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Inflammatory biomarkers of coronary heart disease

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1. ABSTRACT

Coronary heart disease (CHD), characterized by inflammation and accumulation of plaques mainly comprised of lipids, calcium and inflammatory cells in the walls of coronary arteries. CHD is exacerbated by specific cardiovascular risk factors, such as obesity, diabetes mellitus, and hypertension. The current review focuses on the critical role of traditional inflammatory biomarkers, including interleukin-6, C-reactive protein (CRP), complement, CD40 and myeloperoxidase (MPO), in the pathogenesis of CHD.

2. INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death in developed countries, which is associated with stable or unstable angina, myocardial infarction and sudden coronary death (1-2). Records show that 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 can affect individuals at any age, but becomes significantly more common with progressive age, tripling in incidence with each decade of life. Males are affected more often than females (6-8).

CHD is usually appeared as heart attack at first time, and is complicated with heart failure or irregular heartbeat (9-10). The underlying mechanism is arteries atherosclerosis in the heart. Risk factors for CHD include high blood pressure, obesity, diabetes mellitus (DM), increased levels of cholesterol in blood, smoking, lack of exercise, poor diet, excessive consumption of alcohol, and depression (11-14). Thus, atherosclerosis could be assessed by testing cholesterol, triglycerides and lipoproteins levels in blood (15-16). Usually, atherosclerosis in smooth elastic lining of the coronary artery leads to CHD.

In the occurrence of atherosclerosis, the arterial lining becomes hardened and stiffened. And the plaque is formed by calcium and fatty deposition and inflammatory cells infiltrating, which is significant for arteries stiffness in the early stage of coronary arteriosclerosis (17-19). As atherosclerosis develops, myocardial ischemia leads to myocardial hypoxia and finally myocardial death, which is so called “myocardial infarction” (20). Chronic and serious stenos in coronary arteries may cause transient ischemia and then ventricular arrhythmia, which could result in ventricular fibrillation and even death (21, 22).

3. CHARACTERISTICS OF ATHEROSCLEROSIS

Atherosclerosis, the leading cause of peripheral vascular diseases, is characterized by hyperlipidemia and inflammation (23-24). “Atherogenesis” refers to the development of atheromatous plaques, which is characterized by arterial remodeling and fatty accumulation in subendothelia. The plaque development involves into several local vascular factors (25).

