40 Accelerated Atherogenesis and Antiphospholipid Antibodies

Eiji Matsuura, Kazuko Kobayashi, and Luis R. Lopez

Introduction

Atherosclerosis is a major health concern of worldwide importance. The causal relationship between atherosclerosis and cholesterol metabolism is well established. However, newer inflammatory and immunologic mechanisms are emerging as relevant factors for the initiation and progression of atherosclerotic lesions. In particular, the oxidation of low-density lipoprotein (LDL) has been identified as an early pro-atherogenic event that promotes the formation of macrophage derived foam cells [1–4].

The increased cardiovascular morbidity and mortality recently reported in patients with systemic autoimmune diseases is a likely consequence of the accelerated (or premature) development of atherosclerosis. These findings have suggested a contributing role of autoimmunity in the development of atherosclerosis. Antiphospholipid syndrome (APS) is characterized by venous and arterial thromboembolic complications associated with high serum levels of antiphospholipid antibodies. APS is frequently diagnosed in the context of an autoimmune disease [5, 6]. The exact mechanism(s) by which anticardiolipin (aCL), lupus anticoagulants (LA), and/or other antiphospholipid antibodies promote thrombosis is not completely understood. It is now widely agreed that β_2-glycoprotein I (β_2-GPI) plays a central role in APS, and more importantly, represents a major antigenic target for antiphospholipid antibodies [7–11].

Oxidized LDL (oxLDL) is the principal lipoprotein found in atherosclerotic lesions, and it co-localizes with β_2-GPI and immunoreactive lymphocytes [12]. It was also reported that aCL antibodies from patients with systemic lupus erythematosus (SLE) cross-reacted with malondialdehyde (MDA) modified LDL [13], and that anti–β_2-GPI antibodies were associated with arterial thrombosis [14, 15]. These findings further indicated the participation of antiphospholipid antibodies in atherogenesis. More recently, we have demonstrated that oxLDL binds to β_2-GPI, and that these complexes (oxLDL/β_2-GPI) can be found in the blood stream of patients with various autoimmune and chronic inflammatory diseases, such as SLE, APS, chronic renal disease, diabetes mellitus, as well as in some patients with "acute" myocardial infarction [16].

IgG antibodies to oxLDL/β_2-GPI were detected only in SLE and APS patients and were strongly associated with arterial thrombosis. Further, immune complexes con-

taining oxLDL, β_2-GPI, and IgG anti–β_2-GPI antibodies have also been detected in SLE and APS patients [16]. Our recent in vitro experiments showed that oxLDL/β_2-GPI complexes were internalized by macrophages via an anti–β_2-GPI antibody mediated phagocytosis [17–19]. Thus, circulating IgG immune complexes containing oxLDL and β_2-GPI may be atherogenic. In contrast, recent reports indicated that natural antibodies (mainly of the IgM class) derived from hyperlipidemic mice reduced the incidence of atherosclerosis in experimental models [20–23].

Atherogenic Mechanisms

Atherosclerosis is a pathological condition in which arteries undergo thickening of the intima causing a decrease in their elasticity. The aorta, coronary, and cerebral arteries are blood vessels most commonly affected by atherosclerosis. The appearance of lipid laden foam cells is a characteristic hystologic finding in early atherosclerotic lesions. Figure 40.1(A) depicts a current consensus of different events leading to the initial stages of atherosclerosis. Hypercholesterolemia is commonly associated with an elevation of LDL, which is the lipoprotein that accumulates in foam cells. Increasing LDL blood levels together with arterial shear stress may produce a vascular inflammatory response, with the adherence of circulating monocytes to endothelial cells and the migration of these elements (LDL, oxLDL, and monocytes) into the intima. The oxidative modification of LDL may be further catalyzed by inflammatory cells at the site of the arterial lesion, resulting in foam cell formation (oxLDL loaded macrophages). Numerous pro-inflammatory molecules and/or adhesion molecules also participate in the development of atherosclerosis. These molecules participate under complicated interrelated conditions and include: monocyte chemo-attractant protein-1 (MCP-1), macrophage colony-stimulating factor (M-CSF), interferon-γ (IFN-γ , tumor necrosis factor-α (TNF-α), interleukine-4 (IL-4), platelet-derived growth factor (PDGF), heparin-binding EGF-like growth factor (HB-EGF), intercellular adhesion molecules (ICAMs), vascular cell adhesion molecules (VCAM-1), endothelial selectin (E-selectin), and so on [24–27]. In addition, macrophage scavenger receptors and various cell–cell interactions, possibly via CD40 and CD40 ligands, have been reported to be involved in the development of atheroma [28].

When the endothelial surface of the atherosclerotic lesion becomes damaged and unstable, it may rupture. This event is followed by the activation of blood coagulation mechanisms such as platelet aggregation and thrombi formation, which can result in a complete occlusion of the blood vessel and tissue or organ necrosis, as seen in acute myocardial and cerebral infarction.

Macrophages and Scavenger Receptors

Macrophages receptors for the specific uptake of LDL were first described by Goldstein and Brown [29, 30]. Theses receptors are downregulated to prevent lipid overloading. Another type of macrophage receptor was later described for chemically modified LDLs and named scavenger receptors [29, 31]. These scavenger receptors are not downregulated, and may lead to the accumulation of massive