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REVIEW

Molecular and metabolic landscape of adenosine triphosphate-induced cell death in cardiovascular disease

Wei Wang, Xue-Mei Wang, Hao-Long Zhang, Rui Zhao, Yong Wang, Hao-Ling Zhang, Zhi-Jing Song

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Abstract

The maintenance of intracellular and extracellular adenosine triphosphate (ATP) levels plays a pivotal role in cardiac function. In recent years, burgeoning attention has been directed towards ATP-induced cell death (AICD), revealing it as a distinct cellular demise pathway triggered by heightened extracellular ATP concentrations, distinguishing it from other forms of cell death such as apoptosis and necrosis. AICD is increasingly acknowledged as a critical mechanism mediating the pathogenesis and progression of various cardiovascular maladies, encompassing myocardial ischemia-reperfusion injury, sepsis-induced cardiomyopathy, hypertrophic cardiomyopathy, arrhythmia, and diabetic cardiomyopathy. Consequently, a comprehensive understanding of the molecular and metabolic underpinnings of AICD in cardiac tissue holds promise for the prevention and amelioration of cardiovascular diseases. This review first elucidates the vital physiological roles of ATP in the cardiovascular system, subsequently delving into the intricate molecular mechanisms and metabolic signatures governing

AICD. Furthermore, it addresses the potential therapeutic targets implicated in mitigating AICD for treating cardiovascular diseases, while also delineating the current constraints and future avenues for these innovative therapeutic targets, thereby furnishing novel insights and strategies for the prevention and management of cardiovascular disorders.

Key Words: Adenosine triphosphate induced cell death; Cardiovascular diseases; Myocardial ischemia-reperfusion injury; Molecular mechanisms; Metabolic pathways

Core Tip: Understanding the mechanisms behind adenosine triphosphate (ATP)-induced cell death (AICD) is crucial for addressing various cardiovascular diseases. AICD, triggered by elevated extracellular ATP levels, differs from other forms of cell death and has emerged as a significant contributor to conditions such as myocardial ischemia-reperfusion injury, sepsis-induced cardiomyopathy, and diabetic cardiomyopathy. This review explores the physiological roles of ATP in the cardiovascular system and delves into the molecular and metabolic mechanisms underlying AICD. Identifying therapeutic targets to mitigate AICD holds promise for treating cardiovascular diseases, although challenges remain. This review provides valuable insights and strategies for preventing and managing cardiovascular disorders.

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INTRODUCTION

Over the past decade, the Committee on Cell Death Nomenclature has diligently crafted a comprehensive delineation of cell demise, integrating various perspectives encompassing morphology, biochemistry, and functionality[1]. Studies have made novel insights into the mechanisms governing diverse cell death mechanisms. Research has elucidated the intricate interplay of apoptosis, necrotic apoptosis, pyroptosis, and apoptosis in the etiology of cardiovascular disorders[2]. Adenosine triphosphate (ATP) serves as a multifaceted signaling molecule within cells, as it assumes a pivotal role in cellular energy metabolism. There has been a recent surge in investigations delving into ATP-induced cell death (AICD). AICD represents a distinct mode of cellular demise elicited by heightened extracellular ATP (eATP) levels, distinguishing it from conventional forms of cell death like apoptosis and necrosis. Nonetheless, the specific methods and modalities behind AICD continue to be unresolved [3].

Intracellular ATP typically maintains a delicate equilibrium, serving as a pivotal currency for energy transfer, signaling cascades, and cellular metabolism. Both external stimuli or internal insults can perturb this balance, leading to disruptions in intracellular ATP homeostasis, eATP release, and ultimately cellular demise[2]. Concurrently, AICD causes the release of inflammatory mediators, inducing local or systemic inflammatory cascades and causing metabolic dysregulation. Among the myriad metabolic alterations observed in cardiovascular diseases, lipid metabolism disorders prominently stand out [4]. Additionally, lipid metabolism contributes to the deposition of heat-sensitive proteins during disease onset, underscoring the intricate interplay between lipid metabolism and thermal protein deposition. Nevertheless, excessive thermal protein deposition can induce an overwhelming inflammatory response and tissue damage, exacerbating cardiovascular disease progression and prognosis[5,6].

During AICD, alterations in phospholipid distribution across the cell membrane are observed alongside disruptions in ATP homeostasis, culminating in membrane destabilization and rupture. This phenomenon is intricately linked to cellular damage and inflammation in cardiovascular pathologies[7]. Investigations have elucidated the mechanism underlying ATP-mediated T cell demise through P2X7 receptor (P2X7R) activation[8]. Consequently, P2X7R expression emerges as a pivotal determinant of AICD, not only offering insights into the immunomodulatory mechanisms underlying cardiovascular diseases but also presenting novel avenues for therapeutic intervention[9,10].

To date, substantial evidence underscores the intricate association between AICD and cardiovascular disease pathogenesis, implicating inflammatory responses, cellular damage, and immune dysregulation as pivotal mediators. In this comprehensive review, we elucidate the intricate regulation of ATP homeostasis and delineate the underlying mechanisms of lipid metabolism. Moreover, we delve into the progression of AICD in cardiovascular pathologies and explore its potential implications in the context of arrhythmias.

MECHANISM AND REGULATION OF ATP HOMEOSTASIS AND AICD

As a multifaceted signaling molecule, ATP orchestrates pivotal biological activities within cellular microenvironments,

