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From Injury to Heart Failure: Molecular and Cellular Mechanisms of Ischemia-Reperfusion Injury

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ABSTRACT

Background: Myocardial ischemia-reperfusion injury (IRI) represents a significant clinical challenge, contributing to cardiomyocyte death and adverse cardiovascular outcomes. Despite advances in therapeutic strategies, the molecular mechanisms driving IRI remain incompletely understood, hindering the development of effective interventions.

Objective: This review aims to provide a comprehensive overview of the molecular and cellular mechanisms underlying myocardial IRI, emphasizing the roles of programmed cell death pathways, inflammasomes, interleukins, and the intricate balance of autophagy in cardiac injury and repair.

Key Findings: Apoptosis, pyroptosis, and necroptosis contribute to cardiomyocyte death, each characterized by distinct morphological and biochemical features. These pathways are intricately regulated by signaling molecules such as caspases, gasdermin D, and receptor-interacting protein kinases. Activation of the NLRP3 inflammasome and subsequent production of interleukins such as IL-1β and IL-18 exacerbate the inflammatory response, driving further myocardial damage. These pathways are linked to adverse cardiac remodeling and chronic cardiovascular diseases, including heart failure and atherosclerosis. Functional autophagy mitigates cellular stress by removing damaged organelles and misfolded proteins, limiting inflammasome activation. Dysregulated autophagy, however, amplifies cardiac injury during ischemia-reperfusion injury. Targeting these pathways through pharmacological agents such as inflammasome inhibitors, interleukin blockers, and autophagy modulators holds promise for mitigating IRI and improving cardiac outcomes.

Conclusions: A deeper understanding of these molecular mechanisms offers a roadmap for developing targeted interventions to prevent and treat myocardial ischemia-reperfusion injury. Translational efforts focusing on these pathways may enhance therapeutic efficacy and reduce the burden of cardiovascular diseases. Advancing preclinical research and clinical trials is crucial to address knowledge gaps and overcome translational barriers. Integrating molecular insights into personalized therapeutic approaches may redefine the management of myocardial IRI and its long-term sequelae.

Keywords: Myocardial ischemia-reperfusion injury, Programmed cell death, Inflammasome, Interleukins, Pyroptosis, Autophagy, Necroptosis, Cardiovascular inflammation, Therapeutic strategies

Introduction

Myocardial ischemia-reperfusion injury (IRI) represents a paradoxical phenomenon in which restoring blood flow to ischemic myocardium, while essential for salvaging myocardial tissue, can paradoxically exacerbate myocardial damage.[1] Revascularization procedures, including thrombolysis, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG), aim to minimize ischemic damage and improve clinical outcomes. However, the reintroduction of blood flow can induce a cascade of cellular and molecular events that exacerbate myocardial injury, culminating in the death of cardiomyocytes that were viable before reperfusion. This phenomenon demonstrates the dual-edged nature of reperfusion therapy and highlights the complexity of IRI. [2-3]

First described in 1960 by Jennings et al., myocardial reperfusion injury is characterized by histological changes such as cell swelling, contraction band necrosis, and mitochondrial disruptions, observed in canine ischemic myocardium after reperfusion.[4] In 1977–1979, Reimer and Jennings demonstrated that acute myocardial infarction (AMI) develops as a wavefront of necrosis, beginning in the subendocardium and extending to the subepicardium within 3 to 6 hours.[5, 6] Subsequent research identified reperfusion and conditioning as key factors influencing the progression of myocardial ischemic injury.[1, 7] Reperfusion restores oxygen delivery, salvaging mildly ischemic myocardium, but it also exacerbates damage in severely ischemic regions and amplifies the inflammatory response to the ischemic event. These findings, initiated decades of debate regarding whether reperfusion itself contributes to myocardial damage or merely accelerates ischemic injury.[8] Subsequent studies confirmed that reperfusion exacerbates infarct size via mechanisms distinct from ischemic injury alone, supporting the notion of reperfusion injury as an independent pathological process.[9-12]

The mechanisms of IRI are multifactorial and involve a spectrum of processes, including myocardial stunning, the no-reflow phenomenon, reperfusion arrhythmias, and lethal reperfusion injury.[1] Each type contributes uniquely to myocardial dysfunction, with lethal reperfusion injury having the most direct impact on infarct size and clinical outcomes.[1, 13] During ischemia, oxygen deprivation shifts cellular metabolism to anaerobic glycolysis, leading to intracellular acidosis, ion imbalances, and ATP depletion. Reperfusion restores oxygen availability but also triggers calcium overload, oxidative stress, and mitochondrial permeability transition, culminating in cell death via necrosis and apoptosis.[1, 14]

Despite advancements in revascularization strategies, the detrimental effects of reperfusion injury persist, contributing to a mortality rate of nearly 10% and a heart failure (HF) incidence of 25% following AMI.[1, 15] Understanding the molecular mechanisms underlying IRI is crucial for developing targeted interventions to mitigate its impact on myocardial function and improve clinical outcomes. This review aims to explore the intricate molecular pathways of ischemia-reperfusion injury, with an emphasis on cellular disturbances and therapeutic strategies aimed at minimizing its effects.

Materials and Methods

LITERATURE SEARCH STRATEGY

This review was conducted using a structured and comprehensive search strategy to identify relevant studies, reviews, and articles on cellular death pathways, including apoptosis, necroptosis, pyroptosis, and autophagy, with a focus on their roles in myocardial ischemia-reperfusion injury and related cardiovascular diseases. Electronic databases, including PubMed, Scopus, Cochrane and Web of Science, were queried for publications in English from January 2000 to October 2024. Additional relevant references were identified through backward citation tracking of the articles retrieved.

The following Medical Subject Headings (MeSH) terms and keywords were used, alone or in combination: "apoptosis," "pyroptosis," "necroptosis," "autophagy," "ischemia-reperfusion injury," "cardiomyocyte death," "inflammasome," "interleukins," "DAMPs," "oxidative stress," and "cardioprotection."

INCLUSION AND EXCLUSION CRITERIA

Studies included in the review met the following criteria:

- Peer-reviewed original research articles, reviews, or meta-analyses focusing on cellular death mechanisms in myocardial injury.
- Studies discussing mechanistic insights, molecular pathways, or therapeutic interventions targeting apoptosis, pyroptosis, necroptosis, or autophagy.
- Articles published in English.

Exclusion criteria included:

- Studies not relevant to the cardiac context or IRI.
- Case reports, conference abstracts, or publications lacking sufficient experimental or mechanistic data.
- Non-English articles.

