Chapter 4

Vascular Inflammation and Genetic Predisposition as Risk Factors for Cardiovascular Diseases

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Additional information is available at the end of the chapter

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Abstract

Atherosclerosis previously defined as an obstructive disease leads to fatty deposits in the arterial wall. Nowadays, according to the best of our knowledge, specific cells, molecular mechanisms, and genes play crucial roles in the pathogenesis of the disease. Inflammatory reaction contributes to atherosclerotic lesion formation, since fatty streak leads to a plaque erosion or rupture. Experimental and clinical studies have shown that besides well-known risk factors, such as smoking, hypertension, diabetes, and dyslipidemia, genetic variations in certain locuses affect the disease burden. A common genetic variability at the apoE locus has been shown to be associated with a risk for cardiovascular disease. In many studies, a higher cardiovascular risk has been associated with the presence of the apo ε4 allele, whereas the apo ε2 allele has been protective. Recent studies stated that pro-inflammatory cytokines increase the binding of low-density lipoprotein (LDL) to endothelium and smooth muscle cells, so inflammatory response solely increases lipoprotein accumulation within the vessel wall. As a conclusion, cholesterol accumulation leads to atherosclerotic plaque via several mechanisms. Genetic predisposition and inflammatory process may affect disease severity.

Keywords: vascular inflammation, apoE, Lp-PLA2, LDL subtypes, endothelial dysfunction

1. Introduction

Cholesterol is one of the important molecules of the organism due to its strong relationship with cardiovascular disease. In clinical practice, the term of lipids is mainly used instead of lipoprotein metabolism because of its association with atherosclerosis. Certain lipoprotein fractions lead to the deposition and retention of cholesterol in the vessel wall causing atherosclerosis. Different guidelines recommend that lowering plasma cholesterol level by diet or drugs results in the reduction in cardiovascular disease.

Cholesterol is a hydrophobic macromolecule, transported in the circulation by lipoproteins such as chylomicrons, very low-density lipoprotein (VLDL), and high-density lipoprotein (HDL). Low-density lipoprotein (LDL) and intermediate-density lipoprotein (IDL) are synthesized from VLDL. Cholesterol, which is taken from the diet, is absorbed from the intestine and transported via chylomicrons to the liver. In the liver, endogen lipids with cholesterol are packaged into VLDL and secreted to bloodstream. LDL is responsible for peripheral cholesterol transport. Lipoproteins contain different proportions of lipids and proteins and have different physical and chemical properties. Apolipoproteins (apo) are the protein components of lipoproteins. Each lipoprotein class differs by its apoprotein content and proportions. ApoB100 is the main apoprotein of LDL and VLDL. ApoA-I and ApoA-II are the main apoproteins of HDL. ApoC-I, apoC-II, apoC-III, and apoE are present in all lipoproteins in different proportions. These apoproteins have various functions and help in the metabolic pathways of lipoprotein metabolism such as the activation of specific enzymes and the stabilization of the lipoprotein structure and recognized by cell surface of specific cells/ tissues. Among different types of apolipoproteins, ApoE has a crucial importance due to its link with cardiovascular diseases.

1.1. ApoE and its relationship with cholesterol metabolism

Apolipoprotein (apo) E is synthesized mainly by the liver, and less is produced by other cell types such as macrophages. It has a great biological and biomedical importance in lipid metabolism such as cholesterol transportation, triglyceride metabolism, and lipoprotein metabolism. It is a structural component of plasma chylomicrons, very low-density lipoproteins (VLDL) and high-density lipoproteins (HDL), and a ligand for apo B/E (LDL) receptor and LDL receptor-related protein (LRP) [1]. It also facilitates the interlocation of lipoproteins with proteoglycans. ApoE consists of 299 amino acid residue and has three common isoforms apoE2, apoE3, and apoE4 which differ structurally by two amino acid substitutions at residues 112 and 158: ApoE2 (Cys112, Cys158), ApoE3 (Cys112, Arg158), and ApoE4 (Arg112, Arg158) [2]. Each isoform is encoded by three different apoE alleles (ε2, ε3, and ε4), resulting in six different genotypes (E2/2, E3/2, E4/2, E3/3, E4/3, and E4/4) [3] (**Figure 1**).

