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Inflammatory biomarkers of coronary heart disease

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1. ABSTRACT

Coronary heart disease (CHD) is one of the leading causes of death worldwide. CHD is characterized by formation of arterial plaques which are mainly comprised of lipids, calcium and inflammatory cells. These plaques narrow the lumen of coronary arteries leading to episodic or persistent angina. Rupture of these plaques leads to the formation of thrombus, which as a result of cessation of blood flow, causes myocardial infarct and death. CHD is exacerbated by risk factors including obesity, diabetes mellitus, and hypertension. Diagnosis is established by the level of blood cholesterol, triglycerides and lipoproteins Inflammation is considered significant in the pathogenesis of CHD and for this reason, severity and prognosis of CHD is assessed by the levels of inflammatory biomarkers, including interleukin-6, C-reactive protein (CRP), complement, CD40 and myeloperoxidase (MPO).

2. INTRODUCTION

CHD is more common in males than females and is characterized by stable or unstable angina, heart failure, irregular heart beats. CHD can lead to myocardial infarction, which is the leading cause of death in developed countries (1-2, 6–10). CHD was the underlying cause of >8.14 million deaths in 2013, a dramatic increase from 5.2 million CHD-associated deaths reported in 1990 (3–5). CHD affects individuals at any age, but becomes significantly more common with age, tripling in incidence in each decade of life. The underlying mechanism of CHD is atherosclerosis of cornonary arteries. Risk factors for CHD include high blood pressure, obesity, diabetes mellitus, increased blood cholesterol, smoking, lack of exercise, poor diet, excessive consumption of alcohol, and depression (11–14). Diagnosis is established by the level of blood cholesterol, triglycerides and lipoproteins (15–16). CHD is characterized by plaques that develop from accumulation of fatty deposits, inflammatory cells and calcification leading to stiffening of arteries (17–19). Gradual narrowing of the lumen leads to ischemia which may cause ventricular arrhythmia and upon closure of the lumen leads to ventricular fibrillation to infarction (20-22).

3. CHARACTERISTICS OF ATHEROSCLEROSIS

Atherosclerosis, characterized by hyperlipidemia and inflammation, is a leading cause of morbidity and mortality due to peripheral vascular diseases (23–24). “Atherogenesis” refers to the development of atheromatous plaques, characterized by arterial remodeling as a result of subendothelial

accumulation of fatty deposits. An atheromatous plaque develops over several years through a complex series of cellular events that occur within the arterial wall in response to various local factors (25).

Atherogenesis results from endothelial damage by leukocytes infiltrating the arterial wall and fatty deposits (e.g., monocytes, basophils) (26–28). The primary "driver" of this process is considered to be oxidized lipoproteins within the vascular wall. Marginally normal or elevated glucose concentration in blood is also considered to play a major role in this process). The low-density lipoprotein (LDL) in plasma invades the endothelium and get oxidized by a complex set of biochemical reactions involving enzymes (e.g., Lp-LpA2) and free radicals (33–35). Although, the LDL is considered to be a risk factor for the development of cardiovascular disease, its direct role is not clarified since fatty streaks may disappear from the plaques (30–32). Early atherogenesis is characterized by adherence of circulating monocytes to the endothelial lining. These subsequently migrate to the sub-endothelial space, and upon activation convert to tissue macrophages (29). Chemokines, such as monocyte chemoattractant protein (MCP)-1, recruit monocytes from the bloodstream to arterial walls and platelets adhere to the area of insult (36–37). This phenomenon may be promoted by induction of redox signaling factors, such as E-selectin, P-selectin, vascular cell adhesion molecule (VCAM)-1, as well as macrophage colony-stimulating factor (M-CSF) secreted by endothelial cells and smooth muscle cells which are stimulated by oxidized LDL. The macrophages phagocytose and ingest oxidized LDL and ultimately convert to large "foam cells" which as a result of numerous internal cytoplasmic vesicles and high lipid content appear as fatty streaks under microscope (38-40). Ultimately, the foam cells die, further propagating the inflammatory process. Moreover, in response to cytokines secreted by damaged endothelial cells, smooth muscle cells proliferate and migrate from the tunica media into the intima and covert the fatty streaks to a fibrous capsule (41–43).