DATA EXTRACTION AND ANALYSIS

All identified studies were screened by their titles and abstracts for relevance, followed by a full-text review. Information on molecular pathways, key regulatory proteins, therapeutic targets, and experimental outcomes was extracted. Data were synthesized to present an integrated view of the molecular mechanisms underlying cardiomyocyte death and their implications in ischemia-reperfusion injury.

ETHICAL CONSIDERATIONS

As a review article, this study did not involve new experiments or human/animal subjects, and thus no ethical approval was required.

Oxidative Stress and Myocardial Stunning in Ischemia-Reperfusion Injury

OXIDATIVE STRESS IN ISCHEMIA-REPERFUSION INJURY

Oxidative stress plays a pivotal role in the pathogenesis of ischemia-reperfusion injury (IRI), with reactive oxygen species (ROS) such as hydroxyl (OH) and superoxide (O_2^-) radicals being key mediators. Reperfusion induces a burst of ROS, causing direct damage to cardiomyocytes and impairing cardiac contractility.[16] Early experimental studies demonstrated a causal relationship between ROS production and myocardial dysfunction.[17] Efforts to

mitigate this effect have included the use of free radical scavengers such as superoxide dismutase during reperfusion. However, results have been inconsistent, with some studies showing significant cardioprotective effects while others failed to demonstrate benefit.[17, 18]

Beyond direct toxicity, oxidative stress during reperfusion diminishes the bioavailability of nitric oxide (NO), a critical cardioprotective molecule. Nitric oxide donors, such as Nicorandil, have been evaluated as therapeutic agents, showing initial promise in reducing infarct size in animal models. Yet, large clinical trials reported no significant impact on infarct size when Nicorandil was administered during reperfusion.[19, 20] These findings underscore the dual role of NO, which at excessive levels during reperfusion may paradoxically activate apoptotic pathways and exacerbate myocardial damage.[21]

The isoforms of nitric oxide synthase (NOS) — endothelial (eNOS), neuronal (nNOS), and inducible (iNOS) — play distinct roles in NO production during IRI. The timing of interventions is crucial; pre-reperfusion administration of L-arginine, an NO precursor, reduces infarct size via eNOS-derived NO, whereas post-reperfusion administration increases infarct size due to iNOS-derived NO and peroxynitrite formation.[22, 23]

MYOCARDIAL STUNNING: A TRANSIENT DYSFUNCTION

Myocardial stunning refers to the reversible yet prolonged myocardial contractile dysfunction that persists after reperfusion, despite the absence of irreversible damage.[24, 25] This phenomenon is characterized by both systolic and diastolic dysfunction, which gradually resolves over days to weeks. It is commonly observed following brief ischemic episodes and is marked by persistent contractile abnormalities even after coronary flow normalization.[23, 26]

The pathogenesis of myocardial stunning involves multiple mechanisms:

- ROS generation during early reperfusion damages cellular membranes and contractile proteins, impairing calcium homeostasis and reducing myofilament sensitivity to calcium.[27, 28]
- Energy depletion due to anaerobic metabolism during ischemia disrupts ATP production, compounding contractile dysfunction.[29]
- Sarcoplasmic reticulum dysfunction further contributes to excitation-contraction uncoupling.[29, 30]

Myocardial stunning was first described in animal models and later characterized by Braunwald and Kloner as a “hit, run, and stun” process — an ischemic insult followed by recovery without irreversible injury.[24] Clinically, it is commonly seen in patients undergoing percutaneous coronary interventions or experiencing exercise-induced ischemia. Although hemodynamically benign, recurrent stunning in the setting of limited coronary reserve may transition into chronic contractile dysfunction.[30, 31]

Role of the Mitochondrial Permeability Transition Pore in Ischemia-Reperfusion Injury

The mitochondrial permeability transition pore (mPTP) plays a central role in the pathogenesis of ischemia-reperfusion injury, making it a critical therapeutic target for cardioprotection. The mPTP is a non-selective channel in the inner mitochondrial membrane (IMM) that opens in response to pathological stimuli, disrupting mitochondrial function and leading to cell death. This section provides an extended overview of its role during ischemia and reperfusion.[32, 33]

MITOCHONDRIA AND MITOCHONDRIAL PERMEABILITY TRANSITION PORE STRUCTURE

Mitochondria are essential for ATP production via oxidative phosphorylation, maintaining cardiac contractility and ionic homeostasis. Under normal conditions, the IMM is impermeable, allowing efficient energy production. However, under pathological stress, the mPTP opens, allowing the influx of solutes, ions, and water into the mitochondrial matrix. This results in mitochondrial swelling, outer membrane permeabilization, and activation of cell death pathways, including caspase-dependent apoptosis and necrosis.[32, 34]

The molecular components of the mPTP are not fully elucidated but include Cyclophilin D (CyP-D), adenine nucleotide translocase (ANT), and phosphate carrier (PiC) proteins. The pore is highly regulated by factors such as ROS, calcium (Ca^{2+}), and adenine nucleotides, with opening thresholds influenced by the metabolic state of the cell.[35]

MITOCHONDRIAL PERMEABILITY TRANSITION PORE IN ISCHEMIA

During ischemia, oxygen deprivation leads to electron transport chain (ETC) dysfunction, halting oxidative phosphorylation and depleting ATP. To meet energy demands, cells upregulate anaerobic glycolysis, causing lactic acid accumulation, intracellular acidosis, and activation of ion exchangers like Na^+/H^+ antiporters. These changes result in Na^+ and Ca^{2+} overload, along with ROS production due to ETC dysregulation.[34, 36]

Although mPTP opening is minimal during ischemia due to inhibitory effects of ADP and low pH, prolonged Ca^{2+} overload can activate proteases like calpains, leading to cytoskeletal damage and myocardial contracture.[37-39] This ischemic phase primes the mPTP for opening upon reperfusion.

