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REVIEW

Pyroptosis in bone loss

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Abstract

Pyroptosis could be responsible for the bone loss from bone metabolic diseases, leading to the negative impact on people's health and life. It has been shown that osteoclasts, osteoblasts, macrophages, chondrocytes, periodontal and gingival cells may be involved in bone loss linked with pyroptosis. So far, the involved mechanisms have not been fully elucidated. In this review, we introduced the related cells involved in the pyroptosis associated with bone loss and summarized the role of these cells in the bone metabolism during the process of pyroptosis. We also discuss the clinical potential of targeting mechanisms in the osteoclasts, osteoblasts, macrophages, chondrocytes, periodontal and gingival cells touched upon pyroptosis to treat bone loss from bone metabolic diseases as well as the challenges of avoiding potential side effects and producing efficient treatment methods.

Keywords Pyroptosis · NLRP3 · Inflammasome · Bone loss · Osteoclast

Abbreviations

TLR	Toll-like receptors
OVX	Ovariectomy
BMMs	Mouse bone marrow cells
MSCs	Mesenchymal stem cells
BMSCs	Bone marrow stromal cells
NOMID	Neonatal onset multisystem inflammatory disease
HMGB1	High mobility group box 1
PTOA	Post-traumatic osteoarthritis
Lico A	Licochalcone A
ASIC1a	Acid-sensing ion channel 1a
TXNIP	Thioredoxin-interacting protein
HPDLCs	Human periodontal ligament cells
HPDLFs	Human periodontal ligament fibroblasts
PDL	Human periodontal ligament
GCF	Gingival crevicular fluid
HGFs	Human gingival fibroblasts

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Introduction

Over 200 million people worldwide are suffering from bone metabolic diseases that result in bone loss, including osteoporosis, rheumatoid arthritis, psoriatic arthritis, and periodontitis [1, 2], which represents increasing medical and socio-economic challenges [3]. The primary cause of bone loss is an imbalance between osteoclastic bone resorption and osteoblastic bone formation [4]: the increased osteoclast activities and dysregulated osteoblast activities contributes to excessive bone loss [5]. Actually, in bone metabolic diseases, it is clear that multiple inflammatory factors and inflammatory signaling pathways are fundamentally linked to osteoclast and osteoblast activities in the process of bone loss [6, 7]. Moreover, the process of bone resorption and formation can be mediated by the inflammatory response, leading to bone loss caused by a great number of autoinflammatory diseases [8, 9]. For instance, researchers have shown that particular stimulation of the body contributed to an increase in the innate immune function, thus upregulating the tumor necrosis factor α (TNF-α) from activated T cells as an inflammatory factor and facilitating bone loss [10]. The immune system

and bone loss are mutually also influential: an imbalance in the immune system, resulting in inflammatory stimuli may induce an imbalance in bone turnover via induction of osteoclast differentiation and inhibition of osteoblast differentiation, leading to various bone metabolic diseases [11, 12]; meanwhile, bone cells, including osteoblasts, osteoclasts, osteocytes, periodontal and gingival cells influence the cellular functions of immune cells and contribute to immune regulation by modulating immune cell differentiation and/or function through the maintenance of the bone marrow microenvironment [13].

Pyroptosis, a form of programmed cell death accompanied by inflammation and immune response [14], is described as a critical area of interest within the field of the immune system and the accompanying bone loss, which gradually attracts higher attention in the near future [15]. Canonically, pyroptosis launches after pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) were recognized by pattern recognition receptors (PRRs) [16, 17]. Then, PRRs interact and activate the apoptosis-associated speck-like protein (ASC) that then oligomerizes and uses its caspase activation and recruitment domain (CARD) to bind to the CARD of pro-caspase-1 [18]. One common inflammasome consists of nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain containing 3 (NLRP3), ASC and pro-caspase-1 [19, 20]. The assembly of inflammasome triggers the activation of caspase-1 to cleave gasdermin D (GSDMD) and pro-IL-1β/IL-18 into their mature forms [21]. Then, GSDMD interacts preferentially with membrane lipids to form transmembrane pores and induces cells to swell until the cell membrane ruptures, allowing the release of cellular contents (e.g. IL-1β and IL-18), triggering a strong inflammatory response [6, 7]. Additionally, the canonical pathway also exploits toll-like receptors (TLRs) and tumor necrosis factor receptor (TNFR) that are stimulated via aging, infection, estrogen deficiency or inflammatory condition for priming particular PRRs to induce Nuclear factor kappa B (NF-kB) signaling [8, 9], resulting in increased expression of NLRP3, pro-IL-1β, and pro-IL-18 [10], and subsequently NLRP3 is activated, leading to the assembly of inflammasome assembly and the maturation of caspase-1 [22]. Differently, in the noncanonical pathway, intracellular lipopolysaccharides (LPS) of Gram-negative bacteria can be recognized [23], and LPS directly binds to CARD of caspase-11 in rodents or caspase 4/5 in humans (instead of caspase 1), resulting in the activation of caspase-4/5/11 [24, 25]. The caspase-4/5/11 cleaves GSDMD that is oligomerized and transferred to the cell membrane to form plasma membrane pores, leading to the development of pyroptosis [26, 27]. However, caspase-4/5/11 cannot directly cleave pro-IL-1β/pro-IL-18 [16, 26], but they can regulate the maturation and secretion of IL-1β/IL-18 via the NLRP3/caspase-1 pathway.

Appropriate pyroptosis induces strong inflammatory reactions and immune response to aid in host defenses infection, while excessive pyroptosis leads to numerous inflammatory diseases, including bone metabolic disorders [5, 16]. Sartoretto et al. have reported that inflammasome activities including pyroptosis could not only negatively affect host immune defense but also influence osteoclastic bone resorption and osteoblastic bone formation [28]. For instance, during the process of pyroptosis, PAMPs and DAMPs can activate the inflammasome in osteoclasts, promote the production of IL-1β and TNF-α to induce excessive inflammasome activities [29], and stimulate osteoclast differentiation, thus resulting in bone loss [30, 31]. Moreover, the pyroptosis of osteoblasts may induce the release of IL-1β and RANKL, further leading to bone loss [32]. In fact, osteoclasts, osteoblasts, macrophages, chondrocytes, periodontal and gingival cells are all involved in the process of pyroptosis, which eventually leads to bone loss and causes bone metabolic diseases [5, 16, 33].

In this review, we introduced recent advancements and insights into the potential specific mechanisms of pyroptosis in bone loss and summarized the various role of different cells as crucial parts during the process of pyroptosis in osteoclastic bone resorption and osteoblastic bone formation. Furthermore, we discussed the promising potential and underlying challenges of therapeutic strategies for pyroptosis in bone loss and proposed the direction for the development of the identification of therapeutic targets and the development of novel anti-inflammatory drugs.

Pyroptosis

Pyroptosis is defined as a programmed death, which causes cells to swell until the cell membrane ruptures, resulting in the release of cell contents and activating a strong inflammatory response [34]. The process of pyroptosis is classified into the canonical pathway that depends on caspase-1 and the noncanonical pathway that depends on caspase-4/5/11 [16]. As pathogen invasion and tissue damage activate innate immunity, the canonical pathway subsequently commences with the assembly of inflammasomes (an intracellular supramolecular protein complex) that occurs in response to PAMPs and DAMPs(such as toxins, pathogens, metabolites and nucleic acids) [35]. The canonical inflammasome sensors (one component of canonical inflammasome) can be divided into NOD-like receptors (NLRs) [36], melanoma 2 (AIM2)-like receptors (ALRs) [37], and tripartite motif family (TRIM) [38]. Among them, NLRP3 is the well-studied inflammasome sensor in the NLR family and displays an essential role in the innate immune as an important factor of pyroptosis [39], requiring signals to activate: the NF-κB-dependent pathway (an critical pathway in osteoclastic

activities) [32] and varieties of stimulus (e.g. PAMPs and DAMPs) [40]. The TLR and TNFR stimulated by aging, infection, estrogen deficiency or inflammatory condition can also prompt NF-kB signaling, leading to the upregulated expression of NLRP3, pro-IL-1β, and pro-IL-18 [41, 42]. Upon stimulation, NLRP3 recruits the adaptor ASC through PYD-PYD domain association [43]. With NLRP3, ASC further recruits pro-caspase-1 through CARD-CARD domain interaction, forming the signaling ternary complex known as the inflammasome [44]. Activated caspase-1 cleaves GSDMD into a hydrophilic GSDMD-C-terminal domain and a lipophilic GSDMD-N-terminal domain [45] that is anchored on the cell membrane and polymerizes to form a hollow diameter cyclic oligomer (GSDMD pores). Subsequently, the regular permeability barrier of the plasma membrane is disrupted by breaking the concentration gradients of sodium and potassium, resulting in osmotic pressure changes [46], meanwhile, with more pores forming, eventful swelling leads to membrane rupture [47]. Moreover, in this process, the IL-1β and IL-18 precursors are also cleaved into the mature form by caspase-1, and then the mature IL-1β and IL-18 released via the GSDMD pores or later during membrane rupture [48]. It has been reported that IL-1β can stimulate the level of RANKL in osteoblasts or bone marrow mesenchymal stem cells as well as the osteoclasts activities [49]. Furthermore, IL-1β can bind with its receptors on macrophages to induce the expression of RANKL that binds with RANK on the osteoclast precursors to promote osteoclast differentiation [50]. IL-18 are closely concerned with IL-1β since they belong to the same family, and IL-18 also facilitates osteoclast differentiation via various pathways [51]. For example, the increased IL-18 in ovariectomized (OVX) mice promoted the differentiation from peripheral monocytes to osteoclasts and activated the molecules related to NLRP3 inflammasome, as well as suppressed osteoblast activities [52, 53]. Notably, NLRP3 is one of the most prevalent inflammatory bodies linked to numerous disorders, such as cardiovascular disease, diabetes, multiple sclerosis, and cancer [8]. Obviously, IL-1β and IL-18 as well as NLRP3 are critical factors contributing to the release of caspases and resulting in the programmed cell death caused by pyroptosis [21, 32].