4. INFLAMMATION CASCADE INVOLVED IN THE DEVELOPMENT OF ATHEROSCLEROSIS AND CHD

Disruption of normal endothelial function favors vasoconstriction through decreased synthesis of NO and increased synthesis of endothelin I and angiotensin II (44–46). Activation of endothelial cells is mediated by the pro-inflammatory cytokines, interleukin (IL)-1β and tumor necrosis factor (TNF)-α. The activation of endothelial cells upregulates E-selectin, VCAM-1 and intercellular adhesion molecule (ICAM)-1, which facilitates the binding of monocytes and T-cells to the endothelium (47–49).

Migration of inflammatory cells into the intima is promoted by chemokines (including MCP-1), (50). Monocytes once within the intima, are transformed into macrophages that express "scavenger receptors" for modified lipoproteins, such as oxidized LDL (51). Cluster of differentiation (CD)36 and oxidized lectin-like low-density lipoprotein receptor (LOX)-1 allow internalization of oxidized LDL, and promote conversion of macrophages to foam cells. These cells secrete various inflammatory mediators (IL-1β, IL-6, TNF-α) and chemokines (MCP-1) that stimulate expression of endothelial cell adhesion molecules and cause an ongoing leukocyte accumulation in the intima. Recruitment of additional immune cells into the intima, in particular T-lymphocytes and mast cells, contributes to the extravascular inflammatory processes. T-cells within the intima are predominantly T-helper (Th1) cells. These cells secrete cytokines, including interferon (IFN)-γ, IL-2 and TNF-α, and enhance the local inflammatory responses. Mast cells are also recruited to the site of macrophage and T-cell accumulation. These cells secrete various cytokines and chemokines, promote ongoing inflammation and contribute to the formation of foam cells by stimulating with aggregated LDL aggregation which are phagocytosed by macrophages (52–53).

With the production of inflammatory stimuli as well as migration and proliferation of vascular smooth muscle cells (VSMCs) within the intima, the plaques increase in complexity over time (54). VSMCs synthesize and secrete collagen, resulting in expansion of the extracellular matrix (ECM) and formation of a fibrous cap. Additionally, VSMCs secrete cytokines and chemokines that promote recruitment of leukocytes, increase endothelial permeability, and contribute to the expansion of atherosclerotic plaques. Cytokines also stimulate the expression of the coagulation factors such as tissue factor (TF) by macrophages, endothelial cells and VSMCs. TF acts as a potent initiator of the coagulation cascade via interaction with plasma coagulation factor VII, resulting in generation of thrombin and consequent activation of platelets and conversion of fibrinogen to fibrin . Binding of CD40 ligand (CD40L) to CD40 receptors on activated T-cells, endothelial cells, VSMCs, and macrophages that subsequently express TF. Excessive accumulation of oxidized LDL in macrophages ultimately leads to their demise and release of lipids and TF from these cells creates a necrotic plaque (55–56).

5. PREDICTIVE INFLAMMATORY BIOMARKERS IN CHD

The inflammatory mediators contributing to atherosclerosis and CHD are synthesized and secreted in the vicinity of plaques and influence the disease progression.

5.1. C-reactive protein (CRP)

Low plasma level of CRP is an indicator of health while high levels is an indication of inflammation in CHD. After a cardiovascular event, CRP levels may be useful in short-term prognosis and long-term risk assessment of the disease. CRP is an annular, pentameric protein found in plasma that increases in response to inflammation. The protein binds to phosphocholine which is expressed on the surface of dying or dead cells. This interaciton activates the complement system, and promotes phagocytosis by macrophages that clear necrotic and apoptotic cells at the site of injury. CRP is mainly synthesized in the liver, but is also produced by leukocytes and adipocytes (57). This protein has been shown to be a marker of systemic inflammation, injury, infection, and other inflammatory stimuli (58). Serum level of CRP is stable in the absence inflammation, however, its level is increased by hepatocytes by IL-6 stimulation. Patients with elevated basal levels of CRP are at increased risk of diabetes, hypertension and cardiovascular disease (59).