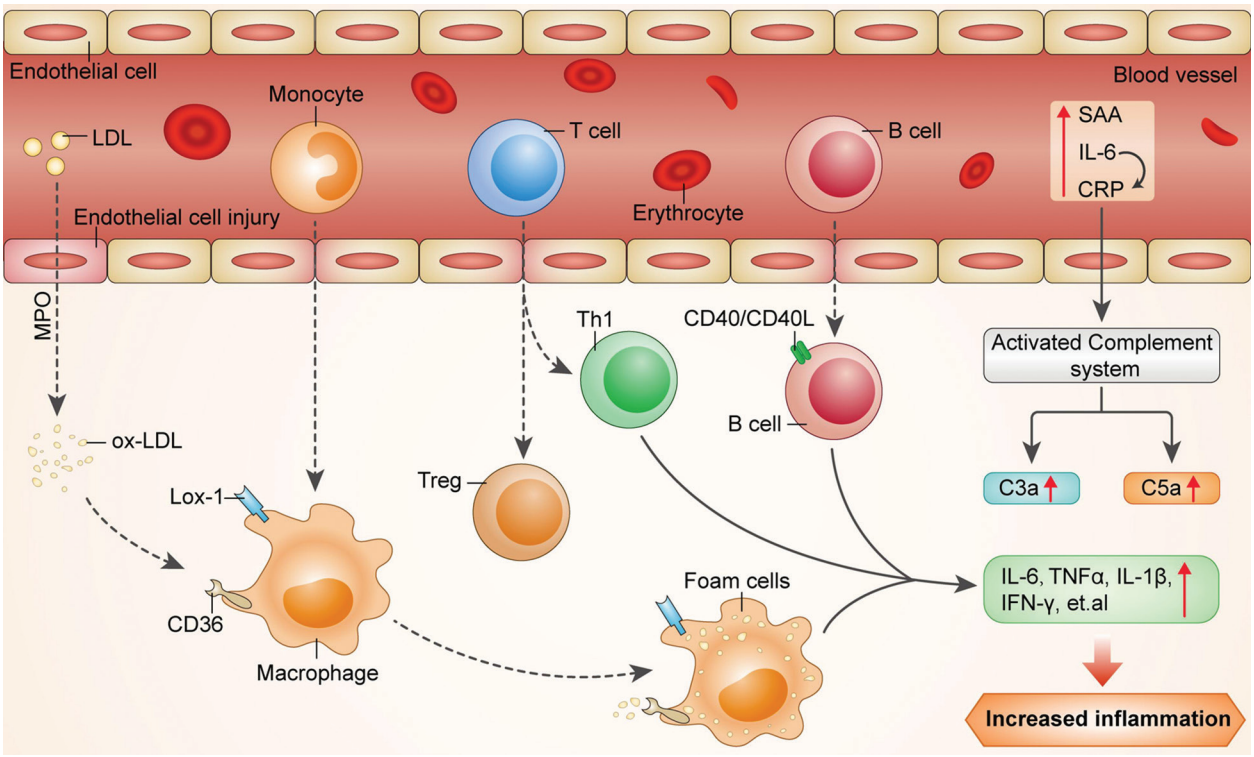

Figure 1. Inflammation cascade in atherosclerosis. Leukocytes such as monocytes, T-cells and B cells begin to attack the endothelium of the artery lumen in cardiac muscle upon endothelial injury. Monocytes differentiate to macrophages and absorb ox-LDL, which in turn are transformed into foam cells. When the latter are overloaded with oxidized-LDL, they die and release lipids. Cholesterol and triglycerides became trapped in vessel walls, resulting in proliferation of smooth muscle cells and formation of atherosclerotic plaques. Several inflammation-related factors are involved in the formation of atherosclerotic plaques and CHD development: oxidized-LDL, CRP, complement, SAA, IL-1β, IL-6, IFN-γ, TNF-α and MPO.

In the development of atherogenesis, it's recently suggested that leukocytes (e.g. monocytes, basophils) attack the endothelium in cardiac arteries (Figure 1), resulting in the formation of atheromatous plaques in the arterial tunica intima (26-28).

In early stage of atherogenesis, monocytes in the circulation adhere to the endothelium, migrate to the sub-endothelial space, and then activate the monocyte-derived macrophages (29). This process is drived by oxidized lipoprotein under endothelium (Figure. 1). An increased glucose concentration in blood contributes to this process. However, the risk factors remain unclear. Fatty streaks are not stable (30-32). Low-density lipoprotein (LDL) in circulation invades the endothelium and is oxidized, which is regulated by enzymes, such as Lp-LpA2, and free radicals in the endothelium (33-34). Thus, atherosclerosis is a chronic inflammatory disorder mainly caused by LDLs and leukocytes (Figure 1) (35). The endothelium damage triggers an inflammatory response. Chemokines, including monocyte chemoattractant protein (MCP)-1, recruit monocytes from the circulation to the arterial walls (36-37), and platelets adhere to the area of insult. Redox signaling factors, such as E-selectin, P-selectin and vascular cell adhesion molecule (VCAM)-1, promote that process, resulting in the recruitment of circulating monocytes and the secretion of macrophage colony-stimulating factor (M-CSF) secreted from endothelial cells and smooth muscle cells when stimulated by oxidized LDL. Furthermore, it's crucial to differentiate monocytes into macrophages, which ingest oxidized LDL molecules and become large "foam cells" (38-39). The foam cells have internal cytoplasmic vesicles and high lipid content (40), and microscopically appears as a fatty streak in lesion. The death of foam cells could promote the inflammation. Moreover, smooth muscle cells proliferate via nitric oxide (NO) release, and then migrate from the tunica media into the intima when stimulated by cytokines from injured endothelial cells (41-43). Those cells finally become a fibrous capsule on the fatty streak. In contrast, uninjured endothelium could prevent proliferation of smooth muscle cells.

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

The injured endothelium promote NO synthesis, whereas reduce the endothelin I and angiotensin II secretion, resulting in vasoconstriction (44-46). The pro-inflammatory cytokines, interleukin (IL)-1β and

tumor necrosis factor (TNF)-α activate endothelial cells, lead to the upregulation of the E-selectin, VCAM-1 and intercellular adhesion molecule (ICAM)-1 (47-49), which bind monocytes and T-cells to the endothelium. And then, these inflammatory cells migrate into the arterial intima with the help of chemokines, such as MCP-1, finally resulting in arterial inflammation (Figure 1) (50).

