International Immunopharmacology 67 (2019) 311–318

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Role of pyroptosis in cardiovascular diseases

Chang Jia[a], Huanwen Chen[c], Jian Zhang[b], Kailiang Zhou[d], Yingzhi Zhuge[b], Chao Niu[a], Jianxin Qiu[b], Xing Rong[b], Zhewei Shi[f], Jian Xiao[e], Yong Shi[g,*], Maoping Chu[a,b,**]

[a] Pediatric Research Institute, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325027, China
[b] Children's Heart Center, Institute of Cardiovascular Development and Translational Medicine, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325027, China
[c] University of Maryland School of Medicine, Baltimore, MD 21201, USA
[d] Department of Orthopaedics, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325027, China
[e] Pharmacology, School of Pharmacy, Wenzhou Medical University, Wenzhou, Zhejiang Province, China
[f] Department of Cardiology, Zhuji People's Hospital of Zhejiang Province, Shaoxing 311800, China
[g] Comprehensive Breast Health Center, Department of Thyroid and Breast Surgery, Lishui People's Hospital, The Six Affiliated Hospital of Wenzhou Medical University, Lishui, Zhejiang 323000, China

ARTICLE INFO

Keywords:
Pyroptosis
Cardiovascular diseases
Caspase-1
Caspase-4/5/11

ABSTRACT

Pyroptosis is a form of programmed necrosis, and is morphologically and mechanistically unique form of programmed cell death compared to others, such as apoptosis and autophagic cell death. More specifically, pyroptosis features gasdermin family-mediated membrane pore formation and subsequent cell lysis, as well as release of pro-inflammatory intracellular contents including IL-1β, IL-18 and HMGB1. Mechanistically, pyroptosis is driven by two main signaling pathways - one mediated by caspase-1 and the other by caspase-4/5/11. Recent studies show that pyroptosis is implicated in several cardiovascular diseases. In this review, we summarize recent scientific discoveries of pyroptosis's involvement in atherosclerosis, myocardial infarction, diabetic cardiomyopathy, reperfusion injury and myocarditis. We also organized new and emerging evidence suggesting that pyroptosis signaling pathways may be potential therapeutic targets in cardiovascular diseases.

1. Introduction

Classically, there are three different types of cell death: apoptosis, autophagic cell death, and necrosis. These categorizations of cell death are largely based on morphological findings. Apoptosis is the first identified form of programmed cell death, featuring DNA fragmentation, chromatin clumping, cell shrinkage, plasma membrane blebbing, as well as apoptotic body formation without loss of cell membrane integrity [1]. Worthy of note, apoptosis is perceived as an immunologically silent process [2]. In contrast, autophagic cell death is closely linked with the process of autophagy, during which cytoplasmic components are enclosed by double-membrane autophagosomes that fuse with lysosomes where these cellular contents are degraded and recycled. While autophagy is usually regarded as a critical pro-survival mechanism, dysregulated autophagy may be harmful and can lead to cell death when the stresses are excessive [3]. Necrosis is a major category of cell death, particularly in disease conditions. While necrosis has traditionally been deemed as an unregulated process specific to injury and disease, it is presently also considered to be highly regulated. More specifically, the identified programmed necrosis mainly encompasses mitochondrial permeability transition (MPT)-dependent necrosis, necroptosis, ferroptosis, and pyroptosis [4–8]. Recently, increasing studies have demonstrated that pyroptosis, a form of programmed necrosis, is involved in various kinds of diseases.

2. Pyroptosis signaling pathways

Pyroptosis, also known as gasdermin-mediated programmed necrosis [9], was first observed in Salmonella-induced macrophage death [10]. Morphologically, pyroptotic cell death combines features of both necrosis and apoptosis. Classical findings include necrosis-like cell-membrane pore formation, cellular swelling, and membrane rupture, leading to massive leakage of the cytosolic contents, as well as apoptosis-like nuclear condensation and DNA fragmentation without DNA

* Corresponding author.
** Correspondence to: M. Chu, Pediatric Research Institute, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325027, China.
E-mail addresses: shiyong111@163.com (Y. Shi), chmping@hotmail.com (M. Chu).

https://doi.org/10.1016/j.intimp.2018.12.028
Received 1 November 2018; Received in revised form 2 December 2018; Accepted 11 December 2018
Available online 17 December 2018

