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Systemic inflammatory response following acute myocardial infarction

Lu FANG[1], Xiao-Lei Moore[1], Anthony M Dart[1,2], Le-Min WANG[3]

[1]*Baker IDI Heart and Diabetes Institute, Melbourne, Vic, Australia*
[2]*Department of Cardiovascular Medicine, the Alfred Hospital, Commercial Road, Melbourne, Vic, Australia*
[3]*Department of Cardiology, Tongji Hospital, Tongji University School of Medicine, Shanghai, China*

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.

Correspondence to: Anthony M Dart, MD, PhD, Department of Cardiovascular Medicine, the Alfred Hospital, Vic, Australia.
E-mail: a.dart@alfred.org.au
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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

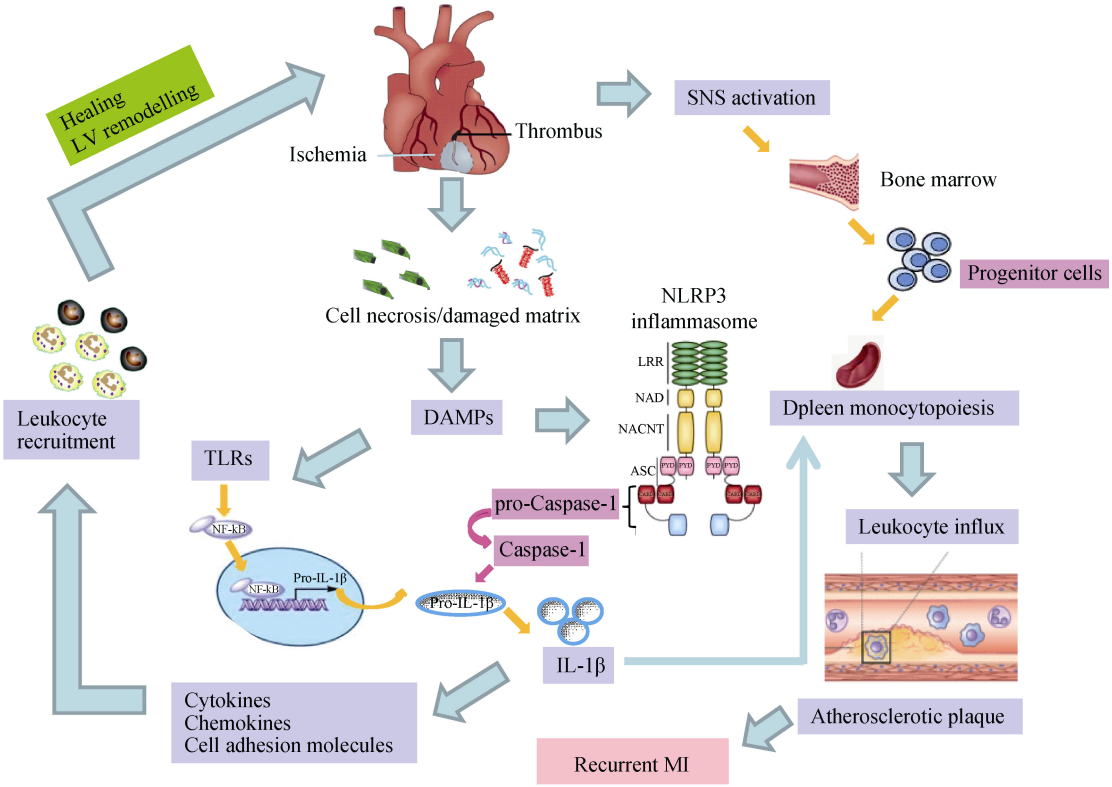

Figure 1. Initiation of inflammatory response following AMI. AMI triggers an intense inflammatory response including elevation of inflammatory mediators, and recruitment of inflammatory cells via DAMPs/TLR/IL-1signaling. Inflammasomes also recognize danger signals and activate caspase-1, and release 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 infarciton; 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)-α 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-1β, as a gatekeeper of inflammation, is an early and prominent mediator for inflammatory response in MI.[8] Increased plasma IL-1β 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 indictors 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)-γ (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-

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 dendric cells produce chemokines 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.[43] 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 dendric 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 symptom.[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.[74] 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.[75] 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.