ApoE consists of two functional domains joined by a flexible hinge region: an amino-terminal domain that contains a highly positively charged receptor-binding region composed mainly of arginine and lysine residues, and a carboxyl-terminal domain which includes a lipid-binding region. Substitutions of two amino acid residues in the three ApoE isoforms significantly alter their receptor-binding and lipid-binding affinities and lead to differences in lipid metabolism [4]. ApoE2 has a lower-binding affinity for low-density lipoprotein (LDL) receptors compared to ApoE3 and ApoE4. ApoE3 and ApoE4 bind similarly to the LDLR; however, compared to apoE3, apoE4 reduces plasma cholesterol less in humans which makes ApoE4 pro-atherogenic lipoprotein than others. Further, ApoE2 and ApoE3 preferentially bind to small, phospholipid-enriched high-density lipoproteins (HDL), whereas ApoE4 preferentially binds to larger, triglyceride-enriched lipoproteins [5, 6]. ApoE isoforms have different binding affinities to different lipoproteins such as ApoE4 that exhibits a better lipid-binding ability with the VLDL particle than apoE3, whereas apoE3 binds preferentially to high-density lipoprotein (HDL) [7].

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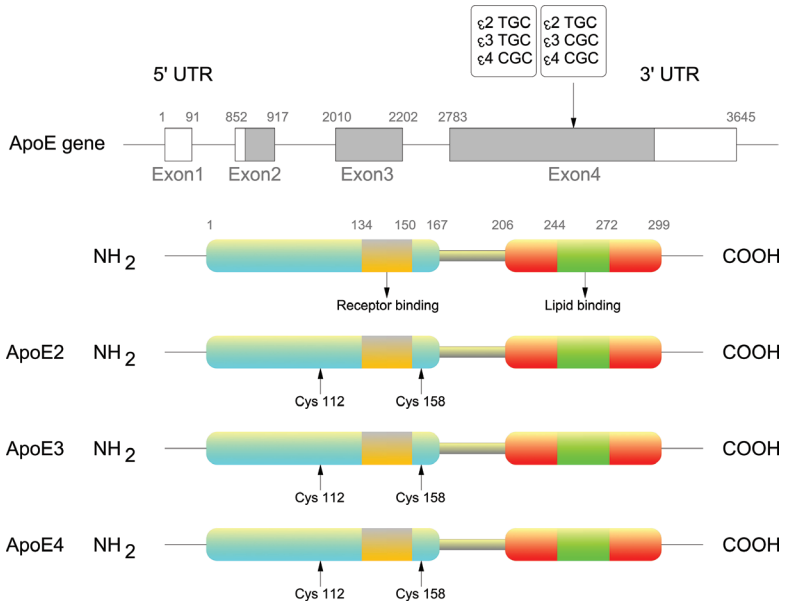

Figure 1. The schematic representation of the structural and functional domains of human apolipoprotein E (ApoE) isoforms.

The three-dimensional structure of apoE differs by Cys-Arg substitution, which causes changes in lipoprotein binding. The human apoE molecule contains the LDLR recognition site in the N-terminal helix bundle domain (residues 1–191) and initiates lipid binding by a C-terminal domain (residues 192–299). The substitution Cys and Arg residues, which differentiates apoE3 and apoE4 in the helix bundle domain, leads to different organizations of the segment spanning residues 261–272 which plays a critical role in the interaction with lipid surfaces; this structural change is the basis for the preferential binding of apoE4 to VLDL than of apoE3 [8–10]. The relative lipid- and lipoprotein-binding abilities of apoE3 and apoE4 have important consequences for the distribution of cholesterol between the VLDL and HDL fractions of plasma [11].

