recent studies have shown that pyroptosis is critical to the progression of pulpitis and its complications. Within this review, effects and roles of pyroptosis in pulpitis are summarized. Inflammasome is a key participant in pyroptosis, while

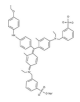
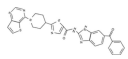
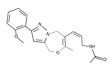
NLRP3, AIM2, and NLRP6 inflammasomes were all detected to be differentially characterized in inflamed dental pulp tissues (Table 1). In pulpitis, pyroptosis can be activated by multiple pathways, causing the cell membrane perforation and inducing the release of IL-1β and IL-18 as well as cellular contents to activate an intense inflammatory response, which may even lead to pain. Notably, the therapeutic strategies of pyroptosis have been shown to attenuate the inflammatory response of pulp cells (Table 2). In previous studies, it has been demonstrated that programmed cell

Table 1 Pathogenic Factors of Pyroptosis Related to Pulpitis

Cells	Pyroptosis Inducers	Inflammasome	Caspases	Gasdermins	Inflammatory Factors	References
HDPCs	Interferon γ and cytoplasmic DNA	AIM2	Caspase-1	N/A	IL-1β	[12]
HDPCs	LPS and LTA	NLRP6	Caspase-1/ 4	N/A	IL-1β and IL-18	[13]
THP-1 cells	LPS	NLRP3, AIM2	Caspase-1	N/A	IL-1β	[15]
HDPCs	Pg+ATP	NLRP3	N/A	N/A	IL-1β	[23]
HDPCs	LTA	NLRP3	Caspase-1	N/A	IL-1β,	[24]
THP-1 cells	Butyrate and Ef. LTA	NLRP3	Caspase-1/4	GSDMD	IL-1β	[25]
PDLFs, DPCs	Cytoplasmic LPS	N/A	Caspase-4	GSDMD	N/A	[26]
HPDLCs	LPS	NLRP6	N/A	N/A	IL-6 and TNF-α	[28]
HDPFs	LPS+ATP	NLRP3	Caspase-1	N/A	IL-1β	[29]
mDPC6T	mtDNA	NLRP3	Caspase-1	GSDMD	IL-1β, CXCL10 and IFN-β	[30]
mDPC6T	LPS+ATP and mitochondrial OS	NLRP3	Caspase-1	N/A	IL-1β, IL-6 and CXCL10	[31]
THP-1 cells	ONCL	NLRP3	Caspase-1	N/A	IL-1β, IL-6, IL-8, TNF-α, IFN-γ and CCL2	[34]
PBMCs	TEGDMA	NLRP3	N/A	N/A	IL-18 and IL-1β	[36]
hDPSCs	LPS+ATP	NLRP3	Caspase-1	N/A	IL-1β	[77]

Abbreviations: HDPCs, human dental pulp cells. PDLFs, periodontal ligament fibroblasts. DPCs, dental pulp cells. HDPFs, human dental pulp fibroblasts. HPDLCs, human periodontal membrane cells. mDPC6T, an odontoblast-like cell line. Mitochondrial OS, mitochondrial oxidative stress. THP-1 cells, human acute monocytic leukemia cell line. PBMCs, peripheral blood mononuclear cells. hDPSCs, human dental pulp stem cells.

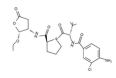
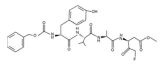
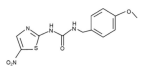
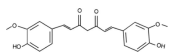
Table 2 Inhibitors of Pyroptosis

Name	Molecular Structure	Description	Mechanism	References
Brilliant Blue G (BBG)		P2X7 inhibitor	Elevates the pain threshold in rats with pulpitis and suppressed the expressions of NLRP3, IL-18 and IL-1β	[53]
MCC950		Alternative inhibitor of NLRP3 inflammasome	Downregulates the levels of GSDMD, IL-1β, caspase-1 p20 and IL-6	[24,54,55,79]
SC75741		NF-κB inhibitor	Reduces the IL-1β and partially inhibited the pyroptosis	[66]
GI-Y1		GSDMD inhibitor	Inhibits the oligomerization and membrane perforation activity of GSDMD-N	[62]
LDC7559		GSDMD inhibitor	Reduces the expression and cleavage of GSDMD	[63]

(*Continued*)

https://doi.org/10.2147/JIR.S516502

Table 2 (Continued).

