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Inflammatory Biomarkers in Ischemic Heart Disease

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1. Introduction

Ischemic heart disease (IHD) is one of the main groups within the class of cardiovascular diseases (CVD), and IHD is the most common single cause of morbidity and mortality in the Western world (Gaziano et al., 2006). According to the American Heart Association Statistics Committee one in three individuals has one or more forms of CVD (Rosamond et al., 2007).

The importance of inflammation in the pathogenesis of IHD, such as, acute myocardial infarct (AMI) and coronary artery disease (CAD), has long been established. A large body of evidence suggests that inflammation plays a key role in CVD, however, the mechanisms in the various stages of the pathological process is not completely understood (Carden and Granger, 2000). Inflammation is a complex of defensive mechanisms reacting to the entry of harmful agents into the organism or cells, in order to eliminate or repair damaged cells or tissue and to restore homeostasis. This broad definition indicates that inflammation does not only accompany infectious diseases, but also other conditions causing cell, tissue or organ damage.

The identified risk factors for IHD include both lifestyle and biological factors, such as smoking, high blood pressure, high cholesterol levels, obesity, and diabetes that all appear to exaggerate many of the vascular alterations elicited by ischemia and reperfusion. Diabetes and CVD often appear as two sides of a coin: on one side, diabetes has been rated as an equivalent of CVD, and conversely, many patients with established CVD suffer from overt or incipient diabetes (Ryden et al., 2007). The mortality from AMI is almost increased five-fold in diabetic patients compared with non-diabetics (Hansen et al., 2007) and diabetes and low-grade inflammation is closely related (Flyvbjerg, 2010). Obesity is seen at epidemic proportions all over the world, and is a significant risk factor for, and contributing factor to increased morbidity and mortality, most importantly from CVD and diabetes (Lavie et al., 2009a). Likewise, obesity is also associated with low-grade inflammation and CVD (Yudkin et al., 1999; Bastard et al., 2006).

Although the combination of traditional risk factors such as age, gender, lifestyle, dyslipidemia, hypertension and diabetes are well established for the prediction of cardiovascular mortality (e.g. the Framingham coronary risk score), these algorithms do not

adequately differentiate individuals at moderate risk. Indeed, not all patients with CVD will have conventional risk factors and not all patients with risk factors will develop CVD (Khot et al., 2003). Both biomarkers of early disease and plaque instability have therefore been sought, and the development of new markers to diagnose and prevent CVD is an important public health goal worldwide. However, a recent report showed that the addition of a multi-marker score including 10 new markers to conventional risk factors added only a moderate increase in the ability to grade the risk in the general population (Wang et al., 2006).

Several inflammatory biomarkers have been shown to represent important cardiovascular risk factors, and this review will primarily focus on the complement system, the acute-phase reactant C-reactive protein (CRP), and the antimicrobial peptides: α-defensins. Whether these inflammatory proteins mediate IHD themselves or solely serve as markers of systemic inflammation and cardiovascular risk stratification is still intensely studied.

2. Inflammation and IHD

Growing evidence indicates that IHD is a broad syndrome with multiple pathogenetic and aetiological components, which may not be the same in all patients. Extensive literature supports the role of inflammation in IHD (Mehta and Li, 1999; Ross, 1999). Inflammatory cells, inflammatory proteins and inflammatory responses from vascular cells are all reported to play crucial roles in various stages of a number of CVD (Carden and Granger, 2000). Some of the inflammatory mechanisms of IHD include, among others, endothelial dysfunction, oxidative stress and vascular calcification, that all seems to play an important role for the development of cardiovascular disease.

Although timely restoration of blood-flow after a myocardial ischemic event is essential to prevent irreversible cellular injury, it is widely recognized that the outcome of tissue injury not only depends on the duration of the ischemic event, but also on reperfusion as a critical factor (Khalil et al., 2006). Paradoxically, the reperfusion exacerbates severe tissue damage, especially after longer periods of ischemia. The intensity of the inflammatory reaction in post-ischemic tissue can be so strong that the injury response to reperfusion can be manifested in distant organs (Carden and Granger, 2000).

The ischemia-reperfusion injury (IRI) results in a local and systemic inflammatory response characterized by the production of reactive oxygen species (ROS), leucocyte-endothelial cell adhesion, complement activation, endothelial leucocyte migration, increased micro-vascular permeability and decreased endothelial-dependent relaxation (Carden and Granger, 2000). Within minutes of reperfusion ROS are generated (Cannon, 2005), stimulating the release of cytokines and expression of adhesion molecules on damaged cells in reperfused tissue. Several hours after onset of reperfusion, neutrophils and other inflammatory cells are activated (Frangogiannis et al., 2002; Frangogiannis, 2007) and adhere to the damaged cell membranes (Zimmerman et al., 1990; Vinten-Johansen, 2004) for further enhancement of the inflammatory response. Thus, IRI poses major problems in the clinic, and effective therapies are required.