In the noncanonical pathways, stimulated by direct interactions between lipid A of cytoplasmic LPS from Gram-negative bacteria and CARD of caspase [54], the caspase-11 in rodents (caspase-4/-5 in human) activated and oligomerized, [55] thus cleaving GSDMD to release its N-terminus, forming pore and resulting in cell rupture [26, 56]. Meanwhile, although caspase-4/5/11 cannot directly cleave pro-IL-1β/pro-IL-18 [16, 26], the enhanced cellular stress induced by noncanonical inflammasome activation may contribute to the activation of the canonical NLRP3/caspase-1 pathway, thereby increasing the secretion of IL-1β and IL-18 [57] (Fig. 1).

Pyroptosis in bone loss

The delicate balance between bone resorption and formation is a complex process involving the regulation of pyroptosis that could be effectively modulated via the activities of osteoclasts, osteoblasts, macrophages, chondrocytes, periodontal and gingival cells. Compelling evidence has demonstrated that canonical inflammasomes are composed to activate caspase-1, produce mature IL-1β and IL-18, and bring about pyroptosis in response to PAMPs and DAMPs, meanwhile noncanonical caspases bind to stimuli including LPS, and contribute to pyroptosis. The improper activation of inflammasomes may lead to a pro-inflammatory microenvironment and excessive cell rupture, thus leading to the involved bone loss in the bone metabolic diseases [39]. Here we summarize various cells that have specific influence on bone loss under the regulation of pyroptosis, and how the mechanisms are engaged in the bone loss related to the pyroptosis.

Pyroptosis in osteoclasts

Osteoclasts are the main functional cells mediating bone resorption [58, 59]. A variety of immune cytokines and receptors participate in bone metabolism by regulating the function of osteoclasts. On the other hand, recent studies point out that certain signals in osteoclast formation (e.g., NFATc1 and NF-κB) also play roles in normal and aberrant immune responses, lymph node formation, and inflammatory arthritis, opening up new frontiers in osteoimmunology [60]. In detail, osteoclasts and osteoclast precursors (OCPs) regulate bone immune responses by means of direct cell–cell contacts through ligands and receptors, such as semaphorins (Semas) and plexins, and Ephs and ephrins [60]. For instance, osteoblast-expressed Sema6d signal through binding to receptor plexin to enhance OC formation by activating NFATc1 and promote OC activation by producing podosome [61]. Moreover, ephrin B2 on the surface of OCPs binding to receptor Eph4 on osteoblastic cells reduces the expression of c-Fos and NFATc1, inhibiting OC formation [62].

According to their immune function of osteoclasts, during inflammatory processes, osteoclasts could serve as major participants and regulators of the pyroptosis to affect bone immune status [63]. PAMPs and DAMPs can activate inflammasomes in osteoclasts and OCPs, prompting hyper multinucleation and IL-1β production [31]. Some essential factors associated with pyroptosis activator of nuclear factor-κB ligand (RANKL), macrophage colony-stimulating factor (M-CSF), TNF-α, and IL family,

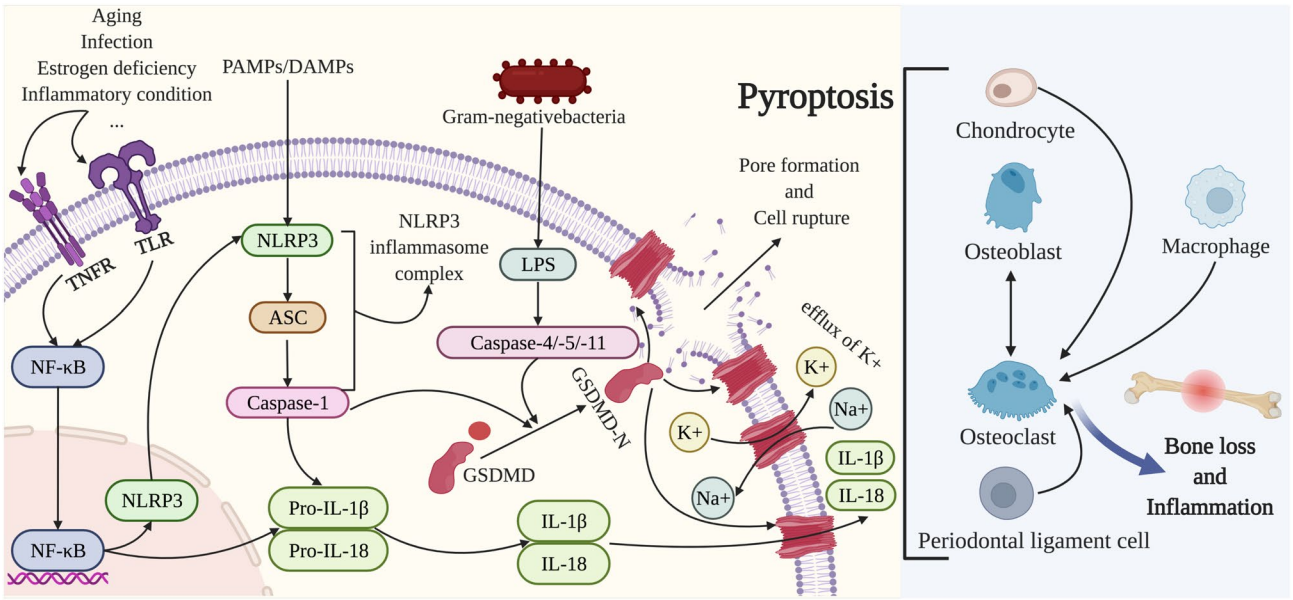

Fig.1 Pyroptosis modulates the activities of osteoclasts, osteoblasts, macrophages, chondrocytes, and periodontal ligament cells to play a non-negligible role in bone loss. In the canonical pathway, after exposure to PAMP and DAMP, NLRP3 inflammasome is activated and followed by the recruitment of ASC and pro-caspase-1, subsequently producing the pro-inflammatory cytokines IL-1β and IL-18. The activation mediated by aging, infection, estrogen deficiency or inflammatory condition of TLR or TNFR prompts NF-kB signaling, causing increased expression of NLRP3, pro-IL-1β, and pro-IL-18. In the noncanonical pathway, caspase-4/-5/-11 is activated upon binding to LPS of Gram-negative bacteria. Caspase-1 and caspase-4/-5/-11 cleave GSDMD into a GSDMD-N-terminal domain which anchors in the cell membrane and results in cell rupture as well as the efflux of K+. In the process of pyroptosis, inflammasomes facilitate osteoclast activities and thus improve the bone resorption ability of osteoclasts. Osteoblasts, chondrocytes, periodontal ligament cells, and macrophages can elevate osteoclast activity in the context of inflammasome activation, meanwhile, the decreased osteoblast activity and increased pyroptosis of osteoblasts and periodontal ligament cells can directly upregulate bone loss and inflammation

stimulate further differentiation and fusion of OCPs into multinucleated osteoclasts, leading to bone loss [64, 65] (Table 1).

As a crucial participant in pyroptosis, NLRP3 can regulate the immune status of bone, ultimately leading to bone resorption, and a hyperactive NLRP3 inflammasome can also enhance osteoclast bone resorption ability by reorganizing the actin cytoskeleton [73]. Recent studies have shown that the intervention on NLRP3 can affect osteoclast pyroptosis and thereby modulate bone loss. The study by Chen et al. showed that NLRP3 could regulate the bone loss in ligature-induced periodontitis by promoting osteoclastic differentiation, while MCC950, a potent inhibitor of the NLRP3 inflammasome, could inhibit bone loss with decreased IL-1β activation and osteoclast differentiation in ligature-induced periodontitis [67]. Moreover, the interference effect of MCC950 on NLRP3 seems to be affected by age. In the age-related alveolar bone loss from periodontitis, Zang et al. found that the treatment with MCC950 significantly suppressed alveolar bone loss with reduced caspase-1 activation in aged mice but not in young mice [68]. However, in the Aggregatibacter actinomycetemcomitans (Aa) induced periodontal disease, results from Rocha et al. suggested that NLRP3 inflammasome did not play a significant role in inflammation and bone resorption in vivo but caspase-1 had an affirmative role in alveolar bone resorption [74].