To date, several epidemiological studies have investigated the relationship between apoE polymorphism and coronary artery disease (CAD) risk, with a significant association [12–17]. It has been shown that apoE polymorphism may contribute to the plasma LDL cholesterol level and apolipoprotein B concentration in the various populations. The effects of apoE genotypes on coronary risk might also be explained as not only the receptor affinity or lipid levels but also apolipoprotein concentrations affecting the CAD phenotype. To the best of our knowledge, it has been shown that the ε2 allele is associated with lower levels of total plasma cholesterol (TC), LDL cholesterol (LDL-C), and apolipoprotein B (apo B) and with elevated levels of triglycerides (TG) as compared to the ε3 allele. An elevated level of TG is related with the impaired clearance of remnant particles containing apo ε2, which might be due to a defective receptor recognition of those particles. Reduced levels of apo B and LDL cholesterol in E2/2 and E2/3 individuals are results of impaired conversion of the intestinal VLDL particles to LDL by interfering with normal lipolytic processing [18, 19]. On the other hand, the ε4 allele

is associated with higher levels of total and LDL-C and apo B because particles with carriers of that allele have a faster catabolic rate than the ε3 counterparts [20]. Meta-analysis has been emphasized that ε2 carriers had a 20% reduced coronary risk as compared to ε3/ε3 genotype [21]. The precise mechanism may be explained by the binding affinity of apoE2 isoform to heparin and small, phospholipid-enriched HDL. These effective binding mechanisms enhance remnant lipoprotein metabolism and also reverse cholesterol transport [5–22]. Further, apo E2 isoforms bind to LDL receptors much more weakly than apo E3 or apo E4 counterparts. Apo E4 isoforms are also related with an increased cholesterol absorption and statin hyporesponsiveness. However, meta-analysis has been suggested that ApoE genetic testing contributes to little information for statin treatment [23].

Numerous effects of apoE genotypes on coronary risk might also be explained by influences on additional lipid-related phenotypes such as lipoprotein subtypes, markers of inflammation, immunity, or oxidative status.

Recently, the atherogenicity of LDL and HDL subclasses and their relationship to coronary heart disease has taken more attention. Various studies revealed that small, dense LDL is more atherogenic and associated with an increased risk of CHD [24, 25] with a high triglyceride level [26]. Researchers reported confusing results about apoE genotypes and LDL, HDL subtypes. Some studies stated a relationship between ε2 allele and smaller LDL particles compared to ε4 allele carriers [27, 28]; others reported contradictory results [29, 30]. As we know that the relationships between apo E polymorphism, serum lipids, and CHD were differed due to different ethnicities, lifestyles, diet habits, and even to age. Epidemiological studies showed that men have more atherogenic profile than women with a low level of HDL cholesterol and an increased triglyceride level. The incidence of first cardiovascular events is also higher among young men and is increasing very fast along with age, than in women [31]. The effect of apo E allelic variants on lipids and lipoprotein particle sizes has been studied in many populations [28, 30, 32, 33]. Several studies suggested that the apo E polymorphism influences lipoprotein particle size and might indirectly increase the CHD risk differently for each gender. Topic and his friends stated that apo ε carriers and its relationship with lipoprotein subtypes differed among sex; men with ε2 allele had the smaller LDL particles and a higher TG/HDL-C ratio [1]. Further, Dobiasova and Frohlich proposed that the Log (TG/HDL-C) be called "atherogenic index of plasma" and used as a marker of plasma atherogenicity because this ratio showed a strong inverse correlation with LDL size [34]. Some researchers have reported an increased LDL-C concentration and a decreased LDL size in subjects with ε4 allele [30]. On the women side, studies showed an association of the ε4 allele with smaller HDL particle and a higher frequency of small HDL phenotype and Framingham Risk Score ("intermediate"). Further, the presence of the ε4 alleles is found to be the independent factor for HDL size variation in women. Others reported different results with ε4 allele; carrier women had the small HDL particles which relates with the severity of CHD [27, 35, 36].

1.2. Endothelial dysfunction and cardiovascular diseases

Despite the strong evidences about lipoproteins and apolipoproteins, it has been shown that chronic oxidative stress and inflammatory changes in the vascular tissue play a crucial role in

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coronary atherosclerosis pathogenesis. Endothelium controls the normal vasomotor balance, the inhibition and stimulation of smooth muscle cell proliferation, migration, thrombogenesis, and fibrinolysis. When these functions of endothelium are impaired, endothelial dysfunction occurs and leads to damage of the wall. Damage to the endothelium promotes substantial events and provokes atherosclerosis by increasing endothelial permeability, platelet aggregation, and leukocyte adhesion.