Name	Molecular Structure	Description	Mechanism	References
VX765		Caspase-1 inhibitor	Suppresses IL-1β, MCP-1, IL-6, and IL-8 through inhibiting caspase-1	[68,69]
Z-YVAD-FMKGA		Caspase-1 inhibitor	Upregulates the mRNA expression of E-cadherin and decreased the caspase-1, IL-18, and IL-1β	[70]
AR-A014418		Inhibitor of glycogen synthase kinase 3b	Inhibits the NLRP3 inflammasome, cleaved caspase-1, TNF-α, IL-6, CXCL1, and IL-1β	[74,75]
Enamel matrix derivative	N/A	Xenograft to promote periodontal regeneration	Downregulates the levels of NLRP3, caspase-1, and IL-1β	[76]
Curcumin		Natural antioxidant	Inhibits the phosphorylation of NF-κB p65 and inactivated NLRP3 inflammasome	[77]

death exists in pulpitis including apoptosis,[80,81] autophagy,[47,82] and necroptosis.[83] However, studies related to the mechanisms of programmed cell death and the crosstalk between different ways of programmed cell death under pulpitis are expected to be enriched and explored in depth.

Also, most studies have only relied on in-vitro models. It is a potential direction to build an in-vivo model of rat pulpitis and explore the effect of pyroptosis on the occurrence and progression of pulpitis in the future.

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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.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Zychlinsky A, Prevost MC, Sansonetti PJ. Shigella flexneri induces apoptosis in infected macrophages. *Nature*. 1992;358(6382):6382):167–9. doi:10.1038/358167a0

