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Review

The Role of Cold-Inducible RNA-Binding Protein in Myocardial Infarction: From a Stress Sensor to an Amplifier of Sterile Inflammation

Yiming Zhang[1,2,†], Hongqiang Yang[3,†], Yongxiang Wang[1,2], Yilin Pan[4], Chengcheng Yi[1,2], Ming Bai[1,2,*], Zheng Zhang[1,2,*]

[1]The First School of Clinical Medicine of Lanzhou University, 730000 Lanzhou, Gansu, China
[2]Heart Center, The First Hospital of Lanzhou University, 730000 Lanzhou, Gansu, China
[3]The First Clinical Medical College, Gansu University of Chinese Medicine, 730000 Lanzhou, Gansu, China
[4]Clinical Medical College of Tianjin Medical University, 300270 Tianjin, China
*Correspondence: baim@lzu.edu.com (Ming Bai); drzzccu@163.com (Zheng Zhang)
[†]These authors contributed equally.
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Abstract

Cold-inducible RNA-binding protein (CIRP) is an evolutionarily conserved, stress-responsive protein that plays a critical, complex dual role in the occurrence and progression of myocardial infarction. As an intracellular stress sensor, CIRP enhances cardiac cell adaptation to ischemic stress and mitigates early injury by regulating messenger ribonucleic acid (mRNA) stability, antioxidant pathways, apoptosis inhibition, and energy metabolism. CIRP expression is induced by signals such as hypothermia, oxidative stress, and hypoxia, and its cytoprotective functions are activated through post-translational modifications, including arginine methylation and phosphorylation, which facilitate nucleocytoplasmic translocation. However, upon cardiac cell necrosis or pyroptosis, CIRP can be actively secreted or passively released into the extracellular space, where it acts as a damage-associated molecular pattern. CIRP then binds to receptors, such as toll-like receptor 4 (TLR4) and triggering receptor expressed on myeloid cells-1 (TREM-1), on the surface of macrophages and neutrophils, activating inflammatory signaling pathways, including nuclear factor kappa-B (NF-κB) and mitogen-activated protein kinase (MAPK), thereby amplifying sterile inflammation, exacerbating myocardial injury, and delaying repair. Furthermore, extracellular CIRP is involved in regulating myocardial fibrosis, angiogenesis, and arrhythmias, with effects that exhibit significant temporal dynamics and cell specificity. Studies have shown that therapeutic strategies targeting CIRP, including receptor antagonists, RNA-binding domain inhibitors, and neutralizing/blocking approaches, can improve cardiac function, reduce infarct size, and attenuate inflammatory responses in animal models. Despite challenges such as its functional duality and clinical translation, CIRP has emerged as a highly promising therapeutic target for myocardial infarction due to the central role of CIRP in disease progression. Thus, future research should further elucidate the dynamic changes associated with CIRP across different repair stages, develop highly specific drugs, and conduct large-scale clinical studies to validate its potential as a diagnostic and prognostic biomarker.

Keywords: myocardial infarction; cold-inducible RNA-binding protein; sterile inflammation

1. Introduction

Acute myocardial infarction (AMI) remains one of the leading causes of death and disability worldwide. Although timely reperfusion has substantially improved survival, myocardial ischemia and subsequent reperfusion still trigger extensive cardiomyocyte death, infarct expansion, maladaptive ventricular remodeling, and progression to heart failure [1]. Increasing evidence indicates that these events are not determined solely by the duration of ischemia, but also by the intensity, timing, and persistence of the sterile inflammatory response elicited after tissue injury. In this context, infarcted myocardium is now recognized not merely as a passive target of ischemic damage, but as an active immunometabolic niche in which danger-associated molecular patterns (DAMPs), innate immune receptors, and recruited inflammatory cells shape both acute injury and long-term repair [2,3].

Among the endogenous alarm signals released during tissue stress, cold-inducible RNA-binding protein (CIRP) was initially characterized as a stress-responsive RNA-binding protein (RBP), whichregulates RNA metabolism and cellular stress adaptation under physiological and moderate stress conditions. Only after translocation and extracellular release following severe cellular injury does CIRP function as a damage-associated molecular pattern (DAMP) that amplifies sterile inflammation [4]. Under physiological or adaptive stress conditions, intracellular CIRP participates in post-transcriptional regulation of target transcripts and contributes to maintenance of redox homeostasis, cell survival, and stress adaptation. In the cardiovascular system, this intracellular form has been implicated in the reg-

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ulation of cardiac electrophysiology, resistance to oxidative injury, and protection against cardiomyocyte apoptosis, suggesting that CIRP may function as an endogenous stress sensor during myocardial injury. However, the biological meaning of CIRP changes fundamentally once it is released into the extracellular milieu. Under severe cellular stress, hypoxia, necrosis, or inflammatory stimulation, CIRP can translocate from the nucleus to the cytoplasm and be actively or passively released outside the cell, where extracellular CIRP (eCIRP) acts as a bona fide DAMP [5,6].

In the context of myocardial infarction (MI), studying CIRP is interesting for several reasons. First, it sits at the interface between cell-intrinsic stress adaptation and cell-extrinsic inflammatory propagation, thereby linking early ischemic stress to secondary immune injury [7]. Second, the known receptors and downstream signaling pathways activated by eCIRP, including toll-like receptor 4-myeloid differentiation factor 2 (TLR4–MD2), triggering receptor expressed on myeloid cells-1 (TREM-1), nuclear factor kappa-B (NF-κB), and potentially nucleotide-binding and oligomerization domain (NOD)-like receptor family pyrin domain containing 3 (NLRP3)-related inflammatory networks, overlap strikingly with the canonical signaling architecture that drives infarct inflammation, pyroptosis, and adverse remodeling [8]. Third, emerging animal and clinical evidence suggests that CIRP is not only mechanistically relevant but also holds considerable translational potential as a diagnostic biomarker and therapeutic target for myocardial infarction. Plasma CIRP levels are elevated in acute coronary syndrome, are higher in ST-elevated myocardial infarction (STEMI) than in non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina, correlate with the Global Registry of Acute Coronary Events (GRACE) score, and independently predict major adverse cardiovascular events [9]. Experimental studies likewise indicate that restoring intracellular CIRP or activating CIRP-related protective programs can attenuate oxidative stress, apoptosis, and post-MI heart failure, underscoring the context-dependent duality of this molecule [5,7].

Despite growing interest, the role of CIRP in MI remains insufficiently synthesized and conceptually fragmented. Existing discussions often focus either on the cytoprotective effects of intracellular CIRP or on the pro-inflammatory properties of eCIRP in systemic inflammatory disorders, whereas a coherent MI-centered framework integrating these two facets is still lacking. In particular, several key questions remain unresolved: When does adaptive intracellular CIRP signaling switch to maladaptive extracellular alarmin signaling? Which cardiac and immune cell populations are the dominant sources and targets of CIRP after infarction? How does CIRP intersect with macrophage polarization, neutrophil activation, inflammasome signaling, microvascular dysfunction, and fibrotic remodeling? And importantly, can the CIRP axis be therapeutically modulated in a compartment-specific manner—preserving intracellular stress-adaptive functions while blocking extracellular inflammatory toxicity? In this review, we summarize current knowledge on CIRP in the setting of MI, with an emphasis on its transition from intracellular stress sensor to extracellular amplifier of sterile inflammation. We discuss the molecular biology of CIRP, the mechanisms governing its release and receptor engagement, and its potential roles in cardiomyocyte death, innate immune activation, infarct healing, and ventricular remodeling. We further highlight the paradoxical dual nature of CIRP in ischemic heart disease and evaluate its promise as both a biomarker and a therapeutic target for precision immunomodulation after MI.

2. Molecular Structure and Functional Properties of CIRP

CIRP is an evolutionarily conserved RNA-binding protein. Its gene is located on human chromosome 19p13.3, encoding a polypeptide of 172 amino acids with a molecular weight of approximately 18–21 kDa [10]. As a member of the RNA-binding protein family, the molecular structure of CIRP comprises two core functional domains: an N-terminal RNA recognition motif (RRM) and a C-terminal arginine-glycine-rich domain (RGG) [11]. The RRM domain contains highly conserved RNP1 and RNP2 motifs, which are responsible for binding to the 3′ untranslated region (3′-UTR) of RNA molecules, thereby regulating the stability and translational efficiency of target mRNAs [12]. For instance, CIRP can bind to the 5′UTR of p27Kip1 messenger ribonucleic acid (mRNA) *via* its RRM domain, enhancing its translational efficiency and subsequently participating in cell cycle regulation [13]. The RGG domain, enriched with arginine and glycine residues, is not only involved in auxiliary regulation of RNA binding but is also closely associated with protein-protein interactions, subcellular localization, and post-translational modifications [14,15].