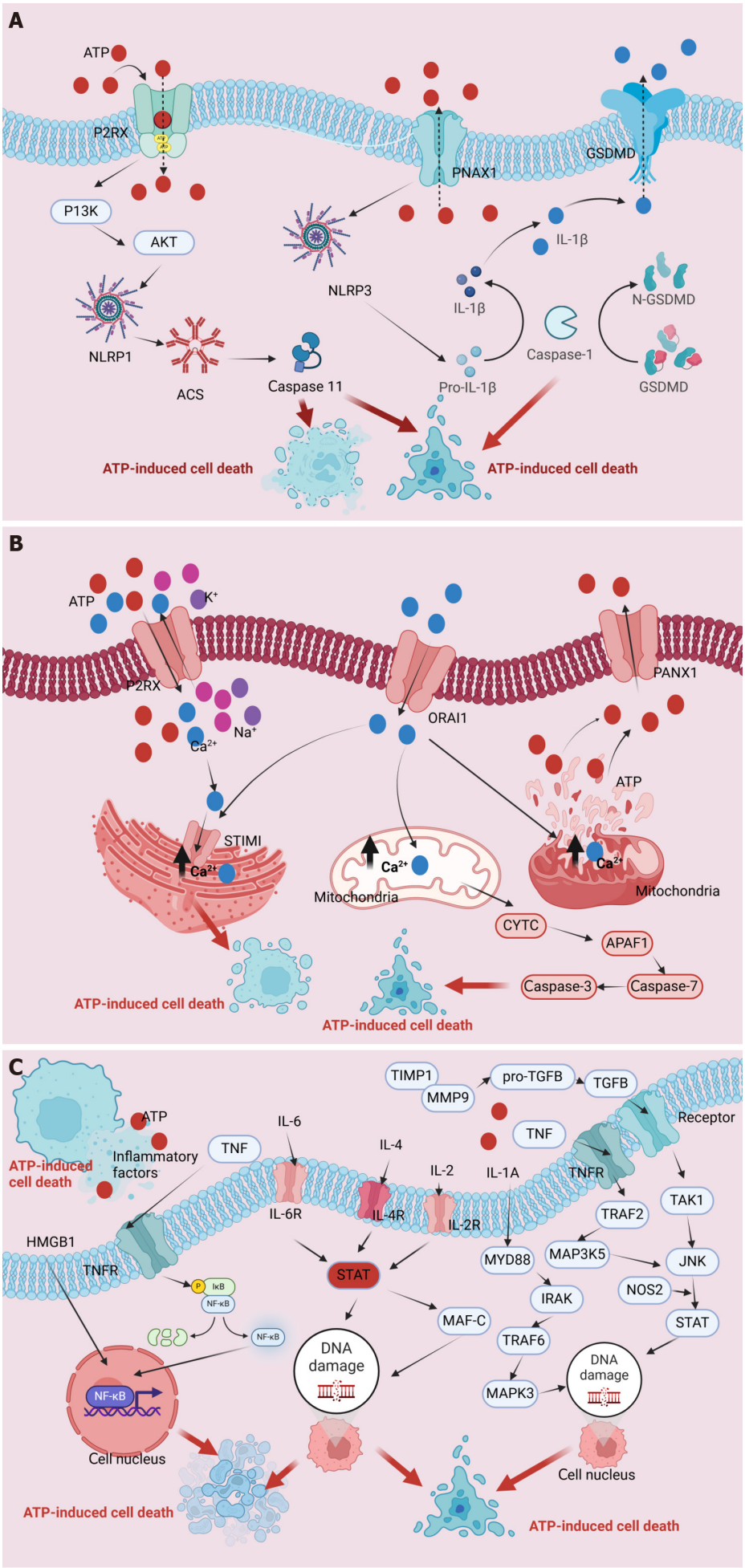
including metabolic processes, signal transduction cascades, and energy transfer. The intricate balance of intracellular ATP levels, termed ATP homeostasis, is meticulously maintained through the interplay of synthesis and utilization processes within cells. However, this equilibrium can be disrupted following internal injuries or external stimuli, leading to elevated extracellular ATP (eATP) levels and subsequent intracellular ATP release[11]. This perturbation results in AICD, mediated by several well-elucidated mechanisms and regulatory pathways. ATP primarily engages with extracellular P2R proteins, particularly the P2X7R family, triggering a cascade of events that includes the activation of associated receptors such as NOD-like receptor family pyrin domain-containing protein 1 (NLRP1) and NLRP3. This activation cascade meticulously coordinates apoptotic signals, encompassing caspases-1, -3, and -11, while also implicating necrotic effectors, such as gasdermin E and gasdermin D, ultimately leading to cellular demise[2]. Secondarily, ATP's interaction with ion channels on the cell membrane modulates ion balance, notably through P2X7R activation-induced opening of ion channels, leading to intracellular calcium ion (Ca^{2+}) accumulation within various cellular compartments, including the Golgi apparatus and mitochondria. This aberrant Ca^{2+} influx induces nuclear DNA damage, precipitating cellular demise. Additionally, ATP triggers mitochondrial dysfunction, evident in the loss of mitochondrial membrane potential, disruption of the mitochondrial respiratory chain, production of reactive oxygen species (ROS), and the disruption of mitochondrial membrane permeability. These aberrations culminate in cellular demise. Moreover, ATP induces immune-inflammatory responses and cell death pathways, leading to the release of inflammatory mediators such as interleukin (IL)-1β, IL-18, tumor necrosis factor (TNF)-α, IL-2, IL-4, IL-6, IL-10, C-C chemokine ligand 5, and CXC motif chemokine ligand 2, ultimately driving cell death (Figure 1)[12].

ATP IN THE HEART INDUCES CELL DEATH

Upon external stimuli or internal injury, elevated eATP levels and intracellular ATP release induces cell demise. ATP induces cellular demise by inducing mitochondrial membrane potential loss through membrane K^+/Na^+ imbalance, mitochondrial respiratory chain disruption, ROS production, and linear membrane permeability alterations. As a result, it coordinates immune-inflammatory reactions, initiates cell death pathways and AICD, leading to the secretion of inflammatory mediators including IL-1β, IL-18, TNF-α, IL-2, IL-4, IL-6, IL-10, C-C chemokine ligand 5, and CXC motif chemokine ligand 2, ultimately resulting in cellular demise[2]. Additionally, P2 receptor-mediated ATP exerts an anti-apoptotic effect, involving pathways such as phosphoinositide 3-kinase, extracellular signal regulated kinase 1 and 2, mitoKATP, and nitric oxide synthase pathway[13]. Moreover, the production of ROS and oxidative stress serve as central mechanisms responsible for cellular damage and dysfunction. Sirtuin 6 (SIRT6), a member of the sirtuin family of NAD^+-dependent class III deacetylases, holds a pivotal role in resisting oxidative stress. SIRT6 upregulates AMP/ATP levels and activates the adenosine 5'-monophosphate-activated protein kinase (AMPK)-forkhead box O3α (FoxO3α) axis, triggering the expression of downstream antioxidant genes, such as manganese superoxide dismutase and catalase. This process alleviates intracellular oxidative stress and confers protection against ischemic heart injury[14]. Furthermore, myocardial ischemia-reperfusion injury (IRI) involves multiple mechanisms, including ROS production, changes in cellular osmotic pressure, and inflammatory reactions. Calcium overload, oxygen level fluctuations, and mitochondrial ROS are major contributors to the irreversible opening of the mitochondrial permeability transition pore (mPTP). These processes are intricately associated with NLRP3 inflammasome activation, governing the maturation and secretion of IL-1β and IL-18[15]. Consequently, upregulation of the caspase-1 pathway and IL-18 release further exacerbates cell death. Moreover, endothelial dysfunction occurs regardless of myocardial IRI presence, resulting from oxygen level fluctuations, reduced nitric oxide production, and excessive ROS generation. This ultimately leads to the expression of adhesion molecules and leukocyte infiltration. The central role of the NLRP3 inflammasome in modulating coronary blood flow alterations *via* endothelial dysfunction underscores its significance in ischemic heart disease pathology[16].

Additionally, ATP interacts with peripheral purine type 2 receptors, specifically P2X7R, while simultaneously activating associated receptors, such as NLRP1 and NLRP3. This activation triggers apoptotic signals involving caspase-1, caspase-3, and caspase-11, and involves necrotic proteins like gasdermin E and gasdermin D[2]. Caspase-1 has emerged as a molecular target with the potential to impede cardiovascular disease progression, notably heart failure (HF), owing to its pivotal role in fostering inflammation and cardiomyocyte loss. Studies suggest that left ventricular assist device implantation modulates caspase-1 expression levels, thus altering inflammatory and apoptotic aspects of the heart. Inflammation appears pivotal in modulating caspase-1 signaling and its downstream effects, including apoptosis. However, caspase-1 deficiency exacerbates myocardial hypertrophy in renal ischemia-reperfusion mouse models[17,18]. Additionally, inflammation assumes a crucial role in HF onset, progression, and prognosis. The NLRP3 inflammatory complex serves as a pivotal hub in chronic inflammatory responses, fostering the generation of pro-inflammatory cytokines IL-1β and IL-18, thereby exacerbating inflammation. Thus, inhibition of downstream factors of the NLRP3 inflammatory complex and its signaling pathway holds promise as a novel intervention strategy for HF treatment[19].

However, pharmacological inhibition of eATP or genetic ablation of P2X7Rs disrupts the function of the myocardial NLRP3 inflammatory complex during stress overload, highlighting the pivotal role of the ATP/P2X7 axis in cardiac inflammation and hypertrophy. eATP induces hypertrophic alterations in cardiomyocytes *via* an NLRP3- and IL-1β-dependent mechanism. Research on the sympathetic nervous system indicates that sympathetic efferent nerves are the main source of eATP. The depletion of ATP released by sympathetic efferent nerves and the elimination of cardiac afferent nerves or lipophilic β receptors lead to reduced cardiac eATP levels, subsequently inhibiting the activation of the NLRP3 inflammatory complex, IL-1β production, and adaptive myocardial hypertrophy in response to pressure overload [20].


