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Review

The pathogenesis of atherosclerosis in autoimmune rheumatic diseases: Roles of inflammation and dyslipidemia

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Abstract

As patients with autoimmune rheumatic diseases live longer due to improved therapies and preventive measures, death and disability from atherosclerosis, particularly myocardial infarcts, are increasing. The relative risks for atherosclerosis vary from approximately 1.6 in ankylosing spondylitis and psoriatic arthritis to 3.0 in rheumatoid arthritis (RA), and 6.0 in systemic lupus erythematosus (SLE). Increased risks are found when analyzed by atherosclerotic events, causes of death, or surrogate measures of atherosclerosis, such as carotid artery plaque, intimal-media thickness, or coronary artery calcification. At all ages among adults, atherosclerosis is increased in patients with SLE or RA compared to healthy controls. For example, in women with SLE under the age of 40 years, approximately 13% have carotid plaque compared to 2% of controls; over age 59 the percentages are 71 and 45, respectively. For patients with RA, prevalence is 7% under the age of 40 in patients compared to zero in controls; over 59 years the prevalences are 80% and 44%, respectively. In this review we will discuss the mechanisms involved as well as an overview of the natural history in pathobiology.

Keywords: Inflammation; Atherosclerosis; Autoimmunity; Rheumatic disease; Dyslipidemia

1. Overview of pathogenesis of atherosclerosis

Major mechanisms that contribute to the complex disease that is atherosclerosis are listed in Table 1. The incidence of atherosclerosis in several key rheumatic diseases has been extensively described [1–9]. The characteristic lesion of acute myocardial infarction is thrombus occurring where the fibrous cap ruptures over a coronary artery plaque. Plaque is composed of a pro-inflammatory, pro-thrombotic lipid core in an area where the artery is thickened by proliferation in its wall, and endothelium is gone, or has been damaged and lost its protective anticoagulant activity. Blood flowing through the coronary artery comes into contact with the lipid core of the plaque; thrombus and occlusion result (reviewed in [10]).

Interactions between the many processes that combine to accelerate atherosclerosis are illustrated in Fig. 1. Several processes occur that damage endothelial cells. Local increased levels of immune complexes containing C1Q decrease cholesterol 27-hydroxylase in arterial endothelium and macrophages, thus reducing ability to catalyze hydroxylation of cholesterol to the more soluble 27-hydroxycholesterol, which is more easily removed from the arterial wall [11]. Exposure of the endothelium and monocytes/macrophages to interferon-gamma (IFNγ) has similar effects on this enzyme. Increased levels of the pro-inflammatory cytokines interleukin (IL)-1, tumor necrosis factor alpha (TNFα) and IFNγ also damage endothelial cells, reducing their anti-coagulant surface receptors (endothelial protein C receptors, ECPR), upregulating their expression of MCP1, VCAM and ICAM, and allowing them to shed and to increase the space between remaining endothelial cells. These altered endothelial cells can be found circulating in patients with active lupus nephritis [12,13]. Increased space permits the entry of cells and low-density

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Table 1
Pathogenesis of atherosclerosis

A. The lesions leading to reduced or absent arterial blood flow	
1	Plaque
2	Thickening and stiffening of the arterial wall
3	Thrombosis
B. The mechanisms that produce the lesions	
1	Inflammation (mediated by cytokines, chemokines, dendritic cells, monocytes, lymphocytes, antibodies and pro-inflammatory lipids)
2	Dyslipidemia with chronic oxidative damage to lipids and tissues
3	Endothelial damage
4	Immune responses, including C1q-fixing immune complexes
5	Proliferation of fibroblasts/smooth muscle
6	Thrombosis
7	Occlusion from plaque, hypertrophy in arterial walls, and thrombus