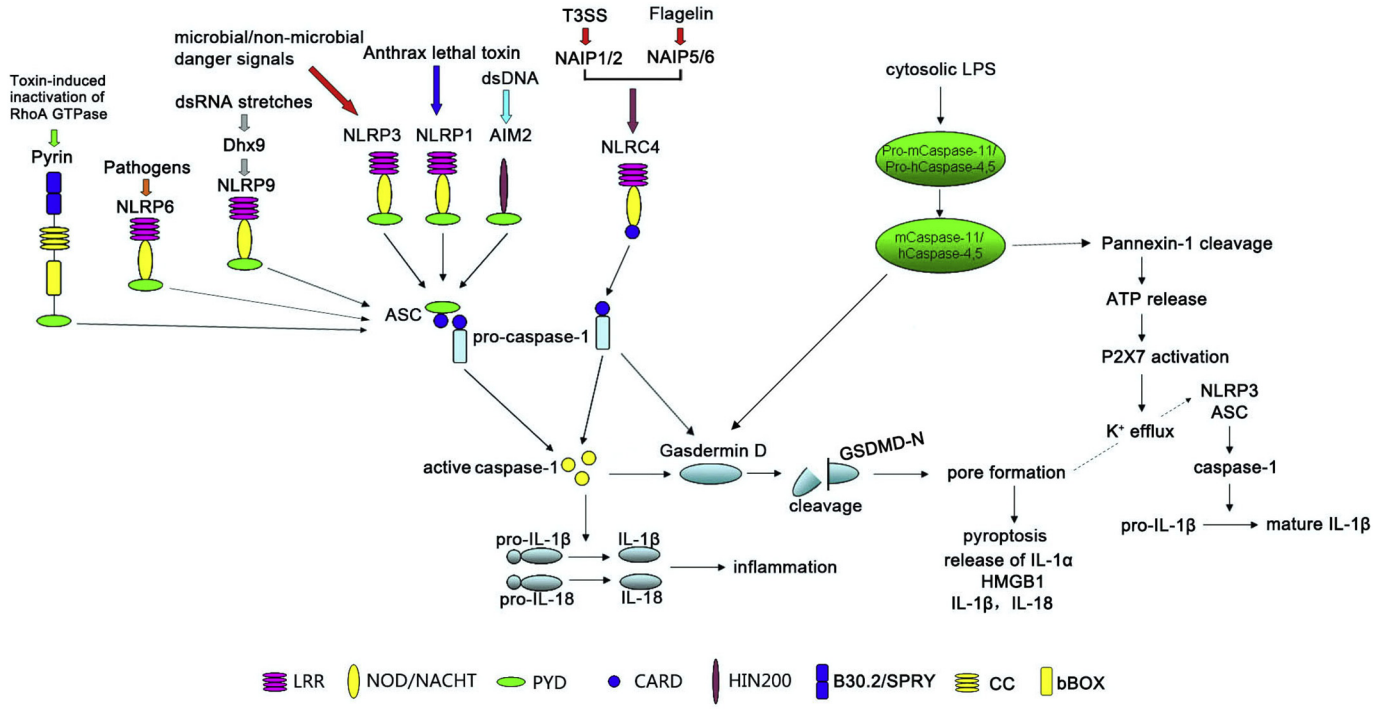

Fig. 1. Canonical caspase-1-dependent and non-canonical caspase-4/5/11-mediated pyroptosis pathways. In the canonical caspase-1 pathway, there are seven kinds of inflammasomes, including NLRP3, NLRP1, NLRP6, NLRP9, AIM2, NLRC4 and Pyrin, which are activated in response to pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). The NLRs (NLRP3, NLRP1, NLRP6, NLRP9, and NLRC4) contain three common domains: C-terminal leucine-rich repeats (LRR), a central nucleotide-binding oligomerization domain (NOD/NACHT), and an *N*-terminal caspase activation and recruitment domain (CARD) or pyrin domain (PYD). The non-NLR AIM2 contains a DNA-binding HIN-200 domain and a PYD signaling domain. The Pyrin consists of the PYD, a zinc finger domain (bBOX), a coiled coil (CC) domain, and/or a B30.2/SPRY domain. The NLRP3 inflammasome could be activated by microbial/non-microbial danger signals, including fungal, bacterial, and viral pathogens, as well as ATP, pore-forming toxins, crystalline compounds, nucleic acids, and hyaluronan. The NLRP1 inflammasome recognizes anthrax lethal toxin. The NLRC4 inflammasome responds to cytosolic bacterial flagellin and type III secretion system (T3SS) components via the NLR family of apoptosis inhibitory proteins (NAIPs), such as NAIP1/2 and NAIP5/6. NLRP6 is activated by microbes and microbial metabolites. NLRP9 recognizes short dsRNA stretches via Dhx9. AIM2 specifically discerns cytosolic double-stranded DNA (dsDNA). Pyrin senses the inactivation of RhoA GTPase that is induced by pathogen. Via homotypic interactions, the signaling domain (PYD or CARD) of AIM2, Pyrin and most of NLRs, binds to ASC, which recruits pro-caspase-1. NLRC4 directly recruits pro-caspase-1. Then the recruited pro-caspase-1 is catalytically activated to generate caspase-1. Active caspase-1 is responsible for processing and maturing IL-1β/18, and cleaving the gasdermin D (GSDMD) to induce pyroptosis. Besides, pro-caspase-1 is also capable of directly cleaving GSDMD to trigger pyroptosis. The non-canonical inflammasome pathway detects cytosolic lipopolysaccharide (LPS) and activates caspase-4/5/11. Active caspase-4/5/11 directly triggers pyroptosis by cleavage of GSDMD or indirectly processes IL-1β via the NLRP3-ASC-caspase-1 pathway mediated by K^+ efflux. During pyroptosis, the mature inflammatory cytokines, such as IL-1β and IL-18, and other DAMPs (IL-1α and HMGB1) are secreted and cause inflammation.

laddering. However, in contrast with apoptosis, the integrity of mitochondria is maintained, and pyroptosis does not involve cytochrome *c* release [11,12].

Pyroptosis-like cell death has been widely reported in various cell types, including macrophages, neutrophils, dendritic cells, endothelial cells, cardiomyocytes and so on [10,13–17]. Mechanistically, the process of pyroptosis is well preserved across cell types, and has been shown to involve the activation of canonical caspase-1 and non-canonical caspase-4/5/11 (human caspase-4/5 and murine caspase-11) [18] (Fig. 1).

In the canonical pyroptosis signaling pathway, pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) are detected by distinct inflammasomes, which consist of the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family (NLRP3, NLRP1, NLRC4, NLRP9 and NLRP6), PYHIN protein families (e.g., absent in melanoma 2 (AIM2)) [19], and Pyrin proteins [20]. These activated inflammasome trigger the activation of caspase-1, leading to pyroptosis.

NLR proteins are comprised of C-terminal leucine-rich repeats (LRRs), a central nucleotide-binding oligomerization domain (NOD/NACHT), and an *N*-terminal caspase activation and recruitment domain (CARD) or pyrin domain (PYD) [21]. The LRR is required for ligand recognition and autoinhibition, the NOD/NACHT domain is responsible for ATP-dependent activation of the signaling complex, and the CARD/PYD mediates homotypic protein-protein interactions [22]. Within the NLR family, NLRP3 has been identified as the critical NOD-like receptor family member that recognizes both microbial and non-microbial danger signals and triggers sterile inflammatory responses under various disease conditions [23,24]. NLRP3 transduces the recognition signal to the inflammasome adaptor ASC (apoptosis-associated speck-like proteins) for caspase-1 activation, and subsequent pro-IL-1β/18 processing and gasdermin D (GSDMD) cleavage [25]. Other NLR family member include NLRP1, which is activated by anthrax lethal toxin [26], NLRP9, which is specifically expressed in intestinal epithelial cells and recognizes short dsRNA stretches via Dhx9 [27], and NLRP6, which is activated by microbes, such as *Porphyromonas gingivalis*, and microbial metabolites, such as the bile acid-derivative taurine [28,29]. Finally, members of the NLR family of apoptosis inhibitory proteins (NAIPs), including NAIP1, NAIP2, and NAIP5/6, can be activated by the needle or rod components of the bacterial type III secretion system (T3SS), as well as cytosolic bacterial flagellin. Activated NAIPs then bind to NLRC4 to form an inflammasome [30–32].

Other types of inflammasome that can trigger pyroptosis include AIM2, which specifically discerns cytosolic double-stranded DNA (dsDNA) [33]. AIM2 proteins typically contain a DNA-binding HIN-200 domain and a PYD-signaling domain [21]. Pyrin, another form of inflammasome, senses the inactivation of RhoA GTPase that is induced by pathogens [20]. Pyrin is encoded by the human/mouse MEFV gene

located on chromosome 16. Human pyrin consists of four functional units: the PYD, a zinc finger domain (bBOX), a coiled coil (CC) domain, and a B30.2/SPRY domain. By contrast, the mouse pyrin contains only PYD, bBOX, and CC, lacking the B30.2/SPRY domain [20].

To trigger pyroptosis, the signaling domains (e.g., PYD) of NLRs, AIM2 and Pyrin bind to ASC, which recruits and activates pro-caspase-1 to generate active caspase-1 [21]. A notable exception to this paradigm is NLRC4 (which can bind activated NAIPs to form inflammasomes), where ASC is not required as NLRC4 activates caspase-1 by directly recruiting pro-caspase-1. Activated caspase-1 not only processes and matures IL-1β/18, but also cleaves the middle linker of GSDMD to release the intramolecular inhibition on the gasdermin-*N* domain, which triggers pyroptosis by oligomerizing to form 10-15-nm diameter pores in the cell membrane [7,34,35]. In addition to cleaved caspase-1, previous studies have also demonstrated that pro-caspase-1 is capable of cleaving and activating GSDMD, ultimately leading to pyroptosis, indicating that the cleavage of GSDMD could be parallel to caspase-1 activation [36]. Through the pore formed by GSDMD-*N* oligomerization in the cell membrane, substrates with a smaller diameter, such as IL-1β and IL-18, are secreted. Pyroptosis and rupture of the membrane ultimately ensues as the number of member pores increases, and cellular contents, such as IL-1α and HMGB1, are released [37].

In the non-canonical pyroptosis pathway, caspase-11 and caspase-4/5 are involved and activated mainly by cytosolic lipopolysaccharide (LPS) via recognizing the lipid A moiety in LPS by the CARD domain [37–40]. Activated caspase-4/5/11 directly initiate pyroptosis and the release of IL-1α and HMGB1 following cleavage of GSDMD-induced membrane pore formation and subsequent cell membrane rupture. Active caspase-4/5/11 also indirectly process IL-1β via the non-canonical NLRP3/ASC/caspase-1 pathway mediated by GSDMD pore formation/K^+ efflux or by pannexin-1 cleavage/ATP release/P2X7/K^+ release [37,39,41–44]. Previous studies have reported that caspase-11 activates NLPR3-dependent caspase-1 inflammasome possibly via K^+ efflux caused by GSDMD-induced membrane pores, since the activation of caspase-1 and the processing and release of IL-1β are suppressed in GSDMD knock-out macrophages stimulated with intracellular LPS [43,44]. However, Yang et al. demonstrated that cleavage of the pannexin-1 channel and ATP release occur via a caspase-11-dependent manner following cytosolic LPS stimulation, ultimately activating the P2X purinoreceptor 7 (P2X7), which leads to K^+ efflux and subsequent NLRP3/ASC/caspase-1 activation in BMDMs [42]. Therefore, active caspase-11-induced noncanonical NLRP3 inflammasome activation may be accomplished through the aforementioned pathways, the common point of which is the induction of K^+ efflux.

In addition to GSDMD, previous studies have discovered five other gasdermins (GSDMs) in human (GSDMA, B, C, E, and PJVK) and nine other GSDMs in mice (GSDMA1-3, GSDMC1-4, GSDME, and PJVK) [45,46]. With the exception of PJVK, all other GSDMs consist of two conserved domains: a C-terminal domain (autoinhibitory domain) and an *N*-terminus [35]. Normally, these two domains are bound, which helps stabilize the conformation of full-length GSDMs [35,47]. However, the *N*-terminus of certain GSDMs is released following proteolytic removal of the C-terminal domain, and binds to inner-leaflet cell membrane lipid components to form oligomeric death-inducing pores. These GSDMs include GSDMA, GSDMA3, GSDMB, GSDMC, GSDMD, and GSDME, the cleavage of which drives cells to undergo pyroptosis [34,35,48–51]. In addition to the induction of pyroptosis, gasdermin pores may also serve as a protein secretion channel (e.g., GSDMD pores for IL-1β secretion) [34,44]. Additionally, proteolytic gasdermin pores allow ion flux prior to plasma membrane rupture [52].

