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The Potential Therapeutic Prospect of PANoptosis in Heart Failure

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Abstract: Heart failure (HF) represents a serious manifestation or advanced stage of various cardiac diseases. HF continues to impose a significant global disease burden, characterized by high rates of hospitalization and fatality. Furthermore, the pathogenesis and pathophysiological processes underlying HF remain incompletely understood, complicating its prevention and treatment strategies. One significant pathophysiological mechanism associated with HF is the systemic inflammatory response. PANoptosis, a novel mode of inflammatory cell death, has been extensively studied in the context of infectious diseases, neurodegenerative disorders, cancers, and other inflammatory conditions. Recent investigations have revealed that PANoptosis-related genes are markedly dysregulated in HF specimens. Consequently, the PANoptosis-mediated inflammatory response may represent a potential mechanism and therapeutic target for HF. This paper conducts a comprehensive analysis of the molecular pathways that drive PANoptosis. We discuss its role and potential therapeutic targets in HF, thereby providing valuable insights for clinical treatment and the development of novel therapies.
Keywords: PANoptosis, pyroptosis, apoptosis, necroptosis, cell death, heart failure

Introduction

HF is an extremely complicated, life-threatening clinical illness characterized by aberrant heart anatomy or function. This condition results in impaired filling of the ventricular and ejection function, as well as the heart's inability to satisfy the systemic circulatory demands. It is the final stage of most cardiovascular diseases.[1] With the progress of population aging, the life expectancy extension, and the improvement of the survival rate of acute myocardial infarction, the prevalence of HF is growing year after year. Upon an investigation of the burden of HF in 195 different nations and regions, it was discovered that the total amount of people suffering HF globally is approximately 33.5 million to 64.3 million.[2] The incidence of HF in Europe is about 3 in 1000 among all age groups and can reach 5 in 1000 among adults.[3,4] Furthermore, HF, with its high rates of hospitalization and mortality, constitutes a considerable global illness burden. According to cohort research conducted between 2000 and 2010, the one-year and 5-years rates of mortality for HF were 20% and 53%, consequently, with an average hospitalization rate of 1.34 per person-year.[5] Despite tremendous breakthroughs in the pharmaceutical and physical therapy of HF after more than half a century, patient clinical outcomes and quality of life remain unsatisfactory, representing a major public health concern. Consequently, identifying new targets for the treatment of HF and developing a more comprehensive and effective strategy for its management remain our current and future challenges.

As a chronic and spontaneously progressive disease, HF is characterized by a systemic proinflammatory state.[6,7] An excessive inflammatory response can exacerbate HF, while elevated levels of inflammatory factors are indicative of poor prognosis in patients. The persistent expression of these inflammatory factors continuously activates the inflammatory cascade, resulting in cardiomyocyte death, cardiac fibrosis, and impaired ventricular remodeling.[8,9] This cascade ultimately leads to both diastolic and systolic dysfunction of the heart, contributing to the onset and progression of

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HF. Therefore, intervening in the inflammatory state associated with HF and regulating cardiomyocyte death to prevent cardiac fibrosis and poor ventricular remodeling may represent a promising therapeutic strategy for the prevention and treatment of this condition.

The inflammatory response mediated by cardiomyocyte death is the key link of myocardial injury and adverse ventricular remodeling.[10,11] Apoptosis, pyroptosis, and necroptosis represent three key pathways of programmed cell death (PCD), which are involved in the onset and progression of HF. However, the course of HF cannot be explained by these three PCD pathways alone, as there is growing evidence of extensive crossover and crosstalk between them. In 2019, Malireddi et al identified the existence of PANoptosis, an inflammatory PCD pathway characterized by key features of apoptosis, pyroptosis, and necroptosis.[12] This discovery offers valuable insights into the interplay and interconnections among various PCD pathways, elucidating their role in the inflammatory cascade associated with HF. This concept was subsequently established in the study by Wang and Kanneganti in 2021: Key elements of pyroptosis, apoptosis, or pyroptosis are present in the inflammatory PCD pathway controlled by the PANoptosome complex; however, none of these PCD routes can account for these properties on their own.[13] Therefore, the inflammatory cascade mediated by PANoptosis is an important target in the fight against HF. However, a large portion of the present PANoptosis research is mostly focused on pathogenic infections, neurodegenerative disorders, cancer, and other inflammatory diseases, as shown in Figure 1. Its role in HF has not been extensively studied. This article provides a brief review of the molecular mechanisms and evidence of cross-talk among apoptosis, pyroptosis, and necroptosis. It summarizes the regulatory mechanisms of PANoptosis and emphasizes the exploration of the inflammatory response mediated by PANoptosis. From this perspective, we interpret the scientific implications for treating HF and identify potential therapeutic targets, aiming to offer more effective and targeted treatment strategies for this condition.

Crosstalk Between Apoptosis, Pyroptosis, and necroptosis—the Emergence of PANoptosis

Apoptosis, pyroptosis, and necroptosis are three PCD pathways with some molecular and genetic characteristics. The molecular mechanisms of apoptosis, pyroptosis, and necroptosis are shown in Figure 2. Apoptosis is a non-inflammatory cell death route triggered by cysteinyl aspartate-specific proteinase (Caspase).[14] Apoptosis pathways include exogenous apoptotic signaling mediated by death receptor (DR) binding ligands, endogenous apoptotic signaling mediated by B-cell lymphoma-2 (BCL-2) family proteins, and Caspase-independent apoptotic signaling triggered by excessive endoplasmic reticulum stress response.[15] Activation of Caspase is the key to regulating apoptosis. Caspase-8, caspase-9, and Caspase-10 are the initiating apoptotic proteases, while executioner Caspase-3, caspase-6, and caspase-7 are the effector apoptotic proteases that execute cell cascade reactions.[16,17] Pyroptosis is a lytic, inflammatory cell death pathway induced by the pore-forming activity of the gasdermins (GSDMs) protein family.[18] The two types of pyroptosis pathways are the conventional pathway, which is triggered by inflammasomes and activates caspase-1, and the non-classical pathway, which is triggered by lipopolysaccharide (LPS) and activates caspase-4/5/11. The creation of inflammasomes, the activation of Caspase, and the large-scale, active release of pro-inflammatory molecules, including Interleukin-1β/18 (IL-18/1β) are important markers of pyroptosis.[19,20] Necroptosis is a cell death pathway mediated by receptor-interacting serine/threonine protein kinase 1 (RIPK1), Receptor-interacting serine/threonine protein kinase 1 (RIPK3), and mixed lineage kinase domain-like protein (MLKL), which has the morphological characteristics of necrotic cells and similar signaling mechanisms to apoptotic cells. It can be used as an alternative, caspase-independent mode of inflammatory PCD that occurs when the normal apoptotic pathway is inhibited.[21]

Prior research has focused on the distinct genetic programs and biochemical processes that comprise each of these three PCD pathways. However, more recent studies have demonstrated that these pathways interact and influence one another, ultimately inducing cell death.The crosstalk between the three PCD pathways is shown in Figure 3. Members of the Caspase family are activated in both pyroptosis and apoptosis. Pyroptosis is a dissolved form of Caspase-1-dependent cell death but leads to activation of apoptotic signals when Caspase-1 function is lost. In the meantime, Caspase-1 triggers apoptosis by activating Caspase-3 and Caspase-7 in the absence of pyroptosis-mediated substrate GSDMD.[22,23] The proteins caspase-3 and GSDME function as regulators between pyroptosis and apoptosis. When GSDME is

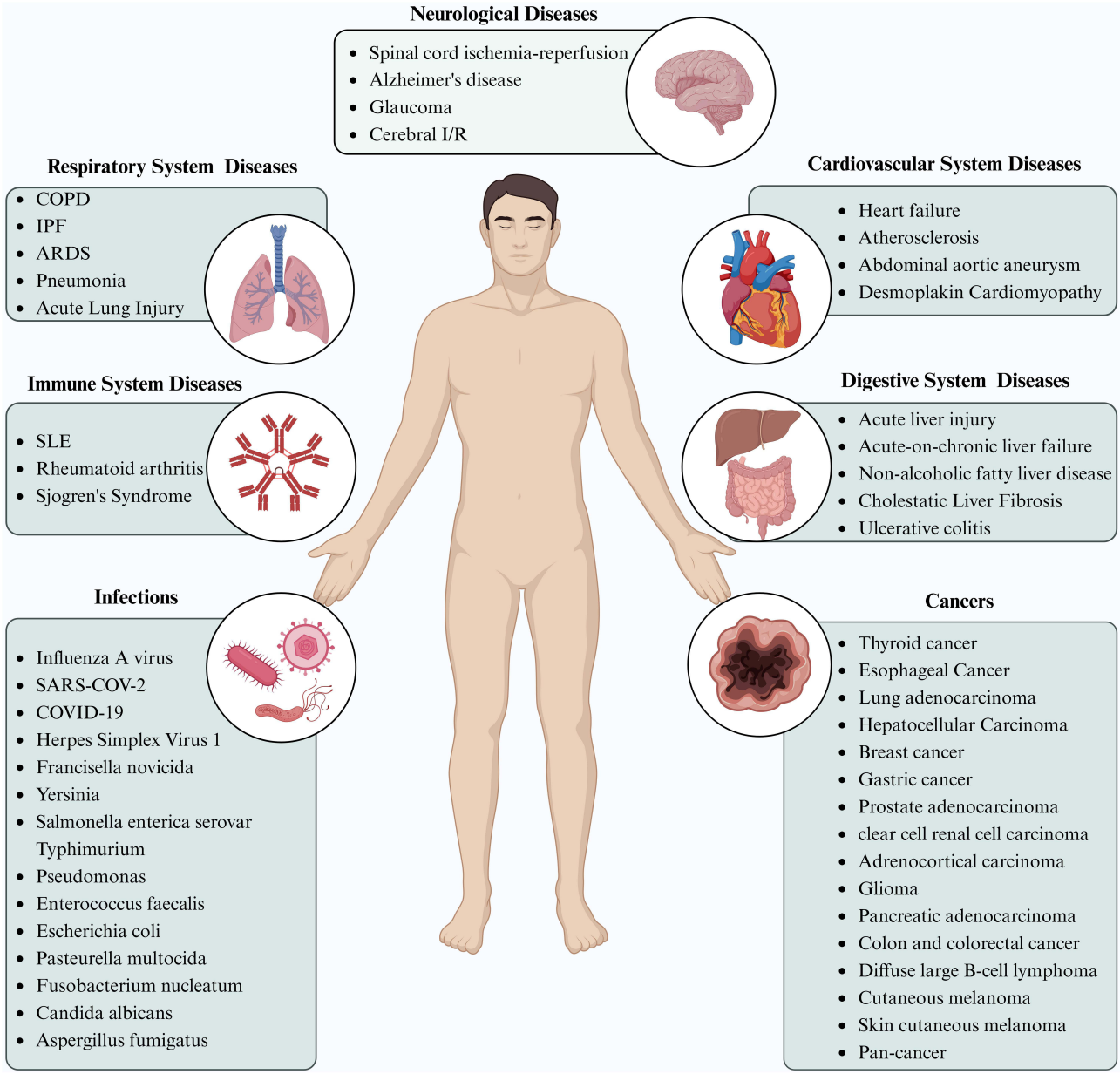

Figure 1 Diseases that may be related to PANoptosis, including Neurological, cardiovascular, respiratory, digestive, immune system, infections, and cancer. The figure is Created in BioRender. Jia, Y. (2024) https://BioRender.com/p99f599.
Abbreviations: I/R, Ischemia/reperfusion; COPD, Chronic obstructive pulmonary disease; IPF, Idiopathic pulmonary fibrosis; ARDS, Acute respiratory distress syndrome; SLE, Systemic lupus erythematosus.

produced at a high level, caspase-3 can cleave GSDME to cause pyroptosis, which would otherwise cause apoptosis.[24,25] Both necroptosis and pyroptosis are fundamentally inflammatory processes that result in lytic cell death. When oligomerized MLKL forms pores in the plasma membrane, it triggers the efflux of potassium ions. It has been demonstrated that this necroptosis-induced ion efflux triggers the NLRP3 inflammasome, activates Caspase activation and recruitment, and processes mature IL-1β and efflux.[26,27] However, in reaction to NLRC4 inflammatory vesicle abnormalities, increased MLKL phosphorylation and activation of necroptosis can work as a compensatory activation mechanism.[28] This further unique mechanism demonstrates the relationship between necroptosis and pyroptosis (the inflammasome) by inducing IL-1β release independently of GSDMD. Necroptosis has been historically recognized as an alternative mechanism for cell death that arises from the suppression of Caspase-8-dependent apoptosis, which is triggered by tumor necrosis factor (TNF) induced Caspase-8 activation and the subsequent inhibition of Caspase-8

