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Review

Possible mechanisms of C-reactive protein mediated acute myocardial infarction

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ABSTRACT

Myocardial infarction is a relevant cardiovascular event worldwide for morbidity and mortality. It has been theorized that acute myocardial infarctions (AMIs) and other acute coronary events that are precipitated by atherosclerosis are due to arterial blockage from fat deposits. It is now known, however, that atherosclerosis involves more than just lipids. Inflammation has also been studied extensively to play a substantial role in myocardial infarction. There have been debates and conflicting reports over the past few years about the value of assessing levels of C-reactive protein and other biomarkers of inflammation for the prediction of cardiovascular events. Several studies have shown that CRP is not only an inflammatory marker, but also involved in the pathogenesis of myocardial infarction. Studies have linked atherogenesis and rupture of atherosclerotic lesion to endothelial dysfunction. CRP directly inhibits endothelial cell nitric oxide (NO) production via destabilizing endothelial NO synthase (eNOS). Decreased NO release causes CRP mediated inhibition of angiogenesis, stimulating endothelial cell apoptosis. CRP can also activate the complement system through the classical pathway. Complement activation plays an important role in mediating monocyte and neutrophil recruitment in an injured myocardium and may therefore lead to increase in infarct size. This article discusses the possible roles of CRP in complement activation, endothelial dysfunction and its impact on the development of myocardial infarction. We also reviewed the possible therapeutic approaches to myocardial infarction.

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1. Introduction

Acute myocardial infarction is the damage and death to heart tissues that occurs due to a blockade to one or more of the coronary arteries of the heart muscles caused by atherosclerotic clot or spasm of the arteries (Libby et al., 2002; Lin et al., 2014). It has been well established that acute myocardial infarction (AMI) is one of the principal causes of death in many developed countries (Matsuzawa and Lerman, 2014). Smoking, hypertension, diabetes and metabolic disorders including hypercholesterolemia have long been considered as the major risk factors for coronary artery diseases including myocardial infarction (Niessen et al., 2003; Calabro et al., 2012). There have been extensive investigations about the role of C-reactive protein (CRP) in coronary heart diseases (CHD) over the past few years. Zacho et al. (Zacho et al., 2008) reported that elevated plasma levels of CRP have a causal association with ischemic diseases, however, polymorphisms associated with elevated CRP levels did not increase the risk of ischemic vascular disease. Further investigations into the biological effects of cellular and genetic variants of CRP are recommended. In recent years, several clinical and preclinical investigations have reported the role of CRP in the progress of atherosclerosis (Strang and Schunkert, 2014). Its clinical applications in the assessment of cardiovascular risk have been studied. Report from Pearson et al. (2003), suggested that, CRP may be used at the discretion of a physician for cardiovascular risk assessment. In 2009, Genest et al. from the Canadian Cardiovascular Society, also recommended CRP assessment in patients at "intermediate risk" (predicted risk of a cardiovascular event over the subsequent 10 years of 10% to less than 20% (Genest et al., 2009)). Moreover, in 2009, Myers et al. reported that measurement of CRP levels might be a useful assessment in patients at intermediate risk for cardiovascular events (Myers et al., 2009). In 2010, a report by the American College of Cardiology Foundation–AHA Task Force on Practice Guidelines stated that assessment of CRP levels is reasonable for patients at intermediate risk (Greenland et al., 2010). The pharmacological events leading to the pathogenesis of atherosclerotic lesions have been associated with those of inflammatory and immunity related diseases. Various similarities have been inferred in the processes leading to the pathogenesis of both conditions. Raising the possibility that inflammation could be the central orchestrator of the formation, progression and eventual rupture of atherosclerotic lesions, leading to the development of myocardial infarction (Calabro et al., 2012; de Faire and Frostegard, 2009). In actual fact, myocardial infarction does not simply result from disorders of pathological lipid deposition leading to atherosclerosis, but it is regarded as a dynamic and progressive pathophysiological process arising from a combination of endothelial dysfunction and inflammation (Brevetti et al., 2010). In effect, studies to identify inflammatory markers to improve our ability to predict MI have intensified (Pearson et al., 2003; Auer et al., 2002; Libby et al., 2002; Mihlan et al., 2011). Several acute phase inflammatory proteins such as C-reactive proteins (Auer et al., 2002; Libby et al., 2002; Pearson et al., 2003; Mihlan et al., 2011), cytokines (Pearson et al., 2003), and intercellular adhesion molecules (Pearson et al., 2003; Brevetti et al., 2010) have been reported as potential pharmacological indicators of atherosclerosis and risk of future cardiovascular events such as AMI (Pearson et al., 2003; Auer et al., 2002; Libby et al., 2002; Mihlan et al., 2011). Elevated levels of C-reactive protein are associated with increased risk of cardiovascular events. Moreover, potentially important associations have been established between elevated markers of inflammation, such as C-reactive protein and increased efficacy of lipid-lowering therapy with the hepatic hydroxymethylglutaryl coenzyme A reductase inhibitors

