

Myeloid Cell–Driven Inflammatory Responses Exacerbate Myocardial Cell Injury in Mice

Rajesh Kumar Sharma¹, Anjali Mehta², Vivek Reddy Narayan³, Sneha Patel^{4*}

All India Institute of Medical Sciences (AIIMS) New Delhi, India.

Postgraduate Institute of Medical Education and Research (PGIMER) Chandigarh, India

Department of Internal Medicine, Christian Medical College (CMC)

Department of Molecular Biology & Biotechnology, Indian Institute of Science (IISc)

Bangalore, Karnataka, India

Corresponding Author: sneha.patel@iisc.ac.in

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ABSTRACT

Myocardial cell injury is a central pathological process underlying acute myocardial infarction, ischemia–reperfusion injury, and inflammatory cardiomyopathies. Although ischemic and metabolic disturbances initiate cardiomyocyte damage, accumulating evidence indicates that immune-mediated inflammatory responses significantly amplify myocardial injury. Among immune populations, myeloid cells—including monocytes, macrophages, and neutrophils—play a dominant role in shaping the inflammatory microenvironment of the injured heart. Experimental murine studies have demonstrated that these cells exacerbate myocardial injury through cytokine production, oxidative stress, inflammasome activation, and direct cellular interactions with cardiomyocytes. Importantly, the temporal dynamics and phenotypic heterogeneity of myeloid cells critically determine whether inflammation promotes injury or facilitates repair. This review provides a comprehensive synthesis of the mechanisms by which myeloid cell–driven inflammation worsens myocardial cell injury in mice, with emphasis on molecular signaling pathways, immunometabolic regulation, and translational implications. Understanding these processes offers opportunities for targeted immunomodulatory therapies aimed at preserving myocardial integrity and improving clinical outcomes.

Keywords: Myocardial injury; Myeloid cells; Inflammation; Macrophages; Neutrophils; Cardiomyocyte death; Oxidative stress; Cytokines.

INTRODUCTION

Myocardial cell injury represents a fundamental event in the pathogenesis of cardiovascular diseases and is the principal determinant of cardiac dysfunction following ischemic and non-ischemic insults [1]. Despite major advances in reperfusion therapy and pharmacological management, the burden of myocardial injury remains substantial, often leading to adverse remodeling and heart failure [2]. Traditionally, myocardial injury has been attributed to ischemia-induced metabolic derangements, including ATP depletion, acidosis, and calcium overload. However, it is now widely recognized that the immune system plays a critical and active role in amplifying myocardial damage beyond the initial insult [3].

Following myocardial injury, the heart rapidly transitions into an inflammatory organ. This response is initiated by the release of damage-associated molecular patterns (DAMPs) from injured cardiomyocytes, including mitochondrial DNA, ATP, and high-mobility group box 1 (HMGB1) [4]. These endogenous signals activate innate immune pathways through pattern recognition receptors (PRRs), leading to the recruitment and activation of immune cells within the myocardium [5]. Among these, myeloid cells are the most abundant and functionally significant contributors to the inflammatory cascade.

Myeloid cells encompass a heterogeneous population that includes neutrophils, monocytes, and macrophages. These cells are rapidly mobilized following myocardial injury and accumulate within the affected tissue in a tightly regulated temporal sequence [6]. While their primary role is to clear necrotic debris and facilitate tissue repair, excessive or dysregulated activation of myeloid cells results in the release of pro-inflammatory cytokines, reactive oxygen species (ROS), and proteolytic enzymes that exacerbate cardiomyocyte injury [7].

Murine models have been instrumental in advancing our understanding of these processes. The use of genetically modified mice, lineage tracing, and immune cell depletion strategies has revealed that myeloid cells are not merely secondary responders but active drivers of myocardial injury [8]. For example, depletion of monocyte-derived macrophages or inhibition of their recruitment significantly reduces infarct size and improves cardiac function in experimental models [9]. These findings highlight the dual role of inflammation in myocardial injury—both protective and detrimental—depending on its magnitude, duration, and cellular composition.

Another critical aspect of myeloid cell biology in myocardial injury is their remarkable phenotypic plasticity. Macrophages, in particular, can adopt a spectrum of activation states ranging from pro-inflammatory (M1-like) to reparative (M2-like) phenotypes [10]. The early inflammatory phase of myocardial injury is dominated by M1-like macrophages, which produce high levels of TNF- α , IL-1 β , and ROS. In contrast, the later reparative phase involves M2-like macrophages that promote tissue repair, angiogenesis, and fibrosis [11]. An imbalance in this transition contributes to persistent inflammation and worsened cardiac outcomes.

In addition to macrophages, neutrophils play a crucial role in early myocardial injury. These cells are rapidly recruited to the site of injury and release ROS, proteases, and neutrophil extracellular traps (NETs), which can damage cardiomyocytes and endothelial cells [12]. Although neutrophils

are essential for host defense and debris clearance, their excessive activation has been linked to increased infarct size and impaired healing [13].

At the molecular level, multiple signaling pathways regulate myeloid cell–driven inflammation in the heart. Key pathways include nuclear factor- κ B (NF- κ B), mitogen-activated protein kinase (MAPK), and the NLRP3 inflammasome [14]. Activation of these pathways leads to the production of pro-inflammatory cytokines and chemokines that perpetuate immune cell recruitment and activation [15]. Importantly, these signaling networks are interconnected and influenced by metabolic changes within immune cells, a concept referred to as immunometabolism [16].

The interplay between myeloid cells and cardiomyocytes further amplifies myocardial injury. Injured cardiomyocytes release signals that recruit and activate myeloid cells, which in turn produce mediators that exacerbate cardiomyocyte dysfunction and death. This creates a self-perpetuating cycle of injury and inflammation [17].

Understanding the mechanisms by which myeloid cells exacerbate myocardial injury is of considerable clinical importance. Targeting inflammatory pathways has emerged as a promising therapeutic strategy, as demonstrated by clinical trials investigating IL-1 β inhibition in cardiovascular disease [18]. However, the complexity of immune responses in the heart necessitates a nuanced approach that balances suppression of harmful inflammation with preservation of reparative processes.

This review aims to provide a comprehensive overview of the role of myeloid cell–driven inflammatory responses in myocardial cell injury, with a focus on mechanistic insights derived from murine models. By integrating current knowledge on cellular dynamics, molecular pathways, and translational implications, we seek to highlight potential therapeutic targets and future research directions.