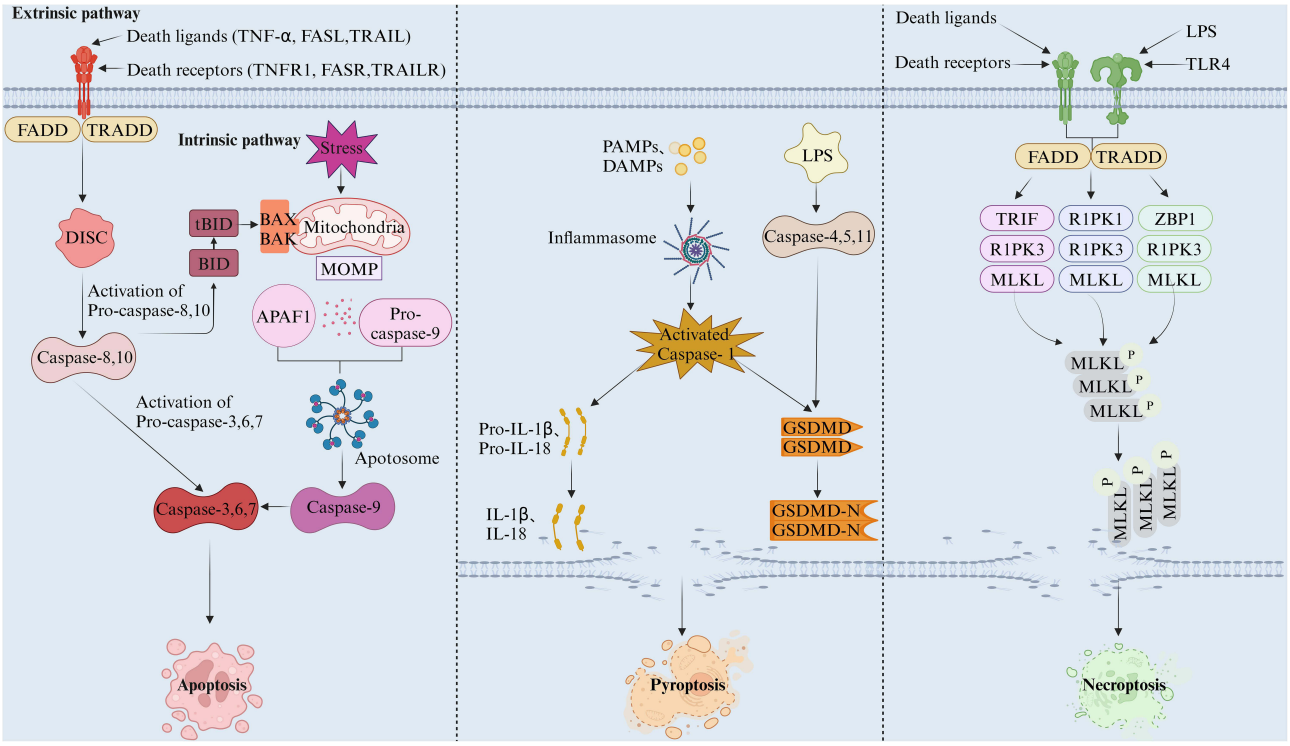

Figure 2 The molecular mechanism of apoptosis, pyroptosis, and necroptosis. Apoptosis mechanisms. The binding of death receptors to ligands initiates exogenous pathways by attracting adaptor proteins, such as tumor necrosis factor receptor type 1-associated DEATH domain protein (TRADD) and fas-associated death domain (FADD). These proteins stimulate downstream Procaspase-8/10 and create the death-inducing signal transduction complex (DISC). Activated Caspase-8 initiates the executive phase of apoptosis by cutting the downstream effector Caspase-3/6/7. In the intrinsic pathway, DNA damage or oxidative stress cause mitochondrial outer membrane permeability (MOMP), resulting in the release of cytochrome C into the cytoplasm. Cytochrome C will form apoptotic bodies with apoptotic protease activating factor-1 (APAF1), activate Caspase-9, and induce endogenous apoptosis. Pyroptosis mechanism: In a classical pathway, Damage-associated molecular patterns (DAMPs) and Pathogen-associated molecular patterns (PAMPs) activate inflammasome and activate Caspase-1. Activating IL −1β/18 and secreting them out of the cell through the pore can amplify the inflammatory response. And it can also cause the shear and polymerization of Gasdermin D (GSDMD) members of the Gasdermin family, resulting in cell membrane perforation and ultimately pyroptosis. In a non-classical pathway, Gram-negative bacteria lipopolysaccharide (LPS) cleaved GSDMD by activating caspase-4/5 in humans or caspase-11 in mice to trigger pyroptosis. Mechanism of necroptosis: When the activity of Caspase-8 is inhibited, RIPK1 and RIPK3 form necrotic complexes and phosphorylate MLKL through RIPK3. The phosphorylated MLKL forms polymers and transfers to the plasma membrane, causing the plasma membrane to break and lead to necroptosis. The figure is Created in BioRender. Jia, Y. (2024) https://BioRender.com/u16f415.

activity.[29–31] Key to both necroptosis and the apoptotic transition, RIPK1's low expression promotes apoptosis while its overexpression tends to cause necroptosis.[32] Furthermore, Caspase-8 plays a crucial role in the non-classical pathway that initiates pyroptosis. Research has demonstrated that in cases when necroptosis is inhibited, inactive Caspase-8 can function as a scaffolding protein to facilitate the creation of an inflammasome, which in turn can result in pyroptosis.[33] Caspase-8 is thus a molecular switch for pyroptosis, apoptosis, and necroptosis and is involved in mediating the switch between various cell death modes.[34] There is growing evidence of extensive crosstalk and cross-regulation among the three, which promotes the establishment of the concept of PANoptosis: Apoptosis, pyroptosis, or necroptosis alone cannot adequately describe the biological effects of PANoptosis. Instead, a distinct innate immunoinflammatory cell death pathway is controlled by PANoptosome—a complex that integrates molecules from other cell death pathways and functions as a molecular scaffold to facilitate signal transduction and interactions between these PCDS. PANoptosis is a novel idea in PCD. Blocking a single PCD during PANoptosis activation will not stop cell death or stop the release of inflammatory cytokines. Consequently, exploring its molecular mechanism is vital as it will advance knowledge of the pathway resulting in cell death and PANoptosis regulation, which is progressively emerging as an innovative target for illness therapy. The differences between apoptosis, pyroptosis, necroptosis, and PANoptosis are shown in Table 1.

Basic Molecular Mechanism of PANoptosis

The formation of the PANoptosome compound—which consists of the inflammasome in pyroptosis, the apoptotic body and lethal signaling complex in apoptosis, and the terrible dead body in necroptosis—is a crucial aspect of PANoptosis.

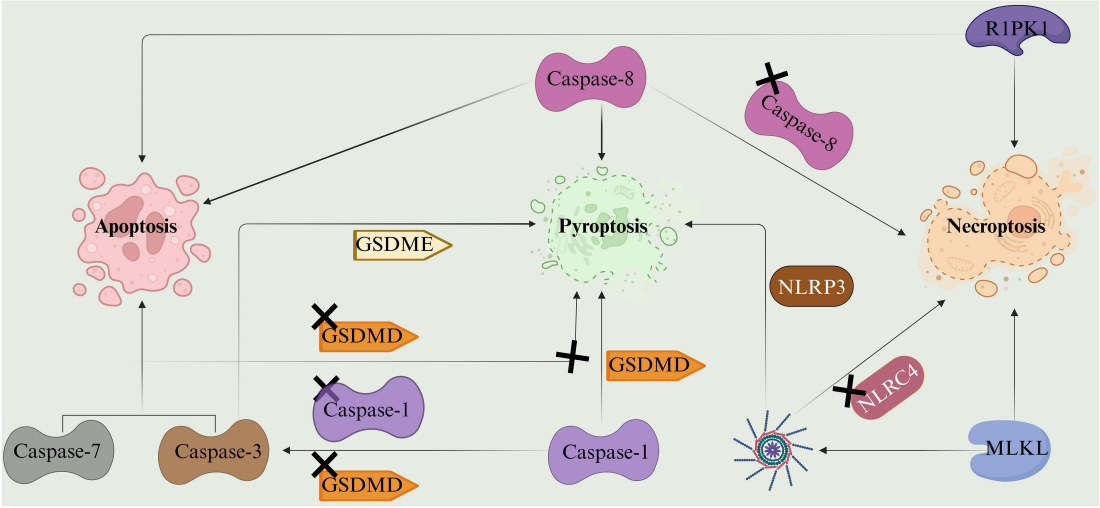

Figure 3 Crosstalk between the three PCD pathways: Crosstalk among apoptosis, pyroptosis, necroptosis. Caspase-8 activation can drive apoptosis, but inhibition of Caspase-8 activity can drive necroptosis. When necroptosis is blocked, enzymatically inactive Caspase-8 can act as a protein scaffold leading to pyroptosis. Crosstalk between pyroptosis and apoptosis: Pyroptosis is activated when Caspase-1 is active, but loss of Caspase-1 function or loss of GSDMD will lead to activation of apoptosis. When GSDME is highly expressed, caspase-3 can cleave GSDME to trigger pyroptosis, which would otherwise trigger apoptosis. During apoptosis, Caspase-3/7 blocks pyroptosis by cleaving GSDMD to inactivate the protein. Crosstalk between pyroptosis and necroptosis: The efflux of potassium ions induced by necroptosis can activate the NLRP3 inflammasome and induce pyroptosis. Enhanced MLKL phosphorylation and activation of necroptosis can be used as compensatory activation strategies when NLRC4 inflammasome is defective. Crosstalk between apoptosis and necroptosis: low expression of RIPK1 is beneficial to apoptosis, while upregulation of expression tends to induce necroptosis. The figure is Created in BioRender. Jia, Y. (2024) https://BioRender.com/u11k548. **X** represents inhibition or inactivation of molecules and inhibition of pathways.

Based on its biological and chemical roles, the composition of PANoptosome is classified into three categories: sensors (eg, Z-DNA-binding protein 1 (ZBP1), absent in melanoma 2 (AIM2), and NLRP3), adapters (eg, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and FADD), and catalytic effects (eg, RIPK1, RIPK3, Caspase-1, and Caspase-8).[35] The host can mount a strong defense against infection by allowing PANoptosome assembly and PANoptosis activation. On the other hand, cytokine storms, excessive inflammation, and damage to tissues and organs can all be caused by abnormal PANoptosis activation.[36–38] The composition of PANoptosome is shown in Figure 4.

ZBP1 PANoptosome

Interferon-induced proteins Z-DNA-binding protein 1 (ZBP1, also known as DNA-dependent activator of IFN regulators (DAI) and DMP-1) is an innate immune sensor that is resistant to pathogen invasion, as well as a key regulator of cell death and inflammation.[39,40] The structure of ZBP1 is characterized by two Z-nucleic acid-binding domains (Zα1 and Zα2), two RIM domains (RHIM1 and RHIM2), and a conserved C-terminal domain.[41] One important molecular switch that initiates PANoptosis is the Zα2 domain. Research indicates that the Zα2 domain is required for ZBP1 activation to trigger NLRP3 inflammasome activation, PANoptosis, and perinatal death in mice.[42] Moreover, deletion of the Zα2 domain removes inflammation and PANoptosis caused by influenza A virus (IAV) infection.[42] ZBP1, a crucial regulator of PANoptosis, is essential in starting the formation of the PANoptosome, which results from an IAV infection. ZBP1 detects IAV during infection and enlists RIPK3 and Caspase-8 to trigger the ZBP1-NLRP3 inflammasome, which in turn triggers the release of IL-1β and IL-18 to start pyroptosis. Concurrently, the ZBP1-RIPK3 complex triggers MLKL-mediated necroptosis, and Caspase-8-dependent apoptosis starts the ZBP1 PANoptosome assembly and causes PANoptosis.[43–45] ZBP1, RIPK3, RIPK1, FADD, caspase-8, ASC, and caspase-1 co-localize and interact to create the PANoptosome, which drives PANoptosis, as demonstrated by immunofluorescence (IF) and Co-immunoprecipitation (Co-IP).[43–45] Multiple studies have demonstrated that, alongside influenza A virus (IAV) infection, infections caused by Candida albicans and Aspergillus fumigatus, as well as interferon (IFN) therapy administered during coronavirus infection, and a combination of IFN with a nuclear export inhibitor (NEI), can trigger the activation of the ZBP1 PANoptosome, thereby initiating PANoptosis.[46–48] However, ADAR1 (adenosine deaminases acting on RNA) can

Table 1 Identification of Cell Death Types

Cell Death Type		Apoptosis	Pyroptosis	Necroptosis	PANoptosis
Morphological feature	Cell morphology	Cell shrinkage	Cell swelling	Cell swelling	Cell swelling/ contraction
	Cell membrane	The cell membrane bubbles to maintain structural integrity	Pores form, cell membranes rupture, and their integrity is lost	Pores form, cell membranes rupture, and their integrity is lost	Pores form, cell membranes rupture, and their integrity is lost
	Nucleus	Nucleolus disappeared, chromatin condensed and broke down into 180–200bp nucleotide fragments	Nucleus is concentrated, chromatin DNA is broken and degraded	Nuclear chromatin does not agglomerate	Nuclear chromatin condensation
	Organelle	Organelle condensation	Mitochondrial and lysosome structures are damaged and gradually dissolved	Mitochondria and endoplasmic reticulum swell and disintegrate	Organelle swelling
	Cytoplasm	Cytoplasmic shrinkage and apoptotic bodies were formed	Osmotic swelling, contents released out of the cell	Osmotic swelling, contents released out of the cell	–
Biochemical characteristics		Activation of caspases, activation of DNA fragments	Caspase-1 activation, GSDMD cleavage, proinflammatory cytokine release	RIPK1, RIPK3 and MLKL are activated, necrotic bodies are formed, and reactive oxygen species are produced	PANoptosome assembly
Immune characteristics		No cell contents are released	Release inflammatory mediators	Release inflammatory mediators	Release inflammatory mediators
Microstructure		Apoptotic body	Pyrogenic corpuscle	Necrosome	PANoptotic body
Sensors/ Regulators		RIPK1, FADD, APAF	NLRP1, NLRP3, NLRC4, AIM2, Pyrin	RIPK1, RIPK3, MLKL	ZBP1, AIM2, NLRC4, R1PK1, NLRP12
Effector protein		Caspase-3, Caspase-6 and Caspase-7	The GSDMD family	MLKL protein	Caspase-3/6/7, Caspase-1/4/5/11, MLKL

adversely influence ZBP1-mediated PANoptosis during the process of PANoptosis caused by IFN and NEI. When ADAR1 is limited to the nucleus by NEI treatment, ZBP1 can promote PANoptosis unfettered in the cytoplasm. ADAR1 is the only protein in mammals, aside from ZBP1, that contains the Zα domain. It is located in the cytoplasm, where it competes with RIPK3 for binding to ZBP1, thereby suppressing cell death.[49] Nevertheless, ZBP1 can promote PANoptosis in the cytoplasm without interference when ADAR1 is restricted to the nucleus to hamper its RNA editing activity by IFN-γ and NEI KPT-330 therapy.[49] Zheng et al demonstrated that caspase-6 is a critical molecule in the regulation of ZBP1-mediated PANoptosis. Through its interaction with RIPK3, caspase-6 facilitates the binding of ZBP1 to itself, thereby promoting the formation of the ZBP1-PANoptosome.[50]

AIM2 PANoptosome

AIM2 is a cytoplasmic innate immunological pattern recognition receptor that functions as an inflammasome sensor in pyroptosis and may identify pathogens and endogenous double-stranded DNA (dsDNA).[51] The AIM2 protein is composed of two domains: the pyrin domain (PYD) and the DNA-binding HIN domain.[52] To facilitate complex formation and PCD induction, the AIM2 hIN domain interacts with ASC via PYD and detects cytoplasmic DNA.[51–54] Following an infection with the herpes simplex virus type 1 (HSV-1) or Francisella novicida, AIM2 PANoptosome is described. In wild-type (WT) bone marrow-derived macrophages (BMDM), infection with HSV1 and Francisella

