

Stem cell-mediated modulation of pyroptosis contributes to tissue repair in noninfective inflammatory-related diseases (Review)

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Abstract. Pyroptosis, a programmed cell death marked by lytic and inflammatory characteristics, plays a crucial role in non-infectious inflammation-related diseases but can lead to detrimental outcomes when dysregulated. Stem cells have emerged as key players in modulating pyroptosis through paracrine signaling, offering a novel avenue for tissue repair and regeneration. The present review delved into previous studies elucidating the intricate interplay between stem cells and pyroptosis, emphasizing the potential of stem cell-based therapies in regulating pyroptotic pathways. The exploration of this dynamic interaction holds promise for developing strategies to harness stem cells for effective tissue repair and regeneration in the context of inflammation-related diseases.

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Abbreviations: AC, articular cartilage; MSCs, mesenchymal stem cells; adMSCs, adipose-derived MSCs; AIM2, absent in melanoma 2; AKI, acute kidney injury; ALI, acute lung injury; BMSCs, bone marrow MSCs; BMSC-CM, BMSCs-conditioned medium; BMSC-Exos, exosomes derived from BMSCs; CA, cardiac arrest; CNS, central nervous system; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; DAMPs, damage-associated molecular patterns; DKD, diabetic kidney disease; DILI, drug-induced liver injury; Dox, doxorubicin; ECM, extracellular matrix; EVs, extracellular vesicles; GSDMD, gasdermin D; hfMSCs, hair follicle MSCs; I/R, ischemia/reperfusion;

1. Introduction

The emergence of systemic chronic inflammation is significantly influenced by lifestyle, psychosocial elements and environmental factors. This intricate interplay fosters a spectrum of non-infectious inflammation-related maladies, including but not limited to cardiovascular and cerebrovascular diseases, diabetes, autoimmune disorders, chronic nephritis, chronic liver diseases, and conditions affecting

HIRI, hepatic I/R injury; hucMSC-EVs, EVs derived from human umbilical cord MSCs; IBD, inflammatory bowel disease; ICH, intracerebral hemorrhage; IVD, intervertebral disc; IVDD, IVD degeneration; LIRI, lung I/R injury; lncRNA, long non-coding RNA; METTL14, methyltransferase like 14; NF- κ B, nuclear factor kappa b; NLRP3, NOD-like receptor family, pyrin domain-containing 3; NPCs, nucleus pulposus cells; NPPCs, nucleus pulposus progenitor cells; OA, osteoarthritis; PRRs, pattern recognition receptors; SCI, spinal cord injury; TBI, traumatic brain injury; TLRs, Toll-like receptors; TNF- α , tumor necrosis factor-alpha

Key words: stem cells, pyroptosis, tissue injury, regeneration, inflammation-related diseases

the osteoarticular and neurodegenerative systems. These diseases collectively represent substantial contributors to global morbidity and mortality rates. Addressing the multifaceted determinants of chronic inflammation is imperative for developing comprehensive strategies to mitigate the impact of these prevalent and debilitating health conditions on a global scale (1).

Studies have shown that pyroptosis is widely involved in the occurrence and development of non-infectious inflammation-related diseases and plays an important role (2). The sterile inflammatory response, devoid of microbial infection, plays a crucial role in organ development, tissue repair and host defense mechanisms. Nonetheless, dysregulation of sterile inflammation can precipitate various inflammatory diseases such as lung inflammation, type 2 diabetes and sterile liver diseases. Pyroptosis is a form of programmed cell death that is distinct from apoptosis and necrosis. It is an inflammatory form of cell death triggered by certain cellular signals, particularly inflammasomes, in response to infection or cellular stress (3). During pyroptosis, the cell undergoes a series of morphological changes, including cell swelling, membrane rupture, and release of pro-inflammatory cytokines and intracellular contents. This process is mediated by gasdermin proteins, which forms pores in the cell membrane, leading to cell lysis and the release of inflammatory molecules (3,4). Given the pivotal influence of pyroptosis on orchestrating inflammation, there exists a hypothesis postulating that pyroptosis may serve as a potential contributor in several sterile inflammatory diseases.

Stem cell therapy, heralded as a groundbreaking approach to treat diverse diseases and injuries, holds tremendous promise for tissue repair and regeneration (5). Their therapeutic prowess lies in their remarkable adaptability to specific tissue environments, fostering healing through the generation of functional cells. This adaptability becomes particularly crucial in scenarios where the body's natural repair mechanisms prove insufficient, as observed in degenerative diseases, injuries, or chronic disorders (6-8). Mesenchymal stem cells (MSCs), for example, exhibit anti-inflammatory and immunomodulatory properties, contributing to tissue repair by reducing inflammation and promoting the regeneration of damaged cells (9).

Previous studies have indicated that the ability of stem cells to regulate pyroptosis has significant implications for tissue repair and regenerative medicine (9,10). Stem cells can secrete various factors, including anti-inflammatory cytokines, growth factors and paracrine factors (Fig. 1), which can play a significant role in reducing inflammation and promoting tissue repair (9,11). These secreted factors carry a cargo of bioactive molecules, such as microRNAs, proteins and lipids, which can directly or indirectly target pyroptosis signaling pathways to influence neighboring cells and modulate their behavior (12,13). Through intricate signaling pathways, stem cells modulate pyroptosis to control the inflammatory response and foster tissue regeneration (14). This regulatory function is crucial in addressing injuries, degenerative diseases and other conditions where pyroptosis may contribute to tissue damage (15).

Understanding the interplay between stem cells and pyroptosis provides insights into innovative therapeutic strategies, offering the potential for targeted interventions that harness

the regenerative capacities of stem cells to promote tissue repair while mitigating excessive inflammatory responses. In the present comprehensive review, it was presented how stem cells regulate pyroptosis to promote tissue repair in various diseases.

2. Canonical and non-canonical pathways of pyroptosis

Stem cells influence pyroptosis by modulating the pyroptosis signaling pathway, thereby further promoting tissue repair or slowing the pathological process (16). Pyroptosis is activated through distinct pathways, the canonical and non-canonical pathways (Fig. 2) (17). Damage-associated molecular patterns (DAMPs), which selectively bind to their complementary membrane protein receptors, including Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors, collectively termed pattern recognition receptors (PRRs). Upon binding to PRRs, DAMPs orchestrate the activation of nuclear factor kappa B (NF- κ B), culminating in the transcriptional upregulation of numerous pro-inflammatory genes, among which are the essential components of the inflammasome pathways (18). The assembly of the NOD-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome facilitates the self-cleavage of pro-caspase-1, transforming it into its enzymatically active form, caspase-1 (19). Subsequently, active caspase-1 cleaves pro-interleukin into its biologically active counterparts, IL-1 β and IL-18 (20). Simultaneously, caspase-1 also cleaves gasdermin D (GSDMD), resulting in the formation of two fragments: GSDMD-N and GSDMD-C. GSDMD-N subsequently assembles into pores within the plasma membrane, initiating pyroptotic cell death and the release of IL-1 β and IL-18 to induce more inflammation (21).

In addition to the canonical pathway, emerging evidence has demonstrated the involvement of caspase-4, caspase-5 and caspase-11 in pyroptosis, particularly in scenarios involving conventional or unconventional inflammasome signaling (22-24). These caspases play a dual role in initiating pyroptotic cell death. Firstly, caspase-4/5/11 can directly cleave GSDMD (25). This direct cleavage leads to the formation of GSDMD-N, which assembles into membrane pores, resulting in pyroptotic cell death (25). Secondly, caspase-4/5/11 can also stimulate the NLRP3 inflammasome/caspase-1 signaling pathway, eventually leading to pyroptosis. In this context, caspase-4/5/11 serves as an upstream activator, triggering the assembly of the NLRP3 inflammasome. This, in turn, leads to the activation of caspase-1, which subsequently cleaves GSDMD, ultimately culminating in the execution of pyroptotic cell death (26).

3. The modulation of pyroptosis by stem cells for alleviating progression in degenerative diseases

Osteoarthritis (OA). (OA) is a chronic joint disease marked by the gradual degradation of articular cartilage (AC), along with subchondral bone sclerosis, synovial hyperplasia, and the formation of osteophytes (27). Emerging evidence suggests that pyroptosis may play a crucial role in the pathogenesis of OA (6). Recent research has revealed that inhibiting pyroptosis in chondrocytes can attenuate the development of OA (28). Excessive inflammation within chondrocytes is a key factor

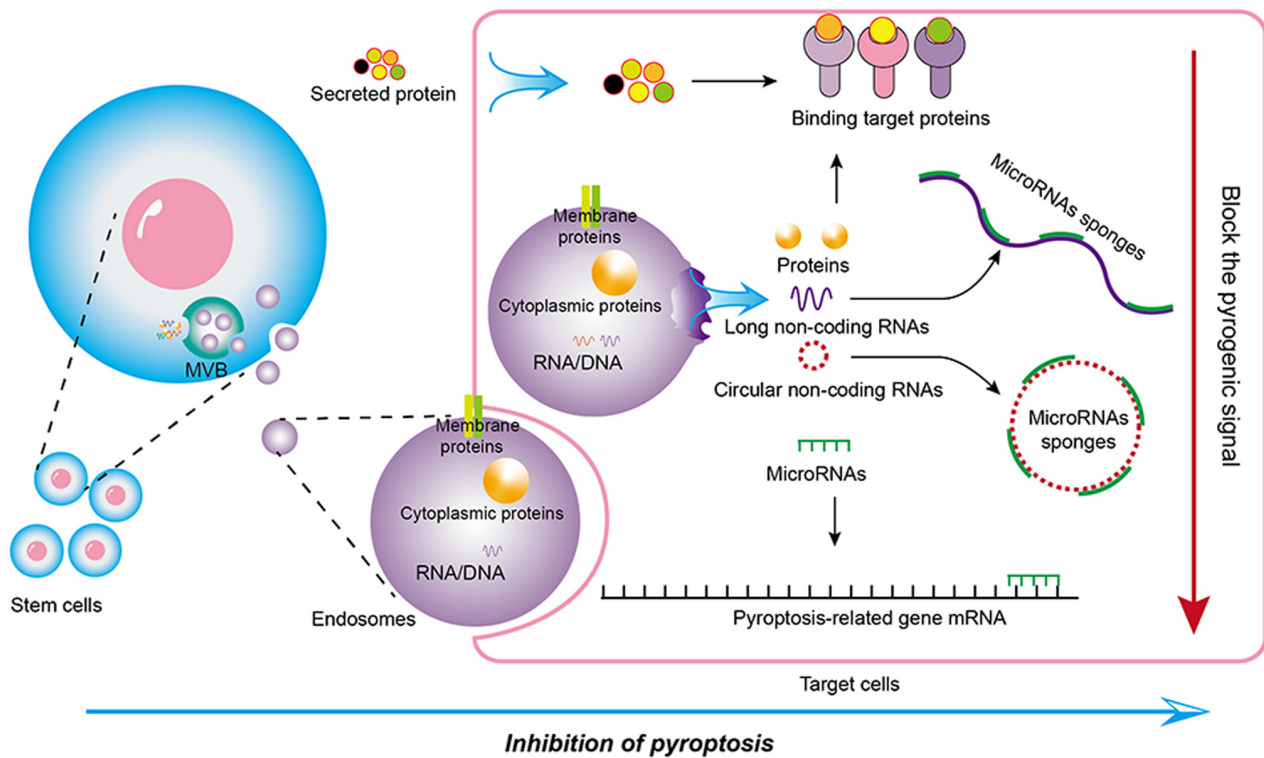


Figure 1. Stem cells inhibit pyroptosis through secrete anti-inflammatory factors and cytokines and paracrine factors, including exosomes and microvesicles.

