Systemic inflammatory response following acute myocardial infarction

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Abstract

Acute cardiomyocyte necrosis in the infarcted heart generates damage-associated molecular patterns, activating complement and toll-like receptor/interleukin-1 signaling, and triggering an intense inflammatory response. Inflammasomes also recognize danger signals and mediate sterile inflammatory response following acute myocardial infarction (AMI). Inflammatory response serves to repair the heart, but excessive inflammation leads to adverse left ventricular remodeling and heart failure. In addition to local inflammation, profound systemic inflammation response has been documented in patients with AMI, which includes elevation of circulating inflammatory cytokines, chemokines and cell adhesion molecules, and activation of peripheral leukocytes and platelets. The excessive inflammatory response could be caused by a deregulated immune system. AMI is also associated with bone marrow activation and spleen monocytopoiesis, which sustains a continuous supply of monocytes at the site of inflammation. Accumulating evidence has shown that systemic inflammation aggravates atherosclerosis and markers for systemic inflammation are predictors of adverse clinical outcomes (such as death, recurrent myocardial infarction, and heart failure) in patients with AMI.

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1 Introduction

Atherosclerosis and acute myocardial infarction (AMI) is a leading cause of death worldwide. Inflammatory response has been known to play an important role in the initiation, progression and destabilization of atherosclerosis. AMI triggers an acute inflammatory response, which serves to repair heart. However, exaggerated inflammatory response leads to adverse left ventricular (LV) remodelling and heart failure. In addition to local inflammation in the myocardium, amplified systemic inflammation response has been documented in patients with AMI, which includes elevation of circulating inflammatory cytokines, chemokines and cell adhesion molecules, activation of various immune cells, and activation of complement system, etc. An increasing body of evidence has suggested that markers for systemic inflammatory response are predictors of adverse clinical outcomes, such as death, recurrent myocardial infarction (MI), and heart failure in patients with AMI.

2 The initiation of inflammatory response following AMI

As illustrated in Figure 1, acute myocardial necrosis and damaged matrix release endogenous alarm signals referred to as damage-associated molecular patterns (DAMPs), which activate the complement cascade and stimulates toll-like receptors (TLRs)/interleukin-1 (IL-1) signalling, resulting in the activation of the nuclear factor-κB (NF-κB) system and induction of cytokines, chemokines, and adhesion molecules. The interactions between chemokines and cell adhesion molecules on endothelial cells and their receptors on leukocytes lead to the recruitment and extravasation of neutrophils and mononuclear cells in the infarcted myocardium.[1] Inflammatory response following AMI serves to clear the wound and facilitate wound healing and scar formation, but excessive inflammatory response causes adverse LV remodelling and heart failure.

TLRs serve as pattern recognition receptors within the innate immune system.[2] Of the 13 known mammalian TLRs, TLR4 has been identified as a key receptor in mediating the inflammatory response in the infarcted heart. TLR4 is a proximal signalling receptor in innate immune responses to lipopolysaccharide of gram-negative pathogens.
Figure 1. Initiation of inflammatory response following AMI. AMI triggers an intense inflammatory response including elevation of inflammatory mediators, and recruitment of inflammatory cells via DAMPs/TLR/IL-1 signaling. Inflammasomes also recognize danger signals and activate caspase-1, and release active IL-1β. Inflammatory response serves to repair the heart, but excessive inflammation leads to adverse LV remodeling and heart failure. AMI is also associated with bone marrow activation via SNS activation and spleen monocytopoiesis, resulting in increased leukocyte influx which aggravates atherosclerosis and contributes to recurrent MI. Spleen monocytopoiesis is also regulated by IL-1β.

AMI: acute myocardial infarction; DAMPs: damage-associated molecular patterns; IL-1: interleukin-1; LV: left ventricular; TLR: toll-like receptor; SNS: sympathetic nervous system.

and also act as a stress sensor and recognize DAMPs in response to non-infectious tissue injury. TLR4-deficient mice sustained smaller infarctions and exhibit less inflammation (fewer neutrophil/monocyte infiltration, decreased cytokine/chemokines production and less complement deposition) after AMI.[3,4] TLR4 deletion also led to a significant reduction in serum levels of TNF-α, IL-1β and IL-6.[5] Thus, TLR4 plays an important role in mediating local and systemic inflammatory response in AMI.