The expression regulation of CIRP is a multi-level and multi-factorial complex process, subject to precise control at transcriptional, post-transcriptional, and post-translational levels. At the transcriptional level, CIRP expression is primarily induced by stress signals, such as hypothermia, hypoxia, ultraviolet radiation, oxidative stress, and nutrient deprivation [10,12]. Hypothermic stress can promote CIRP transcription through a mild-cold responsive element (MCRE) within its 5' regulatory region, where increased recruitment of the transcription factor Sp1 contributes to the induction of CIRP expression [16]. Under hypoxic conditions, HIF-1α directly binds to the hypoxia response element (HRE) in the CIRP promoter, significantly upregulating its mRNA levels. Furthermore, CIRP can enhance its own transcription through an auto-regulatory mechanism: under stress conditions, upregulated CIRP expression can bind to the 3′-UTR of its own mRNA, in-

creasing its stability and forming a positive feedback regulatory loop [17]. Regulation at the post-transcriptional level primarily involves the stability and alternative splicing of CIRP mRNA. Under normal physiological conditions, CIRP mRNA has a short half-life, but its stability is significantly increased under stress conditions. Hypothermic stress can prolong its half-life by activating the RNA-binding protein HuR, which promotes HuR binding to the 3′-UTR of CIRP mRNA [18]. Additionally, CIRP can participate in the coordinated regulation of the stress response by modulating the mRNA stability of other RNA-binding proteins [19]. Under myocardial ischemic conditions, CIRP and RBM3 may participate in stress-adaptive responses through their respective RNA-regulatory functions, thereby contributing to cardiomyocyte cytoprotection [20,21]. Post-translational modifications are crucial for the functional regulation of CIRP, primarily including methylation, phosphorylation, and ubiquitination. Among these, arginine methylation is the most extensively studied. The RGG domain of CIRP is rich in arginine residues and can be methylated by PRMTs, particularly PRMT1, thereby regulating its nucleocytoplasmic shuttling, stress granule recruitment, and subcellular localization [22,23]. Under cold stress, activation of the TRPM8/Ca^{2+}/PKCα/glycogen synthase kinase 3β (GSK3β) signaling cascade promotes the translocation of CIRP from the nucleus to the cytoplasm. In the cytoplasm, CIRP can be recruited into stress granules, whereas methylation of its RGG domain has also been implicated in this relocalization process [15]. Furthermore, ubiquitination can regulate CIRP degradation *via* the proteasomal pathway. Under oxidative stress conditions, CIRP can be recognized and degraded by ubiquitin ligases, thereby terminating its cytoprotective function [6]. As shown in Fig. 1, CIRP exerts a dual role in stressed cardiomyocytes, acting intracellularly as a cytoprotective factor while functioning extracellularly as a pro-inflammatory DAMP that amplifies myocardial injury.

3. CIRP Response Mechanism in Myocardial Ischemic Stress

Myocardial ischemia is the core pathophysiological event in the occurrence of MI, with its essence being an imbalance between oxygen supply and demand in cardiac cells. As a typical cellular stressor, ischemia can induce the expression and functional reprogramming of intracellular stress proteins by activating multiple signaling pathways to adapt to or resist injury. Cold-inducible RNA-binding protein (CIRP), an evolutionarily shared stress-responsive protein, has recently been shown to sense signals associated with ischemia, such as oxidative stress and metabolic disorders, thereby participating in the stress adaptation and injury regulation of cardiac cells [4].

3.1 Effects of Myocardial Ischemia on CIRP Expression

The regulation of CIRP expression is a core aspect of its function as a stress sensor, with changes in its expression levels directly reflecting the cellular perception of and adaptation to ischemic stress. Under physiological conditions, CIRP is expressed at basal levels in cardiac tissue, primarily localized within the nucleus, where it participates in fundamental functions such as mRNA splicing and stabilization [4]. However, when the myocardium is subjected to ischemic stress, the expression pattern of CIRP is markedly altered. A 2019 study reported that CIRP expression was significantly reduced in cardiac tissue from patients with heart failure. Consistently, myocardial tissue from mice with post-MI also exhibited decreased CIRP expression [6]. This finding suggests that myocardial remodeling induced by chronic ischemia may be accompanied by long-term suppression of CIRP expression, potentially related to the exhaustion of adaptive capacity in cardiac cells in response to persistent stress. In contrast, changes in CIRP expression under acute ischemic stress are more complex. In a rat model of MI, Western blot analysis revealed a dynamic change in CIRP expression in cardiomyocytes within the peri-infarct zone during the first week post-infarction: an initial increase followed by a decrease. Within 24 hours post-infarction, CIRP protein levels in the ischemic border zone increased approximately 1.8-fold compared to the sham-operated group, then gradually declined below baseline after 72 hours [5]. This observation is in line with the general stress-response profile of CIRP. In many settings, CIRP is transiently induced during the early stage of acute stress as part of an adaptive cytoprotective response, whereas sustained stress may attenuate CIRP expression, likely owing to maladaptive cellular remodeling and functional deterioration [12,24,25]. *Ex vivo* cellular experiments further validated the direct regulatory effect of ischemia on CIRP expression. In H9C2 cardiomyocytes subjected to simulated oxidative stress, CIRP has been shown to play an important role in regulating cellular survival and apoptosis. Experimental evidence indicates that CIRP downregulation exacerbates oxidative stress-induced cardiomyocyte apoptosis and cell death, suggesting a protective role for intracellular CIRP in myocardial injury [26]. This result indicates that oxidative stress, a core pathological component of ischemia, is a key signal inducing CIRP expression. Research in a mouse model of liver cold exposure indirectly supports this mechanism: oxidative stress induced by cold exposure can upregulate CIRP expression by activating the protein kinase B (AKT) signaling pathway. Given that the AKT pathway is also activated during myocardial ischemia (adaptively in the early phase and suppressed later), it is hypothesized that a similar mechanism may regulate CIRP expression [27].

Notably, in patients undergoing cardiac surgery, the myocardial ischemia-reperfusion process induced by cardiopulmonary bypass (CPB) was observed to significantly

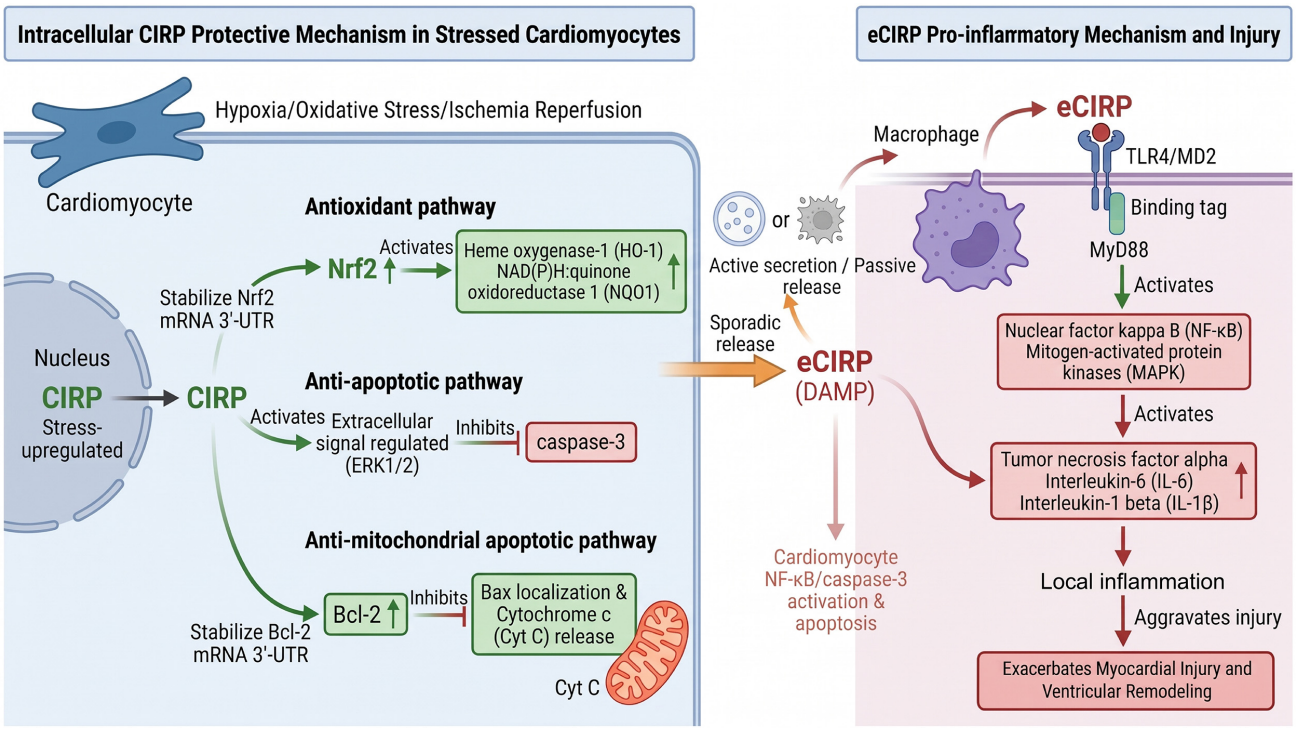


Fig. 1. Dual roles of CIRP in myocardial stress injury. Intracellular CIRP protects stressed cardiomyocytes by promoting antioxidant and anti-apoptotic signaling, whereas extracellular CIRP acts as a DAMP to trigger TLR4/MD2-MyD88-mediated NF-κB/MAPK activation, inflammatory cytokine release, and subsequent myocardial injury and ventricular remodeling. CIRP, cold-inducible RNA-binding protein; eCIRP, extracellular cold-inducible RNA-binding protein; DAMP, damage-associated molecular pattern; TLR4, toll-like receptor 4; MD2, myeloid differentiation protein 2; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase.

elevate serum CIRP levels. In patients who underwent cardiac arrest, postoperative serum CIRP levels increased 26-fold compared to preoperative levels, while those undergoing CPB without arrest showed a 2.7-fold increase. Furthermore, serum CIRP levels showed a significant positive correlation with CPB duration [28]. This clinical evidence directly confirms that acute ischemic stress can induce CIRP release from cardiomyocytes. The elevation of serum CIRP not only reflects the stressed state of cardiomyocytes but may also serve as a biomarker for the severity of ischemia [9]. Integrating the findings from the aforementioned studies, the impact of myocardial ischemia on CIRP expression exhibits bidirectional and time-dependent characteristics [4,29]. In the early phase of acute ischemia (hours to 24 hours), CIRP is rapidly upregulated in response to oxidative stress signals to exert intracellular protective functions. During the intermediate phase (24–72 hours), if ischemia is alleviated, CIRP expression gradually returns to baseline. If ischemia persists (e.g., during post-infarction remodeling in chronic settings), CIRP expression is downregulated due to cellular dysfunction. In the late phase (after 72 hours), suppressed CIRP expression may coincide with the onset of cardiomyocyte apoptosis and fibrosis. This dynamic pattern suggests that CIRP expression levels could serve as a potential indicator for the severity and prognosis of myocardial ischemic injury. Insufficient upregulation of CIRP during acute ischemia or its sustained downregulation during chronic ischemia may both predict aggravated myocardial damage (Fig. 2).