3. Inflammatory biomarkers

Recent research has been focused on identifying biomarkers, which alone or in combination with other risk markers could be useful in monitoring the treatment and as prognostic markers for future coronary syndromes and cardiac death in patients with IHD.

In 2001, a National Institute of Health working group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention (BiomarkersDefinitionsWorkingGroup, 2001). Biomarkers are traditionally specific proteins circulating in the body fluids that become altered as a consequence of disease progression or the effect of a therapeutic intervention and can be divided into different categories:

- Disease-predictive
- Diagnostic
- Prognostic
- Disease-associated
- Therapeutic efficacy.

A number of inflammatory biomarkers have been associated with cardiovascular diseases. Biomarker measurements can help explain empirical results of clinical trials by relating the effects of interventions on molecular and cellular pathways to clinical responses, thus providing an opportunity for researchers to gain a mechanistic understanding.

3.1 The complement system

The complement system is an innate, cytotoxic host defence that normally functions to eliminate pathogens and facilitates the clearance of damaged tissue and apoptotic cells. However, excessive activation of the system may lead to uncontrolled tissue damage. The relevance of complement activation in myocardial ischemia was already proposed more than four decades ago (Hill and Ward, 1971). The inflammatory mechanisms by which tissue injury after an AMI occurs has not been fully elucidated, but strong evidence obtained from animal models, as well as clinical studies, support the hypothesis of a role for the complement system in IHD (Bjerre et al., 2008).

The complement system is a biochemical cascade, which helps clear pathogens from an organism, and is thus one part of a larger immune system. Three pathways of complement activation have been identified (Figure 1), known as the classical, the alternative and the lectin pathway. The classical pathway is initiated by C1q binding to antibody complexes (Cooper, 1985) whereas the alternative pathway is initiated by spontaneous and direct activation of C3 (Muller-Eberhard, 1988). The lectin pathway is initiated either through ficolin (M-, L- or H-ficolin) (Matsushita et al., 2001; Frederiksen et al., 2005), by pattern recognition of N-acetyl-glucosamine-rich polysaccharides or through mannan-binding lectin (MBL) binding to certain carbohydrate structures (Ikeda et al., 1987; Thiel et al., 1997; Holmskov et al., 2003).

Activation of the complement system promotes three main biological activities (Walport, 2001): I) recruitment of inflammatory cells by anaphylatoxins (C3a, C4a, and C5a), leading to accumulation of activated polymorph nuclear leukocytes directly involved in tissue destruction, II) opsonisation of pathogens for phagocytosis by the generation of C3b, and III) lysis of the pathogen by the generation of a membrane attack complex (MAC, C5b-9) penetrating the cell membrane. The loss of membrane integrity destroys the ability to control the concentration of salt within the cell and the cell is killed due to this osmotic instability. MAC formed in the absence of target membranes binds to S-protein, which

inhibits the membrane-damaging effect, and creates a stable non-lytic soluble C5b-9 form (sMAC, sC5b-9) (Fosbrink et al., 2005).