Pathophysiology of Myocardial Cell Injury

Overview of Cellular Injury Mechanisms

Myocardial cell injury is a multifactorial process involving metabolic, ionic, and structural disturbances that ultimately lead to cardiomyocyte dysfunction and death [19]. The initial insult—most commonly ischemia—triggers a cascade of intracellular events that disrupt cellular homeostasis.

Mitochondrial Dysfunction and Energy Failure

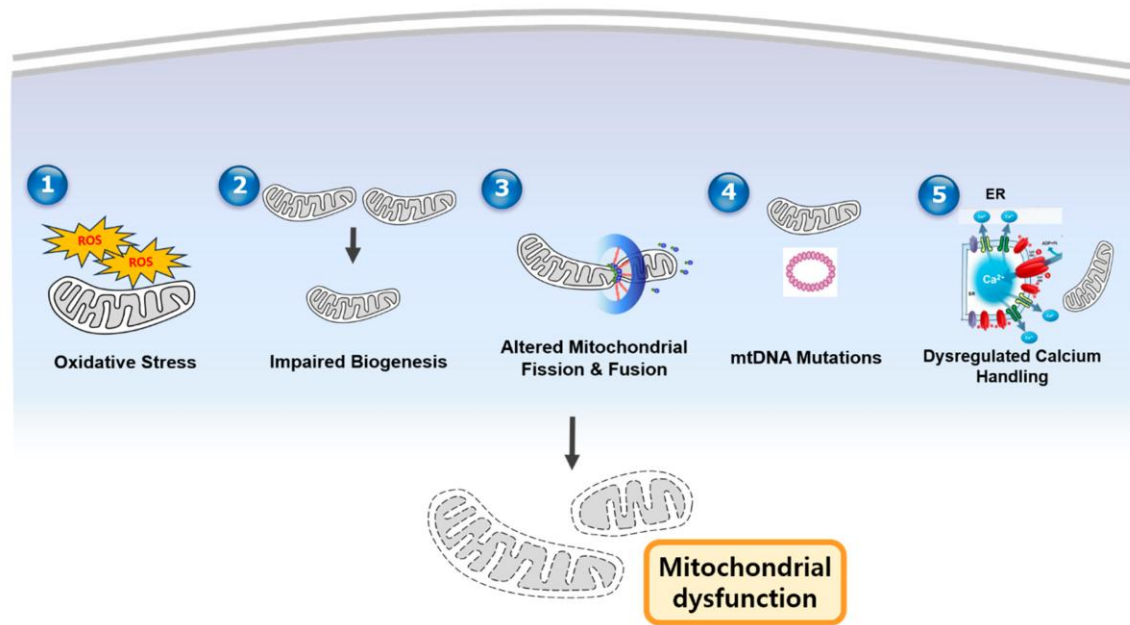


Figure 1. Temporal dynamics of immune cell infiltration following myocardial injury

Schematic representation of the temporal recruitment and functional transitions of immune cells following myocardial injury in murine models. The early phase (0–24 hours) is characterized by rapid neutrophil infiltration and release of reactive oxygen species (ROS) and proteolytic enzymes. The intermediate phase (1–3 days) involves recruitment of circulating monocytes and differentiation into pro-inflammatory macrophages. The late phase (>5 days) is dominated by reparative macrophages that promote tissue repair, angiogenesis, and extracellular matrix remodeling. Dysregulation of this temporal transition leads to persistent inflammation and adverse cardiac remodeling.