3.2 The Role of CIRP in the Stress Adaptation of Cardiac Cells

The function of CIRP within cardiac cells constitutes the core value of its role as a stress sensor. By regulating mRNA stability, translation efficiency, and subcellular localization, CIRP can participate in oxidative stress resistance, energy metabolism adjustment, and apoptosis inhibition in cardiac cells, thereby enhancing cellular adaptation to ischemia.

Oxidative stress is a central mechanism underlying ischemia-induced myocardial injury. CIRP may enhance the reactive oxygen species (ROS)-scavenging capacity of cardiac cells by promoting Nrf2-dependent antioxidant signaling. Among the currently reported CIRP-targeting strategies, only a limited number have been evaluated in the context of myocardial infarction. Therefore, this section focuses on ZR17-2 and A12, which have direct experimental evidence in MI models. In a rat MI model, pretreatment with the CIRP agonist ZR17-2 significantly restored the cardiac expression of antioxidant molecules, including

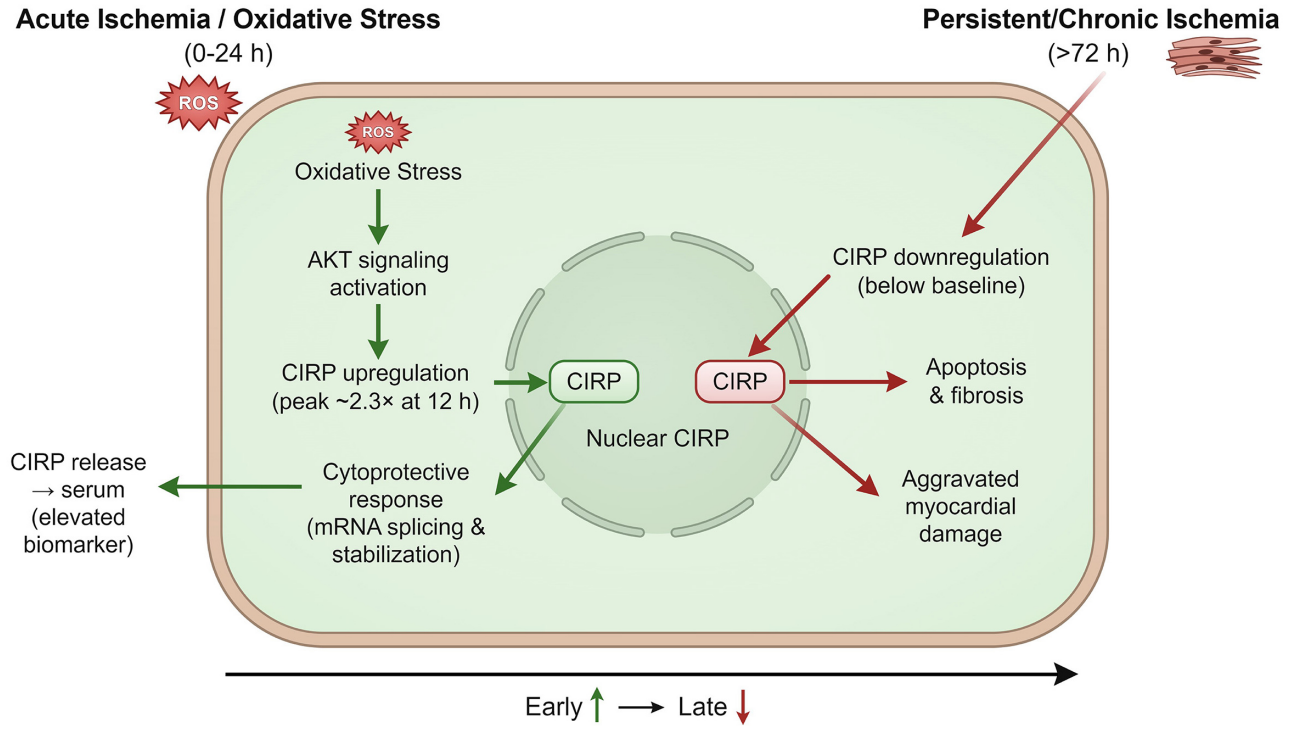


Fig. 2. Dynamic changes and stage-dependent roles of CIRP during myocardial ischemic injury. During the acute phase of ischemia/oxidative stress (0–24 h), oxidative stress activates AKT signaling, which promotes CIRP upregulation, peaking at approximately 2.3-fold at 12 h. Increased nuclear CIRP exerts cytoprotective effects by supporting mRNA splicing and stabilization, while CIRP release into the circulation may contribute to its elevation as a serum biomarker. In contrast, during persistent or chronic ischemia (>72 h), CIRP expression declines below baseline, weakening its protective intracellular functions and thereby promoting apoptosis, fibrosis, and aggravated myocardial damage. Overall, the figure illustrates a gradual temporal shift rather than an abrupt switch. During the early acute phase, intracellular protective signaling and extracellular inflammatory signaling may coexist, although their relative predominance changes over time. CIRP, cold-inducible RNA-binding protein; ROS, reactive oxygen species; AKT, protein kinase B; mRNA, messenger ribonucleic acid.

Nrf2, heme oxygenase 1 (HO-1), and NQO-1, in the peri-infarct region, suggesting that CIRP activation improves myocardial antioxidant capacity [5]. Further mechanistic studies showed that CIRP directly binds Nrf2 mRNA and prolongs its half-life, thereby enhancing Nrf2 expression and activation of downstream antioxidant signaling [30]. Consistent with this, silencing CIRP aggravated oxidative stress and weakened antioxidant defense *in vitro*, supporting the view that the antioxidant effect of CIRP is mediated, at least in part, through post-transcriptional regulation of the Nrf2 pathway [30]. Collectively, these findings support the feasibility of pharmacologically targeting CIRP; however, current evidence remains limited to preclinical studies, and additional CIRP modulators require validation in myocardial infarction models.

Apoptosis is one of the major forms of cell death in ischemic cardiomyocytes, and CIRP appears to play an important anti-apoptotic role. In H9C2 cells, knockdown of CIRP aggravated H_2O_2-induced apoptosis and cell death, accompanied by activation of pro-apoptotic signaling and suppression of anti-apoptotic pathways [6]. This result indicates that CIRP can attenuate oxidative stress-induced apoptosis in cardiac cells. Consistent with this, in a rat MI model, adeno-associated virus serotype 9 (AAV9)-mediated cardiomyocyte-targeted overexpression of CIRP reduced cardiomyocyte apoptosis and alleviated post-infarction cardiac dysfunction and adverse remodeling [7]. Mechanistically, CIRP, as an RNA-binding protein, can regulate cellular stress responses by binding to the 3′-UTR of specific target mRNAs and modulating their stability. In cardiomyocytes, current evidence more directly supports a CIRP–Nrf2 axis, in which CIRP stabilizes Nrf2 mRNA and enhances downstream antioxidant signaling. Through this mechanism, CIRP may indirectly attenuate mitochondrial apoptotic signaling and oxidative stress-induced cell injury [31].

Energy metabolism disturbance is an important contributor to ischemia-induced cardiomyocyte dysfunction. Although direct evidence in the ischemic heart remains limited, studies in a hepatic acute cold exposure model suggest that CIRP may participate in metabolic adaptation by activating AKT-related signaling [27]. Cold exposure in-

creased CIRP expression, enhanced AKT/GSK3β/PFKFB2 phosphorylation, promoted changes in hepatic glycogen utilization and glycolytic metabolism, and was associated with maintenance of hepatocyte energy balance [27]. Although fatty acid oxidation is the predominant energy source in adult cardiomyocytes, ischemia induces marked metabolic reprogramming toward greater reliance on glucose utilization and glycolytic flux. On this basis, the metabolism-regulating role of CIRP observed in other stress models may also be relevant to the ischemic myocardium. However, current evidence in MI models more directly supports antioxidant and cytoprotective effects of CIRP activation than a confirmed role in promoting glycolysis or increasing myocardial adenosine triphosphate (ATP) production [5,32,33]. Further molecular studies suggest that CIRP may regulate glucose metabolism indirectly through AKT-related signaling rather than by directly stabilizing the mRNAs of key glycolytic enzymes. In cold-stress models, CIRP upregulation was associated with increased AKT activation and enhanced phosphorylation of metabolism-related proteins such as PFKFB2, supporting a role for CIRP in metabolic adaptation [27,34]. It should be noted that the intracellular effects of CIRP are highly context-dependent and may vary with stress intensity, cell type, and disease stage. Current evidence in cardiac models generally supports a protective effect of moderate CIRP upregulation, whereas whether excessive overexpression becomes maladaptive remains insufficiently defined [4,5,7]. Furthermore, when ischemic stress exceeds the adaptive capacity of the cells, the protective effect of CIRP becomes ineffective due to cell necrosis. Under these conditions, CIRP is released from the intracellular space into the extracellular environment, where it transitions into an inflammatory mediator [35].