In the intima, monocytes are transformed into macrophages with "scavenger receptors" for modified lipoproteins, such as oxidized LDL (51). Cluster of differentiation (CD)36 and lectin-like oxidized low-density lipoprotein receptor (LOX)-1 internalize oxidized LDL, promoting macrophage conversion to foam cells and then formatting fatty streak. Foam cells secrete inflammatory mediators (IL-1β, IL-6, TNF-α) and chemokines (MCP-1) that stimulate expression of endothelial cell adhesion molecules and recruitment of inflammatory cells in the arterial intima. Recruitment of T-lymphocytes and mast cells are involved into the extravascular inflammation. In the intima, T-helper (Th1) secretes interferon (IFN)-γ, IL-2 and TNF-α to participate in the local inflammation. Around macrophage and Th1 cells, mast cells promote inflammation and foam cell formation by secreting cytokines and chemokines, finally stimulating recruitment of macrophages with LDL aggregation (52–53).

With the stimulation of inflammation, vascular smooth muscle cells (VSMCs) migrate into the intima and proliferation, leading to plaque development (54). Collagen secreted from VSMCs promotes extracellular matrix (ECM) to format plaque fibrous cap. In turn, VSMCs could promote the recruitment of inflammatory cells via secreting cytokines and chemokines and increasing endothelial permeability. Those cytokines could stimulate macrophages endothelial cells and VSMCs to express the coagulation factor and tissue factor (TF). TF is a potent initiator of the coagulation cascade via interacting with plasma coagulation factor VII, leading to thrombin generation, fibrin formation from fibrinogen and finally platelet activation. Those T-cells, macrophages, endothelial cells and VSMCs all participate in plaque development through expressing CD40 ligand (CD40L), which interacts with the CD40 receptors and promotes TF expressed in macrophages. Furthermore, oxidized LDL accumulated in macrophages induces apoptosis, resulting in lipids and TF releasing and subsequent necrotic plaque core formation (55-56).

5. PREDICTIVE INFLAMMATORY BIOMARKERS IN CHD

In atherosclerosis and CHD, inflammatory cells recruit in the injured vascular and secrete inflammatory mediators to promote plaque formation. Thus, the inflammatory factors could be regarded as biomarkers for atherosclerosis and CHD.

5.1. C-reactive protein (CRP)

CRP is an annular, pentameric protein in blood plasma that is increased in response to inflammation. This protein binds to phosphocholine on the surface of dead/dying cells, and activates the complement system, promotes phagocytosis by macrophages. CRP is mainly synthesized in the liver, and could be produced by inflammatory cells and adipocytes (57). This acute-phase protein is a biomarker of systemic inflammation, since it is increased in the condition of injury, infection, and other inflammatory stimuli (58). In liver, CRP production could be directly stimulated by IL-6 stimulation, and its level could be stable in a long term (Figure 1). Recent research found that patients with an increased level of CRP have a higher risk of DM, hypertension and cardiovascular disease (59).

CRP level in circulation is related to several risk factors of cardiovascular disease, such as obesity, smoking, blood pressure, serum levels of triglycerides, apolipoprotein B, fasting blood glucose, heart rate, and serum levels of fibrinogen and high-density lipoprotein (HDL) cholesterol. In addition to be an inflammatory biomarker, CRP directly participates in atherogenesis (60-61). CRP is a well-characterized inflammatory biomarker in CHD. The level of CRP may be useful in short-term prognosis and long-term risk assessment for cardiovascular disease patients.

CRP level is increased in patients with acute and chronic coronary syndromes, which are close with plaque composition and may develop into heart failure (62). Low plasma level may suggest a good health status. Ridker *et al.* (63) showed that CRP is a more effective biomarker for cardiovascular diseases than LDL-cholesterol. Moreover, a combination of CRP and LDL-cholesterol may have a better prognosis than only one. A large-scale prospective study found an association between the CRP and prediction of CHD (63).