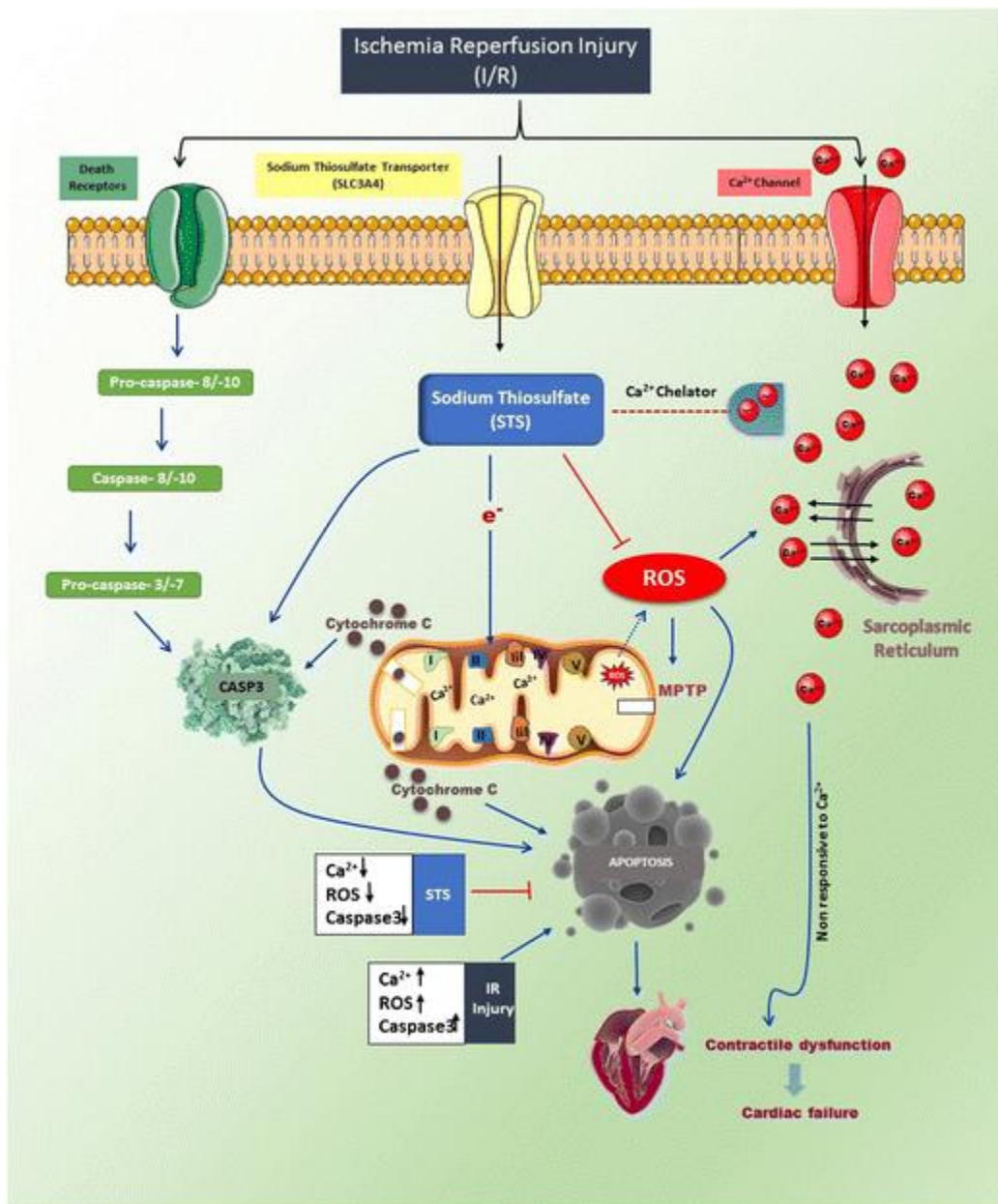


Figure 2. Mechanisms of myeloid cell–driven myocardial injury

Conceptual diagram illustrating the key molecular and cellular pathways through which myeloid cells exacerbate myocardial injury. Following cardiomyocyte damage, damage-associated molecular patterns (DAMPs) activate myeloid cells via pattern recognition receptors (PRRs). Activated neutrophils and macrophages release pro-inflammatory cytokines (TNF- α , IL-1 β), reactive oxygen species (ROS), and proteases, leading to mitochondrial dysfunction, calcium overload, and cardiomyocyte death. Activation of the NLRP3 inflammasome further amplifies inflammatory signaling and promotes pyroptosis.

Mitochondria play a central role in myocardial injury due to their critical function in ATP production. During ischemia, reduced oxygen supply leads to impaired oxidative phosphorylation and ATP depletion [20]. This energy deficit disrupts ion pumps, particularly the Na^+/K^+ -ATPase, resulting in cellular swelling and ionic imbalance.

Upon reperfusion, the sudden restoration of oxygen leads to excessive ROS generation, which damages mitochondrial membranes and DNA [21]. Opening of the mitochondrial permeability transition pore (mPTP) further exacerbates injury by collapsing membrane potential and triggering cell death pathways [22].

Calcium Overload and Ionic Imbalance

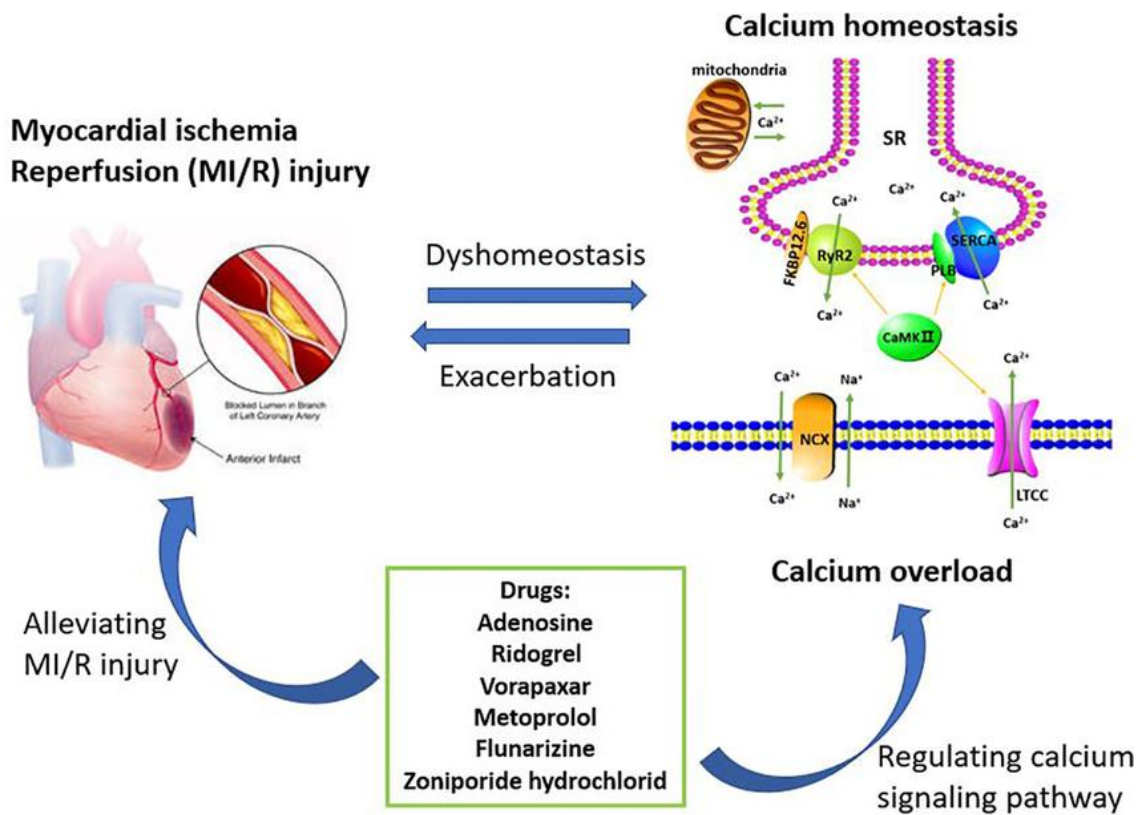


Figure 3. Mitochondrial dysfunction and oxidative stress in cardiomyocyte injury

Illustration of mitochondrial injury during ischemia–reperfusion. Reduced oxygen supply leads to impaired oxidative phosphorylation and ATP depletion. Reperfusion results in excessive generation of reactive oxygen species (ROS), mitochondrial membrane damage, and opening of the mitochondrial permeability transition pore (mPTP). These events trigger cardiomyocyte apoptosis and necrosis and are further exacerbated by inflammatory mediators released from myeloid cells.