In addition, it has been demonstrated that diabetes increases fracture risk and impairs bone repair [79]. Numerous studies have shown a strong link between diabetes and inflammation: diabetes generates higher inflammatory cytokines, which stimulate the development of osteoclasts and suppress fracture healing [80–82]. The inflammatory cascade accelerates the synthesis of advanced glycosylation end products (AGEs) and increases the production of reactive oxidants, causing diabetic patients to experience increased bone resorption and delayed fracture repair [83]. Notably, a high-glucose environment can upregulate the activity of NLRP3, which accordingly promotes bone loss and meanwhile, under diabetic conditions, overexpression of NLRP3 has been demonstrated to cause stronger inflammatory cytokines and subsequently promote diabetic-induced impaired fracture healing [84, 85]. It has been reported that the exposure to high glucose concentrations of mouse bone marrow cells (BMMs) upregulated NLRP3 inflammasome expression via reactive oxygen species (ROS)/MAPKs/NF-kB pathway, while NF-κB inhibitors significantly reduce the expression level of NLRP3 inflammasome and alleviate bone resorption [69]. In a similar pathway, a study by Alippe

Table 1 The regulation of pyroptosis on the osteoclast in the process of bone loss

Target of action	Intervention	Mechanism	Experimental models	Effect	Diseases	References
NLRP3	Signals originating from bone matrix	NLRP3/IL-1β	Mice	Promoted bone loss	Not given	[66]
NLRP3	MCC950	NLRP3/IL-1β	Mice	Inhibited bone loss	Ligature-induced periodontitis	[67]
NLRP3	MCC950	NLRP3/IL-1β	Aged mice	Inhibited bone loss	Periodontitis	[68]
NLRP3	High glucose Induced ROS	ROS/MAPKs/NF-κB/ NLRP3	BMMs	Promoted bone loss	Osteoporosis	[69]
NLRP3	Exosomes from derived MSCs	NLRP3/IL-1β	Diabetic osteoporosis rats	Inhibited bone loss	Osteoporosis	[70]
NLRP3	Glyburide	NLRP3/IL-1β	Mice	Inhibited bone loss	Diabetic-induced fracture	[71]
NLRP3	LncRNA ORLNC1	microRNA-200b-3p/ FoxO3/ CML	BMSCs	Inhibited bone loss	Osteoporosis	[72]
NLRP3	Not given	NLRP3/IL-1β	BMMs	Inhibited bone loss	NOMID	[73]
NLRP3	Not given	NLRP3/IL-1β	Mice	Inhibited bone loss	NOMID	[31]
Caspase-1	Aa	LPS/NLRP3/ caspase-1	Mice	Promoted bone loss	Periodontitis	[74]
RANKL	UA	NF-κB/NLRP3	OVX mice	Inhibited bone loss	Postmenopausal osteoporosis	[75]
IL-1β	Auranofin	IL-1β/RANKL	OVX mice	Inhibited bone loss	Osteoporosis	[76]
Smad3	Alendronate	Smad3/NLRP3/ASC	Murine OCPs	Promoted bone loss	Not given	[77]
RIPK1 / RIPK3	NEC-1 and GSK-872	MAPKs/NF-κB/ NLRP3	OVX mice	Inhibited bone loss	Osteoporosis	[78]

et al. demonstrated that the NLRP3 inflammasome is also activated when exposed to the signals originating from bone matrix under multiple bone turnover states (e.g., estrogen deficiency and persistent parathyroid hormone exposure), resulting in increased NF-κB and MAPK phosphorylation [66]. In osteoclasts, the effect of exposure to high concentrations of glucose could be reversed by exosomes originating from mesenchymal stem cells (MSCs) that inhibited the overactivated NLRP3 inflammasome [70]. Furthermore, glyburide is one of the most commonly prescribed medications for the treatment of diabetes [86], and it has been shown to accelerate the healing of diabetes-induced fractures while inhibiting NLRP3 activation in mouse and human macrophages [87]. Yang et al. proved that treatment of NLRP3 inflammasome inhibitor glyburide significantly decreased the expressions of TNF-α, and IL-6 in the fracture calluses in the diabetic-induced fracture model, as well as increased bone callus volume and bone volume fraction, contributing to diabetic-induced fracture healing [71].

Except for NLRP3, RANKL, IL-1β, and Smad3 are also the target of action to be regulated, affecting bone loss involved in pyroptosis. Tao et al. found that Urolithin A (UA) inhibited RANKL-triggered osteoclastogenesis in a concentration-dependent manner, which finally contributed to downregulated cytoplasmic secretion of IL-1β and IL-18 and reduced pyroptosis to inhibit bone loss [75]. Besides, Kim et al. have demonstrated that the expression of IL-1βmodulated by inflammasomes could be suppressed by auranofin to inhibit osteoclastogenesis induced by RANKL, critically decreasing the bone loss related to pyroptosis [76]. Moreover, Tamai et al. reported that alendronate could directly regulate Smad3 to accelerate IL-1β production and NLRP3-dependent pyroptosis, preventing OCPs from differentiation into osteoclasts and thus inhibiting bone loss [77] (Fig. 2).

Pyroptosis in osteoblasts

Osteoblasts, the bone-forming cells, are indispensable for bone metabolism, and the proliferation and differentiation of osteoblasts are essential elements in the bone loss from bone metabolic diseases [88]. Osteoblasts can differentiate from bone marrow mesenchymal stem cells (BMSCs), and the expression of NLRP3, ASC, caspase-1, IL-1β, and TNF-α can be also upregulated in response to LPS, thereby affecting the potential for osteogenic differentiation [89]. During the progression of bone loss, BMSCs exhibit inhibited osteogenic capacity, resulting in reduced bone formation [90], and it has been demonstrated that the NLRP3 inflammasome is involved in this process by affecting the differentiation of BMSCs via certain active molecules [91]. Besides, NLRP3 also directly inhibits

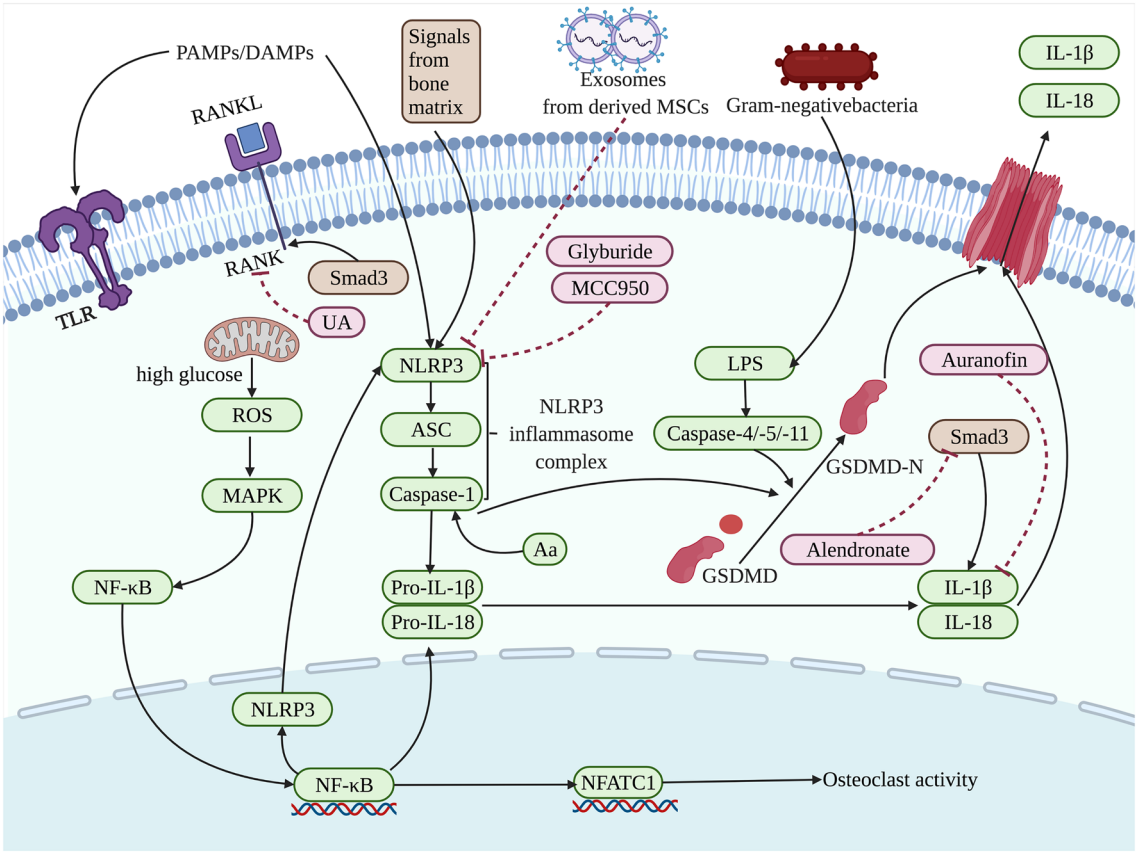

Fig. 2 The pyroptosis related to the osteoclasts in the process of bone loss is affected by the regulation on different targets of actions. Exposure to PAMPs or DAMPs and then influenced by NF-κB, the NLRP3 inflammasome complex assemblies and activates caspase-1 and subsequently results in the cleavage of the proinflammatory cytokines IL-1β and IL-18. Caspase-1 and caspase-4/-5/-11 cleave GSDMD into a GSDMD-N-terminal domain that anchors in the cell membrane, leading to the cell rupture. Signals from bone matrix [66], exosomes from derived MSCs [67], glyburide [71], and MCC950 [67, 68] have been developed in the presented pathway targeting NLRP3. Meanwhile, RANKL, IL-1β, and Smad3 are also the target of action to be regulated to affect bone loss involved in pyroptosis, which can be modulated by Aa [74], UA [75], Auranofin [76] or Alendronate [77], respectively. The factors that promote pyroptosis are indicated in green and pyroptosis-suppressor factors are indicated in pink as well as factors that can have both effects are indicated in brown

osteogenesis by influencing osteoblasts and plays a core role in osteoporosis induced by inflammation. In estrogen-deficient osteoporosis, direct bacterial infection was not observed but NLRP3 levels still rose, while the viability of osteoblasts was significantly increased and the bone loss was also relieved after NLRP3 was inhibited or inactivated [92]. McCall SH et al. also proved that osteoblasts highly expressed NLRP3 that mediated bacterially induced cell death and participated in bone loss during inflammation [93]. Actually, when NLRP3 inflammasomes increase in osteoblasts, the caspase-1 pathway is activated and the expression levels of IL-1 and IL-18 are upregulated, resulting in the death of osteoblasts [94, 95]. Moreover, osteoblasts undergoing pyroptosis will facilitate osteoclastogenesis and the activation of osteoclasts through increased production of cytokines and chemokines, such as RANKL, or decreased OPG levels, leading to increased bone loss [32] (Table 2).

