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REVIEW

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Pyroptosis: candidate key targets for mesenchymal stem cell-derived exosomes for the treatment of bone-related diseases

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Abstract

Bone-related diseases impact a large portion of the global population and, due to their high disability rates and limited treatment options, pose significant medical and economic challenges. Mesenchymal stem cells (MSCs) can differentiate into multiple cell types and offer strong regenerative potential, making them promising for treating various diseases. However, issues with the immune response and cell survival limit the effectiveness of cell transplantation. This has led to increased interest in cell-free stem cell therapy, particularly the use of exosomes, which is the most studied form of this approach. Exosomes are extracellular vesicles that contain proteins, lipids, and nucleic acids and play a key role in cell communication and material exchange. Pyroptosis, a form of cell death involved in innate immunity, is also associated with many diseases. Studies have shown that MSC-derived exosomes have therapeutic potential for treating a range of conditions by regulating inflammation and pyroptosis. This study explored the role of MSC-derived exosomes in modulating pyroptosis to improve the treatment of bone-related diseases.

Keywords Pyroptosis, Mesenchymal stem cells, Exosomes, Osteoarthritis, Spinal cord injury, Disc herniation, Osteoporosis

Background

Data analysis from the Global Burden of Disease (GBD) in 2019 indicated that approximately 1.71 billion individuals worldwide were affected by musculoskeletal disorders (MSDs), which include conditions such as low back pain, neck pain, fractures, osteoarthritis (OA), and rheumatoid arthritis (RA) [1]. These disorders represent a leading cause of disability worldwide. Bone-related diseases, including OA, RA, osteoporosis (OP), disc herniation (DH), and spinal cord injury (SCI), are the primary aetiological factors contributing to MSDs. Most of these conditions can be classified as age-related degenerative diseases or inflammatory disorders resulting from trauma [2]. Bone-related diseases typically present symptoms such as chronic pain and functional limitations. Due to the complexity of their aetiological factors and the

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limitations of current therapies, clinical treatments often alleviate symptoms rather than provide a complete cure [3]. Pathological findings suggest that chronic inflammation is a fundamental cause of various degenerative diseases [4]. Additionally, a newly defined programmed cell death mechanism known as pyroptosis has been identified as a significant driver of harmful chronic inflammation [5]. Pyroptosis has attracted increasing attention because of its critical role in the pathogenesis and progression of several diseases, establishing it as a potential key target for the prevention and treatment of bone-related diseases.

Mesenchymal stem cells (MSCs) are multipotent stem cells derived from the mesoderm that are recognized for their multilineage differentiation potential and robust regenerative and repair capabilities [6]. MSCs present significant promise in the treatment of various bone-related diseases [7]. However, the therapeutic application of MSCs is associated with several potential limitations, including low cell survival rates, tumorigenicity, immune rejection, and genetic variations, which pose significant challenges to clinical research and implementation [8, 9]. Exosomes derived from mesenchymal stem cells (MSC-Exos) not only circumvent the adverse reactions associated with MSCs but also demonstrate more pronounced and effective therapeutic effects [10, 11]. As a result, MSC-Exos have emerged as a key focus of current research in cell-free stem cell therapy [12]. An increasing body of research indicates that pyroptosis serves as a critical pathway through which MSC-Exos exert their regulatory functions [12, 13].

To summarize in this review recent findings concerning how MSC-Exos alleviate bone-related diseases by regulating pyroptosis, we searched the PubMed, Google Scholar, and Web of Science databases up to November 2024 for potentially relevant English-language research. We used specific MeSH terms and keywords related to mesenchymal stem cells, pyroptosis, exosomes, and bone-related diseases (e.g., osteoarthritis, spinal cord injury, disc herniation, osteoporosis, periodontitis). These criteria were extended to include more detailed terms such as osteogenesis, cartilage, chondrocytes, and Nod-like receptor pyrin domain 3 (NLRP3) inflammasome. Originally, 286 resulting articles were found. Duplicates were removed, and 80 articles were then selected according to their title and abstract, excluding studies of non-MSCs and studies referring only to pyroptosis. Based on reading of the full article in detail, we examined those ones focused on bone-related diseases. As a result, 21 articles remained in the present review. This article provides a comprehensive review of research advancements related to the modulation of the pyroptosis pathway by MSCs and their derived exosomes in the alleviation and treatment of bone-related diseases, with the aim of identifying novel and promising therapeutic targets for this category of disorders.

Introduction

Mesenchymal stem cells and exosomes

MSCs are derived from abundant sources and are readily accessible, possess high potential for multilineage differentiation, self-renewal, and secretory abilities [14]. Given their unique advantages, MSCs positively contribute to the treatment of various diseases and injury repair, including cancer, cardiovascular and neurological disorders, pulmonary diseases, and immune dysfunction [15]. Through their capacity to stimulate osteogenesis and angiogenesis, repair and regenerate cartilage, and modulate the inflammatory environment, multiple types of MSCs have beneficial effects on the treatment of various bone-related diseases [16]. For instance, during the management of osteoporosis, MSCs are utilized to increase bone mineral density and improve bone microstructure, alleviating pain and skeletal dysfunction [17]. Another study showed that in addition to direct differentiation, MSCs mediate cartilage repair through paracrine mechanisms by increasing proliferation, promoting survival and inhibiting the inflammatory response [18]. A phase I clinical trial revealed improvements in spinal cord dysfunction with no severe adverse events in 10 SCI patients treated with intrathecal injection of autologous MSCs [19]. As research progresses and technology advances, MSCs are increasingly trending towards becoming important tools for the treatment of bone-related diseases. Furthermore, the robust global expansion of clinical trials involving MSCs, coupled with their high degree of integration in tissue engineering, underscores the promising application prospects of these cells [20, 21]. However, despite the substantial therapeutic potential of MSCs, adverse reactions associated with cell transplantation warrant significant attention and consideration, which may currently limit their clinical translation. As a result, there is heightened focus on the limited differentiation capacity and potential for strong immune responses following allogeneic MSCs transplantation [22, 23]. Moreover, many studies indicate that MSCs primarily exert a series of crucial regulatory functions, including immunoregulation, antifibrotic effects, anti-apoptotic activity, pyroptosis inhibition, and tissue regeneration, through paracrine mechanism [24, 25]. Consequently, the use of cell-free MSC-derived therapies has become a focal point in stem cell research, with extracellular vesicles (EVs) having been identified as the most critical components for therapeutic effects.

EVs are small vesicles characterized by a double lipid membrane structure produced by cells through paracrine secretion [26]. They facilitate the exchange of lipids, proteins, and genetic material between cells and serve as

crucial signal carriers in cell-to-cell communication, playing a vital role in regulating both normal cellular physiological functions and pathological changes. EVs can be broadly categorized into two types: large EVs, which have a diameter greater than 200 nm, and small EVs, which have a diameter of less than 200 nm [27]. Among EVs, microvesicles (MVs) and exosomes have attracted significant attention and research. MVs are produced through the exocytosis of the plasma membrane and are characterized by a diameter ranging from approximately 100 to 1000 nm [28]. Exosomes, on the other hand, are EVs distinguished by a double lipid bilayer structure and diameter ranging from 30 to 150 nm [29]. They carry diverse biomolecules, including nucleic acids (such as DNA, mRNA, microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA)), lipids, proteins, and metabolic waste products. Since their discovery, a growing body of research has revealed the critical role of exosomes in regulating intercellular material transport and signal transmission [30].

Exosomes are derived from the endosomal system through a process involving two steps of membrane invagination. During the initial invagination of the plasma membrane, early-sorting endosomes (ESEs) are formed as the cell membrane undergoes inward folding [31]. Meanwhile, the Golgi apparatus (GA) and the endoplasmic reticulum (ER) also contribute to the formation of ESEs [32]. ESEs have the capacity to fuse with one another, gradually maturing into late-sorting endosomes (LSEs). The subsequent invagination of the plasma membrane occurs within LSEs, leading to the formation of intraluminal vesicles (ILVs) [33]. This process further modifies the cargo intended for future exosomes as LSEs evolve into multivesicular bodies (MVBs). MVBs then fuse with the plasma membrane, releasing the ILVs that they contain as exosomes through exocytosis [34]. Exosomes convey signals to effector cells via processes such as membrane fusion, receptor interaction, and internalization by receptor cells, ultimately participating in the regulation of physiological and pathological processes [35] (Fig. 1). In addition to being naturally released and absorbed by neighbouring cells, they can also be artificially extracted and injected for therapeutic or research purposes. Nanocarrier delivery systems and genetic engineering further expand the potential of MSC-Exos for functional customization [36].

As a significant generator of exosomes, MSCs boast rich source and high proliferative capacity compared with other cells [37]. Notably, they are currently recognized as cell type that produces exosomes in high yields [37]. Studies have demonstrated that MSC-Exos offer several significant advantages over MSCs. They have low immunogenicity, are more accessible, have improved preservation qualities, and potentially have low carcinogenic risks [29]. In addition to their powerful tissue repair function, MSC-Exos also possess immunosuppressive activity and modifiability, resulting in more comprehensive therapeutic ability, which makes them an ideal therapeutic option for disease treatment [38, 39].