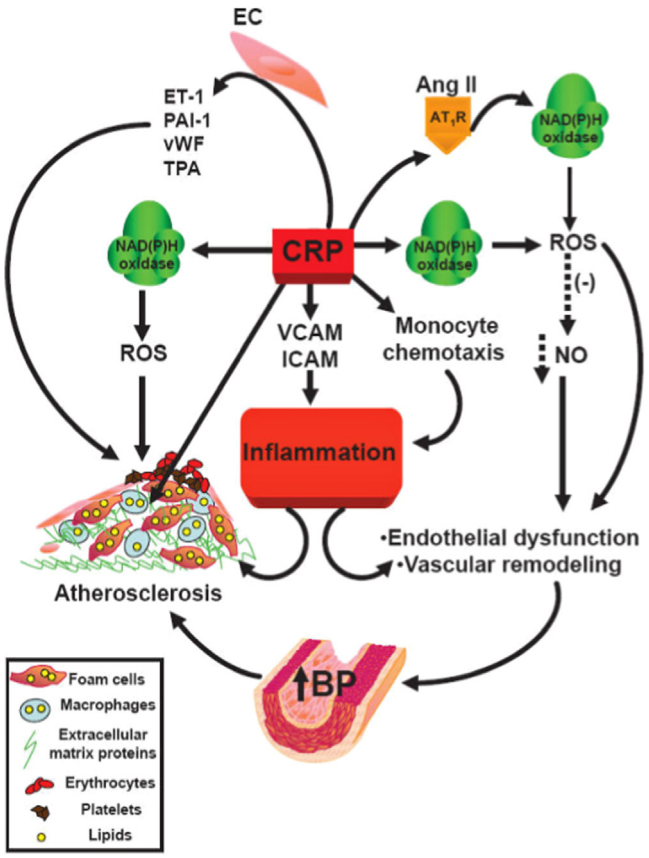

Fig. 1. C-reactive protein-induced inflammation (Savoia and Schiffrin, 2007).

(statins). The therapeutic effects of the statins are not only due to their lipid lowering ability, but also due to their anti-inflammatory effect (Albert et al., 2001; Ridker et al., 1998; Antonopoulos et al., 2012). Many animal studies have shown that inhibiting inflammation using anti-inflammatory agents can markedly reduce infarct size in AMI (Pepys and Hirschfield, 2003; Antonopoulos et al., 2012). Local inflammatory response during myocardial ischemia therefore contributes to myocardial damage and infarct size and plays a major role in tissue remodeling (Nijmeijer et al., 2002; Niessen et al., 2003).

It has been shown that inflammatory reactions in atherosclerotic lesions and infarcted myocardium have a major impact on incidence and outcome of atherosclerosis and its complications such as AMI (Frangogiannisa et al., 2001; Frangogiannisa, 2014; Calabro et al., 2012). CRP amongst other inflammatory mediators play significant role in the activation of the complement system in infarcted myocardium (Haahr-Pedersen et al., 2009). Complement activation may play an important role in the recruitment of neutrophils and cytokines leading to the development of atherosclerosis and reinfarction (Nijmeijer et al., 2004; Krijnen et al., 2003; Frangogiannisa and Rosenzweig, 2012).

Krijnen et al. (Krijnen, 2009) reported that in AMI, cardiac cells undergo apoptosis, many of which convert to necrosis. All these apoptotic and necrotic cells trigger an extensive inflammatory response during reperfusion. Inflammatory mediators including CRP and inflammatory cells flood the jeopardized myocardium (Thiele et al., 2014; Nijmeijer et al., 2004; Nijmeijer et al., 2003). As a result of this inflammatory response, the reversibly damaged cardiomyocytes will change to an irreversibly damaged state, thereby causing more extensive myocardial damage. Recent investigations have shown that increased level of CRP, a marker of inflammation, corresponds to an increased infarct size of patients