In the process of pyroptosis, with the increase of NLRP3 inflammasome, the caspase-1 pathway is activated, and IL-1 and IL-18 are facilitated, contributing to the programmed death of osteoblasts [94, 95]. It has been demonstrated that in the auto-immune diseases including some bone metabolic diseases, NLRP3 inflammasome not only results in the severe bone loss caused by the activation of osteoclasts, but also mediates the osteoblast activity to prevent bone loss from the pyroptosis associated with NLRP3 inflammasome [96]. The results from Wang et al. have proved that NLRP3 inflammasome cascade activation was related to suppressed osteogenesis of MSCs (A type of cell that can differentiate into osteoblasts), while the downregulated capsase-1 induced osteogenic differentiation of MSCs, avoiding bone loss [100]. Recently, Lei et al. have discovered that IL-17 could prompt pyroptosis of osteoblasts involved in NLRP3 inflammasome pathway, which may promote the release of IL-1β as well as RANKL and subsequently further conduce

Table 2 The regulation of pyroptosis on the osteoblast in the process of bone loss

Target of action	Intervention	Mechanism	Experimental models	Effect	Diseases	References
NLRP3	NLRP3 knock-out	NFκB/NLRP3	Osteoblasts	Promoted bone loss	Not given	[96]
NLRP3	IL-17	IL-17/NLRP3	Osteoblasts	Promoted bone loss	Not given	[97]
NLRP3	Wnt/β-catenin signaling	melatonin/ Wnt/β-catenin signaling/ NLRP3	OVX mice	Inhibited bone loss	Osteoporosis	[98]
NLRP3	ROS produced by LPS	LPS/NLRP3	MG63 cells	Promoted bone loss	Periodontitis	[99]
NLRP3	TXNIP	TXNIP/NLRP3/ IL-1β	BMSCs	Inhibited bone loss	Not given	[89]
NLRP3	shRNA	shRNA/NLRP3/caspase-1/IL-1β	Rats	Inhibited bone loss	Diabetes	[85]
NLRP3/ caspase-1	LPS/PA	NLRP3/caspase-1/	MSCs	Promoted bone loss	Osteoporosis	[100]
NLRP3/ caspase-1	IL-18BP	NLRP3/caspase-1/ IL18	Osteoblasts	Promoted bone loss	Postmenopausal osteoporosis	[52]
caspase-1	High glucose	caspase-1/GSDMD/ IL-1β	ME3T3-E1 cells	Promoted bone loss	Alveolar bone disease	[101]
LPS	Necrosulfonamide	NLRP3/caspase-1/ GSDMD	Osteoblasts	Promoted bone loss	Bone fracture	[102]
NF-κB	PKR	PKR/NF-κB/NLRP3	Osteoblasts	Promoted bone loss	Periodontal disease	[103]

to bone loss [97]. Coincidentally, Mansoori et al. have reported that IL-18BP (a natural antagonist of pro-inflammatory IL-18 cytokine related to autoimmune disorders) that displayed the different role from IL-17 could suppress NLRP3 inflammasome and caspase-1, which promoted osteoblast differentiation, reduced osteoclastogenesis, and thus restored trabecular microarchitecture [52]. Beyond IL-18BP, the results from Xu et al. showed that Wnt/β-catenin signaling (participates in osteoblast differentiation) activated by melatonin could also inhibit NLRP3 inflammasome activity, weakening osteogenic differentiation and attenuating the bone loss [98]. Furthermore, it is noteworthy that hyperglycemia-induced exaggerated inflammatory response caused by elevated NLRP3 inflammasome activation impairs diabetic-induced alveolar bone defect healing [85, 104], it has been reported that NLRP3 and the released IL 1β lead to diabetes-associated persistent inflammatory responses that may lead to impaired bone healing of alveolar socket wounds [105]. The results in diabetic rats have proved that a lentiviral short hairpin RNA (shRNA) could negatively target NLRP3 and simultaneously induced the expression of osteogenic markers Runt-related transcription factor 2 and osteocalcin, suggesting that the inhibition of NLRP3 inflammasome could increase alveolar bone defect healing [85].

In the process of osteoblast-related pyroptosis, induced LPS can lead to increased expression of NLRP3, caspase-1, and so on, which promotes pyroptosis and cell migration injury of osteoblasts, contributing to concomitant bone damage. Liu et al. demonstrated that ROS produced by LPS in osteoblasts could lead to the pyroptosis of osteoblasts mediated by NLRP3 inflammasome as well as decreased cell migration, while MCC950, a potent inhibitor of the NLRP3 inflammasome, could enhance osteoblast migration and repair the expression of osteogenic differentiation-related proteins. And the inhibition of ROS with N-acetyl-L-cysteine could also weaken oxidative stress-mediated pyroptosis and improved migration injury in osteoblasts treated with LPS [99]. Moreover, it has been found that necrosulfonamide reversed the influence of LPS on cell viability and pyroptosis, as well as on the mRNA and protein expression of pyroptosis-related genes in osteoblasts, inhibiting the secretion of IL-6, TNF-α and IL-1β [102].

Apart from NLRP3, intervention on the caspase-1 and NF-κB signaling also affects osteoblasts involved in the process of pyroptosis. Yang et al. found that high glucose could produce the pyroptosis through the caspase-1/GSDMD/IL-1β pathway to inhibit the proliferation and differentiation of osteoblast in alveolar bone, resulting in the bone loss, while caspase-1 inhibitor could reverse the negative role of high glucose on the osteoblasts [101]. Additionally, the findings from Yoshida et al. suggested that in the *Porphyromonas gingivalis*-infected osteoblasts, the NF-κB signaling could be induced by double-stranded RNA-dependent kinase (PKR) to facilitate NLRP3, influencing the process of pyroptosis related to bone loss [103] (Fig. 3).

Pyroptosis in macrophages

Macrophages, the essential inflammatory cells involved in the bone metabolic diseases [106], possess the ability to

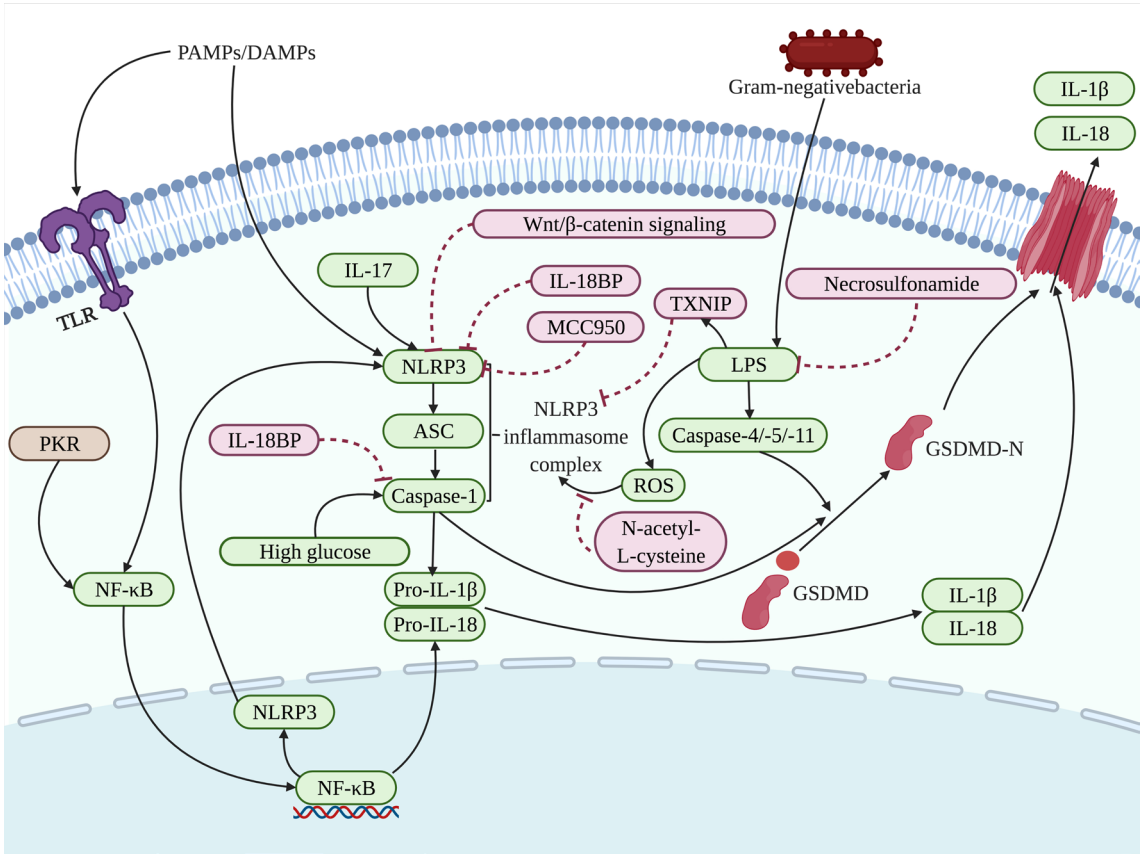

Fig.3 The pyroptosis related to the osteoblasts in the process of bone loss is affected by the regulation on different targets of actions. Exposure to PAMPs or DAMPs and then influenced by NF-κB, the NLRP3 inflammasome complex assemblies and activates caspase-1 and subsequently results in the cleavage of the proinflammatory cytokines IL-1β and IL-18. Caspase-1 and caspase-4/-5/-11 cleave GSDMD into a GSDMD-N-terminal domain that anchors in the cell membrane, leading to the cell rupture. Wnt/β-catenin signaling [98], IL-17 [97], IL-18BP [52], MCC950 [99], TXNIP [89], shRNA [85] and ROS that could be inhibited by N-acetyl-L-cysteine [99], have been developed in the presented pathway targeting NLRP3. Meanwhile, NF-κB, LPS and caspase-1 are also the target of action to be regulated by PKR [103], Necrosulfonamide [102], high glucose [101] or IL-18BP [52], affecting bone loss involved in pyroptosis. The factors that promote pyroptosis are indicated in green and pyroptosis-suppressor factors are indicated in pink as well as factors that can have both effects are indicated in brown