The early lesion of atherosclerosis results in the focal accumulation of lipoproteins in the intimal layer of the artery. The intimal layer contains smooth muscle cell which is embedded in the extracellular matrix, so lipoprotein accumulation often associates with proteoglycans of the arterial extracellular matrix such as heparin sulfate, keratan sulfate, or chondroitin sulfate. These proteoglycan molecules increase the retention of lipoprotein particles in the arterial bed and permit their chemical modification. The extracellular bed of arterial wall is particularly susceptible to oxidative modification. The modification of lipids leads to hydroperoxides, lysophospholipids, oxysterol, and oxidized phospholipids formation which are other stimulators of arterial lesion progression. On the other hand, the apoprotein part of the lipoproteins may undergo similar chemical modification which performs irregular protein moieties that have a pro-inflammatory role during lesion development. The irregular changes of the arterial wall might also activate mononuclear phagocytes. These phagocytes as well as vascular endothelial and smooth muscle cells can produce reactive oxygen species when activated. Then, reactive oxygen species can induce smooth muscle cell growth and trigger inflammatory response.

The second step of the lesion formation is leukocyte recruitment which is the main cell of atheroma of the mononuclear lineage: monocytes and lymphocytes. The vascular endothelium synthesizes certain biomolecules for a regular vascular function. Various adhesion molecules or receptors are synthesized on the endothelial cell surface for leukocytes such as vascular adhesion molecule I (VCAM-I), intercellular adhesion molecule I (ICAM-I), and P-selectin. In normal arteries, the laminar shear stress suppresses the expression of adhesion molecules and stimulates adequate nitric oxide (NO) to maintain vasodilatation. Further, NO production can control adhesion molecules expression such as VCAM-I and show an anti-inflammatory effect. Reactive oxygen species may also react with NO, reduce NO bioavailability, and improve vascular damage indirectly by disrupting adhesion molecule express. In addition to relationship between adhesion molecules and NO, in vitro studies have shown that this relationship is attenuated by apoE [37, 38]. Recently, Ma et al. reported a reduced VCAM-1 and ICAM-1 gene expression in the whole aorta of hyperlipidemic mice at the sub-physiological levels of plasma apoE [39]. As a result of an increased adhesion of certain key molecules to endothelial cells, this leads to the penetration of monocytes and lymphocytes to the subendothelial layer. Besides modified lipoproteins, mediators of inflammation, cytokines can also regulate adhesion molecule expression and promote leukocyte recruitment. For example, VCAM-I and ICAM-I expressions on endothelial cells are stimulated by cytokine interleukin-I (IL-1) and tumor necrosis factor α (TNF-α). As mentioned earlier, the different pathways perform a cumulative effect on endothelial dysfunction and lesion formation. In the intima, the recruitment of mononuclear phagocytes differentiates to macrophages which promote the lipid-loaded foam cell formation. Foam cells have two different features: they either can go to apoptotic pathway or produce cytokines and growth factors which lead to further complicated cellular events

in complicated lesion. Growth factors (platelet growth factor, fibroblast growth factor, etc.) and cytokines again stimulate smooth muscle cell proliferation and induce extracellular matrix formation. Among numerous growth factors, some of them solely trigger interstitial collagen production by smooth muscle cells. These mediators induce lesion progression by inducing transformation of fatty streak into a more complicated lesion with a high fibrous tissue and extracellular matrix by using either paracrine or autocrine pathway. As well as the effect of traditional risk factors and local mediators of various cell types, coagulation and thrombosis also contribute to lesion progression.

Endothelium serves as a barrier between circulating blood and its surrounding tissue. A transmembrane receptor tissue factor (TF) is expressed by blood vessels. An injury of the vascular endothelium leads to exposure of TF and activates the clotting cascade. The imbalance of hemodynamics might also effect the normal activity of endothelial cells. Endothelial cells control platelet function via the synthesis and secretion of Von Willebrand factor (vWF). The vWF is an important glycoprotein in the regulation of hemostasis, stored also in platelets, and can be released as a response to prothrombotic and inflammatory factors. It is a bridge between platelet adhesion and coagulation. VWF contains functional domains for collagen, platelet (GPIb binding), and factor VIII binding. At the site of injury, VWF recognizes collagen in the subendothelial matrix, steer platelet adhesion via collagen, and GPIb-binding sites. Its level increases in plasma as a result of endothelial damage. vWF increases platelet adhesion to subendothelial layer and contributes to thrombus formation [40, 41].

