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Original Article

Cross-Regulation of Hypertrophic Cardiomyopathy and Pan-Apoptosis: Focusing on the Central Role of NLRC5, DRP1 and RIPK Family

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Abstract:

Hypertrophic cardiomyopathy (HCM) is an inherited heart disease caused directly by genetic mutations. From the molecular point of view, the pathogenesis of this disease involves a variety of pathophysiological changes, mainly including cardiac myocyte programmed death, mitochondrial dysfunction and persistent inflammatory response. Recent studies suggest that panapoptosis, a novel cell death mode, may play a key role in the development of HCM.

This article focuses on three important regulatory molecules and the potential link between hypertrophic cardiomyopathy and panapoptosis.

1. NLRC5, in HCM, showed protective effects on the heart muscle, distinct from its role in promoting cell death in other inflammatory responses.
2. DRP1, which may participate in the process of cardiomyocyte death and promote myocardial fibrosis through ZBP1-PANopsis signaling pathway. This finding reveals a potential link between mitochondrial dysfunction and pan-apoptosis.
3. RIPK family members, including RIPK1 and RIPK3. They have dual regulatory properties: on the one hand, they can promote cardiac hypertrophy through necrotic apoptosis pathway and CaMKIIδ-mPTP mechanism; on the other hand, they can integrate multiple death signals to regulate the progress of PANopsis. (Table 1)

Table 1: Regulatory Roles and Mechanistic Associations of PANoptosis-Related Molecules in Hypertrophic Cardiomyopathy.

Molecule	Role in PANoptosis	Role in Hypertrophic Cardiomyopathy (HCM)	Interactions with Other Molecules
NLRC5	Forms PANoptosome complex with NLRP12/NLRP3/ASC/caspase-8/RIPK3; promotes inflammatory PANoptosis during NAD+ depletion	Increased expression in HCM patients and pressure-overload models; deficiency exacerbates cardiac hypertrophy, fibrosis, and inflammation, showing protective	Regulated by NAD+ metabolism; associated with mitochondrial function

		effects in cardiac remodeling	
DRP1	Mediates mitochondrial fission dysfunction to trigger PANoptosis (e.g., ZBP1-PANoptosome signaling cascade)	DNM1L gene variants cause cardiomyopathy; reduced protein levels in FA-HCM promote myocardial hypertrophy	Regulated by HHATL-SHH pathway and SUMO2-SH3GLB1-DRP1 axis; associated with mitochondrial dynamics
RIPK family (RIPK1/RIPK3)	RIPK1 integrates survival/death signals; RIPK3 activates NLRP3 to promote pyroptosis; both form PANoptosome via RHIM domains	Angiotensin II activates RIPK3, promoting myocardial hypertrophy through necroptosis and CaMKII-mPTP mechanisms	Interacts with caspase-8/MLKL/NLRP3; involved in inflammatory responses across multiple diseases

These findings provide new insights into the pathogenesis of HCM and reveal the potential regulatory role of pan-apoptosis in cardiomyopathy.

Key words: Panapoptosis, hypertrophic cardiomyopathy, NLRC5, DRP1, RIPK family

1. Introduction

Pan-apoptosis is a newly discovered cell death pattern, which is essentially a lytic cell death process associated with inflammation. Specific multiprotein complexes called "panapoptotic bodies" perform precise regulatory functions. This death mode is not a simple pathway superposition, but integrates the core components of apoptosis, charred death and necrotic apoptosis.

In 2019, Malireddi's research team first proposed the concept of pan-apoptosis, aiming to clarify the synergistic mechanism of multiple signaling pathways under pathogen infection, inflammatory response and cell stress conditions. Recent studies have shown that this mechanism is involved in a variety of important pathological processes. For example, the Salmonella effector protein SopF exacerbates infection by regulating panapoptosis in intestinal epithelial cells[3]. Pathological ocular hypertension induces panapoptosis of retinal ganglion cells in glaucoma through mitochondrial dynamics disturbance[4]. NINJI proteins are involved in regulating this death process under heat stress and infection conditions[5]. In a study of gastric cancer, YBX1 led to oxaliplatin resistance by inhibiting pan-apoptosis[6]. Yersinia utilizes RIPK1-PANoptosome to trigger cell death[7].