The inflammatory response triggered by tissue damage in AMI is also mediated through inflammasomes. Inflammasomes are multiple cytoplasmic protein complexes that serve as molecular platforms to activate caspase-1 and release IL-1β. Most inflammasomes typically contain one of the NLR family proteins and the NLRP3 inflammasome is the most extensively studied one, which has been shown to recognize danger signals and induce sterile inflammatory responses in MI.[6,7] The NLRP3 inflammasome contains NLRP3 that interact with the adaptor molecule ASC, which recruits and activates caspase-1. Caspase-1 is known to process pro-IL-1β to its active mature form and induce cardiac cell pyoptosis. IL-1β, as a gatekeeper of inflammation, is an early and prominent mediator for inflammatory response in MI.[8] The induction of IL-1β release also requires another signal, that is the transcriptional induction of pro-IL-1β by the TLR/NFκB pathway. Previous studies showed that the NLRP3 inflammasome was predominantly up-regulated in the cardiac fibroblasts of the ischemic myocardium in animal models with MI.[9] Inhibition of NLRP3 preserved myocardial function and reduced infarct size after MI in animal models,[10] suggesting that targeting the NLRP3 inflammasome may be a potential and effective therapeutic strategy to treat MI.

3 Proinflammatory cytokines

Proinflammatory cytokines stimulate chemokines and adhesion molecules, and activate the innate and adaptive immune system. Numerous studies have reported elevated plasma levels of a variety of cytokines/chemokines. Among
the various inflammatory markers, C-reactive protein (CRP) is the most extensively investigated.\[11\] CRP is a strong predictor of adverse outcome in patients with acute coronary syndrome (ACS).\[12,13\] Raised plasma levels of tumour necrosis factor (TNF)-\(\alpha\) and IL-6 are also predictors of mortality and adverse outcomes in patients with ACS.\[14–16\] IL-6 levels are often found to be correlated with CRP levels since IL-6 is the main stimulus for CRP production in the liver. IL-1\(\beta\), as a gatekeeper of inflammation, is an early and prominent mediator for inflammatory response in MI.\[8\]

Increased plasma IL-1\(\beta\) levels were strongly associated with impaired myocardial function and LV hypertrophy following reperfused MI.\[17\] Notably, the work from our group and the others’ has highlighted the role of macrophage migration inhibitory factor (MIF) in acute MI.\[18–20\] MIF is an important regulator of inflammatory and immune response. Takahashi et al.\[19,20\] found elevated serum and plasma MIF levels in patients with AMI. We further reported that plasma levels of MIF were elevated in patients with AMI at the earliest available samples after admission (average 211 min of symptom-sampling time) and admission MIF levels were correlated with cardiovascular magnetic resonance imaging-derived infarct size, LV volumes and ejection fraction at 3 days and 3 months post-MI,\[21,22\] suggesting that MIF is an early diagnostic and prognostic marker of AMI.

4 Chemokines, cell adhesion molecules and cell recruitment

The recruitment of inflammatory cells is a crucial step of inflammatory response after AMI, which is mediated by the interactions between chemokines and cell adhesion molecules expressed on activated endothelial cells and their receptors on inflammatory cells. CC chemokines monocyte chemoattractant protein-1 (MCP-1) induces the infiltration of mononuclear phagocytes while CXC chemokines such as IL-8 and C5a mediate the infiltration of the infarct with neutrophils. Fractalkine/CX3CR1 recruits lymphocytes and monocytes and RANTES/CCR5 is a chemokine mediating the trafficking and homing of T lymphocytes, monocytes, and NK cells. Previous studies reported that plasma levels of chemokines were increased in AMI,\[23–25\] and had prognostic values in the adverse LV remodelling and recurrent MI.\[23,24\] Cell adhesion molecules including selectins and the immunoglobulin superfamily (ICAM-1, VCAM-1, etc) are indicators of activation of endothelial cells, leukocytes, and platelets. Selectins mediate leukocyte capture and rolling on the endothelial surface. The interaction between ICAM-1 and integrins mediate firm adhesion of leukocytes to the endothelial layer. Transmigration of activated leukocyte is dependent on several adhesion molecules, including ICAM-1, members of the junctional adhesion molecule family and vascular-endothelial-cadherin. Previous studies reported that circulating cell adhesion molecules were increased in AMI and were potential predictors of an increased risk for subsequent cardiovascular events.\[26–28\]