differentiate into osteoclasts and function as a part of the innate immune system [107]. Activated macrophages can polarize into pro-inflammatory M1-like macrophages or anti-inflammatory M2-like macrophages, both of which are characterized depending on cytokine release patterns and metabolic signatures [33, 108]. Macrophages can not only mediate bone loss in bone metabolism via their communication with osteoclasts during the pyroptosis, but also participate in the process of inflammasome activation in macrophages to facilitate bone destruction [109, 110]. Exposed to PAMPs/DAMPs or bacteria [111], the M1-like polarization of macrophages can be dependent on inflammasome activation which upregulates the levels of IL-1β and IL-18, causing the pyroptosis in pro-inflammatory microenvironment and thus leading to inflammatory bone loss [112, 113] (Table 3).

In orchestrated innate immune reactions in macrophages, the NLRP3 inflammasome could activate caspase-1 and promote the secretion of IL-1β as well as IL-18, meanwhile the inflammasome activity results in the progress of pyroptosis and the disorders of bone metabolism [114]. Lately, it has been demonstrated that the activation of NLRP3 inflammasome in M1 macrophages could prompt the levels of IL-1β and the development of inflammation and pyroptosis, thereby triggering bone loss [115]. NLRP3 could also be upregulated in macrophages by microorganisms (e.g., porphyromonas gingivalis, mycoplasma salivarium and staphylococcus aureus) to positively mediate the process of pyroptosis, inducing concomitant bone loss [116–119]. In the macrophages from wild-type and NLRP3-deficient mice, Yamaguchi et al. have found that porphyromonas gingivalis could activate innate immune cells through activating

Table 3 The regulation of pyroptosis on the macrophages in the process of bone loss

Target of action	Intervention	Mechanism	Experimental models	Effect	Diseases	References
NLRP3	LPS	NLRP3/caspase-1/IL-1β and IL-18	Mice	Promoted bone loss	Osteoporosis	[114]
NLRP3	HPDLCs stimulated by force	NLRP3/ IL-1β	Periodontal tissues and rats	Promoted bone loss	Root resorption	[115]
NLRP3	Porphyromonas gingivalis	Porphyromonas gingivalis/NLRP3/caspase-1/IL-1β and IL-18	Mice	Promoted bone loss	Periodontal disease	[116]
NLRP3	MARK4	MARK4/NLRP3/caspase-1/IL-1β and IL-18	Healthy and inflamed human gingival tissues	Promoted bone loss	Periodontitis	[117]
NLRP3	Mycoplasma salivarium	NLRP3/caspase-1/IL-1β	BMMs	Promoted bone loss	Periodontal disease	[118]
NLRP3	Staphylococcus aureus	NLRP3/caspase-1/GSDMD	Murine and human infectious bone fragments	Promoted bone loss	Osteomyelitis	[119]
NLRP3	glyburide	glyburide/NLRP3/caspase-1/IL-1β	Human monocyte cells	Inhibited bone loss	Periodontitis	[120]
NLRP3	dioscin	dioscin/NLRP3/caspase-1/IL-1β	BMMs and MC3T3-E1 cells	Inhibited bone loss	Apical periodontitis	[91]
NLRP3	lncRNA_1810058I24Rik lncRNA_Gm12474 lncRNA_Gm41514 Metformin	NLRP3/caspase-1/IL-1β and IL-18	Mice	Inhibited bone loss	Diabetes-associated periodontitis	[121]
NLRP3	resveratrol	Resveratrol/Pink1/Parkin/NLRP3/caspase-1/IL-1β and IL-18	Arthritis rats	Inhibited bone loss	Gouty arthritis	[122]
TLR4	MDP	TLR4/NLRP3/GSDMD	Macrophage of adjuvant arthritis rats	Inhibited bone loss	Adjuvant arthritis	[123]
caspase-1	cyclic stretch	cyclic stretch/AMPK/caspase-1/IL-1β	BMMs	Inhibited bone loss	Not given	[124]
caspase-1	cyclic stretch	cyclic stretch/AMPK/caspase-1/IL-1β	BMMs	Inhibited bone loss	Not given	[125]
caspase-1	DEX	HMGB1/DEX/caspase-1/IL-1β and IL-18	BMMs	Inhibited bone loss	infection and trauma-derived inflammation	[126]
caspase-1	cranberry PACs	cranberry PACs/caspase-1/IL-1β and IL-18	BMMs	Promoted bone loss	Periodontitis	[127]
NF-κB	PUN	PUN/NF-κB/NLRP3/caspase-1/IL-1β and IL-18	BMMs	Inhibited bone loss	rheumatoid arthritis	[128]
NF-κB	cyclic stretch	cyclic stretch/NF-κB/exosomes from HPDLCs/IL-1β	Human macrophages	Inhibited bone loss	Periodontitis	[129]
GSDMD	deficiency	GSDMD deficiency/caspase-1/IL-1β and IL-18	Mice	Inhibited bone loss	PTOA	[130]
AIM2	GSDMD	GSDMD/AIM2/caspase-1/IL-1β and IL-18	BMMs	Promoted bone loss	Francisella novicida infection	[131]

NLRP3 inflammasome, inducing proinflammatory cytokines during pyroptosis and subsequently enhancing alveolar bone loss [116]. Moreover, in the macrophages infected by porphyromonas gingivalis, overexpressed microtubule affinity regulating kinase 4 (MARK4) could further increased inflammasome activation and the pyroptosis, promoting alveolar bone loss [117]. Mycoplasma salivarium had the similar role with porphyromonas gingivalis, which could activate NLRP3 to induce IL-1β and promote periodontal disease accompanying bone loss [118]. Additionally, in the osteomyelitis, *staphylococcus aureus* displayed a key role on upregulating the expressions of NLRP3, caspase-1 as well as GSDMD to enhance pyroptosis and bone disruption, [119].

However, NLRP3 could also be inhibited by glyburide, dioscin, metformin and resveratrol, preventing the bone loss from the progress of pyroptosis. In pyroptosis and inflammation caused by periodontopathic bacteria-infected macrophages, sulfonylureas (such as glyburide) could directly downregulate the expression of NLRP3 and reduce the release of inflammatory cytokines, inhibiting inflammatory bone resorption [120]. Besides, Yin et al. have reported that in the macrophages, dioscin, a new NLRP3 inflammasome inhibitor, could not only suppress inflammatory cell infiltration but also prompt the expression of osteogenic-related factors in osteoblast, which enhanced osteogenesis as well as reduced osteoclastogenesis [91]. Furthermore, in macrophages, NLRP3 leads to a persistent inflammatory response and the release of inflammatory factors including IL-1β and IL-18, which also results in impaired healing of bone wounds induced by diabetes [132]. When it comes to diabetes-associated periodontitis and concomitant bone destruction, it has been proved that metformin could reverse NLRP3-induced pyroptosis and alveolar bone loss in BMMs from diabetes-associated periodontitis mice, and the role of both NLRP3 and GSDMD may also be modulated by lncRNA_1810058I24Rik, lncRNA_Gm12474 and lncRNA_Gm41514 [121]. Differently, resveratrol, a non-flavonoid phenolic substance, inhibited NLRP3 through launching the Pink1/Parkin pathway to induce mitophagy, attenuating bone loss [122]. Moreover, it has been investigated that monomer derivative of paeoniflorin (MDP) could restrain TLR4/NLRP3/GSDMD signaling pathway and decrease the expressions of TLR4, NLRP3, saspase-1, ASC, and GSDMD-N in vivo and in vitro, thereby reducing the ratio of macrophage-related pyroptosis and subsequently mitigating bone loss [123].

Furthermore, different targets of action could directly regulate the caspase-1, affecting the pyroptos related to the macrophages in the process of bone loss. Notably, in pyroptosis associated with macrophages, cyclic stretch could suppress NLRP3 inflammasome-dependent IL-1β secretion in BMMs via the inhibition of caspase-1 activity attributed to weakening the AMPK pathway, attenuating inflammation and concomitant bone loss [124, 125]. Moreover, it has been reported that dexmedetomidine (DEX) could also restrain the expression of caspase-1 and the process of pyroptosis, improving cellular injury in potential bone destruction due to inflammation [126]. However, Lagha et al. have revealed different results in suppressing pyroptosis by the repression of caspase-1: cranberry proanthocyanidins (PACs) could also repress the activation of caspase-1 in BMMs and consequently restrain the secretion of both IL-1β and IL-18, inhibiting pyroptosis, but lead to the development of periodontitis and the differentiation of osteoclasts through cell migration [127].