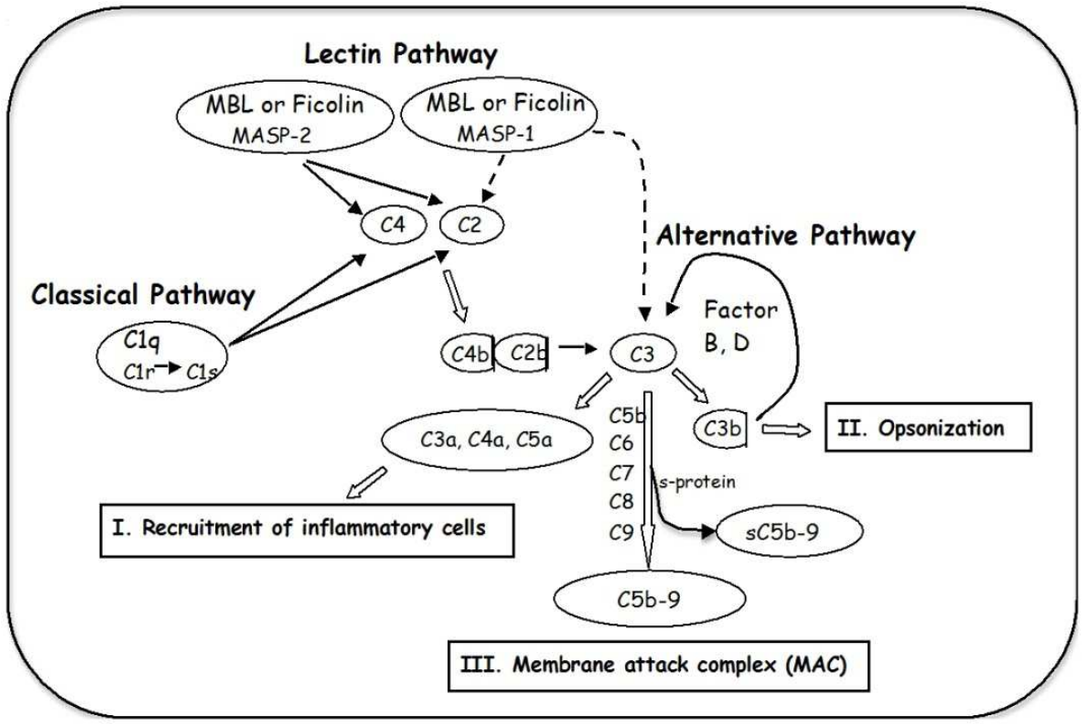

Fig. 1. The complement system can be activated through three pathways, which merge at the cleavage of C3, leading to the effector mechanisms: **I.** recruitment of inflammatory cells, **II.** opsonisation and **III.** the generation of the membrane attack complex (MAC, C5b-9) for cell lysis.

3.1.1 Role of complement in endothelial function

Ischemia and reperfusion are potent activators of the complement system and both clinical and experimental studies in different organs have shown local deposition of complement (Riedemann and Ward, 2003; Arumugam et al., 2004). It has traditionally been assumed that the liver is the source of complement proteins that participate in these events, but complement proteins are produced in several organs of the body, including the heart and the endothelium.

The human heart expresses mRNAs, translated into proteins, for all of the components of the classical complement pathway (Yasojima et al., 1998b). This production is up-regulated in areas of myocardial infarct, and the classical complement pathway was found to be fully activated on injured myocardial tissue. In addition, production of C3 and C9 mRNAs and their protein products was significantly increased in isolated rabbit heart after reperfusion injury, and the production by heart in this circumstance substantially exceeds that of the normal liver (Yasojima et al., 1998a).

Endothelial cells also represent one of the extrahepatic sources of complement components and regulators. Due to the strategic position along the surface of the vessel wall, they may

supply both the circulating blood and the extravascular fluids with these proteins. Most of the information on the production of complement components by endothelial cells has been obtained using human umbilical vein endothelial cells (HUVECs). HUVECs cultured in serum free media were reported to synthesize functional C3, C5, C6, C8, and C9 and assembling of the MAC complex was found, indicating that C7 was produced as well (Johnson and Hetland, 1991). The C7 production was later confirmed (Langeggen et al., 2000) and a small production of C5, C6, C8, and C9 demonstrated by RT-PCR and Northern blot was reported (Langeggen et al., 2001). Activation of the complement cascade leads to the formation of the C5b-9 complex on the cell surface that can cause cell death. However, when the numbers of C5b-9 molecules are limited on host cell membranes, it can activate signalling pathways leading to cell cycle activation and cell survival (Niculescu and Rus, 2001).

The reduction in the capacity of the endothelium to maintain the homeostasis leads to the development of pathological inflammatory processes and vascular diseases. An intact endothelium is a fully biocompatible surface that is not recognized by the complement system. However, blood contact with a damaged endothelium will lead to a certain degree of activation of the defence system. Complement activation results in the formation of several biological active components including C3a, C5a, iC3b, and C5b-9. In addition, to stimulate inflammatory response C5a have been reported to induce production of chemokines and cytokines (Czermak et al., 1999).

3.1.2 Mechanism of complement in IHD

Cardiovascular risk factors (e.g., hypercholesterolemia, hypertension, smoking, diabetes, stress) cause oxidative stress that alters the endothelial cell capacity (Esper et al., 2006; Kyrou and Tsigos, 2007), and thus dysfunction of the endothelium has been implicated in the pathophysiology of different forms of CVD (reviewed by (Endemann and Schiffrin, 2004)). Human endothelial cells have been shown to generate reactive oxygen intermediates in response to hyperglycaemia and lead to dysfunction in type 2 diabetic patients (Bellin et al., 2006). Endothelial dysfunction has been shown to have a prognostic value in patients with chest pain (Neunteufl et al., 2000) and both C-reactive protein (CRP) and C3a were found to be elevated in patients with unstable angina pectoris (Kostner et al., 2006). Elevated plasma levels of C3 was independently associated with MI after accounting for traditional cardiovascular risk factors and CRP in patients with MI, whereas the association of CRP was dependent of C3 (Carter et al., 2009).