Clinical application trials have clearly demonstrated the therapeutic effects of MSC-Exos, which are anticipated to address numerous challenges faced in regenerative medicine [11]. Due to their stability, specificity of molecules, and absorption performance, MSC-Exos provide a promising therapeutic approach for the treatment of bone-related diseases. For example, recent studies have demonstrated the clinical therapeutic potential of these exosomes for SCI and peripheral nerve injury. A single-arm, open-label, phase I clinical trial utilized human umbilical cord mesenchymal stem cell-derived exosomes (hUCMSC-Exos) for allogeneic intrathecal injection to evaluate their efficacy and safety in patients with complete subacute SCI [19]. Significant advances in neurological and functional assessments were observed at 12 months of follow-up after receiving the injection compared with baseline. Notably, a pilot study reported the use of sural autograft repair followed by the delivery of MSC-Exos into the stumps of patients with complete radial nerve damage, which resulted in excellent neural reconstruction outcomes [40]. However, although some current trials have shown encouraging results in the clinical application of MSC-Exos, their overall quantity remains relatively scarce. Thus, it is necessary to promote the development of clinical trials and in-depth research on therapeutic mechanisms to explore the real therapeutic potential of MSC-Exos in bone-related diseases.

Fortunately, MSC-Exos have the potential to alleviate or treat diseases across various systems, including the circulatory, respiratory, and musculoskeletal systems, by modulating the pyroptosis pathway in cells. For example, Zhang et al. reported that bone marrow mesenchymal stem cell-derived exosomes (BMSC-Exos) can inhibit pyroptosis by activating the yes-associated protein (YAP)/ beta-catenin pathway, downregulating the expression of pyroptosis-related proteins, and reducing the secretion of interleukin-18 (IL-18) and interleukin-1β (IL-1β) in alveolar tissue [41]. This mechanism improves the inflammatory response and oxidative stress in lung tissue, thereby alleviating acute lung injury induced by extracorporeal circulation. Yue et al. conducted both in vivo and in vitro studies on myocardial ischaemia/reperfusion (I/R) injury and reported that the delivery of miR-182-5p by MSC-Exos, which target gasdermin D (GSDMD), reduces the production of GSDMD protein and subsequently diminishes NLRP3 inflammasome activation while inhibiting cardiomyocyte pyroptosis, thereby exerting a protective effect against myocardial injury [42]. Furthermore, Yan et al. demonstrated that

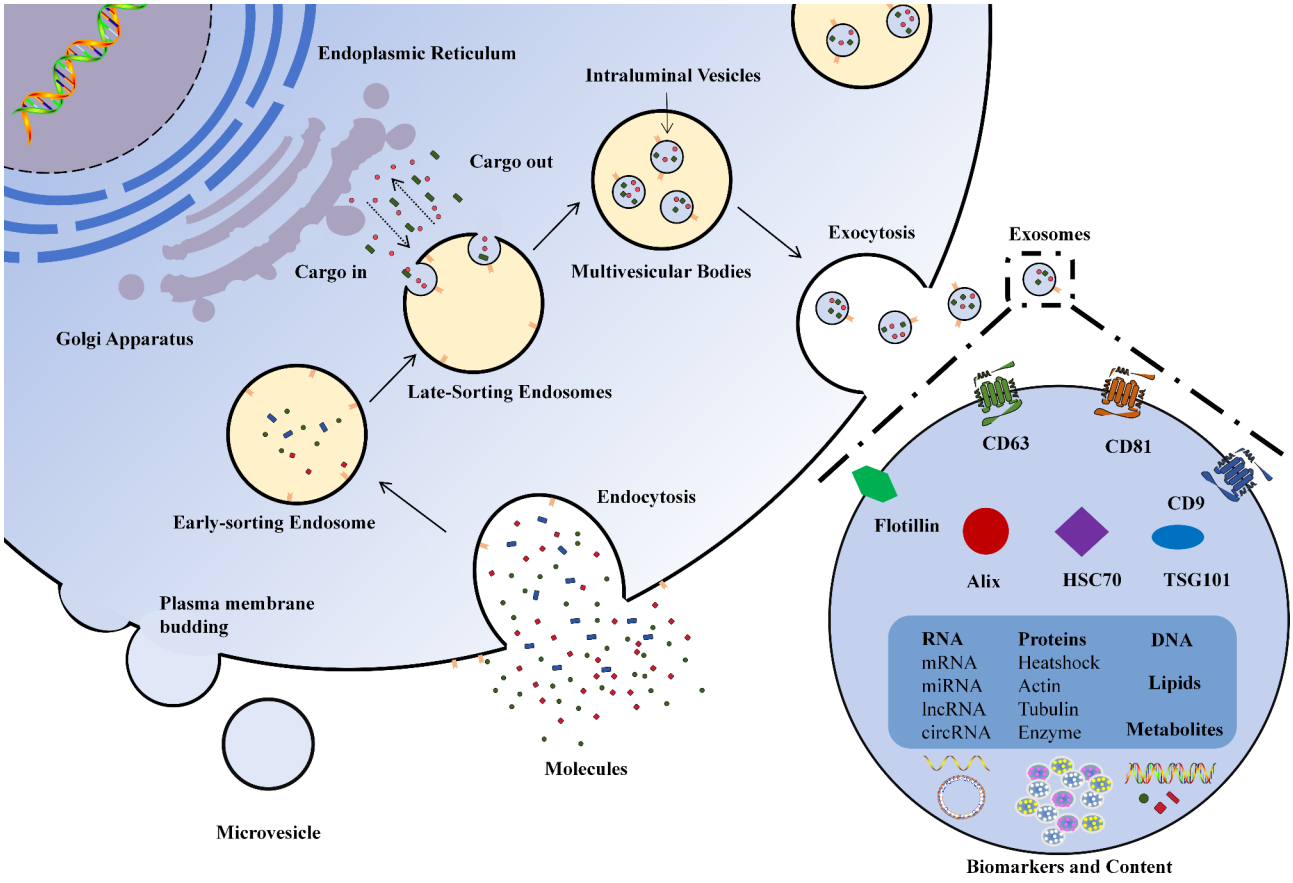

Fig. 1 Mechanisms of exosome formation and secretion. During the initial invagination of the plasma membrane, various extracellular components, including surface proteins, are internalized as the membrane folds inward, resulting in the formation of ESEs. The GA and the ER play critical roles in producing and enabling the fusion of ESEs. During this process, the content carried by the ESEs is transferred, allowing them to mature into LSEs. In the subsequent stage, ILVs of varying sizes and contents form within LSEs through another invagination event, during which the cargo undergoes further modifications. LSEs are transformed into MVBs, which encapsulate ILVs earmarked for release as exosomes. When MVBs fuse with the plasma membrane, ILVs are released into the extracellular space via exocytosis, thereby becoming exosomes. Alternatively, MVBs may also fuse with autophagosomes or lysosomes for degradation and recycling within the cell. Exosomes are formed and released through either an endosomal sorting complex required for the transport (ESCRT)-dependent mechanism or a non-ESCRT-dependent mechanism, depending on the specific cargo and cell type involved. Several proteins serve as exosomal markers, including surface proteins such as CD9, CD63, and CD81, alongside cytoplasmic proteins such as flotillin, tumour susceptibility gene 101 (TSG101), apoptosis linked gene 2 interacting protein X (Alix), and the heat shock protein HSP70. Exosomes are rich in various types of biomolecular information. In contrast, microvesicles bud directly from the plasma membrane and are released into the extracellular space through an outward growth process

hUCMSC-Exos can prevent ischaemic damage to skeletal muscle by delivering circHIPK3, which downregulates miR-421 and subsequently enhances the expression of forkhead box O3a (FOXO3a) but inhibits the expression of pyroptosis proteins, thereby preventing pyroptosis in skeletal muscle [43]. Additionally, Sun et al. showed that exosomes carrying miR-367-3p derived from BMSCs can suppress muscle pyroptosis in a hindlimb I/R injury model in mice by targeting enhancer of zeste homolog 2 (EZH2) [44]. As research has advanced, exploring the mechanisms through which MSC-Exos regulate pyroptosis to increase organ protection in diverse disease states is highly likely to advance the application of this treatment modality.

Pyroptosis

Pyroptosis was first identified in macrophages infected with *Shigella flexneri*; initially, it was misclassified as apoptosis until Brad T. Cookson proposed the term 'pyroptosis' in 2001 to describe this newly recognized form of cell death [45, 46]. Originally, pyroptosis was defined as a type of cell death dependent on the activation of cysteinyl aspartate-specific proteinases (caspase)-1; however, it is now understood to involve multiple caspases, including caspase-1/4/3/5/8/11. In 2018, the Nomenclature Committee on Cell Death (NCCD) classified pyroptosis as a form of regulated cell death (RCD) that is significantly dependent on members of the Gasdermin protein family for the formation of membrane pores activated by the inflammasome [47].

Cells undergoing pyroptosis exhibit distinct morphological changes, including swelling, nuclear condensation, plasma membrane disruption, and the release of inflammatory cytokines [48]. Pyroptosis can be classified into two pathways: the classical pathway, which is mediated by the activation of caspase-1 through inflammasomes, and the nonclassical pathway, which is mediated by the activation of caspases-4/5/11 via lipopolysaccharide (LPS). Both pathways ultimately cleave GSDMD, which is known as the executioner of pyroptosis (Fig. 2).