MITOCHONDRIAL PERMEABILITY TRANSITION PORE IN REPERFUSION

The reperfusion phase triggers dramatic metabolic changes that facilitate mPTP opening:

1. Oxygen Restoration: Resumption of ETC activity generates a surge of ROS, particularly via reverse electron transport at Complex I, exacerbating oxidative stress.[40]
2. Calcium Overload: Persistent mitochondrial Ca^{2+} influx leads to pore opening, disrupting membrane potential and ATP synthesis.[41]
3. pH Normalization: Reperfusion restores intracellular pH, removing the protective inhibition of mPTP by acidic conditions.[41]

Experimental studies have shown that mPTP opening occurs within minutes of reperfusion, driving cardiomyocyte death via mitochondrial swelling, rupture,

and release of pro-apoptotic factors like cytochrome c.[34, 42]

THERAPEUTIC TARGETING OF MITOCHONDRIAL PERMEABILITY TRANSITION PORE

Interventions targeting mPTP have shown promise in mitigating IRI:

- Cyclophilin D Inhibition: Cyclosporin A (CsA) and its analogs reduce mPTP opening, preserving mitochondrial function and reducing infarct size in animal models.[43-45]
- Calcium Homeostasis Modulation: Strategies enhancing mitochondrial Ca^{2+} extrusion, such as overexpressing the Na^{+}/Ca^{2+} exchanger or inhibiting mitochondrial calcium uniporter (MCU), reduce mPTP activation and improve cardiac function.[46-48]
- Antioxidant Therapies: Targeting ROS production at the onset of reperfusion prevents the oxidative burst and subsequent pore opening.[1, 34]

PATHOPHYSIOLOGICAL ROLE AND MOLECULAR MECHANISMS

The mPTP serves as a hub for signaling pathways that link mitochondrial dysfunction to cell death. Elevated mitochondrial Ca^{2+} and ROS levels trigger pore formation, causing mitochondrial membrane potential collapse and release of pro-apoptotic factors, such as SMAC/DIABLO and cytochrome c. These mechanisms drive both apoptotic and necrotic cell death, contributing significantly to myocardial damage during reperfusion.[34, 47, 49]

The mPTP is a pivotal determinant of reperfusion injury, bridging mitochondrial dysfunction to irreversible cardiomyocyte death. Ongoing research into its regulation and targeted therapies holds significant potential for advancing cardioprotection in clinical settings. Further studies are needed to optimize therapeutic strategies and translate these findings into effective interventions for patients with myocardial infarction.[50, 51]

THE REPERFUSION INJURY SALVAGE KINASE PATHWAY IN ISCHEMIA-REPERFUSION INJURY

The Reperfusion Injury Salvage Kinase (RISK) pathway is a collection of pro-survival protein kinases, including Akt and Erk1/2, that play a pivotal role in mitigating ischemia-reperfusion injury.[52] First identified in 2002 by Yellon and colleagues, the RISK pathway has emerged as a key therapeutic target for cardioprotection during myocardial reperfusion. Its activation at the critical moment of reperfusion has been shown to reduce MI size significantly, offering a promising avenue for clinical interventions.[53, 54]

Activation of the RISK pathway provides cardioprotection through multiple mechanisms. Central to its role is the inhibition of the mitochondrial permeability transition pore, which is a primary mediator of cell death during reperfusion. By preventing mPTP opening, the RISK pathway preserves mitochondrial membrane potential and reduces oxidative stress. Furthermore, it enhances calcium uptake into the sarcoplasmic reticulum, stabilizing intracellular calcium levels and preventing calcium overload, a key driver of reperfusion-induced cellular damage. Pro-survival signaling via Akt and Erk1/2 also recruits anti-apoptotic pathways, counteracting the apoptotic cascades that are otherwise activated during reperfusion.[1, 53]

Preclinical studies have demonstrated the robust cardioprotective potential of the RISK pathway when activated by pharmacological agents such as insulin, erythropoietin, adenosine, volatile anesthetics, and statins. These agents, when administered specifically at the time of reperfusion, or combined with mechanical interventions such as ischemic preconditioning and postconditioning, have been shown to reduce infarct size by as much as 50%.[53-56] The therapeutic potential of these approaches highlights the importance of precise timing for the activation of this pathway.

The timing of RISK pathway activation is particularly critical for its effectiveness. Studies indicate that its activation occurs in two distinct phases. The first, termed the "trigger phase," happens during ischemic preconditioning cycles before the ischemic insult. The second, known as the "early reperfusion phase," occurs within the first 15 minutes of reperfusion, a critical window for regulating mPTP activity. If activation is delayed beyond this window, the efficacy of cardioprotective strategies diminishes significantly, even when employing direct mPTP inhibitors such as cyclosporin A.[57-59] This temporal sensitivity underscores the necessity of precisely timed interventions to maximize the benefits of the RISK pathway in clinical settings.

The RISK pathway also serves as a universal signaling cascade, capable of being recruited by a wide array of cardioprotective stimuli. While initially described in the context of ischemic preconditioning, it has since been shown to be activated by various pharmacological agents, including bradykinin, adenosine, and statins. This universality suggests that the RISK pathway constitutes a common mechanism underlying many cardioprotective therapies, further emphasizing its clinical relevance.[1, 58]

Despite its robust cardioprotective potential, the RISK pathway must be carefully regulated to avoid unintended consequences. While acute activation during reperfusion is beneficial, chronic activation of its components, such as the PI3K-Akt cascade, may contribute to pathological conditions like cardiac hypertrophy and HF. The heart appears to mitigate these risks through regulatory mechanisms, including the phosphatase PTEN, which acts as a molecular switch to prevent the deleterious effects of prolonged signalling. This regulatory capacity suggests that the RISK pathway is ideally suited for short-term activation during acute MI, providing targeted protection against IRI without long-term adverse effects.[57, 60-63]

In conclusion, the RISK pathway represents a critical target for therapeutic interventions aimed at mitigating ischemia-reperfusion injury. Its ability to promote cell survival through inhibition of mPTP opening, stabilization of calcium homeostasis, and recruitment of anti-apoptotic mechanisms underscores its central role in cardioprotection.[52] Extensive preclinical research has

demonstrated that activating the RISK pathway, through various pharmacological agents or mechanical interventions such as ischemic preconditioning (IPC) or ischemic postconditioning (IPost), can reduce MI size by up to 50%, primarily by modulating the mitochondrial permeability transition pore (MPTP). Following the step-by-step criteria outlined in the IMproving Preclinical Assessment of Cardioprotective Therapies (IMPACT) initiative, the next phase involves evaluating the effectiveness of RISK pathway activation in small animal models that include confounding comorbidities such as aging or diabetes, as well as in large animal models of IRI.[52, 64] Further research should focus on optimizing the timing and modality of interventions to harness the full potential of the RISK pathway in clinical practice.