5.2. Complement

Complement is a member of the innate immune system, which assists antibodies and phagocytic cells to kill pathogens. The complement system is proteins or glycoproteins mainly synthesized in hepatocytes. The complement could be also produced by macrophages, blood monocytes, and epithelial cells in the genitourinary and gastrointestinal tracts. The classical complement pathway is activated by antibody binding to C1 (comprising C1q, C1r and C1s subunits) *via* the C1q subunit. This action induces a conformational change and promotes C4 cleavage by C1s, and subsequently, C2 to form C4b2b C3 convertase, which cleaves C3 to C3a and C3b. Subsequent formation of C5 convertase activates the common pathway of the complement cascade and leads to the generation of C5b-9 ("membrane attack complex"). 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). However, the alternative pathway is activated at a low level as a result of spontaneous C3 hydrolysis due to breakdown of the internal thioester bond. Unlike other pathways, the alternative pathway does not rely on pathogen-binding antibodies. C3b is generated from C3 by a C3 convertase enzyme complex in the fluid phase, and inactivated rapidly by Factors H and I. C3b-like C3 is the product 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 binds covalently to the surface and is protected from factor H-mediated inactivation. Surface-bound C3b may bind factor B to form C3bB. In the presence of factor D, this complexis cleaved to Ba and Bb. Bb remains associated with C3b to form C3bBb, the alternative pathway of C3 convertase. The C3bBb complex is stabilized via binding to oligomers of factor P. Stabilized C3 convertase, 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 complement activation to a significant extent (66-67). Activation of the complement on a cell surface is limited by endogenous complement regulatory proteins.

The complement system participates in CHD development. CRP has been shown to activate the classical complement cascade through interactions with C1q. In addition, the complement is activated via an alternative pathway with modified lipoproteins, which is enhanced by CRP (Figure 1) (68). Activated complement components are observed to co-localize with CRP in plaques at the early stage of atherosclerotic lesions, suggesting a role of complement in CHD pathogenesis (69-70). When complement cascade is activated via no matter what pathway, complement factors, their products and complexes promote the formation and progression of plaques. Two cleavage products of complement activation, C3a and C5a, are anaphylatoxins, which are potent mediators of inflammation and chemotaxis. C5a is highly chemotactic for monocytes and T-lymphocytes, and promotes these cells to infiltrate into the ECM (71). C5a also stimulates leukocyte synthesis of IL-6, IL-1β and TNF-α to aggravate the inflammatory response (72). Both C3a and C5a can induce degranulation of mast cells, and make plaque unstable. C5a could promote the synthesis of plasminogen activator inhibitor (PAI)-1 to inhibit fibrinolysis in mast cells (73). Though C5b-9 complex is ineffective at lysing nucleated cells, it could promote the release of cytokines and chemokines from VSMCs, and then enhance accumulation of monocytes and T-cells within the ECM. When exposed on cell membrane surfaces, C5b-9 promotes assembly of the prothrombinase complex to participate in thrombus formation upon plaque rupture via potentiating TF-induced thrombin generation (74-75).

5.3. IL-6

IL-6 is a circulating cytokine secreted by activated macrophages, lymphocytes and adipocytes (76). IL-6 is activated by binding to a high-affinity receptor complex. The 80kDa ligand binding component (IL-6R) binds IL-6 with low affinity, whereas a 130kDa signal-transducing component binds gp80-bound IL-6 instead of free IL-6 (77). A ~50kDa soluble IL-6R is generated from proteolytic cleavage of membrane-bound IL-6R (78). When soluble IL-6R interacts with IL-6, the IL-6sR complex binds to membrane-bound gp130.The new complex with gp130 and IL-6R proteins activate IL-6R (79). These complexes initiate a signal transduction cascade through janus kinases (JAKs) and signal transducers and activators of transcription (STATs) (80). Recent evidence has disclosed antagonistic properties of the gp130 receptor (81). However, the mechanisms of soluble receptor release and their function are not well understood.

Risk factors for CHD could upregulate IL-6 level, such as obesity. IL-6 in circulation could be produced in subcutaneous adipose tissue. IL-6 levels both in adipose tissues and circulation are increased when become adiposity. In obesity, the increased IL-6 level in circulation is mainly from adipose tissues. Thus, IL-6 may be associated with body mass index (BMI) and insulin resistance syndrome (82). Obesity, one of risk factors for CHD and DM, has been considered as an inflammatory disorder. Inflammatory cytokines like IL-6 are involved into CHD pathogenesis in patients complicated with obesity (83–84). Moreover, CRP expression could be regulated by IL-6 for an association between circulating concentrations of CRP and IL-6 (85). Thus, IL-6 may be a significant systemic mediator in acute inflammation.