3. Role of pyroptosis in cardiovascular diseases

Cardiovascular disease is a leading cause of both death and patient suffering worldwide. Inflammasome infiltration plays key roles in the pathological processes of various cardiovascular diseases, including atherosclerosis, arteritis, aneurysm, ischemic heart disease, and other nonischemic heart diseases such as diabetic cardiomyopathy, chronic heart failure, and cardiac dysfunction [53]. Recent studies have demonstrated that pyroptosis is associated with the pathogenesis of cardiovascular diseases, including atherosclerosis, myocardial infarction (MI), diabetic cardiomyopathy, reperfusion injury and myocarditis.

3.1. Pyroptosis in atherosclerosis

Atherosclerosis is a well known process involving accumulation of lipids and inflammatory cell infiltrates in the arterial wall [54]. Risk factors, including hyperlipidemia, hyperglycemia, hypercholesterolemia, hypertension, and cigarette smoking, can cause endothelial cell (EC) dysfunction, which triggers monocytes to adhere to vascular ECs. The aggregated chemokines further lead to the migration of monocytes to the endothelium to transform into macrophages, phagocytosing cholesterol-rich lipoproteins in the tissue to form foam cells, and initiating the formation of fatty streaks. Smooth muscle cells (SMCs) that normally reside in the vascular media layer migrate into the intima layer, accumulating around the lipid pool composed of dead foam cells and transforming from contractile to synthetic. Under the stimulation of platelet-derived growth factor (PDGF) or transforming growth factor beta (TGF-β), SMCs forms a fibrous cap that covers the atherosclerotic plaque by producing extracellular matrix molecules such as elastin and collagen [55]. Previous reviews have elucidated that pyroptosis is closely associated with the development of atherosclerosis, referring to pyroptosis in ECs, SMCs, and macrophages [18,56] (Fig. 2).

In ECs, the caspase-1-inflammasome pathway senses increased lipids and inflammatory mediators via DAMP recognization and triggers pyroptosis [57–59]. Yin et al. reported that prior to monocyte recruitment, hyperlipidemia promotes EC activation through the caspase-1-sirtuin 1-activator protein-1 (AP-1) pathway [57], revealing that hyperlipidemic stimulation-activated caspase-1 promotes endothelial activation, causes pyroptosis in ECs, increases the expression level of EC adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), and triggers monocyte adhesion to ECs [57,60]. Besides, pyroptosis of ECs leads to the release of pro-inflammatory cytokines, such as IL-1β and IL-18, resulting in vascular inflammation [57,61]. EC inflammation then attracts monocyte adhesion, and subsequent monocyte migration into the intima. Together, these steps play crucial roles in the initiation of atherosclerosis, and all of these observations indicate that the pyroptosis of ECs is involved in the early stage of atherosclerosis. Wu et al. reported that nicotine, a well known risk factor of atherosclerosis, may induce disease by causing reactive oxygen species (ROS) production and activating the canonical pathway of pyroptosis in ECs [61]. In addition, acrolein and cadmium, which are linked to atherosclerosis, also induce NLRP3 inflammasome-mediated pyroptosis via ROS production in vascular endothelial cells [62,63]. Together, these studies indicate that NLRP3-caspase-1-mediated EC pyroptosis plays pivotal roles in atherosclerosis.

EC pyroptosis may lead to a series of downstream events in atherosclerosis, including the facilitation of SMC migration and deposition due to increased permeability of the endothelium layer caused by reduced number and integrity of ECs. In vascular smooth muscle cells (VSMCs), ox-LDL induces the expression of AIM2, GSDMD-N, ASC, and caspase-1, and DNA fragmentation, indicating that AIM2 may mediate pyroptosis in VSMCs. Overexpression of AIM2 has been shown to lead to an increase in plaque lesion area, the number of TUNEL-positive cells and macrophage accumulation in apolipoprotein E-deficient (ApoE−/−) mice, further substantiating that pyroptosis of VSMCs is associated with AIM2 [17]. Overall, pyroptotic SMCs lead to inflammation by releasing pro-inflammatory cytokines including IL-1β and IL-18, and attenuate the fibrous cap via disturbing collagen and matrix, which could ultimately worsen atherosclerosis, and aggravate plaque instability [18,64,65].

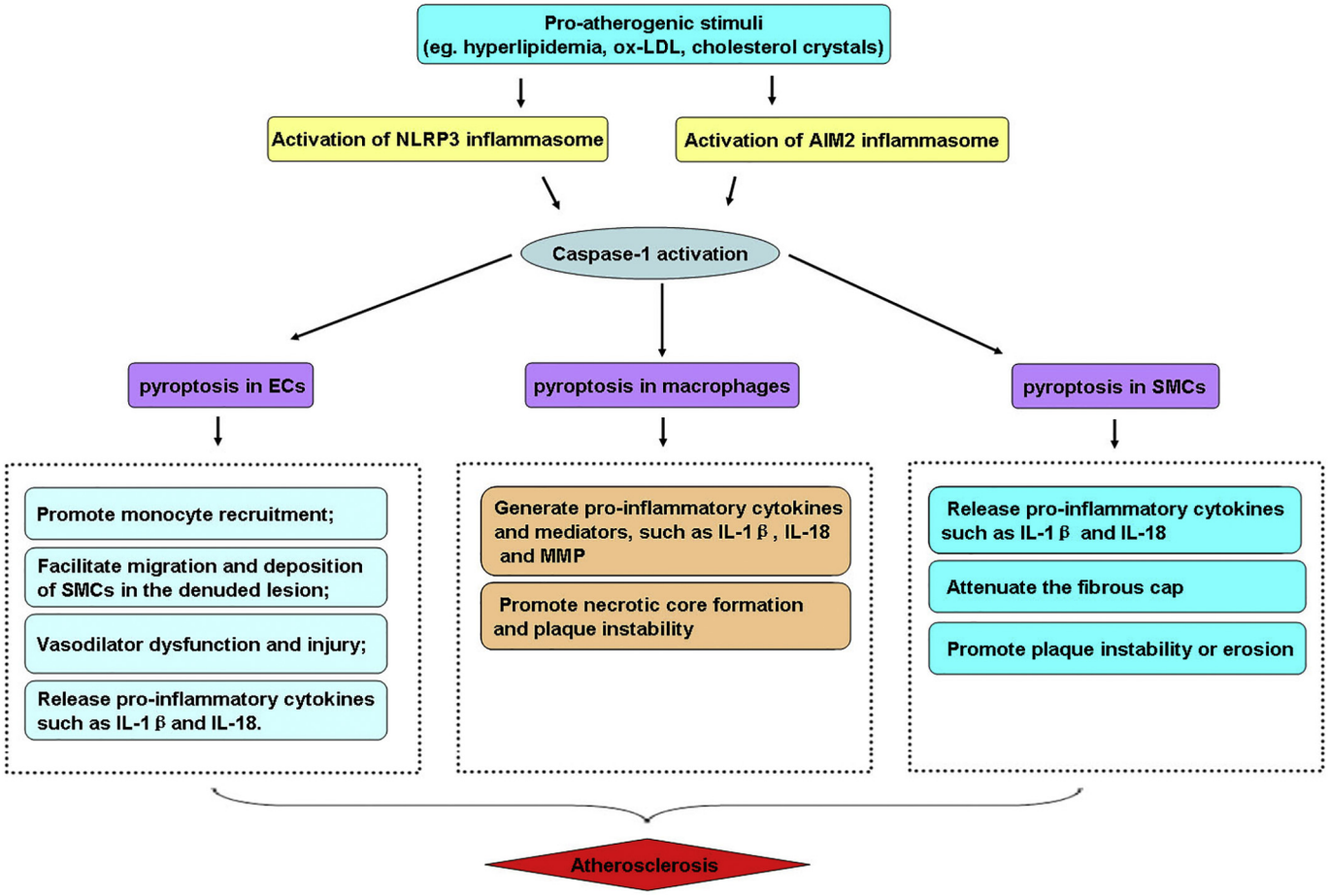

Fig. 2. Pyroptosis is implicated in the development of atherosclerosis.

Pyroptosis in macrophages have also been shown to play a significant role in atherosclerosis. Lin et al. showed that NLRP3-caspase-1 dependent pyroptosis occurs in ox-LDL-induced human macrophages [66], and pyroptotic macrophages produce cytokines such as IL-1β, IL-18, and matrix metalloproteinase (MMP), causing a robust inflammatory response and induce pyroptosis of foam cells that are formed by phagocytosing cholesterol crystals. Together, these events promote the formation of necrotic cores and the fibrous plaque instability in advanced atherosclerotic lesions [18,56].

3.2. Pyroptosis in MI

MI, most commonly attributed to coronary artery atherothrombosis [68], is a clinical syndrome in which the myocardium dies due to ischemia and an imbalance between myocardial oxygen supply and demand. The primary functional consequence caused by MI is the progressive deterioration of the pump function in the left ventricle, which can lead to heart failure. MI is anticipated to become the leading cause of death around the world.