References

1 Frangogiannis NG. The immune system and the remodeling infarcted heart: cell biological insights and therapeutic opportunities. *J Cardiovasc Pharmacol* 2014; 63: 185–195.
2 Feng Y, Chao W. Toll-like receptors and myocardial inflammation. *Int J Inflam* 2011; 2011: 170352.
3 Timmers L, Sluijter JP, van Keulen JK, *et al*. Toll-like receptor 4 mediates maladaptive left ventricular remodeling and impairs cardiac function after myocardial infarction. *Circ Res* 2008; 102: 257–264.
4 Oyama J, Blais C Jr., Liu X, *et al*. Reduced myocardial ischemia-reperfusion injury in toll-like receptor 4-deficient mice. *Circulation* 2004; 109: 784–789.
5 Kim SC, Ghanem A, Stapel H, *et al*. Toll-like receptor 4 deficiency: smaller infarcts, but no gain in function. *BMC Physiol* 2007; 7: 5.
6 Kawaguchi M, Takahashi M, Hata T, *et al*. Inflammasome activation of cardiac fibroblasts is essential for myocardial ischemia/reperfusion injury. *Circulation* 2011; 123: 594–604.
7 Takahashi M. NLRP3 inflammasome as a novel player in myocardial infarction. *Int Heart J* 2014; 55: 101–105.
8 Dinarello CA. A clinical perspective of IL-1beta as the gatekeeper of inflammation. *Eur J Immunol* 2011; 41: 1203–1217.
9 Sandanger O, Ranheim T, Vinge LE, *et al*. The NLRP3 inflammasome is up-regulated in cardiac fibroblasts and mediates myocardial ischaemia-reperfusion injury. *Cardiovasc Res* 2013; 99: 164–174.
10 Mezzaroma E, Toldo S, Farkas D, *et al*. The inflammasome promotes adverse cardiac remodeling following acute myocardial infarction in the mouse. *Proc Natl Acad Sci U S A* 2011; 108: 19725–19730.
11 Calabro P, Golia E, Yeh ET. CRP and the risk of atherosclerotic events. *Semin Immunopathol* 2009; 31: 79–94.
12 Bodi V, Sanchis J, Llacer A, *et al*. Multimarker risk strategy for predicting 1-month and 1-year major events in non-ST-elevation acute coronary syndromes. *Am Heart J* 2005; 149: 268–274.
13 Sheikh AS, Yahya S, Sheikh NS, *et al*. C-reactive protein as a predictor of adverse outcome in patients with acute coronary syndrome. *Heart Views* 2012; 13: 7–12.
14 Valgimigli M, Ceconi C, Malagutti P, *et al*. Tumor necrosis factor-alpha receptor 1 is a major predictor of mortality and new-onset heart failure in patients with acute myocardial infarction: the cytokine-activation and long-term prognosis in myocardial infarction (C-ALPHA) study. *Circulation* 2005; 111: 863–870.
15 Biasucci LM, Liuzzo G, Fantuzzi G, *et al*. Increasing levels of interleukin (IL)-1Ra and IL-6 during the first 2 days of hospitalization in unstable angina are associated with increased risk of in-hospital coronary events. *Circulation* 1999; 99: 2079–2084.
16 Andrie RP, Becher UM, Frommold R, *et al*. Interleukin-6 is the strongest predictor of 30-day mortality in patients with cardiogenic shock due to myocardial infarction. *Crit Care* 2012; 16: R152.
17 Orn S, Ueland T, Manhenke C, *et al*. Increased interleukin-1beta levels are associated with left ventricular hypertrophy and remodelling following acute ST segment elevation myocardial infarction treated by primary percutaneous coronary intervention. *J Intern Med* 2012; 272: 267–276.
18 Dayawansa NH, Gao XM, White DA, *et al*. Role of MIF in myocardial ischaemia and infarction: insight from recent clinical and experimental findings. *Clin Sci* 2014; 127: 149–161.
19 Takahashi M, Nishihira J, Shimpo M, *et al*. Macrophage migration inhibitory factor as a redox-sensitive cytokine in cardiac myocytes. *Cardiovasc Res* 2001; 52: 438–445.
20 Takahashi M, Nishihira J, Katsuki T, *et al*. Elevation of plasma levels of macrophage migration inhibitory factor in patients with acute myocardial infarction. *Am J Cardiol* 2002; 89: 248–249.
21 Chan W, White DA, Wang XY, *et al*. Macrophage migration inhibitory factor for the early prediction of infarct size. *J Am Heart Assoc* 2013; 2: e000226.
22 White DA, Fang L, Chan W, *et al*. Pro-inflammatory action of MIF in acute myocardial infarction via activation of peripheral blood mononuclear cells. *PloS One* 2013; 8: e76206.
23 Orn S, Breland UM, Mollnes TE, *et al*. The chemokine network in relation to infarct size and left ventricular remodeling