A
ATP
P2RX
PNAX1
GSDMD
P13K
AKT
IL-1β
NLRP3
IL-1β
N-GSDMD
NLRP1
ACS
Caspase 11
Caspase-1
Pro-IL-1β
GSDMD
ATP-induced cell death
ATP-induced cell death
B
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K+
P2RX
PANX1
Na+
Ca2+
ORAI1
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Mitochondria
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CYTC
APAF1
Caspase-3
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ATP-induced cell death
ATP-induced cell death
C
TIMP1
MMP9
pro-TGFB
TGFB
Receptor
ATP
IL-6
TNF
TNF
ATP-induced cell death
Inflammatory factors
IL-4
IL-2
IL-1A
TNFR
TAK1
IL-6R
IL-4R
IL-2R
TRAF2
HMGB1
TNFR
STAT
MYD88
MAP3K5
JNK
IκB
NF-κB
IRAK
NOS2
NF-κB
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STAT
DNA damage
TRAF6
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NF-κB
MAPK3
Cell nucleus
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ATP-induced cell death
ATP-induced cell death

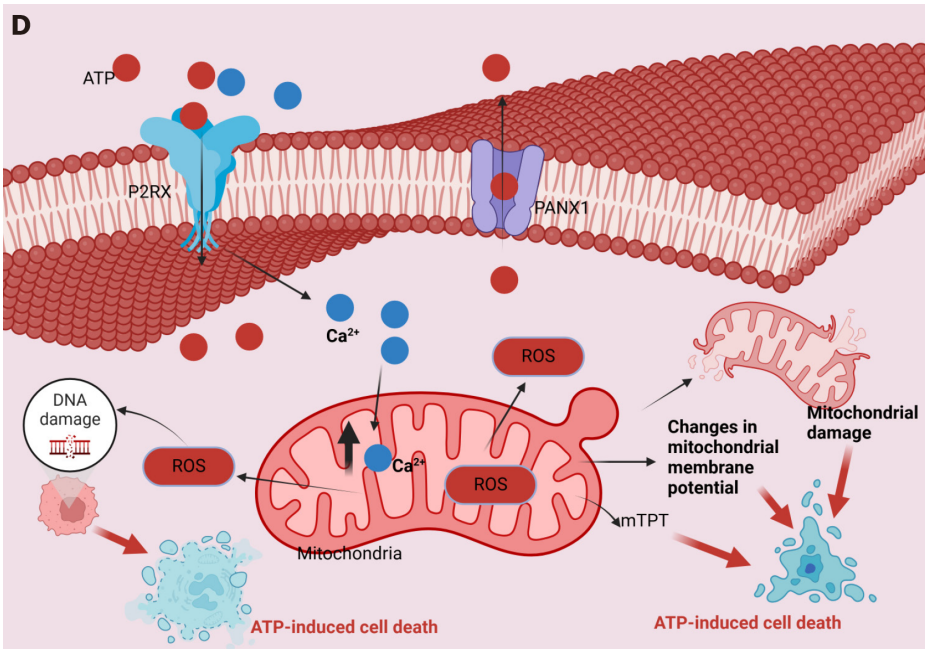

Figure 1 Regulation mechanism of adenosine triphosphate homeostasis and adenosine triphosphate-induced cell death. A: P2 receptor activation pathway; B: Ca^{2+} pathway induces cell death pathways; C: The induction of cell death by adenosine triphosphate results in the release of immune inflammatory factors and activation of immune pathways that further promote cell death; D: The concurrent depletion of mitochondrial membrane potential, disruption of mitochondrial integrity, generation of reactive oxygen species, and alterations in mitochondrial membrane permeability jointly contribute to the ultimate demise of the cell. ATP: Adenosine triphosphate; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; PNAX1: Pannexin-1; GSDMD: Gasdermin D; NLRP3: NOD-like receptor family pyrin domain-containing protein 3; IL: Interleukin; ACS: Apoptosis-associated speck-like protein containing a caspase recruitment domain; ORAI1: Calcium release activated calcium channel protein 1; STIM1: Stromal interaction molecule 1; CYTC: Cytochrome c; APAF1: Apoptotic protease-activating factor 1; HMGB: High-mobility group box; TNF: Tumor necrosis factor; TIMP1: Tissue inhibitor of matrix metalloprotease 1; MMP: Matrix metalloproteinase; TGF: Transforming growth factor; NF-κB: Nuclear factor κB; STAT: Signal transducer and activator of transcription; MYD88: Myeloid differentiation factor-88; TRAF2: Tumor necrosis factor receptor associated factor 2; TAK1: Beta-activated kinase 1; JNK: c-Jun N-terminal kinase; MAP3K5: Mitogen-activated protein kinase kinase kinase 5; IRAK: Interleukin-1 receptor-associated kinase; MAF-C: MAF BZIP transcription factor C; NOS2: Nitric oxide synthase; ROS: Reactive oxygen species; mTPT: Mitochondrial permeability transition.

Moreover, the chloride/bicarbonate ion exchangers AE1, AE2, and AE3 are integral membrane proteins involved in pH regulation across vertebrate tissues, modulated by neurohormonal regulation. Co-expression of AE1 and AE3 in cardiomyocytes facilitates purine agonist ATP-induced cation exchange. ATP stimulates the phosphorylation of tyrosine residues on AE1, leading to the activation of Fyn tyrosine kinase and the binding of Fyn and FAK to AE1. Inhibiting Src-family kinases *in vivo* using compounds like genistein, herbimycin A, or ST638 effectively blocks ATP-triggered AE1 activation. Microinjection of anti-C-terminal Src kinase 1 antibodies or recombinant C-terminal Src kinase, which inhibits Src-family kinase activation, significantly reduces ATP-induced AE1 activation. Moreover, microinjection of anti-FAK antibodies and expression of Phe397 FAK dominant negative mutants in cardiomyocytes impede purine-induced AE1 activation. As a result, tyrosine kinases have emerged as crucial regulators in the acute modulation of intracellular pH and cellular function, particularly in the excitation-contraction coupling of cardiomyocytes[21]. Mild mitochondrial uncoupling in cardiomyocytes triggered by uncoupling agents prompts signal transducer and activator of transcription 3 (STAT3) activation and ATP upregulation. However, excessive mitochondrial uncoupling results in STAT3 inhibition, ATP depletion, and subsequent cellular damage. The development of mitochondrial uncoupling agents with a precisely calibrated dose window that induces mild uncoupling represents a promising approach for enhancing cardiac protection [22].

The human heart relies on a diverse range of energy substrates to maintain its normal contractile function. Under physiological conditions, glucose and long-chain fatty acids (FAs) serve as the primary substrates involved in cardiometabolic processes. However, during stress, there is a shift in substrate preference towards glucose or FAs, which has been implicated in heart disease[23,24]. Research indicates that the pannexin-1 channel is responsible for releasing ATP, subsequently activating fibroblasts within the heart[25]. When cardiac fibroblasts are exposed to ATP or its non-hydrolyzed analog benzoyl ATP, they undergo apoptosis. Similarly, TNF-α, a cytokine linked to the advancement of chronic HF, exacerbates cell death. Similar effects were observed in a murine cardiac muscle cell line, where TNF-α counteracted the decrease in *P2X(6)* mRNA expression typically seen with prolonged exposure to agonists. This indicates that TNF-α disrupts a protective mechanism intended to prevent calcium overload and eventual calcium-dependent cell death by inhibiting ATP-induced P2X6 desensitization[26]. Moreover, stromal interaction molecule 1, a well-known calcium detector within the endoplasmic reticulum calcium reservoir, is increasingly acknowledged as a crucial factor in regulating cardiac hypertrophy and diabetic cardiomyopathy[27,28]. Consequently, a range of proteins involved in regulating cellular ATP homeostasis play crucial roles in AICD[16-20,23-26,29-58] (Table 1).