Hypertrophic cardiomyopathy (HCM) is an inherited heart disease. The main clinical manifestations of HCM include diastolic dysfunction and arrhythmia, and sudden cardiac death may occur in severe cases. Genetic research has made remarkable progress in recent years. It has been established that HCM has a high degree of genetic heterogeneity. The pathogenicity of CSRP3 and TNNI2 genes has been verified by experiments[8-10]. Epidemiological data show that approximately 60% of HCM cases can be identified by current genetic testing techniques. However, there are still a considerable proportion of cases that need to consider complex factors such as deep intron variation, multigene synergy or gene-environment interaction[9]. At the molecular pathological level, the sarcomere hypercontraction hypothesis suggests that HCM-associated mutations (e.g., R403Q of MYH7)

significantly enhance myosine-actin interaction strength. This abnormal intermolecular interaction triggers excessive contraction of sarcomere and results in a disorder of cellular energy metabolism[8]. The theory of abnormal calcium regulation emphasizes that calcium homeostasis imbalance in cardiomyocytes is directly related to arrhythmia and myocardial hypertrophy[11]. However, there is a lack of panapoptotic studies relevant to hypertrophic cardiomyopathy.

By integrating the latest data, we identified three key molecular nodes, which provide new directions for the mechanism of HCM (Figure 1)

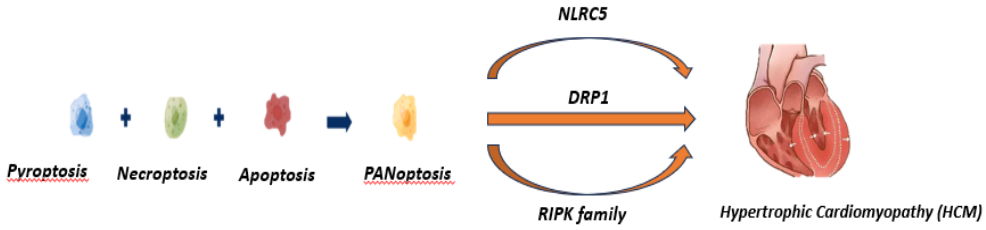

Figure 1

NAD+ is the Metabolic Intersection of NLRC5-Mediated Pan-Apoptosis and Hypertrophic Cardiomyopathy

The relationship between NLRC5 and panapoptotic and hypertrophic cardiomyopathy is a frontier field of cardiovascular disease research in recent years, involving complex mechanisms of inflammation, cell death and myocardial remodeling.

Sundaram et al.(2024) revealed the key role of NLRC5 in inflammatory cell death induced by specific PAMP/DAMP combinations (such as heme +LPS) and proposed the mechanism by which NLRC5 forms PANoptosome complexes with NLRP12, NLRP3 and other molecules to drive PANopsis[12]. The authors compared the cell death response of bone marrow-derived macrophages from wild-type and NLRC5 deficient mice to different stimuli by systematic screening. The results showed that NLRC5-deficient macrophages were significantly reduced in cell death by heme +LPS, heme +R848 and other PAMP/DAMP combinations, indicating that NLRC5 plays a key role in cell death induced by these specific ligands. NLRC5 deficient mice exhibited significant protective effects in phenylhydrazine-and LPS-induced hemolytic disease models, with significantly reduced kidney damage and inflammatory response; NLRC5 deficient mice exhibited significantly reduced inflammatory response and tissue damage in DSS-induced acute colitis models, and significantly reduced mortality in hemophagocytic lymphohistiocytosis models.

NLRC5 also plays an important role in hypertrophic cardiomyopathy. Yu et al.(2023) explored the role and mechanism of NLRC5 in cardiac remodeling in macrophages[13]. The authors found that NLRC5 expression was significantly increased in circulating monocytes and cardiac macrophages in patients with hypertrophic cardiomyopathy and in a mouse model of stress overload. This finding suggests that NLRC5 may play an important role in cardiac remodeling. By immunofluorescence staining and flow cytometry, the authors further confirmed that NLRC5 was highly expressed in cardiac macrophages and almost absent in cardiomyocytes. And in global and myeloid lineage-specific NLRC5 knockout mouse models, NLRC5 deletion was found to exacerbate cardiac hypertrophy, fibrosis, and inflammation induced by pressure overload. These results suggest that NLRC5 expression in macrophages has a protective effect on cardiac remodeling.