Damage-Associated Molecular Patterns in Myocardial Ischemia-Reperfusion Injury

Damage-associated molecular patterns (DAMPs) are endogenous molecules released by stressed or injured cells, such as those experiencing myocardial IRI.[65] These molecules, also referred to as alarmins, activate the immune system by interacting with pattern recognition receptors (PRRs), initiating inflammatory cascades that can be both protective and detrimental.[66, 67] Endothelial cells (ECs) are a focus of immunological research due to their role as sources of various DAMPs and their expression of DAMP-sensing receptors. These receptors include Toll-like receptors (TLRs), NOD-like receptors (NLRs), and receptors for advanced glycation end products (RAGE), which are located on their plasma membrane.[65, 68] Primary human cardiac microvascular endothelial cells (ECs) release a variety of DAMP-associated proteins during simulated ischemia-reperfusion injury, which significantly compromises the integrity of the endothelial plasma membrane.[65]

THE DUAL ROLE OF DAMAGE-ASSOCIATED MOLECULAR PATTERNS IN INFLAMMATION

Damage-Associated Molecular Patterns mobilize inflammatory responses aimed at clearing cellular debris and facilitating tissue repair. However, excessive or disproportionate inflammatory signaling can exacerbate tissue damage, expanding the infarct size and impairing cardiac function. This inflammatory overactivation has been implicated in myocardial remodeling, characterized by fibrosis, loss of cardiomyocytes, ventricular dilation, and eventual HF.[66, 68] Additionally, in heart transplantation, DAMP-mediated signaling worsens ischemic injury, leading to graft dysfunction and rejection through enhanced cytokine release, myocardial edema, and endothelial damage.[66] While experimental models suggest potential for cardioprotective therapies targeting DAMPs and their receptors, clinical translation remains elusive. The next paragraphs present the key DAMP molecules associated with myocardial IRI.

HIGH MOBILITY GROUP BOX 1

High Mobility Group Box 1 (HMGB1), a nuclear protein involved in transcription and DNA repair, functions as a DAMP upon release from stressed or injured cells. It interacts with multiple PRRs, including RAGE, TLR2, and TLR4, to induce immune responses. Experimental studies have demonstrated both protective and harmful roles of HMGB1 in MI. Protective effects include reduced infarct size, enhanced angiogenesis, and improved left ventricular ejection fraction when administered post-MI.[69, 70] Conversely, HMGB1 can exacerbate IRI by increasing pro-inflammatory cytokine levels and infarct size.[71]

Elevated HMGB1 levels in patients post-MI correlate with adverse outcomes such as HF and cardiac rupture.[72, 73] The dual roles of HMGB1 complicate its potential as a therapeutic target, underscoring the need for a nuanced understanding of its mechanisms in cardiovascular disease.[66, 74, 75]

HEAT SHOCK PROTEINS

Heat shock proteins (HSP), primarily HSP60 and HSP70, are chaperone proteins that play critical roles in protein folding and stress responses.[76] These proteins are released during myocardial stress and can act as DAMPs by engaging TLR2 and TLR4. HSP60 has been implicated in apoptosis and inflammation during IRI, with increased release linked to cardiac damage.[77-79]

Heat shock protein 70 (HSP70) demonstrates complex behavior, with studies reporting both protective and harmful effects. Pharmacological inducers of HSP70 expression have shown cardioprotective benefits in animal models, yet elevated serum HSP70 levels in patients post-MI correlate with worse clinical outcomes.[80-84] The ambiguous roles of HSPs in IRI necessitate further research to delineate their mechanisms and therapeutic potential.[66]

FIBRONECTIN CONTAINING EXTRA DOMAIN A

Fibronectin containing Extra Domain A (EDA), an extracellular glycoprotein released by fibroblasts in response to injury, acts as a DAMP by engaging TLR2 and TLR4.[85] Experimental models suggest that targeting fibronectin-EDA reduces adverse cardiac remodeling and infarct size post-MI, although its precise role in inflammation requires further clarification.[86, 87]

HYALURONIC ACID

Hyaluronic acid (HA), a component of the extracellular matrix, plays a dual role in IRI. Fragmented, low molecular weight HA acts as a pro-inflammatory DAMP via TLR2 and TLR4, while high molecular weight HA exhibits anti-inflammatory effects. Early HA responses post-MI appear to support tissue repair, while excessive HA may contribute to harmful cardiac edema.[88-90] Clinical studies indicate elevated HA levels in MI patients, suggesting its potential as a biomarker, though its exact pathogenic role remains uncertain.[91]

MITOCHONDRIAL DNA

Mitochondrial DNA (mtDNA), released during cellular injury, acts as a DAMP by mimicking bacterial DNA and engaging TLR9, RAGE, and inflammasomes.[92] Its oxidative modification during IRI amplifies inflammation and tissue damage. Pharmacological interventions, such as EGCG and mitochondrial-targeted enzymes, have demonstrated reduced infarct size and improved cardiac function by limiting mtDNA release.[93-95] Combined effects of mtDNA and HMGB1 signaling further highlight the complex role of mtDNA in myocardial injury.[94, 95]

EXTRACELLULAR RNA

Extracellular RNA (exRNA), released during IRI, induces strong pro-inflammatory and pro-thrombotic responses through TLR3, TLR7, and TLR8 activation. Experimental models show that RNase treatments reduce infarct size and inflammation, suggesting a potential therapeutic role for exRNA modulation.[96-98]

CARDIAC MYOSIN

Cardiac myosin, a sarcomeric protein unique to the myocardium, acts as a DAMP upon release from necrotic cardiomyocytes. It engages TLR2 and TLR8 to amplify inflammatory responses, though its specific role in IRI warrants further exploration.[99, 100]

Damage-Associated Molecular Patterns play pivotal roles in the inflammatory responses following myocardial IRI. Their contributions to both repair and injury highlight the complexity of these molecules in cardiovascular pathology. While preclinical studies offer promising therapeutic avenues targeting specific DAMPs, further research is needed to translate these findings into clinical applications.[65, 68] Understanding the precise mechanisms and context-dependent roles of DAMPs remains critical to developing effective interventions for IRI.

Inflammasomes: Central Regulators in Cardiovascular Inflammation

Inflammasomes are cytoplasmic multiprotein complexes of the innate immune system that become activated in response to cellular stress or injury, such as through DAMPs (damage or danger-associated molecular patterns) or PAMPs (pathogen-associated molecular patterns).[101, 102] These complexes play a crucial role in inflammatory responses by promoting the maturation and release of pro-inflammatory cytokines, particularly IL-1β and IL-18, and inducing pyroptosis, a form of programmed cell death distinct from apoptosis.[102, 103]

STRUCTURE AND MECHANISM OF INFLAMMASOMES

Inflammasomes are composed of pattern recognition receptors (PRRs), an adaptor protein (ASC), and an effector enzyme, typically caspase-1. Activation triggers caspase-1-mediated cleavage of pro-IL-1β and pro-IL-18 into their active forms, alongside gasdermin D, which facilitates cytokine release and pyroptotic cell death through pore formation in the plasma membrane.[102, 104] Key inflammasomes include NLRP3 (NOD-, LRR-, and PYD-containing 3) and NLRC4 (NOD-, LRR-, and CARD-containing 4), both from the NLR family, and AIM2 (absent in melanoma 2), which detects cytoplasmic double-stranded DNA.[102, 103]