Table 1 Principal modulators of iron metabolism involved in adenosine triphosphate-induced cell death

Gene	Function	Role in AICD	Effects of genetic deletion or overexpression	Ref.
P2RX7	Inflammation and immune regulation, neurotransmission, apoptosis and autophagy	Activates inflammatory mediators and increases calcium ions	Its activation is closely related to the development of cardiac diseases such as cardiomyopathy, myocardial infarction and myocarditis	[29]
CASP3	Execution stage of apoptosis	CASP3 cleavage by CASP1/4/5/11 forms pores, releasing proinflammatory cytokines	Caspase contributes to the progressive decline in systolic function observed in heart failure by facilitating the degradation of myofibrillar protein. Therefore, the selective inhibition of CASP3's proteolytic function may offer a promising strategy for mitigating or reversing the effects of heart failure	[30]
PANX1	Widely involved in ATP and ion permeability, can effectively reduce CCI induced mechanical pain and thermal hyperalgesia	P2X7 activation opens PANX1 channels, releasing ATP and triggering cell death pathways	PANX1 channels release ATP, which then activates fibroblasts in the heart and promotes the development of cardiac fibrosis after myocardial infarction. PANX1 deficiency results in atrioventricular block, delayed ventricular depolarization, significantly prolonged QT interval and rate-corrected QT interval, and an increased incidence of atrial fibrillation following intraatrial burst stimulation	[25,31]
NLRP3	It plays an important role in inflammation and immune responses and can sense various stimuli inside and outside the cell	Upon activation by stimulatory signals, NLRP3 forms an inflammasome, triggering CASP1 activation. This in turn leads to the release of cytokines and apoptosis	Involved in the process of ischemia-reperfusion injury and endothelial dysfunction, affecting the changes of coronary blood flow; participate in chronic inflammatory response and myocardial hypertrophy, accelerate the production of pro-inflammatory cytokines, leading to the occurrence and development of heart failure	[16,19,20]
CASP1	Membrane hyperpolarization; mitochondrial depolarization and positive regulation of IL-1α production	CASP1 triggers the processing of cytokines, pyrosis, and inflammation, thereby orchestrating the inflammatory response	Involved in inflammation and loss of heart muscle cells. LVAD implantation may alter the inflammatory and apoptotic characteristics of the heart by regulating CASP1 expression levels. CASP1 deficiency resulted in more obvious myocardial hypertrophy in renal ischemia-reperfusion mice	[17,18]
P2RY1	Activates downstream signals	P2RY1 has the capacity to elevate calcium ion levels within the Golgi apparatus	*P2RY1* gene is associated with the development of heart disease and the response to anticoagulant therapy. Meanwhile, the polymorphism of *P2RY1* gene is associated with the onset age of myocardial infarction, which may have a protective effect or influence the progression of myocardial infarction	[32]
P2RY11	Immune regulation, neurotransmission, insulin secretion	It plays a role in immune inflammatory mechanisms	The *P2RY11* gene is implicated in the regulation and repair of inflammatory processes in the heart. Enhanced expression of this gene may facilitate myocardial fibrosis and play a crucial role in the restoration of cardiac function following acute myocardial infarction	[20]
ORAI1	Calcium ion coupling is involved in the activation and proliferation of immune cells	Increased intracellular calcium ions	The *ORAI1* gene plays an important role in the heart, especially in cardiac diseases such as cardiac hypertrophy and heart failure, and is involved in regulating the flow of calcium ions in cardiomyocytes, affecting the systolic and diastolic functions of the heart	[33]
STIM1	Calcium ion sensor. It is involved in immune cell activation, muscle contraction and cell cycle regulation	STIM1 responds to ATP-induced calcium influx by activating ORAI1, thereby contributing to cell death	STIM1 plays a pivotal role in regulating SOCE and Ca^{2+} storage replenishment, crucial for heart development and growth. Additionally, the *STIM1* gene modulates energy substrate preferences in the heart, with implications for metabolic disorders like cardiac hypertrophy and diabetic cardiomyopathy. Elucidating its molecular mechanisms could lead to the discovery of novel therapeutic targets for the prevention and treatment of cardiac metabolic diseases	[23,24]
CASP8	Modulating apoptosis	CASP8 causes apoptosis	It is involved in apoptosis and cytokine processing and is crucial for heart development and hematopoietic function. Lack of CASP8 leads to defects in heart muscle development and a decrease in hematopoietic progenitor cells	[34]
CASP9	Modulating apoptosis (programmed	CASP9 causes apoptosis	The *CASP9* gene is involved in mitochondria-	[35]

	cell death)		mediated apoptosis in the heart. As an inhibitor of CASP9, HAX-1 protein protects cardiomyocytes from apoptosis and maintains cardiac function	
CASP7	The executive stage of catalytic apoptosis	CASP7 causes apoptosis	Inhibition of CASP7 can reduce myocardial infarction size and apoptosis, providing a new strategy for the treatment of myocardial ischemia	[36]
P2RX3	Involved in the conduction of sensory neurons and the perception of pain	NA	It is involved in pain signal transduction caused by myocardial ischemia and is a potential therapeutic target	[37,38]
NLRP1	Regulates inflammation and immune response	Upon activation, NLRP1 triggers CASP1 activation, leading to the induction of pyroptosis and the release of IL-1β and IL-18	*NLRP1* gene is closely related to cardiovascular diseases. The NLRP1 inflammatory complex expressed by *NLRP1* gene is involved in the pathogenesis of cardiovascular diseases and may be a potential therapeutic target	[39]
P2RX4	Involved in cellular signaling	P2RX4 promotes AICD (pyroptosis) through the activation of the NLRP3 inflammasome, resulting in the production of IL-1β and IL-18	The *P2RX4* gene in the heart may influence blood pressure and kidney function by regulating vascular tension	[40]
P2RX5	Involved in neurotransmission and pain regulation	NA	*P2RX5* gene may be related to varicose veins and synaptic vesicles in the heart, and it is involved in cardiac development and functional regulation	[41]
SAPK	Involved in cellular stress response and inflammation regulation	ATP triggers cell death through SAPK pathways, modulating apoptosis, necrosis, and stress signaling mechanisms	It plays a role in regulating cardiomyocyte hypertrophy and apoptosis. MiR-350 induces cardiomyocyte hypertrophy by inhibiting the SAPK pathway, suggesting that the *SAPK* gene is a key regulator of pathologic heart hypertrophy and apoptosis	[42]
p38 MAPK	It is involved in cell signaling, cell stress response, inflammation regulation, apoptosis and other biological processes	ATP stimulates p38MAPK, ultimately leading to cell death *via* apoptosis and necrosis	It is involved in the regulation of cardiomyocyte proliferation, apoptosis and hypertrophy. Involved in the regulation of stress response and cardiomyocyte differentiation, its balance in terms of protective and deleterious effects affects cardiac function	[43]
ASK1	It regulates biological processes such as cell survival and death, inflammatory response, cell stress response, and oxidative stress	Elevated levels of ATP trigger cellular stress, activating ASK1 and subsequent downstream pathways, ultimately leading to cell death	ASK1 activation can lead to hypertrophy, fibrosis and dysfunction of the heart	[44]
NOX2	It plays a crucial role in the generation of reactive oxygen species within cells, thereby regulating physiological processes including cell signaling, immune response, and oxidative stress	ATP stimulates NOX2 activation, leading to ROS production, which induces oxidative stress and potentially triggers cell death	Increased NOX2 activity may lead to diaphragmatic dysfunction, which can trigger symptoms of heart failure	[45]
Bax	It is involved in regulating biological processes such as cell development, immune response and tumor suppression	Elevated levels of ATP trigger Bax activation, resulting in mitochondrial dysfunction and apoptotic cell death	It is involved in the process of myocardial apoptosis induced by ischemia	[46]
MLC	It plays a pivotal role in regulating muscle contraction and movement, thereby influencing biological processes including cell morphology and motility	Depletion of ATP impairs muscle contraction by compromising myosin function and cellular viability	Reduced MLC expression is associated with the pathogenesis of heart failure	[47]
ROCK I	It orchestrates biological processes encompassing cell morphology, polarity, and contraction, integral to functions like cell migration, muscle contractility, and cytoskeletal remodeling	ATP stimulates P2X7Rs, triggering apoptosis through the Rho/ROCK pathway, potentially involving ROCK I	It plays a vital role in signal transduction and regulation within cardiomyocytes; involvement in the regulation of Cav 3.2 channels and stabilization of HIF-1α may increase the risk of arrhythmia during ischemia	[48,49]
ERK1/2	It is involved in the regulation of biological processes such as cell growth, proliferation, differentiation and cell survival, and affects cell signaling and cell fate determination	ERK1/2 promotes cell survival and opposes apoptosis, yet sustained activation can ultimately trigger cell death. By activating the ERK1/2 pathway, it plays a pivotal role in determining cell fate	Signaling pathways involved in adaptive or adaptive remodeling; involved in cardiomyocyte hypertrophy and survival	[50,51]
P2X6	It is involved in the regulation of biological processes such as cell	Activation may elevate calcium levels, potentially initiating cell	*P2X6* gene is up-regulated in chronic heart failure, and its activation may be involved in the	[26]

