Research Progress on Inflammatory Response in Patients with Acute Myocardial Infarction: Postprint

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Abstract

Inflammatory response plays a pivotal role in the pathogenesis and prognosis of patients with acute myocardial infarction (AMI), even surpassing the impact of traditional risk factors on AMI; however, systematic summaries of the pathophysiological mechanisms, clinical significance, and current evidence-based medicine evidence regarding inflammatory response in AMI patients are lacking. This article reviews relevant literature to comprehensively explore the mechanisms of action of inflammatory response in AMI patients, related inflammation-derived indicators, and clinical significance, as well as to summarize current research evidence. This article demonstrates that the initial stage of AMI involves an early reactive surge of inflammatory response within the culprit lesion, representing the most destructive phase, whereas subsequent stages involve the coordinated participation of multiple immune cells and cytokines in myocardial repair and healing. Therefore, AMI patients exhibit a complex inflammatory network mechanism that may represent a novel breakthrough target for AMI therapy; nevertheless, our current understanding of the role of immune mechanisms in cardiac remodeling remains incomplete and non-comprehensive, and the greatest dilemma is that initially pro-inflammatory and detrimental cells can also display powerful healing properties, leading to even contradictory research findings; consequently, evidence-based medicine evidence for anti-inflammatory therapy in AMI patients is currently insufficient. Perhaps in the future, AI-assisted inflammatory phenotyping through "machine learning", combined with multi-dimensional inflammatory indicators to identify the specific roles of immune cells in individual patients, could achieve a breakthrough in inflammation regulation from theory to clinical practice and resolve the predicament of residual cardiovascular risk. This article can provide a reference for the in-depth development of anti-inflammatory therapy for AMI patients.

Review and Monograph: Advances in Inflammatory Response Research in Patients with Acute Myocardial Infarction

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Abstract

Inflammatory response plays a crucial role in the pathogenesis and prognosis of acute myocardial infarction (AMI), even surpassing the influence of traditional risk factors. However, there is a lack of systematic summary regarding the pathophysiological mechanisms, clinical implications, and current evidence-based medicine concerning inflammatory response in AMI patients. This article reviews relevant literature to comprehensively explore the mechanisms of inflammatory response in AMI patients, related inflammatory-derived indicators, clinical significance, and a summary of current research evidence. We reveal that the initial stage of AMI is characterized by a rapid surge of inflammatory response within the culprit lesion, representing the most destructive phase, while subsequent stages involve coordinated actions of multiple immune cells and cytokines participating in myocardial repair and healing. Therefore, AMI patients exhibit a complex inflammatory network mechanism that may represent a new therapeutic breakthrough. However, our current understanding of the role of immune mechanisms in cardiac remodeling remains incomplete and non-comprehensive. The greatest challenge is that initially pro-inflammatory and harmful cells can also display powerful healing properties, leading to contradictory research results. Consequently, current evidence-based medicine for anti-inflammatory therapy in AMI patients remains insufficient. In the future, artificial intelligence-assisted inflammatory phenotype classification through "machine learning," combined with multidimensional inflammatory indicators, may identify the specific roles of immune cells in individuals, achieving a breakthrough in inflammatory regulation from theory to clinical practice and solving the dilemma of residual cardiovascular risk. This article provides a reference for the in-depth development of anti-inflammatory therapy for AMI patients.

Keywords: Myocardial infarction; Acute myocardial infarction; Inflammation; Artificial intelligence; Residual risk; Prognosis; Review

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1. Literature Search Strategy

We conducted computerized searches of PubMed, CNKI, Wanfang Data, Embase, Web of Science, Cochrane Library, and Clinical Trials databases from inception to April 2025. Chinese MeSH terms included “acute myocardial infarction” or “acute non-ST-segment elevation myocardial infarction (Non-STEMI)” or “acute ST-segment elevation myocardial infarction (STEMI)” and “inflammation” or “mechanism” or “prognosis.” English MeSH terms included “Myocardial infarction” or “Non-ST Elevated Myocardial Infarction” or “ST Elevation Myocardial Infarction” and “inflammation” or “Inflammation Mediators” or “Mechanism” or “Prognosis.” Inclusion criteria: literature content related to the prognostic impact and pathophysiological mechanisms of inflammatory response in AMI, with no restrictions on article type. Exclusion criteria: literature unrelated to the topic, poor quality, or full text unavailable.