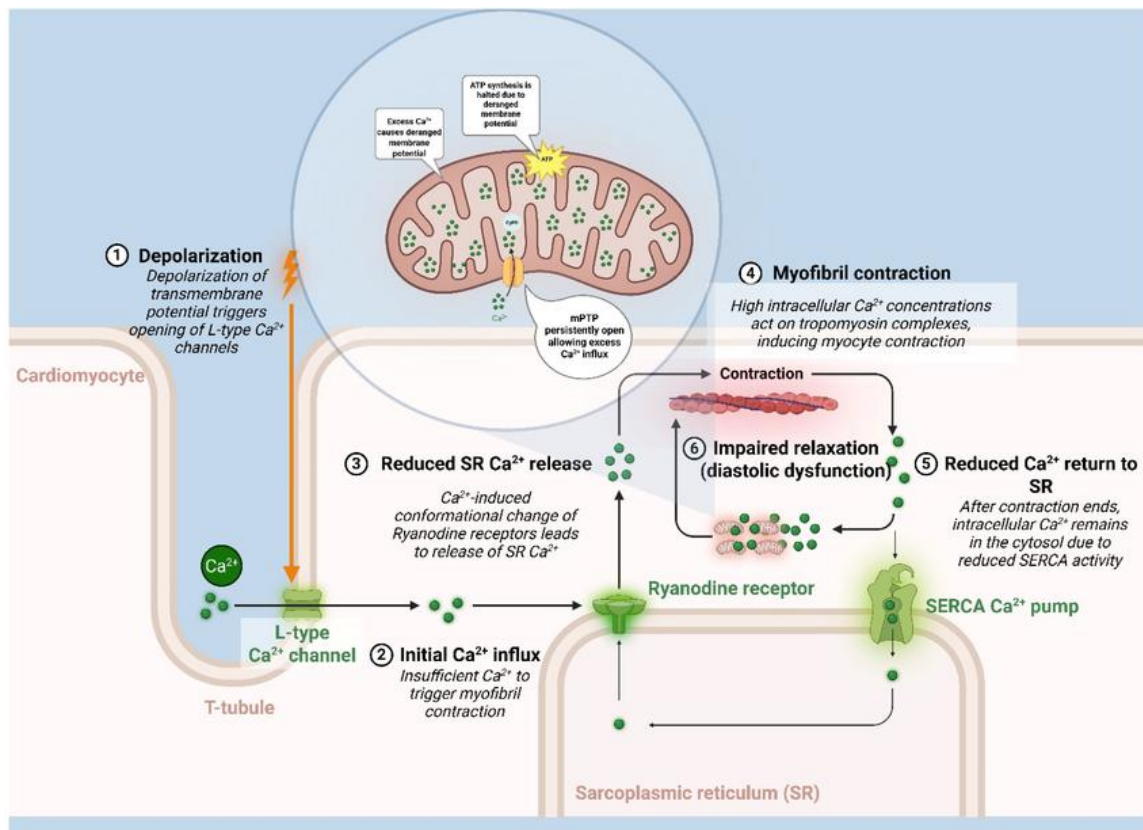


Figure 4. Calcium overload and ionic imbalance in cardiomyocytes

Diagram depicting disruption of calcium homeostasis during myocardial injury. Ischemia-induced ATP depletion impairs ion transporters, leading to intracellular calcium accumulation. Elevated calcium activates proteases, phospholipases, and endonucleases, resulting in structural damage, mitochondrial dysfunction, and activation of cell death pathways.

Calcium homeostasis is tightly regulated in cardiomyocytes. Ischemia disrupts this balance, leading to intracellular calcium accumulation [23]. Elevated calcium levels activate proteases, phospholipases, and endonucleases, which degrade cellular structures and contribute to cell death [24].

Oxidative Stress and Reactive Oxygen Species

ROS are generated from multiple sources, including mitochondria and activated myeloid cells [25]. While low levels of ROS serve signaling functions, excessive ROS production leads to lipid peroxidation, protein oxidation, and DNA damage [26]. Myeloid cells significantly contribute to oxidative stress through NADPH oxidase activity [27].