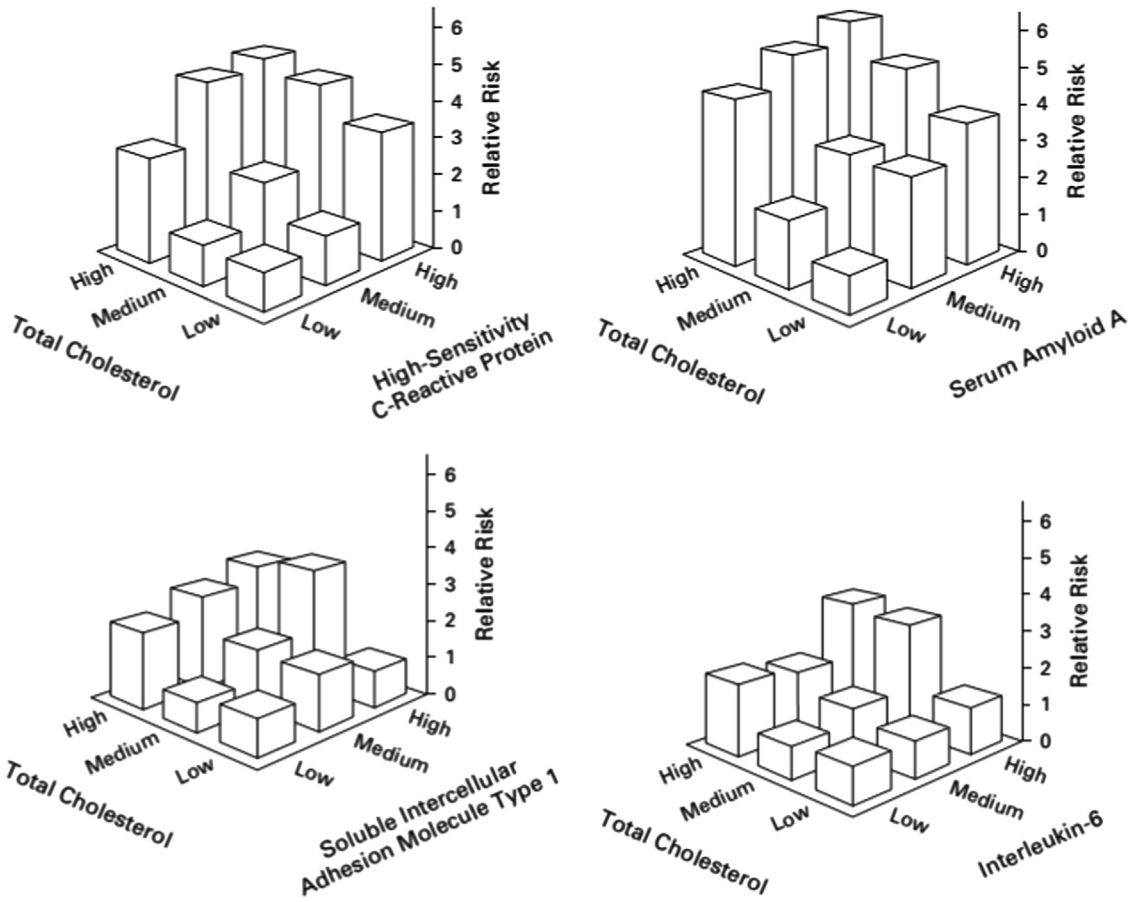

Fig. 2. Relative risk of cardiovascular events among apparently healthy postmenopausal women according to base-line levels of total cholesterol and markers of inflammation. Each marker of inflammation improved risk prediction models based on lipid testing alone, an effect that was strongest for hs-CRP and serum amyloid A (Ridker et al., 2000).

with myocardial infarction and the inhibition of it reduces the size of an infarct (Frangogiannisa et al., 2001; Nijmeijer et al., 2004; Mihlan et al., 2011) (Figs. 1 and 2).

Myocardial infarction is recently regarded as a progressive disease that may arise from plaque rupture and subsequent occlusion of the vessel lumen (thrombosis) after inflammatory response and endothelial dysfunction (Hadi et al., 2005; Matsuzawa and Lerman, 2014). The vascular endothelium, at the interface of blood and tissue, is able to sense changes in hemodynamic forces and blood-borne signals and then synthesizes and releases vasoactive substances. Vascular homeostasis is maintained by a balance between endothelium-derived relaxing and contracting factors (Szmitko et al., 2003). When this balance is disrupted by inflammatory mediators such as CRP and other cardiovascular risk factors (Libby et al., 2002; Szmitko et al., 2003; Dutta et al., 2012), the vasculature becomes susceptible to atheroma formation and also the formation of unstable plaques or plaque ruptures, which eventually elicit coronary artery diseases such as acute myocardial infarction.

As numerous evidence link atherogenesis and eventual rupture of atherosclerotic plaque to markers of inflammation and endothelial dysfunction (Saadeddin et al., 2002; Hein et al., 2009; Matsuzawa and Lerman, 2014), it may be useful to provide additional information on the role of the inflammatory marker CRP in endothelial dysfunction and its impact thereof on the development of acute myocardial infarction. This paper therefore reviews the function and physiological role of CRP in complement activation and endothelial dysfunction in CRP mediation of acute myocardial infarction.

2. Inflammation mediation of myocardial infarction

A large number of experimental and clinical data have demonstrated the effect of inflammation on endothelium activation and the impact of this association on the risk of cardiovascular diseases (Stenvinkel et al., 2000; Kharbanda et al., 2002; Yang et al., 2015; Mccormick et al., 2015; Davignon and Ganz, 2004). Endothelial cells, located at the internal lumen of the vasculature play a wide variety of critical roles in the control of vascular function. They prevent platelet and leukocyte adhesion, regulate blood flow, coagulation, growth of vascular smooth muscle cells, hemostasis, vasodilation and vasoconstriction. Studies suggest that endothelial dysfunction, which is manifested by deficiencies in the production of nitric oxide (NO) and prostacyclin precedes atherogenesis (Matsuzawa and Lerman, 2014; Davignon and Ganz, 2004; Behrendt and Ganz, 2002). When endothelial cells undergo inflammatory activation, leukocytes of the innate immune system migrate to the activated endothelium, whiles naive lymphocytes migrate into draining peripheral lymph nodes through specialized endothelium composed of high endothelial venule cells (Swirski and Nahrendorf, 2013). Within the peripheral lymph nodes, antigen-specific lymphocytes are activated. These lymphocytes migrate across activated endothelium to express adhesion

molecules. The adhesion molecules regulate leukocyte adhesion and leukocyte migration into tissues and arteries (Tseng et al., 2014).