A number of *in vitro* studies using HUVECs have shown that under anoxic conditions the endothelial cells become activators of the complement system. Collard and co-workers showed increased MBL, C3, and iC3b deposition after hypoxia/reoxygenation (Collard et al., 2000; Collard et al., 2001). MBL deposition was attenuated in the presence of MBL ligands indicating the presence of MBL neo-epitopes on the surface of the endothelial cells. Apoptotic endothelial cells deposited C1 and C3d, thus activating the complement system (Mold and Morris, 2001). Experimental studies in porcine and rabbits reported that complement activation attenuates endothelium-dependent relaxation (Stahl et al., 1995; Lennon et al., 1996). The role of complement was mediated by the formation of C5b-9, but not through the generation of the anaphylatoxin C3a and C5a.

Hill et al. were the first to report a role for the complement system after an ischemic event in a rat model of AMI (Hill and Ward, 1971). The association between AMI and complement activation was later confirmed in baboons showing deposition of complement factors in the infarcted tissue (Pinckard et al., 1980; McManus et al., 1983). Later, several studies of experimental myocardial I/R showed deposition of complement; C1 (Vakeva et al., 1994), MBL and C3 (Walsh et al., 2005), C4, C5 (McManus et al., 1983; Crawford et al., 1988), C6 (Ito et al., 1996), and C5b-9 (Vakeva et al., 1994). MBL knock-out (KO) mice were protected from heart I/R injury, but when reconstituted with human recombinant MBL, I/R injury similar to that in wild type mice was found. Mice deficient in C2 and factor B (C2/B KO) were also protected form heart I/R injury but no protection was found in C1q or factor D KO mice (Walsh et al., 2005). In a murine model of coronary artery ischemia the involvement of natural IgM antibodies has been linked to both the classical and the lectin pathways (Zhang et al., 2006a; Zhang et al., 2006b). Mice bearing an altered natural IgM repertoire were significantly protected based on the reduced infarct size, limited apoptosis of cardiomyocytes, and decreased neutrophil infiltration.

In addition to direct lytic activity, C5b-9 also directly attenuates endothelium-dependent (i.e., NO-mediated) relaxation (Stahl et al., 1995). Furthermore, C5b-9 is found to play a role in leucocyte activation, adherence and chemotaxis by induction of different cytokines (Kilgore et al., 1996; Vakeva et al., 1998). Also, activation of endothelial NF-kB and the stimulation of expression of endothelial adhesion molecules have been observed. Furthermore, a role for C5b-9 in mediating myocardial apoptosis after ischemia-reperfusion was demonstrated in a model of rat myocardial IRI (Vakeva et al., 1998). We have shown that increased complement activity as indicated by MBL and sC5b-9 levels, was associated with increased risk of cardiac dysfunction in STEMI patients treated with pPCI (Haahr-Pedersen et al., 2009). High plasma MBL and low plasma sC5b-9 was independently associated with increased risk of cardiac dysfunction, likely due to increased complement activity during the ischemic and reperfusion process. The predictive value of low peripheral plasma sC5b-9 may be explained by an accumulation and activation of sC5b-9 in the infarcted myocardium. Furthermore, an elevated plasma sC5b-9 level was found in patients with chronic heart failure due to IHD (Bjerre et al., 2010). In addition, an independent association between sC5b-9, insulin resistance and endothelial dysfunction was found, which may suggest that insulin resistance leading to endothelial activation results in activation of the complement system thus damaging the heart.

3.1.3 Therapeutic inhibition of complement in IHD

Based on the studies discussed above, regulation of the complement system seems to be of great importance. Indeed, several animal studies point to a possible beneficial role of complement depletion in the treatment of post-ischemic MI; reviewed by (Bjerre et al., 2008; Diepenhorst et al., 2009). Unfortunately, clinical studies focused on complement depletion in humans, especially the use of anti-C5 antibodies, primarily Pexelizumab, have largely been disappointing and not proven effective in the setting of CVD, discussed in details elsewhere: (Bjerre et al., 2008; Diepenhorst et al., 2009; Banz and Rieben, 2011).

Although much of the preclinical work and data accumulated in the past years have been positive, the problem with complement-mediated damage in IR-injury was not “easy to fix”. Thus conclusions drawn from animal studies should be extrapolated to the human settings

with caution. It may lie in the fact that complement activation represents only a part of the cascade of attack directed against the vasculature. An exaggerated blockade of the immune system may increase the susceptibility to infections, thus a well-balanced inhibition of the complement activation is required in order to avoid side effects of pharmaceutically induced modification of the immune system. Direct targeting may be the key to future treatment strategies, including targeting of the complement inhibitor to the site of injury by localized intravascular application.