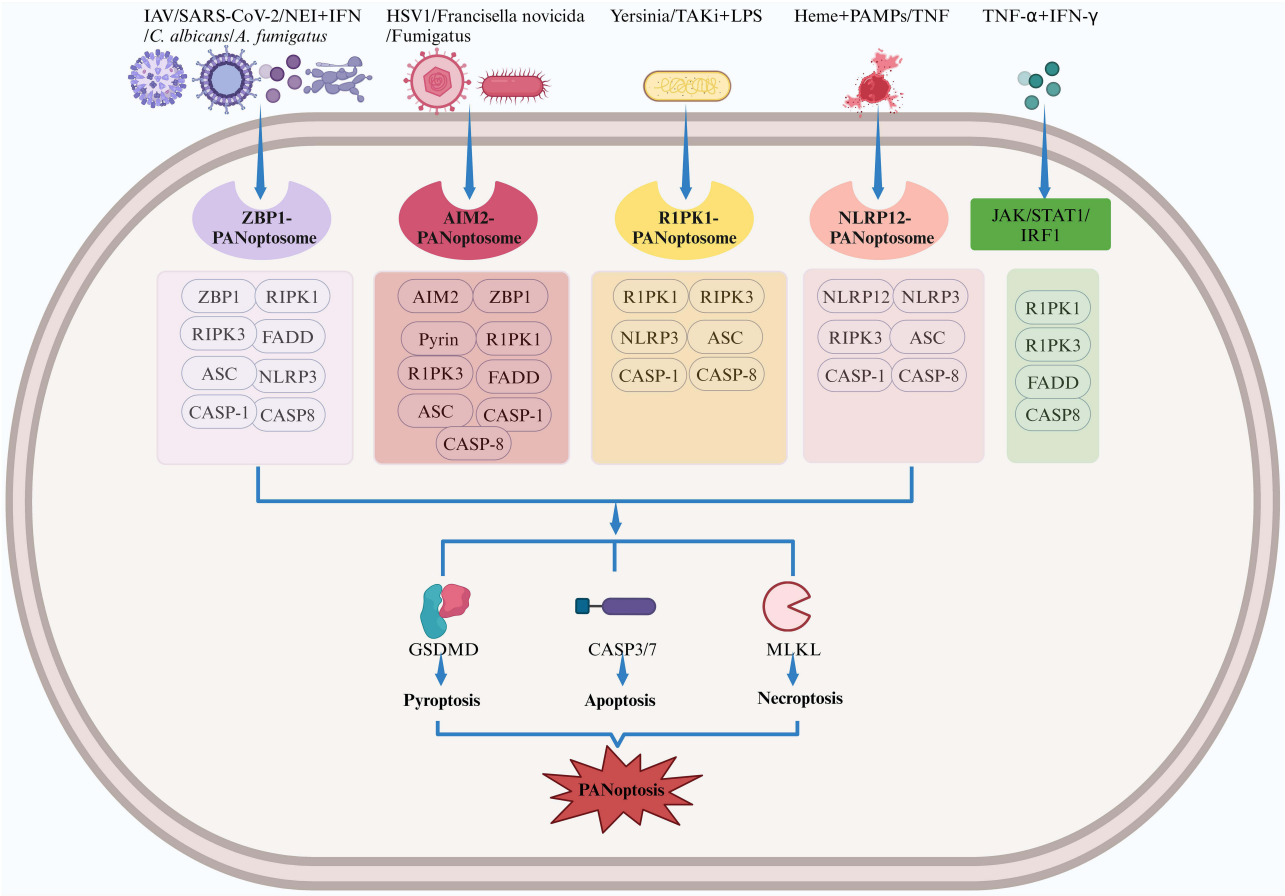

Figure 4 Composition of PANoptosome. Sensors like ZBP1, AIM2, RIPK1, and NLRP12 can interact and recruit many molecules to form PANoptosomes, which are referred to as ZBP1-PANoptosome, AIM2-PANoptosome, RIPK1-PANoptosome, and NLRP12-PANoptosomes, in response to stimuli like multiple microbial infections and changes in cell homeostasis. These PANoptosomes also cause MLKL phosphorylation, GSDMD and GSDME cleavage, and caspase-3/7 activation, which results in membrane hole formation and the advancement of PAN apoptosis. The figure is Created in BioRender. Jia, Y. (2024) https://BioRender.com/y38h055.

novicida was found to activate key molecules of the apoptosis, pyroptosis, and necroptosis pathways.[55] However, in Mefv$^{-/-}$ (the gene encoding Pyrin) and ZBP1$^{-/-}$ BMDMs, there was a decrease in the activity of these important molecules.[55] The complete deactivation of BMDMs from AIM2–/–, Mefv–/–, and ZBP1–/– mice suggests that the synergistic activation of AIM2 in conjunction with Pyrin and ZBP1 is essential for the induction of PANoptosis in response to HSV-1 and Francisella novicida infections.[55] Therefore, AIM2, Pyrin, and ZBP1 bind with ASC to create a multiprotein complex known as the AIM2 PANtosome, which includes ASC, RIPK3, RIPK1, FADD, Caspase-1, and Caspase-8 molecules. This complex is formed after infection. Pyrin and ZBP1 are less expressed when AIM2 is lost, indicating that AIM2-mediated upstream signaling regulates Pyrin and ZBP1 to regulate the formation and initiation of AIM2 PANtosomes.[55] A recent study demonstrated that a shared immune response, along with the activation of PANoptotic pathways mediated by AIM2, pyrin, and ZBP1 at distinct time points, was revealed through time-course transcriptomics.[56] This analysis provided insights into the dynamic immunological landscape of mice with Aspergillus fumigatus-induced fungal keratitis.[56]

RIPK1 PANoptosome

In addition to being a crucial mediator of inflammation and cell death, RIPK1 is also involved in the regulation and activation of necroptosis and apoptosis.[57,58] The assembly of the RIPK1 PANoptosome occurs in response to Yersinia infection. In wild-type bone marrow-derived macrophages (BMDM) infected with Yersinia, we observed the activation

of pyroptosis markers, including Caspase-1 and GSDMD.[59] Additionally, the apoptosis initiator Caspase-8 and executioners Caspase-3 and Caspase-7 were also activated, along with the phosphorylation of MLKL, which is essential for the activation of necroptosis.[59] Yersinia-induced cell death was eliminated as a consequence of the simultaneous loss of important cell death activators, pyroptosis, apoptosis, and necroptosis.[59] In addition, Western blot analysis showed that in order to construct the RIPK1 PANoptosome, RIPK1 joined forces with Caspase-8, FADD, NLRP3, ASC, and RIPK3, thereby regulating the PANoptosis induced by Yersinia infection.[59] Unlike AIM2 and ZBP1-mediated PANoptosis, cell death is not entirely inhibited from activating in the absence of RIPK1. Deletion of RIPK1 resulted in reduced apoptosis and pyroptosis induced by Yersinia, but enhanced necroptosis. Yersinia-induced apoptosis and pyroptosis were decreased when RIPK1 was deleted, whereas necroptosis was increased.[60] While the RIPK1 kinase activity induced by LPS/TNF is not essential for cell death and inflammasome activation in transforming growth factor β-activated kinase 1 (TAK1)-deficient macrophages, it is important to emphasize that both Yersinia infection and TAK1 inhibitor-induced cell death and inflammasome activation depend on RIPK1 kinase activity.[60] In TAK1-deficient cells, this combination promotes PANoptosis and inflammasome activation.[60] Using a whole-genome CRISPR screen, Malireddi et al's study found that RAVER1 and polypyrimidine tract-binding protein 1 (PTBP1) are important regulators of activation of TAK1 inhibition-induced PANoptosis.[61] To completely comprehend the mechanisms of its assembly and activation, more research is necessary as the significance of RIPK1 PANoptosome in TAK1 loss remains unknown.

Other Types of PANoptosome

The components of the PANoptosome react to various infections and endogenous danger signals primarily through specific sensors. Additionally, other infections, including Salmonella typhimurium, Listeria monocytogenes, and vesicular stomatitis virus (VSV), have been demonstrated to activate PANoptosis.[62] The regulatory mechanisms of PANoptosis are closely related to Caspase-1, Caspase-11, RIPK3, and Caspase-8.[62] In addition, other trigger factors can also activate PANoptosis. STING agonists in the airway directly trigger STING and IFN-dependent PANoptosis.[63] Tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ) together induce IRF1-dependent PANoptosis during SARS-CoV-2 infection.[64] The regulatory mechanism involved is associated with the Janus kinase (JAK)/Signal Transducer and Activator of Transcription 1 (STAT1)/IRF1 axis.[63–65] However, the composition and assembly mechanisms of the PANoptosome remain unclear and require further investigation. Recent studies have identified a key role of NLR family pyrin domain containing 12 (NLRP12)-mediated PANoptosis in the innate immune response. Significant upregulation of NLRP12 was observed in both mouse and human macrophages, suggesting that NLRP12 is required to specifically drive inflammatory cell death in response to heme plus PAMPs stimulation in mouse and human cells.[66] The pathway can drive apoptosis in phagocytes through the Caspase-1/Caspase-8/RIPK3-dependent mechanism.[66] Additionally, toll-like receptors 2 (TLR2) and 4 (TLR4) serve as upstream regulators that can induce signal transduction via IRF1, subsequently upregulating the expression of NLRP12.[66]

The Involvement of Apoptosis, Pyroptosis, Necroptosis, and PANoptosis in Heart Failure

Role of Apoptosis in Heart Failure

Apoptosis is a pivotal stage in the course of cardiomyocyte loss, which is a key cause of HF. Research indicates that a substantial association exists between HF and cardiomyocyte apoptosis, as seen by the 0.08% ~ 0.25% apoptosis rate in HF patients, which is 10 to 100 times more than the typical control group's (0.001% ~ 0.01%).[67,68] In a sample of heart muscle drawn from 36 heart transplant recipients and three myocardial infarction patients, the end-stage HF group showed a 232-fold rise in cardiomyocyte apoptosis in contrast to the control group.[69] The hallmark alterations of apoptosis, such as DNA strand breaks, chromatin aggregation, and nuclear fragmentation, were seen by confocal microscopy and histochemical examination.[69] The Western Blot experiment revealed that HF patients had 1.8 times more muscle cells tagged with BCL2, a protein that prevents cells from dying.[69] This finding indicates that cardiomyocyte apoptosis occurs in HF and that Compensatory procedures are triggered in the overworked heart muscle to maintain cell survival.[69] There is mounting evidence that HF can be lessened or perhaps prevented by blocking apoptosis. A rat

model of heart failure (HF) following myocardial infarction was established by ligating the coronary arteries.[70] The rats were subsequently divided into two groups: one group received treatment with caspase inhibitors, while the other group did not.[70] Compared to the untreated group, there was a notable decrease in the cardiac contractile protein troponin-I, the number of apoptotic cardiomyocytes, and the activity of Caspase-3, a key effector in cardiac apoptosis.[70] Furthermore, the use of apoptosis pathway inhibitors may mitigate systolic dysfunction and reduce left ventricular remodeling during myocardial infarction, as evidenced by the observed decrease in myocardial interstitial collagen deposition and the attenuation of left ventricular remodeling.[70] Furthermore, several studies have demonstrated that by blocking apoptosis, HF treatments can have a cardioprotective effect. Zhang et al demonstrated that treatment with the angiotensin-converting enzyme inhibitor captopril in transverse aortic constriction-induced heart failure (HF) exhibits a cardioprotective effect.[71] This effect may be attributed to the inhibition of cardiac hypertrophy and apoptosis, which is mediated by the Jak2/Stat3 and Wnt3a/β-catenin pathways.[71] Sung et al showed that the mechanism by which angiotensin II receptor antagonists (sacubitril/valsartan) ameliorate myocardial ischemia-reperfusion injury is related to the inhibition of cardiomyocyte apoptosis.[72] Ren et al demonstrated that the sodium-glucose cotransporter protein 2 inhibitor, dapagliflozin, mitigate myocardial injury by upregulating SIRT1 expression and inhibiting the PERK-eIF2α-ATF4-CHOP pathway, thereby reducing apoptosis mediated by endoplasmic reticulum stress.[73] Therefore, more information about the processes by which HF regulates apoptosis is needed. Targeting and controlling HF is a promising area for medicinal medicines and the development of pathway inhibitors.

The Role of Pyroptosis in Heart Failure

The activation of inflammatory bodies is a hallmark of pyroptosis, a form of programmed cell death closely linked to inflammation. The death of cardiomyocytes resulting from pyroptosis can directly affect the number of functional cardiomyocytes, thereby influencing the systolic and diastolic function of the myocardium and promoting cardiac remodeling in patients with HF.[74] A study utilizing cardiac specimens from patients with dilated cardiomyopathy (DCM) provides the first evidence of cardiomyocyte pyroptosis in human cardiac tissue in vivo, as derived from the GEO (Gene Expression Omnibus) dataset.[75] The findings indicate that the DCM group exhibited increased GSDMD lysis and significantly elevated expression of the NLRP3 inflammasome/IL-1β axis when compared to healthy controls.[75] This suggests that DCM patients may have active NLRP3 inflammasomes, which could lead to cardiomyocyte pyroptosis and, consequently, accelerate the progression of DCM.[75.] The existence of pyroptosis has been confirmed in various animal models. In calcineurin transgenic (CNTg) mice models of HF, cardiomyocyte pyroptosis is facilitated by elevated levels of NLRP3 messenger RNA (mRNA) and increased cleavage of Caspase-1, ultimately leading to myocardial dysfunction and the progression of HF.[76] Genetic ablation of NLRP3 or the use of IL-1 receptor antagonists can reduce pro-inflammatory cytokine production, inhibit inflammasome activation, and mitigate cardiac inflammation, thereby slowing the progression of HF.[76] Along with pyroptosis pathway inhibitors, pyroptosis's function in various medications' cardiac protection has been gradually identified. Both Singla et al and Zhang et al demonstrated that elevated expression levels of pyroptosis markers and inflammatory vesicles resulted in the activation of pyroptosis in a doxorubicin (Dox)-induced heart failure model.[77,78] In contrast, both embryonic stem cell-derived exosomes (ES-Exos) and bardoxolone methyl mitigated Dox-induced pyroptosis and cardiac remodeling through mechanisms associated with the MyD88/p-P38/p-JNK pathway and the TXNIP-NLRP3 pathway, respectively.[77,78] Audia et al demonstrate a reduction in myocardial infarct size and an improvement in ventricular function through the inhibition of caspase-1 expression, utilizing a P2Y12 receptor antagonist alongside the cysteine aspartic acid protease-1 inhibitor VX-765 in a myocardial ischemia-reperfusion model.[79] Wang et al demonstrated that miR-351 protects against ventricular remodeling in heart failure (HF) by inhibiting the expression of mixed lineage kinase 3 (MLK3) in a mouse model of transverse aortic constriction-induced myocardial fibrosis.[80] This protective mechanism is associated with the NF-κB/NLRP3 signaling pathway-mediated pyroptosis.[80] To avoid cardiac damage from coronary microembolization, rosuvastatin therapy decreased the production of lytic caspase 1, IL-1β, and GSDMD-N.[81] This in turn inhibited the activation of NLRP3 inflammasome.[81] By blocking the TNF-α, IL-6, IL-1β, and NLRP3 inflammasome activation, which inhibits pyroptosis and inflammation, metformin lowers the extent of myocardial infarction and myocardial fibrosis.[82] Targeted modulation of pyroptosis therefore has a beneficial therapeutic implication in slowing the advancement of HF.