3.3 Mechanisms and Regulation of CIRP Release From Cardiac Cells

The release of CIRP from cardiac cells represents a critical transition point where its function shifts from intracellular protection to extracellular amplification of inflammation. Importantly, this transition is unlikely to be an abrupt event. During the early phase of myocardial ischemia, intracellular CIRP continues to exert cytoprotective effects in viable cardiomyocytes, while extracellular CIRP is simultaneously released from severely injured or necrotic cells. Therefore, the protective and pro-inflammatory actions of CIRP may partially overlap in time, with their relative contributions depending on the extent of tissue injury and disease stage [36].

Ischemia-induced cardiomyocyte necrosis is likely an important source of passive CIRP release. In the infarct core, severe ischemic injury causes loss of plasma membrane integrity and necrotic cell death, which may result in the extracellular release of intracellular CIRP together with other damage-associated molecules [4,37,38]. Studies in renal ischemia-reperfusion models suggest that extracellular CIRP is released during renal injury and contributes to acute kidney injury (AKI) progression. Given that eCIRP can be passively released from damaged or necrotic cells, necrotic renal cells may represent an important source of eCIRP during ischemia-reperfusion injury, although a direct quantitative correlation with necrosis severity remains to be fully established [39,40,41]. Passively released CIRP can be non-selectively liberated after loss of membrane integrity during cell injury or necrotic cell death, which may lead to substantial local accumulation of eCIRP. Once released extracellularly, CIRP can activate pattern-recognition receptors, particularly the TLR4/MD2 complex on immune cells, thereby amplifying downstream inflammatory signaling [42]. In addition to passive release, viable stressed cardiac cells can also release CIRP through an active secretory pathway, a process that reflects the cell's active involvement in inflammatory regulation. In cardiac surgery patients, it was found that serum CIRP levels were significantly elevated in patients undergoing CPB, and the extent of elevation was positively correlated with the duration of CPB [43]. The active secretory mechanism of CIRP is further supported by studies showing that eCIRP can be released *via* exosomes. In parallel, hypoxia has been shown to enhance exosome secretion in renal tubular epithelial cells, suggesting that stressed tubular cells may contribute to extracellular CIRP release through an exosomal pathway, although direct quantitative evidence for exosomal CIRP release in HK-2 cells remains limited [44]. Although direct evidence for exosome-mediated CIRP secretion in cardiac cells remains lacking, exosomal release is a conserved pathway for intercellular communication. Thus, it may be hypothesized that stress-induced nuclear-to-cytoplasmic translocation of CIRP is followed by its incorporation into exosomes and subsequent release into the extracellular space [8,45,46]. As shown in Fig. 3, CIRP released passively from necrotic cardiomyocytes or actively from stressed viable cardiac cells can function as a DAMP to activate TLR4/MD2-dependent inflammatory signaling and amplify sterile inflammation after ischemic injury.

4. The Role of CIRP as an Inflammatory Mediator in MI

4.1 Interaction Between CIRP and Immune Cells

The activation of immune cells by eCIRP is the primary step in amplifying the inflammatory response following MI, involving the functional regulation of various immune cells such as macrophages, neutrophils, and lymphocytes. As a DAMP molecule, eCIRP triggers a pro-inflammatory phenotypic transition in immune cells by binding to pattern recognition receptors (PRRs), a process that is particularly critical within the myocardial microenvironment post-MI [8,47]. Macrophage regulation is central to eCIRP-mediated inflammation. Under physiological conditions, macrophage polarization balance maintains tis-

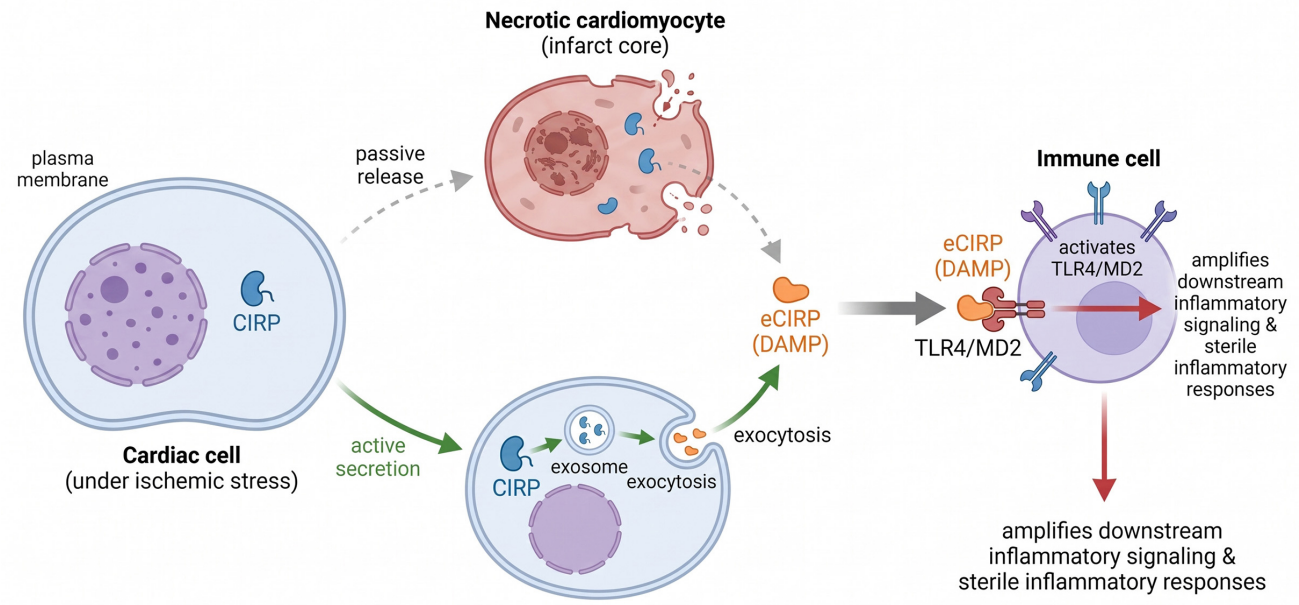


Fig. 3. Release pathways and pro-inflammatory actions of extracellular CIRP during myocardial ischemic injury. Under ischemic stress, CIRP can be released from cardiac cells through two major routes. First, in the infarct core, necrotic cardiomyocytes passively release CIRP into the extracellular space. Second, stressed but still viable cardiac cells can actively secrete CIRP through an exosome- and exocytosis-dependent pathway. Once released, eCIRP acts as a DAMP and binds to the TLR4/MD2 receptor complex on immune cells, thereby activating downstream inflammatory signaling and amplifying sterile inflammatory responses. CIRP, cold-inducible RNA-binding protein; eCIRP, extracellular cold-inducible RNA-binding protein; DAMP, damage-associated molecular pattern; TLR4, Toll-like receptor 4; MD2, myeloid differentiation factor 2.

sue homeostasis. However, the massive release of eCIRP after MI disrupts this equilibrium. In an ischemic muscle tissue model, the proportion of M2-like macrophages was significantly increased in the ischemic tissue of CIRP knockout ($Cirp^{-/-}$) mice, accompanied by a reduction in M1-like macrophages and neutrophil infiltration. This suggests that eCIRP promotes sustained inflammation by inhibiting M2 polarization [48]. Further mechanistic studies revealed that eCIRP can interfere with the trafficking of the erythropoietin receptor (EPOR) to the macrophage surface by damaging Rab26 protein, leading to suppression of the EPOR signaling pathway and ultimately hindering M2 polarization [49]. This process is important for post-MI myocardial repair, as a reduction in reparative M2 macrophages may delay inflammation resolution, impair angiogenesis, and disrupt the balance between extracellular matrix deposition and remodeling, thereby compromising cardiac repair. The enhanced angiogenesis and accelerated tissue regeneration observed in $Cirp^{-/-}$ mice in ischemic models directly confirm that the regulatory role of eCIRP on macrophage polarization is a key mechanism underlying its pro-inflammatory effects [48]. The excessive activation of neutrophils represents another pathway through which eCIRP exacerbates early inflammatory injury post-MI. As the first immune cells to infiltrate the myocardium after MI, the pro-inflammatory activity of neutrophils is directly correlated with myocardial infarct size. eCIRP can enhance the pro-inflammatory phenotype of neutrophils by inducing their trogocytosis behavior. In transendothelial migration (TEM) experiments, eCIRP significantly increased the proportion of neutrophils performing trogocytosis on endothelial cell membranes, and neutrophils that phagocytosed JAM-C exhibited higher pro-inflammatory activity. This trogocytosis is achieved through the polarized activation of macrophage-1 antigen (Mac-1) (integrin αMβ2), enabling neutrophils to acquire adhesion molecule characteristics of endothelial cells, thereby promoting their retention in the ischemic myocardial region and the release of inflammatory mediators [50,51]. In an acute lung injury model, eCIRP-induced JAM-C-positive trogocytic neutrophils have been identified as key effector cells in amplifying inflammation. It is highly probable that this mechanism also operates within the post-MI myocardial microenvironment, leading to neutrophil-mediated direct injury to cardiac cells, such as exacerbated oxidative stress and protease release [51]. The functional regulation of lymphocytes and dendritic cells also participates in the pro-inflammatory network orchestrated by eCIRP. Although direct studies on lymphocytes in MI are limited, eCIRP has been demonstrated to activate pro-inflammatory signaling in T lymphocytes and dendritic cells in models of sepsis and ischemia-reperfusion, promoting the release of cytokines such as interferon-γ (IFN-γ) and interleukin (IL)-12 [52]. Considering the impact of the adaptive immune response on sustained inflammation af-

ter MI, the regulation of lymphocytes by eCIRP may play a role in the chronic inflammation of the later stages of MI, although its specific mechanisms require further investigation. Furthermore, the extracellular transport form of eCIRP influences its interaction efficiency with immune cells. In addition to passive release (e.g., from necrotic cell rupture), eCIRP can be actively secreted *via* exosomes. Under stress conditions, CIRP undergoes methylation modification, translocates from the nucleus to the cytoplasm, and is packaged into multivesicular bodies (MVBs) along with RNA, DNA, *etc*., ultimately being released extracellularly *via* exosomes [53]. Exosome-encapsulated eCIRP exhibits higher stability and target specificity, allowing it to act precisely on surface receptors of immune cells like macrophages and neutrophils. This characteristic endows it with a more potent effect in amplifying local inflammation within the ischemic myocardium.