3.2 C-reactive protein

C-reactive protein (CRP), an acute-phase reactant mainly produced by hepatocytes in response to interleukin (IL) 6, is a nonspecific marker of systemic inflammation, and is the most intensively studied inflammatory biomarker in CVD. In addition, a large number of reports have shown that CRP may be implicated in the pathogenesis of many chronic diseases, including diabetes, cancer and alzheimer dementia, and major CVDs, such as, coronary heart disease (CHD), AMI and IHD (Clyne and Olshaker, 1999; Hirschfield and Pepys, 2003; Lavie et al., 2009b). Of note, CRP levels has been associated with the size of the infarct (de Beer et al., 1982).

The concentration of CRP increases rapidly; it may raise hundreds-fold after acute tissue injury or inflammation, and declines rapidly with resolution of the injurious process. In healthy persons, normal CRP levels are generally considered to be < 3 mg/L (Shine et al., 1981).

3.2.1 High sensitive CRP and IHD

In the 1990s, rapid and more precise methods of quantifying CRP was established and CRP levels measured as low as 0.04 mg/L were possible, referred to as high sensitive (hs) CRP (Jaye and Waites, 1997). Low-grade inflammation is found in IHD, and CRP levels are not as increased as compared to other inflammatory conditions. Therefore, a cardiovascular risk scale according to hsCRP levels is recommended by the American Heart Association and Centers for Disease Control and Prevention (Pearson et al., 2003).

Individuals with hsCRP levels;

- <1 mg/L are at lower relative risk for cardiovascular events,
- 1 to 3 mg/L are at intermediate risk,
- >3 mg/L are at higher relative risk.

In the Copenhagen City Heart study, investigating more than 10,000 apparently healthy participants, elevated hsCRP levels were found to be associated with increased risk of IHD. In fact, the risk of IHD was more than doubled (HR=2.2, 1.6-2.9) in individuals with CRP levels above 3 mg/L as compared to individuals with CRP levels below 1 mg/L (Zacho et al., 2008).

3.2.2 Possible links between hsCRP and IHD

Inflammation clearly plays a clinically significant role in the development of CVD. Consequently, as a marker of inflammation, hsCRP has been studied extensively in patients

with CVD. The predictive value of hsCRP has been widely investigated but the results are contradictive. More than 20 large prospective trials have shown that hsCRP is an independent predictor of future cardiovascular events (Ridker, 2007). In the most recent comprehensive meta-analysis studies of cardiovascular risk factors (more than 50 prospective studies with over 160,000 participants, none of them with a history of coronary heart disease or stroke) (Kaptoge et al., 2010), hsCRP was consistently found to be an independent predictor of CVD. However, the association with ischemic vascular disease depends considerably on conventional risk factors and other markers of inflammation. A critical review by Levinson and colleagues argues that hsCRP is poor discrimination over a wide range of values when used in conjunction with risk factors for lipoprotein lipids, hypertension, metabolic syndrome, and diabetes (Levinson et al., 2004). Danesh and colleagues published a study, performed in a high-risk population with nonfatal myocardial infarct, which questioned the role of CRP in the assessment of cardiovascular risk. However, hsCRP maintained a predictive value after adjustments for smoking and hypertension (Danesh et al., 2004).

A panel of multiple biomarkers, 10 biomarkers in total including hsCRP, was used for prediction of death and major cardiovascular event in more than 3000 participants of the Framingham Off-spring study followed for 10 years (Wang et al., 2006). As a single marker, hsCRP predicted risk of death but no major cardiovascular events after adjusting for other biomarkers, and individuals with high multimarker scores had almost 4 times as great a risk of death. Nonetheless, the authors concluded that the use of contemporary biomarkers adds only moderately to standard risk factors. In the Women's Health Study, CRP was found to be additive to LDL-cholesterol in predicting future CVD in healthy American women (n=28,263 apparently healthy postmenopausal women) (Ridker et al., 2000a). Of the 12 markers measured (including hsCRP and IL-6), hs-CRP was the strongest uni-variant predictor of cardiovascular events, and the only plasma marker predicting risk after adjustment in a multi-variant analysis. This was confirmed in a large meta-analysis of hsCRP as a single biomarker in patients with stable CAD, but the authors concluded that a routine measurement of CRP should not be recommended as a single prognostic biomarker (Hemingway et al., 2010). However, in combination with other biomarkers, hsCRP seems to add significant information to traditional risk factors for CVD, and the value of adding hsCRP to standard risk equations was noted in separate cohorts of asymptomatic (middle-aged or elderly) men and women (Lavie et al., 2009b).