Role of Necroptosis in Heart Failure

A form of necrotic cell death that is not controlled by caspase is called necroptosis. Necroptosis is implicated in the ventricular remodeling process and exacerbates HF, according to recent studies. The research discovered that failing human hearts had higher levels of the major mediators of necroptosis—RIPK1, RIPK3, MLKL, and their phosphorylated forms—than healthy controls did.[83] Furthermore, there was a notable decline in the expression of Caspase-8, the negative regulator of necroptosis, suggesting that necroptosis was activated.[83] Research indicates that following myocardial infarction, RIPK3-dependent necroptosis regulates unfavorable cardiac remodeling in mice models. Moreover, 30 days after myocardial infarction, RIPK3 deletion can lessen ventricular dysfunction, hypertrophy, and inflammation.[84,85] The findings of receiver operating characteristic curve (ROC) and Kaplan-Meier (K-M) survival analyses also suggested that high RIPK3 plasma concentrations were an independent risk factor for a poor prognosis in HF, raising the possibility that it could be used as a biomarker for HF diagnosis and prognosis.[86] Tetsuro et al demonstrated that similar upregulation of necroptosis proteins in a mouse model of chronic heart failure caused by prolonged pressure overload with transverse aortic constriction.[87] Multiple studies have shown that a heat-shock protein (Hsp) 90 inhibitor, catecholamines, hydrogen sulfide, AM404 (N-arachidonoylphenolamine), and GSK2795039 (NADPH oxidase 2 inhibitor) attenuated necroptosis in cardiomyocytes by inhibiting activation of the RIPK1-RIPK3-MLKL pathway.[87–91] In a model of myocardial ischemia/reperfusion (I/R) injury, Gao et al demonstrated that decreased levels of mmu_circ_000338, a cardiac-necroptosis-associated circRNA (CNEACR), were observed alongside increased nuclear activity of histone deacetylase (HDAC7).[92] This resulted in cardiomyocyte necrotic apoptosis during the progression of I/R injury by inhibiting Foxa2 and RIPK3, which in turn causes necroptosis in cardiomyocytes.[92] This suggests that the CNEACR/HDAC7/Foxa2/RIPK3 pathway may be a powerful target for mitigating myocardial injury due to necroptosis in HF.[92] In addition to MLKL as a substrate, it was found that calcium/calmodulin-dependent protein kinase II (CaMKII) can also act as a substrate for RIPK3 and mediate necroptosis in cardiomyocytes through the RIPK3-CaMKII-mitochondrial permeability transition pore (mPTP) signaling pathway.[93] By preventing CaMKII activation, Hua et al found that the RIPK3 inhibitor GSK′872 reduced oxidative stress and necrotic apoptosis and improved cardiomyocyte damage.[94] All things considered, these studies indicate that necroptosis is a key factor in the pathogenesis of HF and cardiac remodeling. It can also participate in the pathophysiology of HF by initiating the signaling pathways RIPK3-CaMKII-mPTP and RIPK1-RIPK3-MLKL mediated necroptosis, which makes necroptosis an encouraging target for HF therapy.

The Function of PANoptosis in Heart Failure

PANoptosis' Involvement in Mediating Inflammation in Heart Failure

HF is characterized as a chronic inflammatory process, with systemic inflammatory response being one of the primary pathophysiological mechanisms underlying the condition. A systemic proinflammatory state is a hallmark of HF, and the inflammatory response plays a critical role in both the onset and progression of the disease. Furthermore, the severity and prognosis of HF are closely correlated with the levels of circulating inflammatory markers.[7] A prospective study enrolled 8089 patients with existing cardiovascular disease but no HF at baseline, with a median follow-up of 9.7 years.[95] The results indicated that patients with higher baseline C-reactive protein (CRP) levels had a significantly increased risk of developing HF; specifically, for each 1 mg/L increase in CRP, the risk of HF increased by 10%.[95] Notably, the risks of HF with reduced ejection fraction and HF with preserved ejection fraction increased by 9% and 12%, respectively.[95] Additionally, another prospective multi-center study demonstrated that 83.7% of patients with acute heart failure exhibited significantly elevated plasma IL-6 concentrations, with quantitative IL-6 levels serving as a powerful and independent predictor of mortality within one year in patients with acute heart failure.[96] Both necroptosis and pyroptosis are inflammatory forms of PCD that can produce substantial quantities of cytokines, thereby promoting inflammation. Initially, apoptosis was considered an immune-silenced form of PCD. However, components of non-inflammatory apoptosis may interact with molecules that facilitate the inflammatory and lytic processes associated with PCD.[24,97] Therefore, PANoptosis plays a crucial function in the inflammatory response by activating associated inflammatory pathways and promoting the release of inflammatory factors.[23,98,99] Research indicates that RNA-binding proteins (RBPs) serve as crucial post-transcriptional regulators of inflammation and immune responses, with dysregulation of

RBPs potentially leading to chronic inflammation and autoimmunity.[100] During inflammatory processes in HF, immune cells infiltrate cardiac tissue, contributing to tissue damage responses.[100] This study screened RBP-based subtype-related genes to identify genes associated with HF risk, termed "characteristic genes".[100] The findings revealed that the majority of characteristic genes were negatively correlated with the abundance of immune cells in HF.[100] However, GRWD1 was positively correlated with most immune cell types.[100] Additionally, the characteristic genes demonstrated significant associations with PANoptosis genes, suggesting their involvement in mediating functions related to cardiac inflammation.[100] Nevertheless, further experiments are required to validate their regulatory roles in inflammation, immune responses, and PANoptosis in the context of HF.[100]

Apoptosis, pyroptosis, and necroptosis influence the development of chronic heart failure through mutual crosstalk and coordinated regulation. In doxorubicin (dox) -induced HF mouse models, simultaneous occurrences of cardiomyocyte apoptosis and pyroptosis have been confirmed.[101] The study observed that levels of NLRP3, ASC, Caspase-1, IL-1β, IL-18, IL-6, and Bax were elevated in the DOX group, while levels of Bcl-2, STAT3, and p-STAT3 were reduced, indicating the activation of apoptosis and pyroptosis.[101] Furthermore, the application of a therapeutic agent for HF, Radix Aconiti Lateralis Preparata, can mitigate inflammation and protect cardiac function in HF mice by inhibiting NLRP3 inflammasome-mediated pyroptosis and the IL-6/STAT3 pathway-induced apoptosis.[101] The simultaneous occurrence of cardiomyocyte apoptosis and necroptosis has been observed in both doxorubicin (dox)-induced HF and post-myocardial infarction HF models.[102,103] Studies have demonstrated that dox can induce HF and diminish cardiomyocyte viability by promoting both apoptosis and necroptosis in vivo and in vitro.[102] Furthermore, Dexrazoxane, a drug that mitigates anthracycline-induced cardiac injury, has been shown to reduce doxorubicin-induced apoptosis and necroptosis in cardiomyocytes, thereby enhancing cardiotoxicity management and preserving cardiac function.[102] Additionally, research involving dox-treated cardiomyocytes revealed that GSK2795039, a novel small molecular inhibitor of NADPH oxidase 2 (Nox2), improved cell viability, decreased apoptosis, and necrosis, and inhibited the phosphorylation of RIP1 and RIP3 while increasing the expression of phosphorylated MLKL.[91] In the context of post-myocardial infarction HF models, the distribution of autophagy, apoptosis, and necroptosis was found to vary across different temporal and spatial contexts following myocardial infarction.[103] Moreover, hepatocyte growth factor (HGF) significantly reduced the levels and activity of caspase 8.[103] The sequestration of Bax by Bcl-2 renders Bax inactive, thereby promoting necroptosis while inhibiting apoptosis.[103] This suggests that HGF enhances recovery from myocardial infarction in rats by facilitating autophagy and necroptosis while suppressing apoptosis. Crosstalk between cardiomyocyte apoptosis, pyroptosis, and necroptosis has been demonstrated in a model of post-myocardial infarction HF.[104] In a rat model of HF induced by permanent left anterior descending coronary artery ligation, simultaneous activation of apoptosis, pyroptosis, and necroptosis was observed, with pyroptosis identified as the predominant pathological component.[104] Furthermore, cardiac mitochondrial dysfunction and imbalances in mitochondrial dynamics have been implicated in mediating myocardial injury and HF following myocardial infarction.[104] To assess the effects of mitochondrial dynamics-targeted therapy on cell death in HF, the study administered enalapril along with mitochondrial dynamics regulators (including Mdivi-1 and M1) to rats with post-myocardial infarction HF.[105] The intervention resulted in a reduction of mitochondrial dynamics imbalance and significantly attenuated the activation of apoptosis, necroptosis, and pyroptosis, leading to improved cardiac pathological remodeling and enhanced left ventricular function.[105] These findings underscore the crosstalk between apoptosis, pyroptosis, and necroptosis in HF, with recent studies further supporting the role of PANoptosis in this condition. PANoptosome complexes are formed in cardiac tissue, including increased levels of AIM2, ZBP1, and Pyrin (a basic member of PANoptosome), in dilated cardiomyopathy sufferers and mice with doxorubicin-induced heart injury.[106] Active versions of Caspase-1 and GSDMD (pyrogenic markers), active types of Caspase-3 and Caspase-8 (apoptotic markers), and phosphorylation of MLKL, RIPK1, RIPK3 (necrotic apoptotic markers).[106] In addition, the dysregulation of PANoptotic genes observed in HF also provides evidence for the involvement of PANoptosis in the process of HF. In a study examining RNA-binding proteins for the diagnosis of HF risk, the dysregulation of PANoptosis genes in left ventricular myocardial specimens from human HF patients, compared to controls, suggests a potential association between PANoptosis and HF.[100] Additionally, there was significant heterogeneity observed in PANoptosis genes across the three subtypes of RNA-binding proteins.[100] Recent studies have demonstrated that PANoptosis occurs in mouse models of HF following myocardial infarction. After treatment with isoproterenol (ISO), markers of pyroptosis

(NLRP3/Cleaved-caspase1/N-GSDMD), apoptosis (Cleaved-caspase3), and necroptosis (p-RIP1/p-RIP3/p-MLKL) were significantly upregulated.[107] Furthermore, the Xian Ling Gu Bao capsule was shown to reverse myocardial damage post-myocardial infarction by inhibiting the NLRP3/Caspase3/RIP1-mediated PANoptosis pathway.[107] Two recent studies confirmed the occurrence of PANoptosis during myocardial ischemia/reperfusion injury.[108,109] One study established a rat model induced by myocardial ischemia-reperfusion injury, revealing that penehyclidine hydrochloride significantly reduced the expression levels of PANoptosis regulatory proteins by inhibiting ZBP1 expression.[108] This suggests that the therapeutic effect of penehyclidine hydrochloride in improving myocardial ischemia/reperfusion injury may be linked to its targeting of ZBP1-mediated PANoptosis.[108] Another study indicated that the mechanosensitive Piezo1 channel exacerbates myocardial ischemia/reperfusion injury by activating caspase-8-mediated PANoptosis.[109] Collectively, these studies provide a foundation for addressing PANoptosis in HF induced by various models.

In addition to the presence of PANoptosis observed in animal and human models of HF, several risk factors associated with HF have also confirmed that PANoptosis contributes to its onset and progression. Olcum M et al induced desmoplakin variant cardiomyopathy by knocking out the DSP gene in MerCreMer mice.[110] They found that the genetic inactivation of β-catenin could prolong the survival of these mice, improve cardiac function, and alleviate myocardial fibrosis. Additionally, they observed cell death in the myocardium caused by apoptosis, necroptosis, and pyroptosis (PANoptosis).[110] On the contrary, the activation of β-catenin has the opposite effect, suggesting that inhibiting but not activating β-catenin may be beneficial to desmosomal macular protein variant cardiomyopathy, and the mechanism may be closely related to PANoptosis.[110] One of the risk factors for HF is atherosclerosis (AS), a chronic inflammatory disease. Recent research indicates that PANoptosis plays a critical role in the development of AS. The study conducted by Chen et al revealed two subtypes of atherosclerosis based on PANoptosis through consensus clustering.[111] Additionally, the researchers screened 36 differential genes linked to these subtypes and identified tartrate-resistant acid phosphatase 5 (ACP5) and heme oxygenase 1 (HMOX) as PANoptosis-related AS through immunoimmune infiltration assay, single-cell analysis, and polymerase chain reaction (PCR) diagnostic genes.[111] These genes may play a role in the pathogenesis of AS by controlling macrophage PANoptosis. The study by Zheng et al identified four additional key differentially expressed genes (ZBP1, SNHG6, DNM1L, and AIM2) associated with PANoptosis, which exhibit significant diagnostic potential for AS and were further validated through animal and cell experiments.[112] Additionally, the study revealed that these key differentially expressed genes are strongly correlated with immune cells, including T cells, macrophages, plasma cells, and mast cells. This study indicates a close relationship between PANoptosis and immune inflammation in the pathogenesis of AS.[112] However, further research is necessary to elucidate the underlying mechanisms of these key differentially expressed genes in relation to PANoptosis in AS. To investigate potential therapeutic targets for PANoptosis-mediated AS, the study also explored the potential candidate small molecule compound/drug signatures and upstream regulatory molecular signatures of the key differentially expressed genes associated with PANoptosis in AS, demonstrating that these genes are intricately linked to 109 distinct interactions between small molecules and drugs.[112] Nonetheless, further validation is required to confirm these findings.[112] The results obtained highlight the critical function of PANoptosis in the pathophysiological course of atherosclerosis, providing a novel target for the diagnosis of atherosclerosis.[111] Nevertheless, additional research and a substantial number of clinical samples are still required to confirm the efficacy of characteristic genes based on the PANoptotic subtype in atherosclerosis diagnosis.[111] PANoptosis plays a crucial role in the onset and progression of HF. Consequently, targeting PANoptosis to modulate inflammation presents promising therapeutic potential for delaying the advancement of HF.

Targeted Regulation of PANoptosis-Mediated Inflammation Plays a Therapeutic Role in HF

This plasticity in the PANoptosis pathway is a necessity for its regulation. Microbiological elements may specifically target the PANoptosis pathway during infection, resulting in different cell death modalities and changes in the composition of PANoptosomes. An essential part of the pathogenesis of HF is cardiac inflammation. It may be possible to delay the progression of HF by controlling important PANoptosis molecules, which inhibit myocardial inflammation and postpone cardiac remodeling. Potential therapeutic targets in HF are shown in Figure 5.

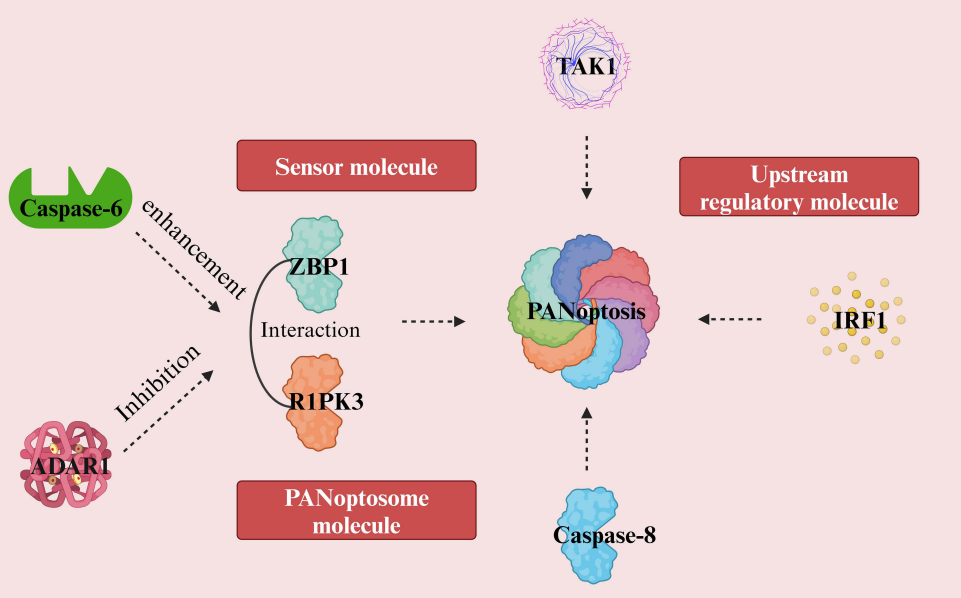

Figure 5 Potential therapeutic targets for regulating PANoptosis in heart failure. The figure illustrates upstream regulatory molecules (IRF1, TAK1), sensors (ZBP1), and associated components of the PANoptosome scaffold (RIPK3, Caspase-8, Caspase-6) as potential therapeutic targets for PANoptosis-mediated heart failure. The interaction between ZBP1 and RIPK3 is crucial for the formation of the ZBP1-PANoptosome, wherein ADAR1 and Caspase-6 exert inhibitory and promotional effects, respectively, on the binding process between ZBP1 and RIPK3. The figure is Created in BioRender. Jia, Y. (2024) https://BioRender.com/u92s643.