	signaling, apoptosis and inflammatory response, and may play a role in neurotransmitter release and pain transmission	death mechanisms	pathological process of chronic heart failure	
CYTC	The electron transport molecules in the mitochondrial respiratory chain are involved in cellular respiration and energy production, as well as regulating the process of apoptosis	During cellular stress, the release of cytochrome c from mitochondria initiates the apoptotic process	Phosphorylation at Thr50 increases with aging, which can inhibit cardiomyocyte apoptosis, especially apoptosis caused by hypoxia/reoxidation, and protect cardiac function	[52]
TNF-α	It plays a crucial role in regulating biological processes encompassing inflammation, immune response, and apoptosis, thereby exerting significant influence on inflammatory conditions, immune disorders, and tumor progression	ATP triggers cell death by activating TNF-α and initiating apoptosis or necroptosis pathways. In response to ATP, immune cells produce TNF-α, thereby amplifying the cellular response	The *TNF-α* gene plays a key role in heart failure, promoting inflammation and cell damage. Increased expression of TNF-α in failing hearts correlates with disease severity and is a potential therapeutic target	[53]
P2RY5	It is involved in cell signaling, skin development, pigmentation and other biological processes, which may be related to hair follicle development and skin pigment distribution regulation	NA	In the heart, it may be associated with inflammation and Crohn's disease activity index, and its expression level may be associated with cardiac dysfunction	[54]
P2RY14	It plays a pivotal role in regulating biological processes including immune and inflammatory responses, potentially contributing to the activation of immune cells and the release of inflammatory mediators	NA	*P2RY14* gene may be involved in the inflammatory process of ischemic acute kidney injury in the heart, and its expression changes are related to the development of AKI after cardiac surgery, which may be a potential therapeutic target for preventing and alleviating ischemic AKI	[55]
P2RY13	It regulates cellular immune response, participates in the regulation of inflammatory response and immune cell activation, and plays a significant role in immune regulation and inflammatory processes	P2Y13 may play a significant role in ADP receptors, primarily implicated in maintaining ATP homeostasis	Variations in the *P2RY13* gene are associated with cardiovascular risk markers that may affect heart health	[56]
P2RY12	It plays a crucial role in platelet aggregation, thrombosis, and hemostasis, thereby contributing significantly to blood coagulation and vascular repair processes	P2Y12 may play a role in ADP receptors, mainly involved in ATP homeostasis	The receptor encoded by the *P2RY12* gene regulates platelet aggregation in the heart, preventing clots from forming. The use of P2Y12 inhibitors protects the heart and reduces the risk of myocardial infarction and reperfusion injury	[57]
P2RY6	It is integral to cell signaling and inflammation regulation, potentially contributing to the activation of immune cells and the secretion of inflammatory mediators	P2Y6 may play a role in calcium signaling processes	In hypertrophic cardiomyopathy, *P2RY6* gene-associated lncRNAs exhibit significant upregulation and may regulate cardiac growth, serving as potential biomarkers and therapeutic targets for hypertrophic cardiomyopathy	[58]

AICD: Adenosine triphosphate-induced cell death; P2RX7: Purinergic receptor P2X7; CASP3: Caspase-3; PANX1: Pannexin-1; NLRP3: NOD-like receptor family pyrin domain-containing protein 3; CASP1: Caspase-1; P2RY1: P2Y purinoceptor 1; P2RY11: P2Y purinoceptor 11; ORAI1: Calcium release activated calcium channel protein 1; STIM1: Stromal interaction molecule 1; CASP8: Caspase-8; CASP9: Caspase-9; CASP7: Caspase-7; P2RX3: Purinergic receptor P2X3; NLRP1: NOD-like receptor family pyrin domain-containing protein 1; P2RX4: P2X purinoceptor 4; P2RX5: P2X purinoceptor 5; SAPK: Stress-activated protein kinase; p38 MAPK: p38 mitogen-activated protein kinases; ASK1: Apoptosis signal regulating kinase 1; NOX2: NADPH oxidase 2; Bax: BCL2 associated X; MLC: Myosin light chain; ROCK I: Rho-associated, coiled-coil containing protein kinase 1; ERK1/2: Extracellular signal regulated kinase 1 and 2; P2X6: P2X purinoceptor 6; CYTC: Cytochrome c; TNF-α: Tumor necrosis factor alpha; P2RY5: P2R purinoceptor 5; P2RY14: P2R purinoceptor14; P2RY13: P2R purinoceptor 13; P2RY12: P2R purinoceptor 12; P2RY6: P2R purinoceptor 6; ATP: Adenosine triphosphate; CCI: Chronic constriction injury; IL: Interleukin; NA: Not available; SAPK: Stress-activated protein kinase; ROS: Reactive oxygen species; TNF: Tumor necrosis factor; LVAD: Left ventricular assist device; HAX-1: Hematopoietic lineage substrate-1-associated protein X-1; MLC: Myosin light chain; HIF-1α: Hypoxia-inducible factor-1α; AKI: Acute kidney injury; lncRNA: Long noncoding RNA.

AICD IN CARDIOVASCULAR DISEASE

The coordinated activation of various gene networks involving energy usage, mitochondrial ATP synthesis, heart muscle contraction, and ion movement is essential for preserving normal heart function. Transcriptional regulators, such as estrogen-related receptors (ERRs), play pivotal roles in coordinating these gene networks, regulating cellular metabolism, and contraction mechanisms. ERRs, particularly ERRα and ERRγ, have emerged as critical regulators of cardiac function, as their deficiency leads to cardiac dysfunction, especially under increased workload conditions. Intriguingly, in diabetic cardiomyopathy, metabolic inflexibility is linked to increased mitochondrial FA oxidation and ERRγ expression, hinting at a possible role of persistent ERRγ expression in cardiogenic outcomes[27]. Furthermore, studies have revealed the regulatory role of pannexin-1 half-channel activity by eATP-sensitive P2X7Rs. Nonetheless, the precise mechanisms

governing how eATP-sensitive P2X7Rs regulate the opening and closing of Px1 half-channels remain largely elusive. Evidence suggests that under pathological conditions like ischemia, P2X7R activation leads to the opening of Px1 half-channels, resulting in the influx of large amounts of extracellular Ca^{2+} and the subsequent release of intracellular ATP, ultimately culminating in cell death[28]. Furthermore, the seamless provision of energy is paramount for maintaining the normal contractile and relaxation functions of the heart. Therefore, metabolic disorders and impaired mitochondrial bioenergy, leading to disruptions in ATP production, are implicated in various heart diseases[59].

Myocardial IRI

IRI represents a prevalent and life-threatening clinical complication affecting various organs, including the heart, liver, kidneys, and brain[60]. Myocardial IRI is characterized by multifaceted mechanisms, including the generation of ROS, alterations in cellular osmotic balance, and inflammatory responses. Excessive calcium, variations in oxygen levels, and the generation of mitochondrial ROS collectively leads to the permanent opening of the mPTP, resulting in harmful effects. ROS generation and subsequent oxidative stress are key mechanisms responsible for cellular damage and dysfunction during cardiac IRI. These processes are intricately connected to NLRP3 inflammasome activation, which facilitates cell demise by enhancing the caspase-1 pathway and IL-18 secretion[15].