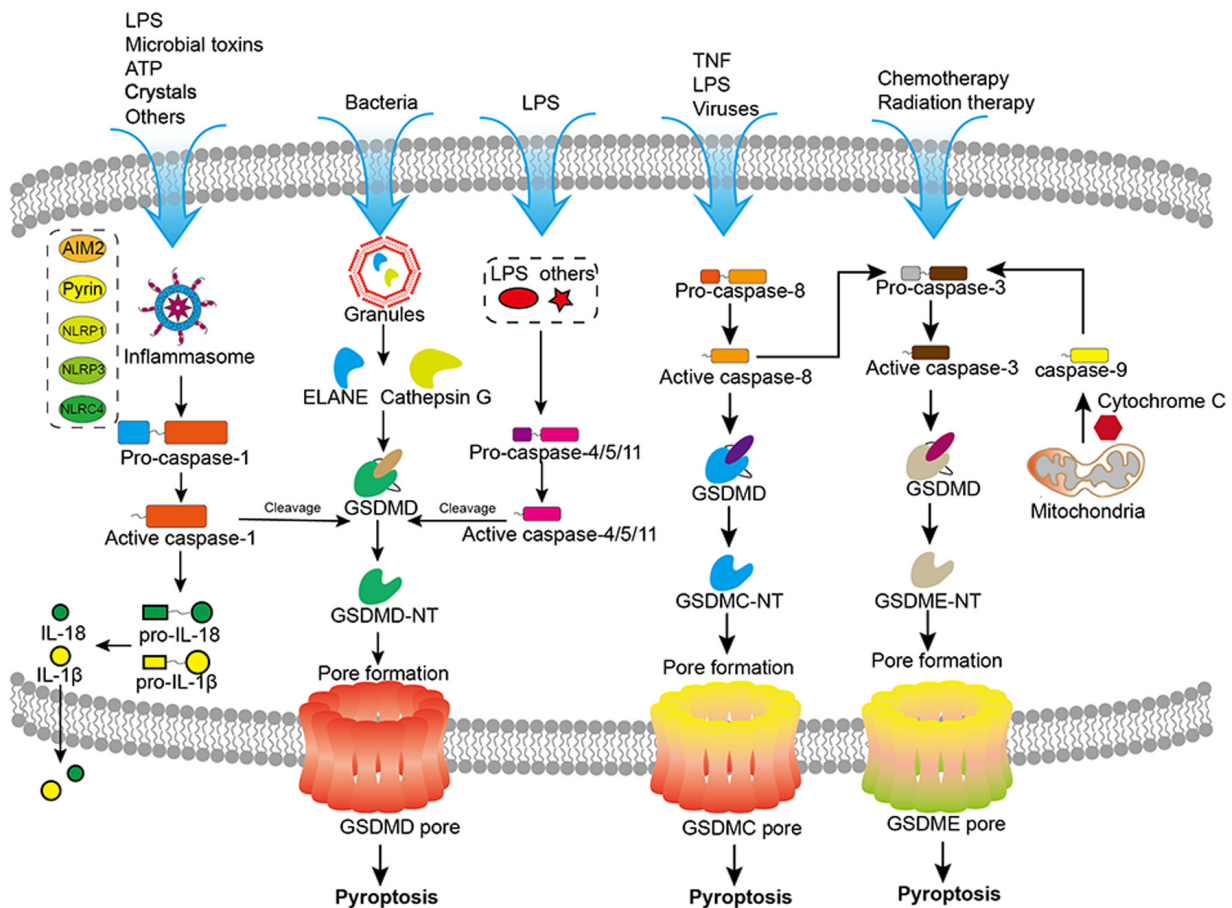


Figure 2. The model diagram of pyroptosis pathway. In response to a variety of danger signals, the assembly of the inflammasome leads to the activation of caspase-1. Activated caspase-1 cleaves gasdermin D, releasing its N-terminal fragment to form membrane pores leading to cell membrane permeabilization. Unlike the canonical pathway, which requires the formation of an inflammasome, non-canonical pyroptosis can be activated directly by cytosolic danger signals. GSDMD, gasdermin D.

contributing to chondrocyte survival and is implicated in the progression of OA. In an adjuvant-induced arthritis model, acid-sensitive ion channel 1a has been identified as a mediator of chondrocyte pyroptosis, shedding light on the underlying mechanisms of OA pathology (29). Furthermore, in knee OA, fibroblast-like synoviocytes have been recognized as the main effector cells responsible for synovial fibrosis. Pyroptosis in these cells has been linked to NOD-like receptor family, pyrin domain-containing 1 and NLRP3 inflammasomes, underscoring the significance of pyroptosis in driving fibroblast-like synoviocyte dysfunction in knee OA (30). An increase in hypoxia-inducible factor-1 α levels has been found to exacerbate synovial fibrosis by promoting fibroblast-like synoviocyte pyroptosis (31). These studies elucidate the critical role of pyroptosis in the pathophysiological processes of OA.

Recently, adipose-derived MSCs (adMSCs) have been demonstrated to exert a protective effect by delaying the development of rat OA. This safeguarding mechanism hinges on the secretion of sTNFR1 by adMSCs, which possesses highly specific neutralizing activity against tumor necrosis factor- α (TNF- α). This inhibition of TNF- α serves to curtail chondrocyte pyroptosis, a pivotal contributor to OA progression (32). In a similar vein, exosomes derived from bone marrow MSCs (BMSC-Exos) have demonstrated the ability to mitigate OA by delivering microRNA (miR)-326 to chondrocytes and cartilage. Through this delivery, BMSC-Exos target HDAC3 and the STAT1/NF- κ B p65 axis, effectively inhibiting chondrocyte and cartilage pyroptosis (15). Likewise, extracellular vesicles derived from human umbilical cord MSCs (hucMSC-EVs) have emerged as a promising avenue for alleviating OA and maintaining chondrocyte homeostasis. A novel therapeutic mechanism was revealed, centered around the pivotal miR-223. This miR directly binds to the 3'-untranslated region of NLRP3 mRNA, exerting profound anti-inflammatory and cartilage-protective effects through hucMSC-EVs (33).

Intervertebral disc degeneration (IVDD). IVDD represents a chronic and degenerative disease characterized by dysregulation of the catabolic and anabolic processes within the extracellular matrix (ECM) and alterations in the microenvironment of the intervertebral disc (IVD) (34,35). The healthy intervertebral disc is a complex tissue composed of a soft inner nucleus pulposus (NP) surrounded by the fibrocartilaginous ring annulus fibrosus and cartilage endplates (36,37). However, during IVDD, there is an aberrant expression of matrix metalloproteinases and a reduction in collagen II secretion from NP cells (NPCs), which disrupts the delicate balance of the ECM (38,39). Consequently, remodeling of the IVDD microenvironment occurs, leading to the accumulation of inflammatory factors and inducing NLRP3-mediated pyroptosis of NPCs (40,41). This cascade of events initiates a series of worsening reactions, contributing to the progression and severity of the disease.

EVs, specifically exosomes, from stem cells play a critical role in paracrine signaling, effectively protecting NPCs from apoptosis, promoting ECM synthesis, and mitigating inflammatory responses in intervertebral discs (42,43). A thermosensitive acellular ECM hydrogel coupled with adMSCs exosomes has shown promise. This approach helps maintain

early IVDD microenvironment homeostasis and ameliorates IVDD (44).

In several studies, the mechanism by which EVs from stem cells inhibit pyroptosis of NPCs has been reported. In IVDD patients, methyltransferase like 14 (METTL14) expression is significantly elevated in NPCs (45). METTL14 stabilizes NLRP3 mRNA in a manner dependent on insulin-like growth factor-binding protein 2 (46,47). Consequently, the increased NLRP3 levels lead to elevated production of IL-1 β and IL-18, triggering pyroptotic cell death in NPCs. However, hope lies in the therapeutic potential of miRs derived from exosomes of different stem cell sources. For instance, miR-26a-5p, found in hucMSCs exosomes, directly degrades METTL14, effectively improving NP cell viability and protecting them from pyroptosis (47). Similarly, MSCs-derived exosomal miR-410 plays an essential role in counteracting pyroptosis by directly binding to NLRP3 mRNA, thereby suppressing the NLRP3 pathway (9). Furthermore, exosomal miR-302c, which originates from ESCs, exhibits anti-pyroptotic properties by inhibiting NLRP3 and consequently alleviating pyroptosis in NPCs (48).

Cartilage regeneration and reconstruction. The regeneration and reconstruction of AC after a defect, including OA and IVDD, pose significant challenges, owing to its inherently restricted intrinsic reparative capabilities (49,50). When AC sustains injury, the afflicted tissue releases damage-associated DAMPs (51), subsequently provoking the neighboring cells and circulating immune cells to secrete pro-inflammatory chemokines (52). These inflammatory cytokines, notably IL-1 and TNF- α , exert a profound inhibitory influence on the proliferation and differentiation of MSCs and chondrocytes. Notably, studies have documented that IL-1 and TNF- α impede the differentiation of growth plate chondrocytes and suppress the expression of chondrogenic-related genes in MSCs (53,54). The crux of addressing AC defects lies in effectively promoting regeneration at the site and controlling the inflammatory response (55).

In recent years, there has been a growing interest in employing an endogenous regenerative approach that mobilizes resident MSCs to the sites of injury—a promising alternative strategy. Research has unveiled a bioactive multifunctional scaffold designed with the aptamer Apt19S as a mediator for the targeted recruitment of MSCs. This scaffold not only enhances cellular chondrogenesis but also exerts effective regulation over the inflammatory response through the incorporation of Mg²⁺ (56). Another noteworthy study has reported that the incorporation of magnesium hydroxide nanoparticles within a poly (lactic-co-glycolic acid) scaffold enhances chondrogenesis by inducing the chondrogenic differentiation of human BMSCs. Furthermore, it diminishes pyroptosis during the early stages of chondrogenic differentiation and curtails the release of inflammatory cytokines (57).