NLRP3 INFLAMMASOME AND MYOCARDIAL INFARCTION

Myocardial infarction serves as a paradigm of sterile injury, where the NLRP3 inflammasome orchestrates inflammatory responses in the absence of pathogens.[102] Following IRI, DAMPs such as extracellular ATP, ROS, and mitochondrial DNA activate the NLRP3 inflammasome, triggering robust recruitment of leukocytes and release of pro-inflammatory cytokines. While this response is crucial for clearing cellular debris and initiating tissue repair, uncontrolled inflammation exacerbates myocardial damage, impeding functional recovery and promoting adverse remodeling, such as fibrosis and ventricular dilation.[105, 106]

The activity of the NLRP3 inflammasome represents a double-edged sword in myocardial healing. While acute activation facilitates debris clearance and repair, chronic and unresolved inflammation perpetuates cardiomyocyte loss, geometric abnormalities, and aneurysm formation, exacerbating the sequelae of MI.[102, 107]

INFLAMMASOMES IN ATHEROSCLEROSIS

The inflammasome, particularly NLRP3, is integrally involved in the pathogenesis of atherosclerosis. Interleukin 1b (IL-1β), a product of inflammasome activation, is one of the earliest cytokines implicated in plaque formation and progression. The NLRP3–IL-1β axis is also recognized as part of "trained immunity," a form of innate immune memory that enhances responses to secondary stimuli, including non-infectious triggers like high-fat diets.[108, 109]

Recent studies demonstrate that NLRP3 deficiency mitigates the adverse effects of Western diets, including decreased plaque formation and reduced IL-1β signaling.[109] Interleukin 1b further amplifies inflammation through induction of IL-6, enhancing thrombosis and inhibiting fibrinolysis, thereby promoting clot formation and arterial occlusion.[110] Pharmacological inhibitors which target NLRP3, have shown promise in reducing atherosclerotic lesions and improving cardiac function in experimental models.[101, 111-113]

INFLAMMASOMES IN AGING AND ATRIAL FIBRILLATION

The NLRP3 inflammasome is also implicated in age-related cardiovascular dysfunction. Elevated IL-1β levels in elderly populations correlate with higher mortality due to metabolic nucleotide dysregulation. Intriguingly, caffeine has been shown to inhibit IL-1β production, suggesting potential therapeutic implications.[114]

Inflammasome NLRP3 activity is heightened in atrial cardiomyocytes of patients with atrial fibrillation (AF), where it contributes to structural and electrical remodeling.[115] In preclinical models, NLRP3 inhibition with MCC950 or genetic deletion prevents atrial dilation and spontaneous arrhythmias, highlighting its potential as a therapeutic target for AF.[115]

INFLAMMASOMES IN CARDIOMYOPATHIES

The role of NLRP3 extends to cardiomyopathy, where its activation originates in cardiomyocytes rather than non-myocyte myocardial cells. This activation is mediated through calcium/calmodulin-dependent protein kinase II (CaMKII) signaling. Early inhibition of CaMKII reduces fibrosis and prevents ventricular dilation, suggesting a narrow therapeutic window for effective intervention.[114, 115]

THERAPEUTIC IMPLICATIONS

Inflammasomes are central players in the inflammatory landscape of cardiovascular diseases, bridging innate immune activation with long-term pathological outcomes. Their dual roles necessitate precise therapeutic targeting to mitigate disease progression while preserving essential repair mechanisms. Inflammasomes, particularly NLRP3,

caspase-1, and IL-1β, represent attractive therapeutic targets in cardiovascular diseases. While experimental agents like MCC950 and other inflammasome inhibitors show promise in preclinical models, their translation to clinical practice requires robust evidence from human trials. Additionally, certain cardiovascular drugs already in use may exert beneficial effects through modulation of inflammasome activity.[108]

Interleukins: Central Mediators of Inflammation in Cardiovascular Disease

Interleukins (ILs) are important cytokines in the inflammatory processes driving cardiovascular diseases, including atheromatosis, ischemia/reperfusion injury, and heart failure. These cytokines not only mediate the local and systemic inflammatory response but also contribute to disease progression by influencing cellular and molecular mechanisms. Their involvement in cardiovascular pathophysiology positions them as critical therapeutic targets.[116]

INTERLEUKINS AND ATHEROMATOSIS

Atheromatosis, characterized by the accumulation of lipids and inflammatory cells in arterial walls, is heavily influenced by interleukins, particularly those of the IL-1 family. The IL-1 family includes 11 cytokines and 10 receptors, with IL-1β and IL-18 being the most studied members due to their pronounced pro-inflammatory roles.[117] These cytokines are central to plaque formation, progression, and rupture, driving atherothrombosis, a major complication of atherosclerosis. IL-1α and IL-1β are produced locally in plaques, where they exert significant effects on endothelial cells. These cytokines impair endothelial function by promoting oxidative stress, reducing vasodilation, and increasing the production of procoagulant mediators. These processes predispose to thrombotic complications. Both IL-1α and IL-1β also influence the inflammatory environment of plaques by stimulating the recruitment of inflammatory cells and enhancing the expression of pro-inflammatory genes. The presence of IL-1β in human atherosclerotic plaques has been well-documented, and its expression is upregulated by oxidized lipoproteins, creating a self-perpetuating cycle of inflammation.[118, 119]

In addition to their direct effects on the vasculature, interleukins modulate plaque stability. IL-1β is associated with plaque destabilization and rupture, while IL-1α appears to play a critical role during early plaque formation. Notably, IL-1Ra, a natural receptor antagonist, counterbalances the effects of IL-1α and IL-1β, highlighting the complex regulatory dynamics of the IL-1 family in atherogenesis.[120]

Cholesterol crystals within plaques activate the NLRP3 inflammasome, a key molecular platform that processes and releases IL-1β and IL-18. This activation is mediated by lysosomal destabilization and the release of cathepsin B, linking lipid metabolism to inflammation. Elevated levels of IL-18 in circulation are strongly predictive of adverse cardiovascular outcomes, further emphasizing its clinical relevance.[121]

IL-37, an anti-inflammatory cytokine, has emerged as a protective factor in atherogenesis. It stabilizes plaques, and its levels are increased in acute coronary syndromes, indicating its potential as a therapeutic target. Similarly, IL-33, through its effects on T helper cells, reduces plaque burden and inflammation, adding another layer of complexity to the interleukin-mediated regulation of atheromatosis.[122, 123]