following acute myocardial infarction. *Am J Cardio* 2009; 104: 1179–1183.

24 Gonzalez-Quesada C, Frangogiannis NG. Monocyte chemoattractant protein-1/CCL2 as a biomarker in acute coronary syndromes. *Curr Atheroscler Rep* 2009; 11: 131–138.

25 Steppich BA, Moog P, Matissek C, *et al*. Cytokine profiles and T cell function in acute coronary syndromes. *Atherosclerosis* 2007; 190: 443–451.

26 Postadzhiyan AS, Tzontcheva AV, Kehayov I, *et al*. Circulating soluble adhesion molecules ICAM-1 and VCAM-1 and their association with clinical outcome, troponin T and C-reactive protein in patients with acute coronary syndromes. *Clin Biochem* 2008; 41: 126–133.

27 Liu WH, Yang CH, Yeh KH, *et al*. Circulating levels of soluble P-selectin in patients in the early and recent phases of myocardial infarction. *Chang Gung Med J* 2005; 28: 613–620.

28 Luc G, Arveiler D, Evans A, *et al*. Circulating soluble adhesion molecules ICAM-1 and VCAM-1 and incident coronary heart disease: the PRIME Study. *Atherosclerosis* 2003; 170: 169–176.

29 Nunez J, Nunez E, Bodi V, *et al*. Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. *Am J Cardio* 2008; 101: 747–752.

30 Wettinger SB, Doggen CJ, Spek CA, *et al*. High throughput mRNA profiling highlights associations between myocardial infarction and aberrant expression of inflammatory molecules in blood cells. *Blood* 2005; 105: 2000–2006.

31 Guasti L, Dentali F, Castiglioni L, *et al*. Neutrophils and clinical outcomes in patients with acute coronary syndromes and/or cardiac revascularisation. A systematic review on more than 34,000 subjects. *Thromb Haemost* 2011; 106: 591–599.

32 Lacraz S, Isler P, Vey E, *et al*. Direct contact between T lymphocytes and monocytes is a major pathway for induction of metalloproteinase expression. *J Biol Chem* 1994; 269: 22027–22033.

33 Bauters A, Ennezat PV, Tricot O, *et al*. Relation of admission white blood cell count to left ventricular remodeling after anterior wall acute myocardial infarction. *Am J Cardio* 2007; 100: 182–184.

34 Aoki S, Nakagomi A, Asai K, *et al*. Elevated peripheral blood mononuclear cell count is an independent predictor of left ventricular remodeling in patients with acute myocardial infarction. *J Cardio* 2011; 57: 202–207.

35 Fang L, Du XJ, Gao XM, *et al*. Activation of peripheral blood mononuclear cells and extracellular matrix and inflammatory gene profile in acute myocardial infarction. *Clin Sci* 2010; 119: 175–183.

36 Mariani M, Fetiveau R, Rossetti E, *et al*. Significance of total and differential leucocyte count in patients with acute myocardial infarction treated with primary coronary angioplasty. *Eur Heart J* 2006; 27: 2511–2515.