Nollet et al.(2023) further analyzed mitochondrial function in patients with hypertrophic cardiomyopathy, revealing the relationship between mitochondrial dysfunction and cardiac cell structural disorder, and proposed therapeutic strategies to correct this dysfunction by improving NADH-driven mitochondrial respiration[14]. The

team found that mitochondrial dysfunction was strongly associated with mitochondrial structural disorders in cardiac myocytes, particularly in genotype negative patients, and was significantly positively correlated with ventricular septal hypertrophy. It is noteworthy that HCM patients (especially the genotype negative subgroup) exhibit significant impairment of NADH-dependent respiratory function, and this specific respiratory impairment is also significantly associated with pathological progression of ventricular septal hypertrophy. By using elamipretide (a drug that stabilizes cardiolipin) and increasing mitochondrial NAD+ levels, the team was able to significantly improve NADH-driven respiratory function. This suggests mitochondrial function has therapeutic potential in HCM. Sundaram et al.(2024) found that NAM significantly inhibited NLRC5-mediated cell death by supplementing NAD+ precursors (e.g., nicotinamide, NAM), further confirming the critical role of NAD+ depletion in PANopsis. NAD+ depletion drives PANopsis[12] by regulating NLRC5 expression and ROS production.

We can see that NLRC5 shows significant tissue-specific differences in its role in PANopsis and HCM. In inflammatory disease models such as hemophagocytic lymphohistiocytosis and colitis, NLRC5 has been shown to promote PANopsis. However, during HCM pathology, the molecule may exert cardioprotective functions by inhibiting excessive inflammation. This functional paradox is manifested by the fact that NLRC5 promotes inflammation and cell death in PANopsis on the one hand, and may inhibit inflammation in HCM on the other. This dual action mechanism still requires more in-depth molecular level studies.

NAD+ metabolism constitutes an important metabolic node linking NLRC5-mediated PANopsis and HCM. Sundaram et al. demonstrated that decreased NAD+ levels promote NLRC5-dependent PANopsis. The Nollet team's work in 2023 found that mitochondrial dysfunction in HCM patients (manifested as impaired NADH respiratory chain) was strongly associated with disease progression. These findings suggest that NAD+ supplementation may simultaneously improve mitochondrial function and inhibit PANopsis processes in HCM patients (Figure 2). However, Yu et al. showed that NLRC5 deletion exacerbates cardiac remodeling, but failed to elucidate its specific regulatory mechanism on macrophage function, especially its potential association with PANopsis. At present, there is no direct evidence to prove whether macrophages in HCM develop PANopsis.