The role of IL-6 in CHD development has been attracted concerns (Figure 1). An animal study demonstrated that IL6 administration to apolipoprotein E (ApoE)$^{-/-}$ mice on a high-fat diet could promote plaque formation (86). Acute stress-induced IL-6 secretion from mast cells is increased in ApoE$^{-/-}$ mice. Furthermore, an increased IL-6 level was found in mast cell-defected mice, suggesting that IL-6 is a mediator of CHD (87). IL-6 may act in the upstream of CRP and complement components, promoting the pro-coagulant state through upregulating fibrinogen expression. However, the predictive value of IL-6 in CHD is limited due to its short half-life time (~5 min). CRP and complement C3 could reflect the secretion of IL-6 (88). In summary, IL-6 levels are increased in systemic inflammation, which may promote the increased level of CRP in person with a risk of CHD.

5.4. Serum amyloid A (SAA)

SAA is a protein produced in acute inflammation. The level of SAA in the circulation is increased in inflammation. SAA activates toll-like receptors (TLRs),

the scavenger receptor SR-BI, and the adenosine triphosphate receptor P_2X_7 (89). SAA also activates the nuclear factor-kappa B (NF-κB) pathway (90). An activation of the NF-κB pathway releases pro-inflammatory factors from M2 macrophages. These functional SAA plays a role in maintaining homeostasis during inflammation. An increased level of SAA has been used to predict the risk of 14-day mortality in CHD patients (91). In the Women's Ischemia Syndrome Evaluation study, elevated levels of SAA were correlated with angiographic severity of CHD and three-year risk for cardiovascular events (92). However, for the prognosis for thrombogenic factors and recurrent coronary events is different. SAA levels in two months after myocardial infarction is not associated with a risk of recurrent cardiovascular events over two years (93).

5.5. The CD40/CD40 Ligand (CD40L) system

CD40, a type I transmembrane protein receptor and member of the TNF super family (94), exists as a dimer and becomes trimerized when binding to CD40L. CD40 is mainly expressed on B-cells, as well as in immune cells, epithelial cells, neuronal cells, fibroblasts, vascular-wall cells and platelets (95). Most of these cells also express CD40L receptor (96). CD40 could be induced by TNF-α and IFNs. The protein is usually upregulated 6-12 h after stimulation, and keeps on the cell surface for 24-72 h. The sCD40L, a truncated soluble form, binds to CD40. Transmembrane CD40L on the platelet surface is cleaved into a 18kDa fragment, and then goes into the circulation. CD40L and sCD40L interact with CD40 and participate in inflammation.

The CD40-CD40L complex plays a key role in the pathogenesis of atherosclerosis. The anti-CD40L antibody could reduce the size and lipid content of atherosclerotic lesions (97). In CD40L knockout $ApoE^{-/-}$ mice, the plaque areas were significantly decreased (98). CD40L can stimulate endothelial cells to express adhesion molecules, which could promote macrophages adhere to endothelial cells in inflammation of atherosclerosis. The level of sCD40L in circulation is an important indicator of cardiovascular diseases, including atherosclerosis and acute coronary syndromes (99–100). The sCD40L participates in lipid deposition and foam cell formation, which is associated with the upregulation of scavenger receptor type A and CD36 (56). Moreover, sCD40L could activate adipocyte enhancer-binding protein 1, cholesterol efflux and activates NF-κB in macrophages, as well as promote foam cell formation via binding to CD40 ligation. It could inhibit foam cell formation in response to sCD40L when blocking the binding between CD40 and CD40L with small interfering RNA or anti-CD40 antibody (56, 101).

5.6. Myeloperoxidase (MPO)

MPO is a peroxidase enzyme produced by leukocytes. It induces oxygen free radical formation. MPO is mainly expressed in neutrophils (102). The lysosomal protein is stored in azurophilic granules of neutrophils and is released into the extracellular space during degranulation. Recent studies have reported an association between elevated levels of MPO and CHD severity (103). In patients with CHD, MPO produced by neutrophils is considered as a biomarker of plaque vulnerability. Yunoki *et al.*(104) observed a negative correlation between MPO levels in plasma and paraoxonase-1 bound to HDL, particularly in patients with angina pectoris. These findings suggest that an unbalance between pro- and anti-oxidants may promote coronary plaque instability.

6. CONCLUSIONS

The inflammation plays a central role in the occurrence and progression of atherosclerosis and CHD. Inflammatory biomarkers could predict cardiovascular risk in population with a high risk or with history of CHD. Traditional biomarkers, such as CRP, complement and IL-6, are associated with CHD. MPO is also an important indicator for CHD. A combination of biomarkers may improve clinical diagnosis and prediction of CHD. Further investigations focusing on the identification of novel CHD-specific factors are required.

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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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