2. Shi J, Gao W, Shao F. Pyroptosis: gasdermin-mediated programmed necrotic cell death. *Trends Biochem Sci*. 2017;42(4):245–254. doi:10.1016/j.tibs.2016.10.004
3. Cookson BT, Brennan MA. Pro-inflammatory programmed cell death. *Trends Microbiol*. 2001;9(3):113–114. doi:10.1016/s0966-842x(00)01936-3
4. Liston A, Masters SL. Homeostasis-altering molecular processes as mechanisms of inflammasome activation. *Nat Rev Immunol*. 2017;17(3):208–214. doi:10.1038/nri.2016.151
5. Shi J, Zhao Y, Wang Y, et al. Inflammatory caspases are innate immune receptors for intracellular LPS. *Nature*. 2014:514(7521):187–92. doi:10.1038/nature13683
6. Schwarzer R, Jiao H, Wachsmuth L, Tresch A, Pasparakis M. FADD and caspase-8 regulate gut homeostasis and inflammation by controlling MLKL- and GSDMD-mediated death of intestinal epithelial cells. *Immunity*. 2020;52(6):978–993.e6. doi:10.1016/j.immuni.2020.04.002
7. Pisciotta A, Bertani G, Bertoni L, et al. Modulation of cell death and promotion of chondrogenic differentiation by Fas/FasL in human dental pulp stem cells (hDPSCs). *Front Cell Dev Biol*. 2020;8:279. doi:10.3389/fcell.2020.00279
8. Aizawa E, Karasawa T, Watanabe S, et al. GSDME-dependent incomplete pyroptosis permits selective IL-1α release under caspase-1 inhibition. *iScience*. 2020;23(5):101070. doi:10.1016/j.isci.2020.101070
9. Wang Y, Gao W, Shi X, et al. Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin. *Nature*. 2017;547(7661):7661):99–103. doi:10.1038/nature22393
10. 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
11. 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
12. 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
13. Tian XX, Li R, Liu C, et al. NLRP6-caspase 4 inflammasome activation in response to cariogenic bacterial lipoteichoic acid in human dental pulp inflammation. *Int Endod J*. 2021;54(6):916–925. doi:10.1111/iej.13469
14. Yaghooti Khorasani MM, Yousefi A, Zainodini N. NLRP1 and NLRC4 inflammasomes are not responsible for the induction of inflammation in pulp tissues from carious teeth. *J Conserv Dent*. 2019;22(1):12–16. doi:10.4103/jcd.Jcd_195_18
15. Ran S, Liu B, Gu S, Sun Z, Liang J. 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
16. 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
17. Durand SH, Flacher V, Roméas A, et al. Lipoteichoic acid increases TLR and functional chemokine expression while reducing dentin formation in in vitro differentiated human odontoblasts. *J Immunol*. 2006;176(5):2880–2887. doi:10.4049/jimmunol.176.5.2880
18. Fawzy El-Sayed KM, Klingebiel P, Dörfer CE. Toll-like receptor expression profile of human dental pulp stem/progenitor cells. *J Endod*. 2016;42(3):413–417. doi:10.1016/j.joen.2015.11.014
19. Keller JF, Carrouel F, Colomb E, et al. Toll-like receptor 2 activation by lipoteichoic acid induces differential production of pro-inflammatory cytokines in human odontoblasts, dental pulp fibroblasts and immature dendritic cells. *Immunobiology*. 2010;215(1):53–59. doi:10.1016/j.imbio.2009.01.009
20. Sakamoto M, Rôças IN, Siqueira JF Jr, Benno Y. Molecular analysis of bacteria in asymptomatic and symptomatic endodontic infections. *Oral Microbiol Immunol*. 2006;21(2):112–122. doi:10.1111/j.1399-302X.2006.00270.x
21. Baumgartner JC, Siqueirajr JF Jr, Xia T, Rôças IN. Geographical differences in bacteria detected in endodontic infections using polymerase chain reaction. *J Endod*. 2004;30(3):141–144. doi:10.1097/00004770-200403000-00004
22. Siqueira JF Jr, Rôças IN. The microbiota of acute apical abscesses. *J Dent Res*. 2009;88(1):61–65. doi:10.1177/0022034508328124
23. 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
24. Al Natour B, Lundy FT, About I, Jeanneau C, Dombrowski Y, El Karim IA. Regulation of caries-induced pulp inflammation by NLRP3 inflammasome: a laboratory-based investigation. *Int Endod J*. 2023;56(2):193–202. doi:10.1111/iej.13855
25. Park OJ, Ha YE, Sim JR, et al. Butyrate potentiates enterococcus faecalis lipoteichoic acid-induced inflammasome activation via histone deacetylase inhibition. *Cell Death Discov*. 2023;9(1):107. doi:10.1038/s41420-023-01404-2
26. 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
27. Zanini G, Bertani G, Di Tinco R, et al. Dental pulp stem cells modulate inflammasome pathway and collagen deposition of dermal fibroblasts. *Cells*. 2024;13(10):836. doi:10.3390/cells13100836
28. 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
29. 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
30. Zhang YF, Zhou L, Mao HQ, Yang FH, Chen Z, Zhang L. 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
31. Wang K, Zhou L, Mao H, Liu J, Chen Z, Zhang L. Intercellular mitochondrial transfer alleviates pyroptosis in dental pulp damage. *Cell Prolif*. 2023;56(9):e13442. doi:10.1111/cpr.13442
32. 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
33. Jiang W, Sun S, Wang D, et al. MicroRNA-22 suppresses NLRP3/CASP1 inflammasome pathway-mediated proinflammatory cytokine production by targeting the HIF-1α and NLRP3 in human dental pulp fibroblasts. *Int Endod J*. 2022;55(11):1225–1240. doi:10.1111/iej.13814
34. 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