Inflammatory Amplification of Injury

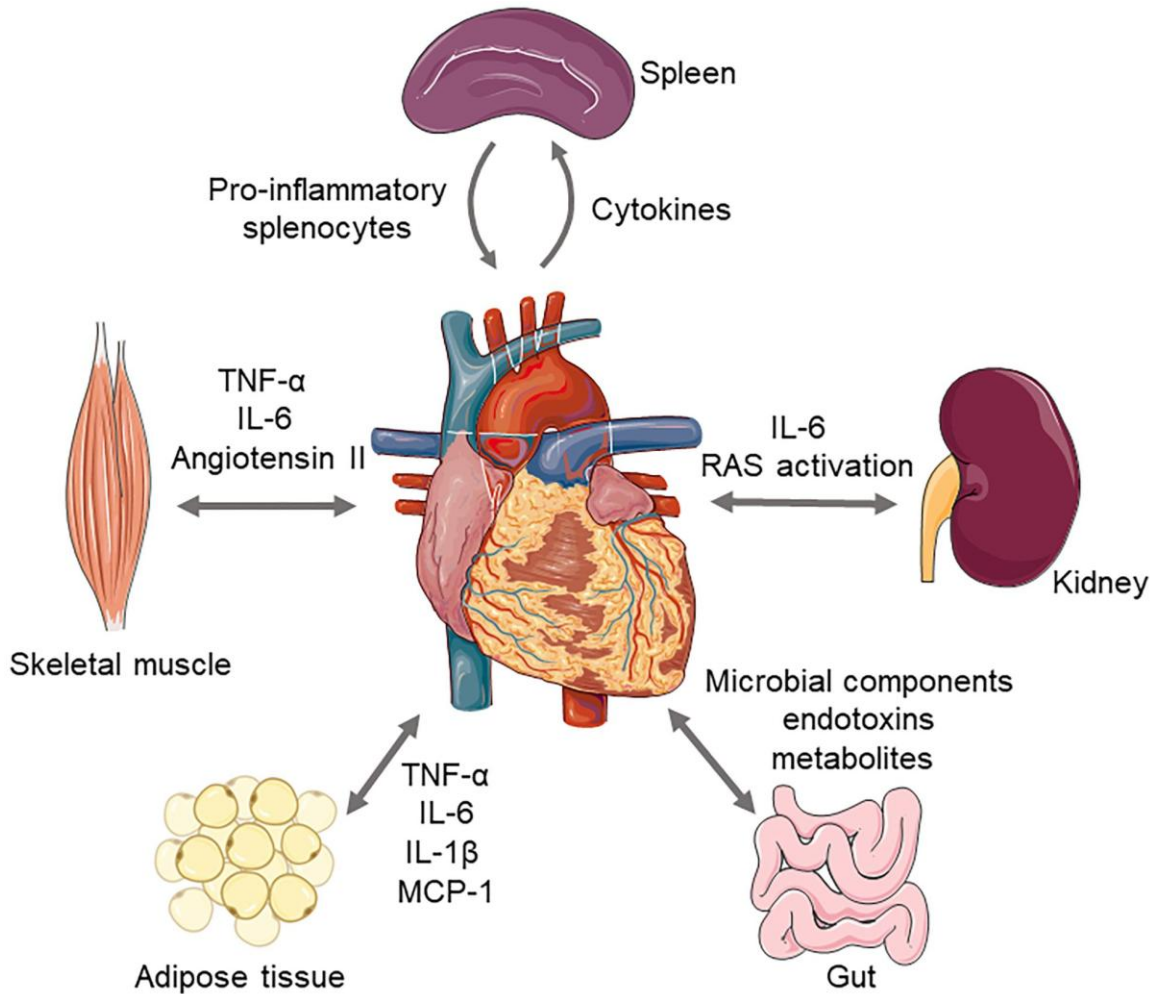


Figure 5. Inflammatory signaling pathways in myocardial injury

Schematic overview of key inflammatory signaling pathways activated in myeloid cells following myocardial injury. Activation of NF- κ B and MAPK pathways leads to transcription of pro-inflammatory cytokines, while NLRP3 inflammasome activation promotes IL-1 β and IL-18 release. These pathways collectively amplify inflammation and contribute to cardiomyocyte injury.

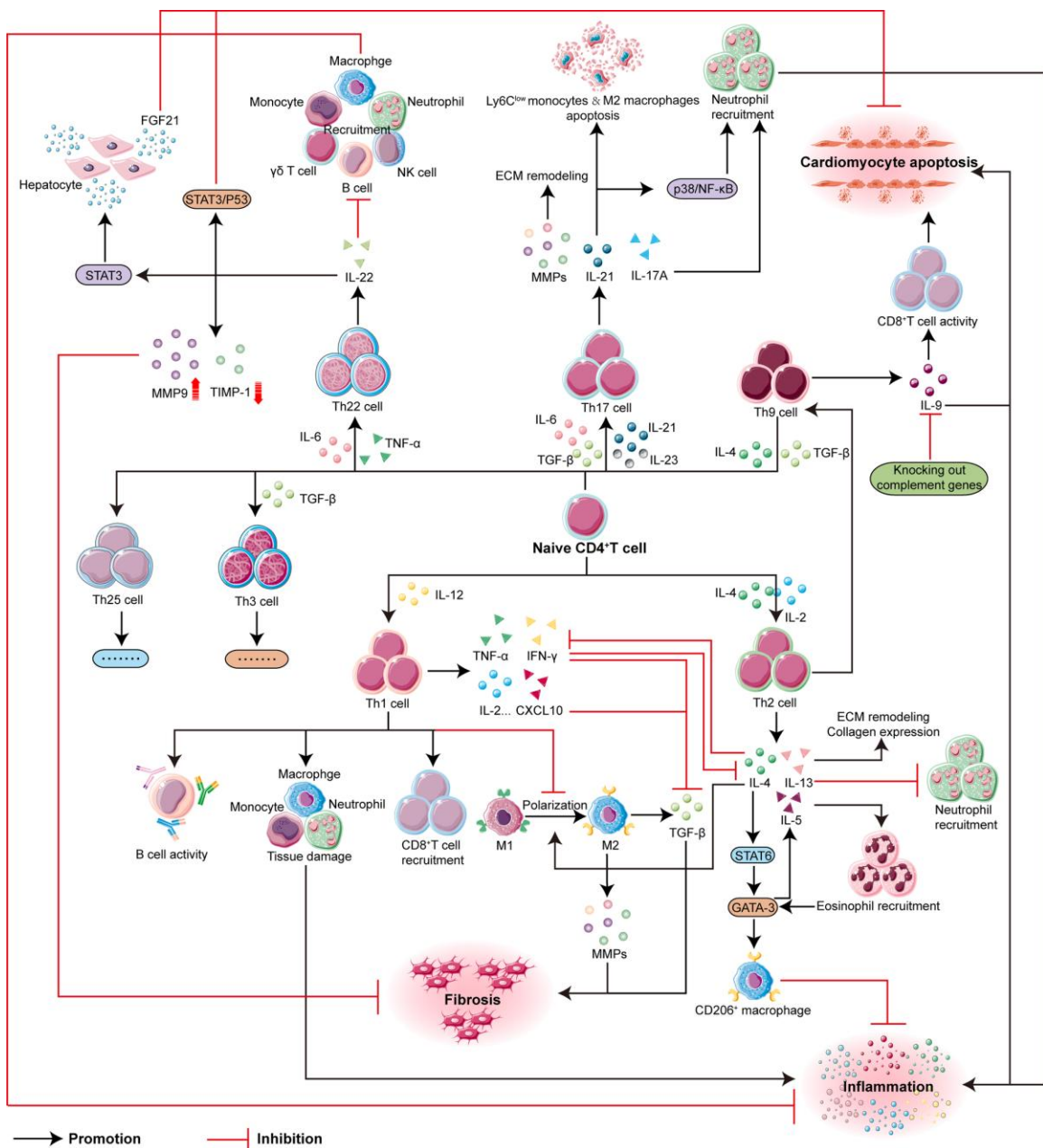


Figure 8. Crosstalk between myeloid cells and cardiomyocytes

Diagram illustrating bidirectional communication between myeloid cells and cardiomyocytes. Injured cardiomyocytes release DAMPs that activate myeloid cells, while activated myeloid cells produce cytokines, ROS, and extracellular vesicles that further impair cardiomyocyte function. This feedback loop contributes to sustained myocardial injury.

Inflammation is a major amplifier of myocardial injury. DAMPs released from injured cardiomyocytes activate innate immune pathways, leading to recruitment of myeloid cells [28]. These cells produce cytokines such as TNF- α and IL-1 β , which directly impair cardiomyocyte function and promote apoptosis [29].

Cell Death Pathways

Three major forms of cell death contribute to myocardial injury:

- Necrosis: characterized by membrane rupture and inflammation
- Apoptosis: regulated cell death involving caspase activation
- Pyroptosis: inflammasome-mediated inflammatory cell death

Pyroptosis is particularly relevant in inflammation-driven injury and is closely linked to NLRP3 activation.

Role of Myeloid Cells in Pathophysiology

Myeloid cells exacerbate myocardial injury through:

- Cytokine release (TNF- α , IL-1 β)
- ROS production
- Protease secretion
- Inflammasome activation

These mechanisms collectively amplify cardiomyocyte injury and impair recovery.