Several lines of evidence indicate that MI is accompanied by sterile inflammatory responses that result in leukocyte accumulation and subsequent wound resorption and scar formation [67]. Furthermore, the accumulated leukocytes at the site of MI, including neutrophils and macrophages, release inflammatory cytokines, chemokines, and proteinases that may further exacerbate the inflammation and promote myocardial damage and remodeling following MI. This sterile inflammatory response could be mediated by Toll-like receptors (TLRs) and NLRs. TLRs regulate IL-1β production by promoting pro-IL-1β synthesis [68]. NLRs are the essential components of the inflammasomes that mediate the release of IL-1β [34], and many studies have revealed that the NLRP3 inflammasome plays an essential role in MI [69]. More specifically, in the context of MI, NLRP3 activation is associated with the leakage of lysosomal enzyme cathepsin B, the induction of K^+ efflux, and the production of ROS and other mediators [70] (Fig. 3).

In a mouse model, Mezzaroma et al. observed the inflammasomes in the heart following acute myocardial ischemia (AMI), and found elevated caspase-1 activity and increased intracytoplasmic ASC, NLRP3, and caspase-1 bordering the infarcted region in scar tissue and cardiomyocytes. The same authors found that inflammasomes are related to increased cell death of cultured cardiomyocytes, although they did not determine whether pyroptosis was involved. ATP receptor P2X7 and NLRP3 inhibition prevent inflammasome formation and limit the infarct size and cardiac enlargement after AMI [71]. In addition to cardiomyocytes, Sandanger et al. found an obvious post-MI increase of NLRP3, IL-1, and IL-18 mRNA in myocardial fibroblasts of the left ventricle. In vitro studies in cells from adult mice have shown that when primed with LPS and exposed to ATP, IL-1 and IL-18 are released by myocardial fibroblasts [72]. These studies indicate that NLRP3 is of paramount importance in MI, but whether pyroptosis functions in this process is still under investigation.

In vivo, Lei et al. showed that cardiomyocyte pyroptosis is mediated by the NLRP3 inflammasome, as substantiated by membrane pore formation, lactate dehydrogenase (LDH) release, and the increased expression of cleaved caspase-1, NLRP3, and ASC. A further study found that pyroptosis is induced by oxidative stress, the suppression of which reduces pyroptosis and the activities of NF-κB and GSDMD. NF-κB inhibition also decreases oxidative stress-regulated pyroptosis via GSDMD. These data indicate that oxidative stress induces NLRP3 inflammasome-mediated cardiomyocyte pyroptosis via the NF-κB-

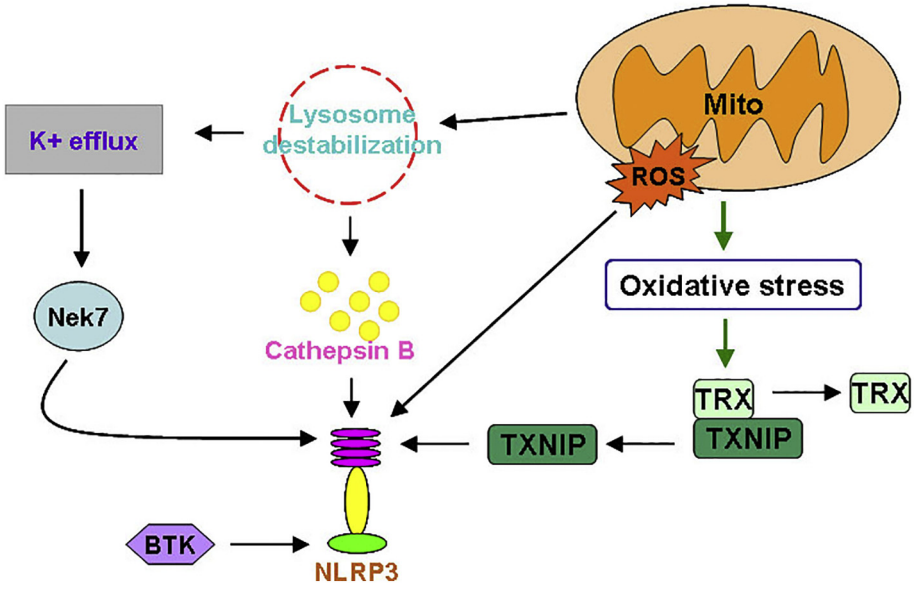

Fig. 3. NLRP3 could be activated by lysosomal enzyme cathepsin B, K^+ efflux, ROS and other mediators. Lysosomal destabilization results in leakage of lysosomal enzyme cathepsin B and induction of K^+ efflux. Cathepsin B could directly activate NLRP3, and the serine/threonine–protein kinase Nek7 senses the K^+ efflux and binds to NLRP3, allowing NLRP3 activation. Oxidative stress can also directly activate the inflammasome, or indirectly mediate by thioredoxin-interacting protein (TXNIP). The production of ROS causes the detachment of TXNIP from thioredoxin (TRX), which then binds to and activate NLRP3 and results in the formation of NLRP3 inflammasome. In addition, the tyrosine–protein kinase BTK could also binds to NLRP3 and trigger inflammasome activation.

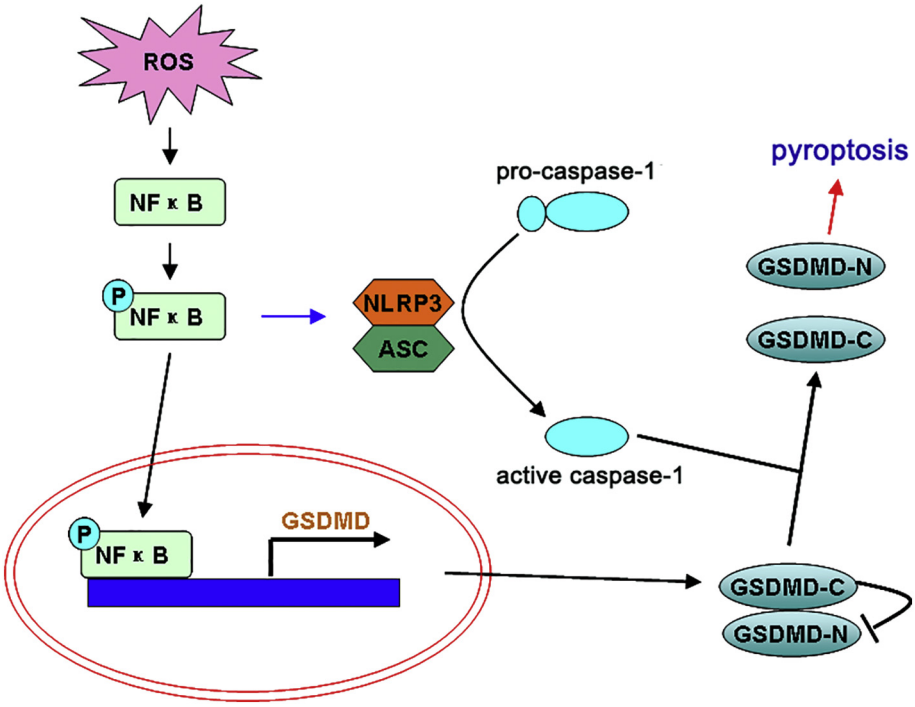

Fig. 4. Oxidative stress induces NLRP3 inflammasome-mediated pyroptosis in myocardial infarction via the NF-kB-GSDMD signaling axis.

GSDMD signaling axis [73] (Fig. 4), which differs from that in macrophages, where the NF-κB pathway upregulates NLRP3 expression while GSDMD is constitutively expressed [74]. These results suggest that pyroptosis is involved in the damage of cardiomyocytes during MI. However, it remains to be delineated whether pyroptosis occurs in other functional cells such as leukocytes, and whether pyroptosis in these cells also participates in MI processes. Therefore, detailed studies that elucidate the roles of pyroptosis in each process following MI are eagerly awaited.

3.3. Pyroptosis in diabetic cardiomyopathy

Diabetes is a frequent problem worldwide, and diabetic cardiomyopathy is a common complication closely associated with chronic inflammation of the heart, which could subsequently lead to heart failure (HF) and eventually result in increased mortality [75]. Several reports have demonstrated that pyroptosis participates in the process of diabetic cardiomyopathy.