35. Hansel C, Leyhausen G, Mai UE, Geurtsen W. Effects of various resin composite (co)monomers and extracts on two caries-associated micro-organisms in vitro. *J Dent Res*. 1998;77(1):60–67. doi:10.1177/00220345980770010601
36. Alizadehgharib S, Östberg AK, Dahlgren U. Triethylene glycol dimethacrylate: adjuvant properties and effect on cytokine production. *Acta Biomater Odontol Scand*. 2018;4(1):1–9. doi:10.1080/23337931.2017.1409075
37. Kaufman G, Skrtic D. N-acetyl cysteine modulates the inflammatory and oxidative stress responses of rescued growth-arrested dental pulp microtissues Exposed to TEGDMA in ECM. *Int J mol Sci*. 2020;21(19):7318. doi:10.3390/ijms21197318
38. Huang Z, Zhang Q, Wang Y, et al. Inhibition of caspase-3-mediated GSDME-derived pyroptosis aids in noncancerous tissue protection of squamous cell carcinoma patients during cisplatin-based chemotherapy. *Am J Cancer Res*. 2020;10(12):4287–4307.
39. Wu F, Du Y, Hou X, Cheng W. A prognostic model for oral squamous cell carcinoma using 7 genes related to tumor mutational burden. *BMC Oral Health*. 2022;22(1):152. doi:10.1186/s12903-022-02193-3
40. Varfolomeev EE, Schuchmann M, Luria V, et al. Targeted disruption of the mouse caspase 8 gene ablates cell death induction by the TNF receptors, Fas/Apo1, and DR3 and is lethal prenatally. *Immunity*. 1998;9(2):267–276. doi:10.1016/s1074-7613(00)80609-3
41. 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
42. Sarhan J, Liu BC, Muendlein HI, et al. Caspase-8 induces cleavage of gasdermin D to elicit pyroptosis during Yersinia infection. *Proc Natl Acad Sci USA*. 2018;115(46):E10888–e10897. doi:10.1073/pnas.1809548115
43. Zhang J, Zhou B, Sun R, et al. The metabolite α-KG induces GSDMC-dependent pyroptosis through death receptor 6-activated caspase-8. *Cell Res*. 2021;31(9):980–997. doi:10.1038/s41422-021-00506-9
44. Rogers C, Fernandes-Alnemri T, Mayes L, Alnemri D, Cingolani G, Alnemri ES. Cleavage of DFNA5 by caspase-3 during apoptosis mediates progression to secondary necrotic/pyroptotic cell death. *Nat Commun*. 2017;8(1):14128. doi:10.1038/ncomms14128
45. Taabazuing CY, Okondo MC, Bachovchin DA. Pyroptosis and apoptosis pathways engage in bidirectional crosstalk in monocytes and macrophages. *Cell Chem Biol*. 2017;24(4):507–514.e4. doi:10.1016/j.chembiol.2017.03.009
46. Tsuchiya K, Nakajima S, Hosojima S, et al. Caspase-1 initiates apoptosis in the absence of gasdermin D. *Nat Commun*. 2019;10(1):2091. doi:10.1038/s41467-019-09753-2
47. 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
48. Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. *Nature*. 2011;469(7329):221–225. doi:10.1038/nature09663
49. Monteleone M, Stanley AC, Chen KW, et al. Interleukin-1β maturation triggers its relocation to the plasma membrane for gasdermin-D-dependent and -independent secretion. *Cell Rep*. 2018;24(6):1425–1433. doi:10.1016/j.celrep.2018.07.027
50. Iula L, Keitelman IA, Sabbione F, et al. Autophagy mediates interleukin-1β secretion in human neutrophils. *Front Immunol*. 2018;9:269. doi:10.3389/fimmu.2018.00269
51. Wu L, Zhao H, Zhang M, et al. Regulated cell death and inflammasome activation in gut injury following traumatic surgery in vitro and in vivo: implication for postoperative death due to multiorgan dysfunction. *Cell Death Discov*. 2023;9(1):409. doi:10.1038/s41420-023-01647-z