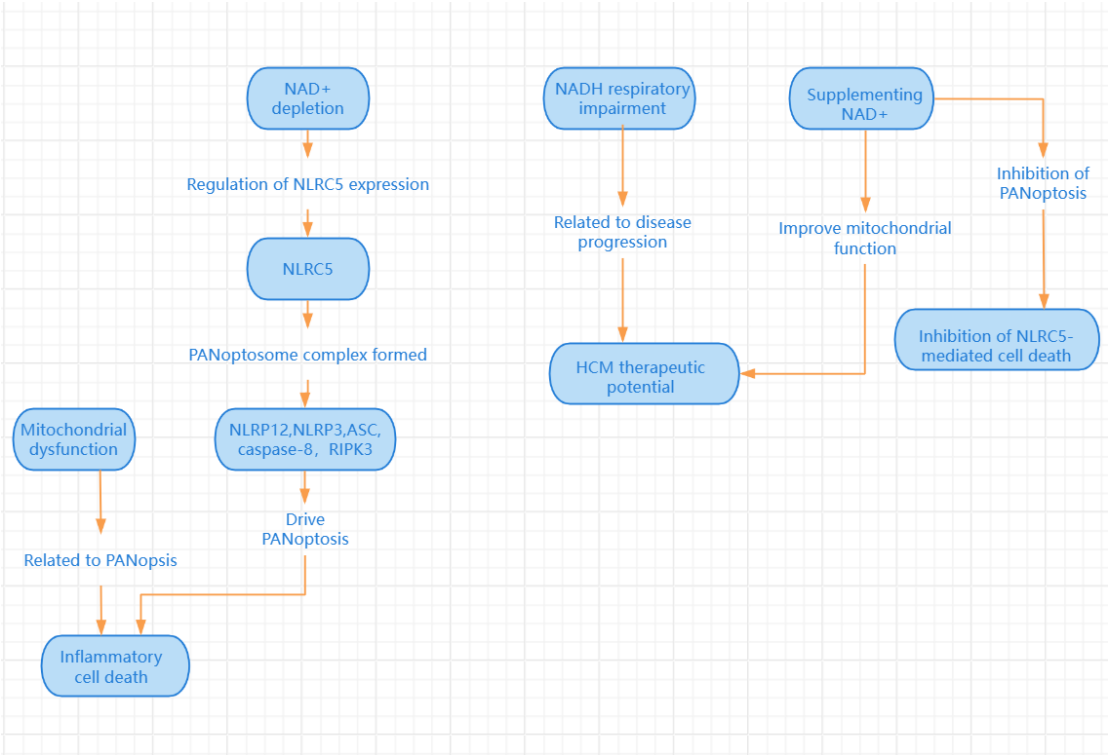

Figure 2: NAD+ Metabolism Regulates PANoptosis via NLRC5: Implications for HCM Treatment

Nollet's study also found that mitochondrial dysfunction was more pronounced in patients with genotypic negative HCM. However, it is still unclear whether the expression or function of NLRC5 varies with HCM genotypes. The existing studies are mainly based on mouse models and in vitro experiments, and no systematic exploration studies have been conducted on the therapeutic potential of NLRC5-targeted interventions in HCM or PANoptosis-related diseases.

From Mitochondrial Dynamics to Cell Death: The Role of DRP1 in Triggering Pan-Apoptosis in Hypertrophic Cardiomyopathy.

DRP1, a member of the dynein superfamily, characterizes GTP enzyme activity. It is mainly involved in the regulatory function of mitochondrial division. DRP1 has been found to play a key role in regulating cellular energy metabolism, executing programmed death pathways, and developing neurodegenerative diseases.

Berti et al.(2024) and Magistrati et al.(2025) found through case reports that DNM1L gene variants can lead to DRP1 functional defects, causing encephalopathy and fatal cardiomyopathy, and suggested that DNM1L be included in mitochondrial hypertrophic cardiomyopathy related genes[15,16]. These results suggest that genetic variation of DRP1 may be directly involved in the pathogenesis of HCM. In Friedrich's ataxia (FA) patients, 60% will develop left ventricular hypertrophic cardiomyopathy (FA-HCM). Chidipi et al.(2022) found that DRP1 protein levels in FA-HCM cardiomyocytes were significantly reduced using a hiPSC-CMs model, ultimately promoting myocardial hypertrophy[17]. This finding reveals a key role of DRP1 posttranslational regulatory abnormalities in FA-HCM. Xu et al.(2024) demonstrated that HHATL gene downregulation promotes cardiac hypertrophy by reducing DRP1 expression leading to mitochondrial fragmentation, and DRP1 overexpression reverses this phenotype[18]. Gao et al.(2022) found that ionizing radiation (IR) modifies SH3GLB1 via SUMO2, enhancing its binding to DRP1, resulting in mitochondrial hyperdivision, ROS burst, and cardiomyocyte hypertrophy[19].