37 Hong YJ, Jeong MH, Ahn Y, *et al*. Relationship between peripheral monocytosis and nonrecovery of left ventricular function in patients with left ventricular dysfunction complicated with acute myocardial infarction. *Circ J* 2007; 71: 1219–1224.

38 Maekawa Y, Anzai T, Yoshikawa T, *et al*. Prognostic significance of peripheral monocytosis after reperfused acute myocardial infarction: a possible role for left ventricular remodeling. *J Am Coll Cardiol* 2002; 39: 241–246.

39 Tapp LD, Shantsila E, Wrigley BJ, *et al*. The CD14++CD16+ monocyte subset and monocyte-platelet interactions in patients with ST-elevation myocardial infarction. *J Thromb Haemost* 2012; 10: 1231–1241.

40 Rogacev KS, Cremers B, Zawada AM, *et al*. CD14++CD16+ monocytes independently predict cardiovascular events: a cohort study of 951 patients referred for elective coronary angiography. *J Am Coll Cardiol* 2012; 60: 1512–1520.

41 Lambert JM, Lopez EF, Lindsey ML. Macrophage roles following myocardial infarction. *Int J Cardiol* 2008; 130: 147–158.

42 Yan X, Anzai A, Katsumata Y, *et al*. Temporal dynamics of cardiac immune cell accumulation following acute myocardial infarction. *J Mol Cell Cardiol* 2013; 62: 24–35.

43 Yilmaz A, Weber J, Cicha I, *et al*. Decrease in circulating myeloid dendritic cell precursors in coronary artery disease. *J Am Coll Cardiol* 2006; 48: 70–80.

44 Fang L, Moore XL, Chan W, *et al*. Decreased fibrocyte number is associated with atherosclerotic plaque instability in man. *Cardiovasc Res* 2012; 95: 124–133.

45 Pasqui AL, Di Renzo M, Bova G, *et al*. T cell activation and enhanced apoptosis in non-ST elevation myocardial infarction. *Clin Exp Med* 2003; 3: 37–44.

46 Liu LL, Lu JL, Chao PL, *et al*. Lower prevalence of circulating invariant natural killer T (iNKT) cells in patients with acute myocardial infarction undergoing primary coronary stenting. *Int Immunopharmacol* 2011; 11: 480–484.

47 Al-Ahmad RS, Mahafzah AM, Al-Mousa EN. Immunological changes in acute myocardial infarction. *Saudi Med J* 2004; 25: 923–928.

48 Blum A, Yeganeh S. The role of T-lymphocyte subpopulations in acute myocardial infarction. *EurJ Intern Med* 2003; 14: 407–410.

49 Cheng X, Liao YH, Ge H, *et al*. TH1/TH2 functional imbalance after acute myocardial infarction: coronary arterial inflammation or myocardial inflammation. *J Clin Immunol* 2005; 25: 246–253.

50 Pasqui AL, Di Renzo M, Auteri A, *et al*. Cytokines in acute coronary syndromes. *Int J Cardiol* 2005; 105: 355–356.

51 Engelbertsen D, Andersson L, Ljungcrantz I, *et al*. T-helper 2 immunity is associated with reduced risk of myocardial infarction and stroke. *Arterioscler Thromb Vasc Biol* 2013; 33: 637–644.

52 Liuzzo G, Goronzy JJ, Yang H, *et al*. Monoclonal T-cell proliferation and plaque instability in acute coronary syndromes. *Circulation* 2000; 101: 2883–2888.