Targeting Upstream Regulatory Molecules

One of the key molecules in the control of inflammation and apoptosis is interferon regulatory factor (IRF), which was first shown to be a transcriptional regulator of type I interferon and IFN-inducible genes.[113] In response to PANoptosis, IRF1—unlike other IRFs—is a crucial regulator of TNF plus IFNγ and triggers PANoptosis. In contrast, human colon cancer cells that lack IRF1 are resistant to PANoptosis caused by TNF plus IFNγ.[65] Furthermore, the Janus kinase-IRF1 signaling pathway, which triggers cytokine storm and inflammatory disease, is responsible for inducing PANoptosis through the release of TNF and IFNγ after Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection.[64] It has been demonstrated that interferon (IFN) and nuclear export inhibitors, like KPT-330, can cause ZBP1-mediated PANoptosis. The study also discovered that IRF1 deletion drastically decreased IFN-γ plus KPT-330 induced PANoptosis and decreased the activation of important PANoptotic markers.[49,114,115] It was also observed that IRF1-deficient cells decreased the expression of ZBP1 mRNA and ZBP1 protein in response to IAV infection.[43] Moreover, AIM2- and RIPK1-dependent PANoptosis have been shown to exhibit a similar pattern.[114] IRF1 is an upstream regulator of NLRP12-PANoptosome activation, which controls NLRP12-mediated PANoptosis, according to recent research.[66] According to these findings, IRF1 triggers ZBP1-, AIM2-, RIPK1-, and NLRP12-dependent PANoptosis in response to inflammatory illnesses and infections.[66] Consequently, it is impossible to overlook IRF1's crucial involvement in HF, and further research is still needed to understand the underlying processes of this role. The expression of interferon regulatory factor 1 (IRF1) was significantly altered in both hypertrophic mouse hearts and failing human hearts. Cardiac-specific transgenic mice overexpressing IRF1 worsened cardiac hypertrophy, ventricular dilatation, fibrosis, and dysfunction; in contrast, mice lacking IRF1 had a significant reduction in hypertrophic response.[116] Therefore, IRF1 may be a useful therapeutic target for cardiac remodeling in HF. However, further research is still needed to fully understand the main mechanisms underlying IRF1's involvement in HF.

Transforming growth factor β-activated kinase 1 (TAK1) is a target for pathogen-mediated immune escape mechanisms and functions as a master regulator of PANoptosis silencing. When TAK1 deficiency results in a loss of cell homeostasis and releases RIPK1 kinase activity-dependent inflammatory signaling, NLRP3 inflammasome activation, and PANoptosis, TAK1 suppression of RIPK1 phosphorylation is pivotal in immune cells to prevent spontaneous activation of PANoptosis.[12] Nonetheless, it has been discovered that when TAK1 is inactivated, microbial triggering circumvents the need for RIPK1 kinase activity to promote PANoptosis, highlighting the difficulty in controlling

inflammatory cell death.[117] Prospective research for controlling TAK1 expression and PANoptosis in disease. Chen et al showed that by up-regulating TAK1 expression, Kongensin A (KA) preserves mitochondrial redox homeostasis, preventing nucleus pulposus cell PANoptosis and delaying the advancement of intervertebral disc degeneration.[118] According to Li et al, up-regulating TAK1 expression successfully prevents lipopolysaccharide-induced hepatocyte apoptosis.[119] Enteroendotoxemia, on the other hand, decreases TAK1 expression by binding to TLR4 molecules and encouraging hepatocyte apoptosis during acute liver damage.[110] Some investigations have demonstrated that cardiac hypertrophy and inflammation are lessened when TAK1 phosphorylation in cardiomyocytes is specifically inhibited.[120–122] Therefore, whether TAK1 delays the progression of HF by regulating PANoptosis still needs exact evidence, but the key role of TAK1 in PANoptosis is beyond doubt.

Targeting Sensors and PANoptosome Molecules

ZBP1 serves as a central regulatory molecule of PANoptosis, overseeing cell death signaling. In addition to this role, it functions as a sensor that detects aberrant signals, thereby promoting the assembly of scaffolds essential for cell death signaling. ZBP1-mediated PANoptosis plays a dual role in disease. While it facilitates the recruitment of immune cells and enhances adaptive immune responses that contribute to host survival, it also restricts the replication of intracellular pathogens.[47,123,124] Conversely, the excessive cell death induced by ZBP1 activation can lead to a detrimental inflammatory cytokine storm, resulting in organ dysfunction and potentially fatal outcomes for the host.[47,123,124] ZBP1-Dependent PANoptosis Forms Complexes with Cyclic GMP-AMP synthase (cGAS) and RIPK to Maintain Type I Interferon Signaling and Drive Cardiotoxicity, Limiting IAV- and SARS-CZBP1-Sensing Mitochondrial Genomic Instability. Mitochondrial DNA (mtDNA)-mediated sterile inflammation is known to play an important role in the development of HF.[125] Nobuyuki et al discovered that ZBP1 plays a protective function in HF and negatively controls mitochondrial DNA (mtDNA)-induced myocardial inflammation by blocking the RIPK3-NF-κB pathway in cardiomyocytes.[126] In contrast, ZBP1 deletion in mice exacerbates post-infarction remodeling.[126] However, in another experiment, when doxorubicin was added to mouse cardiomyocytes, higher levels of Z-type mtDNA, ZBP1 expression, and IFN-I signaling were observed.[127] Additionally, animals that did not express ZBP1 or IFN-I signaling were shielded from the cardiotoxicity caused by doxorubicin.[127] This suggests that ZBP1 acts as a partner to cGAS in maintaining interferon type I (IFN-I) responses to mitochondrial instability within the genome. Furthermore, it identifies ZBP1 as a suitable target for investigating the pathophysiology associated with interferons in HF (HF) and other conditions arising from mitochondrial DNA (mtDNA) stress.[127] Based on these findings, ZBP1 may be a new target for treatment to reduce myocardial inflammation and prevent HF from getting worse. Targeting the critical regulatory elements in ZBP1-mediated PANoptosis may be crucial to slowing the advancement of HF, even if it is unclear how precisely ZBP1 is regulated through the control of various cell death pathways. However, by focusing on crucial regulators in ZBP1-mediated PANoptosis, it might be possible to slow the advancement of HF. A recent study that examined ADAR1's interaction with ZBP1 revealed that ADAR1 constrains the link between ZBP1 and RIPK3 by engaging with ZBP1's Zα2 domain, hence inhibiting ZBP1-mediated PANoptosis.[49] The role of Caspase in the regulation of PANoptosis should not be ignored. Through its association with RIPK3, caspase-6 can facilitate the RHIM-dependent binding of RIPK3 to ZBP1 and the subsequent production of ZBP1-PANoptosomes.[50] A series of processes that culminate in cell death are set in motion when Caspase-8 is activated, functioning as a molecular switch. HF progression is directly linked to the regulation of Caspase-8 activity in PANoptosis, as activation of the enzyme was seen in rat models of myocardial ischemia-reperfusion, which resulted in myocardial remodeling after myocardial ischemia-reperfusion.[128] The evolution of HF is thus strongly associated with the regulation of caspase-8 enzyme activity in PANoptosis.

In conclusion, it is possible to target both upstream molecules of PANoptosis and related molecules of sensors and PANoptosome scaffolds for the regulation of the PANoptotic pathway. However, more research is needed to determine the precise mechanism of this pathway's role in HF, which will likely improve HF prevention and treatment.

The above discussion indicates that PANoptosis holds considerable therapeutic potential for HF. Consequently, it is essential to investigate effective therapeutic agents that target and regulate PANoptosis in the context of HF. Given that PANoptosis encompasses three distinct cell death pathways, traditional Chinese medicine, with its multi-target, multi-link, and multi-level treatment approach, aligns well with the mechanisms underlying PANoptosis. Previous studies have

demonstrated that traditional Chinese medicine offers several advantages in the treatment of HF, including enhanced exercise tolerance, improved quality of life, better cardiac function, delayed myocardial remodeling, and reduced mortality and rehospitalization rates.[129–131] The clinical evidence supporting the use of traditional Chinese medicine in H treatment continues to gain international recognition.[132] Furthermore, due to its diverse ingredients and the presence of various bioactive compounds, numerous studies have shown that both traditional Chinese medicine prescriptions and individual Chinese medicine monomers can influence multiple cell death pathways in the management of HF.[133–135] Recent research demonstrates that traditional Chinese medicine compounds target the PANoptosis signaling pathway to confer myocardial protection.[107] The study established an isoproterenol-induced myocardial infarction model in mice, revealing significant up-regulation of apoptosis markers (Cleaved-caspase3), pyroptosis markers (NLRP3/Cleaved-caspase1/N-GSDMD), and necroptosis markers (p-RIP1/p-RIP3/p-MLKL).[107] Notably, these alterations were significantly reversed by the administration of Xian Ling Gu Bao capsule, which also reduced the levels of inflammatory factors IL-1α, IL-1β, IL-6, and TNF-α.[107] This finding suggests that Xian Ling Gu Bao capsule mediates the PANoptosis signaling pathway to alleviate inflammation and provide cardioprotective effects.[107] However, the precise mechanism by which Xian Ling Gu Bao capsule influences myocardial damage following myocardial infarction remains unclear. Consequently, traditional Chinese medicine holds significant therapeutic potential by targeting PANoptosis-mediated inflammation to mitigate ventricular remodeling in HF. Table 2 summarizes traditional Chinese medicine prescriptions and monomers that target and regulate PANoptosis in the treatment of various diseases.

Summary and Prospect

PANoptosis is a highly coordinated and dynamically balanced programmed cell death pathway. It encompasses not only pyroptosis, apoptosis, and necroptosis occurring simultaneously within cells, but also represents a balanced and complementary cell death mechanism. When these pathways are inhibited, alternative signals may be activated to achieve similar effects or to enhance other death pathways. The systemic inflammatory response is one of the primary pathophysiological mechanisms underlying HF, and PANoptosis plays a significant role in infectious diseases, tumors, neurodegeneration, and other inflammatory conditions. Although apoptosis, pyroptosis, and necroptosis have been extensively studied in the context of HF, the pathogenesis of this condition cannot be fully elucidated through traditional cell death methods alone. PANoptosis integrates the fundamental components of pyroptosis, apoptosis, and necroptosis. In our analysis of PANoptosis and the three cellular pathways involved (pyroptosis, apoptosis, and necroptosis) in HF, we identified that targeting PANoptosis offers a promising avenue for developing more effective treatments for HF. We also propose potential therapeutic targets that regulate upstream signaling pathways, sensors, and components of the PANoptosome to modulate PANoptosis, thereby contributing to therapeutic interventions in HF. However, it remains unclear whether there are any novel sensor molecules or specific components of the PANoptosome implicated in HF. The regulatory mechanisms involved are not well understood, necessitating further research in this area. We believe that the multi-component and multi-target nature of traditional Chinese medicine may effectively address multiple cell death pathways, providing a valuable reference for the identification of effective therapeutic agents for HF. Furthermore, the connections and potential mechanisms linking HF and PANoptosis have yet to be fully elucidated. Current research on PANoptosis predominantly employs genome, transcriptome, proteome, and epigenome sequencing methodologies. Advanced technologies and radiomics can help identify molecular heterogeneity and clarify the relationship between PANoptosis and disease prognosis in a patient-specific context. Future studies should build upon this foundation to investigate the intricate relationship between HF and PANoptosis. Consequently, targeting PANoptosis emerges as a novel strategy for the prevention and treatment of HF, which holds significant implications for advancing treatment paradigms and enhancing therapeutic outcomes in this condition.

Abbreviations

HF, Heart failure; PCD, Programmed cell death; Caspase, cysteinyl aspartate specific proteinase; DR, Death receptor; BCL-2, B-cell lymphoma-2; GSDM, Gasdermin; LPS, lipopolysaccharide; IL-1β/18, Interleukin-1β/18; RIPK1, Receptor-interacting serine/threonine protein kinase 1; RIPK3, Receptor-interacting serine/threonine protein kinase 3; MLKL, Mixed lineage kinase domain like protein; TNF, Tumor necrosis factor; ZBP1, Z-DNA-binding protein 1; AIM2,

Table 2 Therapeutic Effects of Traditional Chinese Medicine Compounds and Monomers in Targeted Regulation of PANoptosis in Diseases

