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Review

Humoral and cellular immune responses in atherosclerosis: Spotlight on B- and T-cells☆,☆☆

Padmapriya Ponnuswamy [a,1], Emily A. Van Vré [a,1], Ziad Mallat [a,b], Alain Tedgui [a,*]

[a] INSERM, U970, Paris-Cardiovascular Research Center (PARCC), Université Paris Descartes, Paris, France
[b] Division of Cardiovascular Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 2QQ, England, UK

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ABSTRACT

Despite more than 1 million basic and clinical investigation reports on the mechanism and clinical outcome of cardiovascular events, the pathogenesis of this multi factorial disease is still incompletely understood, which is illustrated by the fact that it is still the leading cause of death in the western world. Over the decades it has been well approved that in addition to lipid dysfunction and arterial lipid accumulation, inflammation and autoimmune responses are major factors in directing the initiation and progression of atherosclerosis, the underlying cause of cardiovascular diseases. Atherosclerosis involves both humoral and cellular compartments of innate and adaptive immunity making it a very complex disease. This review discusses the innate and adaptive immune responses in atherosclerosis, with a focus on T- and B-cell mediated processes.

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1. Introduction

Cardiovascular diseases, which include stroke, coronary artery diseases (CAD) and myocardial infarction are the leading cause of morbidity and mortality in the western world, despite a decline in incidence and prevalence of these events over recent years (Roger et al., 2011). Atherosclerosis is known to be the primary underlying factor of these cardiovascular events. Though hypercholesterolemia was initially considered to be the major risk factor of atherosclerosis, recent advances in atherosclerosis research have proven beyond doubt that chronic inflammation and autoimmunity play a major role in the initiation and progression of the disease (Hansson and Hermansson, 2011). Both innate and adaptive immune responses are implicated in chronic inflammation, characterized by a complex interplay between different cell types and their products.

One of the triggering events in the initiation of atherosclerotic lesion formation is the oxidation of low density lipoproteins (LDL) which occurs as a result of increased oxidative stress. Generation

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* Corresponding author at: Paris-Cardiovascular Research Center, French National Institute of Health and Medical Research U970, Université Paris Descartes, 56 rue Leblanc, 75015 Paris, France.
E-mail address: alain.tedgui@inserm.fr (A. Tedgui).

[1] Authors contributed equally.

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of oxidized (ox)LDL induces endothelial cell (EC) activation, resulting in the recruitment of several immune cells in the subendothelial space, such as peripheral monocytes, T- and B-lymphocytes. Infiltrated monocytes differentiate into macrophages or dendritic cells (DCs), which can turn into foam cells after excessive lipid uptake (Fig. 1). In the arterial intima these immune cells generate various cytokines and chemotactic factors that lead to a cascade of events, involving recruitment of more inflammatory cells, further lipid accumulation, increased migration, differentiation and proliferation of smooth muscle cells (SMCs), apoptosis and development of a necrotic core, eventually leading to formation of advanced lesions. Advanced, rupture-prone lesions which are associated with clinical events, contain increased numbers of macrophages, T-cells, natural killer cells (NK), neutrophils, mast cells and lesional DCs but fewer SMCs and collagen content (Hansson and Hermansson, 2011; Weber and Noels, 2011).

2. Humoral and cellular immune responses in atherosclerosis

Chronic inflammation and autoimmunity involve both humoral and cellular compartments of innate and adaptive immune responses. Humoral immune responses are initiated when antibodies produced by B-cells recognize foreign or self-antigens and form immune complexes, tagging them for elimination by macrophages. Presence of auto-antibodies and immune complexes against oxLDL within atherosclerotic lesions shows that humoral immunity is involved in the pathogenesis of atherosclerosis (Pereira and Borba, 2008). Furthermore, antibodies against various self-antigens like Hsp-60/65, oxidized phospholipids and β2-glycoprotein (β2-GP) are associated with atherosclerosis (Pereira and Borba, 2008). Innate immune responses in atherosclerosis are mainly governed by monocytes/macrophages and DCs. Abundant macrophages and fewer DCs are detected within both early and advanced atherosclerotic lesions (Moore and Tabas, 2011; Van Vre et al., 2011a). A large body of evidence suggests that macrophages are mainly pro-atherogenic, though certain macrophage subtypes might also exert anti-atherogenic effects (reviewed by Mantovani et al., 2009; Moore and Tabas, 2011). Also, different DC subtypes may have different stimulatory or regulatory functions in atherosclerosis, which are still being investigated (Ju et al., 2010; Van Vre et al., 2011a,b; Weber et al., 2011). Interestingly, though a pro-atherogenic role of DCs was demonstrated (Paulson et al., 2010; Shaposhnik et al., 2007), recently it was proposed that certain subtypes such as plasmacytoid DCs (Daissormont et al., 2011) and FLT3 signaling-dependent DCs (Choi et al., 2011) have a protective role in atherosclerosis. As antigen presenting cells (APCs), macrophages and DCs present atherosclerosis related antigens to T-cells and subsequently generate adaptive immune responses (Lahoute et al., 2011). The power of adaptive immunity resides in the high degree of specificity and its ability to create an immunological memory. Interestingly, T-cells reactive to oxLDL have been described in atherosclerotic patients (Frostegard et al., 1992; Stemme et al., 1995) but most likely many antigens drive the development of atherosclerosis, and research is ongoing to pinpoint atherosclerosis-specific antigens. Though a recent study has shown that unmodified native LDL can itself induce atherosclerosis promoting T-cell responses (Hermansson et al., 2010), in general it is assumed that molecular mimicry and development of neo-antigens through, for instance, oxidation processes trigger the immune system in atherosclerosis (Y. I. Miller et al., 2011). DCs orchestrate naïve T-cell differentiation into specific T helper (Th) subtypes with distinct and adequate immune responses. On the other hand, Th cells participate in humoral immune responses, by "helping" B-cell isotype switching resulting in the generation of antigen specific antibody production, and by induction of B-cells into antibody producing plasma cells, thus resulting in a vicious cycle of inflammatory processes. Earlier studies demonstrated the importance of adaptive immunity in atherosclerosis. Immunodeficient RAG1$^{-/-}$ or scid/scid mice with impaired T- and B-cell development illustrated that the net effect of deficiency in T- and B-cells is 40–80% reduction of the atherosclerotic lesion development (Tedgui and Mallat, 2006). On the contrary transfer of T-cells sensitized to oxLDL into scid/scid/apoE$^{-/-}$ mice accelerated atherosclerotic lesion development (Zhou et al., 2000).