53 Liuzzo G, Biasucci LM, Trotta G, *et al*. Unusual CD4+

CD28null T lymphocytes and recurrence of acute coronary events. *J Am Coll Cardiol* 2007; 50: 1450–1458.
54 Cheng X, Yu X, Ding YJ, *et al*. The Th17/Treg imbalance in patients with acute coronary syndrome. *Clin Immunol* 2008; 127: 89–97.
55 Mor A, Luboshits G, Planer D, *et al*. Altered status of CD4(+)CD25(+) regulatory T cells in patients with acute coronary syndromes. *Eur Heart J* 2006; 27: 2530–2537.
56 Ammirati E, Cianflone D, Banfi M, *et al*. Circulating CD4+ CD25hiCD127lo regulatory T-Cell levels do not reflect the extent or severity of carotid and coronary atherosclerosis. *Arterioscler Thromb Vasc Bio* 2010; 30: 1832–1841.
57 Yan W, Wang L, Duan Q, *et al*. mRNA expression of inhibitory and activating natural killer cell receptors in patients with acute myocardial infarctin and stable angina pectoris. *Exp Clin Cardiol* 2014; 20: 2982–2992.
58 Backteman K, Ernerudh J, Jonasson L. Natural killer (NK) cell deficit in coronary artery disease: no aberrations in phenotype but sustained reduction of NK cells is associated with low-grade inflammation. *Clin Exp Immunol* 2014; 175: 104–112.
59 Zouggari Y, Ait-Oufella H, Bonnin P, *et al*. B lymphocytes trigger monocyte mobilization and impair heart function after acute myocardial infarction. *Nat Med* 2013; 19: 1273–1280.
60 von Hundelshausen P, Weber C. Platelets as immune cells: bridging inflammation and cardiovascular disease. *Circ Res* 2007; 100: 27–40.
61 Furman MI, Barnard MR, Krueger LA, *et al*. Circulating monocyte-platelet aggregates are an early marker of acute myocardial infarction. *J Am Coll Cardiol* 2001; 38: 1002–1006.
62 Sarma J, Laan CA, Alam S, *et al*. Increased platelet binding to circulating monocytes in acute coronary syndromes. *Circulation* 2002; 105: 2166–2171.
63 Liu Y, Gao XM, Fang L, *et al*. Novel role of platelets in mediating inflammatory responses and ventricular rupture or remodeling following myocardial infarction. *Arterioscler Thromb Vasc Bio* 2011; 31: 834–841.
64 Stepien E, Stankiewicz E, Zalewski J, *et al*. Number of microparticles generated during acute myocardial infarction and stable angina correlates with platelet activation. *Arch Med Res* 2012; 43: 31–35.
65 VanWijk MJ, VanBavel E, Sturk A, *et al*. Microparticles in cardiovascular diseases. *Cardiovasc Res* 2003; 59: 277–287.
66 Mahara K, Anzai T, Yoshikawa T, *et al*. Aging adversely affects postinfarction inflammatory response and early left ventricular remodeling after reperfused acute anterior myocardial infarction. *Cardiology* 2006; 105: 67–74.
67 Liu M, Zhang P, Chen M, *et al*. Aging might increase myocardial ischemia/reperfusion-induced apoptosis in humans and rats. *Age* 2012; 34: 621–632.
68 Dutta P, Courties G, Wei Y, *et al*. Myocardial infarction accelerates atherosclerosis. *Nature* 2012; 487: 325–329.
69 Wang H, Eitzman DT. Acute myocardial infarction leads to acceleration of atherosclerosis. *Atherosclerosis* 2013; 229: 18–22.
70 Ridker PM, Rifai N, Pfeffer M, *et al*. Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction. *Circulation* 2000; 101: 2149–2153.
71 Ridker PM, Rifai N, Pfeffer MA, *et al*. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 1998; 98: 839–844.
72 Leuschner F, Rauch PJ, Ueno T, *et al*. Rapid monocyte kinetics in acute myocardial infarction are sustained by extramedullary monocytopoiesis. *J Exp Med* 2012; 209: 123–137.
73 Ruparelia N, Digby JE, Jefferson A, *et al*. Myocardial infarction causes inflammation and leukocyte recruitment at remote sites in the myocardium and in the renal glomerulus. *Inflamm Res* 2013; 62: 515–525.
74 Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. *Cardiovasc Res* 2002; 53: 31–47.
75 Padfield GJ, Din JN, Koushiappi E, *et al*. Cardiovascular effects of tumour necrosis factor alpha antagonism in patients with acute myocardial infarction: a first in human study. *Heart* 2013; 99: 1330–1335.