Inflammatory Leukocyte invasion in the arteries is very crucial to the development of atherosclerosis and its complications such as myocardial infarction (Eriksson, 2004; Verma and Yeh, 2003; Libby et al., 2002). The reader can refer to other sources for general information on inflammation (Østerud and Bjørklid, 2003). The adhesive function of platelets is considered to be an important recruitment mechanism in atherosclerosis (Eriksson, 2004; Libby et al., 2002). CRP and inflammatory cytokines, including interleukin-1 (IL-1) and tumor necrosis factor (TNF), induce the expression of cellular adhesion molecules, which mediate adhesion of leukocytes to the vascular endothelium (Pasceri et al., 2000; Willerson, 2002). Vascular cell adhesion molecule-1 (VCAM-1) mediates the interaction between endothelium and leukocytes (Libby, 2006; Gui et al., 2012; Gidullin et al., 2010). Inflamed endothelial monolayer expresses adhesion molecules that bind cognate ligands on leukocytes. When the luminal endothelium layer is inflamed, selectins such as P-selectin and E-selectin mediate a rolling, or salutary interaction with the inflamed luminal endothelium. Chemokines such as monocyte chemoattractant protein-1(MCP-1) and interleukin-8 (IL-8) recruit leukocytes into the arterial wall. Attachment to the vascular wall is strengthened by membrane integrins. Pro-inflammatory cytokines expressed within atheroma provide a chemotactic stimulus to the adherent leukocytes, directing their migration into the intima. Inflammatory mediators such as macrophage colony-stimulating factor (M-CSF) can augment expression of macrophage scavenger receptors leading to uptake of modified lipoprotein particles and formation of lipid-laden macrophages. Macrophage colony-stimulating factor (M-CSF) and other mediators produced in plaques can promote the replication of macrophages within the intima as well. T-lymphocytes join macrophages in the intima during lesion evolution. These leukocytes and the inherent vascular endothelial cells secrete cytokines, tissue factors (TF), matrix metalloproteinases (MMPs), reactive oxygen species (ROS) and other inflammatory factors that can promote the migration and proliferation of smooth muscle cells (SMCs). SMCs express specialized enzymes that can degrade the elastin and collagen in response to inflammatory stimulation. This degradation of the arterial extracellular matrix permits the penetration of the SMCs through the elastic laminae and collagenous matrix of the growing plaque. Ultimately, inflammatory mediators can inhibit collagen synthesis and evoke the expression of collagenases by foam cells within the intimal lesion. These changes in extracellular matrix metabolism cause the thinning of the fibrous cap, rendering it weaker and susceptible to rupture. Cross-talk between T lymphocytes and macrophages heightens the expression of the potent pro-coagulant tissue factor (Østerud and Bjørklid, 2003). Thus, when the plaque ruptures, the tissue factor induced by the inflammatory signaling leads to thrombus formation and ultimately causes most acute complications of atherosclerosis such as acute myocardial infarction.

3. C-reactive protein (CRP)

C-reactive protein is an acute phase reactant which rises within hours of the onset of inflammation. It has a half-life of 24–48 h during which an inflammation is terminated. Its rate of production is directly correlated with the severity of inflammation. CRP values may be useful in determining disease progress or the effectiveness of treatments (Di Napoli et al., 2011).

Its serum concentration rises in response to inflammation. It binds to phosphocholine with high affinity in the presence of calcium and activates the complement system via the C1Q (Gershov et al., 2000; Yadav et al., 2014). This then promotes phagocytosis by macrophages to target a range of pathogens as well as membranes of damaged and necrotic host cells. This makes CRP, together with other acute-phase proteins, an important component of the first line of innate host defense. It therefore plays a role in innate immunity as an early defense system against infections (Gershov et al., 2000).

CRP may opsonize native low density lipoprotein for macrophages. It enhances uptake of oxidized low density lipoprotein into macrophage through Fcγ receptors (Taskinen et al., 2005), and stimulates macrophage to express tissue factor leading to plaque formation and thrombosis (Stein et al., 2000). Thus, CRP can be suggested to be involved in foam cell formation in atherogenesis (Zwaka et al., 2001). Macrophages cause a rise in the levels of interleukin (IL-6) and adipocytes in response to a wide range of acute and chronic inflammatory conditions such as bacterial, viral, or fungal infections, rheumatic and other inflammatory diseases, malignancy and tissue injury and necrosis. These conditions cause release of interleukin-6 and other cytokines that trigger the synthesis of CRP and fibrinogen by the liver. Thus, the main physiological function of CRP appears to be its ability to recognize pathogens and to facilitate their elimination by activating the complement system and phagocytic cells (Gershov et al., 2000).

Tillet et al. first discovered CRP after its reactivity with the phosphocholine residues of C-polysaccharide of *Streptococcus pneumonia* (Frangogiannisa, 2014). It was initially thought that CRP might be a pathogenic secretion since it was elevated in a variety of illnesses. Its discovery as a product of hepatic synthesis showed that it is an innate protein. The recent development of high-sensitivity assays for CRP (hs-CRP) has led to the belief that CRP is an indicator of micro inflammation.