Circulating levels of CRP increase in response to several cardiovascular risk factors, such as obesity, smoking, high blood pressure, increased heart rate, as well as serum levels of triglycerides, apolipoprotein B, fasting blood glucose, fibrinogen and high-density lipoprotein (HDL) cholesterol. In addition to its role as a powerful inflammatory marker, increasing evidence suggests that CRP participates directly in atherogenesis (60–61). Serum levels of CRP are elevated in patients with acute and chronic coronary heart disease and correlate with the plaque composition as well as in patients who suffer from complications of heart failure (62). A large-scale prospective study has documented a strong association between the predictive power of CRP and CHD risk with CRP levels being a more reliable biomarker of cardiovascular disease than LDL-cholesterol (63). However, a combination of CRP and LDL-cholesterol levels has a higher prognostic value than each factor alone.

5.2. Complement

Complement is a component of the innate immune system that with antibodies and phagocytic cells clear pathogens. By and large, the proteins of the complement system are synthesized by hepatocytes. A significant amount of complement is also produced by tissue macrophages, blood monocytes, and epithelial cells of the genitourinary and gastrointestinal tracts. Complements are activated through a classical as well as an alternate pathway. Activation of the classical complement pathway is, in general, initiated by binding of antibody to C1 (comprising C1q, C1r and C1s subunits) *via* the C1q subunit. This action induces a conformational change and promotes C4 cleavage by C1s. Subsequently, C2 forms C4b2b C3 convertase, which cleaves C3 to C3a and C3b. Factors B or D and properdin are proteins specific for the alternative complement cascade that give rise to C3 convertase, C5 convertase and C5b-9 (64–65). C5 convertase activates the common pathway of the complement cascade and leads to the generation of C5b-9 (“membrane attack complex”). However, the alternative pathway is continuously activated at a low level as a result of spontaneous C3 hydrolysis due to breakdown of the internal thioester bonds. Unlike other pathways, the alternative pathway does not rely on binding of antibodies to pathogens. C3b is generated from C3 by a C3 convertase enzyme complex in the fluid phase, and is inactivated rapidly by Factors H and I. C3b-like C3 is a product that is produced as a result of spontaneous cleavage of the internal thioester. In contrast, when the internal thioester of C3 reacts with a hydroxyl or amino group of a molecule on the surface of a cell or pathogen, C3b covalently binds to the surface and is protected from inactivation by factor H. Surface-bound C3b may bind factor B to form C3bB. In the presence of factor D, this complex is cleaved to Ba and Bb. Bb remains associated with C3b and forms C3bBb complex which represents the stabilized form of C3 convertase. This complex is further stabilized via binding to oligomers of factor P. C3bBbP acts enzymatically to cleave significantly more C3, some of which becomes covalently attached to the same surface as C3b. The newly bound C3b recruits more B, D and P, and amplifies the complement activation to a significant extent (66–67). Depending on the cell type, endogenous complement regulatory proteins, such as CD35, CD46, CD55 and CD59 limit the extent of the activtion of complement pathway.

Because inflammation is an integral part of pathogenesis of CDH, the complement system is integral to the development of the disease. Activated complement components are observed even in early atherosclerotic lesions, and frequently co-localize with CRP in plaques in the vicinity of modified lipoproteins (68-69). CRP is one of the activators of the classical complement cascade that interacts with C1q. Complement pathway is also activated through an alternative pathway that involves modified lipoproteins, which their effects are enhanced by CRP (70). Upon activation of the complement cascade by either pathway, various complexes and cleaved products of complement pathway promote the formation and progression of plaques. Two cleavage products of complement activation, C3a and C5a, are anaphylatoxins, and are potent mediators of inflammation and chemotaxis. C5a, in particular, is highly chemotactic for monocytes and T-lymphocytes, and promotes infiltration of monocytes into the ECM (71). C5a also stimulates leukocyte synthesis of IL-6, IL-1β and TNF-α and further enhances the inflammatory process (72). Both C3a and C5a can