Gasdermin (GSDM) proteins are characterized by diverse functions and the presence of conserved dual domains, consisting of an inhibitory carboxy-terminal domain (GSDMCT) that exhibits self-inhibition, as well as a pore-forming amino-terminal effector domain (GSDMNT) [49]. GSDMCT and GSDMNT are interconnected, maintaining the protein in an autoinhibited state and preventing the formation of pore-forming structures [50]. Activated cysteine proteases cleave aspartic acid residues within the GSDM linker, resulting in the disassembly of GSDMNT from GSDMCT and thereby facilitating its pore-forming activity [51]. This process has attracted significant attention from researchers because of its capacity to induce cell death and inflammatory responses. Given the importance of inflammatory responses in the adverse prognosis of bone-related diseases, the governance of the caspase-dependent pyroptotic pathway involving GSDMD regulation has emerged as a promising tactic for the treatment of these disorders. Therefore, studies on the specific pathogenic mechanisms of pyroptosis in inflammatory diseases are being carried out expeditiously, and the understanding of pyroptosis has increased.

Caspases are conserved cysteine proteases that can be classified into apoptotic caspases and inflammatory caspases, both of which play crucial roles in the occurrence and progression of RCD and inflammation [52]. Inflammatory caspases, specifically human caspases-1/4/5 and mouse caspases-1/11, are pivotal in the activation of pyroptosis, a process ultimately mediated by their ability

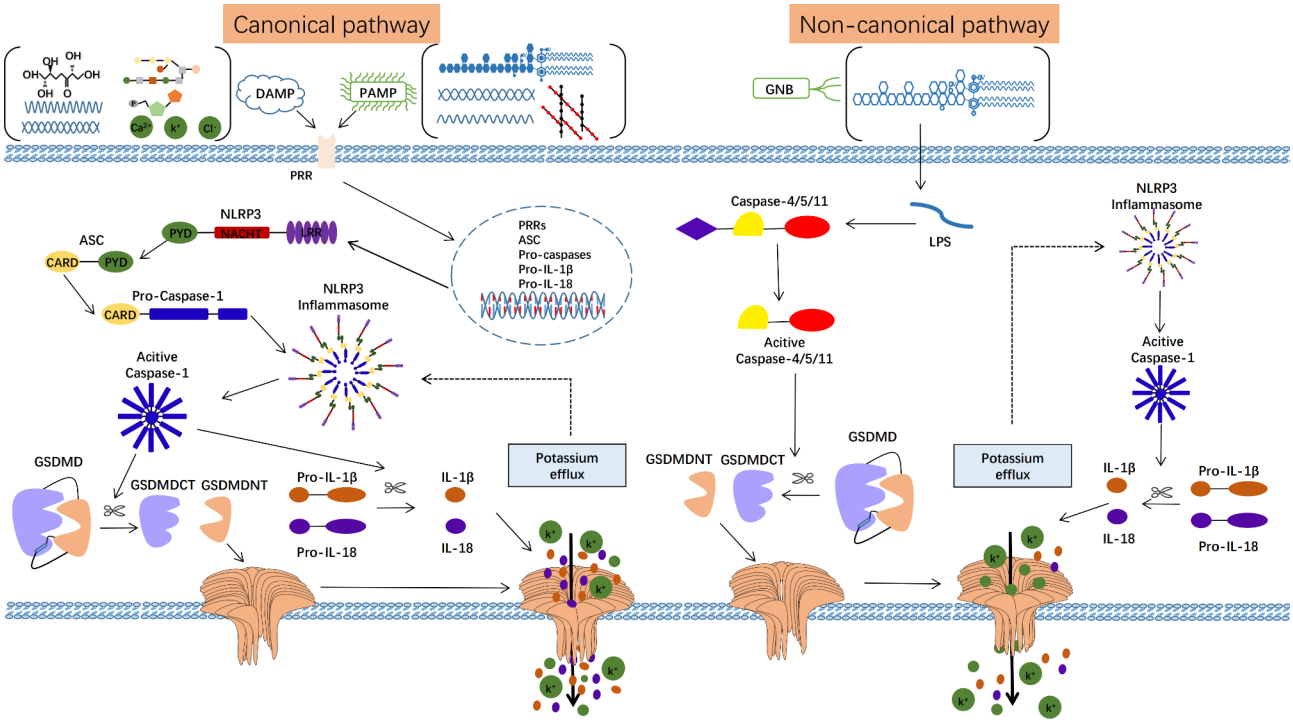

Fig. 2 The classical and nonclassical pathways of pyroptosis. In the classical pathway, the NLRP1, NLRP3, NLRC4, AIM2, and pyrin inflammasomes activate Caspase-1, leading to programmed cell death known as pyroptosis. The NLRP3 inflammasome serves as a primary example of this process. Upon recognition of PAMPs or DAMPs, PRRs trigger the expression of pyroptosis-related proteins, including NLRP3, ASC, caspases, IL-1β, and IL-18. NLRP3 then oligomerizes by binding and hydrolysing ATP through its NACHT domain and recruits ASC via homotypic pyrin domain (PYD)-PYD interactions, resulting in the formation of a prion-like ASC filament. Subsequently, ASC molecules recruit procaspase-1 through CARD-CARD interactions, culminating in the formation of inflammasomes. Procaspase-1 is ultimately cleaved and activated, forming an enzymatically active complex known as active caspase-1. Active Caspase-1 interacts with GSDMDCT, cleaving the linker loop to release GSDMDNT. GSDMDNT selectively interacts with phospholipids in the inner leaflet of the plasma membrane, forming transmembrane pores with an inner diameter of 21.5 nm and an outer diameter of 31 nm. Active Caspase-1 also cleaves pro-IL-1β and pro-IL-18, producing and releasing IL-1β and IL-18 into the extracellular space through these membrane pores. In the nonclassical pathway, Caspase-4/5/11 are activated by LPS and subsequently undergo self-cleavage, generating novel exosites capable of binding GSDMD. This action results in the cleavage of GSDMD and the formation of GSDMDNT, which possesses pore-forming activity, ultimately leading to pyroptosis. In addition, the activation of NLRP3 is closely related to the efflux of potassium ions resulting from the cleavage of the GSDMD

to cleave GSDMD [51, 53]. Importantly, the formation of inflammasomes is a critical step in the activation of caspases, particularly caspase-1. Inflammasomes are multiprotein complexes formed by pattern recognition receptors (PRRs) in response to the detection of pathogenic microorganisms and danger signals by cells and play a vital role in inflammation, immunity, and metabolic disorders. There are five types of inflammasomes, namely, NLRP1, NLRP3, NLRC4, AIM2, and Pyrin, with the NLRP3 inflammasome being the most extensively studied in pyroptosis [54]. The NLRP3 inflammasome consists of the receptor protein NLRP3, a linker protein apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and the effector protein caspase-1 [55]. In this complex, ASCs serve as a bridge linking the receptor and effector proteins. The activation of the NLRP3 inflammasome requires two sequential steps: the priming step and the activation step. During the priming step, the recognition of pathogen-associated molecular patterns (PAMPs) or host-derived damage-associated molecular pattern (DAMPs) by PRRs activates nuclear factor kappa B (NF-κB) or other transcription factors, which leads to the upregulation of NLRP3 and other components of the inflammasome [56]. In the subsequent activation step, NLRP3 senses cellular stress and becomes activated; the underlying mechanisms remain unclear but may be closely related to potassium ion efflux [57]. Additionally, studies have shown that GSDMD is cleaved into GSDMDNT and GSDMDCT, which form membrane pores facilitating potassium ion efflux, resulting in a decrease in the intracellular potassium level that is sufficient to induce NLRP3 inflammasome assembly and activation [58, 59].

In the classical pathway of cell pyroptosis activated by inflammasomes, PRRs identify PAMPs or DAMPs [60]. This recognition leads to the recruitment and activation of Caspase-1. Enzymatically active Caspase-1 associates with GSDMDCT and cleaves the linker loop, resulting in GSDMDNT, which possesses pore-forming capabilities [61]. GSDMDNT selectively interacts with the inner phospholipid leaflet of the target membrane, oligomerizes within the plasma membrane, and creates transmembrane pores with diameters of 21.5 nm on the inner edge and 31 nm on the outer edge [62]. Concurrently, activated Caspase-1 cleaves pro-interleukin-1β (pro-IL-1β) and pro-interleukin-18 (pro-IL-18), which leads to the production of biologically active IL-1β and IL-18 [63]. These cytokines can then be released into the extracellular space through the pores formed during pyroptosis, subsequently inducing and amplifying inflammatory responses. In addition to the classical pathway mediated by Caspase-1, a nonclassical pathway of cell pyroptosis exists that is dependent on Caspase-4/5/11. Caspase-4/5/11 are activated by bacterial LPS within the cytosol, leading to their self-cleavage and the generation of new exosites that can bind to GSDMD [64]. This interaction facilitates the cleavage of GSDMD, resulting in the formation of GSDMDNT, which creates a pore in the membrane and triggers pyroptosis. Recent studies have also demonstrated that Caspase-8 can initiate pyroptosis by cleaving both GSDMC and GSDMD, whereas Caspase-3 can induce pyroptosis by cleaving GSDME [65, 66].