In addition to NLRP3 and caspase-1, the inhibition of NF-κB signaling by punicalagin (PUN) and cyclic stretch also reduces macrophage-related pyroptosis, ameliorating bone disruption [128, 129]. Gao et al. have found that the treatment of PUN could inhibit NF-κB signaling, and subsequently downregulates NLRP3 as well as caspase-1 to attenuate pyroptosis, thereby mitigating inflammatory cell death caused by the secretion of IL-1β and IL-18, while promoting macrophages to switch from an M1 pro-inflammatory phenotype to an M2 anti-inflammatory phenotype, ultimately repressing bone loss [128]. Moreover, NF-κB signaling in LPS-stimulated macrophages could be also retrained by cyclic stretch-induced exosomes from human periodontal ligament cells (PDLCs), which subsequently leads to the repression of IL-1β as well as inhibition of pyroptosis and concomitant alveolar bone loss [129] (Fig. 4).

Pyroptosis in chondrocytes

The immune and bone systems retain homeostasis through interplaying intently with each other, and arthritis is a pathological consequence of their interaction [133], which may be attributed to the immune responses from chondrocytes, resulting in bone loss [134]. In the chondrocytes in osteoarthritis, the expression of genes that encode proteins related to the inflammatory and catabolic responses is increased primarily by signal transduction pathways involving NF-κB and other factors activated via inflammation [135]. Meanwhile, with IL-1β and IL-18 into the synovial fluid following the activation of caspase-1 [136], the process of pyroptosis in chondrocytes and other cells induces proinflammatory cytokines and inflammatory response cascade in chondrocytes and other cells, ultimately contributing to bone loss [137] (Table 4).

In chondrocytes, the NF-κB signaling pathway induces the expression of proteins related to inflammation and metabolic responses, and promotes the role of inflammatory cytokines during pyroptosis, facilitating the development of pyroptosis and the concomitant bone loss [135], while it has been demonstrated that loganin and morroniside that both are the iridoid glycosides could suppress NF-κB

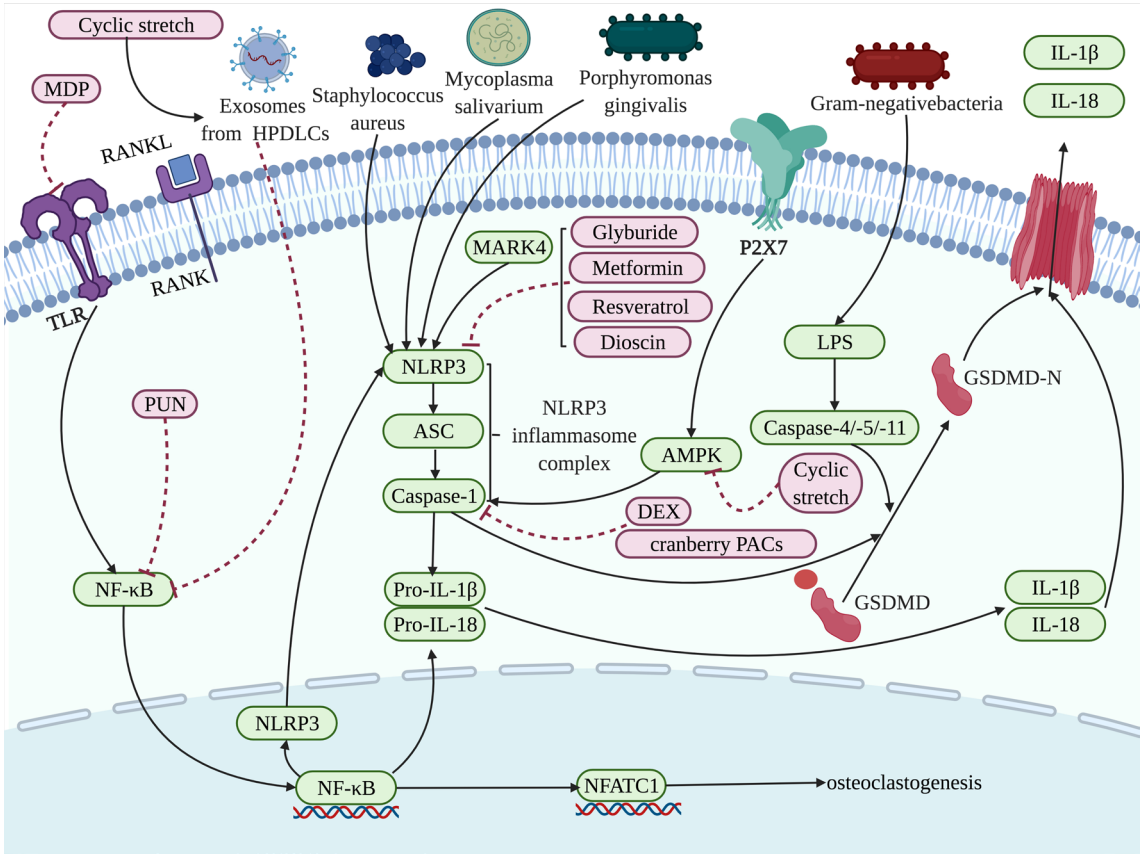

Fig.4 Different targets of action are regulated to affect the pyroptosis related to the macrophages in the process of bone loss. Influenced by NF-κB, the NLRP3 inflammasome complex assemblies and activates caspase-1 and subsequently results in the cleavage of the proinflammatory cytokines IL-1β and IL-18. Caspase-1 and caspase-4/-5/-11 cleave GSDMD into a GSDMD-N-terminal domain that anchors in the cell membrane, leading to the cell rupture. MARK4 [117], mycoplasma salivarium [118], staphylococcus aureus [119], and porphyromonas gingivalis [116] have been found in the presented pathway positively targeting NLRP3 to facilitate pyroptosis, yet glyburide [120], dioscin [91], metformin [121], resveratrol [122] target to suppress NLRP3. Meanwhile, caspase-1 is also the target of action to be modulated by P2X7/AMPK/cyclic stretch [124, 125] and DEX [126], cranberry PACs [127], affecting bone loss involved in pyroptosis. And NF-κB signaling is repressed by PUN [128] and cyclic stretch induced exosomes from human PDLCs [129]. The factors that promote pyroptosis are indicated in green and pyroptosis-suppressor factors are indicated in pink

signaling to inhibit pyroptosis, ameliorating bone loss [138, 139]. The results from mice have shown that loganin and morroniside could directly restrain NF-κB signaling, reducing the expression of MMP, NLRP3 and caspase-1 in chondrocytes, which suppressed the progression of inflammation and attenuated the loss of cartilage [138, 139]. In addition, NF-κB signaling could also be repressed by Licochalcone A through nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling and then NLRP3, ASC, GSDMD, caspase-1, IL-1β and IL-18 was decreased in the LPS-induced chondrocytes, reducing pyroptosis and the degeneration of bone [140]. Moreover, exosomes from BMSCs also target NF-κB signaling via delivering microRNA-326 to inhibit the levels of inflammatory cytokines and pyroptosis-related proteins, participating in the inhibition of chondrocyte-related pyroptosis and reducing bone loss [141]. Differently, the activated P2X7 directly targeted the crosstalk between NF-κB and NLRP3 to prompt pyroptosis, thereby aggravating the secretion of proinflammatory cytokines and the degradation of bone [142].

Beyond NF-κB signaling, NLRP3 can also be mediated by chemical compounds and ions to affect the regulation of pyroptosis on the chondrocytes in the process of bone loss [143, 144]. Wu et al. have found that the expression of the NLRP3 inflammasome could be enhanced by Ca^{2+} in acid-sensing ion channel 1a, inducing the pyroptosis in chondrocytes and causing accompanying bone loss [143]. However, icariin could alleviate the pyroptosis in chondrocytes by suppressing NLRP3 signaling and caspase-1 in vitro and in vivo, suggesting the potential of refraining bone loss [144] (Fig. 5).

Table 4 The regulation of pyroptosis on the chondrocytes in the process of bone loss

Target of action	Intervention	Mechanism	Experimental models	Effect	Diseases	References
NF-κB signaling	Loganin	Loganin/NF-κB/NLRP3/caspase-1	Mice	Inhibited bone loss	Osteoarthritis	[138]
NF-κB signaling	Morroniside	morroniside / NF-κB/NLRP3/caspase-1	Mice	Inhibited bone loss	Osteoarthritis	[139]
NF-κB signaling	Nrf2/HO-1	Licochalcone A / Nrf2/HO-1/NF-κB/LPS/NLRP3	Mice and osteoarthritis chondrocytes	Inhibited bone loss	Osteoarthritis	[140]
NF-κB signaling	MicroRNA-326 delivered by BMSC-derived exosomes	microRNA-326 NF-κB/NLRP3	Osteoarthritis chondrocytes	Inhibited bone loss	Osteoarthritis	[141]
NF-κB/NLRP3 crosstalk	P2X7	P2X7/NF-κB/NLRP3 crosstalk	Osteoarthritis chondrocytes	Promoted bone loss	Osteoarthritis	[142]
NLRP3	Ca 2 +	ASIC1a/ Ca 2 + / NLRP3	Adjuvant arthritis rats	Promoted bone loss	Rheumatoid arthritis	[143]
NLRP3	Icariin	Icariin/NLRP3/caspase-1	Chondrocytes and mice	Inhibited bone loss	Osteoarthritis	[144]

Pyroptosis in periodontal and gingival cells

Periodontal and gingival cells are critically associated with alveolar bone diseases involving apical periodontitis and periodontitis [145]. In the periodontal and gingival cells, the activation of inflammasome can induce inflammatory cytokines that can modulate the process of pyroptosis related to bone loss [33, 146]. The activitated IL-1β that can be produced via caspase-1 induce RANKL production and improve osteoclast activity [147]. Meanwhile, IL-18 can promote protein levels of MMP in PDLCs, increasing osteoclastogenesis [148]. Furthermore, pyroptosis can directly cause the damage of periodontal and gingival cells to lead to the inflammation, ultimately facilitating bone loss [149, 150] (Table 5).