lipoproteins (LDL). When LDL enter the subendothelial area, they undergo modification by oxidation (OxLDL), and those OxLDL activate endothelial cells to express surface adhesion molecules and to upregulate synthesis of cytokines and chemokines, including macrophage chemoattractant protein 1 (MCP-1) [10]. This results in arrest of the monocytes/macrophages that normally circulate through vessels, prowling for danger signals. The monocytes/macrophages (and dendritic cells) are halted by adhesion molecules, spaces between endothelial cells increase, and the cells enter the subendothelial region, where the macrophages engulf OxLDL to form the foam cells that are the nidus of plaque. Macrophages are further activated by this activity; they release cytokines, chemokines, growth factors and metalloproteinases. These proteins degrade the media of the artery and stimulate smooth muscle cells and fibroblasts to proliferate, thus enlarging the area around plaque and creating narrowing of the arterial wall [10]. Activation of monocytes/macrophages to produce additional pro-inflammatory cytokines/chemokines attracts additional cells, including T and B lymphocytes, which contribute to further damage. The contact between monocytes/macrophages and T cells in arterial walls results in production of large amounts of TNFα, and IL-β1 [14]. Not pictured in Fig. 1 is an additional attack on the artery which comes from surrounding lipid (white fat cells). White fat cells are a source of cytokines and chemokines that promote inflammation on the adventitial side of arteries, particularly the neutrophil-attracting IL-8 and the monocyte attractant MCP-1 [15]. Thus the artery wall is attacked from inside and out—endothelial side and adventitial side.

2. Immune responses and pro-inflammatory molecules that promote atherosclerosis

Table 2 lists some of the immune responses that have been associated with promoting atherosclerosis, not only in individuals with autoimmune diseases but also in individuals with clinical atherosclerosis who have no obvious autoimmune or rheumatic diseases. The immune basis of atherosclerosis has been reviewed recently [16,17]. In brief, autoantibodies to several self molecules are increased in individuals with atherosclerosis, as listed in the table. Similarly, autoreactive T cells have been isolated from atherosclerosis lesions and circulation of individuals with atherosclerosis. It is interesting that both antibodies and T cells that recognize particular heat shock proteins, particularly Hsp65, have been implicated in the disease. Since antibodies to phospholipids are essentially antibodies to oxidized lipids, it is no surprise that they are linked to atherosclerosis in some studies, as well as to their better known pro-thrombotic effects. OxLDL themselves are linked to atherosclerosis, with higher levels (expressed as ratio

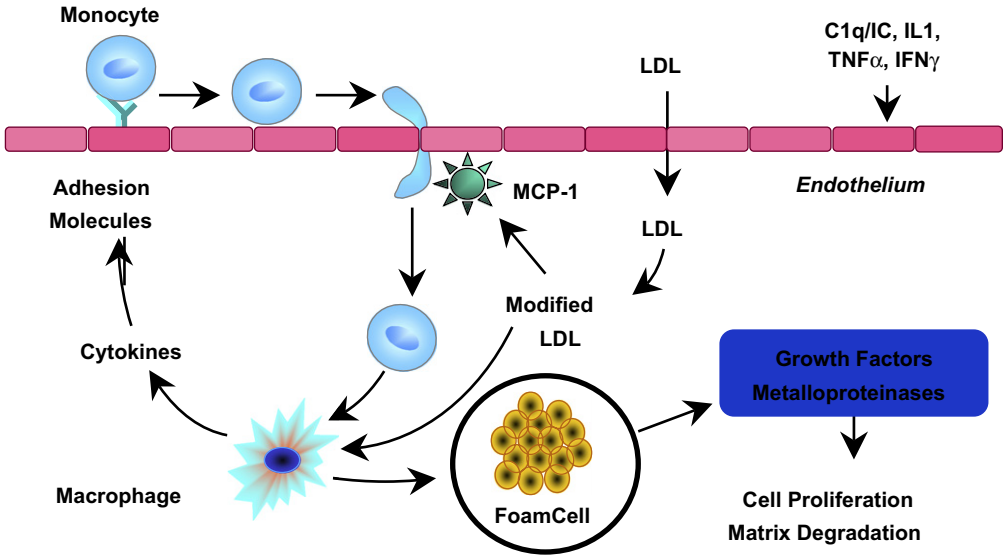

Fig. 1. Lipids and inflammation combine to produce atherosclerotic plaque. See text for description. Adapted by the authors from Mackness et al., Lipids Online 2004.