An appropriate level of pyroptosis can elicit specific immune responses that enhance the host's defence against infections [67]. However, excessive pyroptosis leads to cell lysis and death, accompanied by the secretion of various proinflammatory cytokines. This cascading amplification of inflammatory signals establishes a severe inflammatory environment that can trigger multiple inflammatory diseases. In a pathological bone microenvironment, heightened pyroptosis exacerbates inflammation and leads to cell death, with the intensity of this inflammation being correlated with the positive expression of NLRP3 inflammasomes [68]. Consequently, excessive activation of the NLRP3 inflammasome-mediated chronic inflammation and pyroptosis is highly likely to significantly influence the genesis and progression of various bone-related diseases. During the pathological processes related to these conditions, numerous cell types—including osteoclasts, osteoblasts, macrophages, chondrocytes, and synovial cells—undergo pyroptosis, leading to bone loss, cartilage degeneration, synovial hyperplasia, and disruptions in bone metabolism [5]. Many new studies have focused on the activation of the pyroptosis in normal tissue cells mediated by the NF-κB signalling pathway, which results in a sudden increase in the expression of proinflammatory factors [69]. In addition, immune cells implicated in bone-related diseases, such as macrophages, also undergo extensive pyroptosis during the disease course, giving rise to heightened activation of the NLRP3 inflammasome and further deterioration and degradation of other tissue cells [5]. Further studies have demonstrated that the inhibition of NLRP3 signalling can markedly suppress the levels of proinflammatory factors in macrophages, alleviate the excessive expression of inflammatory factors in tissues, relieve tissue swelling, and inhibit pyroptosis in tissue cells [70]. Efforts have been made to employ natural products or inhibitors targeting NLRP3 or its upstream NF-κB signalling pathway in an attempt to suppress the cytokine storm resulting from pyroptosis in bone-related diseases, and satisfactory therapeutic outcomes have been demonstrated [71, 72].

As our understanding of the anti-inflammatory and tissue cell protection properties of MSC-Exos increases, the cell death protection mechanisms involved are being revealed, with the role of MSC-Exos in pyroptosis

being a particular area of interest. A full understanding of this phenomenon could lead to the development of a new therapeutic use for MSC-Exos and expansion of their clinical scope. Several studies have indicated that MSC-Exos regulate pyroptosis and that NLRP3 inflammasome hyperactivation is achieved through signalling pathways such as the PI3K-AKT, YAP/β-catenin, NF-κB, and STAT3 pathways [41, 73–75]. Furthermore, a number of studies have investigated the manner in which MSC-Exos can regulate certain upstream key upstream targets, such as TRAF6, TXNIP, FOXO3, ELAVL1, and CMPK2, among others, which can be directly targeted by the biologically active substances delivered by exosomes [76–79]. In particular, MSC-Exos regulate the secretion of noncoding RNAs to control the expression of pyroptosis-related genes and proteins, thereby suppressing both pyroptosis and inflammation, as demonstrated by research on bone-related diseases [80–82]. Notably, MSC-Exos seemingly have outstanding regulatory effects on both the classical and nonclassical pathways of pyroptosis in tissue cells, which implies their potential for extensive regulation of pyroptosis. Studies have reported that hUCMSC-Exos can inhibit the activation of caspase-11 and the expression of caspase-4 by delivering miR-203a-3p.2, thereby reducing the secretion of IL-1β and IL-6, significantly alleviating macrophage pyroptosis, and consequently alleviating colitis in mice [83]. Cai et al. demonstrated that hUCMSC-Exos containing miR-378a-5p effectively inhibited the expression of Caspase-1 in a mouse model of colitis, leading to the suppression of NLRP3 inflammasome activation, reduced pyroptosis in macrophages, increased survival rates of histiocytes, and significant alleviation of inflammation in the colon [84]. In summary, MSC-Exos have garnered widespread attention for their anti-inflammatory, anti-death, and tissue repair properties in inflammatory environments, especially by inhibiting pyroptosis and balancing the inflammatory and regenerative microenvironments, which has broad application prospects for significantly inhibiting the progression of inflammatory diseases.

MSC-Exos regulate pyroptosis for the treatment of bone-related diseases

MSC-Exos regulate pyroptosis in osteoarthritis and rheumatoid arthritis

OA is the most prevalent joint disease encountered in clinical practice and is a significant contributor to global disability [85]. In 2019, approximately 528 million individuals worldwide were reported to be affected by OA, with the incidence and prevalence of the disease continuing to rise annually [86]. Patients with OA often experience serious psychological issues, such as depression and anxiety, and are at increased risk of developing other chronic complications, including obesity and diabetes, due to their limited mobility [4]. The prevention and treatment options for OA generally include pharmacological therapies (e.g., topical nonsteroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors, intra-articular corticosteroids, and hyaluronan), complementary arthritis education, structured exercise programs and surgery [87]. However, treatment has not yielded the anticipated level of effectiveness.

OA is characterized as an inflammatory degenerative disorder involving dynamic changes that arise from an imbalance between joint tissue destruction and repair. The primary pathological alterations include cartilage degeneration and loss, osteophyte formation, synovial hyperplasia, and fibrosis [88]. Current research reveals that pyroptosis plays a crucial role in the significant pathological alterations and that suppressing excessive pyroptosis can mitigate OA [87, 89, 90]. The articular cartilage consists of chondrocytes and the extracellular matrix (ECM) [91]. When chondrocytes undergo pyroptosis, they increase the production of matrix metalloproteinases (MMPs) and ADAMTS enzymes, which have been incontrovertibly confirmed as important factors causing structural damage and degradation of the ECM, ultimately resulting in cartilage degradation, which is the characteristic pathological alteration of OA [92]. Synovial cells are activated by DAMPs produced during cartilage degradation, leading to the production and release of inflammatory mediators. This process results in diminished chondrocyte function and degradation of the cartilage matrix, creating a detrimental cycle of damage between cartilage and the synovium [93].

A range of transcription factors, including key regulators of the inflammatory response, such as NF-κB, are activated during this process, leading to the release of degradation-related metabolic factors, cytokines, chemokines, and tissue proteases, all of which are crucial for the pathogenesis of OA [94]. The NF-κB signalling pathway has been widely recognized as a therapeutic target for OA [95]. Importantly, NF-κB signalling is required for NLRP3 activation, and inhibition of chondrocyte pyroptosis has the potential to alleviate cartilage damage and reduce the formation of osteophytes [62]. Furthermore, the pyroptosis of synovial fibroblasts leads to the massive release of high-mobility group box chromosomal protein-1 (HMGB1), which is highly correlated with synovitis and synovial fibrosis [96]. Moreover, other researchers have reported that HMGB1 is released during the pyroptosis of macrophages [97]. These proinflammatory factors act on fibroblast-like synoviocytes (FLSs), amplify the inflammatory response and exacerbate synovial fibrosis, thereby accelerating the pathological progression of OA [97]. Notably, the downstream products of cellular pyroptosis, such as the inflammatory cytokines IL-1β and IL-18, can trigger an inflammatory cascade amplification

reaction [98]. These harmful positive feedback loops in the joint lead to a damaging spiral among different cells, ultimately resulting in the occurrence and further progression of OA.

Studies indicate that MSC-Exos facilitate cartilage repair and regeneration, improve the survival of synovial fibroblasts, and modulate inflammation, thereby playing a significant role in repairing damaged tissues, alleviating symptoms, and impeding OA progression [99, 100]. Notably, pyroptosis serves as a primary target by which MSC-Exos inhibit inflammation associated with OA. Research by Xu et al. demonstrated that human adipose-derived MSCs (hAD-MSCs) could protect cartilage and reduce OA symptoms in a rat model [101]. These findings suggest that hAD-MSCs may bind to tumour necrosis factor-alpha (TNF-α) by secreting sTNFR1, downregulating tumour necrosis factor receptor 1 (TNFR1), and inhibiting the activation of the pyroptosis signalling pathway, thereby reducing chondrocyte pyroptosis. A study conducted by Xu et al. reported that miR-326, carried by BMSC-Exos, was delivered to chondrocytes [75]. This miRNA targets the 3'UTR of histone deacetylase 3 (HDAC3), facilitating the activation of the signal transducer and activator of transcription 1 (STAT1)/NF-κB p65 signalling pathway and inhibiting the expression of pyroptosis-related proteins, such as GSDMD, NLRP3, and ASC, as well as the secretion of the inflammatory factors IL-1β and IL-18. This inhibition significantly suppresses chondrocyte pyroptosis, promotes cartilage regeneration, and maintains cartilage morphology to improve OA symptoms. Liu et al. isolated hUC-derived exosomes (hUCMSC-EVs) from hUC-MSCs that were positive for specific exosomal markers, including CD81, Tsg101, and Alix, and negative for calreticulin, with an average diameter of 142.9 nm [102]. Their study revealed that miR-223, which is carried by hUCMSC-EVs, can directly bind to the 3'UTR of NLRP3 mRNA, thereby inhibiting NLRP3-mediated chondrocyte pyroptosis and subsequent inflammatory responses and contributing to articular cartilage repair in OA. Furthermore, the therapeutic efficacy of the double-engineered hUCMSC-EVs was enhanced.