Recent studies have found that DRP1-mediated mitochondrial dysregulation is the key mechanism triggering PANopsis. In a cardiotoxicity model, Ge et al.(2025) revealed that Rnd3 reduces mitochondrial division by inhibiting Rock1/DRP1 pathway, thus alleviating doxorubicin-induced myocardial PANopsis[20]. In ulcerative colitis, Ye et al.(2024) found that DRP1 triggers PANopsis through sulfuration of ZBP1, whereas the HIV protease inhibitor saquinavir alleviates disease by directly inhibiting DRP1 activity[21]. Among nanomaterial toxicities, Li et al.(2024) demonstrated that SiO2 leads to mtDNA leakage through DRP1 overactivation, activating the ZBP1-PANoptosome complex[22]. In asthma, Ding et al.(2025) found that DRP1-mediated mitochondrial division was regulated by RAB7A in the mechanism of Artemetin-targeted ABCG2/RAB7A axis inhibition of mitochondrial dysfunction in asthma, filling the gap in ABCG2 research in respiratory diseases. Clarify the cascade pathway of ABCG2/RAB7A → DRP1/MFN2 → mitochondrial dynamics → PANopsis, providing a new target for asthma treatment. Association between mitochondrial dysfunction and PANopsis provides new therapeutic ideas for severe asthma[23].

Therefore, DRP1-ZBP1-PANopsis signaling axis may be involved in the pathological basis of hypertrophic cardiomyopathy. When mitochondrial division is abnormal, it can cause mtDNA/ROS leakage phenomenon, which activates ZBP1-dependent PANopsis, which eventually leads to accelerated cardiomyocyte death and fibrosis (Figure 3). The association between DRP1 and panapoptotic processes has been partially supported by HCM studies. However, more confirmatory work is needed to determine whether DRP1-ZBP1 has a direct causal link in myocardial tissue. In particular, DRP1 function may be affected differently in HCM cases with different etiologies, such as genetic mutations, metabolic abnormalities, or radiation therapy. Therefore, it is necessary to establish a disease classification model with higher accuracy, which will provide an important basis for the optimization of treatment strategies. DRP1, a key regulatory factor in mitochondrial dynamics, plays an important role in the development of HCM through mitochondrial homeostasis disruption, ROS imbalance and pan-apoptotic pathway abnormality when its function is disturbed. Future research should focus on analyzing the complex regulatory network system

formed by DRP1 post-translational modification and its possible application value in HCM precision therapy.