INTERLEUKINS AND ISCHEMIA/REPERFUSION INJURY

Ischemia/Reperfusion injury represents a sterile inflammatory response triggered by necrotic cell death and the release of danger-associated molecular patterns, including interleukins such as IL-1α and IL-33. These cytokines initiate and amplify the local and systemic inflammatory response, driving further tissue damage during reperfusion. As mentioned above, the NLRP3 inflammasome plays a central role in the pathogenesis of IRI. During ischemia, intracellular potassium depletion due to ATPase failure serves as a primary trigger for NLRP3 activation. Upon reperfusion, lysosomal destabilization and the release of extracellular ATP (eATP) provide additional stimuli for inflammasome activation. This leads to the processing and release of mature IL-1β and IL-18, which propagate inflammation and exacerbate tissue damage.[118, 124]

Interleukins IL-1β and IL-18 exert detrimental effects on various cell types involved in IRI. In neutrophils, these cytokines stimulate the production of reactive oxygen species (ROS) and proteolytic enzymes, further injuring cardiomyocytes. In endothelial cells, IL-1β and IL-18 impair vasodilation and promote vascular dysfunction, limiting coronary blood flow. In fibroblasts, IL-1β drives pro-fibrotic changes, contributing to scar expansion and adverse remodeling.[124]

Interestingly, while cardiomyocytes harbor active caspase-1, they exhibit limited secretion of IL-1β, suggesting that the primary damage in these cells arises from pyroptosis rather than cytokine release.[118] This distinction highlights the multifaceted role of interleukins in IRI, involving both direct cellular injury and systemic inflammatory amplification.

INTERLEUKINS AND HEART FAILURE

Heart failure (HF) is a final common pathway for many cardiovascular diseases and is increasingly recognized as an inflammatory condition. Interleukins IL-1β and IL-18 are key mediators in HF, contributing to both its pathogenesis and progression through direct and indirect mechanisms. IL-1β and IL-18 influence HF progression by impairing myocardial contractility, promoting maladaptive remodeling, and exacerbating systemic inflammation. These cytokines reduce inotropy and lusitropy in cardiomyocytes by disrupting calcium handling and altering protein synthesis. Additionally, IL-1β has been implicated in arrhythmogenesis, adding another layer of complexity to its pathological effects.[125]

The impact of IL-1β and IL-18 extends beyond the myocardium. By mobilizing inflammatory cells from the bone marrow, these cytokines drive pathological myocardial healing following AMI, favoring scar

expansion and increasing the risk of ventricular rupture.[118]

Targeting interleukins has shown promise in the management of HF. Pharmacological inhibitors such as anakinra (IL-1 receptor antagonist) and canakinumab (anti-IL-1β monoclonal antibody) have demonstrated efficacy in improving cardiac function and reducing hospitalizations in HF patients. These findings underscore the potential of interleukin-directed therapies as a novel approach for HF management.[117, 118]

In conclusion, interleukins are nowadays considered crucial players in the inflammatory networks underlying cardiovascular diseases. From their role in atherogenesis and plaque rupture to their contribution to IRI and HF, these cytokines represent a double-edged sword, driving pathology while offering therapeutic opportunities. A deeper understanding of their mechanisms will pave the way for innovative interleukin-based treatments, potentially transforming cardiovascular care.

Pyroptosis: A Distinct Form of Programmed Cell Death in Cardiovascular Disease

Pyroptosis, a form of programmed cell death (PCD), is characterized by its association with inflammatory responses, setting it apart from other forms such as apoptosis and autophagy. This process is integral to maintaining homeostasis and combating microbial infections, but it also plays a critical role in the pathogenesis of cardiovascular diseases (CVDs) like atherosclerosis and MI. Pyroptosis involves the activation of specific molecular pathways leading to membrane rupture, release of inflammatory mediators, and eventual cell death.[126, 127]

MECHANISM AND CHARACTERISTICS OF PYROPTOSIS

Pyroptosis occurs primarily in immune and vascular cells, including monocytes, macrophages, vascular smooth muscle cells (VSMCs), vascular endothelial cells (VECs), and cardiomyocytes (CMs). It is triggered by pathological stimuli such as oxidative stress, hyperglycemia, and chronic inflammation. Unlike apoptosis, which is a non-inflammatory PCD mediated by caspase-2, -8, -9, and -10 (initiators) and caspase-3, -6, and -7 (executioners), pyroptosis relies on inflammatory caspases, notably caspase-1, -4, -5, and -11. These caspases mediate the cleavage of gasdermin D (GSDMD), producing an N-terminal fragment (GSDMD-N) that forms pores in the plasma membrane.[128, 129]

The process is marked by cellular swelling, membrane rupture, and the release of pro-inflammatory cytokines IL-1β and IL-18. Morphologically, pyroptosis combines features of apoptosis (nuclear condensation) and necrosis (membrane disruption). These events result in a highly inflammatory microenvironment that contributes to tissue damage and disease progression in CVDs.[129, 130]

PYROPTOSIS IN ATHEROSCLEROSIS

In atherosclerosis, pyroptosis plays a critical role in plaque development and destabilization. The internalization of oxidized low-density lipoproteins (oxLDL) by macrophages via CD36 receptors leads to the intracellular accumulation of cholesterol crystals within lysosomes. These crystals activate the NLRP3 inflammasome by inducing lysosomal rupture and the release of cathepsin B. Simultaneously, oxLDL activates NLRP3 through the TLR/NF-κB pathway, further promoting the release of mature IL-1β and IL-18.[131] These cytokines drive the recruitment of inflammatory cells, exacerbate local inflammation, and increase pyroptosis in vascular cells, destabilizing plaques and predisposing them to rupture.[131]

Targeting pyroptosis pathways, particularly through NLRP3 inhibition, has shown potential in reducing plaque instability. Experimental interventions such as NLRP3 inhibitors and ASC (apoptosis-associated speck-like protein containing a CARD) blockade have demonstrated reduced plaque burden and improved outcomes in preclinical models.[132]

PYROPTOSIS AND MYOCARDIAL INFARCTION

Myocardial infarction is another major cardiovascular event where pyroptosis is a key driver of myocardial injury and remodeling. During ischemia, the initial cell death is predominantly necrotic. However, the subsequent release of DAMPs during reperfusion triggers the activation of the NLRP3 inflammasome, leading to a second wave of cell death mediated by pyroptosis.[105]