In the periodontal and gingival cells, pyroptosis is dominantly triggered by a non-canonical pathway, which usually involves the activation of LPS. It has been demonstrated that LPS can activate the NLRP3 inflammasome and subsequently induce IL-1β secretion, thereby inducing tissue inflammation, which may lead to bone loss [150]. Moreover, the results of gingival crevicular fluid and periodontium from periodontitis patients and healthy patients have proved that the pyroptosis modulated by the caspase-4/GSDMD lead to the death of periodontal ligament stem cells, which was attributed to the periodontal bacteria and cytoplasmic LPS, and subsequently, IL-1β was released into the tissue microenvironment to enhance inflammation and induce osteoclastogenesis [39]. Li et al. have found that LPS released by porphyromonas gingivalis could promote the pyroptosis of gingival fibroblasts with increasing inflammatory cytokines associated with pyroptosis, may inducing alveolar bone loss [13]. The regulation of LPS on pyroptosis could be inhibited via eldecalcitol (ED-71), in which upregulated Nrf2/HO-1 signaling displayed the role on suppressing pyroptosis, as well as the levels of NLRP3, caspase-1 and IL-1β decreased [151].

Except for LPS, NLRP3 inflammasome and GSDMD can be activated by cyclic stretch to prompt the process of pyroptosis. Zhao et al. have investigated that in the human PDLCs, cyclic stretch could positively stimulate the NLRP3 inflammasome and then induce the secretion of IL-1β, thereby enhancing pyroptosis and bone loss [152]. Besides, GSDMD could also be activated via cyclic stretch, and subsequently IL-1β as well IL-18 were liberated, leading to bone loss related to pyroptosis [153]. Additionally, it has been reported that the role of caspase-1 and IL-1β in the process of pyroptosis could be directly restrained by VX765, suppressing the development of apical periodontitis and the concomitant bone resorption [154] (Fig. 6).

Pyroptosis in other cells

Apart from osteoclasts, osteoblasts, macrophages, chondrocytes, periodontal and gingival cells, in the process of pyroptosis associated with bone loss, osteocytes, fibroblast-like synoviocytes as well as cholesteatoma keratinocytes are also included. Zhang et al. reported that the pyroptotic death of osteocytes could be attributed to Bisphenol A which launched the pyroptosis through ROS/NLRP3/caspase-1 pathway, promoting bone erosion [155]. Besides, in the fibroblast-like synoviocytes, pyroptosis could be triggered

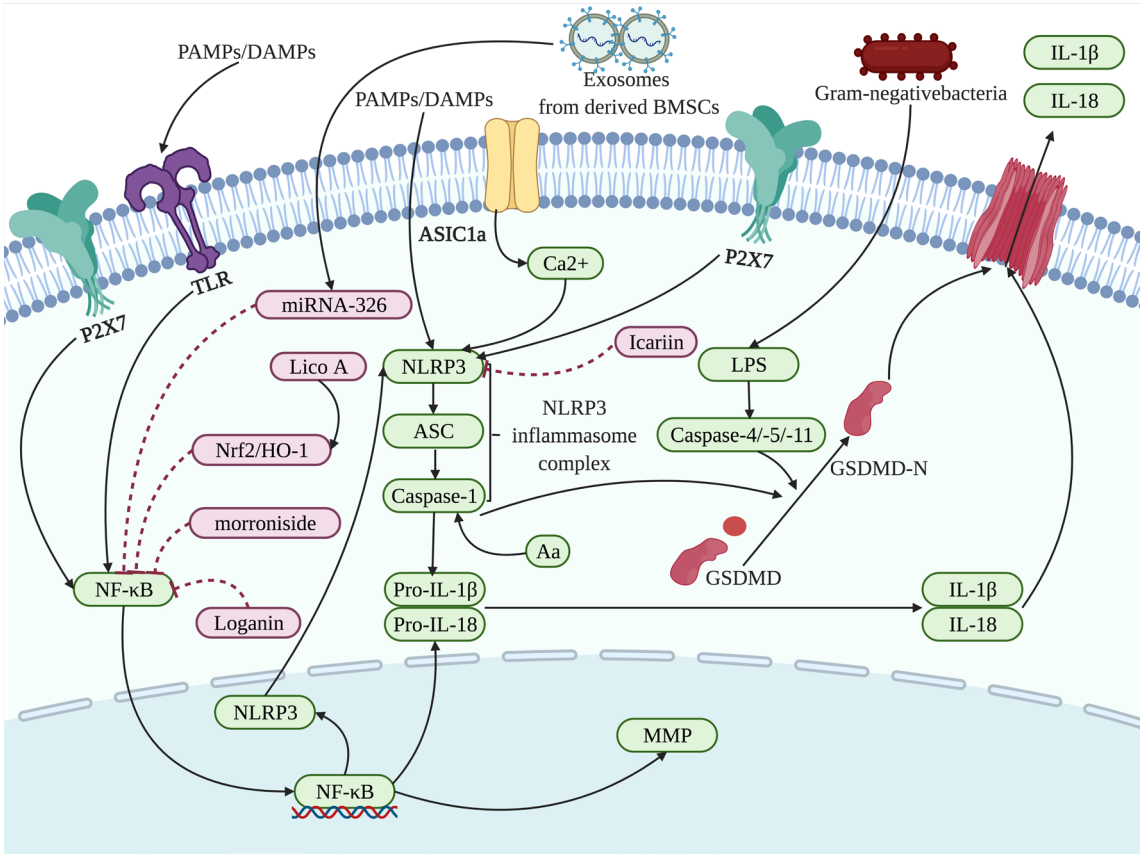

Fig.5 Different targets of action are regulated to affect the pyroptosis related to the chondrocytes in the process of bone loss. Exposure to PAMPs or DAMPs and then influenced by NF-κB, the NLRP3 inflammasome complex assemblies and activates caspase-1 and subsequently results in the cleavage of the proinflammatory cytokines IL-1β and IL-18. Caspase-1 and caspase-4/-5/-11 cleave GSDMD into a GSDMD-N-terminal domain that anchors in the cell membrane, leading to the cell rupture. Loganin [138], morroniside [139], Nrf2/HO-1 induced by Lico A (Licochalcone A) [140], and microRNA-326 delivered by BMSC-derived exosomes [141], have been developed in the presented pathway targeting NF-κB signaling, and P2X7 directly targeted the crosstalk between NF-κB and NLRP3 [142]. Meanwhile, NLRP3 are also the target of action to be regulated by Ca^{2+} [143] and icariin [144], affecting bone loss involved in pyroptosis. The factors that promote pyroptosis are indicated in green and pyroptosis-suppressor factors are indicated in pink

via NLRP3/caspase-1/GSDMD signaling pathways, which were mediated by LPS as well as the NF-κB signaling that induced the activation of inflammasomes, promoting inflammation and accompanying bone loss [156]. While the activated inflammasome is distinct from NLRP3, it has been reported that the pyroptosis of cholesteatoma keratinocytes could be also induced by AIM2, which facilitated the development of cholesteatoma (a kind of the non-permanent bone lesion) as well as bone loss [157] (Table 6).

Perspectives and conclusion

This review summarizes recent shreds of evidences that the pyroptosis in bone loss is associated with osteoclasts, osteoblasts, macrophages, chondrocytes, periodontal and gingival cells. The targets in the process of pyroptosis related to these cells have the potential to become an effective approach for future interventions in bone metabolic diseases, with implications for the prevention and treatment of bone metabolic diseases caused by pyroptosis.

However, some obstacles significantly hamper the application of the targets at this phase, mainly concerning the far from enough understanding of the clear association between pyroptosis and the bone loss, as well as lacking the further research of involved underlying mechanisms. For instance, a breakthrough of the restrictive assembly, activation, or other response mechanisms is required to interfere with pyroptosis by inhibiting the inflammasome, as well as the possible other roles of inflammasome-mediated pyroptosis in bone metabolic function in addition to the modulation on maturation of IL-1β, IL-18 and GSDMD. Meanwhile, for the prevention of bone metabolic diseases related to pyroptosis, it is of a notable necessity that clinical studies should be deeply investigated, which involve exploring effective strategies for integrating the Wnt/β-catenin pathway, MAPK pathway

Table 5 The regulation of pyroptosis on the periodontal and gingival cells in the process of bone loss

Target of action	Intervention	Mechanism	Experimental models	Effect	Diseases	References
LPS	Periodontal bacteria	LPS/caspase-4/GSDMD	GCF and periodontium	Promoted bone loss	Periodontitis	[39]
LPS	Porphyromonas gingivalis	LPS/caspase-4/GSDMD	HGFs and gingival tissues	Promoted bone loss	Periodontitis	[13]
LPS	ED-71	Nrf2/HO-1/ LPS/caspase-4/GSDMD	Gingival fibroblasts	Inhibited bone loss	Periodontitis	[151]
NLRP3	LPS	LPS/NLRP3/caspase-1/IL-1β	HPDLFs	Promoted bone loss	Apical periodontitis	[150]
NLRP3	Cyclic stretch	cyclic stretch/NLRP3 /caspase-1/IL-1β and IL-18	PDL tissues from teenagers	Promoted bone loss	Periodontitis	[152]
GSDMD	Cyclic stretch	caspase-1/GSDMD/IL-1β and IL-18	PDL tissues from teenagers	Promoted bone loss	Periodontitis	[153]
Caspase-1 and IL-1β	VX765	caspase-1/GSDMD/IL-1β and IL-18	HPDLFs	Inhibited bone loss	Apical periodontitis	[154]

as well as other signaling pathways to block the NLRP3 inflammasome and repressing pyroptosis [158]. Furthermore, despite the fact that the combination of numerous treatments as well as various drugs developed on the basis of NLRP3, caspase, or the GSDMD may contribute to more hope for healing bone loss in bone metabolic diseases, it is still significant to evaluate the potential negative interaction mechanisms of these treatments that could trigger the disturbing effects on pyroptosis and thus reducing the therapeutic effect. In particular, the prospective association of versatile medication strategies should be balanced with the advantageous dedication of pyroptosis activation in host defense, preventing from mutually antagonistic intervention.