Stem cell-based transplantation holds immense promise as a therapeutic approach for IVDD (58). MSCs transplantation, in particular, has gained traction as a representative cell therapy for IVDD (59). However, the intra-discal injection of 'naked' MSCs faces challenges due to the harsh IVDD microenvironment, resulting in poor survival rates and altered activity (60,61). To address this, a novel strategy

involving the use of embryo-derived long-term expandable NP progenitor cells (NPPCs) and esterase-responsive ibuprofen nano-micelles (PEG-PIB) was devised for synergistic transplantation. The PEG-PIB micelles were endocytosed to pre-modify the NPPCs, rendering them adaptable to the harsh IVDD microenvironment by inhibiting pyroptosis of NPPCs through the COX2/NF- κ B/Caspase-1 signaling pathway. This synergistic transplantation approach demonstrated effective functional recovery, histological regeneration, and inhibition of pyroptosis during the process of IVDD regeneration (62).

Pyroptosis plays a pivotal role in degenerative diseases, with a specific emphasis on its impact on OA and IVDD (41,63). Stem cells exhibit dual functionality in mitigating degenerative diseases. Firstly, they impede pyroptosis at lesion sites through paracrine pathways, thereby decelerating the pathological progression. Secondly, the hostile microenvironment at lesion sites induces pyroptosis in transplanted stem cells. Several innovative designs are required to inhibit stem cell pyroptosis, enhancing the efficacy of lesion repair.

4. Stem cell-mediated modulation of pyroptosis for tissue repair in ischemia/reperfusion (I/R) injury

Myocardial I/R injury. Myocardial I/R injury is a complex pathological process that occurs when blood flow to the heart muscle (myocardium) is temporarily reduced or interrupted (ischemia), followed by the restoration of blood flow (reperfusion) (64). This intricate phenomenon is observed in various cardiac conditions, such as acute myocardial infarction (heart attack) and coronary artery bypass grafting (65).

During myocardial I/R, the activation of inflammasomes and the subsequent release of pro-inflammatory cytokines can trigger pyroptosis, a highly regulated form of cell death (66). This cascade of events contributes to the progression of tissue damage and inflammation, exacerbating the consequences of myocardial I/R injury. Understanding the mechanisms underlying pyroptosis in the context of myocardial I/R injury is of utmost importance for devising novel therapeutic interventions and mitigating the impact of cardiovascular diseases (67).

Recent evidence highlights the significant role of exosomes derived from MSCs in conferring protective effects against myocardial I/R injury by inhibiting myocardial pyroptosis (7). These exosomes act as carriers of endogenous molecules, including non-coding RNA, which play a crucial role in suppressing pyroptosis following I/R (68). Specifically, exosomal miR-320b targets NLRP3 (69), miR-100-5p targets FOXO3 (16), and miR-182-5p targets GSDMD (7), leading to downregulation of these target proteins and subsequent inhibition of pyroptosis. Additionally, the lncRNA KLF3-AS1, competes with miR-138-5p to regulate Sirt1 expression, contributing to the attenuation of pyroptosis (70). Another lncRNA, XIST, serves as a competing endogenous RNA of miR-214-3p, leading to upregulation of its target gene Arl2, which in turn attenuates myocardial pyroptosis (71). Moreover, MSC-derived exosomes exhibit their protective role in preventing ischemic injury through the release of circHIPK3, a circular non-coding RNA. CircHIPK3 downregulates miR-421, resulting in increased expression of FOXO3a, which effectively inhibits pyroptosis and the release of pro-inflammatory cytokines such as IL-1 β and IL-18 (72).

Neuronal I/R injury. Cerebral ischemic stroke stands as the most prevalent cause of death and disability among central nervous system (CNS) diseases (73). This ischemic insult is often accompanied by a robust inflammatory response. In the face of cerebral I/R injury, various forms of programmed cell death, including apoptosis and pyroptosis, emerge as prominent contributors to the ensuing tissue damage (74). Microglia, as the resident immune cells in the central nervous system, play a pivotal role in the initiation and progression of I/R injury (75). Notably, prior investigations have shown that inhibiting microglial pyroptosis in neonatal mice subjected to cerebral I/R promotes neuronal survival and ultimately ameliorates brain injury (76).

In the realm of neuroprotection, a distinct class of MSCs called olfactory mucosa MSCs demonstrate their capacity to confer neuroprotection by mitigating apoptosis and pyroptosis in microglial cells, employing an oxygen-glucose deprivation/reperfusion model that closely mimics I/R conditions (77). Moreover, emerging research highlights the significance of MSC-derived exosomes in inhibiting microglial pyroptosis. These exosomes facilitate FOXO3a-dependent mitophagy, a cellular process responsible for clearing damaged mitochondria, thereby mediating neuroprotection (78). Additionally, MSC-derived exosomes modulate microglial polarization, shifting them from an M1 phenotype (pro-inflammatory) to an M2 phenotype (anti-inflammatory), further contributing to the amelioration of cerebral I/R injury (79). Another noteworthy finding pertains to BMSCs-derived exosomal miR193b-5p, which plays a pivotal role in reducing microglia pyroptosis post-ischemic stroke. The miR targets the absent in melanoma 2 (AIM2) pathway, effectively suppressing AIM2-mediated pyroptosis (12).

A recent study suggested that retinal I/R injury may initiate pyroptosis in retinal neurons (80). Throughout retinal I/R injury, various cellular processes, including oxidative stress, mitochondrial dysfunction and activation of inflammasomes, contribute to the induction of pyroptosis in retinal neurons. Interventions targeting pyroptosis could prove to be an effective strategy in preventing I/R-induced retinal damage and subsequent visual impairment (81). The neuroprotective effects of intravitreal injection of MSCs and MSC-conditioned medium in rats during retinal ischemia are noteworthy (82,83). These effects are primarily mediated by EVs (84). While both MSCs and MSC-derived EVs have demonstrated neuroprotective effects following retinal I/R injury, direct evidence confirming this protective effect's association with the modulation of pyroptosis is currently lacking.

Cardiac and cerebral injuries after cardiopulmonary resuscitation (CPR). After CPR, cardiac and cerebral injuries often lead to unfavorable outcomes in cardiac arrest (CA) victims (85). The pathogenesis of these injuries may involve cell pyroptosis and ferroptosis. However, promisingly, MSCs have also emerged as a potential therapeutic strategy for providing cardiac and cerebral protection for I/R injury. MSCs have been identified to effectively reduce post-resuscitation cardiac and cerebral pyroptosis and ferroptosis, offering hope for improving the prognosis and overall outcome of CA patients (10). Although the mechanism by which MSCs reduce pyroptosis in post-resuscitation cardiac and brain cells

is unclear, there is evidence that MSCs downregulate the level of M1 macrophages and upregulate the level of M2 macrophages after CA (86). Given the link between pyroptosis and inflammation, the modulation of post-resuscitation cardiac and cerebral pyroptosis by MSCs may involve the regulation of the inflammatory microenvironment.

Lung I/R injury (LIRI). LIRI represents a pathological phenomenon triggered by various clinical conditions, including lung transplantation, hemorrhagic shock and pulmonary embolism (87). A key contributing factor to LIRI is the heightened release of IL-1 β and IL-6, leading to pyroptosis in lung epithelial cells (88). Remarkably, treatment with human BMSCs has shown significant efficacy in alleviating hypoxia-induced pulmonary epithelial injury, offering promise for LIRI intervention (89). Recent investigations have identified a crucial mechanism by which BMSC-derived exosomes exert their protective effects against LIRI. Specifically, the exosomal miR-202-5p plays a central role in repressing pulmonary epithelial pyroptosis, thereby inhibiting the progression of LIRI (90). The targeted molecule of miR-202-5p is CMPK2, a mitochondrial nucleotide monophosphate kinase known for its regulatory role in macrophage activation and inflammatory responses (91).

Hepatic I/R injury (HIRI). HIRI is a significant contributor to liver injury and failure following liver surgery. This condition is characterized by massive cell death, severe inflammation and oxidative stress (92). adMSCs and their exosomes have been demonstrated to reduce pyroptosis in the injured liver and promote the expression of factors associated with liver regeneration. Additionally, they can inhibit the NF- κ B pathway while activating the Wnt/ β -catenin pathway, both of which play crucial roles in inflammation and tissue repair (93).

These elucidate the crucial role of pyroptosis in I/R injuries, particularly focusing on cardiac and cerebral injuries, lung I/R injury, and hepatic I/R injury (85,87,92,94). In summary, stem cell-based therapies, particularly involving MSCs and their exosomes, showcase promising outcomes in alleviating I/R injuries.

5. Stem cell-mediated modulation of pyroptosis for tissue repair in drugs-induced injury

Doxorubicin (Dox)-induced cardiotoxicity. Dox is a potent antineoplastic agent widely used for cancer treatment. However, its use can lead to cardiotoxicity and muscle toxicity due to the escalation of oxidative stress and inflammation, ultimately culminating in pyroptosis. Encouragingly, the protective effects of exosomes derived from ESCs on Dox-induced myocardial pyroptosis have been previously demonstrated (95). At a mechanistic level, Dox treatment significantly upregulates the expression of inflammasome markers, such as TLR4 and NOD-like receptor protein 3 (NLRP3), as well as pyroptotic markers, including caspase-1, IL-1 β and IL-18 (96). Additionally, Dox treatment leads to an increase in cell signaling proteins, such as myeloid differentiation primary response 88 (MyD88), phosphorylated (p-)P38, and p-JUN N-terminal kinase, which play pivotal roles in inflammation and cell signaling (96,97). Moreover,

the treatment with Dox promotes the pro-inflammatory M1 macrophages and the secretion of TNF- α cytokine, further contributing to the pro-inflammatory environment and pyroptotic response (96,97).

However, the adverse effects induced by Dox, including pyroptosis, inflammation and cell signaling protein expression, are effectively counteracted by the application of ESCs-exosomes or ESCs themselves (97). These protective interventions demonstrate promising potential in mitigating Dox-induced cardiac and muscle damage by attenuating the pyroptotic response and dampening the inflammatory signaling (96,98).

Drugs-induced liver injury (DILI). DILI involves liver damage resulting from the use of certain medications. Some drugs may trigger the activation of inflammasomes, leading to the release of pro-inflammatory cytokines and initiating pyroptotic pathways in liver cells. This process can exacerbate liver damage and contribute to the progression of DILI.