2.1 Pathophysiological Mechanisms of Inflammatory Response in AMI Patients

Following AMI, ischemic cardiac tissue injury triggers involvement of both innate and adaptive immune cells in the early inflammatory response [Figure 1: see original paper]. The inflammatory response continuously evolves throughout the AMI timeline, showing significant changes within hours, days, and weeks post-infarction. During the initial phase of plaque rupture and coronary occlusion, myocardial necrosis begins, followed by interstitial congestion and edema, releasing damage-associated molecular patterns (DAMPs) that activate the innate immune system and trigger inflammatory cell infiltration. Within hours after ischemia, polymorphonuclear neutrophils (PMNs) rapidly infiltrate the infarcted area, initiating inflammatory responses. PMN activation and monocyte recruitment release pro-inflammatory mediators such as interleukin (IL)-6 and reactive oxygen species (ROS), generating an early inflammatory surge within the culprit lesion that represents the most destructive phase post-AMI, causing local congestion and edema [8]. Additionally, cytokine surges promote neutrophil activation and myeloperoxidase (MPO) release, forming neutrophil extracellular traps (NETs) [9], which induce inflammatory cell recruitment to the MI area and enhance pro-inflammatory and immune responses after AMI. Infiltrating inflammatory cells can induce cardiomyocyte death by targeting the viable border zone of the infarct, thereby extending ischemic injury beyond the original MI area. During the pro-inflammatory phase, complement cascade activation, ROS production, and DAMPs synergistically exacerbate the pro-inflammatory response [10]. The initial inflammatory response peaks on day

3 and subsequently begins to decline. This process is amplified immediately after coronary reperfusion, leading to reperfusion injury. This process includes: (1) PMN activation and NET formation [9]: neutrophils release MPO and elastase to form NETs, aggravating tissue damage and thrombosis; (2) monocyte recruitment: chemokines such as monocyte chemotactic protein-1 (MCP-1) attract monocytes to differentiate into pro-inflammatory M1 macrophages, which further release IL-1β and tumor necrosis factor (TNF)-α; (3) inflammasome activation: persistent NLRP3 pathway activation promotes IL-18 and other cytokine release [11]. The process also involves synergistic damage mechanisms including: (1) ROS burst: mitochondrial dysfunction leads to ROS accumulation, causing lipid peroxidation and cell membrane damage; (2) reperfusion injury: if blood flow is restored, it leads to calcium overload and oxidative stress, amplifying the inflammatory response.

The second phase of post-AMI immune response (around day 5) is a complex repair process involving coordinated actions of multiple immune cells and cytokines. Early M1 macrophages dominate, clearing necrotic cell debris but potentially exacerbating inflammatory damage. Meanwhile, T cells are activated early after AMI [5], possibly induced by autoantigens generated from intracellular proteins released during myocardial injury. Regulatory T cells (Tregs) are activated and subsequently form granulation tissue dominated by fibroblasts, new capillaries, and inflammatory cells, providing a temporary scaffold that gradually fills the necrotic area and establishes a structural foundation for scar formation. Eventually, type I/III collagen deposition gradually replaces granulation tissue, forming dense fibrous scars that promote healing. During this process, Tregs secrete IL-10 and transforming growth factor β (TGF-β), while Th2 cells release IL-4/IL-13, driving the transformation of M1 macrophages (pro-inflammatory) to M2 macrophages (anti-inflammatory) [12]. Tregs also directly inhibit effector T cells through cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and IL-10, and promote M2 polarization, thereby promoting healing after AMI. Bone marrow-derived NK cell expansion in AMI reduces myocardial apoptosis by inhibiting the caspase pathway, regulates matrix metalloproteinase (MMP)/tissue inhibitor of metalloproteinase (TIMP) balance to reduce fibrosis/collagen deposition, and secretes vascular endothelial growth factor (VEGF) to promote neovascularization, thereby protecting the heart [14]. After M2 macrophage polarization, they secrete IL-10/TGF-β to promote repair, phagocytize necrotic debris, and initiate angiogenic signals. Smooth muscle cells promote angiogenesis and collagen production. This repair mechanism advances from the infarct periphery toward the core, requiring 4-8 weeks overall, and possibly extending to 12 weeks for large infarcts.