induce degranulation of mast cells, and progressively contribute to the destabilization of plaques. C5a has been shown to promote the synthesis of plasminogen activator inhibitor (PAI)-1 and inhibits fibrinolysis in mast cells (73). The C5b-9 complex is relatively ineffective in lysing nucleated cells but exerts several non-lytic effects, including promotion of release of cytokines and chemokines from VSMCs, further enhancing accumulation of monocytes and T-cells within the ECM. Upon plaque rupture, C5b-9 leads to exposure of cell membranes, promoting assembly of the prothrombinase complex which potentiates formation of TF-induced thrombin (74–75).

5.3. IL-6

IL-6 is a circulating cytokine that is secreted largely by activated macrophages and lymphocytes (76). The biologic activities of IL-6 are initiated upon its binding to a high-affinity receptor complex consisting of two membrane glycoproteins. The 80 kDa ligand binding receptor (IL-6R) binds IL-6 with low affinity, whereas a second 130 kDa signal-transducing component (gp130) is required for high-affinity binding of gp80-bound IL-6 (77). gp-130 does not interact with or bind free IL-6. A ~50 kDa soluble form of IL-6R is generated from proteolytic cleavage of membrane-bound IL-6R (78). Recombinant soluble IL-6R interacts with IL-6 in solution and augments the activity of IL-6 as a result of binding of the IL-6:IL-6sR complex to membrane-bound gp130. Elevated levels of IL-6 are associated with increased production of IL-6R. Binding and interaction of IL-6 with its receptors, gp130 and IL-6R proteins, leads to the formation of an activated signaling complex (79). These complexes bring together the intracellular regions of gp130 to initiate a signal transduction cascade through janus kinases (JAKs) and signal transducers and activators of transcription (STATs) (80). More recently, a soluble form of the gp130 receptor has been shown to be antagonistic in IL-6 signaling (81). However, the regulatory mechanisms of soluble receptor release and its functional significance are not yet clearly understood.

Obesity contributes to increased IL-6 levels and a proportion of circulating IL-6 is thought to be produced by subcutaneous adipose tissue in humans. Thus, serum level of IL-6 is correlated with body mass index (BMI) and is correlated with insulin resistance (82). Inflammation and production of IL-6 and other inflammatory proteins may be key contributing mechanisms to the development of obesity, diabetes and CHD (83–84). IL-6 along with other inflammatory proteins are systemic mediators of acute response to infection and inflammation (85). Apolipoprotein E $(ApoE)^{-/-}$ mice on a high-fat diet responded to stress by elevation of serum IL6 levels and showed an enhanced plaque formation (86). Increased IL-6 levels have also been reported in mice deficient in mast cells (87). As one of the key mediators in the inflammatory process, IL-6 may act upstream of CRP and complement components and contributes to a pro-coagulant state through upregulation of fibrinogen expression. The value of IL-6 as a predictor of CHD is limited due to its labile nature (half-life of ~5 min). However, other inflammatory predictors of CHD, such as CRP and complement C3, may act as surrogates for enhanced secretion of IL-6 (88). Clearly, IL-6 levels are elevated in systemic infection and inflammation, which may contribute to increased CRP in at-risk CHD patients.

5.4. Serum amyloid A (SAA)

SAA is a major protein produced in large quantities during the acute-phase response. Increased concentration of SAA in the blood is a marker of active inflammation. SAA activates multiple receptors, including toll-like receptors (TLRs), the scavenger receptor SR-BI, and the adenosine triphosphate receptor P_2X_7 (89). Recent studies have shown that SAA activates transcription factors, including the nuclear factor-kappa B (NF-κB) pathway (90). It is postulated that activation of the NF-κB pathway promotes release of pro-inflammatory factors expressed by M2 macrophages. These functional properties distinguish SAA from the well-characterized inflammatory factors, such as lipopolysaccharide and TNF-α, suggesting a role in maintaining homeostasis during inflammation. Elevated SAA were correlated with severity of CHD as assessed by angiography and increased risk of complications and has been used to predict increased risk of mortality in CHD patients (91-92). However, measurement of SAA level after myocardial infarction was not correlated with an increased risk of recurrent cardiovascular events (93).