Luo et al. reported that diabetic rats exhibit upregulation of NLRP3, ASC, pro-caspase-1, activated caspase-1, and mature IL-1β. NLRP3 silencing or ROS inhibition in H9c2 cardiomyocytes suppresses pyroptosis induced by high glucose [76]. Jeyabal et al. demonstrated that hyperglycemic treatment upregulates the caspase-1 and IL-1 expression, as well as ELAVL1, in human heart and ventricular cardiomyocytes. A further study found that ELAVL1 is a direct target of miR-9, and the inhibition of miR-9 increases the expression of ELAVL1 and causes caspase-1 activation. MiR-9 mimics treatment significantly inhibits ELAVL1 expression in hyperglycemia and subsequently suppresses pyroptosis in cardiomyocytes. This study revealed that targeting miR-9/ELAVL1 would be a potential therapeutic strategy in diabetic HF by

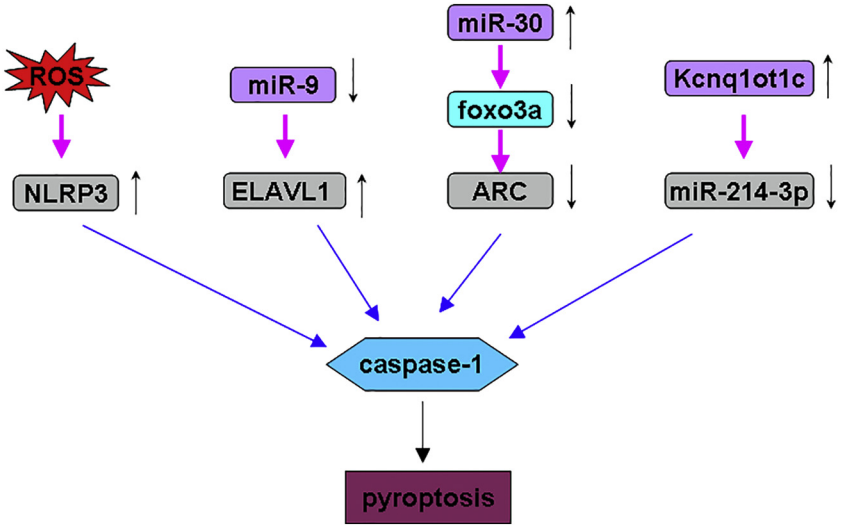

Fig. 5. Pyroptosis is involved in diabetic cardiomyopathy. In diabetic cardiomyopathy, caspase-1-mediated pyroptosis could be activated by ROS/NLRP3, miR-9/ELAVL1, miR-30/foxo3a/ARC, and Kcnq1ot1c/miR-214-3p signaling.

preventing cardiomyocyte death [77]. Li et al. demonstrated that miR-30d is substantially upregulated in the heart from instreptozotocin-induced diabetic rats and in cardiomyocytes treated with high glucose, and that in diabetic cardiomyopathy, miR-30d upregulation promotes cardiomyocyte pyroptosis. Subsequent investigations demonstrated that the miR-30d/foxo3a/ARC/caspase-1/IL-1β/18/pyroptosis pathway mediates cardiomyocyte pyroptosis under hyperglycemic conditions [78]. Yang et al. observed pyroptosis and Kcnq1ot1 activation in cardiac fibroblasts treated with high glucose, and Kcnq1ot1 knockdown by small interfering RNAs downregulates the expression of caspase-1. Further assays showed that Kcnq1ot1 sponges miR-214-3p and regulates caspase-1 expression by acting as a competing endogenous RNA. Kcnq1ot1 silencing inhibits the GSDMD cleavage and IL-1β secretion, and represses the TGF-β1/Smad signaling pathway in cardiac fibroblasts treated with high glucose. Thus, the Kcnq1ot1/miR-214-3p/caspase-1/TGF-β1 signaling pathway can be a potential therapeutic target and represents a novel mechanism of disease progression in diabetic cardiomyopathy [79] (Fig. 5).

Together, these studies indicate that in diabetic cardiomyopathy, caspase-1-induced pyroptosis could be mediated by non-coding RNA in addition to known inflammasomes, which expands the potential therapeutic targets in the pyroptosis signaling pathway for treatment of this disease.

3.4. Pyroptosis in reperfusion injury

Reperfusion injury is described as the damage to tissues caused by return of the blood supply following a hypoxia or ischemia, leading to ROS accumulation, dysregulation of cellular ion homeostasis, and inflammatory responses [80]. Reperfusion-induced oxidative stress is elaborated in ischemia-reperfusion injury (IRI). The induction of different types of cell death triggered by ROS plays an important role in IRI in multiple organs. Early literature revealed that necroptosis and apoptosis are involved in IRI [81]. Recent evidence shows that pyroptosis is also typically observed in cardiac IRI.

Lou et al. demonstrated that miR-424 promotes cardiac IRI injury by inducing cardiomyocyte pyroptosis. Under IRI conditions, miR-424 is significantly upregulated, which downregulates CRISPLD2 that leads to the upregulation of IL-1β, IL-18, and caspase-1 [82]. Qiu et al. reported that, under hyperglycemic conditions, NLRP3 inflammasome-mediated pyroptosis is induced and plays a critical role in myocardial IRI, while inhibition of the inflammasome with specific inhibitors or ROS scavengers reduces pyroptosis-like cell death and attenuates myocardial IRI [16]. These studies indicate that pyroptosis is involved in myocardial IRI. In addition to cardiac injury, pyroptosis-mediated IRI has also been widely reported in other organs (e.g., hepatic, cerebral, and renal IRI) [83–86]. Therefore, targeting pyroptosis may be a novel treatment strategy for reperfusion injury in the heart and beyond.

3.5. Pyroptosis in myocarditis

Myocarditis is described as an inflammatory disease of the myocardium. In addition to necroptosis, pyroptosis is also of great importance in the process of myocardium inflammation. Wang et al. reported that coxsackievirus B3-induced myocarditis is aggravated by cathepsin B via activating the inflammasome and promoting pyroptosis [87]. Liu et al. reported that cholecalciterol cholesterol emulsion (CCE) downregulates pyroptosis signaling pathways and improves autoimmune myocarditis [88]. These findings confirm that pyroptosis participates in the myocarditis process, and inhibiting the pyroptosis signaling pathway may be a possible strategy for treating this disease.

4. Potential therapies targeting pyroptosis for cardiovascular diseases

The crucial role of pyroptosis in the initiation of cardiovascular diseases has led to the significant development of specific inhibitors or agents that target pyroptosis pathway-related proteins, such as NLRP3, caspase-1, GSDMD, and other molecules.

Several NLRP3 inflammasome inhibitors have been identified, such as colchicine, glyburide derivatives, MCC950, INF4E, Dapansutrile/OLT1177, 16673-34-0 and CY-09. These agents could inhibit ATPase activity, prevent NLRP3 oligomerization, block opening of the P2X7 channel and destabilization of the lysosome, interfere with ASC polymerization, or affect ATP/dATP binding in the central NACHT domain [69,89,90]. In addition to these aforementioned agents that directly affect NLRP3, there are other drugs and molecules that indirectly suppress NLRP3 activity. For instance, Zhang et al. found that melatonin rescues EC pyroptosis by decreasing levels of pyroptosis-related proteins via the MEG3/miR-223/NLRP3 signaling axis in atherosclerosis [14]. Chen et al. reported that liraglutide alleviates pyroptosis mediated by NLRP3 inflammasome by downregulating the SIRT1/NOX4/ROS pathway in H9c2 cells [91]. MicroRNA-30c-5p inhibits NLRP3 inflammasome-dependent EC pyroptosis by downregulating FOXO3 in atherosclerosis [92]. Together, these studies provide potential NLRP3-inhibiting targets that could suppress pyroptosis.

Caspase-1 inhibitors are also agents that can inhibit pyroptosis, and they include VX-765, Ac-WEHD-CHO, ac-YVAD-cmk, and Pralnacasan [93–96]. Among them, VX-765 is widely used to inhibit pyroptosis in cardiovascular diseases, and when administered at reperfusion, VX-765 inhibits caspase-1 in P2Y receptor antagonist-treated rats and leads to a sustained reduction in infract size. Furthermore, VX-765 reduced MI in IRI [93,97], indicating that inhibiting caspase-1 is a reasonable method for the treatment of pyroptosis-triggered cardiovascular diseases.

GSDMD is an essential pyroptosis executor and is required for IL-1β release [36]. As a small-molecule inhibitor, necrosulfonamide (NSA) directly binds to GSDMD and leads to the inhibition of p30-GSDMD oligomerization, which impedes pyroptotic cell death and IL-1 secretion in monocytes/macrophages. However, NSA neither inhibits other innate immune pathways, such as TLR signaling and GSDME–dependent cell death, nor interferes with inflammasome formation [98]. Furthermore, disulfiram and Bay 11-7082 are also capable of blocking GSDMD pore formation and pyroptosis by covalently modifying a conserved Cys (Cys192 in mouse and Cys191 in human GSDMD) that is essential for the formation of membrane pores [99]. These findings indicate that drugs that target GSDMD could inhibit pyroptosis and pyroptosis-related diseases.