In summary, eCIRP constructs a pro-inflammatory network of immune cells post-MI by targeting macrophage polarization, neutrophil function, and lymphocyte activity. Its inhibition of macrophage M2 polarization and induction of neutrophil trogocytosis are key to amplifying early inflammatory injury. The molecular interactions described above are summarized in Fig. 4 and provide potential targets for subsequent intervention strategies.

4.2 CIRP-Mediated Inflammatory Signaling Pathways

eCIRP amplifies the sterile inflammatory response following MI by activating multiple classic inflammatory signaling pathways, among which the TLR4-MD2, TREM-1, and NF-κB pathways serve as the core mediating mechanisms. The synergistic activation of these pathways constitutes the molecular basis for the pro-inflammatory effects of eCIRP [54]. The TLR4–MD2 pathway is the primary receptor mechanism through which eCIRP activates immune cells. Although TLR4 was originally identified as the canonical receptor for lipopolysaccharide (LPS) from Gram-negative bacteria, accumulating evidence has demonstrated that it also recognizes endogenous DAMPs, including eCIRP, thereby mediating sterile inflammatory responses after tissue injury. eCIRP triggers signal transduction by binding to the MD2 subunit of TLR4. In models of sepsis, acute lung injury, and ischemia-reperfusion, the binding of eCIRP to TLR4 activates the myeloid differentiation primary response 88 (MyD88)-dependent signaling pathway, leading to NF-κB nuclear translocation and the release of pro-inflammatory cytokines [55]. This mechanism may also be relevant to MI, as eCIRP released after myocardial ischemia can activate TLR4-mediated inflammatory signaling in cardiac macrophages and infiltrating neutrophils, thereby promoting the production of pro-inflammatory mediators such as IL-6 and tumor necrosis factor-α (TNF-α). Anti-CIRP antibodies or TLR4 inhibitors have been shown to significantly mitigate inflammatory injury [36,56]. Notably, the RNA-binding domain of eCIRP is the critical region for its interaction with TLR4. Oligonucleotide inhibitors developed based on this principle can competitively bind to the RNA-binding domain of eCIRP, blocking its interaction with TLR4, and have successfully suppressed inflammatory responses in models of hemorrhagic shock and intestinal ischemia-reperfusion [57]. This strategy provides a direct reference for targeting the eCIRP-TLR4 pathway in MI.

The TREM-1 pathway is an important synergistic mechanism through which eCIRP amplifies the inflammatory response. TREM-1, an activating receptor on the surface of immune cells, can enhance target lesion revascularization (TLR) signaling in both infectious and sterile inflammation. eCIRP has been identified as an endogenous ligand for TREM-1. In a neonatal sepsis model, recombinant CIRP (rmCIRP) was shown to upregulate TREM-1 expression in cardiac cells, accompanied by increased secretion of TNF-α and IL-6. This effect was significantly inhibited by a TREM-1 inhibitor, which improved cardiac function and increased survival rates [58]. This mechanism may also be involved in MI, as TREM-1 expression has been reported to increase after myocardial infarction, particularly in activated immune cells. Given that eCIRP can amplify inflammatory signaling through TREM-1-related pathways, the eCIRP–TREM-1 axis may contribute to post-infarction inflammation and adverse cardiac remodeling. Their interaction can further activate NF-κB *via* the spleen tyrosine kinase (Syk)-PI3K-Akt pathway, forming a TLR4-TREM-1 synergistic amplification loop that exacerbates inflammation. In a model of hypothermia-induced acute lung injury, CIRP knockout significantly reduced the expression of TREM-1 and NF-κB, further confirming the cascade activation effect of the eCIRP-TREM-1-NF-κB pathway [54].

The NF-κB pathway represents a major downstream hub of eCIRP-mediated inflammatory signaling. Activation through either TLR4/MD2 or TREM-1 converges on pro-inflammatory transcriptional programs centered on NF-κB. In a renal ischemia-reperfusion model, $Cirp^{-/-}$ mice exhibited significantly reduced renal injury and inflammatory responses compared with wild-type mice, including lower IL-6 levels and attenuated oxidative stress and apoptosis [36,39,40,59]. Similarly, studies in acute lung injury have shown that CIRP deficiency or inhibition attenuates pulmonary inflammation and injury, with NF-κB-related signaling being implicated as an important downstream pathway [54,60]. Indirect evidence for the involvement of this pathway in myocardial injury comes from LPS-induced septic cardiomyopathy, in which CIRP knockdown attenuated cardiomyocyte apoptosis, oxidative stress, and inflammation through suppression of TLR4/NF-κB signaling; given that extracellular CIRP is a recognized pro-inflammatory mediator upstream of TLR4/TREM-1. Collectively, these findings identify the TLR4–MD2 pathway as the principal mediator of eCIRP-induced inflammatory signaling in myocardial injury [8,53,56]. Furthermore,

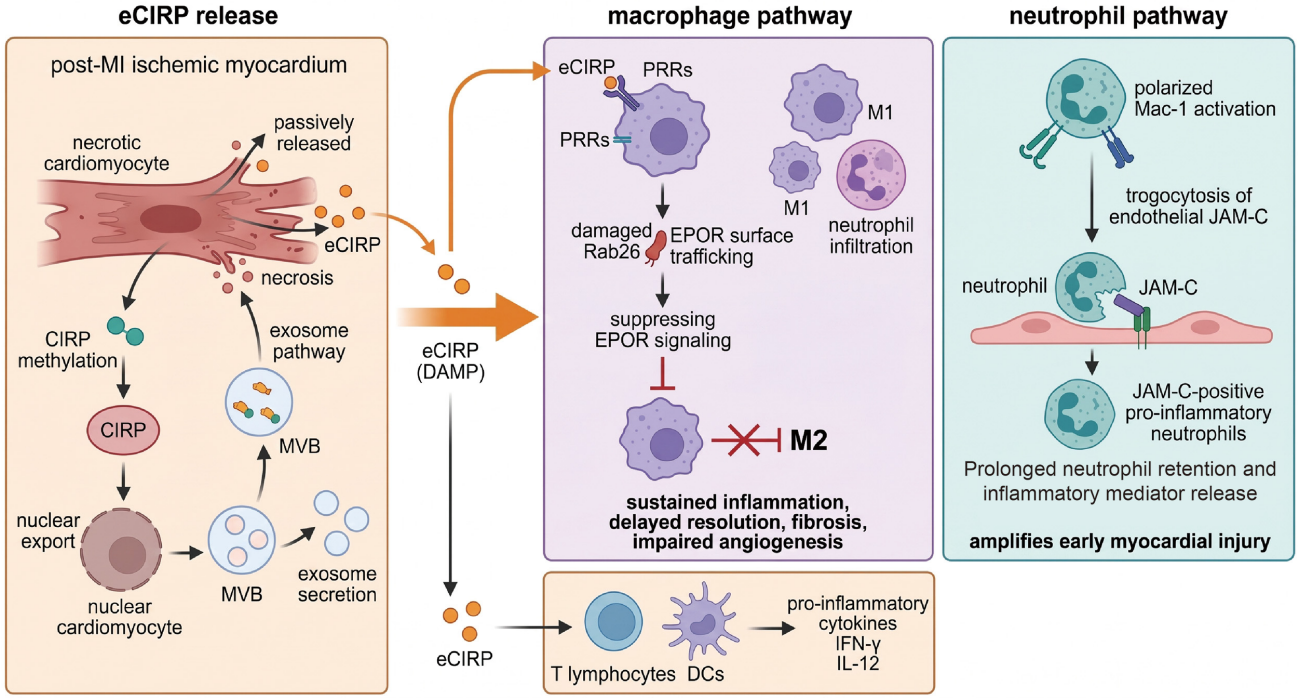


Fig. 4. Mechanisms of eCIRP-mediated inflammatory aggravation after myocardial infarction. After MI, CIRP is released from injured cardiomyocytes through necrosis and exosome-mediated secretion, releasing eCIRP. As a DAMP, eCIRP amplifies post-MI inflammation through multiple immune pathways. In macrophages, eCIRP impairs EPOR signaling, inhibits M2 polarization, and promotes sustained inflammation, delayed resolution, fibrosis, and impaired angiogenesis. In neutrophils, eCIRP induces polarized Mac-1 activation and trogocytosis of endothelial JAM-C, generating JAM-C-positive pro-inflammatory neutrophils that aggravate early myocardial injury. eCIRP may also enhance pro-inflammatory cytokine production by T lymphocytes and DCs. CIRP, cold-inducible RNA-binding protein; eCIRP, extracellular cold-inducible RNA-binding protein; MI, myocardial infarction; DAMP, damage-associated molecular pattern; EPOR, erythropoietin receptor; Mac-1, macrophage-1 antigen; JAM-C, junctional adhesion molecule-C; DCs, dendritic cells.

eCIRP can amplify inflammatory signaling by inducing endoplasmic reticulum stress (ERS). In sepsis-related lung injury, CIRP was shown to promote endoplasmic reticulum (ER) stress in pulmonary endothelial cells, while ERS is known to intersect with NF-κB signaling, including through the protein kinase RNA-like endoplasmic reticulum kinase (PERK)-eukaryotic initiation factor 2α (eIF2α)-activating transcription factor 4 (ATF4) axis, thereby further aggravating inflammation [60,61,62].