Activated NLRP3 induces the cleavage of pro-caspase-1, generating active caspase-1, which processes pro-IL-1β and pro-IL-18 into their mature forms. These cytokines, along with other inflammatory mediators, exacerbate myocardial injury by increasing oxidative stress, recruiting neutrophils, and promoting fibroblast activation.[128] The release of GSDMD-N-mediated membrane pores facilitates the efflux of cytokines, amplifying the inflammatory response and expanding the infarct size.[129]

Therapeutic interventions targeting pyroptosis have demonstrated promise in experimental models. Activated protein C (aPC), an endogenous anti-inflammatory molecule, inhibits NLRP3 activation in macrophages, cardiomyocytes, and fibroblasts. This effect is mediated through the proteinase-activated receptor 1 (PAR-1) pathway, which is involved in reducing inflammatory responses and limiting myocardial injury.[133] Additionally, NLRP3 inhibitors have shown efficacy in minimizing infarct size and improving cardiac function post-MI.[132]

PYROPTOSIS AND FIBROBLASTS IN ISCHEMIA/REPERFUSION INJURY

Cardiac fibroblasts (CFs), the most abundant cell type in the adult human heart, play a pivotal role in maintaining cardiac structure and function. During IRI, upregulation of NLRP3 in CFs drives pyroptotic cell death, contributing to myocardial dysfunction and fibrosis. The pro-inflammatory milieu created by pyroptosis in CFs exacerbates adverse remodeling, leading to reduced contractility and increased scar formation.[134]

Notably, pyroptosis is a delayed response in IRI, with minimal inflammasome activity observed during the early hours (<3 hours) of reperfusion. This delay offers a critical therapeutic window for interventions aimed at preventing pyroptosis-mediated damage.[105]

Autophagy: A Fundamental Cellular Process in Cardiovascular Health and Disease

Autophagy is a critical cellular mechanism that facilitates the degradation and recycling of intracellular components, including misfolded proteins and damaged organelles, through lysosomal pathways. Initially observed in the 1950s by Christian de Duve, autophagy has since been recognized as a key regulator of cellular homeostasis and a vital player in the response to myocardial ischemia and inflammation. This process operates through three main pathways—macroautophagy, microautophagy, and chaperone-mediated autophagy—each with distinct mechanisms and roles in cellular health.[135, 136]

MECHANISMS AND TYPES OF AUTOPHAGY

Macroautophagy, the most common form of autophagy, involves the formation of a double-membrane vesicle known as an autophagosome, which sequesters cytoplasmic components and subsequently fuses with lysosomes for degradation. This process is essential for clearing organelles and macromolecules, including lipids, sugars, nucleic acids, and proteins.[136, 137] Autophagosomes merge with lysosomes to form autolysosomes, where hydrolytic enzymes break down the cargo.[138]

Microautophagy entails the direct invagination of the lysosomal membrane to engulf and degrade intracellular contents. This form of autophagy bypasses the formation of autophagosomes, making it a more direct degradation pathway.[139]

Chaperone-mediated autophagy (CMA) involves a selective process where specific substrates are identified by molecular chaperones, which then deliver them to lysosomes for degradation. Unlike macroautophagy, CMA is highly selective and primarily degrades proteins rather than organelles.[140]

These three forms of autophagy operate in coordination to maintain cellular integrity, adapt to stress, and manage damaged cellular components, forming a critical axis of cellular maintenance and protection.

ROLE OF AUTOPHAGY IN MYOCARDIAL ISCHEMIA AND INFLAMMASOME ACTIVATION

Autophagy plays a pivotal role in the pathophysiology of myocardial ischemia and its subsequent inflammation. The primary function of autophagy is the removal and recycling of damaged proteins and organelles, which is essential for tissue homeostasis and minimizing cellular damage. Dysregulated autophagy can exacerbate myocardial injury, while functional autophagy has been shown to mitigate damage following AMI.[141, 142]

Experimental evidence highlights that autophagic processes suppress inflammasome activation by eliminating dysfunctional mitochondria through mitophagy. By clearing damaged mitochondria, autophagy prevents the accumulation of reactive oxygen species (ROS) and mitochondrial DNA, which are potent activators of the NLRP3 inflammasome. Consequently, functional autophagy reduces the secretion of inflammatory cytokines, such as IL-1β, thereby limiting the inflammatory cascade in myocardial tissues.[141, 143]

However, impairment in autophagic pathways, often resulting from extensive cellular injury, leads to incomplete or ineffective autophagy. This dysfunction not only fails to resolve mitochondrial damage but also contributes to the activation of the NLRP3 inflammasome, exacerbating myocardial injury through the release of pro-inflammatory cytokines and amplification of tissue damage.[105, 144]

AUTOPHAGY AS A THERAPEUTIC TARGET IN CARDIOVASCULAR DISEASE

Given its dual role in cellular maintenance and inflammation, autophagy represents a promising therapeutic target in cardiovascular disease. Enhancing autophagic activity during the early stages of myocardial ischemia may limit inflammasome activation, reduce cytokine release, and preserve myocardial function. Conversely, addressing autophagic dysfunction in the later stages of injury could prevent the accumulation of cellular debris and further tissue damage.[145]

Future research is needed to unravel the molecular mechanisms governing autophagy in the heart and to develop pharmacological interventions that can selectively modulate this pathway. Targeting autophagy could provide a novel approach to mitigating myocardial injury, improving outcomes in conditions like AMI, and addressing chronic inflammatory states in cardiovascular diseases.[146]

Necroptosis: A Regulated Form of Inflammatory Cell Death

Necroptosis, a programmed form of necrosis or inflammatory cell death, has emerged as a critical mechanism in the interplay between cell survival and immune defense. Unlike classical necrosis, which is unregulated and triggered by external insults, necroptosis is a genetically programmed process that serves as an alternative to apoptosis, particularly in conditions where caspase activity is inhibited. This mechanism plays vital roles in host defense against pathogens, regulation of inflammation, and pathogenesis of several diseases, including MI and chronic inflammatory disorders.[147]

MECHANISMS OF NECROPTOSIS

Necroptosis is initiated through death receptors such as tumor necrosis factor receptor 1 (TNFR1), which upon activation recruits intracellular adaptor proteins like receptor-interacting protein kinase 1 (RIPK1). This process is a crucial checkpoint where the cell fate decision between apoptosis and necroptosis is determined. In the presence of functional caspase-8, apoptosis is executed by cleavage and activation of executioner caspases, such as caspases 3, 6, and 7. However, when caspase-8 activity is absent or inhibited, RIPK1 interacts with RIPK3 to form the necrosome (or ripoptosome), a complex that drives necroptosis.[148, 149]

The necrosome phosphorylates mixed-lineage kinase domain-like protein (MLKL), causing its oligomerization and translocation to plasma membranes and organelles.