52. Li H, Guan J, Chen J, et al. Necroptosis signaling and NLRP3 inflammasome cross-talking in epithelium facilitate Pseudomonas aeruginosa mediated lung injury. *Biochimica Et Biophysica*. 2023;1869(3):166613. doi:10.1016/j.bbadis.2022.166613
53. 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
54. Zhao Z, Ming Y, Li X, et al. Hyperglycemia aggravates periodontitis via autophagy impairment and ROS-inflammasome-mediated macrophage pyroptosis. *Int J mol Sci*. 2023;24(7). doi:10.3390/ijms24076309
55. Huang C, Zhang C, Yang P, et al. Eldecalcitol inhibits LPS-induced NLRP3 inflammasome-dependent pyroptosis in human gingival fibroblasts by activating the Nrf2/HO-1 signaling pathway. *Drug Des Devel Ther*. 2020;14:4901–4913. doi:10.2147/dddt.S269223
56. Han SX, He ZJ, Hu X, et al. Inhibiting NLRP3 inflammasome activation by CY-09 helps to restore cerebral glucose metabolism in 3xTg-AD mice. *Antioxidants*. 2023;12(3):722. doi:10.3390/antiox12030722
57. Jiang H, He HB, Chen Y, et al. Identification of a selective and direct NLRP3 inhibitor to treat inflammatory disorders. *J Exp Med*. 2017;214 (11):3219–3238. doi:10.1084/jem.20171419
58. Lonnemann N, Hosseini S, Marchetti C, et al. The NLRP3 inflammasome inhibitor OLT1177 rescues cognitive impairment in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci USA*. 2020;117(50):32145–32154. doi:10.1073/pnas.2009680117
59. Marchetti C, Swartzwelter B, Gamboni F, et al. OLT1177, a ß-sulfonyl nitrile compound, safe in humans, inhibits the NLRP3 inflammasome and reverses the metabolic cost of inflammation. *Proc Natl Acad Sci USA*. 2018;115(7):E1530–E1539. doi:10.1073/pnas.1716095115
60. Teng JF, Mei QB, Zhou XG, et al. Polyphyllin VI induces caspase-1-mediated pyroptosis via the induction of ROS/NF-κB/NLRP3/GSDMD signal axis in non-small cell lung cancer. *Cancers*. 2020;12(1):193. doi:10.3390/cancers12010193
61. Hu JJ, Liu X, Xia SY, et al. FDA-approved disulfiram inhibits pyroptosis by blocking gasdermin D pore formation. *Nat Immunol*. 2020;21(7):736–+. doi:10.1038/s41590-020-0669-6
62. Zhong L, Han J, Fan X, et al. Novel GSDMD inhibitor GI-Y1 protects heart against pyroptosis and ischemia/reperfusion injury by blocking pyroptotic pore formation. *Basic Res Cardiol*. 2023;118(1):40. doi:10.1007/s00395-023-01010-4
63. Cai W, Wu Z, Lai J, et al. LDC7559 inhibits microglial activation and GSDMD-dependent pyroptosis after subarachnoid hemorrhage. *Front Immunol*. 2023:141117310. doi:10.3389/fimmu.2023.1117310
64. Humphries F, Shmuel-Galia L, Ketelut-Carneiro N, et al. Succination inactivates gasdermin D and blocks pyroptosis. *Science*. 2020;369 (6511):1633–+. doi:10.1126/science.abb9818
65. Yang X, Wu YL, Zhang ML, et al. Piceatannol protects against age-related hearing loss by inhibiting cellular pyroptosis and inflammation through regulated Caspase11-GSDMD pathway. *Biomed Pharmacother*. 2023:163114704. doi:10.1016/j.biopha.2023.114704
66. Sun B-J, Chen M-H, Zhang W-H, et al. Palmitic acid induces GSDMD-mediated pyroptosis in periodontal ligament cells via the NF-κB pathway. *Oral Dis*. 2023;30(4):2546–2557. doi:10.1111/odi.14648
67. Pang Y, Liu L, Wu S, Wang J, Liu L. Synoviolin alleviates GSDMD-mediated periodontitis by suppressing its stability. *Immun Inflam Dis*. 2023;11 (7). doi:10.1002/iid3.880