In addition to the core pathways described above, eCIRP may promote necroinflammatory signaling through mitochondrial DNA (mtDNA) damage. In sepsis and hemorrhagic shock models, eCIRP has been shown to induce mtDNA fragmentation/release in macrophages and activate stimulator of interferon genes (STING) signaling. Given that mtDNA-STING activation can drive receptor-interacting protein kinase 3 (RIPK3)/MLKL-dependent necroptotic signaling in other inflammatory settings, this mechanism may contribute to sustained inflammation and secondary cardiomyocyte injury after MI [63,64,65]. Moreover, eCIRP can enhance the pro-inflammatory effects of the IL-6/STAT3 pathway by binding to IL-6R, further expanding the inflammatory network [53]. In summary, eCIRP constructs an amplification loop for inflammatory signaling after MI through the cascade activation of the TLR4-MD2, TREM-1, and NF-κB pathways. The synergistic interactions among these pathways and their downstream effects collectively exacerbate myocardial inflammatory injury. Targeted interventions against these pathways have demonstrated potential therapeutic value. As illustrated in Fig. 5, eCIRP released after myocardial infarction may amplify sterile inflammation through coordinated activation of the TLR4/MD2–MyD88–NF-κB and TREM-1–Syk–PI3K–Akt pathways.

4.3 Regulation of Inflammatory Cytokine Release by CIRP

The regulatory effect of eCIRP on the inflammatory cytokine network represents a plausible mechanism by which it may amplify inflammation after MI. eCIRP is known to induce the production of pro-inflammatory cytokines and chemokines through TLR4- and TREM-1-dependent signaling, while also promoting secondary paracrine amplification *via* immune cell activation. Given the central role of cytokine and chemokine imbalance in post-MI inflammation, these actions may contribute to sustained inflammatory cascade activation and adverse cardiac

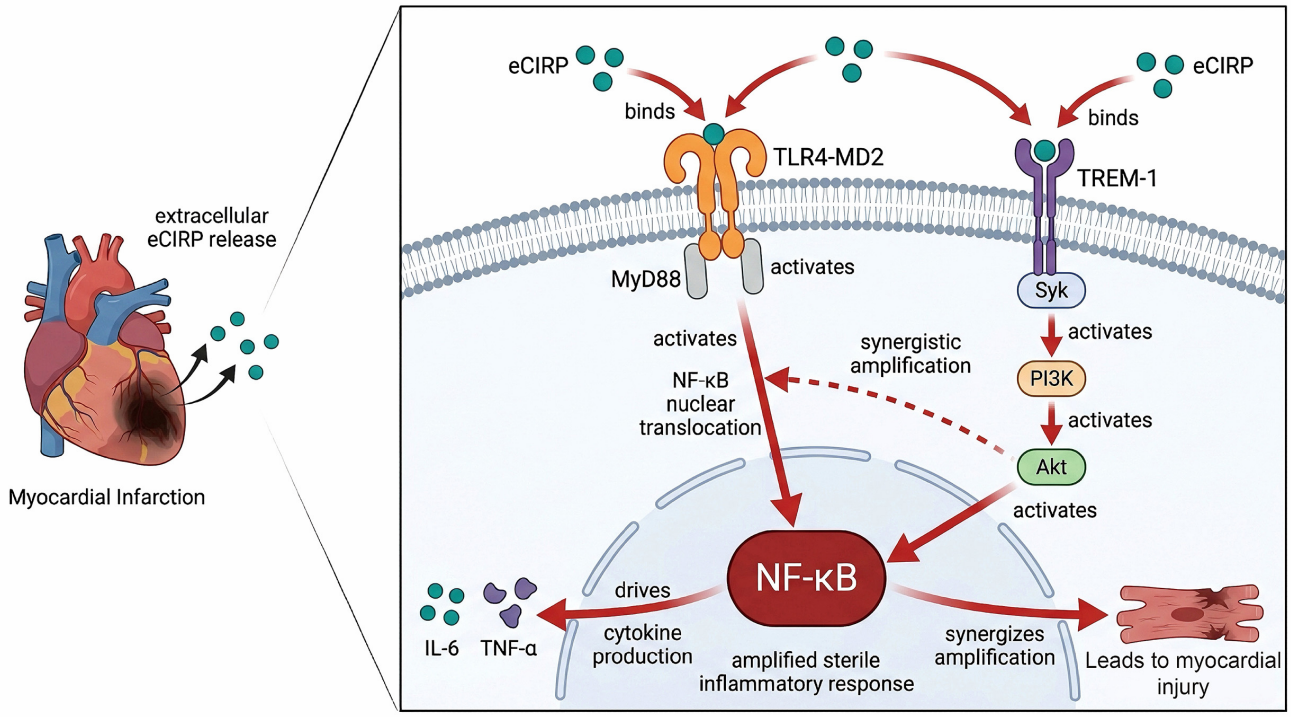


Fig. 5. eCIRP-mediated inflammatory amplification after myocardial infarction. Following myocardial infarction, eCIRP is released from injured myocardium and binds to TLR4/MD2 and TREM-1. TLR4/MD2 activates the MyD88–NF-κB pathway, whereas TREM-1 activates the Syk–PI3K–Akt axis, synergistically enhancing NF-κB nuclear translocation. This signaling cascade promotes IL-6 and TNF-α production, amplifies sterile inflammation, and contributes to myocardial injury. eCIRP, extracellular cold-inducible RNA-binding protein; TLR4, Toll-like receptor 4; MD2, myeloid differentiation factor 2; TREM-1, triggering receptor expressed on myeloid cells-1; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa B; Syk, spleen tyrosine kinase; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; IL, interleukin.

remodeling [66,67]. Excessive release of pro-inflammatory cytokines is a central manifestation of eCIRP-driven inflammation. In ischemia-reperfusion-related injury models, eCIRP can directly or indirectly promote the production of key pro-inflammatory mediators, including TNF-α, IL-6, and IL-1β, all of which contribute to the inflammatory response following myocardial ischemia/reperfusion injury [68]. In a renal ischemia/reperfusion (I/R) model, serum IL-6 levels in $Cirp^{-/-}$ mice were 70% lower than those in wild-type mice, accompanied by significant reductions in tissue injury markers, supporting CIRP as an important regulator of IL-6 release and inflammatory tissue injury [36,58,69]. In a model of septic myocardial injury, CIRP knockdown significantly reduced the levels of TNF-α and IL-6 in myocardial tissue and serum, improving cardiac function [56]. Furthermore, eCIRP can promote the maturation and release of IL-1β by activating the inflammasome. In a sepsis model, eCIRP induced NLRP3 inflammasome activation in macrophages, while CIRP knockout inhibited this process and reduced IL-1β secretion [8]. This mechanism may be particularly relevant in MI, where ischemia/reperfusion injury releases inflammasome activators such as ATP and uric acid. eCIRP has been shown to enhance inflammasome activity, suggesting a potential positive feedback loop between inflammatory cytokines and inflammasome signaling. In addition, induction of chemoattractants represents an important mechanism by which eCIRP promotes immune cell infiltration. After MI, chemoattractants guide neutrophils and macrophages toward the ischemic myocardium, and eCIRP may amplify this process by upregulating their expression. In a hemorrhagic shock model, treatment with the eCIRP antagonist A12 significantly reduced lung MIP-2 and KC mRNA levels and attenuated neutrophil infiltration [55,70]. Similarly, in an intestinal I/R model, A12 treatment suppressed eCIRP, lowered the expression of IL-6, IL-1β, and MIP-2 in lung tissue, and ameliorated lung injury [57]. These findings suggest that eCIRP promotes immune cell recruitment to ischemic tissue by regulating the chemoattractant network, thereby aggravating local inflammatory injury. In addition to enhancing pro-inflammatory signaling, CIRP deficiency has been associated with a shift toward inflammation-resolving macrophage polarization. In an ischemic muscle tissue model, $Cirp^{-/-}$ mice exhibited a higher proportion of M2-like macrophages and less tissue damage than wild-type mice, suggesting that CIRP may hinder inflammation resolution by maintaining a more pro-inflammatory tissue microenvironment [48]. Moreover, ev-

idence from hypothermia-induced acute lung injury indicates that CIRP aggravates inflammation primarily through the TREM-1/NF-κB pathway rather than through a clearly established transforming growth factor-β (TGF-β)/small mothers against decapentaplegic (Smad) mechanism. Although CIRP has been linked to TGF-β-related signaling in other injury settings, direct evidence that eCIRP suppresses anti-inflammatory responses *via* TGF-β/Smad signaling in hypothermic lung injury remains limited [54,71,72].