In terms of the current treatment targeting pyroptosis in bone metabolic diseases, developing direct inhibitors that directly target the NLRP3 protein and other indirect inhibitors that target components of the NLRP3 inflammasome, such as caspase-1, IL-1β, and IL-18, are currently reported to be more commonly therapies targeted against pyroptosis [158]. New drugs and related inhibitor molecules that directly target NLRP3 include MCC950 [68], glyburide [71], irisin [159], melatonin [98], dioscin [91], etc., which are effective in osteoporosis, impaired fracture healing caused by diabetes, osteoarthritis, osteomyelitis, and so on, displaying certain clinical therapeutic potential. In addition, VX765 targets Caspase-1 [154], and IL-18BP targets IL-18 [52], both of which have been found to partially reduce bone resorption, while the oral drug auranofin effectively inhibits IL-1β to suppress the progression of osteoclasts differentiation [76]. Some studies have focused on the post-transcriptional control of microRNA based on NLRP3, in which NLRP3 targeting miRNA is a relatively successful treatment method for rheumatoid arthritis, etc. [160], but it is not yet widely used in some specific bone metabolic diseases including osteoporosis [161]. Moreover, attenuating inflammasome activity through other indirect means has also shown some clinical therapeutic effects: using E and D series resolvins decreases NF-κB activity to suppress inflammasome activation [162]; using antioxidant drugs that target intracellular ROS regulates upstream signaling linked to inflammasome oligomerization and activation [163].

When it comes to the development direction of targets on pyroptosis therapy into clinics in the future, it is progressive for bone metabolic diseases to obtain suitable drugs which should be decreased the possibility of side effects that include the osteolytic inflammatory responses contemporaneous with targeted regulation of the NLRP3 inflammasome. Additionally, since it has been found that the activation of inflammasome in infected macrophages could trigger the release of IL-1 and IL-18 and the process of pyroptosis, driving the inflammatory process in covid-19, the concomitant effects on pulmonary inflammatory pathology can be referred in further application on the production and development of therapeutic strategies targeting pyroptosis [164]. Moreover, since current drugs are administered orally or subcutaneously [146], drug delivery methods that comply with the stability, specificity and efficacy of targeting are needed to develop. For example, in terms of drug delivery carriers, appropriate materials with excellent drug emancipate dynamics is advocated to devise and produce to prompt local delivery of potential anti-inflammatory drugs [5], exquisite candidates of which may include hydrogels. Carriers such as hydrogels are supplied with modifiable tunable physicochemical characteristics, effectively dominating

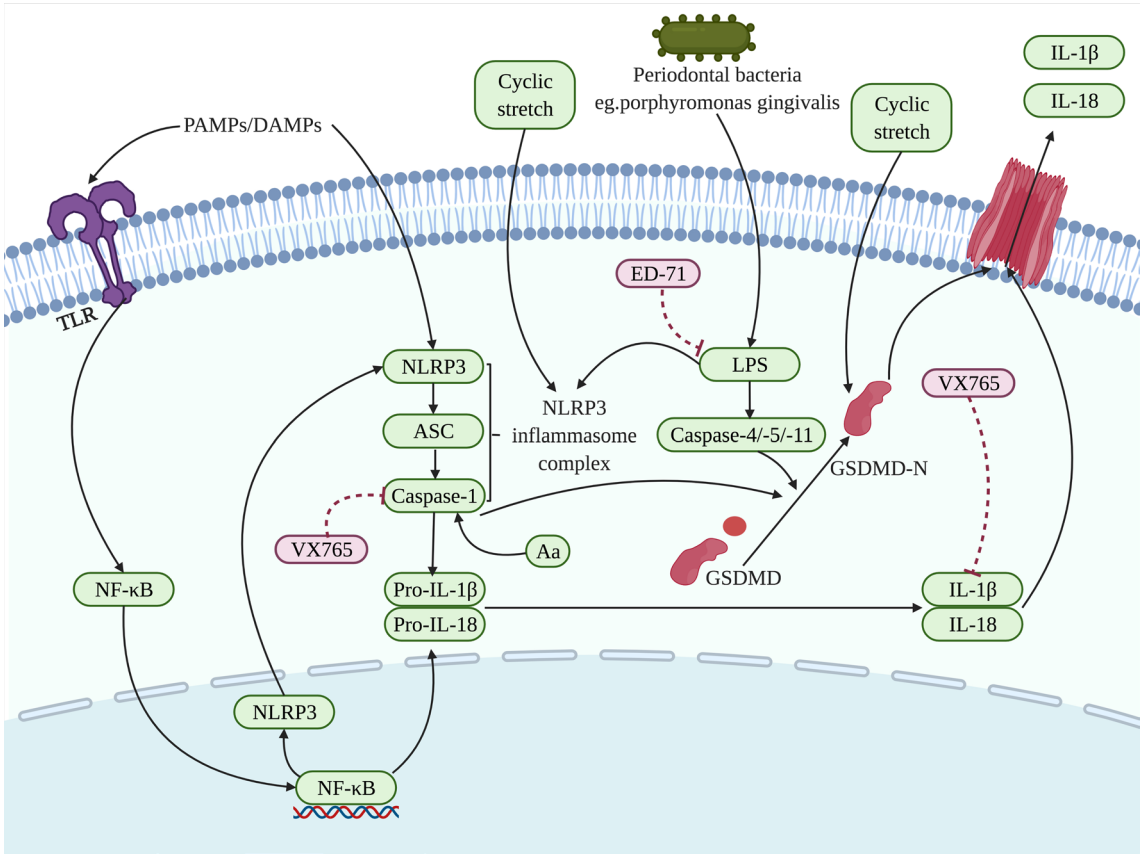

Fig.6 Different targets of action are regulated to affect the pyroptosis related to the periodontal and gingival cells in the process of bone loss. Exposure to PAMPs or DAMPs and then influenced by NF-κB, the NLRP3 inflammasome complex assemblies and activates caspase-1 and subsequently results in the cleavage of the proinflammatory cytokines IL-1β and IL-18. Caspase-1 and caspase-4/-5/-11 cleave GSDMD into a GSDMD-N-terminal domain that anchors in the cell membrane, leading to the cell rupture. Periodontal bacteria [39] including porphyromonas gingivalis [13] and ED-71 [151] have been found in the presented pathway targeting LPS. Meanwhile, NLRP3 and GSDMD are also the target of action to be regulated through cyclic stretch [152, 153], and Caspase-1 as well as IL-1β are negatively targeted by VX765 [154], affecting bone loss involved in pyroptosis. The factors that promote pyroptosis are indicated in green and pyroptosis-suppressor factors are indicated in pink

Table 6 The regulation of pyroptosis on other cells in the process of bone loss

Target of action	Intervention	Mechanism	Experimental models	Effect	Diseases	References
ROS	Bisphenol A	ROS/NLRP3/caspase-1	MLO-Y4 cells	Promoted bone loss	Not given	[155]
NLRP3 and caspase3	LPS the NF-κB signaling	NLRP3/caspase-1/GSDMD and caspase-3/gasdermin E	fibroblast-like synoviocytes	Promoted bone loss	Rheumatoid arthritis	[156]
AIM2	IFN-γ	IFN-γ/AIM2/caspase-1/IL-1β and IL-18	Cholesteatoma tissue	Promoted bone loss	Cholesteatoma	[157]

drug release kinetics as well as probably solving the conundrum of systemic side effects [165, 166]. Besides, it is critical to design adequate and effective regulatory inhibitors to restrain pyroptosis and accompanying bone loss, which could be achieved through the regulation of inflammasome components, inflammasome initiation, inflammasome oligomerization as well as activation, proinflammatory influence on inflammasome-dependent cytokines. As described above, for instance, utilizing VX765 to target caspase-1 and utilizing MCC950 to target NLRP3, nevertheless, more potent inhibitors against different targets need to be developed to alleviate bone metabolic diseases related to pyroptosis in the future. Since it has been demonstrated that classical pathway and nonclassical pathway of pyroptosis will interact as well as activate each other, and subsequently their interdependent activation could enhance the expression of

the NLRP3 inflammasome, suggesting that the development of vaccine needs to target both pathways to achieve superior consequent in treatment [167].

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Author contributions XYL and LJ wrote the manuscript with feedback from all authors. XRM, XYC and MHZ polished the manuscript. SSH and SC gave their comments and suggestions to the manuscript. All authors read and approved the manuscript.

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Data availability All data relevant to this review is included in the text, references, and figures.

Declarations

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

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication All authors approve the submission of the manuscript.

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