Stem cell-based therapy has exhibited promise in treating liver diseases due to the regenerative and paracrine secretion properties of stem cells (99). Notably, MSCs have anti-inflammatory effects and have been investigated for their therapeutic potential in various liver diseases. For instance, the injection of interleukin-10 or transplantation of MSCs has been found to ameliorate liver injury induced by D-galactosamine, as evidenced by reduced levels of liver injury markers, inflammatory cytokines and NH3 (100). Moreover, when adMSCs are preincubated with green tea theanine, they demonstrate an enhanced therapeutic effect in rats with liver injury induced by N-nitrosodiethylamine, significantly suppressing pyroptosis markers, such as caspase-1 and IL-1 β (101).

Various drugs can activate inflammasomes, triggering the release of pro-inflammatory cytokines and initiating pyroptotic pathways in affected cells. This process exacerbates tissue damage and contributes to the progression of drug-induced injuries. These findings highlight the potential of stem cell-based interventions in mitigating drug-induced injuries by suppressing pyroptosis.

6. Stem cell-mediated modulation of pyroptosis for tissue repair in diabetes complications

Diabetes is a chronic metabolic disorder characterized by elevated blood sugar levels, which can result from inadequate insulin production or ineffective insulin utilization. This condition can lead to various complications, including cardiovascular diseases, kidney damage, nerve damage, and issues with the skin and eyes (102).

Diabetic skin wounds. In diabetes, skin wounds become a major medical concern. High blood sugar levels and impaired wound healing mechanisms can lead to chronic wounds that heal slowly and are prone to infections (103). Pyroptosis, a type of cell death triggered by inflammation, can exacerbate the inflammatory response at the wound site and hinder tissue repair, further delaying the healing process (104). Hair follicle MSCs (hfMSCs) have shown promise in promoting skin wound healing in diabetic mice.

Exosomes from hfMSCs containing long non-coding RNA (lncRNA) H19 have been found to enhance the proliferation and migration of HaCaT cells (a human keratinocyte cell line) and inhibit pyroptosis by reversing the stimulation of the NLRP3 inflammasome (105). Moreover, the use of BMSCs-conditioned medium (BMSC-CM) has revealed positive effects in diabetic foot ulcers. MSC-CM accelerates wound closure, promotes cell proliferation and angiogenesis (formation of new blood vessels), enhances cell autophagy (a process that supports cell survival and renewal), and reduces cell pyroptosis. By modulating these cellular processes, MSC-CM facilitates a more efficient wound healing process in diabetic foot ulcers (13).

In regenerative therapy, providing a conducive microenvironment is crucial to increasing the survival of transplanted stem cells. However, hyperglycemia can lead to stem cell death, hindering the effectiveness of stem cell therapy. A previous study reported that hyperglycemia-induced oxidative stress contributes to apoptosis and pyroptosis in human cardiac stem cells (106). Downregulation of NLRP3 in adipose-derived stem cells has been found to improve the effects of stem cell therapy under hyperglycemic conditions by suppressing pyroptosis (107).

Diabetic kidney disease (DKD). DKD is a serious complication of diabetes characterized by kidney damage and impaired function resulting from prolonged high blood sugar levels. It stands as a leading cause of chronic kidney disease and kidney failure worldwide (108). Promisingly, research has revealed that BMSCs-derived exosomal miR-30e-5p can effectively inhibit caspase-1-mediated pyroptosis in HK-2 cells induced by high glucose. The discovery of this regulatory mechanism opens up new possibilities for treating DKD (109). By attenuating pyroptosis, which is known to contribute to kidney damage and dysfunction, BMSCs-derived exosomal miR-30e-5p offers a promising new strategy for the management and treatment of diabetic kidney disease.

Diabetes poses various complications, including skin wounds with impaired healing mechanisms. Pyroptosis, an inflammation-triggered cell death, exacerbates inflammatory responses in diabetic skin wounds. In conclusion, stem cells, including hfMSCs and BMSCs, along with their secreted factors and exosomes, play pivotal roles in mitigating these complications by inhibiting pyroptosis.

7. Stem cell-mediated modulation of pyroptosis for tissue repair in inflammation-related diseases

Inflammatory bowel disease (IBD). IBD comprises chronic inflammatory disorders primarily affecting the gastrointestinal tract, including Crohn's disease and ulcerative colitis (110). Pyroptosis plays a significant role in contributing to the pathogenesis of IBD (111). In the context of IBD, immune cells in the gut, such as macrophages and epithelial cells, undergo pyroptosis, releasing pro-inflammatory molecules that lead to intestinal inflammation and tissue damage. This process exacerbates the symptoms of IBD, including abdominal pain, diarrhea and ulcers, emphasizing the importance of understanding and targeting pyroptosis as a potential therapeutic approach for managing IBD (112).

hucMSCs-derived exosomes have emerged as novel cell-free therapeutic agents for IBD. These exosomes have demonstrated the ability to inhibit the activation of macrophage NLRP3 inflammasomes, thereby suppressing the secretion of IL-18, IL-1 β and cleaved caspase-1, resulting in reduced cell pyroptosis. Furthermore, miR-378a-5p, highly expressed in hucMSCs-derived exosomes, plays a vital role in promoting colitis repair (113). Additionally, miR-203a-3p.2 in hucMSC-derived exosomes, acts as an effective mediator in the interaction with caspase-4 in THP-1 macrophage pyroptosis (114).

Lung injury. Acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), are characterized by widespread inflammation and injury to the lungs, often leading to respiratory failure. Pyroptosis is implicated in various factors-induced ALI/ARDS, such as lipopolysaccharide and sepsis (115). Emerging evidence suggests that pyroptosis is involved in the pathogenesis of ALI/ARDS, contributing to the amplification of the inflammatory response in the lungs (116). Influenza A virus infection triggers an exaggerated immune response in the host, leading to caspase-3-GSDME-mediated pyroptosis of lung alveolar epithelial cells. This process contributes to the onset of a cytokine storm, ultimately resulting in ALI or ARDS. Notably, BMSCs exhibit a therapeutic effect by mitigating ALI through the inhibition of caspase-3-GSDME-mediated pyroptosis in lung alveolar epithelial cells (117). Furthermore, MSCs-derived exosomes play a crucial role in inhibiting pyroptosis. This inhibition is achieved through miRNAs targeting the caspase-1-mediated pathway and proteins with immunoregulatory functions, thereby suppressing alveolar macrophage pyroptosis and alleviating ALI (118). Specifically, exosomes derived from BMSCs act as carriers for delivering miR-125b-5p, which downregulates STAT3. This, in turn, inhibits macrophage pyroptosis, demonstrating a potential therapeutic avenue for alleviating sepsis-associated ALI (119). Besides, cardiopulmonary bypass (CPB) has been widely used to support the heart and lung during cardiac surgery. It has been reported that BMSCs-derived exosomes ameliorate macrophage infiltration and oxidative stress, and downregulate expression of pyroptosis-related proteins in CPB-ALI model, as well as promote YAP interaction with β -catenin and regulate its transcription activity (120).

Silicosis is induced by prolonged inhalation of silica particles, resulting in lung cell injury and disruptions to the intracellular environment. It is characterized by collagen deposition and the development of pulmonary fibrosis (121). Pyroptosis and apoptosis play vital roles in the pathogenesis of silicosis (122). Recently, it has been revealed that BMSCs possess the ability to mitigate silica-induced pulmonary fibrosis by inhibiting both apoptosis and pyroptosis (123).

Kidney injury. Acute kidney injury (AKI) is characterized by a sudden and rapid deterioration in kidney function, leading to an impaired ability to filter waste and fluid from the blood (124). The involvement of pyroptosis has been recognized in regulating homeostasis in kidney tissues, thus playing a significant role in the development of AKI (125). It has been reported that EVs released by BMSCs might carry a specific

miR, miR-223-3p, to mitigate inflammation and pyroptosis induced by AKI through the modulation of the HDAC2/SNRK axis (126). Furthermore, another study has demonstrated the beneficial effects of BMSCs in sepsis-induced AKI. These stem cells promote mitophagy and inhibit apoptosis and pyroptosis of renal tubular epithelial cells within kidney tissues. This therapeutic action is attributed to the upregulation of SIRT1/Parkin, which plays a crucial role in protecting against AKI in the context of sepsis (127).

Traumatic injury. The CNS is particularly vulnerable to external mechanical damage. Traumatic brain injury (TBI) can result from direct impacts or blows to the head, often caused by factors such as motor vehicle accidents, crush injuries, or assaults (128). The pathophysiology of TBI involves both primary and secondary injury mechanisms. The primary injury occurs at the time of impact and involves mechanical damage to brain tissue. Secondary injury mechanisms follow the primary injury and involve processes such as inflammation, oxidative stress and excitotoxicity. In recent developments, exosomes derived from hucMSCs have shown significant potential in suppressing neuron cell apoptosis, pyroptosis and ferroptosis in cases of TBI. This therapeutic effect is mediated through the PINK1/Parkin pathway, facilitating mitophagy, a process that removes damaged mitochondria and aids in cellular recovery (129).

Spinal cord injury (SCI) involves damage to the spinal cord, leading to functional impairment. The trauma induces a cascade of events, activating pyroptosis-related molecules and triggering an inflammatory response. Excessive pyroptosis exacerbates secondary injury processes, contributing to tissue damage and neurological deficits. Inhibiting the pyroptosis-regulated cell death and inflammasome components is a promising therapeutic approach for the treatment of SCI (130). BMSCs have been previously reported to exhibit a promising therapeutic effect in treating SCI by mitigating inflammasome-related pyroptosis. The underlying mechanism involves BMSCs' exosome-derived circ_003564, a circular RNA, which has been identified to decrease the expression of inflammasome-related pyroptosis markers, including cleaved caspase-1, GSDMD, NLRP3, IL-1 β and IL-18 in neurons (14). This reduction in pyroptosis markers indicates a potential protective effect of BMSC-derived exosomal circ_003564 on neurons in the context of SCI.

Intracerebral hemorrhage (ICH). Another cerebrovascular disease with high morbidity and mortality is ICH, often resulting from the rupture of blood vessels (131). Hemoglobin and its breakdown products released from erythrocytes during hemorrhage can activate inflammasomes, initiating the pyroptotic pathway. Pyroptosis is strongly related to neuroinflammation, which plays a crucial role in the pathophysiological processes of secondary brain injury after ICH. Pyroptosis causes the releases of inflammatory cytokines and DAMPs can exacerbate neuronal injury and affect surrounding tissue. It has been reported that stem cell-derived exosomes have demonstrated a protective effect in ICH by inhibiting pyroptosis. Specifically, exosomal miR-23b from BMSCs exhibits antioxidant properties through the inhibition of PTEN, thereby alleviating NLRP3 inflammasome-mediated pyroptosis. This

process promotes neurologic function recovery in rats with ICH (132).

Extensive research demonstrates their effectiveness in treating diverse inflammation-related diseases by targeting signals associated with inflammation and pyroptosis (Table I). There is a basis for optimism that stem cells and the factors they release may exert favorable effects in various other inflammatory diseases.