The other anticoagulant functions of the endothelium are inhibition of coagulation by TFPI, keeping balance between thrombin- thrombomodulin secretion and regulation of coagulation factors by antitrypsin. On the other hand, the endothelium controls the activation and regulation of fibrinolysis by the secretion of tPA and PAIs. tPA is released in response to thrombin which is controlled by PAI-1. Various complex functions of endothelium are controlled strictly with high fidelity to maintain vascular health.

Based on the robust relationship between lipoprotein metabolism and basic endothelium functions, it has been recommended that different types of inflammatory reactions might be involved in the initiation and progression stages of atherosclerosis and contribute to vascular events.

Numerous epidemiologic studies reported that 20% of the coronary events occurred in the absence of the classical risk factors: hyperlipidemia, diabetes, hypertension, and smoking. In this situation, a question raises whether traditional risk factors are adequate to predict CVD risk. To solve this issue, new biomarkers are proposed for daily practice for better identification of the risk, including hemostatic system markers (the best identified ones, tissue plasminogen activator inhibitor—PAI-I, tissue plasminogen activator—tPA, fibrinogen, von Willebrand Factor—vWF, etc.) and inflammatory markers (high sensitive C reactive protein—HsCRP, lipoprotein-associated phospholipase II—Lp-PLA2, myeloperoxidase, pentraxin III—PTX3, serum amyloid A, etc.). Together with these, interleukins, inflammatory cytokines, adhesion molecules, homocysteine, and heat shock proteins can be used as appropriate. All these factors participate in the atherosclerotic process and show an abnormal behavior in individuals at high risk, or suffered from a cardiovascular event.

1.3. Vascular inflammation as a risk factor for cardiovascular diseases

Among the wide range of markers, C-reactive protein (CRP) was recommended as a comprising marker for the evaluation of CVD risk in 2009 by the common declaration of the Laboratory Medicine Practice Guideline of National Academy of Clinical Biochemistry (NACB) and American Heart Association and the CDC (AHA/CDC) [42]. CRP is an acute-phase protein, which is primarily produced in the liver during acute inflammation or infection. CRP is stimulated by interleukin 6 (IL-6) and also detected at local sites of inflammation or injury. It is not specific for vascular inflammation. Then, more sensitive types of CRP have been developed to detect the small changes of the protein, called hs-CRP. Since hs-CRP has been increased, the predictive accuracy of risk evaluation with other risk-scoring systems is still inadequate. Hs-CRP levels are known to be systemic inflammatory marker and increased by infection and tissue damage, malignancies, obesity, aging, hypertension, diabetes mellitus, smoking, and other cardiovascular risks [43].

As described earlier, the increased expression of endothelial adhesion molecules, which trigger subendothelial penetration of LDL, is more susceptible to oxidation and stimulates inflammatory cytokines. Great attention has been recently given to myeloperoxidase (MPO), released systemically and locally by activated leukocytes. It has been shown that this enzyme is present in atherosclerotic lesions with higher concentrations and also contributes to LDL oxidation by different mechanisms via radical and non-radical mechanisms either lipid or apoprotein moieties [44]. Moreover, MPO limits the bioavailability of nitric oxide (•NO) and contributes to endothelial dysfunction [45, 46]. Unlike CRP, MPO is more involved in different stages of atherosclerosis such as foam cells, endothelial dysfunction and apoptosis, the activation of matrix metalloproteinases, and the expression of tissue factor which could address the patients with vulnerable plaques, and the potential burden of such plaques in clinical practice [47]. The members of the inflammatory cytokine family IL-6 and tumor necrosis factor (TNF)-α, released from the main cells of the plaque, vascular smooth muscle cells, endothelial cells, monocytes, and macrophages, are highly involved in atherosclerosis [48]. Ridker and colleagues reported from 14,916 healthy male; blood IL-6 concentrations were significantly elevated in individuals who had myocardial infarction as compared with those who did not [49]. Another prospective study reported a relationship between IL-6 levels and the incidences of ischemic cardiac disease, stroke, and heart failure events from middle-aged participants [50]. The other important player of the inflamed plaque is chemokines, leading to the recruitment of leukocytes to the damaged area of the arterial wall, as well as other systemic inflammatory markers, particularly monocyte chemoattractant protein 1 (MCP-1), which is again non-specific for interpreting CV risk [51].

