



Review

Possible mechanisms of C-reactive protein mediated acute myocardial infarction



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ARTICLE INFO

Article history:

Received 4 February 2015

Received in revised form

1 April 2015

Accepted 1 April 2015

Available online 18 April 2015

Keywords:

C-reactive protein

Myocardial infarction

Complement activation

Endothelial dysfunction

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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Contents

1. Introduction	73
2. Inflammation mediation of myocardial infarction	74
3. C-reactive protein (CRP)	75
3.1. CRP and the risk of acute myocardial infarction	75
4. The complement system	76
4.1. CRP activation of the complement system	76
4.2. Complement activation in myocardial infarction	76
5. Endothelial dysfunction	77
5.1. Role of CRP in endothelial dysfunction	78
6. Concluding remarks	78
Acknowledgments	78
References	78

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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

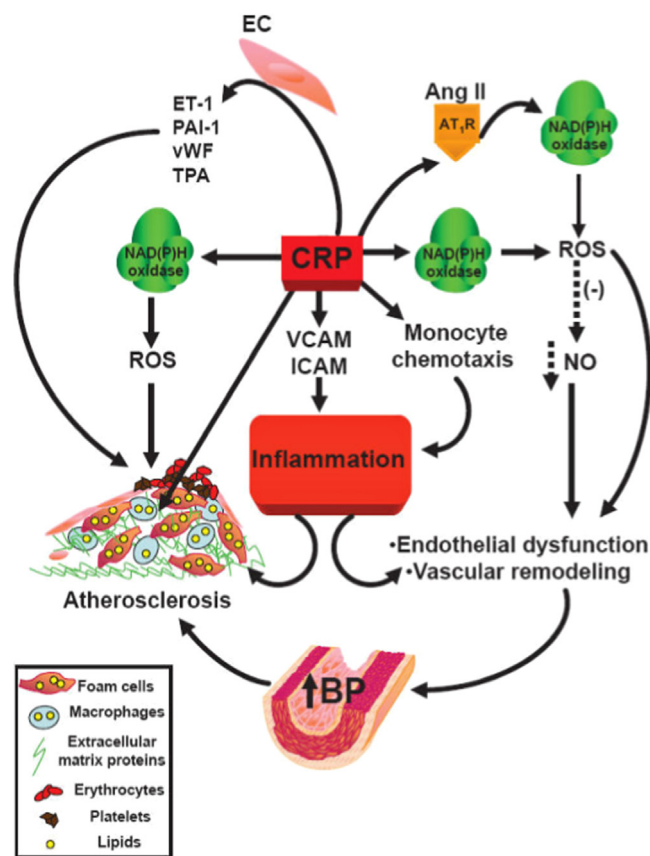


Fig. 1. C-reactive protein-induced inflammation (Savoia and Schiffrin, 2007).

(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

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