8. Prospect

Stem cells are unique cells with the ability to differentiate into various cell types and self-renew, making them an attractive option for repairing damaged or diseased tissues (133). However, its clinical application also faces numerous challenges and risks (134). On the one hand, the potential for tumorigenesis, particularly teratoma formation, is a significant concern associated with the clinical use of ESCs (135). Teratomas are tumors that contain a mixture of differentiated tissues from all three germ layers (ectoderm, mesoderm and endoderm). They can be benign, but they represent a significant risk associated with the transplantation of undifferentiated pluripotent cells, including ESCs (136). While ESC therapy has immense potential, the risk of teratoma formation underscores the importance of rigorous safety and quality control measures in the development and application of these therapies. Researchers and clinicians are actively working to address these challenges to make ESC-based treatments safer and more effective (137). On the other hand, autologous transplantation offers the advantage of using a patient's own cells, thereby eliminating the risk of immune rejection, but allogeneic stem cell treatments involve donor cells and carry a distinct set of potential risks and complications (138). These must be carefully considered due to the inherent differences between the donor and recipient, which include factors such as genetic disparities, tissue compatibility and immunological variations. Overall, ensuring the safety and efficacy of stem cell treatments, as well as addressing issues related to immune rejection and ethical considerations, remain important areas of research (139).

Exosomes derived from stem cells in therapy is their potential to overcome the limitations associated with stem cell transplantation, such as potential immune rejection and ethical concerns. Exosomes can be delivered directly to the target site, and they have a lower risk of immune response compared with whole cells. While exosomes hold great promise, further research is needed to optimize their isolation, characterization and therapeutic application (8). Additionally, understanding the precise mechanisms of exosome-mediated effects will help enhance their efficacy in stem cell-based therapy and pave the way for more effective regenerative treatments.

The protective mechanisms employed by stem cells are remarkably complex, and current understanding only provides a glimpse of their full potential. In addition to inhibiting apoptosis, stem cells have been found to suppress pyroptosis and regulate autophagy (140,141). While they hold great promise in therapeutic applications, stem cell therapy is still in its nascent stages and requires extensive research and clinical practice before it can be fully realized in clinical settings. Creating an environment that maximizes stem cell

Table I. Stem cells inhibit pyroptosis in inflammation-related diseases.

Disease types	Classification of stem cells	Targeted cells	Pyroptotic signaling molecules	Effectors	(Refs.)
Osteoarthritis	adMSCs	Chondrocyte	TNF- α	sTNFR1	(32)
	BMSCs	Chondrocyte	HDAC3	miR-326 (exosomes)	(15)
	hucMSCs	Chondrocyte	NLRP3	miR-223 (exosomes)	(33)
Intervertebral disc degeneration	MSCs	Nucleus pulposus	METTL14	miR-26a-5p (exosomes)	(47)
	hucMSCs	Nucleus pulposus	NLRP3	miR-410 (exosomes)	(9)
	ESCs	Nucleus pulposus	NLRP3	miR-302c (exosomes)	(48)
Myocardial ischemia/reperfusion injury	MSCs	Myocardial cell	NLRP3	miR-320b (exosomes)	(69)
		Myocardial cell	GSDMD	miR-182-5p (exosomes)	(7)
	hucMSCs	Myocardial cell	FOXO3	miR-100-5p (exosomes)	(16)
		Myocardial cell	FOXO3a	Circular non-coding RNA, circchipk3 (exosomes)	(72)
	hMSCs	Myocardial cell	Sirt1	Long non-coding RNA, KLF3-AS1 (exosomes)	(70)
	adMSCs	Myocardial cell	Arl2	Long non-coding RNA, XIST (exosomes)	(71)
Cerebral ischemic stroke	omMSCs	Microglial cells		Exosomes	(77,78)
Lung ischemia-reperfusion injury	BMSCs	PC12 cells	AIM2	miR193b-5p (exosomes)	(12)
	BMSCs	Pulmonary epithelial cells	CMPK2	miR-202-5p (exosomes)	(90)
Hepatic ischemia-reperfusion injury	adMSCs	Hepatocyte	NF- κ B pathway and Wnt/ β -catenin pathway ^a	Exosomes	(93)
Doxorubicin-induced cardiotoxicity	ESCs	Myocardial cell		Exosomes	(97)
Drugs-induced liver injury	ADSCs	Hepatocyte	Caspase-1 and IL-1 β ^a		(101)
Diabetic skin wounds	hfMSCs	HaCaT cells	NLRP3	Long non-coding RNA, H19 (exosomes)	(105)
	BMSCs			Bone marrow-derived mesenchymal stem cell-conditioned medium	(13)
Diabetic kidney disease	BMSCs	Renal proximal tubular cells	ELAVL1	miR-30e-5p (exosomes)	(109)
Inflammatory bowel disease	hucMSCs	THP-1 cells and mouse peritoneal macrophages	NLRP3	miR-378a-5p (exosomes)	(113)
		Macrophage	Caspase-4	miR-203a-3p.2 (exosomes)	(114)
Acute lung injury	BMSCs	Lung cells	YAP/ β -catenin axis ^a	Exosomes	(120)
Silicosis	BMSCs	Lung cells			(123)
Acute kidney injury	BMSCs	HK-2 cells	HDAC2/SNRK	miR-223-3p (extracellular vesicles)	(126)
		Renal tubular epithelial cells	SIRT1/Parkin ^a		(127)
Traumatic brain injury	hucMSCs	Neuron	PINK1/Parkin	Exosomes	(129)
Spinal cord injury	BMSCs	Neuron	pathway ^a caspase-1, GSDMD, NLRP3, IL-1 β and IL-18 ^a	Circular non-coding RNA, circ_003564 (exosomes)	(14)
Intracerebral hemorrhage	BMSCs	Microglial cells	PTEN	miR-23b (exosomes)	(132)

^a represents an indirect effect. MSCs, mesenchymal stem cells; BMSCs, bone marrow MSCs; adMSCs, adipose-derived MSCs; hucMSCs, human umbilical cord MSCs; hfMSCs, hair follicle MSCs; NLRP3, NOD-like receptor family, pyrin domain-containing 3; GSDMD, gasdermin D; miR, microRNA.

protection and harnessing their potential for therapeutic benefits necessitate a rigorous and comprehensive approach to furthering understanding and advancing stem cell-based treatments.

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Availability of data and materials

Not applicable.

Authors' contributions

YiWe and LL conceptualized the study, wrote the original draft, conducted formal analysis, and wrote, reviewed and edited the manuscript. YiWa, YC, ZL and CH reviewed and edited the manuscript. YaW developed methodology. CJ contributed to study conceptualization, writing the original draft, and writing, reviewing and editing the manuscript. ZW and JL supervised the study. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, Ferrucci L, Gilroy DW, Fasano A, Miller GW, *et al*: Chronic inflammation in the etiology of disease across the life span. *Nat Med* 25: 1822-1832, 2019.
- Li T, Zheng G, Li B and Tang L: Pyroptosis: A promising therapeutic target for noninfectious diseases. *Cell Proliferat* 54: e13137, 2021.
- Yu P, Zhang X, Liu N, Tang L, Peng C and Chen X: Pyroptosis: Mechanisms and diseases. *Signal Transduct Tar* 6: 128, 2021.
- Kovacs SB and Miao EA: Gasdermins: Effectors of pyroptosis. *Trends Cell Biol* 27: 673-684, 2017.
- Dekoninck S and Blanpain C: Stem cell dynamics, migration and plasticity during wound healing. *Nat Cell Biol* 21: 18-24, 2019.
- Mapp PI and Walsh DA: Mechanisms and targets of angiogenesis and nerve growth in osteoarthritis. *Nat Rev Rheumatol* 8: 390-398, 2012.
- Yue R, Lu S, Luo Y, Zeng J, Liang H, Qin D, Wang X, Wang T, Pu J and Hu H: Mesenchymal stem cell-derived exosomal microRNA-182-5p alleviates myocardial ischemia/reperfusion injury by targeting GSDMD in mice. *Cell Death Discov* 8: 202, 2022.
- Hade MD, Suire CN and Suo Z: Mesenchymal stem cell-derived exosomes: Applications in regenerative medicine. *Cells-Basel* 10: 1959, 2021.
- Zhang J, Zhang J, Zhang Y, Liu W, Ni W, Huang X, Yuan J, Zhao B, Xiao H and Xue F: Mesenchymal stem cells-derived exosomes ameliorate intervertebral disc degeneration through inhibiting pyroptosis. *J Cell Mol Med* 24: 11742-11754, 2020.
- Xu J, Zhang M, Liu F, Shi L, Jiang X, Chen C, Wang J, Diao M, Khan ZU and Zhang M: Mesenchymal stem cells alleviate post-resuscitation cardiac and cerebral injuries by inhibiting cell pyroptosis and ferroptosis in a swine model of cardiac arrest. *Front Pharmacol* 12: 793829, 2021.
- Li K, Yan G, Huang H, Zheng M, Ma K, Cui X, Lu D, Zheng L, Zhu B, Cheng J and Zhao J: Anti-inflammatory and immunomodulatory effects of the extracellular vesicles derived from human umbilical cord mesenchymal stem cells on osteoarthritis via M2 macrophages. *J Nanobiotechnol* 20: 38, 2022.
- Wang Y, Chen H, Fan X, Xu C, Li M, Sun H, Song J, Jia F, Wei W, Jiang F, *et al*: Bone marrow mesenchymal stem cell-derived exosomal miR-193b-5p reduces pyroptosis after ischemic stroke by targeting AIM2. *J Stroke Cerebrovasc* 32: 107235, 2023.
- Xu YF, Wu YX, Wang HM, Gao CH, Xu YY and Yan Y: Bone marrow-derived mesenchymal stem cell-conditioned medium ameliorates diabetic foot ulcers in rats. *Clinics (Sao Paulo)* 78: 100181, 2023.
- Zhao Y, Chen Y, Wang Z, Xu C, Qiao S, Liu T, Qi K, Tong D and Li C: Bone marrow mesenchymal stem cell exosome attenuates Inflammasome-Related pyroptosis via delivering circ_003564 to improve the recovery of spinal cord injury. *Mol Neurobiol* 59: 6771-6789, 2022.
- Xu H and Xu B: BMSC-Derived exosomes ameliorate osteoarthritis by inhibiting pyroptosis of cartilage via delivering miR-326 targeting HDAC3 and STAT1/NF-kappaB p65 to chondrocytes. *Mediat Inflamm* 2021: 9972805, 2021.
- Liang C, Liu Y, Xu H, Huang J, Shen Y, Chen F and Luo M: Exosomes of human umbilical cord MSCs protect against Hypoxia/Reoxygenation-Induced pyroptosis of cardiomyocytes via the miRNA-100-5p/FOXO3/NLRP3 pathway. *Front Bioeng Biotech* 8: 615850, 2020.
- Broz P, Ruby T, Belhocine K, Bouley DM, Kayagaki N, Dixit VM and Monack DM: Caspase-11 increases susceptibility to Salmonella infection in the absence of caspase-1. *Nature* 490: 288-291, 2012.
- Strowig T, Henao-Mejia J, Elinav E and Flavell R: Inflammasomes in health and disease. *Nature* 481: 278-286, 2012.
- He Y, Hara H and Nunez G: Mechanism and regulation of NLRP3 inflammasome activation. *Trends Biochem Sci* 41: 1012-1021, 2016.
- Cookson BT and Brennan MA: Pro-inflammatory programmed cell death. *Trends Microbiol* 9: 113-114, 2001.
- Chen X, He WT, Hu L, Li J, Fang Y, Wang X, Xu X, Wang Z, Huang K and Han J: Pyroptosis is driven by non-selective gasdermin-D pore and its morphology is different from MLKL channel-mediated necroptosis. *Cell Res* 26: 1007-1020, 2016.
- Kayagaki N, Stowe IB, Lee BL, O'Rourke K, Anderson K, Warming S, Cuellar T, Haley B, Roose-Girma M, Phung QT, *et al*: Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. *Nature* 526: 666-671, 2015.
- Boise LH and Collins CM: Salmonella-induced cell death: Apoptosis, necrosis or programmed cell death? *Trends Microbiol* 9: 64-67, 2001.
- Li J and Yuan J: Caspases in apoptosis and beyond. *Oncogene* 27: 6194-6206, 2008.
- Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H, Zhuang Y, Cai T, Wang F and Shao F: Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. *Nature* 526: 660-665, 2015.
- Matikainen S, Nyman TA and Cypryk W: Function and regulation of noncanonical Caspase-4/5/11 inflammasome. *J Immunol* 204: 3063-3069, 2020.
- O'Neill TW and Felson DT: Mechanisms of osteoarthritis (OA) pain. *Curr Osteoporos Rep* 16: 611-616, 2018.