It is noteworthy that eCIRP's regulation of inflammatory cytokines exhibits characteristics of post-transcriptional regulation. As an RNA-binding protein, intracellular CIRP can stabilize the mRNA of pro-inflammatory cytokines by binding to their 3′-UTR regions, thereby promoting their translation. In an airway inflammation model, cold stress-induced CIRP overexpression increased the stability and protein expression of MUC5AC and IL-6 mRNA by binding to their 3′-UTRs, whereas CIRP knockdown promoted the degradation of these mRNAs [12]. Although direct evidence is currently lacking that intracellular CIRP promotes inflammatory cytokine expression *via* post-transcriptional regulation in MI, this mechanism may contribute to the rapid release of inflammatory factors in the early phase of MI, considering the nucleocytoplasmic translocation of intracellular CIRP and stress granule (SG) formation during myocardial ischemia. Intracellular CIRP may bind to pro-inflammatory cytokine mRNAs within SGs, protecting them from degradation. Upon cell rupture, these are released alongside eCIRP, further amplifying the inflammatory response [53]. In summary, eCIRP constructs an imbalanced network of inflammatory factors post-MI by promoting the release of pro-inflammatory cytokines, inducing chemoattractant expression, and suppressing anti-inflammatory factor signaling. Its characteristics of post-transcriptional regulation and synergistic effects with immune cell activation position it as a key amplifier of the inflammatory cascade. Potential intervention points targeting the eCIRP–TLR4/TREM-1 signaling axis are illustrated in Fig. 6.

5. The Role of CIRP in Cardiac Repair and Remodeling After MI

5.1 The Relationship Between CIRP and Cardiac Cell Death

Massive cardiomyocyte death constitutes a central pathological basis of cardiac dysfunction after MI, with oxidative stress, inflammatory activation, and mitochondrial dysfunction serving as key mechanisms driving apoptosis and necrosis. As an intracellular stress-response protein, CIRP appears to support cardiomyocyte survival under ischemic or oxidative stress conditions. Studies have shown that CIRP expression is reduced in myocardial tissue from patients with heart failure and in post-MI animal hearts, and that this reduction is associated with increased cardiomyocyte apoptosis [6]. In H_2O_2-stimulated H9c2 cells, CIRP knockdown markedly increased apoptosis, accompanied by upregulation of cleaved caspase-3 and Bcl-2-associated X protein (Bax) and downregulation of Bcl-2, indicating that CIRP deficiency enhances cardiomyocyte susceptibility to oxidative stress-induced apoptosis [4,6].

The anti-apoptotic effect of CIRP is closely linked to its regulation of intracellular redox homeostasis. A recent study showed that pretreatment with the CIRP agonist Zr17-2 upregulated Nrf2 and its downstream antioxidant genes, including HO-1 and NQO-1, in post-MI hearts and in oxidatively injured cardiomyocytes. In H_2O_2-treated cardiomyocytes, Zr17-2 attenuated oxidative injury and apoptosis, whereas CIRP silencing abolished these antioxidant effects, indicating that CIRP is required for the cytoprotective action of Zr17-2 [5,73]. CIRP exerts context-dependent effects on cell survival. In cardiomyocytes, intracellular CIRP generally acts as a cytoprotective RNA-binding protein that limits stress-induced apoptosis, whereas extracellular CIRP functions as a pro-inflammatory DAMP after release from injured cells. Experimental studies have shown that CIRP deficiency increases cardiomyocyte susceptibility to oxidative stress-induced apoptosis, while earlier mechanistic work indicates that CIRP can suppress apoptosis-associated caspase signaling, at least in part through extracellular signal-regulated kinase (ERK) activation. By contrast, once released extracellularly, CIRP activates innate immune signaling through receptors such as TLR4 and TREM-1, thereby promoting inflammatory mediator release and indirectly worsening cardiomyocyte injury [8,56,74,75]. This double-edged sword effect suggests that the role of CIRP in cardiomyocyte death depends on its form of existence and the inflammatory state of the local microenvironment.

5.2 The Role of CIRP in the Process of Myocardial Fibrosis

Following MI, the clearance and replacement of necrotic myocardial tissue rely on the fibrotic process, during which fibroblasts proliferate and produce large amounts of extracellular matrix (ECM) components, leading to scar formation and maintenance of cardiac structural integrity. However, excessive fibrosis leads to ventricular wall stiffening, diastolic dysfunction, and ultimately progression to heart failure. CIRP participates in the dynamic equilibrium of post-infarction fibrosis by regulating inflammatory responses, fibroblast activation, and ECM metabolism. Current research on the direct regulation of fibroblast function by CIRP is relatively limited, but substantial evidence indicates that CIRP indirectly modulates the fibrotic process by influencing the inflammatory microenvironment [76]. After cardiomyocyte-targeted overexpression of CIRP in a rat MI model, the inflammatory response in cardiac tissue of the MI model was significantly attenuated: macrophage infiltration decreased by 35%, and mRNA levels of pro-inflammatory factors such as TNF-α and IL-1β were re-

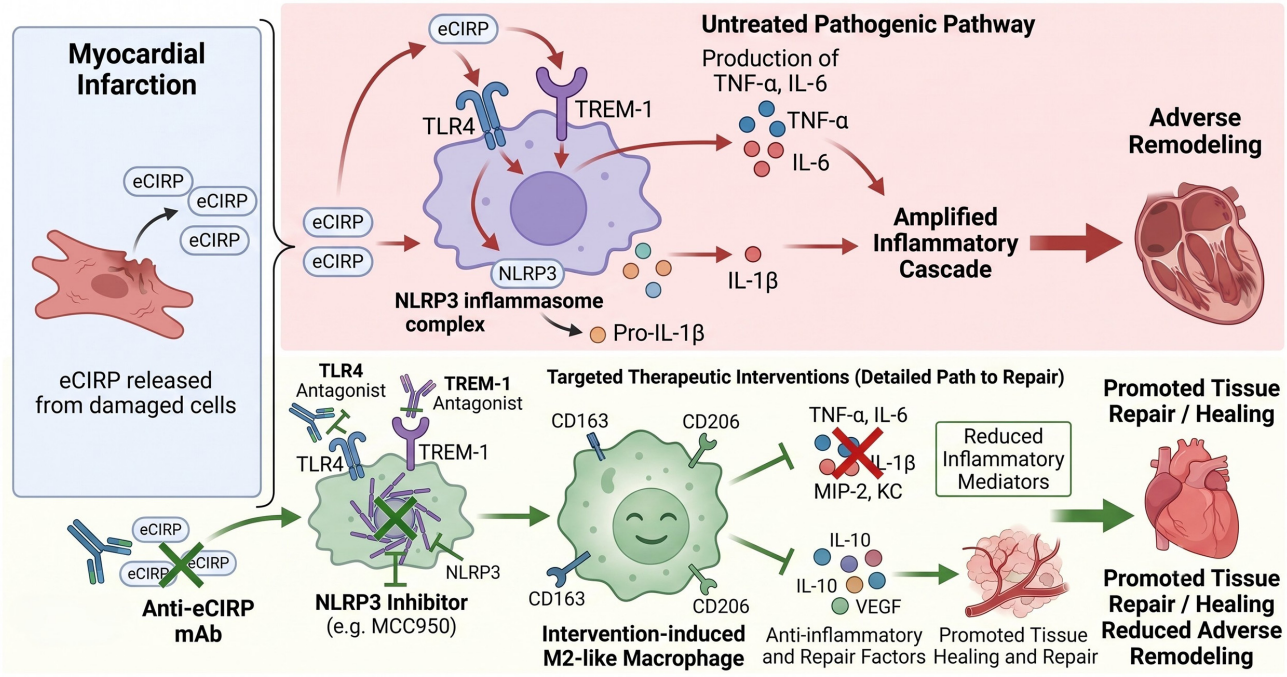


Fig. 6. eCIRP-driven inflammatory amplification and adverse remodeling after myocardial infarction. Myocardial infarction induces the release of eCIRP from damaged cells. eCIRP activates TLR4, TREM-1, and the NLRP3 inflammasome, thereby promoting the production of TNF-α, IL-6, IL-1β, and chemokines such as MIP-2 and KC. These mediators enhance neutrophil and macrophage recruitment, amplify sterile inflammation, and contribute to ischemic tissue injury and adverse cardiac remodeling. In contrast, CIRP deficiency may favor M2-like macrophage polarization, inflammation resolution, and tissue repair. eCIRP, extracellular cold-inducible RNA-binding protein; CIRP, cold-inducible RNA-binding protein; TLR4, Toll-like receptor 4; TREM-1, triggering receptor expressed on myeloid cells-1; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3; TNF-α, tumor necrosis factor-α; IL, interleukin; MIP-2, macrophage inflammatory protein-2; KC, keratinocyte-derived chemokine.

duced by over 40%. The attenuation of the inflammatory response directly led to the inhibition of fibroblast activation—immunohistochemical results showed that the number of α-smooth muscle actin-positive cells in CIRP-overexpressing cardiac tissue decreased by 52% compared to the control group, while the deposition area of collagen I and collagen III decreased from 38.7% to 21.3% [7]. These results suggest that CIRP indirectly reduces fibroblast activation and ECM synthesis by suppressing the inflammatory response [7].