Temporal Integration of Injury and Inflammation

The progression of myocardial injury is tightly linked to immune cell dynamics:

- Early phase: neutrophil-mediated damage
- Intermediate phase: macrophage-driven inflammation
- Late phase: repair and fibrosis

Disruption of this balance leads to chronic injury and heart failure [38].

Immunometabolic Regulation

Metabolic reprogramming of myeloid cells influences their function. Pro-inflammatory cells rely on glycolysis, whereas reparative cells utilize oxidative metabolism [30]. This metabolic shift affects cytokine production and inflammatory signaling.

Integration of Mechanisms

Myocardial injury is the result of a complex interplay between metabolic stress and immune activation. Mitochondrial dysfunction, calcium overload, oxidative stress, and inflammation converge to drive cardiomyocyte death [31].

DISCUSSION

The present review synthesizes accumulating evidence that myeloid cell-driven inflammatory responses play a central and active role in exacerbating myocardial cell injury in murine models. While myocardial injury has traditionally been attributed to ischemic and metabolic stress, it is increasingly clear that the immune system, particularly the myeloid compartment, is a critical determinant of both the magnitude and progression of cardiomyocyte damage. The findings discussed herein support a paradigm in which inflammation is not merely a consequence of injury but a dynamic and self-amplifying driver of myocardial pathology.

Myeloid Cells as Central Amplifiers of Myocardial Injury

A major conceptual advance in cardiovascular immunology is the recognition that myeloid cells actively amplify myocardial injury through multiple converging mechanisms. Experimental evidence from murine models demonstrates that monocytes, macrophages, and neutrophils are rapidly recruited to the injured myocardium, where they orchestrate inflammatory signaling cascades that extend beyond the initial ischemic insult [31].

Importantly, depletion or inhibition of myeloid cell recruitment consistently results in reduced infarct size, improved cardiac function, and decreased cardiomyocyte death [32]. These findings strongly support a causal role for myeloid cells in exacerbating myocardial injury. Rather than acting as passive responders, these cells function as central regulators of tissue damage, integrating signals from injured cardiomyocytes and translating them into sustained inflammatory responses. The spatial co-localization of myeloid cells with regions of cardiomyocyte injury further underscores their pathogenic role. Areas of dense macrophage infiltration frequently correspond to zones of maximal cellular disruption, suggesting a direct relationship between immune cell activity and tissue damage [33].

Temporal Dynamics: A Double-Edged Sword

The temporal dynamics of myeloid cell responses are critical in determining whether inflammation is beneficial or harmful. In the early phase of myocardial injury, neutrophils and inflammatory monocytes dominate the immune landscape. These cells are essential for debris clearance and host defense; however, their excessive activation leads to substantial collateral damage [34].

Neutrophils, in particular, contribute to early myocardial injury through the release of reactive oxygen species (ROS), proteases, and neutrophil extracellular traps (NETs), which can disrupt endothelial integrity and exacerbate cardiomyocyte death [35]. This initial wave of inflammation sets the stage for subsequent macrophage-driven responses.

During the intermediate phase, monocyte-derived macrophages accumulate and adopt predominantly pro-inflammatory phenotypes. These cells produce high levels of TNF- α , IL-1 β , and IL-6, which impair cardiomyocyte contractility and promote apoptotic and necrotic cell death [36]. Failure to resolve this inflammatory phase leads to persistent immune activation and progressive myocardial injury.

Conversely, the late phase of myocardial injury is characterized by the emergence of reparative macrophages that promote tissue repair, angiogenesis, and extracellular matrix remodeling [37]. The transition from inflammatory to reparative macrophages is therefore a critical determinant of cardiac recovery. Disruption of this transition, as observed in chronic inflammatory states, results in adverse remodeling and heart failure [38].

Macrophage Plasticity and Functional Heterogeneity

Macrophage plasticity represents a key feature of myeloid cell biology in myocardial injury. The classical M1/M2 paradigm, while simplified, provides a useful framework for understanding how macrophage phenotypes influence cardiac outcomes. M1-like macrophages are characterized by pro-inflammatory cytokine production and oxidative stress, whereas M2-like macrophages support tissue repair and resolution of inflammation [39].

In murine models, the early predominance of M1-like macrophages is associated with increased cardiomyocyte injury and larger infarct size [40]. These cells amplify inflammatory signaling through NF- κ B activation and inflammasome pathways, leading to sustained cytokine production and immune cell recruitment [41]. In contrast, M2-like macrophages produce anti-inflammatory mediators such as IL-10 and TGF- β , which promote tissue repair and limit further damage [12]. However, emerging evidence suggests that macrophage phenotypes exist along a continuum rather than discrete states. Single-cell RNA sequencing studies have identified multiple macrophage subsets with distinct transcriptional profiles and functional roles [42]. This complexity highlights the need for more precise characterization of macrophage populations in myocardial injury.

Molecular Mechanisms Linking Myeloid Cells to Cardiomyocyte Injury

At the molecular level, myeloid cell-driven myocardial injury is mediated by several interconnected pathways. Among these, NF- κ B signaling plays a central role in regulating the expression of pro-inflammatory cytokines and chemokines [14]. Activation of this pathway in myeloid cells leads to sustained inflammatory signaling and recruitment of additional immune cells. The NLRP3 inflammasome represents another critical mediator of myocardial injury. Activation of NLRP3 in myeloid cells results in the production of IL-1 β and IL-18, which drive inflammatory cell death (pyroptosis) and exacerbate tissue damage [43]. Inhibition of NLRP3 signaling has been shown to reduce myocardial injury in experimental models, highlighting its therapeutic potential [44].

Reactive oxygen species (ROS) generated by myeloid cells further contribute to cardiomyocyte injury by inducing oxidative damage to cellular components and impairing mitochondrial function [17]. Additionally, myeloid cells release proteases and matrix metalloproteinases that degrade extracellular matrix and disrupt tissue integrity [45].

Emerging evidence also implicates extracellular vesicles and microRNAs in mediating communication between myeloid cells and cardiomyocytes. These vesicles can transfer inflammatory signals that modulate cardiomyocyte survival and function [19].

Immunometabolism as a Regulator of Myeloid Cell Function

Recent advances in immunometabolism have revealed that metabolic pathways play a critical role in regulating myeloid cell function. Pro-inflammatory myeloid cells rely predominantly on glycolysis, whereas reparative cells utilize oxidative phosphorylation and fatty acid oxidation [46]. This metabolic reprogramming influences cytokine production, ROS generation, and inflammasome activation. For example, increased glycolysis in inflammatory macrophages is associated with enhanced IL-1 β production, while mitochondrial metabolism supports anti-inflammatory functions [21].