NLRP3 belongs to the nucleotide-binding domain (NOD)-like receptor family and is expressed by various immune and non-immune cells. When activated, NLRP3, together with apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and procaspase-1, come together to create the NLRP3 inflammasome complex. This assembly regulates inflammation by cleaving pro-inflammatory cytokines IL-1β and IL-18, promoting pyroptotic cell death[61]. Significantly, targeting the NLRP3 inflammasome holds promise as a therapeutic strategy for ischemic stroke, with MCC950 demonstrating potential clinical efficacy[62]. Moreover, in hypertensive target organ damage, various triggers such as oxidative stress and inflammation activate the NLRP3 inflammasome, leading to the release of pro-inflammatory cytokines that worsen tissue damage and dysfunction[63].

Research using heterozygous SIRT6 knockout [SIRT6 (+/-)] mice and cardiomyocyte models *in vitro* has elucidated SIRT6's role in modulating oxidative stress and myocardial damage during IRI. Partial loss of SIRT6 exacerbates myocardial damage, ventricular remodeling, and oxidative stress. In mice subjected to myocardial I/R, restoring SIRT6 expression *via* direct cardiomyocyte injection of adenovirus vectors to reexpress it rescues the adverse effects of SIRT6 knockout on ischemic hearts. Partial SIRT6 deletion hinders myocardial function recovery after I/R. Importantly, SIRT6 increases AMP/ATP levels, activates the AMPK-FoxO3α axis, and boosts the expression of downstream antioxidant genes, such as manganese superoxide dismutase and catalase. This sequence mitigates intracellular oxidative stress, leading to the protective effect against ischemic heart damage. Thus, SIRT6 activation of FoxO3α in an AMP/ATP-driven, AMPK-dependent manner enhances antioxidant defense mechanisms and suppresses oxidative stress, thereby shielding the heart from IRI[14].

Furthermore, investigations have demonstrated that the reversal of calcium ion entry into cardiac cells can lead to a decrease in mechanical function, disruption of cell ultrastructure, depletion of ATP levels, increase in intracellular calcium ions, and initiation of cell apoptosis. Intracellular calcium overload influences various pathways involved in the apoptotic cascade. Exposure of the heart to a brief period without calcium followed by reintroduction of calcium results in significant structural and functional changes in the myocardium, a phenomenon commonly known as the "calcium paradox". The heart experiencing the calcium paradox serves as an exemplary model for understanding the mechanisms of cellular injury caused by intracellular calcium overload at the cardiomyocyte level after reoxygenation following hypoxia or ischemia. A study aimed to determine whether cardiomyocytes undergo apoptosis after 5 minutes of calcium depletion followed by 30 minutes of calcium restoration. It is important to note that cardiomyocytes subjected to 30 minutes of ischemia followed by 60 minutes of reperfusion have exhibited apoptotic cell death[64].

Diabetic cardiomyopathy

Diabetes is a common comorbidity in cardiovascular disease, heightening the heart's susceptibility to IRI. As a result, individuals with diabetes often have a worse prognosis following acute myocardial infarction compared to those without diabetes. Importantly, diabetes exacerbates myocardial IRI by activating the NADPH oxidase pathway in an AMPK-dependent manner, ultimately resulting in different types of programmed cell death[65,66]. Additionally, diabetic cardiomyopathy, a condition marked by heart muscle dysfunction regardless of coronary artery disease and hypertension, is worsened by diabetes. Mitochondrial dysfunction emerges as a key feature of diabetic cardiomyopathy, with mitochondria exerting varied effects on cardiomyocyte function, including oxidative stress, metabolic shifts, intracellular signaling, and cell death. Normally, damaged mitochondria undergo mitophagy, a process that breaks down dysfunctional mitochondria for lysosomal degradation. However, impaired mitophagy leads to the buildup of dysfunctional mitochondria, resulting in cardiomyocyte death[60,67].

Type 2 diabetes mellitus (T2DM) is a rapidly spreading condition, with cardiovascular issues being the leading cause of death among diabetic patients. Prolonged high blood sugar levels impair vascular function by affecting the function of vascular smooth muscle cells (VSMCs) and intracellular calcium dynamics. To investigate intracellular calcium signaling in VSMCs from Zucker diabetic obese rats, Fura-2/AM calcium imaging was performed. The findings revealed that T2DM reduces calcium release from the sarcoplasmic reticulum while increasing the activity of store-operated channels. Additionally, key calcium export mechanisms (SERCA, PMCA, and NCX) show heightened activity during the initial stages of ATP-induced calcium transients. However, during later stages, calcium entry increases alongside a decrease in NCX, SERCA, and PMCA activity, resulting in a shortened decay time of ATP-induced calcium transients during the early phase and an increased amplitude during the subsequent plateau. Elevated cytoplasmic calcium levels in VSMCs may contribute to vascular dysfunction associated with T2DM[68].

Heart damage due to sepsis

Sepsis stands as a prominent global cause of mortality and morbidity. Autophagy is a cellular process that facilitates the degradation and recycling of damaged organelles and proteins, and it is posited to confer a protective effect against sepsis-induced myocardial dysfunction (SIMD). Experimental models of septicemia were established in male Sprague-Dawley rats *via* cecal ligation and puncture. Assessment of cardiac damage involved examining serum markers, echocardiographic parameters, histological analysis with hematoxylin and eosin staining, evaluating cardiac mitochondrial health using transmission electron microscopy, measuring ATP and mitochondrial DNA levels, and quantifying cardiac oxidative stress using REDOX markers in cardiac tissue samples. To assess gene and protein expression levels, real-time polymerase chain reaction and western blotting techniques were utilized. Chromatin co-immunoprecipitation and quantitative real-time polymerase chain reaction were utilized to analyze the binding of histone deacetylase (HDAC) to the phosphatase and tensin homolog (PTEN) promoter and the histone acetylation level of the PTEN promoter.

The results revealed that valproic acid (VPA) alleviated mitochondrial impairment, oxidative stress, and inflammation in septic rats, thereby reducing SIMD by enhancing myocardial autophagy levels. This effect was mediated by VPA-induced autophagy, which downregulated PTEN expression through HDAC1 and HDAC3 in septic rat myocardial tissue. Furthermore, VPA promoted myocardial autophagy by upregulating PTEN expression and inhibiting the protein kinase B/mammalian target of rapamycin pathway, thereby ameliorating SIMD[69]. Moreover, research has highlighted the protective effects of irisin against both acute and chronic myocardial injury. Treatment with irisin mitigated cardiomyocyte death and myocardial dysfunction induced by lipopolysaccharide (LPS). Mechanistically, LPS exposure induced mitochondrial oxidative damage, resulting in ATP depletion in cardiomyocytes and activating apoptosis through caspase. Conversely, irisin preserved mitochondrial function by inhibiting LPS-induced mitochondrial fission mediated by dynamin-related protein 1. Notably, irisin restored the c-Jun N-terminal kinase-large tumor suppressor kinase 2 signaling pathway associated with dynamin-related protein 1-mediated mitochondrial fission activation induced by LPS, suggesting its potential as a promising therapeutic approach for SIMD[70]. Furthermore, exogenous carbon monoxide can regulate mitochondrial energy metabolism by influencing the expression of peroxisome proliferator-activated receptor-gamma coactivator 1-alpha, nuclear respiratory factor 1, and mitochondrial transcription factor A. As a result, it improved cardiac function in sepsis[71].