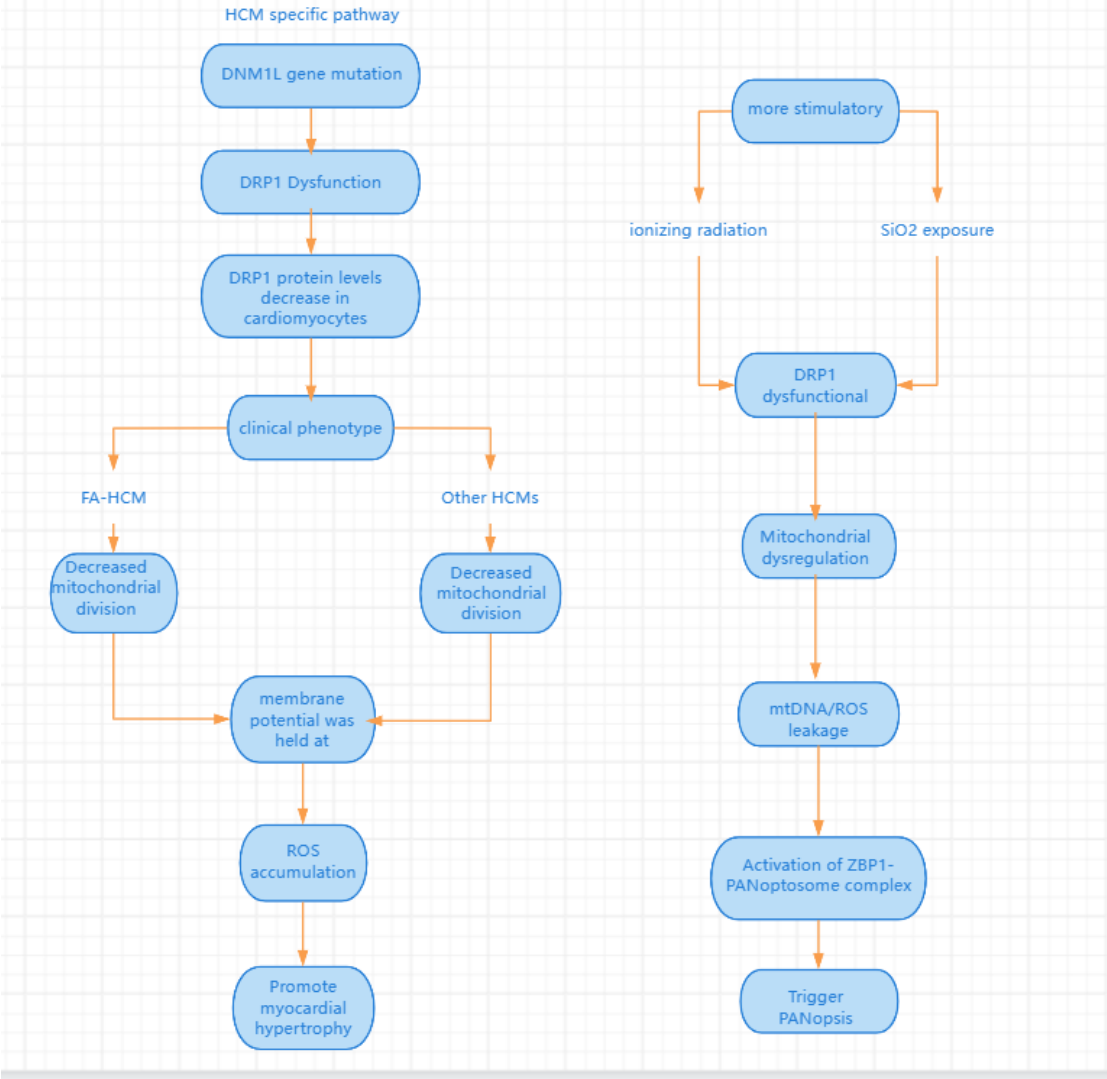

Figure 3: The Role of DRP1-Mitochondrial Pathway Dysfunction in the Pathogenesis of Hypertrophic Cardiomyopathy.

RIPK Family: Core Molecular Switch Linking Hypertrophic Cardiomyopathy and Pan-Apoptosis

RIPK family (RIPK1/RIPK3), as death domain protein kinases, plays a central regulatory role in pan-apoptosis, a new type of programmed inflammatory cell death. RIPK1, as a signal integration hub, can promote cell survival through NF-κB pathway, regulate apoptosis through caspase-8 or induce necrotic apoptosis in cooperation with RIPK3; RIPK3 can activate NLRP3 inflammatory body to promote apoptosis in addition to necrotic apoptosis through phosphorylation of MLKL. RIPK1/RIPK3 binds to pattern recognition receptors such as ZBP1 or TRIF through RHIM domain to form dynamic PANoptosome complex, which flexibly switches cell death mode according to caspase-8 activity state: RIPK3-MLKL axis dominates necrotic apoptosis when caspase-8 is inhibited; when caspase-8 is activated, it turns to apoptosis, and at the same time, it forms cooperative apoptosis by enhancing GSDMD pore. RIPK family becomes a key molecular switch connecting apoptosis, charred apoptosis and necrotic apoptosis.

Recent studies have revealed the central role of RIPK family in the PANopsis regulatory network and its pathological mechanisms in a variety of diseases. Sundaram et al.(2024) and Malireddi et al.(2024) were the first to elucidate the underlying mechanism by which NOD-like receptors (NLRs) form PANoptosome complexes by integrating key