MLKL insertion into the membranes results in permeabilization, leading to cell swelling, rupture, and the release of damage-associated molecular patterns (DAMPs). These DAMPs amplify the inflammatory response, recruiting immune cells and exacerbating tissue damage.[149]

MORPHOLOGICAL AND BIOCHEMICAL FEATURES

Morphologically, necroptosis exhibits characteristics of both necrosis and apoptosis. Cells undergoing necroptosis display organelle and cellular swelling, plasma membrane rupture, and mild chromatin condensation without nuclear fragmentation. These features distinguish necroptosis from apoptosis, where nuclear fragmentation and membrane blebbing are hallmark traits.[147, 148]

Biochemically, the process involves the phosphorylation and activation of RIPK1 and RIPK3, culminating in MLKL-mediated membrane disruption. The release of intracellular contents, including pro-inflammatory cytokines and DAMPs, underscores the immunogenic nature of necroptosis, setting it apart from non-inflammatory apoptosis.[148, 149]

ROLE OF NECROPTOSIS IN CARDIOVASCULAR DISEASES

Necroptosis is increasingly recognized as a contributor to cardiovascular pathology, particularly in IRI and MI. During ischemia, inhibition of caspase-8 promotes necroptosis, allowing necrosome formation and subsequent cell death. This programmed necrotic pathway exacerbates myocardial injury by releasing DAMPs, which trigger robust inflammatory responses that further damage cardiac tissue.[148, 149]

Pharmacological inhibitors of necroptosis, such as necrostatin-1 (Nec-1), have demonstrated potential in reducing tissue damage in experimental models of MI. Nec-1 inhibits RIPK1, thereby preventing necrosome assembly and MLKL activation. This strategy holds promise for mitigating ischemia/reperfusion injury, where necroptosis significantly contributes to the expansion of MI and post-infarction remodeling.[149]

THERAPEUTIC IMPLICATIONS

Given its inflammatory and immunogenic profile, targeting necroptosis offers therapeutic opportunities in cardiovascular and inflammatory diseases. Modulation of necroptosis through inhibitors of RIPK1, RIPK3, or MLKL may mitigate excessive inflammation and reduce tissue damage in conditions such as MI, HF, and chronic inflammatory states. Furthermore, understanding the molecular interplay between necroptosis and other forms of cell death, such as apoptosis and pyroptosis, could pave the way for combinatorial therapies to restore cellular homeostasis and improve outcomes in various pathological contexts.[150, 151]

Necroptosis represents a fascinating paradigm in programmed cell death, bridging cellular demise and immune activation. While its evolutionary role in pathogen defense is evident, its dysregulation poses significant challenges in cardiovascular and inflammatory diseases. Future research into the molecular mechanisms and clinical applications of necroptosis modulation will be instrumental in harnessing its potential for therapeutic benefit.[152]

Cardiomyocyte Injury and Pathological Myocardial Remodeling in Heart Failure

Heart failure is a complex syndrome characterized by impaired ventricular filling or ejection, classified into systolic HF, with reduced ejection fraction, and diastolic HF, marked by a stiff ventricle with preserved ejection fraction.[4, 153, 154] Despite advances in medical management, HF remains a significant public health issue, with mortality rates of 30–40% at one year and exceeding 50–60% at five years.[153]

Heart failure typically begins with an acute insult or chronic stress, initiating secondary damage and activating compensatory neurohumoral mechanisms. In systolic HF, progressive myocardial remodeling, characterized by changes in cardiomyocyte (CMC) contractility and calcium regulation, is a pivotal feature.[4, 155] Remodeling involves structural and functional alterations, including CMC hypertrophy, increased cell death, fibrosis, and chamber dilation, culminating in symptomatic HF.[156]

PATHOPHYSIOLOGY AND PROGRESSION OF MYOCARDIAL REMODELING

Pathological remodeling is driven by mechanisms such as apoptosis, autophagy, and necrosis, which contribute to increased CMC loss, fibrosis, and hypertrophy. In conditions like idiopathic dilated cardiomyopathy, these processes predict adverse outcomes, while myocardial fibrosis exacerbates systolic and diastolic dysfunction.[157] Both ischemic and non-ischemic cardiomyopathies exhibit severe fibrosis, hypertrophy, and myocytolysis, emphasizing their shared endpoint of advanced myocardial remodeling in HF.[158]

THERAPEUTIC STRATEGIES AND CHALLENGES

Despite promising developments, cardiac regenerative therapies, including stem cell-based approaches, have shown limited success in reversing myocardial damage.[159] Current strategies focus on mitigating pathological remodeling through therapies targeting inflammation, fibrosis, and metabolism. Advanced HF often necessitates left ventricular assist devices (LVADs) or heart transplantation. LVADs, used as bridge-to-transplantation or destination therapy, can halt or reverse pathological remodeling, as evidenced by reductions in CMC hypertrophy and receptor re-localization during ventricular unloading [4]. Nonetheless, the challenge lies in understanding and intervening in the fundamental biological processes underpinning HF to develop transformative therapies.[160]

Limitations

This review synthesizes existing knowledge on cellular death pathways in myocardial ischemia-reperfusion injury and related cardiovascular diseases. However, certain limitations must be acknowledged. First, while extensive effort was made to include comprehensive and up-to-date literature, the reliance on published studies may inherently introduce a bias towards well-documented mechanisms, potentially overlooking less explored or emerging pathways. Second, the review primarily focuses on findings from preclinical models and in vitro studies, which may not fully translate to clinical settings. Third, given the rapid pace of research in this

field, some recent developments may not have been captured due to the time frame of the literature search. Lastly, therapeutic implications discussed are largely theoretical or based on experimental data, necessitating further validation through robust clinical trials.

Conclusions

Myocardial ischemia-reperfusion injury involves complex molecular mechanisms that drive cardiomyocyte death and inflammation, significantly contributing to adverse outcomes in cardiovascular diseases. Apoptosis, pyroptosis, necroptosis, and dysregulated autophagy represent distinct yet interconnected cell death pathways, each playing a role in exacerbating myocardial damage. The activation of inflammasomes, interleukins, and damage-associated molecular patterns further amplifies the inflammatory response, linking acute injury to chronic conditions like heart failure and atherosclerosis. While preclinical studies highlight the potential of targeting these pathways for therapeutic benefit, significant challenges remain in translating these findings into clinical practice. Future efforts should focus on refining molecular interventions and integrating them into personalized treatment strategies to mitigate IRI, promote cardiac repair, and improve patient outcomes.

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