28. Yu H, Yao S, Zhou C, Fu F, Luo H, Du W, Jin H, Tong P, Chen D, Wu C and Ruan H: Morroniside attenuates apoptosis and pyroptosis of chondrocytes and ameliorates osteoarthritic development by inhibiting NF-kappaB signaling. *J Ethnopharmacol* 266: 113447, 2021.
29. Wu X, Ren G, Zhou R, Ge J and Chen FH: The role of Ca²⁺ in acid-sensing ion channel 1a-mediated chondrocyte pyroptosis in rat adjuvant arthritis. *Lab Invest* 99: 499-513, 2019.
30. Zhao LR, Xing RL, Wang PM, Zhang NS, Yin SJ, Li XC and Zhang L: NLRP1 and NLRP3 inflammasomes mediate LPS/ATP-induced pyroptosis in knee osteoarthritis. *Mol Med Rep* 17: 5463-5469, 2018.
31. Zhang L, Zhang L, Huang Z, Xing R, Li X, Yin S, Mao J, Zhang N, Mei W, Ding L and Wang P: Increased HIF- α in knee osteoarthritis aggravate synovial fibrosis via Fibroblast-Like synoviocyte pyroptosis. *Oxid Med Cell Longev* 2019: 6326517, 2019.
32. Xu L, Zhang F, Cheng G, Yuan X, Wu Y, Wu H, Wang Q, Chen J, Kuai J, Chang Y, *et al*: Attenuation of experimental osteoarthritis with human adipose-derived mesenchymal stem cell therapy: Inhibition of the pyroptosis in chondrocytes. *Inflamm Res* 72: 89-105, 2023.
33. Liu W, Liu A, Li X, Sun Z, Sun Z, Liu Y, Wang G, Huang D, Xiong H, Yu S, *et al*: Dual-engineered cartilage-targeting extracellular vesicles derived from mesenchymal stem cells enhance osteoarthritis treatment via miR-223/NLRP3/pyroptosis axis: Toward a precision therapy. *Bioact Mater* 30: 169-183, 2023.
34. Sergio MR, Godinho C, Guerra L, Agapito A, Fonseca F and Costa C: TSH anti-receptor antibodies in Graves' disease. *Acta Medica Port* 9: 229-231 (In Portuguese).
35. Buckley CT, Hoyland JA, Fujii K, Pandit A, Iatridis JC and Grad S: Critical aspects and challenges for intervertebral disc repair and regeneration-Harnessing advances in tissue engineering. *Jor Spine* 1: e1029, 2018.
36. Zhao CQ, Wang LM, Jiang LS and Dai LY: The cell biology of intervertebral disc aging and degeneration. *Ageing Res Rev* 6: 247-261, 2007.
37. Basso M, Cavagnaro L, Zanirato A, Divano S, Formica C, Formica M and Felli L: What is the clinical evidence on regenerative medicine in intervertebral disc degeneration? *Musculoskelet Surg* 101: 93-104, 2017.
38. Binch A, Fitzgerald JC, Growney EA and Barry F: Cell-based strategies for IVD repair: Clinical progress and translational obstacles. *Nat Rev Rheumatol* 17: 158-175, 2021.
39. Francisco V, Pino J, Gonzalez-Gay MA, Lago F, Karppinen J, Tervonen O, Mobasher A and Gualillo O: A new immunometabolic perspective of intervertebral disc degeneration. *Nat Rev Rheumatol* 18: 47-60, 2022.
40. Ge Y, Chen Y, Guo C, Luo H, Fu F, Ji W, Wu C and Ruan H: Pyroptosis and intervertebral disc degeneration: Mechanistic insights and therapeutic implications. *J Inflamm Res* 15: 5857-5871, 2022.
41. Luo J, Yang Y, Wang X, Chang X and Fu S: Role of pyroptosis in intervertebral disc degeneration and its therapeutic implications. *Biomolecules* 12: 1804, 2022.
42. Zhang X, Cai Z, Wu M, Huangfu X, Li J and Liu X: Adipose stem Cell-Derived exosomes recover impaired matrix metabolism of torn human rotator cuff tendons by maintaining tissue homeostasis. *Am J Sport Med* 49: 899-908, 2021.
43. Shi Y, Wang Y, Li Q, Liu K, Hou J, Shao C and Wang Y: Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases. *Nat Rev Nephrol* 14: 493-507, 2018.
44. Xing H, Zhang Z, Mao Q, Wang C, Zhou Y, Zhou X, Ying L, Xu H, Hu S and Zhang N: Injectable exosome-functionalized extracellular matrix hydrogel for metabolism balance and pyroptosis regulation in intervertebral disc degeneration. *J Nanobiotechnol* 19: 264, 2021.
45. Zhu B, Chen HX, Li S, Tan JH, Xie Y, Zou MX, Wang C, Xue JB, Li XL, Cao Y and Yan YG: Comprehensive analysis of N6-methyladenosine (m6A) modification during the degeneration of lumbar intervertebral disc in mice. *J Orthop Transl* 31: 126-138, 2021.
46. Shen C, Xuan B, Yan T, Ma Y, Xu P, Tian X, Zhang X, Cao Y, Ma D, Zhu X, *et al*: m⁶A-dependent glycolysis enhances colorectal cancer progression. *Mol Cancer* 19: 72, 2020.
47. Yuan X, Li T, Shi L, Miao J, Guo Y and Chen Y: Human umbilical cord mesenchymal stem cells deliver exogenous miR-26a-5p via exosomes to inhibit nucleus pulposus cell pyroptosis through METTL14/NLRP3. *Mol Med* 27: 91, 2021.
48. Yu Y, Li W, Xian T, Tu M, Wu H and Zhang J: Human embryonic stem-cell-derived exosomes repress NLRP3 inflammasome to alleviate pyroptosis in nucleus pulposus cells by transmitting miR-302c. *Int J Mol Sci* 24: 7664, 2023.
49. Hunziker EB: Articular cartilage repair: Basic science and clinical progress. A review of the current status and prospects. *Osteoarthr Cartilage* 10: 432-463, 2002.
50. Lin F, Zhang W, Xue D, Zhu T, Li J, Chen E, Yao X and Pan Z: Signaling pathways involved in the effects of HMGB1 on mesenchymal stem cell migration and osteoblastic differentiation. *Int J Mol Med* 37: 789-797, 2016.
51. Bertheloot D and Latz E: HMGB1, IL-1 α , IL-33 and S100 proteins: Dual-function alarmins. *Cell Mol Immunol* 14: 43-64, 2017.
52. Koh TJ and DiPietro LA: Inflammation and wound healing: The role of the macrophage. *Expert Rev Mol Med* 13: e23, 2011.
53. Han SA, Lee S, Seong SC and Lee MC: Effects of CD14 macrophages and proinflammatory cytokines on chondrogenesis in osteoarthritic synovium-derived stem cells. *Tissue Eng Pt A* 20: 2680-2691, 2014.
54. Wehling N, Palmer GD, Pilapil C, Liu F, Wells JW, Muller PE, Evans CH and Porter RM: Interleukin-1 β and tumor necrosis factor α inhibit chondrogenesis by human mesenchymal stem cells through NF-kappaB-dependent pathways. *Arthritis Rheum* 60: 801-812, 2009.
55. Yang Z, Li H, Yuan Z, Fu L, Jiang S, Gao C, Wang F, Zha K, Tian G, Sun Z, *et al*: Endogenous cell recruitment strategy for articular cartilage regeneration. *Acta Biomater* 114: 31-52, 2020.
56. Liao Z, Fu L, Li P, Wu J, Yuan X, Ning C, Ding Z, Sui X, Liu S and Guo Q: Incorporation of magnesium ions into an Aptamer-Functionalized ECM bioactive scaffold for articular cartilage regeneration. *Acs Appl Mater Inter* 15: 22944-22958, 2023.
57. Park KS, Kim BJ, Lih E, Park W, Lee SH, Joung YK and Han DK: Versatile effects of magnesium hydroxide nanoparticles in PLGA scaffold-mediated chondrogenesis. *Acta Biomater* 73: 204-216, 2018.
58. Barakat AH, Elwell VA and Lam KS: Stem cell therapy in discogenic back pain. *J Spine Surg* 5: 561-583, 2019.
59. Sakai D and Andersson GB: Stem cell therapy for intervertebral disc regeneration: Obstacles and solutions. *Nat Rev Rheumatol* 11: 243-256, 2015.
60. Yu C, Li D, Wang C, Xia K, Wang J, Zhou X, Ying L, Shu J, Huang X, Xu H, *et al*: Injectable kartogenin and apocynin loaded micelle enhances the alleviation of intervertebral disc degeneration by adipose-derived stem cell. *Bioact Mater* 6: 3568-3579, 2021.
61. Zhou X, Wang J, Fang W, Tao Y, Zhao T, Xia K, Liang C, Hua J, Li F and Chen Q: Genipin cross-linked type II collagen/chondroitin sulfate composite hydrogel-like cell delivery system induces differentiation of adipose-derived stem cells and regenerates degenerated nucleus pulposus. *Acta Biomater* 71: 496-509, 2018.
62. Xia KS, Li DD, Wang CG, Ying LW, Wang JK, Yang B, Shu JW, Huang XP, Zhang YA, Yu C, *et al*: An esterase-responsive ibuprofen nano-micelle pre-modified embryo derived nucleus pulposus progenitor cells promote the regeneration of intervertebral disc degeneration. *Bioact Mater* 21: 69-85, 2023.
63. Yang J, Hu S, Bian Y, Yao J, Wang D, Liu X, Guo Z, Zhang S and Peng L: Targeting cell death: Pyroptosis, ferroptosis, apoptosis and necroptosis in osteoarthritis. *Front Cell Dev Biol* 9: 789948, 2021.
64. Tibaut M, Mekis D and Petrovic D: Pathophysiology of myocardial infarction and acute management strategies. *Cardiovasc Hematol Agents Med Chem* 14: 150-159, 2017.
65. Zhou M, Yu Y, Luo X, Wang J, Lan X, Liu P, Feng Y and Jian W: Myocardial Ischemia-reperfusion injury: Therapeutics from a mitochondria-centric perspective. *Cardiology* 146: 781-792, 2021.
66. Toldo S, Mauro AG, Cutter Z and Abbate A: Inflammasome, pyroptosis, and cytokines in myocardial ischemia-reperfusion injury. *Am J Physiol-Heart C* 315: H1553-H1568, 2018.
67. Qiu Z, Lei S, Zhao B, Wu Y, Su W, Liu M, Meng Q, Zhou B, Leng Y and Xia ZY: NLRP3 inflammasome activation-mediated pyroptosis aggravates myocardial ischemia/reperfusion injury in diabetic rats. *Oxid Med Cell Longev* 2017: 9743280, 2017.
68. Kalluri R and LeBleu VS: The biology, function, and biomedical applications of exosomes. *Science* 367: eaau6977, 2020.