In recent years, there have been a lot of investigations about the value of assessing levels of C-reactive protein (CRP) and other biomarkers of inflammation for the prediction of first cardiovascular events (Kaptoge et al., 2012; Greenland et al., 2010; Graham et al., 2007; Calabro et al., 2012; Genest et al., 2009; Myers et al., 2009). However, a lot of discoveries have suggested that CRP is associated with high risk of coronary artery diseases and that CRP inhibition can be a safe and effective therapy for myocardial infarction (Ji et al., 2006; Choi et al., 2004; Vivona et al., 2009; Saadeddin et al., 2002; Sun et al., 2005). Its role in endothelial dysfunction and complement activation is also very important in the development of cardiovascular events.(Wang et al., 2011).

3.1. CRP and the risk of acute myocardial infarction

In recent years, the view on the role of CRP has shifted from an innocent acute phase protein to a mediator of tissue damage (Kaptoge et al., 2012). It has been observed that elevated levels of circulating CRP after an infarction correlated with prognosis of cardiovascular events (Ridker et al., 2000). CRP may directly interact with atherosclerotic vessels or ischemic myocardium by activation of the complement system, thereby promoting inflammation and thrombosis (Riedemann and Ward, 2003; Dutta et al., 2012). The observation of the impact of elevated blood CRP levels in patients with AMI intensified the investigation about the relations between CRP and acute myocardial infarction (AMI). Paraskevas and Mikhailidis (2008) made an observation that CRP is not only an innocent bystander but actively involved in the pathogenic process of AMI and reperfusion injury and that CRP was also found to be localized in infarcted rabbit myocardium. Nijmeijer et al. (2004) however discovered that CRP and activated complement fragments co-localize in infarcted myocardium, but not in normal myocardium of patients with AMI. This means that inflammatory response in the damaged myocardium can cause

complement activation which ultimately leads to acute myocardial infarction. These results therefore reveal the relationship between cardiomyocyte-bound CRP and local complement activation in AMI. Case control studies conducted by Ridker et al. (Willerson and Ridker, 2004; Koenig, 2001) postulated that markers of inflammation predict risk of recurrent events. A prospective nested case-control study was conducted among 28,263 apparently healthy postmenopausal women over a mean follow-up period of three years to assess the risk of cardiovascular events such as myocardial infarction associated with base-line levels of markers of inflammation. The markers included high-sensitivity C-reactive protein (hs-CRP), serum amyloid A, interleukin-6, and soluble intercellular adhesion molecule type 1 (sICAM-1). Of all the markers of inflammation measured, CRP was the strongest predictor of the risk of cardiovascular events; the relative risk of events for women in the highest quartile, as compared with the lowest quartile for this marker (CRP) was 4.4 (95% confidence interval, 2.2–8.9), serum amyloid A (relative risk for the highest as compared with the lowest quartile, 3.0), sICAM-1 (2.6), interleukin-6 (2.2), homocysteine (2.0), total cholesterol (2.4), low-density lipoprotein (LDL) cholesterol (2.4), apolipoprotein B-100 (3.4), high-density lipoprotein (HDL) cholesterol (0.3), and the ratio of total cholesterol to HDL cholesterol (3.4) (Ridker et al., 2000).

Other investigations have also shown that elevated levels of CRP corresponded to enlarged infarct size (Pearson et al., 2003; Mihlan et al., 2011); injection of human CRP into rats after ligation of the coronary artery reproducibly enhanced infarct size by approximately 40% (Kluft, 2004). On the basis of this evidence, it can be postulated that CRP predicts risk of recurrent events after myocardial infarction.

CRP, amongst other factors, also mediates complement activation in infarcted myocardium (Krijnen et al., 2006a, 2006b; Mihlan et al., 2011). CRP-C3d and CRP-C4d complexes have been found to be higher in patients with AMI compared to those in controls (normal group) or in patients with unstable angina pectoris (Nijmeijer et al., 2002). Moreover, multiple studies have shown that inhibiting inflammation by anti-inflammatory agents can markedly reduce infarct size in AMI and that effectiveness of statins in treating AMI is not only due to their lipid lowering ability but also due to their anti-inflammatory effect (Albert et al., 2001; Antonopoulos et al., 2012). de Beer and Webb (2006) indicated that several components of the inflammatory response are associated with the initiation and progression of atherosclerosis. Studies in stable and unstable angina patients unexpectedly revealed that the baseline value of CRP significantly predicted future coronary events. In the unstable angina studies, increased baseline CRP values were associated with significantly increased risk of future coronary events (Nijmeijer et al., 2002). Studies performed on the general population without known pre-existing coronary artery disease showed independently that baseline CRP measurements were associated with future coronary events. The above studies and results strongly suggest that CRP is a mediator of the recurrent and development of myocardial infarction.