In the Caerphilly Prospective Heart Disease Study, Mendall and colleagues, showed a significant and positive association between CRP and incidents of IHD, not affected by ischemia history (Mendall et al., 2000). However, after adjustment of lifestyle risk factors (such as smoking and obesity) only the association with all-cause mortality remained significant. Plasma hsCRP was not found as an independent predictor of long-term IHD risk in a 13-year-follow-up study of men with no previous history of IHD (n=1982) (St-Pierre et al., 2005). The authors thus concluded that neither CRP nor the systemic inflammation appeared to have a direct role in the development of IHD. But the association of hsCRP with IHD may be that CRP levels are raised non-specifically by a variety of exposures that are themselves implicated in the pathogenesis of IHD (Figure 2).

A connection between CRP and activation of the complement system was proposed more than 35 years ago, after the discovery of aggregated or ligand-complexed human CRP was

able to bind to C1q and activate the classical pathway (Kaplan and Volanakis, 1974; Siegel et al., 1974; Jiang et al., 1991), thus mediating the functions summarized in Figure 1. CRP was later found to co-localize with activated complement fragments in atherosclerotic lesions (Bhakdi et al., 1999; Yasojima et al., 2001) and CRP-mediated complement activation in the arterial wall may be considered as an important pathogenic feature in CVD.

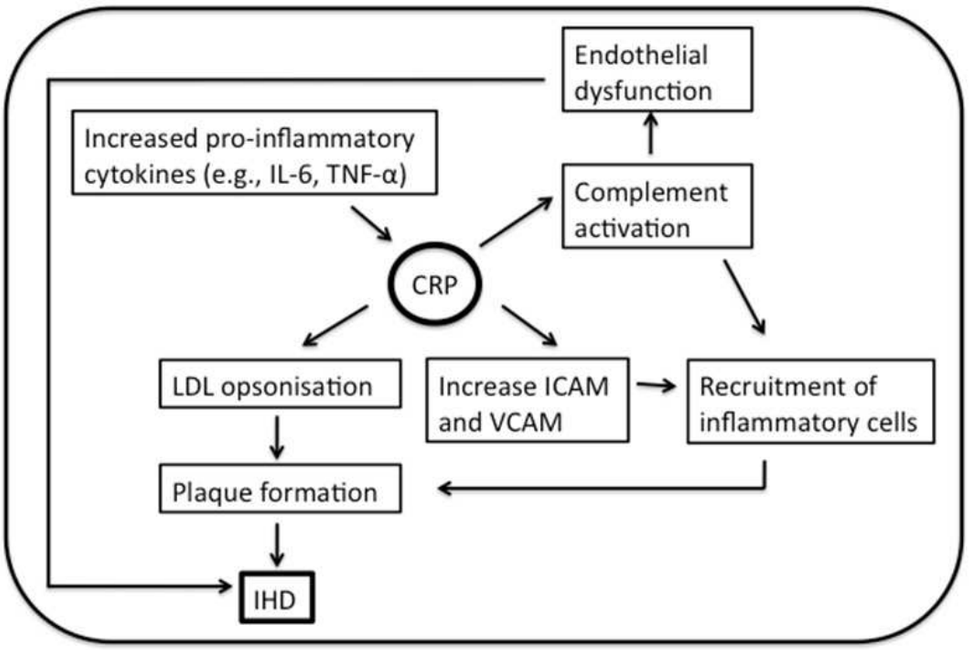

Fig. 2. Schematic depiction of potential mechanisms of CRP involvement in the pathogenesis of IHD.

A number of pro-inflammatory cytokines have been shown to play roles in the process leading to IHD, but IL-6, in particular, appears to have a central role, e.g. by stimulating the liver to increase the CRP production. However, even with a strong correlation between IL-6 and CRP, IL-6 was found to predict future AMI in a group of apparently healthy men (Ridker et al., 2000b).

CRP binds to apolipoprotein-containing lipoproteins like LDL (de Beer et al., 1982) and very low-density lipoprotein (VLDL) (Rowe et al., 1984), which may be of considerable importance in the pathogenesis of CVD. More recent studies revealed that CRP preferentially binds to modified forms of LDL; enzymatically modified LDL (Bhakdi et al., 1999) and oxidized LDL (Chang et al., 2002), and CRP was reported to mediate LDL uptake by macrophages (Zwaka et al., 2001). Opsonisation of LDL lead to monocyte infiltration and the formation of foam cells resulting in plaque formation and eventually IHD.

CRP was found to cause expression of cell adhesion molecules with a significant dose-dependent expression of ICAM-1, VCAM-1 and E-selectin in human umbilical vein endothelial cells (HUVEC) following CRP stimulation (Pasceri et al., 2000). Furthermore, production of chemokines monocyte chemoattractant protein-1 (MCP-1), which plays an important role in recruitment of monocytes into the vessel wall and thus the formation of plaques, was directly induced by CRP (Pasceri et al., 2001).