69. Tang J, Jin L, Liu Y, Li L, Ma Y, Lu L, Ma J, Ding P, Yang X, Liu J and Yang J: Exosomes derived from mesenchymal stem cells protect the myocardium against ischemia/reperfusion injury through inhibiting pyroptosis. *Drug Des Devel Ther* 14: 3765-3775, 2020.
70. Mao Q, Liang XL, Zhang CL, Pang YH and Lu YX: LncRNA KLF3-AS1 in human mesenchymal stem cell-derived exosomes ameliorates pyroptosis of cardiomyocytes and myocardial infarction through miR-138-5p/Sirt1 axis. *Stem Cell Res Ther* 10: 393, 2019.
71. Yan B, Liu T, Yao C, Liu X, Du Q and Pan L: LncRNA XIST shuttled by adipose tissue-derived mesenchymal stem cell-derived extracellular vesicles suppresses myocardial pyroptosis in atrial fibrillation by disrupting miR-214-3p-mediated Arl2 inhibition. *Lab Invest* 101: 1427-1438, 2021.
72. Yan B, Zhang Y, Liang C, Liu B, Ding F, Wang Y, Zhu B, Zhao R, Yu XY and Li Y: Stem cell-derived exosomes prevent pyroptosis and repair ischemic muscle injury through a novel exosome/circHIPK3/ FOXO3a pathway. *Theranostics* 10: 6728-6742, 2020.
73. Feigin VL, Norrving B, George MG, Foltz JL, Roth GA and Mensah GA: Prevention of stroke: A strategic global imperative. *Nat Rev Neurol* 12: 501-512, 2016.
74. Jayaraj RL, Azimullah S, Beiram R, Jalal FY and Rosenberg GA: Neuroinflammation: Friend and foe for ischemic stroke. *J Neuroinflamm* 16: 142, 2019.
75. Madore C, Yin Z, Leibowitz J and Butovsky O: Microglia, lifestyle stress, and neurodegeneration. *Immunity* 52: 222-240, 2020.
76. Li W, Shen N, Kong L, Huang H, Wang X, Zhang Y, Wang G, Xu P and Hu W: STING mediates microglial pyroptosis via interaction with NLRP3 in cerebral ischaemic stroke. *Stroke Vasc Neurol*: svn-2023-002320, 2023 doi: 10.1136/svn-2023-002320.
77. Huang Y, Tan F, Zhang Y, Liu J, He J, Duan D, Lu M and Hu Z: Hypoxia-preconditioned olfactory mucosa mesenchymal stem cells abolish cerebral ischemia/reperfusion-induced pyroptosis and apoptotic death of microglial cells by activating HIF-1 α . *Aging (Albany NY)* 12: 10931-10950, 2020.
78. Hu Z, Yuan Y, Zhang X, Lu Y, Dong N, Jiang X, Xu J and Zheng D: Human umbilical cord mesenchymal stem Cell-Derived exosomes attenuate Oxygen-Glucose Deprivation/Reperfusion-Induced microglial pyroptosis by promoting FOXO3a-dependent mitophagy. *Oxid Med Cell Longev* 2021: 6219715, 2021.
79. Liu X, Zhang M, Liu H, Zhu R, He H, Zhou Y, Zhang Y, Li C, Liang D, Zeng Q and Huang G: Bone marrow mesenchymal stem cell-derived exosomes attenuate cerebral ischemia-reperfusion injury-induced neuroinflammation and pyroptosis by modulating microglia M1/M2 phenotypes. *Exp Neurol* 341: 113700, 2021.
80. Huang Y, Wang S, Huang F, Zhang Q, Qin B, Liao L, Wang M, Wan H, Yan W, Chen D, *et al*: c-FLIP regulates pyroptosis in retinal neurons following oxygen-glucose deprivation/recovery via a GSDMD-mediated pathway. *Ann Anat* 235: 151672, 2021.
81. Zhou Z, Shang L, Zhang Q, Hu X, Huang JF and Xiong K: DTX3L induced NLRP3 ubiquitination inhibit R28 cell pyroptosis in OGD/R injury. *Bba-Mol Cell Res* 1870: 119433, 2023.
82. Dreixler JC, Poston JN, Balyasnikova I, Shaikh AR, Tupper KY, Conway S, Boddapati V, Marcet MM, Lesniak MS and Roth S: Delayed administration of bone marrow mesenchymal stem cell conditioned medium significantly improves outcome after retinal ischemia in rats. *Invest Ophthalmol Vis Sci* 55: 3785-3796, 2014.
83. Mathew B, Poston JN, Dreixler JC, Torres L, Lopez J, Zelkha R, Balyasnikova I, Lesniak MS and Roth S: Bone-marrow mesenchymal stem-cell administration significantly improves outcome after retinal ischemia in rats. *Graef Arch Clin Exp* 255: 1581-1592, 2017.
84. Mathew B, Ravindran S, Liu X, Torres L, Chennakesavalu M, Huang CC, Feng L, Zelka R, Lopez J, Sharma M and Roth S: Mesenchymal stem cell-derived extracellular vesicles and retinal ischemia-reperfusion. *Biomaterials* 197: 146-1460, 2019.
85. Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Bottiger BW, Callaway C, Clark RS, Geocadin RG, Jauch EC, *et al*: Post-cardiac arrest syndrome: Epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation* 118: 2452-2483, 2008.
86. Yu Y, Wang D, Li H, Fan J, Liu Y, Zhao X, Wu J and Jing X: Mesenchymal stem cells derived from induced pluripotent stem cells play a key role in immunomodulation during cardiopulmonary resuscitation. *Brain Res* 1720: 146293, 2019.
87. Weyker PD, Webb CA, Kiamanesh D and Flynn BC: Lung ischemia reperfusion injury: A bench-to-bedside review. *Semin Cardiothorac Vasc Anesth* 17: 28-43, 2013.
88. Fei L, Jingyuan X, Fangte L, Huijun D, Liu Y, Ren J, Jinyuan L and Linghui P: Preconditioning with rHMGB1 ameliorates lung ischemia-reperfusion injury by inhibiting alveolar macrophage pyroptosis via the Keap1/Nrf2/HO-1 signaling pathway. *J Transl Med* 18: 301, 2020.
89. Shologu N, Scully M, Laffey JG and O'Toole D: Human mesenchymal stem cell secretome from bone marrow or Adipose-Derived tissue sources for treatment of hypoxia-induced pulmonary epithelial injury. *Int J Mol Sci* 19: 2996, 2018.
90. Sun ZL, You T, Zhang BH, Liu Y and Liu J: Bone marrow mesenchymal stem cell-derived exosomes miR-202-5p inhibited pyroptosis to alleviate lung ischemic-reperfusion injury by targeting CMPK2. *Kaohsiung J Med Sci* 39: 688-698, 2023.
91. Luo Y, Zheng D, Mou T, Pu J, Huang Z, Chen W, Zhang Y and Wu Z: CMPK2 accelerates liver ischemia/reperfusion injury via the NLRP3 signaling pathway. *Exp Ther Med* 22: 1358, 2021.
92. Hirao H, Nakamura K and Kupiec-Weglinski JW: Liver ischaemia-reperfusion injury: A new understanding of the role of innate immunity. *Nat Rev Gastro Hepat* 19: 239-256, 2022.
93. Piao C, Sang J, Kou Z, Wang Y, Liu T, Lu X, Jiao Z and Wang H: Effects of exosomes derived from adipose-derived mesenchymal stem cells on pyroptosis and regeneration of injured liver. *Int J Mol Sci* 23: 12065, 2022.
94. Shi H, Gao Y, Dong Z, Yang J, Gao R, Li X, Zhang S, Ma L, Sun X, Wang Z, *et al*: GSDMD-Mediated cardiomyocyte pyroptosis promotes Myocardial I/R injury. *Circ Res* 129: 383-396, 2021.
95. Tavakoli DZ, Singla R, Johnson T, Kukreja R and Singla DK: Exosomes derived from embryonic stem cells inhibit doxorubicin and inflammation-induced pyroptosis in muscle cells. *Can J Physiol Pharm* 96: 304-307, 2018.
96. Tavakoli DZ and Singla DK: Embryonic stem cell-derived exosomes inhibit doxorubicin-induced TLR4-NLRP3-mediated cell death-pyroptosis. *Am J Physiol Heart Circ Physiol* 317: H460-H471, 2019.
97. Singla DK, Johnson TA and Tavakoli DZ: Exosome treatment enhances anti-inflammatory M2 macrophages and reduces inflammation-induced pyroptosis in doxorubicin-induced cardiomyopathy. *Cells-Basel* 8: 1224, 2019.
98. Dessouki F, Kukreja RC and Singla DK: Stem Cell-Derived Exosomes ameliorate Doxorubicin-Induced muscle toxicity through counteracting pyroptosis. *Pharmaceuticals (Basel)* 13: 450, 2020.
99. Wang J, Sun M, Liu W, Li Y and Li M: Stem cell-based therapies for liver diseases: An overview and update. *Tissue Eng Regen Med* 16: 107-118, 2019.
100. Wang J, Ren H, Yuan X, Ma H, Shi X and Ding Y: Interleukin-10 secreted by mesenchymal stem cells attenuates acute liver failure through inhibiting pyroptosis. *Hepatol Res* 48: E194-E202, 2018.
101. Chen TS, Lai YA, Lai YJ and Chien CT: Adipose stem cells preincubated with theanine exert liver regeneration through increase of stem cell paracrine VEGF and suppression of ROS, pyroptosis as well as autophagy markers in liver damage induced by N-nitrosodiethylamine. *Life Sci* 308: 120969, 2022.
102. Forbes JM and Cooper ME: Mechanisms of diabetic complications. *Physiol Rev* 93: 137-188, 2013.
103. Kunkemoeller B, Bancroft T, Xing H, Morris AH, Luciano AK, Wu J, Fernandez-Hernando C and Kyriakides TR: Elevated thrombospondin 2 contributes to delayed wound healing in diabetes. *Diabetes* 68: 2016-223, 2019.
104. Mu X, Wu X, He W, Liu Y, Wu F and Nie X: Pyroptosis and inflammasomes in diabetic wound healing. *Front Endocrinol* 13: 950798, 2022.
105. Yang H, Zhang Y, Du Z, Wu T and Yang C: Hair follicle mesenchymal stem cell exosomal lncRNA H19 inhibited NLRP3 pyroptosis to promote diabetic mouse skin wound healing. *Aging (Albany NY)* 15: 791-809, 2023.
106. Yadav SK, Kambis TN, Kar S, Park SY and Mishra PK: MMP9 mediates acute hyperglycemia-induced human cardiac stem cell death by upregulating apoptosis and pyroptosis in vitro. *Cell Death Dis* 11: 186, 2020.