Chinese Medicine Name	Diseases	Models	Inducing Factors	Effects	Mechanisms	Ref
XiaoChaiHu decoction	SIC	Male SD rats, Male C57/BL6J mice, H9c2 cells	LPS	The expression of inflammatory cytokines (IL-6, IL-1β, and TNF-α)↓, the expression of PANoptosis markers (ZBP1, MLKL, Cleaved-caspase-3, Caspase-8, and NLRP3)↓	Mitigate inflammation-related myocardial damage by obstructing the PANoptosis pathway activated by ZBP1	[136]
Shengxian decoction	IPF	Male SD rats	Bleomycin	The expression of inflammatory factor (TNF-α, IFN-γ, IL-1β, IL-18)↓, the expression of PANoptosis-related proteins [ZBP1↓, (apoptotic pathway proteins, such as Bax, cleaved caspase-3, caspase-3↓, Bcl-2↑), (pyroptosis pathway proteins, such as NLRP3, cleaved caspase-1, caspase-1, and GSDMD↓), (necroptosis pathway proteins, such as RIPK1, RIPK3, p-MLKL, and MLKL↓)]	Improves lung function by inhibiting PANoptosis.	[137]
Si-Wu-Tang	NAFLD	Male and female C57BL/6 J mice, RAW264.7 cells, AML12 cells	MCD	The expression of pyroptosis (CASPASE 1 and NLRP3)↓, apoptosis (caspase-3, caspase-6)↓, and necrosis (MLKL, p-MLKL, IL-1β and p- RIPK3)↓, mtDNA synthesis and release from PANoptotic hepatocytes to macrophages↓	Suppress hepatocyte PANoptosis and macrophage M1 polarization by influencing intrahepatic release and intercellular transfer of mtDNA	[138]
Xian Ling Gu Bao capsule	MI	Male C57BL/6J mice	ISO	The expression of PANoptosis-related proteins [pyroptosis (NLRP3/Cleaved-caspase1 /N-GSDMD)↓, apoptosis (Cleaved-caspase-3)↓ and necroptosis (p-RIP1/p-RIP3/p-MLKL)↓, the expression of inflammatory cytokines (IL-1α, IL-1β, IL-6, and TNF-α)↓, mitochondrial ROS as well as MDA↓, CAT, SOD, GSH, and GSH-Px↑	Reverse myocardial damage following MI by inhibiting the NLRP3/Caspase3/RIP1-mediated PANoptosis	[107]
Dachengqi decoction dispensing granule	ALI	Alb/c mice, BEAS-2B cells	LPS	The expression of TNF-α, IL-1β and IL-18↓, the expression of PANoptosis-related proteins [ZBP1, RIPK1↓, pyroptosis (NLRP3, CASP1, and ASC)↓, apoptosis (CASPase8, CASPase3, Cleaved-caspase8, Cleaved-caspase3)↓ and necroptosis (p-MLKL)]↓, display co-localization of ZBP1 and RIPK1	Attenuate PANoptosis by inhibiting ZBP1-RIPK1-PANoptosome	[139]
Quercetin	Erebellum tissue damage	Male C57BL/6J mice, NS20Y	SiO_2	Cytoplasmic vacuolization, and inflammatory cell infiltration↓, oxidative stress↓, the activation of TLR4 pathway↓, the activation of ZBP-1 PANoptosome↓	Reduce cerebellum injury induced by ZBP-1 PANoptosis of mouse neuronal cells through ROS/TLR4/MyD88/TRAF6/NF-κB axis	[140]
Echinacea Polyphenols	ALI	Male C57BL/6J mice, J774A.1 macrophage cell line	LPS	The expression of NLRP3, GSDMD, caspase-8, caspase-3↓	Attenuate PANoptosis by suppressing NO Production	[141]
Curcumin	Cerebral I/R	Male C57BL/6J mice, MouseBV2, Mouse HT22	MCAO, OGD/R	The expression of [PANoptosome (AIM2, ZBP1 and pyrin)↓, pyroptosis (Pro-caspase-1, cleaved caspase-1, and GSDMD)↓, apoptosis (Pro-caspase-3, cleaved caspase-3, and caspase-8)↓ and necroptosis (RIPK1, RIPK3, and MLKL)]↓, the levels of pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6)↓, M2 polarization↑, M1 microglial polarization↓	Mitigate cerebral ischemia/reperfusion injury-induced neuronal PANoptosis by modulating microglial polarization	[142]
Curcumin	Human CEC injury	Male SD rats	TNF-α plus IFN-γ	Cleaved caspase-3, cleaved caspase-6, cleaved caspase-7, and cleaved poly (ADP-ribose) polymerase↓, MLKL, RIP3↓, cleaved caspase-1, IL1β and MCP-1, and MPO↓, the expression of intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1↓	Relieve CECs by inhibiting PANoptosis and reducing monocyte adhesion to CECs.	[143]
Scutellarin	HLH	BDMDs, J774A.1 macrophage cells	OXO plus LPS	The activation biomarkers for pyroptotic (Caspase-1p10 and GSDMD-NT)↓, apoptotic (cleaved Casp3/8/9 and GSDME-NT)↓, and necroptotic (phosphorylated MLKL)↓, block the assembly of PANoptosome that encompasses ASC, RIPK3, Caspase-8 and ZBP1, inhibit mitochondrial damage and mtROS generation	Inhibit inflammatory PANoptosis by diminishing mitochondrial ROS generation and blocking PANoptosome formation	[144]
Baicalin	HLH	BMDMs, J774A.1 macrophage cells	5Z-7-oxozeaenol (OXO) in combination with TNF-α or LPS	Prevent mitochondrial injury, block mtDNA release, Z-DNA formation and PANoptosome assembly (ZBP1, RIPK3, ASC, and caspase-8)↓, the levels of serum TNF-α and IFN-γ↓	Inhibits PANoptosis by blocking mitochondrial Z-DNA formation and ZBP1-PANoptosome assembly in macrophages	[145]

Notes: ↑ represents a decrease; ↓ represents an elevation.

Abbreviations: SIC, Sepsis-induced cardiomyopathy; SD, Sprague-Dawley; LPS, Lipopolysaccharide; IPF, Idiopathic pulmonary fibrosis; NAFLD, Non-alcoholic fatty liver disease; MCD, Methionine/choline-deficient diet; MI, Myocardial infarction; ISO, Isoprenaline; ROS, Reactive oxygen species; MDA, malondialdehyde; CAT, Catalase; SOD, GSH, Glutathione; and GSH-Px, glutathione peroxidase; ALI, Acute lung injury; SiO2, Silicon dioxide; NS20Y, Neuroblastoma cell; I/R, Ischemia-reperfusion; BV2, Microglia cells; HT22, Hippocampal neurons; MCAO, Middle cerebral artery occlusion; OGD/R, Oxygen and glucose deprivation/reoxygenation; CEC, Corneal endothelial cell; TNF-α, Tumor necrosis factor-alpha; IFN-γ, Interferon-gamma; BDMDs, Bone marrow-derived macrophages; HLH, Hemophagocytic lymphohistiocytosis; OXO, TAK1 inhibitor; mtROS, Mitochondrial reactive oxygen species.

Absent in melanoma 2; ASC, Apoptosis-associated speck-like protein containing a caspase recruitment domain; DAI, DNA-dependent activator of IFN regulators; IAV, Influenza A virus; IF, Immunofluorescence; Co-IP, Co-immunoprecipitation; IFN, Interferon; NEI, Nuclear export inhibitor; ADAR1, Adenosine deaminases acting on RNA; dsDNA, double-stranded DNA; PYD, Pyrin domain; HSV-1, Herpes simplex virus 1; WT, Wild-type; BMDM, Bone marrow-derived macrophages; TAK1, Transforming growth factor β-activated kinase 1; VSV, Vesicular stomatitis virus; IFN-γ, Interferon γ; IRF1, Interferon Regulatory Factor 1; JAK, Janus kinase; STAT1, Signal transducer and activator of transcription 1; NLRP12, NLR family pyrin domain containing 12; TLR2, Toll-like receptors 2; TLR4, Toll-like receptors 2; PTBP1, Polypyrimidine tract-binding protein 1; DCM, Dilated cardiomyopathy; GEO, Gene Expression Omnibus; CNTg, Calcineurin transgenic; mRNA, messenger RNA; IL-6, Interleukin-6; ROC, Receiver operating characteristic curve; K-M, Kaplan-Meier; MLK3, mixed lineage kinase 3; TAC, Transverse aortic constriction; ES-Exos, Embryonic stem cell-derived exosomes; Dox, Doxorubicin Hsp90, Heat shock protein 90; I/R, Ischemia/reperfusion; HDAC7, Histone deacetylase; mPTP, Mitochondrial permeability transition pore; CNEACR, Cardiac- necroptosis-associated circRNA; CaMKII, Calcium calmodulin dependent protein kinase II; RBP, RNA-binding protein; ACP5, Acid phosphatase 5; HMOX, Heme oxygenase 1; KA, Kongensin A; cGAS, Cyclic GMP-AMP synthase; MtDNA, mitochondrial DNA.

Data Sharing Statement

No data was used for the research described in the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

References

1. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Circulation*. 2022;145(18):e895–e1032. doi:10.1161/CIR.0000000000001063
2. Bragazzi NL, Zhong W, Shu J, et al. Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. *Eur J Prev Cardiol*. 2021;28(15):1682–1690. doi:10.1093/eurjpc/zwaa147
3. Brouwers FP, de Boer RA, van der Harst P, et al. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J*. 2013;34(19):1424–1431. doi:10.1093/eurheartj/eht066
4. Meyer S, Brouwers FP, Voors AA, et al. Sex differences in new-onset heart failure. *Clin Res Cardiol*. 2015;104(4):342–350. doi:10.1007/s00392-014-0788-x
5. Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med*. 2015;175(6):996–1004. doi:10.1001/jamainternmed.2015.0924
6. Murphy SP, Kakkar R, McCarthy CP, Januzzi JL. Inflammation in heart failure: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75(11):1324–1340. doi:10.1016/j.jacc.2020.01.014
7. Dutka M, Bobiński R, Ulman-Włodarz I, et al. Various aspects of inflammation in heart failure. *Heart Fail Rev*. 2020;25(3):537–548. doi:10.1007/s10741-019-09875-1
8. Aimo A, Castiglione V, Borrelli C, et al. Oxidative stress and inflammation in the evolution of heart failure: from pathophysiology to therapeutic strategies. *Eur J Prev Cardiol*. 2020;27(5):494–510. doi:10.1177/2047487319870344
9. Hanna A, Frangogiannis NG. Inflammatory cytokines and chemokines as therapeutic targets in heart failure. *Cardiovasc Drugs Ther*. 2020;34(6):849–863. doi:10.1007/s10557-020-07071-0

10. Briasoulis A, Androulakis E, Christophides T, Tousoulis D. The role of inflammation and cell death in the pathogenesis, progression and treatment of heart failure. *Heart Fail Rev*. 2016;21(2):169–176. doi:10.1007/s10741-016-9533-z
11. Martini E, Kunderfranco P, Peano C, et al. Single-cell sequencing of mouse heart immune infiltrate in pressure overload-driven heart failure reveals extent of immune activation. *Circulation*. 2019;140(25):2089–2107. doi:10.1161/CIRCULATIONAHA.119.041694
12. Malireddi RKS, Kesavardhana S, Kanneganti TD. ZBP1 and TAK1: master regulators of NLRP3 inflammasome/pyroptosis, apoptosis, and necroptosis (PAN-optosis). *Front Cell Infect Microbiol*. 2019;9:406. doi:10.3389/fcimb.2019.00406
13. Wang Y, Kanneganti TD. From pyroptosis, apoptosis and necroptosis to PANoptosis: a mechanistic compendium of programmed cell death pathways. *Comput Struct Biotechnol J*. 2021;19:4641–4657. doi:10.1016/j.csbj.2021.07.038
14. Kinloch RA, Treherne JM, Furness LM, Hajimohamadreza I. The pharmacology of apoptosis. *Trends Pharmacol Sci*. 1999;20(1):35–42. doi:10.1016/s0165-6147(98)01277-2
15. Wong RSY. Apoptosis in cancer: from pathogenesis to treatment. *J Exp Clin Cancer Res*. 2011;30(1):87. doi:10.1186/1756-9966-30-87
16. Hengartner MO. Apoptosis: corralling the corpses. *Cell*. 2001;104(3):325–328. doi:10.1016/s0092-8674(01)00219-7
17. Xu X, Lai Y, Hua ZC. Apoptosis and apoptotic body: disease message and therapeutic target potentials. *Biosci Rep*. 2019;39(1):BSR20180992. doi:10.1042/BSR20180992
18. Bertheloot D, Latz E, Franklin BS. Necroptosis, pyroptosis and apoptosis: an intricate game of cell death. *Cell Mol Immunol*. 2021;18(5):1106–1121. doi:10.1038/s41423-020-00630-3
19. Shi J, Gao W, Shao F. Pyroptosis: gasdermin-mediated programmed necrotic cell death. *Trends Biochem Sci*. 2017;42(4):245–254. doi:10.1016/j.tibs.2016.10.004
20. Kovacs SB, Miao EA. Gasdermins: effectors of Pyroptosis. *Trends Cell Biol*. 2017;27(9):673–684. doi:10.1016/j.tcb.2017.05.005
21. Galluzzi L, Kepp O, Chan FKM, Kroemer G. Necroptosis: mechanisms and relevance to disease. *Annu Rev Pathol*. 2017;12:103–130. doi:10.1146/annurev-pathol-052016-100247
22. Puri AW, Broz P, Shen A, Monack DM, Bogyo M. Caspase-1 activity is required to bypass macrophage apoptosis upon Salmonella infection. *Nat Chem Biol*. 2012;8(9):745–747. doi:10.1038/nchembio.1023
23. Rogers C, Erkes DA, Nardone A, Aplin AE, Fernandes-Alnemri T, Alnemri ES. Gasdermin pores permeabilize mitochondria to augment caspase-3 activation during apoptosis and inflammasome activation. *Nat Commun*. 2019;10(1):1689. doi:10.1038/s41467-019-09397-2
24. Wang Y, Gao W, Shi X, et al. Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin. *Nature*. 2017;547(7661):99–103. doi:10.1038/nature22393
25. Jiang M, Qi L, Li L, Li Y. The caspase-3/GSDME signal pathway as a switch between apoptosis and pyroptosis in cancer. *Cell Death Discov*. 2020;6:112. doi:10.1038/s41420-020-00349-0
26. Gutierrez KD, Davis MA, Daniels BP, et al. MLKL activation triggers NLRP3-mediated processing and release of IL-1β independently of gasdermin-D. *J Immunol*. 2017;198(5):2156–2164. doi:10.4049/jimmunol.1601757
27. Conos SA, Chen KW, De Nardo D, et al. Active MLKL triggers the NLRP3 inflammasome in a cell-intrinsic manner. *Proc Natl Acad Sci U S A*. 2017;114(6):E961–E969. doi:10.1073/pnas.1613305114
28. Sundaram B, Karki R, Kanneganti TD. NLRC4 deficiency leads to enhanced phosphorylation of MLKL and necroptosis. *ImmunoHorizons*. 2022;6(3):243–252. doi:10.4049/immunohorizons.2100118
29. Holler N, Zaru R, Micheau O, et al. Fas triggers an alternative, caspase-8-independent cell death pathway using the kinase RIP as effector molecule. *Nat Immunol*. 2000;1(6):489–495. doi:10.1038/82732
30. Li H, Zhu H, Xu CJ, Yuan J. Cleavage of bid by caspase 8 mediates the mitochondrial damage in the fas pathway of apoptosis. *Cell*. 1998;94(4):491–501. doi:10.1016/s0092-8674(00)81590-1
31. Newton K, Wickliffe KE, Dugger DL, et al. Cleavage of RIPK1 by caspase-8 is crucial for limiting apoptosis and necroptosis. *Nature*. 2019;574(7778):428–431. doi:10.1038/s41586-019-1548-x
32. Li X, Zhong CQ, Wu R, et al. RIP1-dependent linear and nonlinear recruitments of caspase-8 and RIP3 respectively to necrosome specify distinct cell death outcomes. *Protein Cell*. 2021;12(11):858–876. doi:10.1007/s13238-020-00810-x
33. Newton K, Wickliffe KE, Maltzman A, et al. Activity of caspase-8 determines plasticity between cell death pathways. *Nature*. 2019;575(7784):679–682. doi:10.1038/s41586-019-1752-8
34. Fritsch M, Günther SD, Schwarzer R, et al. Caspase-8 is the molecular switch for apoptosis, necroptosis and pyroptosis. *Nature*. 2019;575(7784):683–687. doi:10.1038/s41586-019-1770-6
35. Samir P, Malireddi RKS, Kanneganti TD. The PANoptosome: a deadly protein complex driving pyroptosis, apoptosis, and necroptosis (PANoptosis). *Front Cell Infect Microbiol*. 2020;10:238. doi:10.3389/fcimb.2020.00238
36. Yuan H, Zhou L, Chen Y, et al. Salmonella effector SopF regulates PANoptosis of intestinal epithelial cells to aggravate systemic infection. *Gut Microbes*. 2023;15(1):2180315. doi:10.1080/19490976.2023.2180315
37. Karki R, Kanneganti TD. The "cytokine storm": molecular mechanisms and therapeutic prospects. *Trends Immunol*. 2021;42(8):681–705. doi:10.1016/j.it.2021.06.001
38. C W, Jm G, Re T, Td K. Innate immune inflammatory cell death: pANoptosis and PANoptosomes in host defense and disease. *Eur J Immunol*. 2023. doi:10.1002/eji.202250235
39. Kuriakose T, Kanneganti TD. ZBP1: innate sensor regulating cell death and inflammation. *Trends Immunol*. 2018;39(2):123–134. doi:10.1016/j.it.2017.11.002
40. Takaoka A, Wang Z, Choi MK, et al. DAI (DLM-1/ZBP1) is a cytosolic DNA sensor and an activator of innate immune response. *Nature*. 2007;448(7152):501–505. doi:10.1038/nature06013
41. Rebsamen M, Heinz LX, Meylan E, et al. DAI/ZBP1 recruits RIP1 and RIP3 through RIP homotypic interaction motifs to activate NF-kappaB. *EMBO Rep*. 2009;10(8):916–922. doi:10.1038/embor.2009.109
42. Kesavardhana S, Malireddi RKS, Burton AR, et al. The Zα2 domain of ZBP1 is a molecular switch regulating influenza-induced PANoptosis and perinatal lethality during development. *J Biol Chem*. 2020;295(24):8325–8330. doi:10.1074/jbc.RA120.013752
43. Kuriakose T, Man SM, Malireddi RKS, et al. ZBP1/DAI is an innate sensor of influenza virus triggering the NLRP3 inflammasome and programmed cell death pathways. *Sci Immunol*. 2016;1(2):aag2045. doi:10.1126/sciimmunol.aag2045