Hypertrophic cardiomyopathy

M-iPSC-CMs were obtained from a patient harboring a mitochondrial 16S rRNA gene (MT-RNR2). Hypertrophic cardiomyopathy (HCM) represents a condition characterized by cardiac hypertrophy, diastolic dysfunction, and sudden cardiac death, particularly prevalent among young individuals. The involvement of mitochondrial DNA mutations in HCM pathogenesis has been recognized. Induced pluripotent stem cell-derived cardiomyocytes have diminished mitochondrial protein levels, thereby resulting in mitochondrial dysfunction and ultrastructural aberrations. Simultaneously, the mutation resulted in a decrease in the ATP/ADP ratio and mitochondrial membrane potential, ultimately leading to an increased intracellular Ca^{2+} concentration, a characteristic feature of various HCM-specific electrophysiological abnormalities[72]. Furthermore, phosphorus-31 magnetic resonance spectroscopy studies conducted in rats revealed a significant impairment in cardiac energy metabolism, characterized by a reduced phosphocreatine to ATP ratio (-31%, $P < 0.05$)[73]. The *MYBPC3* gene, which encodes myocardial myosin-binding protein C, stands as the predominant genetic factor underlying HCM. Remarkably, myocardial fibrosis (MF) emerged as a pivotal player in HCM development. Nevertheless, the precise mechanism by which mutant MYBPC3 contributes to MF remains unclear. A model featuring R495Q mutant pigs was established using cytosine base editing technology, leading to early onset MF shortly after birth. Intriguingly, the "heart-specific" MYBPC3 gene was transcribed and expressed at the protein level not only in cardiac fibroblasts across different species but also in NIH3T3 fibroblasts. CRISPR-mediated ablation of Mybpc3 in NIH3T3 fibroblasts triggered nuclear factor κB signaling pathway activation, resulting in enhanced expression of transforming growth factor-beta 1 and other proinflammatory genes. Increased levels of transforming growth factor-beta 1 led to the upregulation of hypoxia-inducible factor-1 alpha and its downstream glycolytic targets, such as GLUT1, PFK, and LDHA. This resulted in enhanced aerobic glycolysis and elevated ATP production rates, accelerating cardiac fibroblast activation and ultimately contributing to HCM progression[74].

Potential link between AICD and arrhythmia

Approximately one-third of individuals afflicted with mitochondrial disease experience some manifestation of cardiomyopathy, often characterized by symptoms such as HF and arrhythmias. The primary source of ATP production occurs *via* oxidative phosphorylation of FAs and carbohydrates within the mitochondrial respiratory chain[75]. Mitochondria serve as the principal ATP suppliers, crucial for fulfilling the heart muscle's energy requirements to sustain continuous electrical activity and contractile function. Emerging evidence suggests that mitochondrial dysfunction can deleteriously affect cardiac electrical function by reducing ATP synthesis and triggering excessive ROS production. This disrupts intracellular ion homeostasis and membrane excitability, ultimately increasing the risk of arrhythmias[76]. Furthermore, ventricular fibrillation is closely associated with myocardial ischemia. Sudden cardiac death can be the initial clinical presentation of myocardial ischemia or infarction in approximately 20%-25% of patients. Fatal arrhythmias often result from a complex sequence of pathophysiological abnormalities, arising from intricate interactions among coronary vascular events, myocardial injury, changes in autonomic tone, metabolic conditions, and cardiac ion status. The timing of ischemic onset also plays a crucial role, with a substantial surge in ventricular arrhythmias typically observed within the first few minutes, persisting for about 30 minutes[77].

In large animal hearts, regional ischemia generally induces two distinct stages of ventricular arrhythmia. The first stage (1A), occurring around 5 to 7 minutes after perfusion cessation, is characterized by membrane depolarization, slight

acidification in intracellular and extracellular spaces, and minor disturbances in membrane potential. The subsequent stage of ventricular arrhythmia (1B) emerges between 20 and 30 minutes post-perfusion cessation, during which ischemia-induced changes in K^+ and pH stabilize. The onset of arrhythmia in this stage is presumed to be associated with electrolytic coupling between cells, evident from the rapid rise in tissue impedance preceding arrhythmia. Research has demonstrated that interventions like ischemic preconditioning can attenuate the effects of subsequent ischemia by postponing the emergence of electrolytic coupling between cells, thereby delaying the occurrence of ischemia-induced arrhythmias[78]. Additionally, acute ischemia triggers the opening of K(ATP) channels, inducing cardiomyocyte acidosis and hypoxia, resulting in significant repolarization dispersion across the boundary region. Concurrently, abnormalities in intracellular Ca^{2+} handling manifest within the initial minutes of acute myocardial ischemia, potentially serving as a significant contributor to arrhythmogenesis in individuals with coronary artery disease[77].

AICD IS A PROMISING THERAPEUTIC TARGET IN THE CARDIOVASCULAR SYSTEM

Due to its crucial role in heart disease pathogenesis, AICD holds significant promise as a therapeutic target in the cardiovascular field. Here, we present an overview of diverse small molecules that impede AICD pathways and discuss their potential applications across various heart disease models[30,36,63,79-109] (Table 2). Persistent low-level inflammation is a fundamental factor in various diseases, particularly cardiovascular conditions. While efforts to address inflammation in cardiovascular disease are still in their early stages, they are an area of significant interest. P2X7R, an ATP-activated ion channel, stands out as a promising target for the development of new drugs, primarily involved in regulating inflammatory responses and cell death mechanisms[110]. Due to its pivotal function in inflammation and immune responses, P2X7R stands out as a promising target for treating inflammatory conditions. Research has shown that Rhein hinders ATP/BZATP-triggered calcium increase, pore formation, ROS production, reduced phagocytosis, IL-1β release, and cell death by blocking P2X7Rs in rat peritoneal macrophages[111]. Stimulation of P2X7 and the resulting increase in IL-1β and IL-18 levels are linked to the development of several cardiovascular conditions, such as high blood pressure, artery hardening, tissue damage from restricted blood flow followed by restoration, and heart weakening. However, medications that block P2X7 have shown effectiveness in lowering blood pressure in individuals with hypertension and slowing down artery hardening in experimental animals. Trials in clinical settings have revealed that drugs inhibiting IL-1β and IL-18 can notably lower the likelihood of major negative heart events, including heart attacks and HF[79]. Additionally, P2X7 stands out among P2X receptors because it can operate as both a typical receptor activated by a molecule and a channel that allows substances to pass through, causing cell death when exposed to ATP for extended periods[112]. Furthermore, mild disruption of mitochondrial coupling provides protective effects against various diseases. However, identifying mild disruption induced by chemical agents remains uncertain. Research has shown that typical chemical agents such as FCCP, niacinamide, and BAM15 induce two-phase changes in STAT3 activity in heart muscle cells - boosting STAT3 at low concentrations while suppressing it at high concentrations, albeit with different ranges of doses. Low doses of these agents activate STAT3 by slightly increasing mitochondrial ROS production and subsequently activating JAK/STAT3 in heart muscle cells. Conversely, high doses of these agents lead to STAT3 suppression, reduced ATP production, and heart muscle cell death. Excessive disruption triggers STAT3 inhibition through excessive mitochondrial ROS production and reduced AMPK activation induced by ATP. Low doses of mitochondrial uncoupling agents alleviate doxorubicin-induced STAT3 inhibition and heart muscle cell death, with STAT3 activation playing a crucial role in the cardiac protective effects of these agents. Mild disruption of mitochondrial coupling in heart muscle cells by these agents is characterized by STAT3 activation and increased ATP levels. Conversely, excessive disruption leads to STAT3 inhibition, decreased ATP levels, and cellular damage. Developing mitochondrial uncoupling agents with an optimal dose range to induce mild disruption represents a promising approach for protecting the heart[22].

Studies indicate that simultaneous exposure to LPS and ATP leads to pronounced ASC speck formation, caspase-1 activation, cell death, and ROS production. Inhibiting the ATP-gated purinergic receptor P2X7 significantly reduces caspase-1 activation, while sodium vanadate effectively induces caspase-1 activation. Moreover, adjunctive therapy with ethanol reverses caspase-1 activation, ASC speck formation, and ROS production triggered by LPS and ATP. In HepG2 cells, both LPS and ATP signaling are required for ASC speck formation and caspase-1 induction. Additionally, P2X7 may play a critical role in inflammasome activation, and ethanol's acute effects on the inflammasome may involve reduced ROS production, thereby enhancing tyrosine phosphatase activity[113].