4. The complement system

The complement system essentially can be activated by three distinct routes of activation; the classical, alternative and lectin pathways. The classical pathway (involving C1q, C1r, C1s, C4, C2 and C3) is activated primarily by the interaction of C1q with immune complexes but can also be initiated upon interaction of C1q with other proteins, such as, CRP. The activation of the alternative pathway (involving C3, factor B, factor D and properdin) is not dependent on the presence of immune complexes but is affected by interactions with carbohydrate-rich particles that lack sialic acid. Mannose-binding lectin (MBL) binds to terminal mannose groups on a variety of bacteria and subsequently, activates the lectin pathway (MASP1, MASP2, C4, C2 and C3) (Sajanti et al., 2014; Degn et al., 2013). Previous studies have postulated that C-reactive protein can exacerbate ischemic necrosis in a complement-dependent fashion (Sun et al., 2005; Agrawal et al., 2010; Wang et al., 2011).

4.1. CRP activation of the complement system

CRP can bind to the plasma membrane of necrotic cells and activate complement through the classical pathway by binding to C1q. Binding of C1q initiates conformational changes in C1, leading to cleavage of C1r followed by C1s, which is then able to cleave C2 and C4, resulting in the formation of the C4b2a complex. This complex enhances C3 cleavage; thereafter, C3b joins with C4b2a to form C4b2a3b. This then cleaves C5b from C5, which forms C5b67complex by joining C6 and C7. Together with C8, this complex forms the membrane attack complex (MAC), leading to lysis of the cell and recruits multiple C9 molecules to the membrane. This may eventually lead to complement-mediated I/R-induced tissue injury and subsequently result in acute myocardial infarction (Willerson and Ridker, 2004). Studies have revealed that co-localization of CRP in infarcted myocardium induces complement activation to enhance inflammation in ischemic myocardium. Nijmeijer et al. (2003) conducted an experiment to establish whether CRP activates complement in infarcted human myocardium. It was reported that CRP activates the complement system and that the relationship between this activation and the duration of infarction was more than 12 h. This suggests that assessment of CRP level can be incorporated in the treatment of myocardial infarction patients.

4.2. Complement activation in myocardial infarction

Complement system is an important mediator of inflammation in patients with acute myocardial infarction (Ridker et al., 2000; Frangogiannisa, 2014) and thus plays a major role in the development, progression and recurrence of acute myocardial infarction. As early as 1971, Hill and Ward (Frangogiannisa, 2014) demonstrated in a rat model that complement was activated locally in ischemic myocardium and contributed to the local inflammatory response. Afterwards, enormous evidence have accumulated supporting the role of the complement system as an important mediator of inflammation and subsequent cell death in AMI (Peisajovich et al., 2008; Hansson, 2005; Frangogiannisa, 2014; Pearson et al., 2003). Complement is activated locally in the heart by complement proteins during myocardial infarction (Nijmeijer et al., 2004). C-reactive protein (CRP) and complement, are inflammatory mediators and possible cardiovascular risk factors that may contribute to the pathogenesis of atherosclerosis (Niessen et al., 2003; Krijnen et al., 2006a, 2006b). The complement split product, C5a, and the terminal membrane attack complex, C5b-9 (MAC), are believed to be responsible for complement-mediated I/R-induced tissue injury (Riedemann and Ward, 2003) which may eventually result in acute myocardial infarction (Krijnen et al., 2002; Frangogiannisa et al., 2001; Willerson and Ridker, 2004; Nijmeijer et al., 2004). During myocardial necrosis, CRP amongst other inflammatory mediators induces complement activation. Myocardial necrosis induced complement activation and free radical generation trigger-cytokine cascade initiated by Tumor Necrosis Factor (TNF)-α release. If reperfusion of the infarcted area is initiated, it is attended by an intense inflammatory reaction. Interleukin (IL)-8 synthesis and C5a activation have a crucial role in recruiting

neutrophils in the ischemic and reperfused myocardium. Neutrophil infiltration is regulated through a complex sequence of molecular steps involving the selectins and the integrins, which mediate leukocyte rolling and adhesion to the endothelium. Marginated neutrophils exert potent cytotoxic effects through the release of proteolytic enzymes and the adhesion with Intercellular Adhesion Molecule (ICAM)-1 expressing cardiomyocytes.

The complement system inhibition causes a decrease in myocardium infarct size (Frangogiannisa et al., 2001; Krijnen et al., 2006a, 2006b; Mihlan et al., 2011). Acute phase response in the innate immune system can be provoked by myocardial infarction (Krijnen et al., 2006a, 2006b). Within the infarct, C-reactive protein (an acute-phase protein) is an important component of the first line of innate host defense deposited together with complement (Nijmeijer et al., 2002; Krijnen et al., 2006a, 2006b). In vivo complement depletion, produced by cobra venom factor, completely attenuates this effect (Frangogiannisa, 2014). These observations demonstrate that human CRP and complement activation are major mediators of ischemic myocardial injury and raises the possibility that their inhibition can improve cardiovascular diseases such as myocardial infarction. Local activation of the classical pathway of complement occurs in various animal models of AMI as exhibited by deposition of activated fragments of this pathway in infarcted myocardium (Frangogiannisa et al., 2001). This activation occurs independently of reperfusion. Subsequent studies have demonstrated that myocardial cell necrosis results in the release of subcellular membrane constituents that are rich in mitochondria, and are capable of triggering the early acting components (C1, C4, C2 and C3) of the complement cascade (Nah and Rhee, 2009). Further studies suggested that during myocardial ischemia, mitochondria extruded through breaks in the sarcolemma unfold and release membrane fragments rich in cardiolipin and protein. By binding C1 and supplying sites for the assembly of later acting complement components, these subcellular fragments provide the means to relay the complement-mediated inflammatory response to ischemic injury. mRNA and proteins for all the components of the classical complement pathway are up-regulated in areas of myocardial infarcts (Frangogiannisa et al., 2001).

