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REVIEW

Dendritic cells: An important link between antiphospholipid antibodies, endothelial dysfunction, and atherosclerosis in autoimmune and non-autoimmune diseases

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Abstract The presence of dendritic cells, antigen-presenting cells that link innate and adaptive immunity, is necessary to generate and maintain the production of antiphospholipid antibodies in response to exposed intracellular phospholipids on the outer surface of apoptotic cells. In turn, antiphospholipid antibodies enhance dendritic cell-induced inflammatory and proatherogenic responses in a number of conditions that are associated with accelerated atherosclerosis, including diabetes, chronic kidney disease, periodontal infections, and aging. While altering dendritic cells by modifying the ubiquitin–proteasome system enhances antiphospholipid antibody production and leads to development of accelerated atherosclerosis and autoimmune features, inducing tolerance by dendritic cell manipulation leads to decreased atherosclerosis and thrombosis. Therefore, further translational studies are needed to understand the interplay between dendritic cells and antiphospholipid antibodies, and to develop potential new therapies for antiphospholipid syndrome and atherosclerosis. Here we review current experimental and translational studies that have examined the role of dendritic cells in antiphospholipid antibody formation and in antiphospholipid-associated atherosclerosis and thrombosis.

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Contents

1. Introduction

Antiphospholipid antibodies (aPL Abs) are a heterogeneous group of Abs against phospholipids or phospholipid-binding proteins found not only in individuals with autoimmune diseases, but also in individuals without overt autoimmune diseases [1]. Antiphospholipid syndrome (APS) is characterized by the presence of persistent aPL Abs associated with arterial and/or venous thrombosis and increased pregnancy morbidity [2,3]. While not all aPL Abs are pathogenic, it has been well established that Abs against cardiolipin (aCL Abs) and particularly Abs against beta2 glycoprotein I (anti-β2-GPI Abs), a plasma protein that binds to negatively charged phospholipids, play an instrumental role in the pathogenesis of APS [4–7]. While an association between aPL Abs and accelerated atherosclerosis with and without APS has also been proposed, the exact mechanisms are not well understood [8–14].

Atherosclerosis is a complex process that is initiated when low density lipoprotein (LDL) molecules are deposited in the arterial walls, where they become oxidized by reactive oxygen species or enzymes, such as myeloperoxidase or lipoxygenase. Oxidized LDL (oxLDL) particles are phagocytosed by macrophages and become foam cells that are subsequently deposited within arterial walls, where they release pro-inflammatory cytokines such as TNF-α and IL-1, matrix metalloproteinases and oxygen-activated radicals. In addition to macrophages, monocytes, neutrophils and dendritic cells (DCs) also contribute to endothelial activation and increased expression of adhesion molecules including E-selectin and VCAM-1, which leads to further immune system activation and plaque formation. Acute plaque rupture and thrombus formation can cause stroke or acute myocardial infarction [15–20].

APS and atherosclerosis share several similar features: increased levels of Abs to oxLDL, phospholipids and heat shock proteins, endothelial dysfunction, platelet activation and thrombus formation, increased oxidative stress and increased immune cell activation (Fig. 1). Several more potential contributions of aPL Abs in atherosclerosis have been proposed, including proatherogenic modification of LDL and high density lipoprotein (HDL), increased endothelial damage and immune system activation [8–11,13]. However, the epidemiologic evidence that the presence of aPL Abs may be a serologic marker or an independent risk factor for atherosclerosis is inconclusive [21,22].

Here we review experimental and translational evidence suggesting that DCs may play an important role in the generation and maintenance of aPL Abs, and illustrate a key connection between DCs, aPL Abs, innate and adaptive immunity and atherosclerosis.

2.1. The role of DCs in autoimmunity and atherosclerosis

DCs are antigen-presenting cells that link innate and adaptive immunity, and play an important role in the pathogenesis of atherosclerosis [20] and autoimmune diseases [23]. Conventional DCs search peripheral tissues for pathogens, secrete cytokines, present antigen, and activate naive T-cells. In addition, conventional DCs play a role in inducing and maintaining central and peripheral self-tolerance and minimizing autoimmune reactions. Plasmacytoid DCs (pDCs)

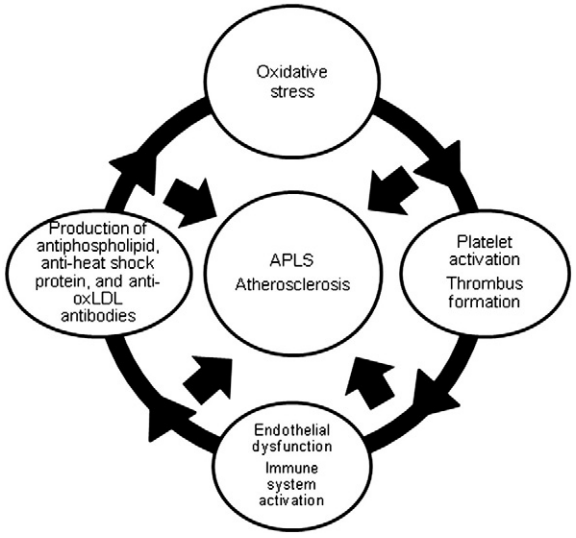

Figure 1 Common pathways in antiphospholipid syndrome and in atherosclerosis. APLS and atherosclerosis share several common pathways including production of antibodies to phospholipids, heat shock proteins, and oxidized LDL; endothelial dysfunction; immune cell activation; oxidative stress; and platelet activation and thrombus formation.