5. Conclusions

Until now, two types of pyroptosis signaling pathways have been described, the canonical caspase-1-dependent pathway and the non-canonical caspase-4/5/11-mediated pathway. Among conventional signaling pathways, NLRP3 complex-mediated pyroptosis is the most widely studied in cardiovascular diseases. Studies highlighted in this review have presented exciting new evidence that pyroptosis plays a significant role in various cardiovascular diseases, such as atherosclerosis, MI, reperfusion injury, and myocarditis. Furthermore, pyroptosis signaling pathways may be potential targets for novel therapeutic interventions, with many experimental therapeutics already under development. However, despite these new advances, studies concerning pyroptosis are still few. Thus, efforts should be taken to further elucidate the role of pyroptosis in cardiovascular disease for a better understanding of its mechanisms and how it can be leveraged for therapeutic benefit.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

This study was supported by the Natural Science Foundation of China (81601705, 81770502), the Natural Science Foundation of Zhejiang Province (LQ18C010003, LY18H020012), and Zhejiang Provincial Medicine and Health Technology Project (No. 2017KY472, 2019329308).

References

[1] K. Konstantinidis, R.S. Whelan, R.N. Kitsis, Mechanisms of cell death in heart disease, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 1552.
[2] A. Rongvaux, R. Jackson, C.C.D. Harman, T. Li, A.P. West, M.R. de Zoete, et al., Apoptotic caspases prevent the induction of type I interferons by mitochondrial DNA, Cell 159 (2014) 1563–1577.
[3] N. Hariharan, P. Zhai, J. Sadoshima, Oxidative stress stimulates autophagic flux during ischemia/reperfusion, Antioxid. Redox Signal. 14 (2011) 2179–2190.
[4] H. Zhu, A. Sun, Programmed necrosis in heart disease: molecular mechanisms and clinical implications, J. Mol. Cell. Cardiol. 116 (2018) 125–134.
[5] R. Weinlich, A. Oberst, H.M. Beere, D.R. Green, Necroptosis in development, inflammation and disease, Nat. Rev. Mol. Cell Biol. 18 (2016) 127.
[6] B.R. Stockwell, J.P. Friedmann Angeli, H. Bayir, A.I. Bush, M. Conrad, S.J. Dixon, et al., Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease, Cell 171 (2017) 273–285.
[7] X. Liu, Z. Zhang, J. Ruan, Y. Pan, V.G. Magupalli, H. Wu, et al., Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores, Nature 535 (2016) 153.
[8] M. Bonora, M.R. Wieckowski, C. Chinopoulos, O. Kepp, G. Kroemer, L. Galluzzi, et al., Molecular mechanisms of cell death: central implication of ATP synthase in mitochondrial permeability transition, Oncogene 34 (2015) 1475–1486.
[9] J. Shi, W. Gao, S. Feng, Pyroptosis: gasdermin-mediated programmed necrotic cell death, Trends Biochem. Sci. 42 (2016) 245.
[10] M. Brennan, B. Cookson, Salmonella induces macrophage death by caspase-1-dependent necrosis, Mol. Microbiol. 38 (2000) 31–40.
[11] S. Fink, B. Cookson, Caspase-1-dependent pore formation during pyroptosis leads to osmotic lysis of infected host macrophages, Cell. Microbiol. 8 (2006) 1812–1825.
[12] J. Cervantes, T. Nagata, M. Uchijima, K. Shibata, Y. Koide, Intracytosolic *Listeria monocytogenes* induces cell death through caspase-1 activation in murine macrophages, Cell. Microbiol. 10 (2008) 41–52.
[13] J. Edgeworth, J. Spencer, A. Phalipon, G. Griffin, P. Sansonetti, Cytotoxicity and interleukin-1beta processing following Shigella flexneri infection of human monocyte-derived dendritic cells, Eur. J. Immunol. 32 (2002) 1464–1471.
[14] Y. Zhang, X. Liu, X. Bai, Y. Lin, Z. Li, J. Fu, et al., Melatonin prevents endothelial cell pyroptosis via regulation of long noncoding RNA MEG3/miR-223/NLRP3 axis, J. Pineal Res. 64 (2018).
[15] J.C. Ryu, M.J. Kim, Y. Kwon, J.H. Oh, S.S. Yoon, S.J. Shin, et al., Neutrophil pyroptosis mediates pathology of *P. aeruginosa* lung infection in the absence of the NADPH oxidase NOX2, Mucosal Immunol. 10 (2017) 757–774.
[16] Q. Zhen, S. Lei, Z. Bo, W. Yang, W. Su, L. Min, et al., NLRP3 inflammasome activation-mediated pyroptosis aggravates myocardial ischemia/reperfusion injury in diabetic rats, Oxidative Med. Cell. Longev. 2017 (2017) 1–17.
[17] J. Pan, L. Han, J. Guo, X. Wang, D. Liu, J. Tian, et al., AIM2 accelerates the atherosclerotic plaque progressions in ApoE−/− mice, Biochem. Biophys. Res. Commun. 498 (2018) 487–494.
[18] Y. Xu, L. Zheng, Y. Hu, Q. Wang, Pyroptosis and its relationship to atherosclerosis, Clin. Chim. Acta 476 (2018) 28–37.
[19] V.A.K. Rathinam, Z. Jiang, S.N. Waggoner, S. Sharma, L.E. Cole, L. Waggoner, et al., The AIM2 inflammasome is essential for host-defense against cytosolic bacteria and DNA viruses, Nat. Immunol. 11 (2010) 395–402.
[20] R. Heilig, P. Broz, Function and mechanism of the pyrin inflammasome, Eur. J. Immunol. 48 (2017) 230–238.
[21] Y. Aachoui, V. Sagulenko, E. Miao, K. Stacey, Inflammasome-mediated pyroptotic and apoptotic cell death, and defense against infection, Curr. Opin. Microbiol. 16 (2013) 319–326.
[22] F. Martinon, K. Burns, J. Tschopp, The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta, Mol. Cell 10 (2002) 417–426.
[23] R. Malireddi, S. Ippagunta, M. Lamkanfi, T. Kanneganti, Cutting edge: proteolytic inactivation of poly(ADP-ribose) polymerase 1 by the Nlrp3 and Nlrc4 inflammasomes, J. Immunol. 185 (2010) 3127–3130.
[24] A. Afrasyab, P. Qu, Y. Zhao, K. Peng, H. Wang, D. Lou, et al., Correlation of NLRP3 with severity and prognosis of coronary atherosclerosis in acute coronary syndrome patients, Heart Vessel. 31 (2016) 1218–1229.
[25] O. Gross, H. Poeck, M. Bscheider, C. Dostert, N. Hannesschläger, S. Endres, et al., Syk kinase signalling couples to the Nlrp3 inflammasome for anti-fungal host defence, Nature 459 (2009) 433–436.
[26] S. Fink, T. Bergsbaken, B. Cookson, Anthrax lethal toxin and Salmonella elicit the common cell death pathway of caspase-1-dependent pyroptosis via distinct mechanisms, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 4312–4317.
[27] S. Zhu, S. Ding, P. Wang, Z. Wei, W. Pan, N.W. Palm, et al., Nlrp9b inflammasome restricts rotavirus infection in intestinal epithelial cells, Nature 546 (2017) 667–670.
[28] M. Levy, C.A. Thaiss, D. Zeevi, L. Dohnalovã, G. Zilberman-Schapira, J.A. Mahdi, et al., Microbiota-modulated metabolites shape the intestinal microenvironment by regulating NLRP6 inflammasome signaling, Cell 163 (2015) 1428–1443.
[29] W. Liu, J. Liu, W. Wang, Y. Wang, X. Ouyang, NLRP6 induces pyroptosis by activation of caspase-1 in gingival fibroblasts, J. Dent. Res. 97 (2018) 1391–1398.
[30] E. Kofoed, R. Vance, Innate immune recognition of bacterial ligands by NAIPs determines inflammasome specificity, Nature 477 (2011) 592–595.
[31] R.E. Vance, The NAIP/NLRC4 inflammasomes, Curr. Opin. Immunol. 32 (2015) 84–89.
[32] J. Tenthorey, E. Kofoed, M. Daugherty, H. Malik, R. Vance, Molecular basis for specific recognition of bacterial ligands by NAIP/NLRC4 inflammasomes, Mol. Cell 54 (2014) 17–29.
[33] V. Hornung, A. Ablasser, M. Charrel-Dennis, F. Bauernfeind, G. Horvath, D. Caffrey, et al., AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC, Nature 458 (2009) 514–518.
[34] J. Shi, Y. Zhao, K. Wang, X. Shi, Y. Wang, H. Huang, et al., Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death, Nature 526 (2015) 660–665.
[35] J. Ding, K. Wang, W. Liu, Y. She, Q. Sun, J. Shi, et al., Pore-forming activity and structural autoinhibition of the gasdermin family, Nature 535 (2016) 111.
[36] W. He, H. Wan, L. Hu, P. Chen, X. Wang, Z. Huang, et al., Gasdermin D is an executor of pyroptosis and required for interleukin-1β secretion, Cell Res. 25 (2015) 1285–1298.
[37] J. Shi, Y. Zhao, Y. Wang, W. Gao, J. Ding, P. Li, et al., Inflammatory caspases are innate immune receptors for intracellular LPS, Nature 514 (2014) 187–192.
[38] J. Yang, Y. Zhao, F. Shao, Non-canonical activation of inflammatory caspases by cytosolic LPS in innate immunity, Curr. Opin. Immunol. 32 (2015) 78–83.
[39] K. Cheng, S. Xiong, Z. Ye, Z. Hong, A. Di, K. Tsang, et al., Caspase-11-mediated endothelial pyroptosis underlies endotoxemia-induced lung injury, J. Clin. Invest. 127 (2017) 4124–4135.
[40] P. Broz, D.M. Monack, Noncanonical inflammasomes: caspase-11 activation and effector mechanisms, Plos Pathog. 9 (2013) e1003144.
[41] N. Kayagaki, S. Warming, M. Lamkanfi, L. Vande Walle, S. Louie, J. Dong, et al., Non-canonical inflammasome activation targets caspase-11, Nature 479 (2011)

