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REVIEW

Accelerated vascular disease in systemic lupus erythematosus: Role of macrophage

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Abstract Atherosclerosis is a chronic inflammatory condition that is considered a major cause of death worldwide. Striking phenomena of atherosclerosis associated with systemic lupus erythematosus (SLE) is its high incidence in young patients. Macrophages are heterogeneous cells that differentiate from hematopoietic progenitors and reside in different tissues to preserve tissue integrity. Macrophages scavenge modified lipids and play a major role in the development of atherosclerosis. When activated, macrophages secret inflammatory cytokines. This activation triggers apoptosis of cells in the vicinity of macrophages. As such, macrophages play a significant role in tissue remodeling including atherosclerotic plaque formation and rupture. In spite of studies carried on identifying the role of macrophages in atherosclerosis, this role has not been studied thoroughly in SLE-associated atherosclerosis. In this review, we address factors released by macrophages as well as extrinsic factors that may control macrophage behavior and their effect on accelerated development of atherosclerosis in SLE.
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Contents

Abbreviations: SLE, systemic lupus erythematosus; CVD, cardiovascular disease; oxLDL, oxidized low-density lipoprotein; oxLDL-IC, oxidized low-density lipoprotein immune complex; HDL, high-density lipoprotein; dsDNA, double stranded DNA; IFNγ, interferon gamma; TNFα, tumor necrosis factor alpha; IL-1α, interleukin 1 alpha; IL-1β, interleukin 1 beta; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemotactic protein-1; MIF, macrophage migration inhibitory factor; CRP, C-reactive protein; SK, sphingosine kinase; S1P, sphingosine 1-phosphate; dh-S1P, dihydrosphingosine 1-phosphate; RA, rheumatoid arthritis; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; M-CSF, macrophage colony stimulating factor; ONOO−, peroxynitrate; HSP70B′, heat shock protein 70B′; NK cells, natural killer cells.

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1. Introduction

Atherosclerosis is a chronic inflammatory disease affecting the arterial intima [1], involving adaptive and innate immunological responses [2,3]. Noninvasive investigations have shown increases in intima–media thickness, carotid plaque build-up, and coronary artery calcifications in subjects with SLE [4]. Atherosclerosis has been recognized as a major co-morbid condition in systemic lupus erythematosus (SLE) with a 5–10 fold increase in risk of developing cardiovascular disease (CVD) compared to age-matched controls [5]. Women with SLE in the 35–44 year age group have an estimated 50-fold increased risk of myocardial infarction compared to age and sex-matched controls [6]. Although patients with SLE are subject to the same traditional CVD risk factors (e.g., hypertension, dyslipidemia, diabetes, old age, tobacco use, and postmenopausal status) as the general population, several studies showed that these factors do not sufficiently account for the increased level of CVD in SLE patients (reviewed in 7–9). Controlling for traditional risk factors as defined by the Framingham studies, there is a substantial and statistically significant increase in CVD and stroke among SLE patients [10]. It has been found, however, that 53% of patients with SLE had at least three traditional CVD risk factors [11]. Some traditional risk factors may also interact with the management of SLE disease activity (e.g., smoking, diabetes and hyperlipidemia) [7]. Systemic inflammation, antiphospholipid antibodies, and low levels of the natural antiphosphorylcholine antibodies are examples of non-traditional CVD risk factors in lupus [7–9]. Anti-phospholipid antibodies (anticardiolipin antibody, anti-β2-glycoprotein I, and lupus anticoagulant), which are usually generated against phospholipid binding proteins, have been associated with myocardial infarction in the general population [12]. However, the association of anti-phospholipid antibodies with CVD in patients with SLE has been inconsistent [7]. The underlying mechanisms responsible for the increase in morbidity and mortality due to SLE-related CVD remain unclear.

Atherosclerosis is identified by a passive accumulation of lipids in the vessel wall forming an atherosclerotic plaque. However, inflammation plays a role not only in the development of the atherosclerotic lesion but also in acute plaque ruptures resulting in acute myocardial ischemic events [13,14]. Lupus is an autoimmune disease in which the immune system attacks its own cells and tissues causing inflammation. A hallmark of both atherosclerosis and SLE-related inflammation is increased modification of lipoproteins and increased production of autoantibodies [15–18]. In addition, SLE patients have a tendency to develop pro-atherogenic lipids [19,20], and/or a defect in endothelial cell function [21]. More specifically, SLE patients show decreased levels of high-density lipoproteins (HDL) with increased triglycerides and oxidized low-density lipoproteins (oxLDL) levels compared to healthy controls [22–24], thus predisposing them to coronary artery disease. Moreover, modified lipoproteins and circulating antibodies act in concert, accelerating chronic inflammation and the development of atherosclerosis largely by the transformation of monocytes into foam cells [25]. While it is established that foam cell accumulation is a critical event in atherogenesis, the underlying mechanisms responsible for CVD intensification in SLE are not yet fully understood. Numerous studies have improved our understanding of the diverse components of immune dysregulation in SLE; however, the pathophysiologic role(s) of monocytes/macrophages remains unclear.

The macrophage is a heterogeneous cell that differentiates from hematopoietic progenitors which can generate dendritic cells, osteoclasts, and monocytes as well as macrophages [26]. Monocytes circulate in the blood, but when activated reside in tissues as macrophages. Macrophages are active in both innate and adaptive immune responses, in addition to their known role in reverse cholesterol transport [27]. They are also involved in normal tissue homeostasis through the uptake and clearance of apoptotic cells, and in resorption of bone during normal bone remodeling [26]. A classically activated macrophage requires both interferon gamma (IFN-γ) and either the induction of tumor necrosis factor alpha (TNF-α), or the engagement of toll-like receptors typically by a microbial product [28]. In response, the macrophage secretes inflammatory cytokines such as interleukin-1β (IL-1β) and TNF-α, and chemokines that drive an immune reaction [29].

Theories formulated in the 1980s proposed that monocytes/macrophages in lupus display a defective phagocytic function, enabling the aberrant accumulation of apoptotic debris. This in turn can lead to a sequel of autoimmune events. However, studies exploring lupus nephritis suggested a more active role of monocytes/macrophages in mediating

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