The anti-inflammatory effect of CIRP appears to be closely associated with activation of the Nrf2 antioxidant pathway. Studies have shown that pharmacologic upregulation of CIRP by Zr17-2 enhances cardiac Nrf2 signaling and increases the expression of downstream antioxidant genes such as HO-1 and NQO-1 in MI models. Given the well-established anti-inflammatory and antifibrotic roles of Nrf2, CIRP may indirectly modulate post-infarction inflammatory and fibrotic remodeling. However, a direct CIRP–Nrf2–IL-10–TGF-β1 signaling axis has not yet been conclusively established [5,77,78]. Furthermore, the regulation of cardiac cell apoptosis by CIRP also influences the extent of fibrosis. As previously mentioned, the anti-apoptotic effect of CIRP reduces the number of cardiac cell deaths, thereby diminishing the recruitment and activation signals for fibroblasts from necrotic tissue. Research by Chen et al. [6]. indirectly supports this view: low expression of CIRP in myocardial tissue from heart failure patients coexists with high apoptosis rates and severe fibrosis, suggesting that the absence of CIRP may indirectly promote fibrosis progression by exacerbating cardiac cell death.

It is important to note that the impact of CIRP on fibrosis may depend on its cellular localization and the inflammatory context. Intracellular CIRP generally exhibits cytoprotective effects, including anti-oxidative, anti-inflammatory, and anti-apoptotic actions, which may secondarily restrain fibrotic remodeling. In contrast, extracellular CIRP (eCIRP), acting as a pro-inflammatory DAMP, has been implicated in profibrotic responses, including inflammatory activation of fibroblasts and promotion of tissue fibrosis in experimental models. These context-dependent effects may partly explain the discrepant findings regarding CIRP in fibrosis, although the specific contributions of intracellular versus extracellular CIRP to post-MI fibrosis remain to be clarified [79,80].

5.3 The Impact of CIRP on Angiogenesis

One study examined the role of CIRP in angiogenesis using a murine hindlimb ischemia model and found that CIRP deficiency enhanced ischemia-induced angiogenesis and tissue regeneration. This was accompanied by an increased capillary-to-muscle fiber ratio, more proliferating endothelial cells, reduced inflammatory M1-like macrophage accumulation, increased regenerative M2-like macrophages, and upregulated vascular endothelial growth factor (VEGF) expression in ischemic tissue, suggesting that CIRP may modulate angiogenesis through macrophage polarization and microenvironmental remodeling [48]. These findings suggest that CIRP may indirectly impede angiogenesis by inhibiting M2 macrophage polarization. However, because the available evidence was obtained in a skeletal muscle ischemia model rather than in post-infarction myocardium, its relevance to myocardial angiogenesis remains to be validated. Given the distinct inflammatory milieu of the infarcted heart, the role of CIRP in myocardial angiogenesis is likely to be more complex. Extracellular CIRP may impair endothelial-supportive remodeling by sustaining pro-inflammatory macrophage activation, whereas intracellular CIRP may indirectly favor angiogenesis by preserving cardiac cell viability and improving the local reparative microenvironment. In addition, pharmacologic upregulation of CIRP by Zr17-2 enhances cardioprotective signaling in MI models, suggesting that intracellular CIRP may support post-ischemic repair, although direct evidence that CIRP may promote myocardial angiogenesis through VEGF regulation is still limited [5,81]. Taken together, the currently available evidence suggests that CIRP may participate in the regulation of post-infarction angiogenesis. However, this hypothesis is largely inferred from indirect evidence and studies performed in non-cardiac ischemic models. Therefore, whether intracellular and extracellular CIRP exert distinct effects on myocardial angiogenesis remains to be established.

6. Limitations and Future Directions

Although significant progress has been made in recent years regarding the role of CIRP in MI, several limitations persist. These limitations constrain a comprehensive understanding of CIRP's biological functions and its potential for clinical translation. Firstly, the dynamic changes in CIRP expression and its functional switching across different post-MI stages remain incompletely understood. Most current studies focus on the role of CIRP during the acute phase of MI, while its specific functions during the post-infarction recovery phase are poorly characterized. Furthermore, the cell type-specific roles of CIRP and its regulatory networks require further investigation. Secondly, as a DAMP molecule, the mechanisms underlying the interactions between CIRP and other inflammatory mediators are not fully elucidated. The sterile inflammatory response following MI constitutes a complex network involving multiple DAMP molecules and inflammatory signaling pathways. Current research primarily focuses on signaling pathways mediated by CIRP through receptors such as TLR4 and TREM-1. However, whether synergistic or antagonistic interactions exist between CIRP and other DAMP molecules, and how these interactions influence post-MI inflammation and tissue healing, necessitates systematic investigation. These findings suggest that CIRP may indirectly impede angiogenesis by inhibiting M2 macrophage polarization. However, because the available evidence was obtained in a skeletal muscle ischemia model rather than in post-infarction myocardium, its relevance to myocardial angiogenesis remains to be validated. Given the distinct inflammatory milieu of the infarcted heart, the role of CIRP in myocardial angiogenesis is likely to be more complex. Extracellular CIRP may impair endothelial-supportive remodeling by sustaining pro-inflammatory macrophage activation, whereas intracellular CIRP may indirectly favor angiogenesis by preserving cardiac cell viability and improving the local reparative microenvironment. In addition, pharmacologic upregulation of CIRP by Zr17-2 enhances cardioprotective signaling in MI models, suggesting that intracellular CIRP may support post-ischemic repair, although direct evidence that CIRP promotes myocardial angiogenesis through VEGF regulation is still limited [5,81].

Another important limitation is that much of the current mechanistic understanding of CIRP in myocardial infarction remains hypothesis-generating rather than conclusively established. Although numerous experimental and clinical studies have demonstrated significant associations between altered CIRP expression and myocardial injury, inflammation, and cardiac remodeling, most available evidence is based on correlation, pharmacological modulation, or conventional gain- and loss-of-function approaches. Direct causal evidence demonstrating that CIRP independently drives specific pathological processes in myocardial infarction, particularly through cell type-specific and temporally controlled genetic models, remains limited. Therefore, several mechanistic pathways discussed in this review should be regarded as plausible working models rather than fully validated mechanisms, and further studies are required to establish causal relationships.

Based on the current research status and limitations, future studies on the role of CIRP in myocardial infarction should focus on the following directions to provide new strategies and targets for the treatment of MI. First, a thorough elucidation of the dynamic changes of CIRP in different stages after myocardial infarction and the molecular mechanisms underlying its functional switching. Future research should employ multi-omics technologies (such as transcriptomics, proteomics, and metabolomics) to systematically analyze the expression patterns, post-translational modifications, and interaction networks of CIRP during the

acute, subacute, and chronic phases post-infarction. For example, single-cell RNA sequencing technology could be utilized to map the expression profiles of CIRP in various cell types within cardiac tissues at different time points after myocardial infarction, clarifying its specific functions in cardiomyocytes, fibroblasts, endothelial cells, and immune cells. Furthermore, attention should be paid to the regulatory role of post-translational modifications of CIRP on its subcellular localization, RNA-binding activity, and release processes, which may provide novel targets for modulating in CIRP function. Second, post-infarction myocardial repair involves the coordinated action of multiple cell types, including the survival and proliferation of cardiomyocytes, angiogenesis by endothelial cells, and the activation of fibroblasts and matrix remodeling. Future studies should focus on investigating how CIRP appears to regulate these processes. Third, conducting clinical research on CIRP as a diagnostic and prognostic biomarker for myocardial infarction. Although correlations between CIRP levels and the severity of myocardial infarction have been observed in animal models and limited clinical studies, large-scale clinical data supporting its clinical value as a biomarker are currently lacking. Future research should carry out multicenter, large-sample clinical studies to systematically evaluate the relationship between serum or plasma CIRP levels in myocardial infarction patients and disease severity, treatment response, and long-term prognosis. Fourth, focus on the role of CIRP in myocardial infarction among special populations. The pathophysiological processes and treatment responses may differ among myocardial infarction patients of different genders, ages, and with comorbidities. Future research should emphasize exploring the role of CIRP in these special populations. For example, studying the expression patterns of CIRP in female myocardial infarction patients and its interaction with estrogen; or investigating the mechanisms of CIRP in patients with diabetes mellitus and myocardial infarction, and whether modulating CIRP can improve the prognosis of such patients. Finally, strengthening research on the interactions between CIRP and other DAMP molecules. The sterile inflammatory response after myocardial infarction is a complex network system involving the synergistic action of multiple DAMP molecules. Future studies should focus on exploring the interactions between CIRP and other DAMP molecules and their regulatory mechanisms on the inflammatory response. Additionally, the role of CIRP in modulating immune cell function and how it affects post-infarction immune tolerance and the resolution of inflammation can be explored [82,83,84,85,86]. The precise temporal overlap between intracellular protective CIRP and extracellular pro-inflammatory CIRP remains insufficiently defined because most available studies measured total CIRP rather than simultaneously distinguishing intracellular and extracellular pools at serial time points after myocardial infarction.

In summary, CIRP, as a stress-responsive protein with dual roles, plays a profound role in the occurrence and development of myocardial infarction. A deep understanding of the molecular mechanisms of CIRP and the development of specific targeted therapeutic strategies will provide new hope for the treatment of myocardial infarction. Future research requires interdisciplinary collaboration, integrating basic research and clinical translation to continuously advance this field. It is believed that with the deepening of research, CIRP is expected to become a novel therapeutic target for myocardial infarction, making important contributions to improving the prognosis of patients with myocardial infarction.

Author Contributions

YZ and HY contributed equally to this work. YZ and HY performed the literature search, organized the manuscript framework, drafted the initial manuscript, and prepared the figures. YW, YP, and CY contributed to literature collection, reference management, content refinement, and manuscript revision. MB and ZZ conceived and supervised the work. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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