117–121.
[42] Dahai Yang, Yuan He, Raul Muñoz-Planillo, et al., Caspase-11 requires the pannexin-1 channel and the purinergic P2X7 pore to mediate pyroptosis and endotoxic shock, Immunity 43 (2015) 923–932.
[43] S. Rühl, P. Broz, Caspase-11 activates a canonical NLRP3 inflammasome by promoting K+ efflux, Eur. J. Immunol. 45 (2015) 2927–2936.
[44] N. Kayagaki, I.B. Stowe, B.L. Lee, K. O'Rourke, K. Anderson, S. Warming, et al., Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling, Nature 526 (2015) 666–671.
[45] S.B. Kovacs, E.A. Miao, Gasdermins: effectors of pyroptosis, Trends Cell Biol. 27 (2017).
[46] S. Feng, D. Fox, S. Man, Mechanisms of gasdermin family members in inflammasome signaling and cell death, J. Mol. Biol. 430 (2018) 3068–3080.
[47] S. Kuang, J. Zheng, H. Yang, S. Li, S. Duan, Y. Shen, et al., Structure insight of GSDMD reveals the basis of GSDMD autoinhibition in cell pyroptosis, Proc. Natl. Acad. Sci. U. S. A. 114 (2017) 10642.
[48] R.A. Panganiban, M. Sun, A. Dahlin, H.R. Park, M. Kan, B.E. Himes, et al., A functional splicing variant associated with decreased asthma risk abolishes the ability of gasdermin B (GSMDB) to induce epithelial cell pyroptosis, J. Allergy Clin. Immunol. 142 (2018) 1469–1478.e2.
[49] Y. Wang, W. Gao, X. Shi, J. Ding, W. Liu, H. He, et al., Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin, Nature 547 (2017) 99–103.
[50] Y. Wang, B. Yin, D. Li, G. Wang, X. Han, X. Sun, GSDME mediates caspase-3-dependent pyroptosis in gastric cancer, Biochem. Biophys. Res. Commun. 495 (2017) 1418.
[51] B. Zhou, J.Y. Zhang, X.S. Liu, H.Z. Chen, Y.L. Ai, K. Cheng, R.Y. Sun, et al., Tom20 senses iron-activated ROS signaling to promote melanoma cell pyroptosis[J], Cell Res. (2018) 1.
[52] N.M.D. Vasconcelos, N.V. Opdenbosch, H.V. Gorp, E. Parthoens, M. Lamkanfi, Single-cell analysis of pyroptosis dynamics reveals conserved GSDMD-mediated subcellular events that precede plasma membrane rupture, Cell Death Differ. 1 (2018).
[53] W. Zhou, C. Chen, Z. Chen, L. Liu, J. Jiang, Z. Wu, et al., NLRP3: a novel mediator in cardiovascular disease, J Immunol Res 2018 (2018) 5702103.
[54] C. Zhu, M. Ichetovkin, M. Kurtz, E. Zycband, D. Kawka, J. Woods, et al., Cholesterol in human atherosclerotic plaque is a marker for underlying disease state and plaque vulnerability, Lipids Health Dis. 9 (2010) 61.
[55] G. Mensah, Healthy endothelium: the scientific basis for cardiovascular health promotion and chronic disease prevention, Vasc. Pharmacol. 46 (2007) 310–314.
[56] W. Chang, J. Lin, J. Dong, D. Li, Pyroptosis: an inflammatory cell death implicates in atherosclerosis, Med. Hypotheses 81 (2013) 484–486.
[57] Y. Yin, X. Li, X. Sha, H. Xi, Y. Li, Y. Shao, et al., Early hyperlipidemia promotes endothelial activation via a caspase-1-sirtuin 1 pathway, Arterioscler. Thromb. Vasc. Biol. 35 (2015) 804–816.
[58] Y. Yin, J. Pastrana, X. Li, X. Huang, K. Mallilankaraman, E. Choi, et al., Inflammasomes: sensors of metabolic stresses for vascular inflammation, Front. Biosci. (Landmark Ed.) 18 (2013) 638–649.
[59] T. Fernandes-Alnemri, J. Wu, J. Yu, P. Datta, B. Miller, W. Jankowski, et al., The pyroptosome: a supramolecular assembly of ASC dimers mediating inflammatory cell death via caspase-1 activation, Cell Death Differ. 14 (2007) 1590–1604.
[60] J. Lopez-Pastrana, L. Ferrer, Y. Li, X. Xiong, H. Xi, R. Cueto, et al., Inhibition of caspase-1 activation in endothelial cells improves angiogenesis: a novel therapeutic potential for ischemia, J. Biol. Chem. 290 (2015) 17485–17494.
[61] X. Wu, H. Zhang, W. Qi, Y. Zhang, J. Li, Z. Li, et al., Nicotine promotes atherosclerosis via ROS-NLRP3-mediated endothelial cell pyroptosis, Cell Death Dis. 9 (2018) 171.
[62] C. Jiang, L. Jiang, Q. Li, X. Liu, T. Zhang, L. Dong, et al., Acrolein induces NLRP3 inflammasome-mediated pyroptosis and suppresses migration via ROS-dependent autophagy in vascular endothelial cells, Toxicology 410 (2018) 26–40.
[63] H. Chen, Y. Lu, Z. Cao, Q. Ma, H. Pi, Y. Fang, et al., Cadmium induces NLRP3 inflammasome-dependent pyroptosis in vascular endothelial cells, Toxicol. Lett. 246 (2016) 7–16.
[64] P. Lacolley, V. Regnault, A. Nicoletti, Z.L. Li, J.B. Michel, The vascular smooth muscle cell in arterial pathology: a cell that can take on multiple roles, Cardiovasc. Res. 95 (2012) 194–204.
[65] S. Lim, S. Park, Role of vascular smooth muscle cell in the inflammation of atherosclerosis, BMB Rep. 47 (2014) 1–7.
[66] J. Lin, X. Shou, X. Mao, J. Dong, N. Mohabeer, K.K. Kushwaha, et al., Oxidized low density lipoprotein induced caspase-1 mediated pyroptotic cell death in macrophages: implication in lesion instability? PLoS One 8 (2013) e62148.
[67] M. Takahashi, Role of the SDF-1/CXCR4 system in myocardial infarction, Circ. J. 74 (2010) 418.
[68] M.G. Netea, A. Simon, F. Van dV, B.J. Kullberg, Jw VDM, L.A. Joosten, IL-1beta processing in host defense: beyond the inflammasomes, PLoS Pathog. 6 (2010) e1000661.
[69] S. Toldo, A. Abbate, The NLRP3 inflammasome in acute myocardial infarction, Nat. Rev. Cardiol. 15 (2018) 203–214 (nrcardio.2017.161).
[70] A. Liu, X. Gao, Q. Zhang, L. Cui, Cathepsin B inhibition attenuates cardiac dysfunction and remodeling following myocardial infarction by inhibiting the NLRP3 pathway, Mol. Med. Rep. 8 (2013) 361–366.
[71] E. Mezzaroma, S. Toldo, D. Farkas, I. Seropian, B. Van Tassell, F. Salloum, et al., The inflammasome promotes adverse cardiac remodeling following acute myocardial infarction in the mouse, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 19725–19730.
[72] Ø. Sandanger, T. Ranheim, L. Vinge, M. Bliksøen, K. Alfsnes, A. Finsen, et al., The NLRP3 inflammasome is up-regulated in cardiac fibroblasts and mediates myocardial ischaemia-reperfusion injury, Cardiovasc. Res. 99 (2013) 164–174.