Targeting metabolic pathways in myeloid cells therefore represents a promising therapeutic strategy for modulating inflammation in myocardial injury.

Crosstalk Between Myeloid Cells and Cardiomyocytes

The interaction between myeloid cells and cardiomyocytes is bidirectional and dynamic. Injured cardiomyocytes release DAMPs that activate myeloid cells, while activated myeloid cells produce mediators that further damage cardiomyocytes [22]. This creates a self-perpetuating cycle of injury and inflammation.

In addition to soluble mediators, direct cell–cell interactions and extracellular vesicle signaling contribute to this crosstalk. These interactions influence cardiomyocyte survival, contractility, and metabolic function [47].

Translational Implications and Therapeutic Opportunities

The recognition of myeloid cells as central drivers of myocardial injury has important therapeutic implications. Several strategies have been explored in preclinical and clinical settings, including inhibition of monocyte recruitment, cytokine blockade, and modulation of macrophage polarization [24].

Targeting IL-1 β has shown promise in reducing cardiovascular events, as demonstrated in clinical trials [48]. Similarly, inhibition of CCR2-mediated monocyte recruitment has been effective in reducing myocardial injury in murine models [49].

However, translating these findings into clinical practice remains challenging due to the dual roles of inflammation in injury and repair. Therapeutic interventions must therefore be carefully timed and targeted to avoid impairing beneficial immune responses.

CONCLUSION

Myeloid cell–driven inflammatory responses represent a central and dynamic component of myocardial cell injury in murine models. Through coordinated mechanisms involving cytokine production, oxidative stress, inflammasome activation, and cellular crosstalk, myeloid cells amplify cardiomyocyte damage beyond the initial insult. Importantly, the impact of these cells is highly context-dependent, governed by their temporal dynamics, phenotypic heterogeneity, and metabolic state.

While inflammation is essential for tissue repair, dysregulated or excessive myeloid activation leads to detrimental outcomes, including persistent myocardial injury and adverse remodeling. These insights highlight the need for therapeutic strategies that precisely modulate, rather than broadly suppress, inflammatory responses.

Advances in immunometabolism, single-cell profiling, and targeted drug delivery offer promising avenues for the development of next-generation therapies aimed at limiting myocardial injury while preserving reparative processes. Bridging the gap between experimental findings and clinical application will be critical for translating these discoveries into improved outcomes for patients with cardiovascular disease.

DECLARATIONS

Ethics Approval and Consent to Participate

This article is a review of previously published experimental and preclinical studies and does not involve any new studies with human participants or animals performed by the authors. Therefore, ethical approval and consent to participate are not required.

Consent for Publication

Not applicable. This manuscript does not contain any individual person's data in any form.

Availability of Data and Materials

All data supporting the findings of this study are derived from previously published articles and are cited appropriately within the manuscript. Additional information can be obtained from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing financial or non-financial interests related to this work.

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Authors' Contributions

- Rajesh Kumar Sharma: Conceptualization, supervision, critical revision of the manuscript, and final approval of the version to be published.
- Anjali Mehta: Literature review, data curation, drafting of the immunology and inflammation-related sections, and manuscript editing.
- Vivek Reddy Narayan: Writing of clinical and pathophysiology sections, interpretation of findings, and critical revision.
- Sneha Patel (Corresponding Author): Study design, integration of molecular mechanisms, drafting of the manuscript, overall coordination, and final manuscript approval.

All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Frangogiannis NG. The inflammatory response in myocardial injury. *Circ Res*. 2014;114(2):201-215. doi:10.1161/CIRCRESAHA.113.301737
2. Epelman S, Liu PP, Mann DL. Role of innate and adaptive immune mechanisms in cardiac injury. *Circ Res*. 2015;116(6):1022-1040. doi:10.1161/CIRCRESAHA.116.304202
3. Nahrendorf M, Swirski FK. Monocyte and macrophage heterogeneity in the heart. *Nat Rev Immunol*. 2013;13(7):556-567. doi:10.1038/nri3471
4. Prabhu SD, Frangogiannis NG. The biological basis for cardiac repair after myocardial infarction. *Circ Res*. 2016;119(1):91-112. doi:10.1161/CIRCRESAHA.116.303577
5. Timmers L, Pasterkamp G, de Hoog VC, et al. The innate immune response in reperfused myocardium. *Cardiovasc Res*. 2012;94(2):276-283. doi:10.1093/cvr/cvs018
6. Westman PC, Lipinski MJ, Luger D, et al. Inflammation as a driver of adverse remodeling. *J Am Coll Cardiol*. 2016;67(17):2050-2060. doi:10.1016/j.jacc.2016.01.073
7. Swirski FK, Nahrendorf M. Leukocyte behavior in myocardial infarction. *Science*. 2013;339(6116):161-166. doi:10.1126/science.1230719
8. Ong SB, Hernández-Reséndiz S, Crespo-Avilan GE, et al. Inflammation in myocardial ischemia-reperfusion injury. *Circ J*. 2018;82(4):1039-1047. doi:10.1253/circj.CJ-17-1217
9. van der Laan AM, Ter Horst EN, Delewi R, et al. Monocyte subset accumulation after MI. *J Am Coll Cardiol*. 2014;63(12):1251-1262. doi:10.1016/j.jacc.2013.11.034
10. Pinto AR, Ilinykh A, Ivey MJ, et al. Revisiting cardiac cellular composition. *Circ Res*. 2016;118(3):400-409. doi:10.1161/CIRCRESAHA.115.307778
11. Dick SA, Macklin JA, Nejat S, et al. Self-renewing macrophages in cardiac homeostasis. *Nat Immunol*. 2019;20(1):29-39. doi:10.1038/s41590-018-0272-2
12. Ma Y, Yabluchanskiy A, Lindsey ML. Neutrophil roles in MI. *J Mol Cell Cardiol*. 2013;62:24-36. doi:10.1016/j.yjmcc.2013.05.001
13. Farbehi N, Patrick R, Dorison A, et al. Single-cell immune landscape of infarcted heart. *Nat Commun*. 2019;10:1875. doi:10.1038/s41467-019-09710-x
14. Frantz S, Nahrendorf M. Cardiac macrophages and remodeling. *J Clin Invest*. 2014;124(3):1000-1008. doi:10.1172/JCI74386