5.5. The CD40/CD40 Ligand (CD40L) system

CD40 is a type of I transmembrane protein receptor and is a member of the TNF superfamily (94). CD40 exists as a dimer that, after binding of CD40L, is trimerized. CD40 is expressed mainly on B-cells and in other immune cells, epithelial cells, neuronal cells, fibroblasts, vascular-wall cells and platelets (95-96). CD40 is induced by pro-inflammatory stimuli, such as TNF-α and IFNs. CD40 is usually upregulated 6–12 hr after an initial stimulation, and remains on the cell surface for 24–72 hr. CD40L is shed in a truncated soluble form (sCD40L) which then binds CD40. Transmembrane CD40L on the platelet surface is cleaved into a 18kDa fragment, and provides the major source of circulating sCD40L. CD40L and sCD40L interact with CD40 in a range of cell types, leading to various inflammatory processes.

Increasing evidence suggests that the CD40-CD40L complex plays a pivotal role in the

pathogenesis of atherosclerosis. In 1998, an anti-CD40L antibody was shown to markedly reduce the size and lipid content of atherosclerotic lesions (97). Subsequent studies reported significantly decreased plaque in CD40L knockout ApoE$^{-/-}$ mice (98). CD40L by stimulation of endothelial cells to express adhesion molecules accelerates adhesion of macrophages to these cells. Circulating level of sCD40L is an important marker for existence of cardiovascular disease, including atherosclerosis and acute coronary syndromes (99–100). sCD40L upregulates scavenger receptor type A and CD36, stimulates the levels of adipocyte enhancer-binding protein 1 and cholesterol efflux, activates NF-κB in macrophages, promotes formation of foam cells via CD40 ligation and enhances lipid deposition (56). Contribution of CD40 to the formation of foam cells has been established by disruption of binding of CD40 and CD40L with small interfering RNA or blockage of anti-CD40 antibody (56, 101).

5.6. Myeloperoxidase (MPO)

MPO is a peroxidase, which most abundant in leukocytes, induces free oxygen radicals (102). This lysosomal protein is stored in azurophilic granules of neutrophils and released into the extracellular space by degranulation. Recent studies have reported an association between elevated levels of MPO and severity of CHD (103). In patients with CHD, MPO produced by neutrophils is a marker for instability of plaques. Particularly in patients with stable and unstable angina pectoris, Yunoki *et al.* observed a significant inverse correlation between levels of plasma MPO and paraoxonase-1 bound to HDL (104) These findings suggest that a mismatch between pro- and anti-oxidants contributes to progression of coronary plaque instability.

6. CONCLUSIONS

Advances in our understanding of the mechanisms underlying atherosclerosis have implicated inflammation as a central contributor to the initiation and progression of this disease including CHD. Inflammatory biomarkers may have prognostic value for predicting cardiovascular risk in high risk patients. Traditional biomarkers, such as CRP, complement and IL-6 as well as MPO can be used for detection and assessment of severity of CHD. A combination of biomarkers are utilized in clinical diagnosis and in prognosis of CHD.

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Abbreviations: ApoE, apolipoprotein E; BMI, body mass index; CD40L, CD40 ligand; CHD, coronary heart disease; CRP, C-reactive protein; ECM, extracellular matrix; ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon-gamma; IL, interleukin; JAKs, janus kinases; LDL, low-density lipoprotein; MCP-1, monocyte chemoattractant protein-1; M-CSF, macrophage colony-stimulating factor; MPO, myeloperoxidase; NF-κB, nuclear factor-kappa B; NO, nitric oxide; SAA, serum amyloid A; STATs, signal transducers and activators of transcription; TF, tissue factor; TLRs, toll-like receptors; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1; VSMCs, vascular smooth muscle cells

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