molecules such as RIPKs and caspases[24,26]. On this basis, several studies have confirmed the key role of RIPK-PANopsis axis in different diseases: in acute lung injury, Xiao et al.(2025) found that RIPK3-mediated necrotizing apoptosis aggravated the inflammatory response by releasing DAMPs[25]; in asthma model, Bai et al.(2025) confirmed that DEK protein participated in airway inflammation by regulating RIPK1-PANopsis pathway[27]; In terms of neurological diseases, Jiajia et al.(2025) demonstrated that PGAM5 drives neuronal panapoptosis after subarachnoid hemorrhage by activating RIPK1. In addition, Liu et al.(2025) extended this concept to ageing-related diseases, suggesting that the "aging-PANopsis-inflammation" axis is a key mechanism for osteoarthritis progression[28]. The study by Lu et al.(2024) provides new ideas for therapeutic intervention against these pathological processes, demonstrating that chlorogenic acid blocks bacterial infection-induced PANopsis[29] by inhibiting RIPK1/3 expression. These studies not only systematically clarify the central role of RIPK-PANopsis networks in infectious diseases, neurological diseases and degenerative diseases, but also provide a theoretical basis for the development of novel therapies targeting RIPK kinase inhibitors and regulating PANoptosome assembly.

Recent studies in recent years have also revealed that RIPK family plays an important role in hypertrophic cardiomyopathy. Zhang et al.(2022) first identified the central role of RIPK3-CaMKIIδ signaling axis in pressure overload myocardial hypertrophy. It has been found that angiotensin II (AngII) and other stimuli activate RIPK3 and drive myocardial lesions through dual pathways: one is to form RIPK1-RIPK3 necrotic bodies, triggering MLKL-mediated necrotic apoptosis; the other is to directly phosphorylate CaMKIIδ and promote ROS production, resulting in abnormal activation and splicing disorder of CaMKIIδ, and finally induce myocardial hypertrophy and cardiac function damage. The specific inhibitor GSK'872 was demonstrated to reverse hypertrophic phenotype by blocking RIPK3 activity, restoring CaMKII delta splicing balance and reducing necrotic apoptosis, providing a new target for HCM therapy[31]. Chen et al.(2023) further systematized the universal role of the RIPK3-CaMKII-mPTP pathway in a variety of cardiovascular diseases, especially in HCM, where the pathway accelerates disease progression by promoting cardiac hypertrophy, necrotic apoptosis, and fibrosis. Both clinical samples and animal models (AngII/phenylephrine-induced) showed significantly increased RIPK3 expression and phosphorylation levels in hypertrophic myocardium. GSK'872 (RIPK3 inhibitor) and Necrostatin-1 (RIPK1 inhibitor) are effective in reducing hypertrophy and necrotizing apoptosis, suggesting that RIPK1-RIPK3 interaction is a key regulatory node[32] of HCM. In the same year, Bencze et al.(2023) extended their vision to multi-organ lesions and found that RIPK3-mediated necrotic apoptosis not only participates in cardiomyopathy in DMD models, but also drives skeletal muscle and respiratory muscle dysfunction. Gene knockout or drug inhibition of RIPK3 can improve myocardial hypertrophy, fibrosis and cardiac function without impairing muscle regeneration, highlighting its therapeutic potential[33].

In conclusion, the functional properties of RIPK family of death domain protein kinases (RIPK1/RIPK3) have significant regulatory significance in hypertrophic cardiomyopathy syndrome (HCM) and panapoptosis. Activated by pathological stimuli such as angiotensin II (AngII), RIPK3 molecule is particularly prominent in the course of HCM, which promotes the damage process of myocardial tissue through necrotic apoptosis pathway and CaMKII-mPTP mechanism (Figure 4).

In addition, the RIPK3-CaMKII signaling pathway may exacerbate myocardial inflammation through the synergistic effect of PANoptosome structural components (such as NLRP3/caspase-1, etc.), a phenomenon that may constitute a key intersection between HCM and pan-apoptosis research. The RIPK family has dual biological identities--both as a pathogenic driver of HCM and as a central regulatory switch for PANopsis--making it an important mediator linking myocardial pathology to systemic inflammation.