5 Leukocytes

Leukocytosis is a hallmark of inflammatory reactions in patients with AMI and it has emerged as a powerful predictor of death in patients with AMI.\[29\] Leukocytes are also activated in patients with MI as evidenced by being more active in transcription of inflammatory genes.\[30\] There are also profound changes in relation to the number and status of different leukocyte subpopulations. Neutrophils are an important component of innate immunity, and neutrophils infiltrate coronary plaques and the infarcted myocardium and mediate tissue damage by releasing matrix-degrading enzymes and reactive oxygen species. A high neutrophil count was found to be related to mortality rate and to major clinical adverse outcomes in patients with ACS.\[29,31\]

Peripheral blood mononuclear cells (PBMCs) include monocytes and lymphocytes, both being major sources of proinflammatory cytokines and matrix metalloproteinases (MMPs). Direct contact of monocytes with T lymphocytes, or interferon (IFN)-\(\gamma\) (produced by T lymphocytes) exposure to monocytes induces the expression of proinflammatory cytokines and MMPs by monocytes,\[32,33\] The number of PBMCs was increased after AMI, which was significantly correlated with LV remodelling.\[34\] We also demonstrated that PBMCs were activated in patients with AMI, and PBMCs from patients with AMI showed unregulated expression of inflammatory cytokines, cell adhesion molecules and MMP-9.\[35\]

6 Monocytes

Monocytes, the most abundant immune cell type found in atherosclerotic plaques, play a major role in atherosclerosis and acute coronary event. The recruitment of monocytes into the infarcted heart regulates inflammatory and reparative cascades. Peripheral monocytosis after AMI was associated with LV dysfunction and adverse cardiovascular events.\[36–38\] It is well known that monocytes display substantial heterogeneity and 3 distinct monocyte subsets exist: namely classical CD14\(^+\)CD16\(^-\) monocytes, intermediate CD14\(^+\)CD16\(^+\) monocytes, and non-classical CD14\(^+\)CD16\(^+\) monocytes. Notably, a prominent increase in the number of intermediate CD14\(^+\)CD16\(^+\) monocytes with more promi-

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nent NFκB pathway activity was observed in AMI.\[39\] Furthermore, intermediate CD14++CD16– monocytes count independently predicted cardiovascular events in subjects referred for elective coronary angiography.\[40\] So, CD14++ CD16– monocytes may become a potential target cell population for new therapeutic strategies in atherosclerosis and AMI.

In response to the dynamic alterations in cytokines and growth factor expression in the infarct, infiltrating monocytes are transformed into macrophages. Macrophages produce a variety of cytokines and chemokines (TNF-α, IL-6, IL-1, IFN-γ, MIF and MCP-1, etc), growth factors, and proteases such as MMPs, mediating wound healing and LV remodeling.\[41\] Macrophages are functionally heterogeneous, classified into M1 (those related to pro-inflammatory processes) and M2 (those involved in resolution and repair) macrophages. Macrophages were numerically the predominant cells infiltrating the infarcted myocardium, with M1 macrophages dominating at 1–3 days post-MI, whereas M2 macrophages representing the predominant macrophage subset after 5 days.\[42\]

Monocytes also give rise to dendritic cells. The role of dendritic cells in cardiovascular disease is receiving increasing interest. Activated dendritic cells produce cytokines such as IFN-γ and thus regulate immune cells trafficking and also promote T cell activation. Significantly more myeloid dendritic cell (mDC) precursors were observed in vulnerable carotid plaques than in stable ones. mDC was also the predominant subset of dendritic cells infiltrating into the infarcted myocardium, which peaked in number on day 7.\[42\] However, circulating mDC precursors were significantly reduced in patients with ACS compared with control patients, which were inversely correlated with CRP or interleukin-6.\[41\] The decrease of mDC precursors in blood could be due to their recruitment into atheroma or infarcted myocardium.