3.2.3 Is CRP a potential therapeutic in prevention of IHD?

As described in the previous section, CRP is reported to be associated with a wide range of biomarkers and risk factors of IHD. Thus, overestimating of the true effect of hsCRP on CVD risk, because of confounding effects, constitute a challenge. Support for a role of CRP in the pathogenesis of CVD comes primary from epidemiologic studies, which in general have observed an association between elevated plasma CRP and cardiovascular events.

Although hsCRP may not be the ideal marker of IHD, it seems to be very reliable, and hsCRP is a simple, non-invasive, commercially available, inexpensive and reproducible biomarker. CRP measurement has a lot of advantages; the protein is stable and the concentration is not subjected to time-of-the day variations (Meier-Ewert et al., 2001). Thus, determination of baseline hsCRP for cardiovascular risk prediction may be performed without concern for diurnal variation.

Availability of drugs to block CRP binding and its effects *in vivo* would provide a powerful tool for determining whether CRP is just a marker or does indeed participate in the pathogenesis of CVD complications. Griselli and colleagues (Griselli et al., 1999) showed that injection of human CRP in a rat model of AMI enhanced the infarct size, of note rat CRP does not activate rat complement, whereas human CRP activate both rat and human complement. However, in vivo complement depletion, by cobra venom factor, completely abrogated this. A similar effect was later found by administration of a specific synthetic CRP-inhibitor, 1,6-bis(phosphocholine)-hexane, which reduced the infarct size and thus provided promising results for therapeutic inhibition of CRP (Pepys et al., 2006).

Statins lower the levels of LDL-cholesterol and CRP. Ridker and colleagues showed, in a sub-population (n= 3745) derived from the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) study, that patients with low hsCRP levels after statin treatment had improved cardiovascular outcome (Ridker et al., 2005). Patients in whom statin therapy resulted in hsCRP levels below 2 mg/L overall had better clinical outcomes regardless of the LDL-cholesterol level achieved. Recently, a study JUPITER: Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (n=17802), of healthy individuals without history of CVD but hsCRP > 2 mg/L and low LDL concentration, showed beneficial effect of Rosuvastatin (Ridker et al., 2007; Kones, 2010; Ridker et al., 2010). The study was terminated due to a great risk-reduction in AMI, CVD and death from cardiovascular causes, indicating that part of the statin effect may be mediated through lowering CRP.

Aside from whether measurement of CRP is useful in assessments of CVD, studies are needed to help determine if CRP is a mediator or a marker of CVD. Zacho et al. showed that genetic variants that are associated with a lifelong increased plasma CRP level are not associated with increased risk of IHD (Zacho et al., 2008), indicating CRP as a marker but not as an actual contributor.

3.3 Anti-microbial peptides

The involvement of polymorphonuclear neutrophils (PMNs) in the pathogenesis of CVD has received relatively little attention, despite their presence in the atherosclerotic plaques (Quinn et al., 2008). PMN counts have been reported as independent risk factors for

cardiovascular outcome (Madjid et al., 2004) and during inflammation PMNs are activated in order to enhance the inflammatory response and releases antimicrobial peptides into circulation.

Anti-microbial peptides are polypeptides of fewer than 100 amino acids. The human innate immune system includes two main families; defensins and cathelicidins. Defensins, also termed human neutrophil peptides (HNP) as they are found in large amounts in neutrophils, are secreted during phagocytosis as a first line of defence against invading organisms (Ganz, 2003).

3.3.1 α-defensins

Three different classes of defensin are identified in mammals, two of which are found in humans; α- and β-defensin (Ganz, 1987). The human family of α-defensins are composed of 3 closely related gene products, also referred to as human neutrophil peptides 1-3 (HNPs-1-3) and HNP4, HNP5 and HNP6. The α-defensins are cationic peptides, cysteine-rich peptides of approximately 3 kDa and are normally sequestered in the granules of neutrophils, where they constitute 5% of the total cellular protein and are involved in the intracellular killing of prokaryotic organisms (Ganz, 1987). Under normal conditions, only small amounts of α-defensins (nanomolar range) are found in plasma. However, during inflammatory reactions, α-defensins are released extracellularly, which could exert harmful effects on host cells. Increased plasma concentrations of α-defensins have been described in several inflammatory diseases (Ganz, 2003; Klotman and Chang, 2006; de Leeuw and Lu, 2007).

3.3.2 Possible link between α-defensins and IHD

The cationic nature of the α-defensins prefers the negatively charged phospholipids of the bacterial membrane as target and avoids the more neutral charged mammalian cell membrane. However, both a direct and an indirect chemoattracting role of α-defensins has been reported for a number of cells (Oppenheim et al., 2003). In addition, α-defensin was found to promote oxidative stress and induces endothelial dysfunction by reducing the endothelium-dependent relaxation in porcine coronary arteries (Kougias et al., 2006). This effect is associated with increased superoxide radical production and decreased eNOS expression. Also, α-defensins is capable of forming complexes with C1q and MBL, thus playing a role in the regulation of both the classical and the lectin pathway of complement activation (Groeneveld et al., 2007).