In conclusion, the ability of MSC-Exos to alleviate OA via the suppression of pyroptosis and inflammatory responses in chondrocytes is promising. However, there are relatively few reports on the pyroptosis of other cells, such as synovial fibroblasts and macrophages, that undergo key changes during the progression of OA. Therefore, the study of exosomes that target pyroptosis in these cells will be the direction of future research on exosome therapy.

The GBD study also revealed that the global prevalence of RA was 0.27% in 2017 [103]. Notably, the prevalence among females was 2–4 times higher than that among males [104]. RA is a chronic, systemic autoimmune inflammatory disorder characterized by progressive joint damage and persistent synovial inflammation [105]. RA patients typically require lifelong treatment, with disease-modifying antirheumatic drugs (DMARDs) and NSAIDs functioning as the first-line treatment [106]. Research has revealed that several key cells, including fibroblast-like synoviocytes, chondrocytes, monocytes/macrophages, and CD4 + T-cells, contribute to the progression of RA through pyroptosis [107]. Inhibiting pyroptosis in macrophages or fibroblast-like synoviocytes can help alleviate the inflammatory response in joints [108]. Shin et al. demonstrated that human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) can dramatically suppress the activation of NLRP3 inflammasome, the release of IL-1β, and the downregulation of TNF-α secretion in macrophages [109]. This effect inhibits the activation of M1 phenotype macrophages and promotes the polarization of M2 phenotype macrophages, consequently alleviating RA symptoms. Additionally, Huang et al. reported that microRNA-223 carried by MSC-Exos binds to the 3′UTR of NLRP3, inhibiting the generation and activation of NLRP3 inflammasome in macrophages and reducing the release of IL-1β, IL-18, and TNF-α [110]. This action helps relieve synovitis in RA animal models. These studies indicate that MSC-Exos may ultimately improve RA by suppressing NLRP3 inflammasome activation and the production and release of inflammatory factors.

Research indicates that MSC-Exos may alleviate or treat RA through targeting T cells, macrophages, dendritic cells, and FLSs. Given that the excessive pyroptosis of these cells plays a crucial role in the adverse pathological progression of RA, targeting the regulation of multicellular pyroptosis has emerged as a promising therapeutic strategy for the treatment of this disease, with MSC-Exos serving as a viable option. Additional experimental studies are needed to validate these findings, thereby further facilitating the promising clinical application of MSC-Exos for the treatment of RA in the future.

MSC-Exos regulate pyroptosis in disc herniation

DH is one of the most prevalent degenerative disorders in clinical practice and the leading cause of neck, back, and leg pain, typically resulting from intervertebral disc degeneration (IVDD) [111]. The intervertebral disc (IVD) consists of two major components: the nucleus pulposus (NP) and the annulus fibrosus. Rupture of the annulus fibrosus followed by protrusion of the nucleus pulposus can compress the nerves, leading to a range of symptoms, including neck and back pain, numbness and pain in the limbs, sympathetic nerve compression symptoms, neurogenic claudication, and cauda equina syndrome [112,

113]. The current principal treatment options include surgical treatment (e.g., intervertebral disc fusion, total disc replacement), pharmacological therapies (e.g., NSAIDs, opioid painkillers), and nonpharmacological approaches (e.g., bed rest, stent fixation, electromagnetic, electrothermal therapy), with the aims of alleviating symptoms and enhancing functional status [114]. Although clinical treatment has improved, it still cannot effectively protect against IVDD.

An increasing amount of evidence suggests that the progression of IVDD is closely related to pyroptosis [5]. Pyroptosis stimulates the generation of diverse cytokines, which induce inflammation and aggravate intervertebral disc degeneration, promote ECM degradation, and facilitate angiogenesis as well as the ingrowth of nerves and lymphatic vessels into IVD tissues [115]. Moreover, researchers have reported that pyroptosis in cartilaginous endplate (CEP) tissue can contribute to CEP degeneration and tear, which are initiating factors of IVDD [116]. In addition, clinical measurements conducted on patients with lumbar intervertebral DH revealed that NLRP3 inflammasome is activated in NP tissue and that its expression is correlated with the severity of IVDD [117]. These findings indicate that NLRP3 is a critical target for treating IVDD and that the pyroptosis of NP cells (NPCs) plays a pivotal role in this process.

Given the importance of pyroptosis in the pathological progression of IVDD, various antipyroptosis strategies have been explored in animal models, with those involving MSC-Exos particularly noteworthy [67, 115]. Zhang et al. reported that miR-410 within MSC-Exos directly interacts with the 3'UTR of NLRP3, leading to a decrease in NLRP3 expression and a subsequent decrease in pyroptosis-related proteins [118]. This action inhibits the pyroptosis of NPCs and reduces the symptoms associated with IVDD. Yuan et al. demonstrated that miR-26a-5p carried by hUCMSC-Exos could inhibit the pyroptosis of NPCs and decrease proinflammatory cytokine synthesis by targeting the METTL14/NLRP3 pathway [119]. These findings indicate that miR-26a-5p decreases the expression of the mRNA methyltransferase METTL14, subsequently reducing the methylation of NLRP3 mRNA. This reduction leads to decreased binding of IGF2BP2 to NLRP3 mRNA, lowering NLRP3 protein expression, mitigating pyroptosis, and decreasing the production of proinflammatory cytokines, thereby exerting a protective effect on NP tissue. Dong et al. reported the alleviative effects of miR-155-5p in human adipose tissue stem cells (hASC)-Exos for rats with IVDD [80]. This effect was achieved through the targeting of transforming growth factor beta receptor 2 (TGFβR2) by miR-155-5p, which facilitated autophagy in NPCs, inhibited pyroptosis, and alleviated the symptoms of IVDD in a rat model. Xing et al. conducted experiments on the development of a thermosensitive acellular extracellular matrix hydrogel combined with adipose-derived stem cell exosomes (ADSC-Exos) [120]. In their study, ADSC-Exos effectively inhibited the pyroptosis of NPCs, maintained the stability of the IVD microenvironment, and ameliorated IVDD in rats.

The findings of these studies demonstrate that MSC-Exos effectively alleviate IVDD by regulating the pyroptosis of NPCs. However, studies on the roles of other cells in the IVD are relatively limited. Reports have shown that aberrant mechanical loading stress in the spine triggers intervertebral disc degeneration by inducing pyroptosis of AF and CEP tissues [121]. These findings indicate that pyroptosis of other cells also occurs during IVDD. Although there are significant differences in embryonic origin and anatomical structure between EP and articular cartilage tissues, many similarities exist in terms of their cellular physiological characteristics and ECM features [122]. Furthermore, the pathological changes that occur during the processes of cartilage degradation and degeneration are similar in both tissues [122]. As mentioned above concerning the mitigation of intra-articular chondrocyte pyroptosis by MSC-Exos, it is possible that MSC-Exos could alleviate IVDD by inhibiting pyroptosis in CEP. A deeper understanding of this regulatory mechanism may provide new therapeutic targets for IVDD and pave the way for innovative treatment strategies for DH.

MSC-Exos regulate pyroptosis in spinal cord injury

SCI is a condition that significantly impairs the quality of life of affected individuals. In 2019, the incidence of SCI worldwide was 0.91 million new cases, with a prevalence of 20.64 million and 6.20 million estimated years lived with disability [123]. SCI can lead to numerous severe complications, such as sensory impairment, motor dysfunction, and autonomic dysfunction [124]. Axonal degeneration and neuronal injury are prominent characteristics of SCI [125]. Despite the greatest efforts of many investigators to devise frontier therapeutic treatments, the main clinical options are still early surgical decompression and the administration of high-dose methylprednisolone; effective and feasible neuroprotective approaches remain elusive [126].

The integrity of the blood-spinal cord barrier (BSCB) is crucial for maintaining normal physiological functions within the spinal cord. Damage to the BSCB and neuroinflammation are critical events in the pathogenesis of SCI, as they inhibit axon regeneration and hinder nerve function recovery [127]. Pericytes, which are vascular wall cells that surround endothelial cells in capillaries and veins throughout the body, facilitate communication with endothelial cells via direct contact and paracrine signalling [128]. Research has highlighted the essential role of pericytes in preserving the integrity of the BSCB, and a

reduction in pericytes disrupts the BSCB, increases its permeability, intensifies the inflammatory response, and ultimately exacerbates the pathological changes associated with SCI [129]. A study conducted by Zhou et al. demonstrated that BMSC-Exos inhibit pericyte pyroptosis by suppressing the activation of the Nod1 inflammasome [130]. This action is beneficial for maintaining the integrity of the BSCB, reducing blood component leakage, alleviating oedema following SCI, promoting neuronal survival, and ultimately enhancing the motor function of SCI rats.

Microglia are the primary immune cells involved in the inflammatory response following SCI, and their depletion can disrupt scar healing and hinder neuronal regeneration, ultimately delaying functional recovery [131]. In experiments conducted by Sheng et al., EVs derived from MSCs (MSC-EVs) were isolated; these EVs positively expressed CD63, CD81, and ALIX and had a diameter of approximately 100 nm. The miRNA-22 contained within these vesicles can alleviate the neuroinflammatory response after SCI by inhibiting microglial pyroptosis, thereby facilitating damage repair and partially restoring neural function in rats post-SCI [132]. Research by Gu et al. demonstrated that miR-21a-5p, carried by BMSC-Exos, binds directly to the 3'UTR of PELI1, inhibiting its expression [133]. This interaction enhances autophagy in macrophages and microglia, reducing pyroptosis, mitigating neuroinflammation after SCI, and promoting motor function recovery.