Complement activation may have an important role in mediating neutrophil and monocyte recruitment in the injured myocardium. Studies have shown the complement system to be activated locally in infarcted myocardium, and that complement activation products contribute to the infiltration of neutrophils (Nijmeijer et al., 2004). Inhibition of complement activation in rat models not only attenuates infiltration of the jeopardized myocardium by neutrophils, but also reduces infarct size (Krijnen, 2009). Studies conducted by Dreyer et al. (Frangogiannisa, 2014) show that neutralizing antibodies to C5a in vitro completely inhibits post-ischemic cardiac lymph. Other studies show that monocyte chemotactic activity in cardiac lymph collected in the first hour of reperfusion is attributable to C5a. Depletion of Complement using cobra venom in a variety of animal models in experimental coronary artery occlusion has been shown to attenuate myocardial necrosis (Frangogiannis et al., 2000; Mihlan et al., 2011).

5. Endothelial dysfunction

The endothelium maintains vascular homeostasis through multiple complex interactions with cells in the vessel wall and lumen. Specifically, the endothelium regulates vascular tone by balancing production of vasodilators, including nitric oxide (NO), and vasoconstrictors. Endothelial dysfunction is the reduced amount of the production of nitric oxide and the imbalance between endothelium-derived relaxing and contracting factors. The resulting imbalance may lead to an impairment of endothelium-dependent vasodilation, which is a clear demonstration of endothelial dysfunction (Hadi et al., 2005). Endothelial dysfunction is a well-established response to cardiovascular risk factors and precedes the development of atherosclerosis, so it is important in the pathogenesis of acute coronary syndrome (Matsuzawa and Lerman, 2014). Endothelial dysfunction promotes both the early and late stages of atherosclerosis such as up-regulation of adhesion molecules, increased chemokine secretion and leukocyte adherence, increased cell permeability, enhanced low-density lipoprotein oxidation, platelet activation, cytokine elaboration, and vascular smooth muscle cell proliferation and migration (Hadi et al., 2005).

Plaque rupture can be as a result of endothelial dysfunction and may contribute to the development of acute coronary syndrome such as AMI. Increased oxidative stress is related to endothelial dysfunction (Napoli et al., 2001). NO may reduce endothelial expression of several inflammatory mediators and adhesion molecules that increase plaque rupture (Krijnen et al., 2003). The relationship between endothelial dysfunction and atherosclerosis has raised the possibility that the status of an individual endothelial function may reflect the propensity to develop atherosclerotic disease, and thus may serve as a marker of an unfavorable cardiovascular event (Al Suwaidi et al., 2001).

Evidence of reduced endothelial nitric oxide availability and elevated levels of inflammatory mediators suggest that vascular endothelial dysfunction and inflammation contribute to the development of cardiovascular diseases (Taddei et al., 2006; Allanore et al., 2001). Low grade chronic inflammation has been reported to cause endothelial dysfunction and decreased availability of nitric oxide which leads to increased production of oxidative stress (Taddei et al., 2006). Nitric oxide is a chemically unstable radical formed by the reduction of nitric oxide synthase by tetrahydrobiopterin (cofactor for all the three isoforms of nitric oxide synthase) and hydroxylation of L-arginine in the vascular endothelium. Nitric oxide causes relaxation of Vascular Smooth Muscle Cell by activating cytosolic guanylate cyclase and also inhibits leukocyte adhesion, platelet adhesion and aggregation (Bauer and Sotnikova, 2010). Its biological effects make it an important factor in the endogenous defense against vascular occlusion and thrombosis. Therefore, nitric oxide elicits flow-dependent vasodilation that increases blood flow in conduit arteries. Endothelial formation of nitric oxide contributes to vasodilator mechanisms both physiologically and pharmacologically (Quillon et al., 2015). Endothelial dysfunction can therefore be defined as failure of the vascular endothelium to elicit nitric oxide-mediated vasodilation which may be due to inflammation mediated decreased formation, decreased sensitivity to the nitric oxide formed and increased degradation or a combination of these factors. Endothelial dysfunction can therefore lead to an impaired coronary blood flow, impaired tissue perfusion, increased local vascular resistance, decreased defense against thrombus formation and promotion of platelet adherence and aggregation (Puzserova et al., 2008). Based on the aforementioned biological actions of nitric oxide, numerous therapies have been investigated to assess the possibility of reversing endothelial dysfunction by enhancing the release of nitric oxide from the endothelium, either by stimulating the synthesis of nitric oxide or averting the oxidative inactivation and conversion of nitric oxide to toxic substances (Tousoulis et al., 2012). With this knowledge, we can infer that the loss of nitric oxide production could explain why inflammation mediated endothelial dysfunction is considered to be a risk factor for the development and clinical expression of atherosclerosis and myocardial infarction.