[73] Q. Lei, T. Yi, C. Chen, NF-κB-gasdermin D (GSDMD) axis couples oxidative stress and NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome-mediated cardiomyocyte pyroptosis following myocardial infarction, Med. Sci. Monit. 24 (2018) 6044–6052.
[74] Y. Qiao, P. W, J. Q, L. Z, C. G, TLR-induced NF-κB activation regulates NLRP3 expression in murine macrophages, FEBS Lett. 586 (2012) 1022–1026.
[75] Zhong-Shu Liang, Kan Yang, He-Ling Wen, Anti-inflammatory effects of triptolide improve left ventricular; function in a rat model of diabetic cardiomyopathy, Cardiovasc. Diabetol. 12 (2013) (50-).
[76] B. Luo, B. Li, W. Wang, X. Liu, Y. Xia, C. Zhang, et al., NLRP3 gene silencing ameliorates diabetic cardiomyopathy in a type 2 diabetes rat model, PLoS One 9 (2014) e104771.
[77] P. Jeyabal, R.A. Thandavarayan, D. Joladarashi, S.S. Babu, S. Krishnamurthy, A. Bhimaraj, et al., MicroRNA-9 inhibits hyperglycemia induced cardiac pyroptosis in human ventricular cardiomyocytes by targeting ELAVL1, Biochem. Biophys. Res. Commun. 471 (2016) 423–429.
[78] X. Li, N. Du, Q. Zhang, J. Li, X. Chen, X. Liu, et al., MicroRNA-30d regulates cardiomyocyte pyroptosis by directly targeting foxo3a in diabetic cardiomyopathy, Cell Death Dis. 5 (2014) e1479.
[79] F. Yang, Y. Qin, J. Lv, Y.Q. Wang, H. Che, X. Chen, et al., Silencing long non-coding RNA Kcnq1ot1 alleviates pyroptosis and fibrosis in diabetic cardiomyopathy, Cell Death Dis. 9 (2018).
[80] H. Li, Z. Xia, Y. Chen, D. Qi, Z. Hong, Mechanism and therapies of oxidative stress-mediated cell death in ischemia reperfusion injury, Oxidative Med. Cell. Longev. 2018 (2018) 2910643.
[81] J. Wang, X. Zhang, Q. Li, K. Wang, Y. Wang, J. Jiao, et al., MicroRNA-103/107 regulate programmed necrosis and myocardial ischemia/reperfusion injury through targeting FADD, Circ. Res. 117 (2015) 352–363.
[82] Y.P. Lou, S.Y. Wang, J.L. Qu, J.H. Zheng, W.W. Jiang, Z.F. Lin, et al., miR-424 promotes cardiac ischemia/reperfusion injury by direct targeting of CRISPLD2 and regulating cardiomyocyte pyroptosis, Int. J. Clin. Exp. Pathol. 11 (2018) 3222–3235.
[83] Z.Y. Li, F.Z. Zhao, Y.G. Cao, J.Y. Zhang, P.L. Shi, X.Y. Sun, et al., DHA attenuates hepatic ischemia reperfusion injury by inhibiting pyroptosis and activating PI3K/Akt pathway, Eur. J. Pharmacol. 835 (2018) 1–10.
[84] P. Xia, Y. Pan, F. Zhang, N. Wang, E. Wang, Q. Guo, et al., Pioglitazone confers neuroprotection against ischemia-induced pyroptosis due to its inhibitory effects on HMGB-1/RAGE and Rac1/ROS pathway by activating PPAR-É¤, Cell. Physiol. Biochem. 45 (2018) 2351–2368.
[85] H. Zhao, H. Huang, A. Alam, Q. Chen, K.C. Suen, J. Cui, et al., VEGF mitigates histone induced pyroptosis in the remote liver injury associated with renal allograft ischemia-reperfusion injury in rats, Am. J. Transplant. 18 (2018) 1890–1903.
[86] J.R. Yang, F.H. Yao, J.G. Zhang, Z.Y. Ji, K.L. Li, J. Zhan, et al., Ischemia-reperfusion induces renal tubule pyroptosis via the CHOP-caspase-11 pathway, Am. J. Physiol. Renal Physiol. 306 (2014) 75–84.
[87] Y. Wang, L. Jia, J. Shen, Y. Wang, Z. Fu, S.A. Su, et al., Cathepsin B aggravates coxsackievirus B3-induced myocarditis through activating the inflammasome and promoting pyroptosis, PLoS Pathog. 14 (2018) e1006872.
[88] N. Liu, H. Su, Y. Zhang, Z. Liu, J. Kong, Cholecalciterol cholesterol emulsion attenuates experimental autoimmune myocarditis in mice via inhibition of the pyroptosis signaling pathway, Biochem. Biophys. Res. Commun. 493 (2017).
[89] S. Toldo, A. Mauro, Z. Cutter, A. Abbate, Inflammasome, pyroptosis, and cytokines in myocardial ischemia-reperfusion injury, Am. J. Physiol. Heart Circ. Physiol. 315 (2018) H1553–H1568.
[90] H. Jiang, H. He, Y. Chen, W. Huang, J. Cheng, J. Ye, et al., Identification of a selective and direct NLRP3 inhibitor to treat inflammatory disorders, J. Exp. Med. 214 (2017) 3219.
[91] A. Chen, Z. Chen, Y. Xia, D. Lu, X. Yang, A. Sun, et al., Liraglutide attenuates NLRP3 inflammasome-dependent pyroptosis via regulating SIRT1/NOX4/ROS pathway in H9c2 cells, Biochem. Biophys. Res. Commun. 499 (2018).
[92] P. Li, X. Z, J. L, H. L, X. M, R. H, Y. Z, MicroRNA-30c-5p inhibits NLRP3 inflammasome-mediated endothelial cell pyroptosis through FOXO3 down-regulation in atherosclerosis, Biochem. Biophys. Res. Commun. 503 (2018) 2833–2840.
[93] J. Audia, X. Yang, E. Crockett, N. Housley, E. Haq, K. O'Donnell, et al., Caspase-1 inhibition by VX-765 administered at reperfusion in P2Y receptor antagonist-treated rats provides long-term reduction in myocardial infarct size and preservation of ventricular function, Basic Res. Cardiol. 113 (2018) 32.
[94] Y. Hayashi, I. Jikihara, T. Yagi, M. Fukumura, Y. Ohashi, Y. Ohta, et al., Immunohistochemical investigation of caspase-1 and effect of caspase-1 inhibitor in delayed neuronal death after transient cerebral ischemia, Brain Res. 893 (2001) 113.
[95] G. Mathiak, G. Grass, T. Herzmann, T. Luebke, C.C. Zetina, S.A. Boehm, et al., Caspase-1-inhibitor ac-YVAD-cmk reduces LPS-lethality in rats without affecting haematology or cytokine responses, Br. J. Pharmacol. 131 (2000) 383–386.
[96] K. Rudolphi, N. Gerwin, N. Verzijl, P.V.D. Kraan, W.V.D. Berg, K. Rudolphi, et al., Pralnacasan, an inhibitor of interleukin-1 converting enzyme, reduces joint damage in two murine models of osteoarthritis, Osteoarthr. Cartil. 11 (2003) 738–746.
[97] H. Do Carmo, S. Arjun, O. Petrucci, D. Yellon, S. Davidson, The caspase 1 inhibitor VX-765 protects the isolated rat heart via the RISK pathway, Cardiovasc. Drugs Ther. 32 (2018) 165–168.
[98] J. Rathkey, J. Zhao, Z. Liu, Y. Chen, J. Yang, H. Kondolf, et al., Chemical disruption of the pyroptotic pore-forming protein gasdermin D inhibits inflammatory cell death and sepsis, Sci. Immunol. (2018) 3.
[99] J.J. Hu, X. Liu, J.X. Zhao, S.Y. Xia, J.B. Ruan, X.M. Luo, et al., Identification of pyroptosis inhibitors that target a reactive cysteine in gasdermin D, bioRxiv (2018) 365908.