Neuronal damage is a key contributor to the development of motor, sensory, and autonomic dysfunctions following SCI, with the extent of neuronal damage and the efficacy of regeneration and repair processes directly influencing the recovery of neural function [134]. Zhao et al. confirmed that BMSC-Exos have a protective effect on rats with SCI [82]. Specifically, the circular RNA circ_003564 carried by these exosomes inhibits cellular pyroptosis and protects neurons by decreasing the expression of pyroptosis-related proteins, thereby facilitating recovery after SCI. Furthermore, Lu et al. reported that BMSC-Exos can effectively address SCI by reducing LPS-induced pyroptosis in neuronal cells through the activation of the uncoordinated 5B (UNC5B)/phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway [135]. Additionally, engineered exosomes designed to carry Netrin-1 modified RNA (modRNA) exhibited enhanced effects.

In summary, MSC-Exos mitigate SCI injury and promote recovery by regulating the pyroptosis of pericytes, microglia, and neurons. Investigating the modulation of pyroptosis pathways in these cells by MSC-Exos may pave the way for new treatment strategies addressing motor, sensory, and autonomic dysfunctions, as well as various complications arising from SCI.

MSC-Exos regulate pyroptosis in osteoporosis

OP is the most prevalent bone disorder worldwide. A systematic review and meta-analysis revealed that the global prevalence of OP is 18.3%, with a higher rate of 23.1% among females [136]. A comprehensive observational study conducted in China indicated that the prevalence of OP among women aged 65 and older can reach as high as 48.55% and suggested that the number of OP patients may exceed 120 million by 2050 [137]. Currently, the range of medications available for the treatment of OP in clinical practice is somewhat limited [138]. Treatment options include stimulatory therapies that promote bone formation, such as teriparatide, and anti-bone resorption therapies aimed at inhibiting bone loss, including bisphosphonates and oestrogens. However, these treatments often do not achieve optimal results. Therefore, there is an urgent need for the development of novel anti-OP drugs to effectively address the increasing severity of bone loss and improve bone strength.

OP is characterized by a reduction in bone strength, which includes decreases in both bone mineral density and overall bone quality [139]. This condition ultimately leads to increased fragility and a heightened risk of fractures. Disruption of bone homeostasis is central to the pathogenesis of OP [140]. Bone homeostasis is maintained through a series of complex signalling pathways that establish a delicate balance between osteoclast-mediated bone resorption and osteoblast-driven bone matrix formation [141]. Moreover, osteoblasts, osteoclasts, and other bone cells interact with one another through the secretion of specific cytokines, which are essential for the coordinated maintenance of bone homeostasis [142, 143].

Cellular pyroptosis plays a critical role in the pathological processes underlying the onset and progression of OP. This includes the inhibition of osteoblastogenesis, the promotion of osteoclast formation, and the enhancement of bone resorption [144, 145]. Research indicates that pyroptosis in osteoblasts, osteoclasts, and bone marrow-derived macrophages is closely associated with bone loss in OP, suggesting that inhibiting pyroptosis may enhance osteogenesis and slow the progression of this disease [146–148]. Furthermore, the inflammasome activated during pyroptosis, along with the subsequent release of IL-1β and IL-18, contributes to bone destruction, thereby facilitating the onset and progression of OP [149]. Among these cytokines, IL-1β serves as a critical mediator that regulates the differentiation of osteoblasts and osteoclasts, disrupts the balance between these cell types, and consequently contributes to the development of OP [150, 151]. Research indicates that following

pyroptosis, IL-1β secreted by bone marrow-derived macrophages promotes the differentiation and maturation of osteoclasts [152]. Moreover, research has confirmed that inhibition of the NLRP3/caspase-1/IL-1β/IL-18 signalling pathway can mitigate bone loss and improve outcomes in individuals with OP [150, 153].

MSC-Exos can enhance osteoblast differentiation and activity through multiple signalling pathways, upregulate the secretion of osteogenesis-related proteins, increase mineral deposition levels, increase bone density, and promote bone repair [154]. Adipose derived mesenchymal stem cells (ADMSC)-Exos inhibit the activation of the NLRP3 inflammasome in osteoclasts, thereby reducing bone resorption, restoring bone mass, and alleviating diabetes-related OP [155]. Additionally, BMSC-Exos can alleviate OP by modulating bone immunity [156]. This effect is mediated through the inhibition of M1 macrophage polarization and the suppression of inflammatory levels, alongside the increase in osteoblast differentiation and activity, ultimately enhancing osteogenesis. HMGB1 is known to polarize monocytes into having an M1 macrophage phenotype and skew their differentiation away from the M2 phenotype [157]. Pan et al. reported that the expression of long noncoding RNA small nucleolar RNA host gene 1 (SNHG1) and HMGB1 was elevated in patients with OP [158]. Further investigations indicated that SNHG1 promotes HMGB1 expression, facilitates pyroptosis in BMSCs, and consequently inhibits their osteogenic differentiation. Notably, research has demonstrated that miR-548x-3p, delivered by BMSC-Exos, inhibits pyroptosis in vascular tissue by targeting HMGB1 [159]. This finding agrees with the research showing that ADMSC-Exos are rich in osteoprotegerin and that miR-21-5p can inhibit the osteoclast differentiation of macrophages and attenuated bone loss in OP mice, suggesting that inhibiting the pyroptosis of macrophages to prevent their polarization to the M1 phenotype represents a favourable therapeutic strategy for OP and that MSC-Exos might play a highly promising role in preventing inflammatory bone loss by the pyroptosis pathway in immune cells [160].

During ossification, bone remodelling, and repair processes, angiogenesis plays a critical role. Vascularization supplies essential nutrients and oxygen for bone regeneration, whereas endothelial cells—integral components of blood vessels—are essential for maintaining bone homeostasis [161]. Endothelial cells and osteoblasts secrete a range of growth factors and cytokines, including fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), which promote the proliferation, migration, and angiogenesis of bone cells, ultimately enhancing bone formation [162, 163]. This positive feedback mechanism, which mutually promotes angiogenesis and bone formation, is referred to as "angiogenesis–osteogenesis coupling" [164]. Therefore, vascular neovascularization and remodelling represent crucial directions for the treatment of OP.

Research has demonstrated that BMSC-Exos can enhance bone formation by promoting angiogenesis [165, 166]. Numerous studies have confirmed that BMSC-Exos can inhibit pyroptosis in vascular endothelial cells (VECs) through various pathways, thus facilitating angiogenesis and protecting blood vessels. Pei et al. discovered that miR-548x-3p, which is carried by BMSC-Exos, inhibits pyroptosis in VECs induced by heatstroke by regulating the HMGB1/NLRP3 axis [159]. Additionally, miR-223-3p, which is carried by BMSC-Exos, diminishes the expression of NLRP3 through a competitive endogenous RNA (ceRNA) regulatory mechanism, leading to reduced levels of ASC and GSDMD, which in turn inhibit LPS-induced pyroptosis and inflammation in endothelial progenitor cells (EPCs), thereby promoting angiogenesis [167]. BMSC-Exos can stimulate the proliferation and osteogenic differentiation of BMSCs, facilitating both osteogenesis and neovascularization [168]. Therefore, it is reasonable to believe that MSC-Exos can protect the inner wall of blood vessels by inhibiting pyroptosis in endothelial cells, promoting angiogenesis, and facilitating ossification, bone remodelling, and bone repair processes.

The demonstration in multiple cell types that pyroptosis has a profound influence on the progression of OP diseases highlights the importance of pyroptosis as a potential key target. Furthermore, MSC-Exos have exhibited considerable promise in regulating this process and possess a targeted delivery capability. Whether exosomes can be used as delivery carriers of more proangiogenic factors and anti-inflammatory factors to further strengthen the intervention in the imbalance of pyroptosis in OP may be a future the next research direction.

MSC-Exos regulate pyroptosis in other bone-related diseases

Growing evidence indicates that inappropriate inflammatory reactions play essential roles in the damage caused by bone-related diseases, even extending to periodontitis. Considering this point, pyroptosis has gradually become considered a fatal regulator of bone-related inflammation and subsequent disorganization, and increasing research has reported the overactivation of the inflammasome in chronic inflammation [169]. Excessive inflammation can lead to the destruction of connective tissue and the loss of alveolar bone, which can result in periodontitis [170]. A study comparing NLRP3 knockout mice and their wild-type littermates with periodontitis revealed that the loss of NLRP3 inflammasome significantly inhibited osteoclast differentiation and alveolar bone loss, and that

the pathological changes associated with periodontitis were obviously ameliorated. Furthermore, these findings are in accordance with showing that human periodontal ligament stem cell-derived EVs (hPDLSC-EVs) relieve periodontal inflammation damage and alveolar bone destruction. Following the transplantation of these exosomes, periodontal macrophage pyroptosis is suppressed by the inhibition of NLRP3 activation via the binding of miR-590-3p to the Toll-like receptor 4 (TLR4) transcription [171]. In summary, MSC-Exos therapy has shown effective and safe therapeutic potential for periodontitis through improving regeneration and regulating inflammation in preclinical studies. Moreover, there is reason to believe that pyroptosis, as an important target of exosomes, will be a promising new approach and idea for the treatment of various bone-related diseases (Table 1; Fig. 3).