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) or platelet-activating factor acetylhydrolase is a unique pro-inflammatory biomarker, specific for vascular inflammation and atherosclerosis [52, 53]. Lp-PLA_2 was discovered in 1980, and it was classified as a Ca^{2+}-independent PLA_2 [54] produced by a wide range of inflammatory and non-inflammatory cells [55] (**Figure 2**).

Lp-PLA_2 shows a positive correlation with CV events by various scientific and clinical studies [56–58]. Lavi et al. found that patients with early coronary atherosclerosis had higher

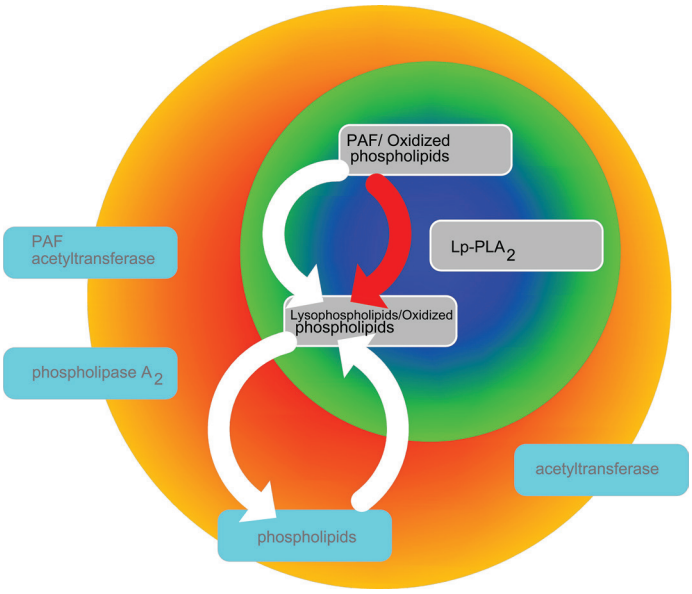

Figure 2. Relationship of Lp-PLA2 action with phospholipids. Platelet-activating factor (PAF) is an active phospholipid related to many pathologic and physiologic reactions. The PAF is formed through two reactions: firstly, the cytosolic phospholipase A2 (cPLA2) acts on membrane phospholipids producing lysophospholipids; then, the lysophospholipids are modified by PAF acetyltransferase, Thus, PAF concentration is modulated by Lp-PLA2 activity.

lysophosphatidylcholine when compared with control subjects [59]. Herrmann et al. showed that carotid artery plaques of patients with cardiac events presented higher Lp-PLA2, lysophospholipids, macrophage, and collagen content when compared to patients without events [60]. Kuniyasu et al. demonstrated that oxLDL and, particularly, the lysophosphatidylcholine present in this particle enhance the plasminogen activator inhibitor-1 expression [61].

Moreover, the difference in the distribution and association of Lp-PLA_2 activity and index with apoB containing lipoproteins across lipoprotein subfractions has also been reported [62]. Further, Lp-PLA_2 has been recommended as an adjunct to traditional risk factors for individuals at a moderate or a high CV risk by the Adult Treatment Panel III (ATP III) guideline [63].

Lp-PLA_2 is synthesized mainly by macrophages of atherosclerotic plaque, then enters the circulation, and binds to LDL, HDL, and Lp(a). In the atherosclerotic plaque, Lp-PLA_2 hydrolyzes oxLDL into Lyso-PC and oxidized nonesterified fatty acids (oxNEFAs), both of which have a pro-inflammatory role (**Figure 3**). The degradation products, Lyso-PC and oxNEFAs, hydrolyzed by Lp-PLA_2 play crucial roles on the development of atherosclerosis. Both Lyso-PC and oxNEFAs induce the recruiting of leukocytes, upregulating inflammatory cytokine such as TNF-a and IL-6, amplifying oxidation, and increasing matrix metalloproteinase expression. During the process, the presence of OxLDL, as well as lysophospholipids and oxNEFAS, stimulates the growth of the plaque [64, 65]. As mentioned earlier, Lp-PLA2 resides on different types of lipoproteins, so dyslipidemia effects the enzyme mass and activity and alters its