In addition to maturation into macrophages and dendritic cells, monocytes also differentiate into bone-marrow-derived circulating mesenchymal progenitors. We previously found that the number of circulating fibrocytes was reduced in AMI and PBMCs from AMI have reduced ability to differentiate into fibrocytes while enhanced ability to differentiate into macrophages.\[44\] Taken together, circulating monocytes display profound changes (including their number, subpopulations, function, and differentiation) in AMI.

7 Lymphocytes

Unlike neutrophils and monocytes, a lower lymphocyte count has been observed in AMI. A lower lymphocyte count and a higher neutrophil/lymphocyte ratio were found to be related to more cardiovascular events during the follow-up.\[29\] T cells are a key component of the adaptive immune system and T cells can be divided into helper T cells (CD4: Th1, Th2, Th17, etc), cytotoxic T cells (CD8), and regulatory T cells according to the role of immune response. Previous studies demonstrated activation of peripheral T lymphocytes evidenced by increased expression of markers HLADR and CD69 in AMI.\[25,45\] However, patients with AMI had lower CD4+ but higher CD8+ T lymphocytes in both the percentages and absolute numbers,\[46,47\] leading to an inverted CD4/CD8 ratio.\[47,48\] A prolonged depressed CD4/CD8 ratio was a poor prognostic factor.\[48\]

CD4+ T lymphocytes are able to differentiate into Th1 and Th2 lineage in response to the local milieu of cytokines. The frequency of IFN-γ-producing T-cells (Th1) was significantly increased in patients with ACS within 24 h after the onset of symptoms.\[49\] A significant increase of IFN-γ and TNF-α production (Th1) and a significant decrease of IL-10 production (Th2) in cultures of lymphocytes taken from patients with ACS were also observed,\[50\] suggesting a predominance of the proinflammatory Th1 cells and cytokines in AMI. In clinical setting, high numbers of Th2 cells were independently associated with decreased carotid intima-media thickness and a reduced risk of AMI, suggesting a protective role of Th2 cells in AMI.\[51\]

CD4+CD28− T cells are unusual T lymphocytes which are also able to secret IFN-γ. CD4+CD28− T cells were found in unstable coronary plaques,\[52\] and the frequency of CD4+CD28− T cells was related to patients at risk of future acute coronary events.\[53\]

A proinflammatory Th1/Th2 imbalance and the expansion of CD4+CD28− cells could be due to decreased T regulatory (Treg) cells. Treg cells are centrally involved in maintaining self-tolerance and suppress aberrant or excessive immune response. A decrease in the number of CD4+ CD25 Foxp3+ Treg cells producing anti-inflammatory IL-10 and TGF-β was identified in the peripheral blood of ACS patients,\[54,55\] leading to a loss of regulation of immune system, which in turn trigger and amplify an exaggerated inflammatory response in AMI. Thus, Treg cells could be a key target for immunomodulation of AMI. However, non-univocal variations in Treg cell number were also observed in patients suffering an ACS (with an increase in ST-elevation AMI but a decrease in non-ST-elevation AMI).\[56\]

Natural killer (NK) cells are a type of cytotoxic lymphocyte critical to the innate immune system. A reduction in both the absolute number and the cell fraction of NK cells was documented in patients with AMI.\[46\] The expression of NK cell receptors was also down regulated in AMI.\[57\] A recent study reported that sustained NK cell deficit was as-
sociated with low-grade inflammation, suggesting a protective role of NK cells in atherosclerosis and AMI.[58]

Much less is known about B lymphocytes in AMI. Unlike T lymphocytes, increased peripheral B lymphocytes in both the percentages and absolute numbers were reported in patients with AMI.[46,47] Recent studies also showed that B lymphocytes promote monocyte mobilization and recruitment and enhance tissue injury.[59] However, more work needs to be done to investigate the associations between B lymphocytes and AMI.