Conclusion and future perspectives

Bone-related diseases are leading cause of disability worldwide [1]. Patients often endure chronic pain and functional impairments for extended periods, leading

Table 1 MSCs and Exos affect bone-related diseases by regulating pyroptosis in different cells

Origin	Mechanisms	Effector cells	Outcomes	References
hAD-MSCs	Inhibiting the pyroptosis signalling pathway mediated through TNFR1/NF-κB by secreting sTNFR1 to combine with TNF-α	Chondrocytes	Reducing cartilage damage and mitigating the pathological changes of arthritis, delaying the development of OA	[101]
BMSC-Exos	miR-326 targets HDAC3, thereby activating the STAT1/NF-κB p65 signalling pathway	Chondrocytes	Inhibiting the occurrence of pyroptosis and protecting chondrocytes from osteoarthritis	[75]
hUCMSC-EVs	miR-223 binds with the 3'UTR of NLRP3 mRNA and inhibits the activation of NLRP3	Chondrocytes	Inhibiting chondrocyte pyroptosis, promoting cartilage repair and inhibiting inflammation	[102]
BMSC-Exos	miR-223 targets and inhibits the expression of NLRP3	Macrophages	Inhibiting inflammation and alleviating the symptoms of RA	[110]
MSC-Exos	miR-410 binds to NLRP3 mRNA	NPCs	Weakening NPCs pyroptosis to alleviate IVDD	[118]
hUCMSC-Exos	miR-26a-5p inhibits the METTL14/NLRP3 pathway	NPCs	Effectively improving the viability of NPCs, protecting them from pyroptosis	[119]
hASC-Exos	miR-155-5p targets TGFβR2	NPCs	Promoting autophagy and inhibiting pyroptosis in NPCs to alleviate IVDD	[80]
ADSC-Exos	Mitigating the expression of NLRP3, GSDMD, cleaved caspase-1 and IL-1β	NPCs	Inhibiting pyroptosis, modulating MMPs, and maintaining IVD microenvironment homeostasis	[120]
BMSC-Exos	Inhibiting pyroptosis in pericytes by inhibiting Nod1	Pericytes	Attenuating BSCB leakage and reducing oedema after SCI	[130]
MSC-EVs	Inhibiting the expression of GSDMD	Microglias	Inhibiting the occurrence of pyroptosis in microglias	[132]
BMSC-Exos	Inhibiting macrophage/microglia pyroptosis by increasing autophagy through the miR-21a-5p/peli1 axis	Macrophages/Microglias	Alleviating neuroinflammation after SCI	[133]
BMSC-Exos	circ_003564 reduces inflammasome-related pyroptosis marker levels	Neurons	Attenuating inflammasome-related pyroptosis to improve SCI recovery	[82]
BMSC-Exos	Activating the Unc5b/PI3K/AKT/mTOR axis	Neurons	Promoting axonal growth in SCI by attenuating inflammation and pyroptosis	[135]
ADMSC-Exos	Suppressing NLRP3 activation	Osteoclasts	Rescuing diabetes-induced bone loss	[155]
MSC-Exos	miR-548x-3p regulates the HMGB1/NLRP3 axis	VECs	Inhibiting the pyroptosis of VECs, alleviating the injury of tissues, and decreasing the pro-inflammatory cytokine levels	[159]
BMSC-Exos	Degrading NLRP3 in a ceRNA mechanism-dependent manner	EPCs	Inhibiting pyroptosis and inflammation in EPCs and promoting EPCs-mediated angiogenesis	[167]
hPDLSC-EVs	Inhibiting NLRP3 activation by binding miR-590-3p to the TLR4 transcript	Periodontal macrophages	Ameliorating periodontal inflammatory injury by repressing pyroptosis	[171]
hUCMSC-Exos	circHIPK3 downregulates miR-421, resulting in increased expression of FOXO3a	Skeletal muscle cells	Preventing pyroptosis and repairing ischaemic muscle injury	[43]
BMSC-Exos	miR-367-3p targets EZH2	Skeletal muscle cells	Safeguarding mouse skeletal muscle against pyroptosis-induced I/R injury	[44]

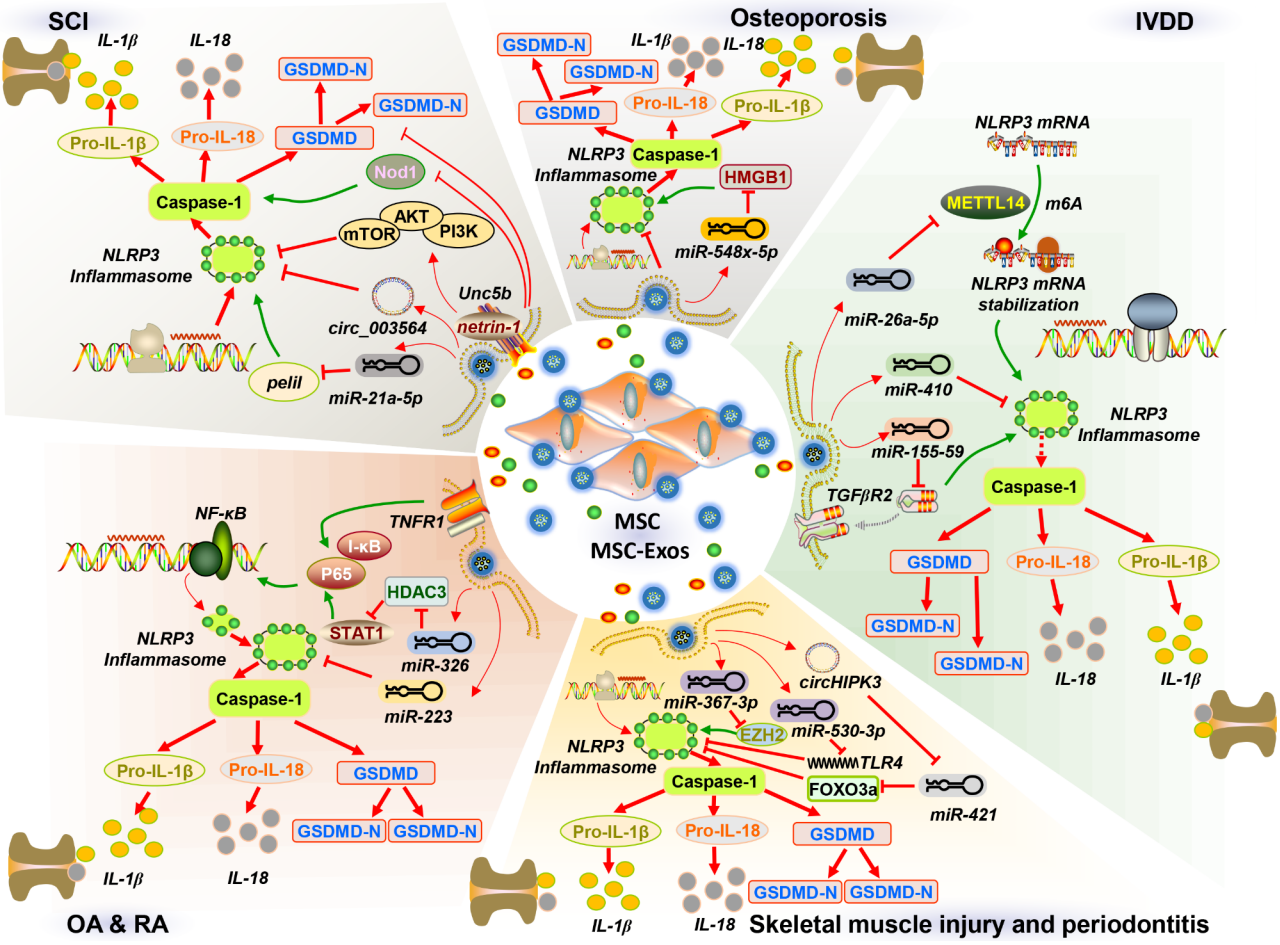

Fig. 3 The roles and mechanisms by which various MSCs and their derivatives affect bone- related diseases by regulating pyroptosis in different cells. In OA, MSCs and their derivatives can inhibit chondrocyte pyroptosis through multiple approaches, thus reducing the cartilage damage and delaying the development of OA. BMSC-Exos inhibit the expression of NLRP3 to inhibit inflammation and alleviate the symptoms of RA. In DH, various MSC-Exos act through multiple signalling pathways, weakening NPCs pyroptosis to alleviate IVDD. BMSC-Exos alleviate neuroinflammation and improve SCI recovery by inhibiting the pyroptosis in multiple cell types. ADMSC-Exos rescue the diabetes-induced bone loss by suppressing NLRP3 inflammasome activation. By inhibiting the NLRP3 activation via the binding of miR-590-3p to the TLR4 transcription, hPDLSC-EVs protected periodontal macrophages and thereby ameliorated periodontal inflammatory injury. MSC-Exos can prevent skeletal muscle cell pyroptosis and alleviate muscle injury through various pathways

to mental health challenges and social isolation [172, 173]. Additionally, the difficulty in achieving complete cures for these conditions results in significant medical expenses and a loss of labour resources for both individuals and society [174, 175]. Pyroptosis is a recently identified form of programmed cell death characterized by cellular lysis, subsequent cell death, and the release of various proinflammatory cytokines, thereby initiating or exacerbating inflammatory responses [48]. Pyroptosis and chronic inflammation are critical processes in numerous degenerative diseases and significantly contribute to the onset and progression of bone-related diseases [176].