68. Cheng R, Feng Y, Zhang R, Liu W, Lei L, Hu T. The extent of pyroptosis varies in different stages of apical periodontitis. *Biochimica Et Biophysica*. 2018;1864(1):226–237. doi:10.1016/j.bbadis.2017.10.025
69. McKenzie BA, Mamik MK, Saito LB, et al. Caspase-1 inhibition prevents glial inflammasome activation and pyroptosis in models of multiple sclerosis. *Proc Natl Acad Sci USA*. 2018;115(26):E6065–E6074. doi:10.1073/pnas.1722041115
70. Li Y, Li B, Liu Y, et al. Porphyromonas gingivalis lipopolysaccharide affects oral epithelial connections via pyroptosis. *J Dental Sci*. 2021;16(4):1255–1263. doi:10.1016/j.jds.2021.01.003
71. Parajuli B, Sonobe Y, Horiuchi H, Takeuchi H, Mizuno T, Suzumura A. Oligomeric amyloid β induces IL-1β processing via production of ROS: implication in Alzheimer's disease. *Cell Death Dis*. 2013;4e975. doi:10.1038/cddis.2013.503
72. Pan P, Shen MM, Yu ZY, et al. SARS-CoV-2 N protein promotes NLRP3 inflammasome activation to induce hyperinflammation. *Nat Commun*. 2021;12(1):4664. doi:10.1038/s41467-021-25015-6
73. Sorolla A, Yeramian A, Dolcet X, et al. Effect of proteasome inhibitors on proliferation and apoptosis of human cutaneous melanoma-derived cell lines. *Br J Dermatol*. 2008;158(3):496–504. doi:10.1111/j.1365-2133.2007.08390.x
74. Xie H, Lin Y, Fang F. Glycogen synthase kinase-3β inhibitor promotes the migration and osteogenic differentiation of rat dental pulp stem cells via the β-catenin/PI3K/Akt signaling pathway. *J Dent Sci*. 2022;17(2):802–810. doi:10.1016/j.jds.2021.09.035
75. Xie H, Lin Y, Fang F. AR-A014418, a glycogen synthase kinase-3β inhibitor, mitigates lipopolysaccharide-induced inflammation in rat dental pulp stem cells via NLR family pyrin domain containing 3 inflammasome impairment. *J Dent Sci*. 2023;18(4):1534–1543. doi:10.1016/j.jds.2023.03.010
76. Sordi MB, Cabral da Cruz AC, Panahipour L, Gruber R. Enamel matrix derivative decreases pyroptosis-related genes in macrophages. *Int J mol Sci*. 2022;23(9):5078. doi:10.3390/ijms23095078
77. Lan C, Qian Y, Wang Y, et al. The protective role of curcumin in human dental pulp stem cells stimulated by lipopolysaccharide via inhibiting NF-κB p65 phosphorylation to suppress NLRP3 inflammasome activation. *Clin Oral Investig*. 2023;27(6):2875–2885. doi:10.1007/s00784-023-04885-8
78. 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
79. 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
80. Li Z, Wu M, Liu S, et al. Apoptotic vesicles activate autophagy in recipient cells to induce angiogenesis and dental pulp regeneration. *Mol Ther*. 2022;30(10):3193–3208. doi:10.1016/j.ymthe.2022.05.006
81. Ni C, Wu G, Miao T, Xu J. Wnt4 prevents apoptosis and inflammation of dental pulp cells induced by LPS by inhibiting the IKK/NF-κB pathway. *Exp Ther Med*. 2023;25(2):75. doi:10.3892/etm.2022.11774
82. Wang X, Wu Z, Zhang Y, Lian B, Ma L, Zhao J. Autophagy induced by hypoxia in pulpitis is mediated by HIF-1α/BNIP3. *Arch Oral Biol*. 2024;159105881. doi:10.1016/j.archoralbio.2024.105881
83. Tanaka A, Hayano S, Nagata M, Kosami T, Wang Z, Kamioka H. Ruxolitinib altered IFN-β induced necroptosis of human dental pulp stem cells during osteoblast differentiation. *Arch Oral Biol*. 2023;155105797. doi:10.1016/j.archoralbio.2023.105797