Localization of α-defensins were analysed by the use of immunohistochemical staining of coronary arteries from patients with severe CVD or normal donor heart tissue (Barnathan et al., 1997). Of interest, α-defensin was found most prominently in association with intima smooth muscle cells of both normal or atherosclerotic vessels. α-defensins has been reported as an atherogenic agent by enhancing and promoting stable complexes with LDL particles, thus stimulating the binding to endothelial and smooth muscle cells (Higazi et al., 1997). In addition, in human cerebral vessels obtained during autopsy, α-defensin and LDL co-localized primary within the atherosclerotic areas, and the staining intensity correlated with the severity of the disease. The authors hypothesize that the small α-defensins may rapidly cross the endothelial barrier and gain access to sub-endothelial matrix and affording the binding of LDL

and a complex relative resistant to degradation. Retention of LDL in the arteries may predispose to pro-atherogenic modifications, such as, oxidation and internalization by foam cells. In addition, an independent negative relationship between high-density lipoprotein (HDL) has later been described (Saraheimo et al., 2008). Furthermore, α-defensins were found to inhibit the fibrionolytic activity by binding to tissue plasminogen activator molecule (Kougias et al., 2005). In a small study of patients undergoing elective coronary artery catheterization, an accumulation of α-defensin in the human skin was described and the accumulated amount correlated with the severity of coronary artery disease (Nassar et al., 2007). Of note, no correlation between CRP and α-defensin was found in this study.

Chronic low-grade inflammation is a hallmark of obesity and diabetes, and has been causally linked to the development of premature CVD. In a group of type-1 diabetic patients, with a 10-year-follow-up-period of cardiovascular end-points, elevated baseline plasma α-defensin levels were an independent predictor for cardiovascular morbidity and mortality (Joseph et al., 2008). In a recent study, the risk of cardiovascular mortality was significantly increased with elevated plasma α-defensin levels in patients admitted for elective lower extremity artery surgery (Urbonaviciene et al., 2011). Surprisingly, patients with high α-defensin levels combined with high hs-CRP levels had a five time increased risk of cardiovascular death compared to patients in whom only one or none of the peptides was elevated.

4. Perspectives

Inflammatory biomarkers may have prognostic value for future cardiovascular risk stratification among individuals with high risk or a history of IHD, but they may also in particular be useful in apparently healthy individuals who might be at higher risk than estimated by the traditional risk factor scores. Using a biomarker profile that covers various aspects of the complex pathophysiology of IHD may increase the rational basis for cardiovascular risk assessment. As decribed above, a multiple inflammatory role of the combination of complement activation, CRP, LDL and α-defensins may participate in the pathogenesis of IHD and other CVD.

With the emergence of novel biomarkers for inflammation and vascular damage it may be possible to characterize different contributions of each of these major mechanisms to short- and long-term prognosis following CVD. Hopefully, patients may benefit from different therapeutic strategies depending on their personal biomarker profile in the future. So far, however, results about which biomarkers are the most suitable for diagnosis or prognosis of IHD remain conflicting, and further research within this field is needed.

5. References

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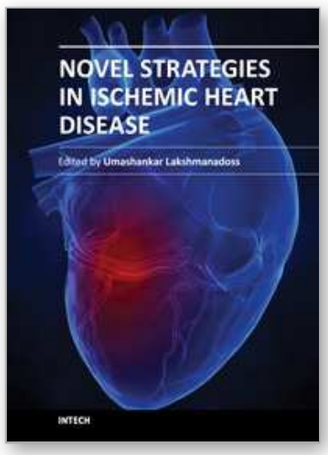

Novel Strategies in Ischemic Heart Disease

Edited by Dr. Umashankar Lakshmanadoss

ISBN 978-953-51-0184-0
Hard cover, 450 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

The first edition of this book will provide a comprehensive overview of ischemic heart disease, including epidemiology, risk factors, pathogenesis, clinical presentation, diagnostic tests, differential diagnosis, treatment, complications and prognosis. Also discussed are current treatment options, protocols and diagnostic procedures, as well as the latest advances in the field. The book will serve as a cutting-edge point of reference for the basic or clinical researcher, and any clinician involved in the diagnosis and management of ischemic heart disease. This book is essentially designed to fill the vital gap existing between these practices, to provide a textbook that is substantial and readable, compact and reasonably comprehensive, and to provide an excellent blend of "basics to bedside and beyond" in the field of ischemic heart disease. The book also covers the future novel treatment strategies, focusing on the basic scientific and clinical aspects of the diagnosis and management of ischemic heart disease.

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