107. Luo C, Peng Y, Zhou X, Fan J, Chen W, Zhang H and Wei A: NLRP3 downregulation enhances engraftment and functionality of adipose-derived stem cells to alleviate erectile dysfunction in diabetic rats. *Front Endocrinol* 13: 913296, 2022.
108. Alicic RZ, Rooney MT and Tuttle KR: Diabetic kidney disease: Challenges, progress, and possibilities. *Clin J Am Soc Nephro* 12: 2032-2045, 2017.
109. Lv J, Hao YN, Wang XP, Lu WH, Xie LY and Niu D: Bone marrow mesenchymal stem cell-derived exosomal miR-30e-5p ameliorates high-glucose induced renal proximal tubular cell pyroptosis by inhibiting ELAVL1. *Renal Failure* 45: 2177082, 2023.
110. Zhang YZ and Li YY: Inflammatory bowel disease: Pathogenesis. *World J Gastroentero* 20: 91-99, 2014.
111. Zhen Y and Zhang H: NLRP3 Inflammasome and inflammatory bowel disease. *Front Immunol* 10: 276, 2019.
112. Zhang S, Liang Y, Yao J, Li DF and Wang LS: Role of pyroptosis in inflammatory bowel disease (IBD): From gasdermins to DAMPs. *Front Pharmacol* 13: 833588, 2022.
113. Cai X, Zhang ZY, Yuan JT, Ocansey D, Tu Q, Zhang X, Qian H, Xu WR, Qiu W and Mao F: hucMSC-derived exosomes attenuate colitis by regulating macrophage pyroptosis via the miR-378a-5p/NLRP3 axis. *Stem Cell Res Ther* 12: 416, 2021.
114. Xu Y, Tang X, Fang A, Yan J, Kofi WOD, Zhang X and Mao F: HucMSC-Ex carrying miR-203a-3p.2 ameliorates colitis through the suppression of caspase11/4-induced macrophage pyroptosis. *Int Immunopharmacol* 110: 108925, 2022.
115. Jiao Y, Zhang T, Zhang C, Ji H, Tong X, Xia R, Wang W, Ma Z and Shi X: Exosomal miR-30d-5p of neutrophils induces M1 macrophage polarization and primes macrophage pyroptosis in sepsis-related acute lung injury. *Crit Care* 25: 356, 2021.
116. Feng Y, Li M, Yangzhong X, Zhang X, Zu A, Hou Y, Li L and Sun S: Pyroptosis in inflammation-related respiratory disease. *J Physiol Biochem* 78: 721-737, 2022.
117. Zhang M, Xu G, Zhou X, Luo M, Ma N, Wang X, Wang Z, Tang H, Wang X, Li Y, *et al*: Mesenchymal stem cells ameliorate H9N2-induced acute lung injury by inhibiting caspase-3-GSDME-mediated pyroptosis of lung alveolar epithelial cells. *Eur J Pharmacol* 960: 176148, 2023.
118. Liu P, Yang S, Shao X, Li C, Wang Z, Dai H and Wang C: Mesenchymal stem cells-derived exosomes alleviate acute lung injury by inhibiting alveolar macrophage pyroptosis. *Stem Cell Transl Med*: szad094, 2024 doi: 10.1093/stcltm/szad094 (Epub ahead of print).
119. Tao Y, Xu X, Yang B, Zhao H and Li Y: Mitigation of sepsis-induced acute lung injury by BMSC-Derived exosomal miR-125b-5p through STAT3-Mediated suppression of macrophage pyroptosis. *Int J Nanomed* 18: 7095-7113, 2023.
120. Zhang T, Lu L, Li M, Zhang D, Yu P, Zhang X, Zhang Z and Lei C: Exosome from BMMSC attenuates cardiopulmonary bypass-induced acute lung injury via YAP/beta-catenin pathway: Downregulation of pyroptosis. *Stem Cells* 40: 1122-1133, 2022.
121. Li C, Lu Y, Du S, Li S, Zhang Y, Liu F, Chen Y, Weng D and Chen J: Dioscin exerts protective effects against crystalline silica-induced pulmonary fibrosis in mice. *Theranostics* 7: 4255-4275, 2017.
122. Song M, Wang J, Sun Y, Pang J, Li X, Liu Y, Zhou Y, Yang P, Fan T, Liu Y, *et al*: Inhibition of gasdermin D-dependent pyroptosis attenuates the progression of silica-induced pulmonary inflammation and fibrosis. *Acta Pharm Sin B* 12: 1213-1224, 2022.
123. Zhao Q, Hao C, Wei J, Huang R, Li C and Yao W: Bone marrow-derived mesenchymal stem cells attenuate silica-induced pulmonary fibrosis by inhibiting apoptosis and pyroptosis but not autophagy in rats. *Ecotox Environ Safe* 216: 112181, 2021.
124. Levey AS and James MT: Acute Kidney Injury. *Ann Intern Med* 167: ITC66-ITC80, 2017.
125. Li N, Wang Y, Wang X, Sun N and Gong YH: Pathway network of pyroptosis and its potential inhibitors in acute kidney injury. *Pharmacol Res* 175: 106033, 2022.
126. Xie Z, Tang J, Chen Z, Wei L, Chen J and Liu Q: Human bone marrow mesenchymal stem cell-derived extracellular vesicles reduce inflammation and pyroptosis in acute kidney injury via miR-223-3p/HDAC2/SNRK. *Inflamm Res* 72: 553-576, 2023.
127. Guo J, Wang R and Liu D: Bone marrow-derived mesenchymal stem cells ameliorate sepsis-induced acute kidney injury by promoting mitophagy of renal tubular epithelial cells via the SIRT1/Parkin axis. *Front Endocrinol* 12: 639165, 2021.
128. Reddi S, Thakker-Varia S, Alder J and Giarratana AO: Status of precision medicine approaches to traumatic brain injury. *Neural Regen Res* 17: 2166-2171, 2022.
129. Zhang L, Lin Y, Bai W, Sun L and Tian M: Human umbilical cord mesenchymal stem cell-derived exosome suppresses programmed cell death in traumatic brain injury via PINK1/Parkin-mediated mitophagy. *Cns Neurosci Ther* 29: 2236-2258, 2023.
130. Al MA, Wu Y, Monalisa I, Jia C, Zhou K, Munir F and Xiao J: Role of pyroptosis in spinal cord injury and its therapeutic implications. *J Adv Res* 28: 97-109, 2021.
131. Sheth KN: Spontaneous intracerebral hemorrhage. *New Engl J Med* 387: 1589-1596, 2022.
132. Hu LT, Wang BY, Fan YH, He ZY and Zheng WX: Exosomal miR-23b from bone marrow mesenchymal stem cells alleviates oxidative stress and pyroptosis after intracerebral hemorrhage. *Neural Regen Res* 18: 560-567, 2023.
133. Giri TK, Alexander A, Agrawal M, Saraf S, Saraf S and Ajazuddin: Current status of stem cell therapies in tissue repair and regeneration. *Curr Stem Cell Res Ther* 14: 117-126, 2019.
134. Yamanaka S: Pluripotent stem cell-based cell therapy-promise and challenges. *Cell Stem Cell* 27: 523-531, 2020.
135. Masuda S: Risk of teratoma formation after transplantation of induced pluripotent stem cells. *Chest* 141: 1120-1121, 2012.
136. Chour T, Tian L, Lau E, Thomas D, Itzhaki I, Malak O, Zhang JZ, Qin X, Wardak M, Liu Y, *et al*: Method for selective ablation of undifferentiated human pluripotent stem cell populations for cell-based therapies. *JCI Insight* 6: e142000, 2021.
137. Alessandrini M, Preynat-Seauve O, De Bruin K and Pepper MS: Stem cell therapy for neurological disorders. *S Afr Med J* 109: 70-77, 2019.
138. Trounson A and McDonald C: Stem cell therapies in clinical trials: Progress and challenges. *Cell Stem Cell* 17: 11-22, 2015.
139. Liu XY, Yang LP and Zhao L: Stem cell therapy for Alzheimer's disease. *World J Stem Cells* 12: 787-802, 2020.
140. Al-Ghadban S and Bunnell BA: Adipose Tissue-Derived stem cells: Immunomodulatory effects and therapeutic potential. *Physiology* 35: 125-133, 2020.
141. Li Q, Wang Z, Xing H, Wang Y and Guo Y: Exosomes derived from miR-188-3p-modified adipose-derived mesenchymal stem cells protect Parkinson's disease. *Mol Ther Nucleic Acids* 23: 1334-1344, 2021.