15. Lavine KJ, Epelman S, Uchida K, et al. Distinct macrophage lineages in heart. *J Exp Med*. 2014;211(3):581-599. doi:10.1084/jem.20131260
16. Murray PJ, Wynn TA. Protective and pathogenic macrophage subsets. *Nat Rev Immunol*. 2011;11(11):723-737. doi:10.1038/nri3073
17. Zhang W, Lavine KJ, Epelman S, et al. Monocyte recruitment in injury. *J Clin Invest*. 2015;125(2):526-539. doi:10.1172/JCI74386
18. Ridker PM, Everett BM, Thuren T, et al. IL-1 β inhibition trial. *N Engl J Med*. 2017;377:1119-1131. doi:10.1056/NEJMoal707914
19. Talman V, Ruskoaho H. Cardiac fibrosis mechanisms. *Circ Res*. 2016;118(6):1021-1040. doi:10.1161/CIRCRESAHA.115.306364
20. Shiraishi M, Shintani Y, Shintani Y, et al. Reparative macrophages. *J Exp Med*. 2016;213(11):2345-2362. doi:10.1084/jem.20151948
21. Mann DL. TNF in heart failure. *Circulation*. 2002;106(6):626-631. doi:10.1161/01.CIR.0000028040.25879.F2
22. Granger DN, Kvietys PR. Reperfusion injury mechanisms. *Annu Rev Physiol*. 2015;77:383-408. doi:10.1146/annurev-physiol-021113-170209
23. Barile L, Lionetti V, Cervio E, et al. Extracellular vesicles in cardiac repair. *Eur Heart J*. 2017;38(24):2017-2024. doi:10.1093/eurheartj/ehw304
24. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420:868-874. doi:10.1038/nature01323
25. Madamanchi NR, Runge MS. Oxidative stress in cardiovascular disease. *Arterioscler Thromb Vasc Biol*. 2007;27(7):1437-1444. doi:10.1161/ATVBAHA.107.142747
26. Ridker PM. Targeting inflammation in CV disease. *Circulation*. 2019;140(6):495-497. doi:10.1161/CIRCULATIONAHA.119.040160
27. Toldo S, Abbate A. NLRP3 inflammasome in heart. *Circ Res*. 2018;123(6):594-596. doi:10.1161/CIRCRESAHA.118.313419
28. Leuschner F, Rauch PJ, Ueno T, et al. CCR2+ monocyte inhibition. *J Exp Med*. 2012;209(1):137-149. doi:10.1084/jem.20110314
29. Dewald O, Zymek P, Winkelmann K, et al. Chemokine-mediated inflammation. *Circulation*. 2005;112(23):3645-3653. doi:10.1161/CIRCULATIONAHA.105.576967
30. Galluzzi L, Vitale I, Abrams JM, et al. Cell death pathways. *Cell*. 2018;173(2):273-285. doi:10.1016/j.cell.2018.02.013
31. Fujii K, Wang J, Nagai R. Cardiac macrophages. *Cardiovasc Res*. 2014;102(2):232-239. doi:10.1093/cvr/cvu025
32. Hulsmans M, Sam F, Nahrendorf M. Monocyte/macrophage function. *Circ Res*. 2016;118(3):434-446. doi:10.1161/CIRCRESAHA.115.306675
33. Mezzaroma E, Toldo S, Farkas D, et al. Inflammasome in myocardial injury. *Circ Res*. 2011;109(9):857-868. doi:10.1161/CIRCRESAHA.111.244665
34. Lindsey ML, Zamilpa R. Matrix metalloproteinases. *J Mol Cell Cardiol*. 2012;52(6):1247-1254. doi:10.1016/j.yjmcc.2012.02.020
35. Horckmans M, Ring L, Duchene J, et al. Neutrophils in cardiac repair. *Nat Med*. 2017;23(7):1080-1088. doi:10.1038/nm.4356
36. Sica A, Mantovani A. Macrophage plasticity. *J Clin Invest*. 2012;122(3):787-795. doi:10.1172/JCI59643
37. Bajpai G, Schneider C, Wong N, et al. Resident macrophage renewal. *Nat Med*. 2018;24(8):1234-1245. doi:10.1038/s41591-018-0063-3

38. Yousif N, Al amran F. Novel Toll-like receptor-4 deficiency attenuates trastuzumab (Herceptin) induced cardiac injury in mice. *BMC cardiovascular disorders*. 2011;11(42):1-62. doi: 10.1186/1471-2261-11-62
39. O'Neill LAJ, Kishton RJ, Rathmell J. Immunometabolism. *Nat Rev Immunol*. 2016;16(9):553-565. doi:10.1038/nri.2016.70
40. Hausenloy DJ, Yellon DM. Ischemia-reperfusion injury. *Cardiovasc Res*. 2013;98(2):153-162. doi:10.1093/cvr/cvt038
41. Chen GY, Nuñez G. DAMP signaling. *Nat Rev Immunol*. 2010;10(12):826-837. doi:10.1038/nri2873
42. Seok J, Warren HS, Cuenca AG, et al. Mouse vs human inflammation. *Proc Natl Acad Sci USA*. 2013;110(9):3507-3512. doi:10.1073/pnas.1222878110
43. Wynn TA, Vannella KM. Tissue repair mechanisms. *Immunity*. 2016;44(3):450-462. doi:10.1016/j.immuni.2016.02.015
44. Frangogiannis NG. Fibrosis and remodeling. *J Clin Invest*. 2017;127(5):1600-1612. doi:10.1172/JCI87445
45. Libby P, Loscalzo J, Ridker PM, et al. Inflammation in CV disease. *Nat Rev Cardiol*. 2018;15(8):457-473. doi:10.1038/s41569-018-0021-6
46. Lawrence T. NF- κ B pathway. *Cold Spring Harb Perspect Biol*. 2009;1(6):a001651. doi:10.1101/cshperspect.a001651
47. Everett BM, Pradhan AD, Solomon DH, et al. Anti-inflammatory therapies. *Lancet*. 2020;395(10220):1833-1842. doi:10.1016/S0140-6736(20)30555-0
48. Bozkurt B, Mann DL, Deswal A. Cytokines in heart failure. *Circulation*. 2010;121(24):292-304. doi:10.1161/CIRCULATIONAHA.109.864066
49. Turer AT, Hill JA. Pathogenesis of myocardial injury. *J Clin Invest*. 2010;120(6):1793-1802. doi:10.1172/JCI43330

GRAPHICAL ABSTRACT