5.1. Role of CRP in endothelial dysfunction

Elevated levels of CRP elicit a multitude of effects on endothelial function favouring a pro-inflammatory and pro-atherosclerotic phenotype and may be used to predict vascular disease (Danesh et al., 2004). Dysfunction of endothelial activity represents a key early step in the development of atherosclerosis and it is also involved in plaque progression and rupture, leading to the development of acute coronary syndrome and myocardial infarction (Libby, 2001). Hein et al. (2009) examined the effect of CRP on endothelial function and its underlying mechanisms in rats. It was revealed that dilation of mesenteric arterioles was significantly reduced following CRP treatment. The endothelial nitric oxide synthase (eNOS) activity and eNOS dimer/monomer ratio were significantly lower in aortic tissue homogenates from CRP-treated rats. There were also significant reductions in guanosine triphosphate cyclohydrolase 1 (GTPCH1) expression and tetrahydrobiopterin (BH4) levels in rat aortic tissues following CRP administration. GTPCH 1 and BH4 are involved in endothelial nitric oxide production and that, their depletion may lead to decreased availability of NO (Verhaar et al., 2004). It was therefore concluded that, C-reactive protein induces endothelial dysfunction and uncoupling of eNOS and inhibits endothelium-dependent nitric oxide (NO)-mediated vasodilation. The possible mechanism may be the CRP-mediated decreased expression of GTPCH1 and the CRP induced deficiency of tetrabiopterin (BH4).

CRP stimulates endothelin-1 and interleukin-6 release from endothelial cells and up-regulates adhesion molecules such as intercellular adhesion molecule-1(ICAM-1), vascular cell adhesion molecule-1(VCAM-1), and E-selectin and stimulates the release of monocyte chemotactic protein-1. The inhibition of endothelin and interleukin-6 may also attenuate the pro-atherogenic effects of C-Reactive Protein (Verma et al., 2002a). CRP facilitates endothelial cell apoptosis and blocks angiogenesis by inhibiting NO production (Verma et al., 2002a; Szmitko et al., 2003; Verma et al., 2002b). Furthermore, CRP augments CD14-induced endothelial cell activation as a compensatory mechanism in myocardial ischemic injury and thus, increases the propensity to develop various cardiovascular diseases (Verma et al., 2002b). It up-regulates nuclear factor-κB, and inhibits bone marrow-derived endothelial progenitor cell survival and differentiation. Nuclear factor-κB is a key nuclear factor that facilitates the transcription of numerous pro-atherosclerotic genes. Endothelial progenitor cells have been suggested to play an important role in postnatal neovascularization. The ability of CRP to inhibit progenitor cells may be an important inhibiting compensatory angiogenesis mechanism in chronic ischemia (Verma et al., 2002b).

6. Concluding remarks

The role of inflammation in acute myocardial infarction has been established over the years in studies describing the pathogenesis of atherosclerosis. Its involvement in the various aspects of atherogenesis from the initial foam cell activation to the development of atherosclerotic lesion and the rupture of the vulnerable fibrous cap have been well noted. All these eventually lead to coronary artery diseases such as acute myocardial infarction. Thus, inflammation may directly increase the risk of atherosclerotic plaque already present in an artery. Plaque rupture leads to the formation of a blood clot, blocking the blood flow in the artery and causing acute myocardial complications.

It is now widely accepted that C-reactive protein, an inflammatory marker is involved in the development of myocardial infarction. It may induce endothelial dysfunction and activate the complement system to enhance atherosclerosis and plaque ruptures which may eventually, lead to myocardial infarction.

Prolonged myocardial ischemic insult causes an indirect attack on the jeopardized tissue through activation of the complement system. The complement response to ischemia attracts neutrophils to the area of myocardial injury which participates in extending the area of necrosis. Components of the complement system can damage the myocardium by the formation of neutrophil chemoattractants as well as through an assembly of the membrane attack complex. This abrupt complement activation entails leukocyte sequestration in the microcirculation in addition to anaphylatoxin-mediated vasoconstriction, resulting in interruption of blood supply and subsequent irreversible myocardial damage and necrosis.

Endothelial dysfunction is a term that covers diminished production/availability of nitric oxide and/or an imbalance in the relative contribution of endothelium-derived relaxing and contracting factors. It is involved in lesion formation by the promotion of both the early and late mechanisms of atherosclerosis, including up-regulation of adhesion molecules, increased chemokine secretion and leukocyte adherence, increased cell permeability, enhanced low-density lipoprotein oxidation, platelet activation, cytokine elaboration, and vascular smooth muscle cell proliferation and migration. When cardiovascular risk factors such as CRP are treated, the endothelial dysfunction and its associated complications may be reversed. Individual's blood levels of the acute phase protein may therefore be a reflection on the propensity to develop myocardium infarction. Thus, inhibition of CRP in cardiovascular disease assessment may be a possible therapeutic approach for the treatment of myocardial infarction. Based on the reported consistency between clinical and preclinical data, we conclude that CRP plays a major role in the development and clinical expression of myocardial infarction. We therefore recommend further studies on CRP-targeting drug since currently there are no CRP-specific drugs available.

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