The third phase involves necrotic myocardial fibers dissolving under enzymatic action to form characteristic myocytolysis lesions, followed by granulation tissue formation and eventual replacement by dense fibrous scars. During this process, natural killer (NK) cells interact with M1 macrophages through interferon-γ (IFN-γ) to enhance inflammatory responses [13], but also appear to indirectly promote an anti-inflammatory environment by participating in IL-10 and IL-2-

mediated immune cell interactions. IL-10 and IL-2 are key cytokines in myocardial wound repair, coordinating interactions between T cells and macrophages to promote tissue healing. Th2 helper cell-derived cytokines such as IL-4 and IL-13 induce M2 macrophage phenotype through signal transducer and activator of transcription 6 (STAT6) signaling pathways [12]. Once activated by Th2 cells and Tregs, M2 macrophages produce a series of mediators [such as insulin-like growth factor 1, fibronectin, TGF-β, IL-10, and VEGGF] that promote angiogenesis, collagen deposition, and tissue repair.

2.2 Inflammatory Signaling Pathways Involved in AMI Inflammatory Response

2.2.1 Plaque Instability and Rupture Stage **(1) Toll-like receptor (TLR)/nuclear factor kappa-B (NF- B) pathway:** The NF- B pathway plays a key role in regulating pro-inflammatory signaling cascades, triggered by DAMPs [such as high mobility group box 1 protein (HMGB1)] released from necrotic cells within plaques [15]. TLR2/4 activation initiates both MyD88-dependent and MyD88-independent intracellular pathways, which activate NF- B translocation to the nucleus, leading to expression of pro-inflammatory factors (TNF-α, IL-6, IL-1β) that promote macrophage infiltration and MMP-2/9 secretion, resulting in fibrous cap degradation. **(2) NLRP3 inflammasome pathway:** The NLRP3 inflammasome is part of the nucleotide-binding oligomerization domain-like receptor (NLR) family [17], activated by cholesterol crystals, ROS, and ATP in the hypoxic microenvironment within plaques. Its effect is caspase-1-mediated cleavage of pro-IL-1β/pro-IL-18, producing mature cytokines IL-18 and IL-1β release [11], which exacerbates intravascular inflammatory responses.

2.2.2 Ischemia-Reperfusion Injury Stage **(1) Complement system activation:** Exposure of phospholipids (such as cardiolipin) on ischemic cell membranes promotes complement cascade activation through classical, alternative, and lectin pathways, promoting complement C1q or C3 deposition and forming membrane attack complexes (MAC) [18], leading to cardiomyocyte lysis. Complement C5a can chemoattract neutrophils and promote ROS burst. **(2) Neutrophil NETosis pathway:** Neutrophils release MPO and elastase to form NETs, composed of chromatin, histones, and protease-containing granules. Once formed, NETs exacerbate local inflammation and plaque erosion by promoting macrophage accumulation, IL-1α activation, and plasmacytoid dendritic cell release of type I interferon (IFN-1), thereby promoting coagulation [19]. NET cross-linking with plasma fibrinogen leads to thrombosis and "no-reflow" phenomenon [20]. **(3) Cell death-related pathways:** Including pyroptosis and necroptosis. Pyroptosis involves Gasdermin D pore formation, dependent on NLRP3-mediated IL-1β release, triggering programmed cell death [11]. Necroptosis is mediated by the receptor-interacting protein kinase

1/receptor-interacting protein kinase 3/mixed-lineage kinase domain-like pseudokinase (RIPK1/RIPK3/MLKL) pathway [21], leading to membrane rupture and DAMPs release.

2.2.3 Pro-inflammatory and Anti-inflammatory Imbalance **(1) Cytokine storm:** Many pro-inflammatory cytokines secreted by surviving cardiac cells and circulating inflammatory cells can enhance pro-inflammatory responses, with core molecules including TNF-α and IL-6. TNF-α inhibits myocardial contraction through tumor necrosis factor receptor-associated factor 1 (TNFR1) activation of c-Jun N-terminal kinase/p38 (JNK/p38) [22]. IL-6 promotes hepatocyte production of C-reactive protein (CRP) through the glycoprotein 130/Janus kinase/signal transducer and activator of transcription 3 (gp130/JAK/STAT3) pathway [23], while also promoting monocyte chemoattractant protein (MCP-1), leading to more macrophage infiltration. **(2) Anti-inflammatory repair pathway (insufficient inhibition):** In the IL-10 signaling pathway, STAT3-mediated NF- B inhibition fails. In the TGF-β pathway, delayed Smad2/3 activation leads to lagging fibrotic repair [11,24].

Note: Figure translations are in progress. See original paper for figures.

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