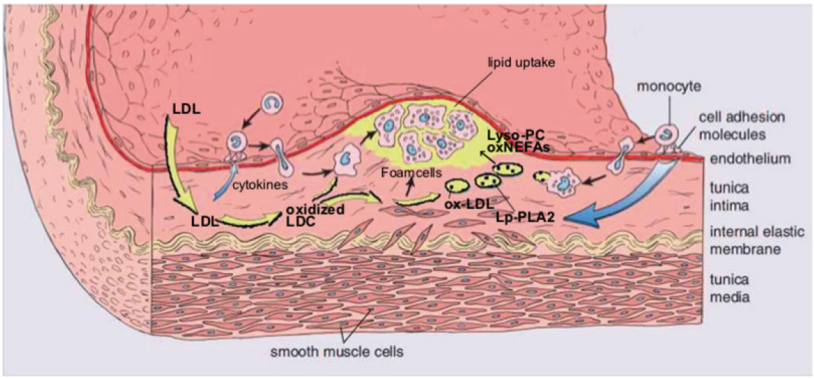

Figure 3. The role of Lp-PLA$_2$ on atherosclerotic plaque.

distribution between apo B- and apo AI-containing lipoproteins, as reported by Tsimihodimos et al. The same study also demonstrated inducing the increase of HDL-Lp-PLA2 activity and the reduction of LDL-Lp-PLA$_2$ activity by atorvastatin treatment [66].

Lp-PLA$_2$ quantitatively reflects the degree of inflammatory reaction of the plaque in the plasma. Lp-PLA$_2$ measurement can be classified into enzyme activity and enzyme mass; however, Berglund and colleagues recommended an integrated measure of Lp-PLA$_2$ activity and mass as Lp-PLA$_2$ index which showed an independent predictor of CAD in different ethnicity [58]. Since the first report, many epidemiological studies and meta-analysis have also proved the significant associations between Lp-PLA$_2$ atherogenesis and CV-risk stratification [52, 67, 68]. A meta-analysis of 32 clinical studies evaluated the association of Lp-PLA$_2$ mass or activity with the future risk of CHD, emphasizing strongly that Lp-PLA$_2$ is a reliable indicator for the future CV-risk assessment. The study also revealed that the association of the enzyme activity with lipid markers is stronger than the association with mass [69]. Further, Gungor et al. demonstrated an association between apoE genotype and Lp-PLA$_2$, for the first time. The Lp-PLA$_2$ index, an integrated measure of Lp-PLA$_2$ mass and activity, was higher in apo E4 carriers irrespective of ethnicity and underlines the importance of assessing the relationship between genetic predisposition and inflammation, in the assessment of cardiovascular disease risk [70]. The genetic variation of Lp-PLA$_2$ activity and mass and relationship with 13 common single nucleotide polymorphisms (SNPs) of the PLA2G7 gene was investigated in the community-based Framingham Heart Study. The study reported that Lp-PLA2 activity is influenced by variation in the genomic region of PLA2G7. Further, it has been underlined that different pathophysiological roles of Lp-PLA$_2$ activity and mass conveyed different clinical outcome. The strong association is seen for Lp-PLA$_2$ activity with cardiovascular risk factors compared to Lp-PLA$_2$ mass [71].

Pentraxin 3 (PTX3) is a protein from acute-phase reactant family. It belongs to long pentraxins and possesses numerous properties in the field of inflammation. Pentraxin 3 transcription is upregulated by tumor necrosis factor and interleukins (IL-1) in different cell types such as endothelial cells, phagocytes, smooth muscle cells, and fibroblasts which are involved in the different stages of atherosclerosis. PTX3 represents a specific and sensitive marker connecting inflammation with CVD.