44. Kesavardhana S, Kuriakose T, Guy CS, et al. ZBP1/DAI ubiquitination and sensing of influenza vRNPs activate programmed cell death. *J Exp Med*. 2017;214(8):2217–2229. doi:10.1084/jem.20170550
45. Zhang T, Yin C, Boyd DF, et al. Influenza virus Z-RNAs induce ZBP1-mediated necroptosis. *Cell*. 2020;180(6):1115–1129.e13. doi:10.1016/j.cell.2020.02.050
46. Banoth B, Tuladhar S, Karki R, et al. ZBP1 promotes fungi-induced inflammasome activation and pyroptosis, apoptosis, and necroptosis (PANoptosis). *J Biol Chem*. 2020;295(52):18276–18283. doi:10.1074/jbc.RA120.015924
47. Karki R, Lee S, Mall R, et al. ZBP1-dependent inflammatory cell death, PANoptosis, and cytokine storm disrupt IFN therapeutic efficacy during coronavirus infection. *Science Immunology*. 2022;7(74):eabo6294. doi:10.1126/sciimmunol.abo6294
48. Karki R, Kanneganti TD. ADAR1 and ZBP1 in innate immunity, cell death, and disease. *Trends Immunol*. 2023;44(3):201–216. doi:10.1016/j.it.2023.01.001
49. Karki R, Sundaram B, Sharma BR, et al. ADAR1 restricts ZBP1-mediated immune response and PANoptosis to promote tumorigenesis. *Cell Rep*. 2021;37(3):109858. doi:10.1016/j.celrep.2021.109858
50. Zheng M, Karki R, Vogel P, Kanneganti TD. Caspase-6 is a key regulator of innate immunity, inflammasome activation, and host defense. *Cell*. 2020;181(3):674–687.e13. doi:10.1016/j.cell.2020.03.040
51. Briard B, Place DE, Kanneganti TD. DNA sensing in the innate immune response. *Physiology*. 2020;35(2):112–124. doi:10.1152/physiol.00022.2019
52. Man SM, Karki R, Kanneganti TD. AIM2 inflammasome in infection, cancer, and autoimmunity: role in DNA sensing, inflammation, and innate immunity. *Eur J Immunol*. 2016;46(2):269–280. doi:10.1002/eji.201545839
53. Sharma BR, Karki R, Kanneganti TD. Role of AIM2 inflammasome in inflammatory diseases, cancer and infection. *Eur J Immunol*. 2019;49(11):1998–2011. doi:10.1002/eji.201848070
54. Hornung V, Ablasser A, Charrel-Dennis M, et al. AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. *Nature*. 2009;458(7237):514–518. doi:10.1038/nature07725
55. Lee S, Karki R, Wang Y, Nguyen LN, Kalathur RC, Kanneganti TD. AIM2 forms a complex with pyrin and ZBP1 to drive PANoptosis and host defence. *Nature*. 2021;597(7876):415–419. doi:10.1038/s41586-021-03875-8
56. Xu X, Wei Y, Pang J, et al. Time-course transcriptomic analysis reveals the crucial roles of PANoptosis in fungal keratitis. *Invest Ophthalmol Visual Sci*. 2023;64(3):6. doi:10.1167/iovs.64.3.6
57. Mifflin L, Ofengeim D, Yuan J. Receptor-interacting protein kinase 1 (RIPK1) as a therapeutic target. *Nat Rev Drug Discov*. 2020;19(8):553–571. doi:10.1038/s41573-020-0071-y
58. Newton K. RIPK1 and RIPK3: critical regulators of inflammation and cell death. *Trends Cell Biol*. 2015;25(6):347–353. doi:10.1016/j.tcb.2015.01.001
59. Malireddi RKS, Kesavardhana S, Karki R, Kancharana B, Burton AR, Kanneganti TD. RIPK1 distinctly regulates Yersinia-induced inflammatory cell death, PANoptosis. *Immunohorizons*. 2020;4(12):789–796. doi:10.4049/immunohorizons.2000097
60. Malireddi RKS, Gurung P, Kesavardhana S, et al. Innate immune priming in the absence of TAK1 drives RIPK1 kinase activity–independent pyroptosis, apoptosis, necroptosis, and inflammatory disease. *J Exp Med*. 2019;217(3):jem.20191644. doi:10.1084/jem.20191644
61. Malireddi RKS, Bynigeri RR, Mall R, et al. Whole-genome CRISPR screen identifies RAVER1 as a key regulator of RIPK1-mediated inflammatory cell death, PANoptosis. *iScience*. 2023;26(6):106938. doi:10.1016/j.isci.2023.106938
62. Christgen S, Zheng M, Kesavardhana S, et al. Identification of the PANoptosome: a molecular platform triggering pyroptosis, apoptosis, and necroptosis (PANoptosis). *Front Cell Infect Microbiol*. 2020;10:237. doi:10.3389/fcimb.2020.00237
63. Messaoud-Nacer Y, Culerier E, Rose S, et al. STING agonist diABZI induces PANoptosis and DNA mediated acute respiratory distress syndrome (ARDS). *Cell Death Dis*. 2022;13(3):269. doi:10.1038/s41419-022-04664-5
64. Karki R, Sharma BR, Tuladhar S, et al. Synergism of TNF-α and IFN-γ triggers inflammatory cell death, tissue damage, and mortality in SARS-CoV-2 infection and cytokine shock syndromes. *Cell*. 2021;184(1):149. doi:10.1016/j.cell.2020.11.025
65. Subbarao Malireddi RK, Karki R, Sundaram B, et al. Inflammatory cell death, PANoptosis, mediated by cytokines in diverse cancer lineages inhibits tumor growth. *Immunohorizons*. 2021;5(7):568–580. doi:10.4049/immunohorizons.2100059
66. Sundaram B, Pandian N, Mall R, et al. NLRP12-PANoptosome activates PANoptosis and pathology in response to heme and PAMPs. *Cell*. 2023;186(13):2783–2801.e20. doi:10.1016/j.cell.2023.05.005
67. Gao E, Lei YH, Shang X, et al. A novel and efficient model of coronary artery ligation and myocardial infarction in the mouse. *Circ Res*. 2010;107(12):1445–1453. doi:10.1161/CIRCRESAHA.110.223925
68. Guerra S, Leri A, Wang X, et al. Myocyte death in the failing human heart is gender dependent. *Circ Res*. 1999;85(9):856–866. doi:10.1161/01.RES.85.9.856
69. Olivetti G, Abbi R, Quaini F, et al. Apoptosis in the failing human heart. *N Engl J Med*. 1997;336(16):1131–1141. doi:10.1056/NEJM199704173361603
70. Chandrashekhar Y, Sen S, Anway R, Shuros A, Anand I. Long-term caspase inhibition ameliorates apoptosis, reduces myocardial troponin-I cleavage, protects left ventricular function, and attenuates remodeling in rats with myocardial infarction. *Journal of the American College of Cardiology*. 2004;43(2):295–301. doi:10.1016/j.jacc.2003.09.026
71. Zhang Y, Zhang L, Fan X, et al. Captopril attenuates TAC-induced heart failure via inhibiting Wnt3a/β-catenin and Jak2/Stat3 pathways. *Biomed Pharmacother*. 2019;113:108780. doi:10.1016/j.biopha.2019.108780
72. Sung PH, Chai HT, Yang CC, et al. Combined levosimendan and Sacubitril/Valsartan markedly protected the heart and kidney against cardiorenal syndrome in rat. *Biomed Pharmacother*. 2022;148:112745. doi:10.1016/j.biopha.2022.112745
73. Ren FF, Xie ZY, Jiang YN, et al. Dapagliflozin attenuates pressure overload-induced myocardial remodeling in mice via activating SIRT1 and inhibiting endoplasmic reticulum stress. *Acta Pharmacol Sin*. 2022;43(7):1721–1732. doi:10.1038/s41401-021-00805-2
74. Chai R, Xue W, Shi S, et al. Cardiac remodeling in heart failure: role of pyroptosis and its therapeutic implications. *Front Cardiovasc Med*. 2022;9:870924. doi:10.3389/fcvm.2022.870924
75. Zeng C, Duan F, Hu J, et al. NLRP3 inflammasome-mediated pyroptosis contributes to the pathogenesis of non-ischemic dilated cardiomyopathy. *Redox Biol*. 2020;34:101523. doi:10.1016/j.redox.2020.101523

76. Bracey NA, Beck PL, Muruve DA, et al. The Nlrp3 inflammasome promotes myocardial dysfunction in structural cardiomyopathy through interleukin-1β. *Exp Physiol*. 2013;98(2):462–472. doi:10.1113/expphysiol.2012.068338
77. Singla DK, Johnson TA, Tavakoli Dargani Z. Exosome treatment enhances anti-inflammatory M2 macrophages and reduces inflammation-induced pyroptosis in doxorubicin-induced cardiomyopathy. *Cells*. 2019;8(10):1224. doi:10.3390/cells8101224
78. Zhang W, Shi C, Yao Z, Qian S. Bardoxolone methyl attenuates doxorubicin-induced cardiotoxicity by inhibiting the TXNIP–NLRP3 pathway through Nrf2 activation. *Environ Toxicol*. 2024;39(4):1936–1950. doi:10.1002/tox.24075
79. Audia JP, Yang X, Crockett ES, et al. Caspase-1 inhibition by VX-765 administered at reperfusion in -P2Y12 receptor antagonist-treated rats provides long-term reduction in myocardial infarct size and preservation of ventricular function. *Basic Res Cardiol*. 2018;113(5):32. doi:10.1007/s00395-018-0692-z
80. Wang J, Deng B, Liu Q, et al. Pyroptosis and ferroptosis induced by mixed lineage kinase 3 (MLK3) signaling in cardiomyocytes are essential for myocardial fibrosis in response to pressure overload. *Cell Death Dis*. 2020;11(7):574. doi:10.1038/s41419-020-02777-3
81. Chen A, Chen Z, Zhou Y, et al. Rosuvastatin protects against coronary microembolization-induced cardiac injury via inhibiting NLRP3 inflammasome activation. *Cell Death Dis*. 2021;12(1):1–12. doi:10.1038/s41419-021-03389-1
82. Zhang J, Huang L, Shi X, et al. Metformin protects against myocardial ischemia-reperfusion injury and cell pyroptosis via AMPK/NLRP3 inflammasome pathway. *Aging*. 2020;12(23):24270–24287. doi:10.18632/aging.202143
83. Szobi A, Gonçalvesová E, Varga ZV, et al. Analysis of necroptotic proteins in failing human hearts. *J Transl Med*. 2017;15(1):86. doi:10.1186/s12967-017-1189-5
84. Luedde M, Lutz M, Carter N, et al. RIP3, a kinase promoting necroptotic cell death, mediates adverse remodelling after myocardial infarction. *Cardiovasc Res*. 2014;103(2):206–216. doi:10.1093/cvr/cvu146
85. Guo X, Chen Y, Liu Q. Necroptosis in heart disease: molecular mechanisms and therapeutic implications. *J Mol Cell Cardiol*. 2022;169:74–83. doi:10.1016/j.yjmcc.2022.05.006
86. Hu X, Li H, Chen X, et al. Plasma concentration of receptor-interacting protein kinase-3 as a potential biomarker for diagnosis and prognosis in heart failure. *Clin Chim Acta*. 2020;509:273–279. doi:10.1016/j.cca.2020.06.039
87. Marunouchi T, Nishiumi C, Iinuma S, Yano E, Tanonaka K. Effects of Hsp90 inhibitor on the RIP1-RIP3-MLKL pathway during the development of heart failure in mice. *Eur J Pharmacol*. 2021;898:173987. doi:10.1016/j.ejphar.2021.173987
88. Wu P, Cai M, Liu J, Wang X. Catecholamine surges cause cardiomyocyte necroptosis via a RIPK1–RIPK3-dependent pathway in mice. *Front Cardiovasc Med*. 2021;8:740839. doi:10.3389/fcvm.2021.740839
89. Ma F, Zhu Y, Chang L, et al. Hydrogen sulfide protects against ischemic heart failure by inhibiting RIP1/RIP3/MLKL-mediated necroptosis. *Physiol Res*. 2022;71(6):771. doi:10.33549/physiolres.934905
90. Bai JQ, Li PB, Li CM, Li HH. N-arachidonoylphenolamine alleviates ischaemia/reperfusion-induced cardiomyocyte necroptosis by restoring proteasomal activity. *Eur J Pharmacol*. 2024;963:176235. doi:10.1016/j.ejphar.2023.176235
91. Zhang XJ, Li L, Wang AL, et al. GSK2795039 prevents RIP1-RIP3-MLKL-mediated cardiomyocyte necroptosis in doxorubicin-induced heart failure through inhibition of NADPH oxidase-derived oxidative stress. *Toxicol Appl Pharmacol*. 2023;463:116412. doi:10.1016/j.taap.2023.116412
92. Gao XQ, Liu CY, Zhang YH, et al. The circRNA CNEACR regulates necroptosis of cardiomyocytes through Foxa2 suppression. *Cell Death Differ*. 2022;29(3):527–539. doi:10.1038/s41418-021-00872-2
93. Zhang T, Zhang Y, Cui M, et al. CaMKII is a RIP3 substrate mediating ischemia- and oxidative stress–induced myocardial necroptosis. *Nat Med*. 2016;22(2):175–182. doi:10.1038/nm.4017
94. Hua Y, Qian J, Cao J, Wang X, Zhang W, Zhang J. Ca2+/calmodulin-dependent protein kinase II regulation by inhibitor of receptor interacting protein kinase 3 alleviates necroptosis in glycation end products-induced cardiomyocytes injury. *Int J Mol Sci*. 2022;23(13):6988. doi:10.3390/ijms23136988
95. Burger PM, Koudstaal S, Mosterd A, et al. C-reactive protein and risk of incident heart failure in patients with cardiovascular disease. *J Am Coll Cardiol*. 2023;82(5):414–426. doi:10.1016/j.jacc.2023.05.035
96. Michou E, Wussler D, Belkin M, et al. Quantifying inflammation using interleukin-6 for improved phenotyping and risk stratification in acute heart failure. *Eur J Heart Fail*. 2023;25(2):174–184. doi:10.1002/ejhf.2767
97. Rogers C, Fernandes-Alnemri T, Mayes L, Alnemri D, Cingolani G, Alnemri ES. Cleavage of DFNA5 by caspase-3 during apoptosis mediates progression to secondary necrotic/pyroptotic cell death. *Nat Commun*. 2017;8:14128. doi:10.1038/ncomms14128
98. Orning P, Weng D, Starheim K, et al. Pathogen blockade of TAK1 triggers caspase-8-dependent cleavage of gasdermin D and cell death. *Science*. 2018;362(6418):1064–1069. doi:10.1126/science.aau2818
99. Sarhan J, Liu BC, Muendlein HI, et al. Caspase-8 induces cleavage of gasdermin D to elicit pyroptosis during Yersinia infection. *Proc Natl Acad Sci U S A*. 2018;115(46):E10888–E10897. doi:10.1073/pnas.1809548115
100. Li J, Zhang X, Ren P, et al. Landscape of RNA-binding proteins in diagnostic utility, immune cell infiltration and PANoptosis features of heart failure. *Front Genetics*. 2022;13:1004163. doi:10.3389/fgene.2022.1004163
101. Xiong F, Pu L, Wang D, et al. Investigation of polysaccharide from radix aconiti lateralis preparata (Fuzi) cardio protective effect on doxorubicin-induced chronic cardiotoxicity. *J Pharm Pharmacol*. 2024;76(4):391–404. doi:10.1093/jpp/rgae001
102. Yu X, Ruan Y, Huang X, et al. Dexrazoxane ameliorates doxorubicin-induced cardiotoxicity by inhibiting both apoptosis and necroptosis in cardiomyocytes. *Biochem Biophys Res Commun*. 2020;523(1):140–146. doi:10.1016/j.bbrc.2019.12.027
103. Liu J, Wu P, Wang Y, et al. Ad-HGF improves the cardiac remodeling of rat following myocardial infarction by upregulating autophagy and necroptosis and inhibiting apoptosis. *Am J Transl Res*. 2016;8(11):4605.
104. Piamsiri C, Maneechote C, Jinawong K, et al. GSDMD-mediated pyroptosis dominantly promotes left ventricular remodeling and dysfunction in post-myocardial infarction: a comparison across modes of programmed cell death and mitochondrial involvement. *J Transl Med*. 2023;21:16. doi:10.1186/s12967-023-03873-6
105. Piamsiri C, Maneechote C, Jinawong K, et al. Chronic mitochondrial dynamic-targeted therapy alleviates left ventricular dysfunction by reducing multiple programmed cell death in post-myocardial infarction rats. *Eur J Pharmacol*. 2024;977:176736. doi:10.1016/j.ejphar.2024.176736