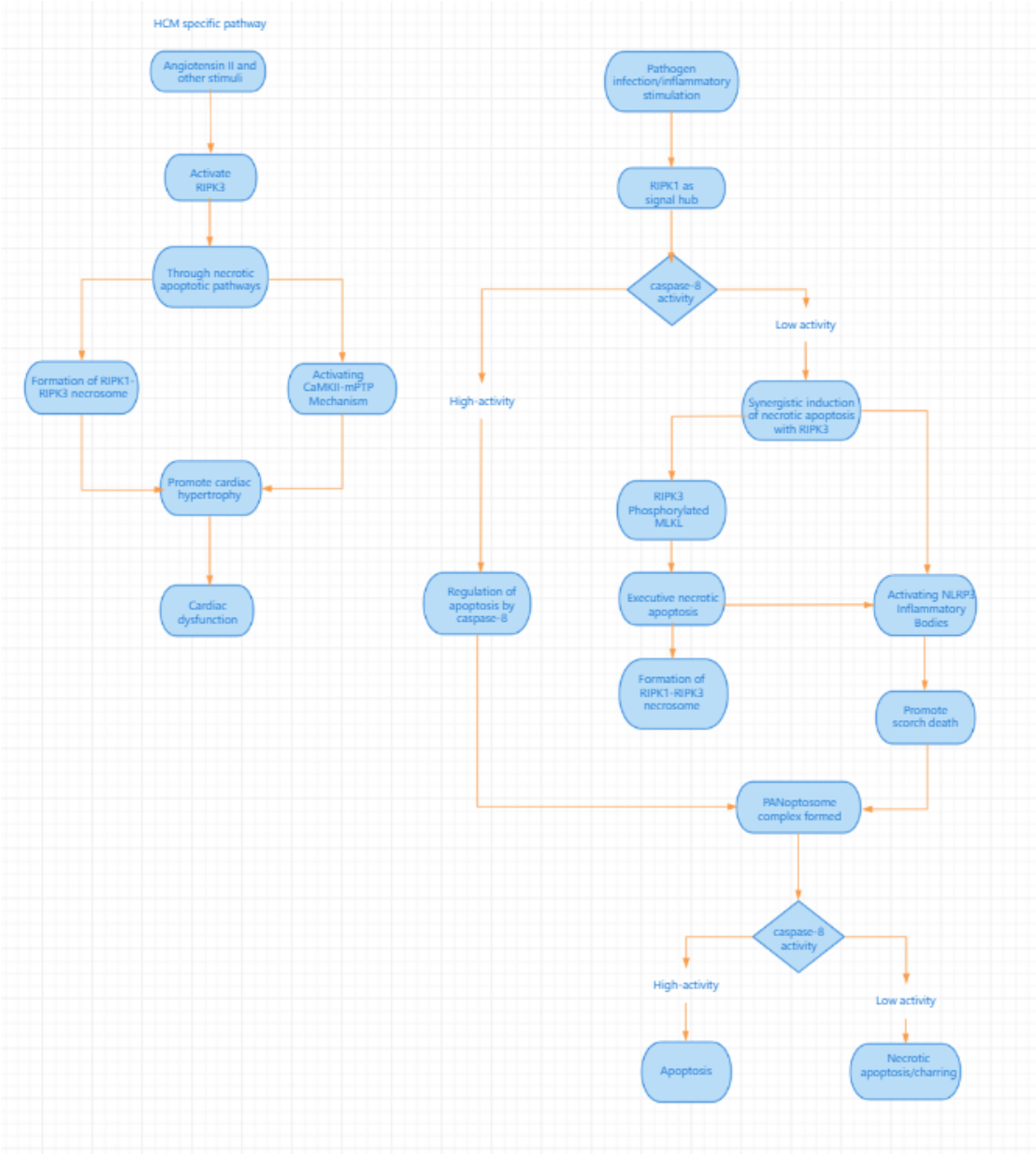

Figure 4: Comparative Analysis of RIPK Family-Mediated Cell Death Pathways in Hypertrophic Cardiomyopathy and Infection.

Conclusion:

As a new cell death model, pan-apoptosis may play an important role in hypertrophic cardiomyopathy. However, there are still many difficulties in the study of these pathways, such as insufficient tissue targeting specificity and disease heterogeneity. Interventions at these critical nodes, such as NAD+ complementary therapy, precise regulation of DRP1 activity, or specific inhibition of RIPK kinase, have shown promise. To achieve clinical application goals, multidisciplinary research teams need to further explore the spatiotemporal specific regulation of PANopsis in hypertrophic cardiomyopathy, thus gaining momentum for the development of precision medicine strategies to provide new treatment possibilities for this major human health threat.

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