2.1. Humoral immune responses in atherosclerosis

Maintenance of normal vascular homeostasis is important for a healthy vessel and the endothelium plays a crucial role in serving as a first line of defense, preventing infiltration of immune cells in the intima. Classical risk factors like hyperlipidemia, smoking, disturbed blood flow and oxidative stress are known to cause endothelial cell dysfunction (Munzel et al., 2008). In addition to these risk factors, anti-endothelial cell antibodies (AECA), a heterogeneous group of auto-antibodies, detected in a variety of disorders, are implicated with disruption of the endothelial barrier (Elsheikh et al., 2010). High titres of AECA and auto-antibodies against endothelial protein C receptor (EPCR) were observed in patients with myocardial infarction compared to controls (Elsheikh et al., 2010; Montes et al., 2005). Following inflammatory stimuli, auto-antibodies generated against sialic acid N-glycolylneuraminic acid (Neu5Gc, expressed on the endothelium and sub-endothelium of atherosclerotic plaques), lead to endothelial activation, increased cytokine secretion, complement deposition and monocyte binding (Pham et al., 2009). Also, auto-antibodies to self-antigen beta2-glycoprotein 1 (β2-GP 1) expressed on endothelial cells may cause cellular damage (Xu, 2002). Due to molecular mimicry, immune responses against microbial heat shock proteins (Hsp)-65 and Hsp-60 can lead to cross reactivity of microbial antibodies against human Hsp-60, which is expressed by stressed vascular cells. Indeed, more than a decade ago it was shown that high titres of Hsp-65 auto-antibodies are associated with atherosclerosis, independent of other risk factors in humans (Xu et al., 1999; Xu et al., 1993a,b) and animals (Xu et al., 1993a,b). The capacity of Hsp-60 auto-antibodies to directly induce atherosclerosis was demonstrated by injection of human and murine Hsp-60 auto-antibodies in apoE$^{-/-}$ mice (Foteinos et al., 2005). Similarly, several studies have reported the association of Hsp-70 auto-antibodies with atherosclerosis (Kocsis et al., 2002; Zhang et al., 2010).

In addition, oxidized epitopes on apoptotic cells and oxLDL may reveal antigenic sequences that are normally absent or concealed and will generate humoral immune response by inducing auto-antibodies against these antigens (Miller et al., 2011). Also, circulating antibodies that recognize peptides of apoB-100, the primary apolipoprotein of native LDL have been identified and shown to have an inverse correlation with atherosclerosis (Sjogren et al., 2008). Interestingly, several studies demonstrated a positive correlation of circulating oxLDL specific auto-antibodies and atherosclerosis in both humans and mice (van Leeuwen et al., 2009). Moreover, plasma oxLDL IgG and IgA antibodies correlated with myocardial infarction (Wu et al., 1997). On the other hand, attenuated atherosclerosis following lipid lowering therapy was associated with a reduction in oxLDL auto-antibody levels (Kural et al., 2004; Orem et al., 2002). IgM and IgG antibodies are present within human atherosclerotic lesions. The role of IgM antibodies has been studied in detail in mouse atherosclerosis and was shown to play a protective role (Binder et al., 2004; Faria-Neto et al., 2006). Clinical studies showed a positive correlation of oxLDL IgG antibodies with cardiovascular events, and an inverse correlation of IgM oxLDL antibodies, independent of other risk factors (Dotevall et al., 2001; Hulthe et al., 2001; Tsimikas et al., 2007). In LDLr$^{-/-}$ mice, blocking of TNF receptor super family 4 (OX40 ligand) resulted in reduced atherosclerosis associated with low serum anti-oxLDL specific IgG1 and high atheroprotective IgM levels against oxLDL (van Wanrooij et al., 2007). Based on the current knowledge on oxLDL antibodies in atherosclerosis, it can be hypothesized that oxLDL specific IgM antibodies are anti-atherogenic whereas the IgG response to the oxLDL is pro-atherogenic (Shoenfeld et al., 2004; van Leeuwen et al., 2009).