Moreover, another investigation demonstrated that CORM-3 effectively impedes NLRP3 inflammasome activation by obstructing the interaction between NLRP3 and the adaptor protein ASC, thereby alleviating myocardial dysfunction in septic mice[15]. Moreover, when J774 cells are stimulated with LPS and ATP, they display characteristics akin to pyroptosis, including increased expression of *IL-1β* mRNA and protein, activation of caspase-1, assembly of the inflammasome, and cell death. Cathelicidin LL-37 (LL-37) effectively inhibits LPS/ATP-induced IL-1β expression, caspase-1 activation, inflammasome assembly, and cell death. Notably, LL-37 disrupts the binding of LPS to target cells and reduces ATP-induced/P2X7-mediated caspase-1 activation. These findings suggest that LL-37 can counteract LPS activity and suppress P2X7 response to ATP, thereby mitigating LPS/ATP-induced pyroptosis. Hence, leveraging LL-37's dual actions on LPS binding and P2X7 activation may present novel strategies for managing sepsis[114].

P2X7R assumes a pivotal function in diverse pathological states linked to tissue damage and inflammation, rendering human P2X7R an appealing therapeutic target. Through evaluation of human P2X7R-mediated Ca^{2+} responses, three compounds (C23, C40, and C60) were identified from a pool of 73 top-ranked compounds. These compounds underwent additional characterization utilizing Ca^{2+} imaging, patch clamp current recording, YO-PRO-1 uptake, and propyl iodide

Table 2 Summary of small-molecule modulators in adenosine triphosphate-induced cell death-related diseases

Drug	Mechanism	Targets	Ref.
P2X7 antagonist	Inhibit P2RX7 function	High blood pressure; atherosclerosis	[79]
IL-1β and IL-18 inhibitors	Inhibit the release of IL-1β and IL-18	Myocardial infarction and heart failure	[79]
Caspase-3 inhibitors	Inhibit the proteolysis of caspase-3	Reduces or reverses heart failure	[30]
S-propranolol	Decreased caspase-3 activity	I/R injury	[80]
Spirolactone	Inhibits alpha-adrenergic vasoconstriction in the arteries	Drug-resistant hypertension	[81]
Prosulfanilone and carbenolone	Blocking thrombin-induced calcein outflow and reducing Ca^{2+} inflow, ATP release, platelet aggregation, and thrombosis at the *in vitro* arterial shear rate	Arterial thrombus	[82]
Curcumin, resveratrol, notoginseng lactone and allicin	Inhibition of NLRP3 inflammasome	Hypertension TOD	[63]
Pubescenoside A active compound	It inhibited NLRP3 inflammatory activation and induced Nrf2 signaling pathway	I/R injury	[83]
Resveratrol (PIC)	TG storage and caspase 1 activity were inhibited	Atherosclerosis	
MRS-2179	Inhibit platelet aggregation	Thrombotic syndrome	[84,85]
MRS2500	Inhibit P2RY1	Thrombus	[86]
NF157	Inhibit inositol phosphate accumulation	I/R injury	[87]
SKF96365	The entry of orai1 Ca^{2+} was inhibited	Atherosclerosis	[88]
ML9	Inhibition of STIM1	Hypertrophy and Ca^{2+} overload due to I/R; cardiomyocyte death	[89]
TDCPP	Decreased STIM1 expression of and increased GSK3β phosphorylation	I/R injury	[90]
MMPSI	Selective inhibition of caspase 3/7	Myocardial ischemic injury	[36]
Acetyl-tyr-val-ala-asp chloro-methyl ketone	They blocked caspase activation	Myocardial injury induced by ischemia and reperfusion; myocardial infarction	[91]
Hypericin	Up-regulation of autophagy after myocardial infarction	Myocardial infarction	[92]
MRS-2339	Activated the heart P2X receptor	Heart failure	[93]
Propofol	Induced autophagy	I/R injury	[94]
Carvedilol	Novel vasodilator beta-adrenergic receptor antagonist and potent antioxidant	Myocardial I/R induced apoptosis	[95]
Midazolam	Inhibit p38 MAPK	Myocardial I/R injury	[96]
Ulinastatin	Inhibit inflammation, oxidative stress and apoptosis	Chronic heart failure	[97]
Kaempferol	Inhibition of ASK1	Cardiac hypertrophy	[98]
KN-93	Inhibition of NOX2	Cardiac remodeling and heart failure	[99]
Acacetin	Inhibit oxidative stress, inflammation and apoptosis	Diabetic cardiomyopathy	[100]
CETP inhibitor	Elevated phosphorylation levels of vascular myosin light chain and myosin phosphatase target subunit 1, a protein that promotes contractility, along with enhanced reactive ROS production	Hypertension	[101]
Fasudil	ROCKI inhibition	Coronary vasospasm, angina pectoris, hypertension, heart failure	[102,103]
Isosteviol (STV)	ERK1/2 is selectively activated in cells exposed to stress	Myocardial ischemia-reperfusion	[103]
Adriamycin (DOX)	Induced oxidative stress	Heart failure	[105]
Plasminogen activator inhibitor 1	Release the pro-inflammatory cytokine TNF-α	Thromboembolism complication	[106]
Rosuvastatin	MG53 up-regulation was induced	Myocarditis	[107]
Na^+/H^+ exchanger 1	Catalyze increased intracellular Na uptake	Hypertrophy of heart; heart failure	[108]
Prasugrel	Inhibit P2RY12	ST-segment elevation myocardial	[109]

	infarction following primary percutaneous coronary intervention

P2RX7: Purinergic receptor P2X7; IL: Interleukin; I/R: Ischemia/reperfusion; ATP: Adenosine triphosphate; NLRP3: NOD-like receptor family pyrin domain-containing protein 3; TOD: Target organ damage; Nrf2: NF-E2-related factor-2; P2RY1: P2Y purinoceptor 1; STIM1: Stromal interaction molecule 1; GSK: Glycogen synthase kinase; MAPK: Mitogen-activated protein kinases; ASK1: Apoptosis signal regulating kinase 1; NOX2: NADPH oxidase 2; ROS: Reactive oxygen species; ROCK I: Rho-associated, coiled-coil containing protein kinase 1; ERK1/2: Extracellular signal regulated kinase 1 and 2; TNF: Tumor necrosis factor.

cell death assay. The findings revealed that all three compounds effectively inhibited BZATP-induced Ca^{2+} response and demonstrated potent protective effects against AICD[115]. Moreover, the anti-inflammatory effects of P2X7R antagonists stem from their ability to inhibit P2X7R-mediated secretion of pro-inflammatory cytokines from activated macrophages. P2X7R antagonists reliably hinder ATP-triggered casein release, a phenomenon not observed in P2X7R(-/-) mouse macrophages and unrelated to cellular apoptosis. Nevertheless, our findings indicate that P2X7R activation may independently contribute to tissue injury by facilitating protease release, distinct from its pro-inflammatory actions mediated by IL-1 cytokines[116]. Furthermore, recent studies have shown that exposure of HeLa cells to interferon-gamma leads to increased expression of *P2X7* mRNA and full-length protein, altering ATP-dependent calcium flux and rendering the cells susceptible to ATP-induced apoptosis. Importantly, P2X7 antagonists hold promise in attenuating this apoptotic reaction[117].

CONCLUSION

In summary, AICD plays a prominent role in the pathogenesis of cardiovascular disease, contributing to tissue damage, inflammation, and adverse remodeling. Understanding the molecular and metabolic landscape of AICD provides valuable insights into disease mechanisms and identifies potential therapeutic targets. Future research efforts should focus on addressing the limitations, advancing our understanding of these pathways, and developing targeted interventions to improve clinical outcomes in cardiovascular patients. Continued exploration of small molecules, biologics, and gene-based therapies targeting AICD pathways may lead to the development of innovative treatments for cardiovascular diseases. Conducting well-designed clinical trials to evaluate the efficacy and safety of novel therapeutic interventions targeting AICD is essential for translating preclinical findings into clinical practice.

FOOTNOTES

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