106. Bi Y, Xu H, Wang X, et al. FUNDC1 protects against doxorubicin-induced cardiomyocyte PANoptosis through stabilizing mtDNA via interaction with TUFM. *Cell Death Dis*. 2022;13(12):1020. doi:10.1038/s41419-022-05460-x
107. Wu X, Wei J, Zhang W, et al. Targeting the PANoptosis signaling pathway for myocardial protection: therapeutic potential of Xian Ling Gu Bao capsule. *Front Pharmacol*. 2024;15:1391511. doi:10.3389/fphar.2024.1391511
108. Cui B, Qi Z, Liu W, Zhang G, Lin D. ZBP1-mediated PANoptosis: a possible novel mechanism underlying the therapeutic effects of penehyclidine hydrochloride on myocardial ischemia–reperfusion injury. *Int Immunopharmacol*. 2024;137:112373. doi:10.1016/j.intimp.2024.112373
109. Li PB, Bai JQ, Jiang WX, Li HH, Li CM. The mechanosensitive Piezo1 channel exacerbates myocardial ischaemia/reperfusion injury by activating caspase-8-mediated PANoptosis. *Int Immunopharmacol*. 2024;139:112664. doi:10.1016/j.intimp.2024.112664
110. Olcum M, Fan S, Rouhi L, et al. Genetic inactivation of β-catenin is salubrious whereas its activation is deleterious in desmoplakin cardiomyopathy. *Cardiovasc Res*. 2023:cvad137. doi:10.1093/cvr/cvad137
111. Chen H, Xie X, Xiao H, et al. A pilot study about the role of panoptosis-based genes in atherosclerosis development. *J Inflamm Res*. 2023;16:6283–6299. doi:10.2147/JIR.S442260
112. Zheng Z, Li K, Yang Z, et al. Transcriptomic analysis reveals molecular characterization and immune landscape of PANoptosis-related genes in atherosclerosis. *Inflamm Res*. 2024;73(6):961–978. doi:10.1007/s00011-024-01877-6
113. Zhao GN, Jiang DS, Li H. Interferon regulatory factors: at the crossroads of immunity, metabolism, and disease. *BBA*. 2015;1852(2):365–378. doi:10.1016/j.bbadis.2014.04.030
114. Sharma BR, Karki R, Rajesh Y, Kanneganti TD. Immune regulator IRF1 contributes to ZBP1-, AIM2-, RIPK1-, and NLRP12-PANoptosome activation and inflammatory cell death (PANoptosis). *J Biol Chem*. 2023;299(9):105141. doi:10.1016/j.jbc.2023.105141
115. Kuriakose T, Zheng M, Neale G, Kanneganti TD. IRF1 is a transcriptional regulator of ZBP1 promoting NLRP3 inflammasome activation and cell death during influenza virus infection. *J Immunol*. 2018;200(4):1489–1495. doi:10.4049/jimmunol.1701538
116. Jiang DS, Li L, Huang L, et al. Interferon regulatory factor 1 is required for cardiac remodeling in response to pressure overload. *Hypertension*. 2014;64(1):77–86. doi:10.1161/HYPERTENSIONAHA.114.03229
117. Malireddi RKS, Gurung P, Kesavardhana S, et al. Innate immune priming in the absence of TAK1 drives RIPK1 kinase activity-independent pyroptosis, apoptosis, necroptosis, and inflammatory disease. *J Exp Med*. 2020;217(3). doi:10.1084/jem.20191644
118. Chen Y, Hu B, Ni F, et al. Kongensin a attenuates intervertebral disc degeneration by inhibiting TAK1-mediated PANoptosis of nucleus pulposus cells. *Int Immunopharmacol*. 2024;129:111661. doi:10.1016/j.intimp.2024.111661
119. Li W, Zhang W, Zhang D, Shi C, Wang Y. Effect of lipopolysaccharide on *TAK1*-mediated hepatocyte PANoptosis through *Toll*-like receptor 4 during acute liver failure. *Int Immunopharmacol*. 2024;129:111612. doi:10.1016/j.intimp.2024.111612
120. Li J, Yan C, Wang Y, et al. GCN5-mediated regulation of pathological cardiac hypertrophy via activation of the TAK1-JNK/p38 signaling pathway. *Cell Death Dis*. 2022;13(4):421. doi:10.1038/s41419-022-04881-y
121. Dai C, Luo W, Chen Y, et al. Tabersonine attenuates Angiotensin II-induced cardiac remodeling and dysfunction through targeting TAK1 and inhibiting TAK1-mediated cardiac inflammation. *Phytomedicine*. 2022;103:154238. doi:10.1016/j.phymed.2022.154238
122. Guo S, Liu Y, Gao L, et al. TBC1D25 regulates cardiac remodeling through TAK1 signaling pathway. *Int J Biol Sci*. 2020;16(8):1335–1348. doi:10.7150/ijbs.41130
123. Upton JW, Kaiser WJ, Mocarski ES. DAI complexes with RIP3 to mediate virus-induced programmed necrosis that is targeted by murine cytomegalovirus vIRA. *Cell Host Microbe*. 2012;11(3):290–297. doi:10.1016/j.chom.2012.01.016
124. Hao Y, Yang B, Yang J, et al. ZBP1: a powerful innate immune sensor and double-edged sword in host immunity. *Int J Mol Sci*. 2022;23(18):10224. doi:10.3390/ijms231810224
125. Nakayama H, Otsu K. Mitochondrial DNA as an inflammatory mediator in cardiovascular diseases. *Biochem J*. 2018;475(5):839–852. doi:10.1042/BCJ20170714
126. Enzan N, Matsushima S, Ikeda S, et al. ZBP1 protects against mtDNA-induced myocardial inflammation in failing hearts. *Circ Res*. 2023;132(9):1110–1126. doi:10.1161/CIRCRESAHA.122.322227
127. Lei Y, VanPortfliet JJ, Chen YF, et al. Cooperative sensing of mitochondrial DNA by ZBP1 and cGAS promotes cardiotoxicity. *Cell*. 2023;186(14):3013–3032.e22. doi:10.1016/j.cell.2023.05.039
128. Fauconnier J, Meli AC, Thireau J, et al. Ryanodine receptor leak mediated by caspase-8 activation leads to left ventricular injury after myocardial ischemia-reperfusion. *Proc Natl Acad Sci U S A*. 2011;108(32):13258–13263. doi:10.1073/pnas.1100286108
129. Guo H, Zhu M, Yu R, Li X, Zhao Q. Efficacy of Chinese traditional patent medicines for heart failure with preserved ejection fraction: a Bayesian network meta-analysis of 64 randomized controlled trials. *Front Cardiovasc Med*. 2023;10:1255940. doi:10.3389/fcvm.2023.1255940
130. Wu X, Guo M, Shi S, et al. Efficacy and safety of shenqisuxin granule for non-st-segment elevation acute coronary syndrome: study protocol for a randomized, double-blinded, placebo-controlled trial. *Front Cardiovasc Med*. 2022;9:888724. doi:10.3389/fcvm.2022.888724
131. Lv S, Wang Y, Zhang W, Shang H. The chemical components, action mechanisms, and clinical evidences of YiQiFuMai injection in the treatment of heart failure. *Front Pharmacol*. 2022;13:1040235. doi:10.3389/fphar.2022.1040235
132. Cheang I, Yao W, Zhou Y, et al. The traditional Chinese medicine Qiliqiangxin in heart failure with reduced ejection fraction: a randomized, double-blind, placebo-controlled trial. *Nat Med*. 2024;30(8):2295–2302. doi:10.1038/s41591-024-03169-2
133. Yoon JJ, Tai AL, Kim HY, et al. TongGuanWan alleviates doxorubicin- and isoproterenol-induced cardiac hypertrophy and fibrosis by modulating apoptotic and fibrotic pathways. *Int J Mol Sci*. 2024;25(19):10573. doi:10.3390/ijms251910573
134. Qin J, Yang Q, Wang Y, Shi M, Zhao X, Zhou Y. The role of pyroptosis in heart failure and related traditional Chinese medicine treatments. *Front Pharmacol*. 2024;15:1377359. doi:10.3389/fphar.2024.1377359
135. Zhang ZY, Yang ZH, Wang S, Feng SL, Wang XL, Mao JY. Regulation of optimized new Shengmai powder on cardiomyocyte apoptosis and ferroptosis in ischemic heart failure rats: the mediating role of phosphatidylinositol-3-kinase/protein kinase B/tumor protein 53 signaling pathway. *J Ethnopharmacol*. 2024;330:118264. doi:10.1016/j.jep.2024.118264
136. Wang Y, Fu X, Shang Z, et al. In vivo and in vitro study on the regulatory mechanism of XiaoChaiHu decoction on PANoptosis in sepsis-induced cardiomyopathy. *J Ethnopharmacol*. 2025;336:118740. doi:10.1016/j.jep.2024.118740

137. Liang Y, Yan Y, Liu N, Wang J, Fang C. Shengxian decoction improves lung function in rats with bleomycin-induced idiopathic pulmonary fibrosis through the inhibition of PANoptosis. *J Ethnopharmacol*. 2024;329:118153. doi:10.1016/j.jep.2024.118153
138. Ma Z, Xie K, Xue X, et al. Si-Wu-Tang attenuates hepatocyte PANoptosis and M1 polarization of macrophages in non-alcoholic fatty liver disease by influencing the intercellular transfer of mtDNA. *J Ethnopharmacol*. 2024;328:118057. doi:10.1016/j.jep.2024.118057
139. Zhang M, Shang L, Zhou F, et al. Dachengqi decoction dispensing granule ameliorates LPS-induced acute lung injury by inhibiting PANoptosis in vivo and in vitro. *J Ethnopharmacol*. 2025;336:118699. doi:10.1016/j.jep.2024.118699
140. Liu M, Gao M, Shi X, et al. Quercetin attenuates SiO2-induced ZBP-1-mediated PANoptosis in mouse neuronal cells via the ROS/TLR4/NF-κb pathway. *J Environ Manage*. 2024;370:122948. doi:10.1016/j.jenvman.2024.122948
141. Guo J, Luo Y, Zuo J, Teng J, Shen B, Liu X. Echinacea polyphenols inhibit NLRP3-dependent pyroptosis, apoptosis, and necroptosis via suppressing NO production during lipopolysaccharide-induced acute lung injury. *J Agric Food Chem*. 2023;71(19):7289–7298. doi:10.1021/acs.jafc.2c08382
142. Lan Z, Tan F, He J, et al. Curcumin-primed olfactory mucosa-derived mesenchymal stem cells mitigate cerebral ischemia/reperfusion injury-induced neuronal PANoptosis by modulating microglial polarization. *Phytomedicine*. 2024;129:155635. doi:10.1016/j.phymed.2024.155635
143. Guo R, Yu Y, Xu C, et al. Protective effects of curcumin on corneal endothelial cell PANoptosis and monocyte adhesion induced by tumor necrosis factor-alpha and interferon-gamma in rats. *Exp Eye Res*. 2024;245:109952. doi:10.1016/j.exer.2024.109952
144. Yuan T, Yang HY, Li YP, et al. Scutellarin inhibits inflammatory PANoptosis by diminishing mitochondrial ROS generation and blocking PANoptosome formation. *Int Immunopharmacol*. 2024;139:112710. doi:10.1016/j.intimp.2024.112710
145. ping YY, Yan L, yu KH, et al. Baicalin inhibits PANoptosis by blocking mitochondrial Z-DNA formation and ZBP1-PANoptosome assembly in macrophages. *Acta Pharmacol Sin*. 2024;45:1–18. doi:10.1038/s41401-024-01376-8