During inflammation, the blood vessel produces large amounts of PTX3; its high level in circulation related with pathological conditions affects cardiovascular system. Recently, epidemiological and clinical data showed that PTX3 is a valid biomarker for atherosclerosis [72] and its high plasma levels were found to be related with the severity of coronary atherosclerosis [34]. It has been demonstrated that PTX3 increases the tissue factor (TF) expression in mononuclear and endothelial cells. The increased level of TF activates the coagulation cascade and causes the thrombus formation [73]. PTX3 might also bind to growth factor 2 (FGF2) and interfere with plaque stability via effect of the proliferation and migration of smooth muscle cells [74]. Based on such findings, PTX3 is more specific for coronary plaque instability than for atherosclerosis. In addition, the elevated plasma level of PTX3 has been found in patients with high systolic and diastolic blood pressure levels [75]. On the other hand, in patients with acute myocardial infarction, PTX3 was shown to be produced by the neutrophils penetrating into unstable coronary plaques. This underscored the fact that PTX3 might be more accurate predictor of cardiovascular events after myocardial infarction than other markers [76].

As conclusion, it is well known that atherosclerosis is a chronic inflammatory disease of the vessel wall. This chapter reviewed the relationship between atherosclerosis and the various effects of different inflammatory biomarkers and possible roles of genetic predisposition on the development and progression of coronary artery diseases (**Figure 4**). Atherosclerotic disease mostly starts

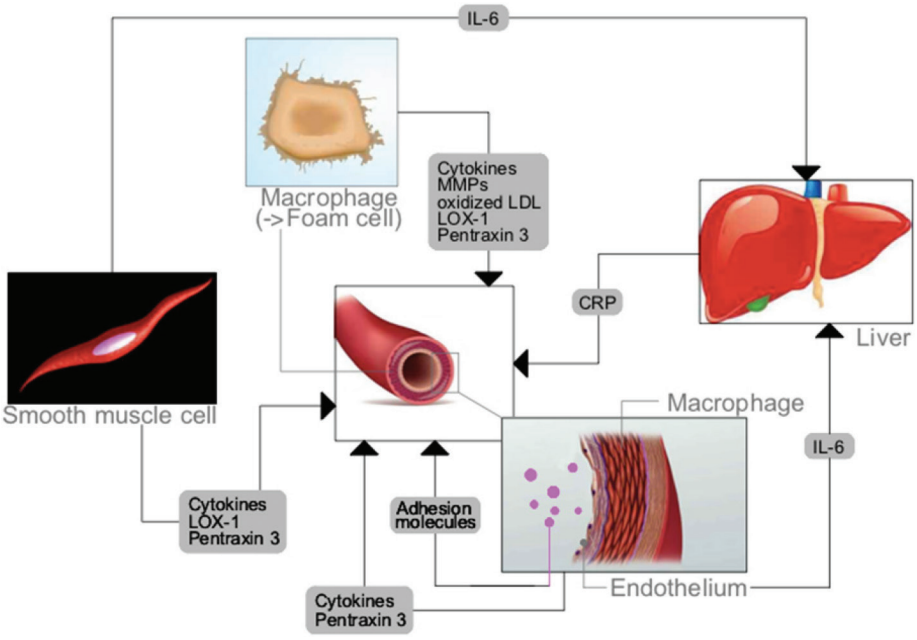

Figure 4. Inflammatory markers secreted from various cells in atherosclerotic lesion. Pro-inflammatory markers such as cytokines, pentraxin-3, MMPs, and LOX-1 are produced by macrophages, endothelial cells, and vascular smooth muscle cells in atherosclerotic lesion. CRP is mainly produced in the liver stimulated by IL-6. CRP indicates C-reactive protein; IL-6, interleukin-6; LDL, low-density lipoprotein; LOX-1, lectin-like oxidized LDL receptor-1; and MMP, matrix metalloproteinase.

as asymptomatic, however, when it gives symptoms; the life quality is effected significantly and sometimes it will be life threatening. In these circumstances, the early detection of the disease or prediction of the individuals with a high CV risk becomes very important. The evaluation of a CV risk or a disease progression by an accurate biomarker either vascular inflammation or genetic markers would be promising and underscores their diagnostic importance in clinical practice.

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Conflict of interest

The author declares that there is no conflict of interest.

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