8 Platelets

In addition to their well-established role in thrombotic process, platelets have been recognized as inflammatory and immune cells.[60] Platelets contribute to inflammatory responses through release of inflammatory mediators and platelet-leukocyte interactions by which platelets mediate leukocyte activation and infiltration into inflamed tissues. Several studies by other groups reported elevated peripheral platelet-leukocyte aggregation in patients with AMI.[61,62] Our group further demonstrated that early increase in circulating platelet-leukocyte aggregation in AMI was mediated by P-selectin/P-selectin glycoprotein ligand-1 and anti-platelet interventions inhibited circulating platelet/leukocyte aggregation and reduced the severity of myocardial inflammation.[63]

Platelet activation in AMI is associated with increased generation of circulating microparticles.[64] Microparticles are now acknowledged as intercellular communicators and links between inflammation and thrombosis.[65] Platelet-derived microparticles enhance monocyte arrest on activated endothelium, and P-selectin/P-selectin glycoprotein ligand-1 also enhances the production of leukocyte-derived microparticles. Leukocyte-derived microparticles in turn induce inflammatory marker expression by endothelial cells. Thus microparticles mediate interactions between platelets, leukocytes and endothelial cells, which play important roles in AMI.

9 Influence of aging

Aging has the effect on the post-infarction inflammatory response and LV remodeling. Previous study found a higher peak CRP level and higher IL-6 levels at 2 weeks and 6 months after AMI in patients > 70 years old compared to patients < 70 years old, in association with exaggerated LV remodeling.[66] The elderly AMI patients (> 65 years) also manifested decreased cardiac function and increased plasma apoptotic marker levels.[67]

10 Systemic inflammation aggravate atherosclerosis

Survivors of AMI are at increased risk of subsequent MI, which is associated with high mortality rate. Systemic inflammatory response to ischaemic injury could be responsible for recurrent MI through triggering leukocyte influx into atherosclerotic plaques, thus aggravating existing atherosclerosis lesions by accelerating their growth and/or promoting plaque destabilization.[68,69] Previous studies showed that elevations of several biomarkers (CRP, TNF-α, MCP-1, etc) reflecting inflammatory activity indicate increased risk of recurrent MI.[70,71]

11 Involvement of other organs

Activation of bone marrow and spleen as lymphoid organs also plays key roles in the systemic inflammatory response to myocardial damage.[68] As illustrated in Figure 1, following MI, haematopoietic stem and progenitor cells are liberated from bone marrow niches via sympathetic nervous system and seeded the spleen. Spleen monocytopoiesis following MI yields a sustained boost in monocyte production, which could contribute to recurrent MI through inducing leukocyte influx into atherosclerotic plaques.[68,72] A previous study also showed spleen monocytopoiesis was regulated by IL-1β,[72] suggesting a key role of IL-1β in triggering extramedullary monocytopoiesis after AMI. AMI also results in acute renal inflammation as evidenced by upregulated inflammatory markers and the recruitment of leukocytes in the kidney.[73]

12 Questions to be answered and future direction

Systemic inflammatory response in AMI is very complex, involving many different blood cell types and different plasma inflammatory mediators (cytokines, chemokines, cell adhesion molecules, and complement system). A number of markers of systemic inflammatory response have been demonstrated as predictors of adverse clinical outcomes in AMI patients. Such information is very useful for risk stratification of patients with AMI since peripheral markers are easy to bed measured and readily available. However, it is still very difficult to identify patients at risk for AMI prior to the events. Future work needs to be done to assess the predictive values of different component of systemic inflammatory response. Although inflammation response plays important roles in atherosclerosis and AMI, immunomodulation therapies have not been successful ac-
cording to previous studies. A recent study showed that TNF-α antagonist etanercept reduced neutrophil count and plasma IL-6 concentrations but increased platelet-monocyte aggregation in patients with AMI. Uncovering the most critical steps of inflammatory response involved in AMI is very important to introduce better treatments.

13 Conclusions

AMI is associated with profound systemic inflammatory response including elevated levels of circulating inflammatory mediators, and activation of peripheral leukocytes and platelets. The excessive inflammatory response in AMI could be caused by a deregulated immune system. AMI is also associated with bone marrow activation and spleen monocytopoiesis, which yields a sustained boost in monocyte production. Systemic inflammation aggravates atherosclerosis and markers for systemic inflammation are predictors of adverse clinical outcomes (such as death, recurrent MI, and heart failure) in patients with AMI. While many of peripheral markers could be used for risk stratification of patients with AMI, future studies need to assess the value of these markers to identify patients at risk of AMI. With more understanding of inflammation response in AMI, we are close to developing new immunomodulation therapies.

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