Many studies have demonstrated that mesenchymal stem cells play crucial roles in anticancer and anti-inflammatory processes, tissue protection, and tissue repair through the release of exosomes containing a wide range of soluble factors and beneficial cargo [177–181]. Several of these applications have been translated into clinical practice, highlighting promising avenues for both experimental and clinical investigations [182]. As research on MSCs has progressed, the focus has increasingly shifted towards "cell-free therapy," with exosomes serving as a crucial mechanism through which MSCs mediate this therapeutic approach [183].

In clinical applications, several potential advantages of MSC-Exos are evident [11]. First, nanosized exosomes can traverse various biological barriers, including the blood–brain barrier, the blood–cerebrospinal fluid barrier, and the placental barrier, effectively facilitating the delivery of diverse therapeutic agents [184]. Second, the utilization of MSC-Exos can yield higher concentrations of therapeutic agents than traditional MSCs transplantation [185].

However, bone tissue exhibits innate rigidity, low permeability, and reduced blood flow, features that result in poor retention and lower therapeutic concentrations, further impeding the effective treatment of bone diseases [186]. This necessitates that we pay special attention to the method of local drug administration [187]. Exosomes are highly biocompatible, have low immunogenicity, and are targeted, thereby rendering them exceptional natural biological carriers for the treatment of bone-related diseases [187]. Carriers that deliver exosomes can offer the advantages of localized, quantitative drug delivery and sustained release. Currently, exosomes are increasingly being combined with new biomaterials, including composite hydrogels, bioceramic bone substitutes, bioactive metals, and composite scaffolds, which is currently one of the most promising research directions [188].

Although exosomes therapies present safer and superior advantages in comparison with cell transplantation, numerous difficulties remain in moving from laboratory research to clinical application. First, regardless of whether they are used directly as natural exosomes or as carriers for drugs, difficulties exist in the processes of large-scale exosome production, isolation, and purification [189]. Second, highly specific identification approaches for exosomes are lacking [190]. Additionally, guaranteeing consistency in the dosage and efficacy of exosomes across diverse production batches, technical conditions, and environmental factors is an urgent need. The resolution of these problems demands that we further upgrade or generate new production and identification technologies and establish standardized manufacturing practices and a comprehensive regulatory framework. Furthermore, when systemic administration methods are employed, exosomes are promptly cleared from the bloodstream and accumulate in the lungs and liver [191]. We can improve therapeutic effects and safety through the creation of diverse biomaterials to assist in the local delivery of exosomes. Additionally, in future clinical applications, potential side effects, such as general toxicity and immunotoxicity, should be considered. Therefore, the adverse reactions and safety of exosomes are worthy of further research. Foremost, the majority of the applications of exosomes in disease treatment remain in the preclinical research stage involving cell and animal experiments, with scarce clinical efficacy data, thereby rendering it challenging for this technology to genuinely function as a therapy in clinical practice. However, this is our chance to explore and develop it as a new treatment option.

While exosome therapy remains in its nascent stage in clinical treatment and numerous pressing problems await resolution, fortunately, in light of the alluring prospects manifested by the research in this field, related clinical studies are becoming increasingly prevalent. Currently, most clinical research is focused on respiratory system diseases, whereas research on bone-related diseases includes studies on osteoarthritis (NCT05060107), degenerative meniscal injury (NCT05261360), and bone loss/bone grafts (NCT04998058) [11]. This implies that the majority of preclinical studies with outstanding results have not yet advanced to clinical trials, and we should exert greater efforts to validate these potential treatment modalities in clinical trials, with the aim of uncovering novel therapeutic approaches for these intractable diseases. In addition, when addressing the challenges faced in translating MSC-Exos therapy from the laboratory to clinical application, one frontier worth exploring is the utilization of Artificial Intelligence (AI) technology to optimize the design, production, purification, and therapeutic application of MSC-Exos [192]. AI can not only enhance the efficiency and purity of large-scale MSC-Exos production through advanced algorithms, minimizing batch-to-batch variations, but potentially also enable more precise modulation of MSC-Exos in balancing pyroptosis in bone-related diseases, thereby ensuring stable therapeutic outcomes. This could serve as a powerful catalyst in advancing the application of MSC-Exos therapy in the future.

The aetiology and pathological changes of bone-related diseases are complex and often involve the pyroptosis of multiple cell types, which makes it difficult to block pyroptosis in a single cell type using conventional strategies. Fortunately, MSC-Exos offer a new perspective for the treatment of such diseases because of their unique ability to regulate multiple cell types. In recent years, the broader "PANoptosis" concept has emerged that encompasses pyroptosis, representing a completely new type of inflammatory RCD that was initially explored in the context of bone-related diseases. Excitingly, MSCs have already shown initial regulatory effects on PANoptosis [193]. So, are MSC-Exos not far off?

This paper reviews recent evidence regarding the inhibition of pyroptosis in bone-related diseases by MSC-Exos, along with investigations into the targets and regulatory mechanisms associated with this process. Such insights are highly important for the prevention and treatment of these diseases via MSC-Exos. Current research unequivocally indicates that MSC-Exos inhibit pyroptosis and reduce inflammatory levels by modulating the expression of key genes and proteins associated with pyroptosis, thereby providing alleviative or therapeutic effects in bone-related diseases. With an ageing population and increasing injury rates, the incidence and prevalence of bone-related diseases continue to increase [194, 195]. Therefore, investigating and elucidating the mechanisms and pathways through which MSC-Exos regulate pyroptosis has become essential for the development of novel and more effective drugs and therapeutic strategies.

The treatment of bone-related diseases through the modulation of pyroptosis presents both opportunities and challenges, and significant work remains to achieve this objective effectively.

Abbreviations

ADSC-Exos	Adipose-derived stem cell exosomes
AKT	Protein kinase B
Alix	Apoptosis linked gene 2 interacting protein X
BMSC-Exos	Bone marrow mesenchymal stem cell-derived exosomes
BSCB	Blood–spinal cord barrier
CEP	Cartilaginous endplate
ceRNA	Competitive endogenous RNA
DAMPs	Danger-associated molecular patterns
DH	Disc herniation
DMARDs	Disease-modifying antirheumatic drugs
EPCs	Endothelial progenitor cells
ER	Endoplasmic reticulum
ESCRT	Endosomal sorting complexes required for transport
ESEs	Early-sorting endosomes
EVs	Extracellular vesicles
EZH2	Enhancer of zeste homologue 2
FGF	Fibroblast growth factor
FLSs	Fibroblast-like synoviocytes
FOXO3a	Forkhead box O3a
GA	Golgi apparatus
GSDMCT	Carboxy-terminal domain
GSDMD	Gasdermin D
GSDMNT	Amino-terminal effector domain
hAD-MSCs	Human adipose-derived mesenchymal stem cells
hASC	Human adipose tissue stem cells
HDAC3	Histone deacetylase 3
HMGB1	High-mobility group box chromosomal protein-1
hPDLSC-EVs	Human periodontal ligament stem cell-derived exosomes
hUC-MSCs	Human umbilical cord mesenchymal stem cells
hUCB-MSCs	Human umbilical cord blood-derived MSCs
hUCMSC-EVs	Extracellular vesicles derived from hUC-MSCs
hUCMSC-Exos	Human umbilical cord MSC-Exos
I/R	Injury Ischaemia/Reperfusion injury
ILVs	Intraluminal vesicles
IVD	Intervertebral disc
IVDD	Intervertebral disc degeneration
LSEs	Late sorting endosomes
MSC-EVs	EVs derived from MSCs
MSC-Exos	Exosomes derived from mesenchymal stem cells
MSCs	Mesenchymal stem cells
MSDs	Musculoskeletal disorders
mTOR	Mammalian target of rapamycin
MVBs	Multivesicular bodies
MVs	Microvesicles
NCCD	The Nomenclature Committee on Cell Death
NP	Nucleus pulposus
NPCs	NP cells
NPCs	NP cells
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
OP	Osteoporosis
PAMPs	Pathogen-associated molecular patterns
PDGF	Platelet-derived growth factor
PI3K	Phosphatidylinositol 3-kinase
pro-IL-1β	Pro-interleukin-1β
pro-IL-18	Pro-interleukin-18
PRRs	Pattern recognition receptors
RA	Rheumatoid arthritis
RCD	Regulated Cell Death
SCI	Spinal cord injury
SNHG1	Long noncoding RNA small nucleolar RNA host gene 1
STAT1	Signal transducer and activator of transcription 1
TGFβR2	Transforming growth factor beta receptor 2
TLR4	Toll-like receptor 4
TNF-α	Tumour necrosis factor-alpha
TNFR1	Tumour necrosis factor receptor 1
UNC5B	Uncoordinated 5B
VECs	Vascular endothelial cells
VEGF	Vascular endothelial growth factor

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