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Survey

Cytokines in atherosclerosis: Key players in all stages of disease and promising therapeutic targets

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ABSTRACT

Atherosclerosis, a chronic inflammatory disorder of the arteries, is responsible for most deaths in westernized societies with numbers increasing at a marked rate in developing countries. The disease is initiated by the activation of the endothelium by various risk factors leading to chemokine-mediated recruitment of immune cells. The uptake of modified lipoproteins by macrophages along with defective cholesterol efflux gives rise to foam cells associated with the fatty streak in the early phase of the disease. As the disease progresses, complex fibrotic plaques are produced as a result of lysis of foam cells, migration and proliferation of vascular smooth muscle cells and continued inflammatory response. Such plaques are stabilized by the extracellular matrix produced by smooth muscle cells and destabilized by matrix metalloproteinase from macrophages. Rupture of unstable plaques and subsequent thrombosis leads to clinical complications such as myocardial infarction. Cytokines are involved in all stages of atherosclerosis and have a profound influence on the pathogenesis of this disease. This review will describe our current understanding of the roles of different cytokines in atherosclerosis together with therapeutic approaches aimed at manipulating their actions.

Contents

Abbreviations: ABC, ATP-binding cassette; ACAT-1, acyl-CoA acyl transferase-1; ADRP, adipocyte differentiation related protein; Apo, apolipoprotein; BMT, bone marrow transplantation; CANTOS, Canakinumab Anti-inflammatory Thrombosis Outcomes Study; CIRT, Cardiovascular Inflammation Reduction Trial; CCR2, CC-chemokine receptor-2; CR, chemokine receptor; CVD, cardiovascular disease; CSF, colony-stimulating factor; DCs, dendritic cells; ECs, endothelial cells; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; Fn14, fibroblast growth factor-inducible 14; G-CSF, granulocyte colony-stimulating factor; GDF-15, growth differentiation factor-15; GM-CSF, granulocyte macrophage colony-stimulating factor; ICAM-1, intercellular adhesion molecule-1; IFN, interferon; IL, interleukin; IL-18BP, IL-18 binding protein; IL-1RA, IL-1 receptor antagonist; LDL, low-density lipoprotein; LDLr, low-density lipoprotein receptor; LFA1, lymphocyte function-associated antigen 1; LIGHT, homologous to lymphotoxin, exhibits inducible expression, and competes with HSV glycoprotein D for herpes virus entry mediator, a receptor expressed by T lymphocytes; M-CSF, macrophage-colony stimulating factor; MHC, major histocompatibility complex; MIF, macrophage migration inhibitory factor; miRNA, micro RNA; mmLDL, minimally modified LDL; MMP, matrix metalloproteinase; LXR, liver X receptors; NK, natural killer; NOD, nucleotide-binding oligomerization domain; NLR, NOD-like receptor; NLRP3, NLR family, pyrin domain containing 3; NPC, Niemann-Pick disease, type C; OxLDL, oxidized LDL; PAI, plasminogen activator inhibitor; PECAM-1, platelet endothelial cell adhesion molecule-1; PRR, pattern recognition receptor; RCT, reverse cholesterol transport; ROS, reactive oxygen species; SMCs, smooth muscle cells; SOCS, suppressor of cytokine signaling; SR, scavenger receptor; SREBP, sterol response element binding protein; SR-PSOX, SR that binds phosphatidyl serine and oxidized lipoprotein; STAT1, signal transducer and activator of transcription-1; TF, tissue factor; TGF, transforming growth factor; Th, T-helper; TIMP, tissue inhibitor of metalloproteinases; TNF, tumor necrosis factor; TL1A, TNF-like protein 1A; TNFSF12, TNF superfamily member 12; TLR, Toll-like receptor; TRAIL, TNF-related apoptosis-inducing ligand; Tregs, regulatory T cells; TWEAK, TNF-related weak inducer of apoptosis; VCAM-1, vascular cell adhesion molecule-1; VLA4, very late antigen 4; wt, wild type.

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1. Introduction

Cardiovascular disease (CVD) is responsible for most mortality worldwide and accounted for about 31.9% of all deaths in 2010 in the United States alone [1]. The total direct and indirect costs from CVD in 2010 were estimated at $315.4 billion [1]. Although morbidity and mortality from CVD has decreased in the last two decades, at least in the western world, it is expected that this will reverse in the future because of a global increase in diabetes and obesity along with an alarming rise in CVD in developing countries in part due to acquisition of a westernized lifestyle.

Atherosclerosis, the underlying cause of myocardial infarction, cerebrovascular accident or peripheral vascular disease, is the major cause of deaths from CVD. Atherosclerosis is now recognized as an inflammatory disorder of medium and large arteries initiated by risk factors such as high plasma cholesterol levels and hypertension [2]. Atherosclerosis develops during the lifespan of an individual and involves a number of steps: activation of the endothelium and recruitment of immune cells; monocyte differentiation and foam cell formation; development of fibrotic plaques due to death of foam cells and migration and proliferation of smooth muscle cells (SMCs); and plaque rupture and thrombosis [2] (Fig. 1). Both the innate and adaptive immune response in atherosclerosis is orchestrated by a range of cytokines, which regulate all stages of the disease [2–4].

Cytokines are a diverse group of low-molecular weight proteins with over 100 identified so far. Cytokines are clustered into several classes such as the interleukins (IL), chemokines, colony-stimulating factors (CSF), tumor necrosis factors (TNF), the interferons (IFN) and transforming growth factors (TGF) [2–4]. Many cytokines are expressed in atherosclerotic plaques and all cells involved in the disease are capable of producing cytokines and responding to them [2]. They can be generally classified as pro- or anti-atherogenic though the roles of some are not as clear-cut and often context-dependent [2–4]. This review will discuss the roles of key cytokines in different stages of atherosclerosis. Although *in vitro* studies using cell culture model systems have made a major contribution in advancing our understanding of the roles of cytokines in the cellular processes associated with atherosclerosis, the major focus of this review will be on the outcome from studies using animal model systems. In particular, two mouse models, the apolipoprotein (Apo) E-deficient mice and the low-density lipoprotein receptor (LDLr)-deficient mice [5,6], have been particularly useful in advancing our understanding of the molecular basis of atherosclerosis and the roles of various cytokines in the disease [2–4]. The use of bone marrow transplantation (BMT) approaches in such models also informs on whether a particular phenotype is driven by hematopoietic or non-hematopoietic cells [5,6]. These mice can spontaneously form atherosclerotic lesions on a standard chow diet but feeding of a high fat, western-type diet can markedly speed up the development of the disease [5,6]. It should be noted that caution needs to be exerted in the extrapolation of outcomes from such mouse models to humans because of many differences between the two species, including in lipoprotein metabolism and the inflammatory response [7,8]. In addition, existing mouse models are not particularly useful for investigating the steps involved in the clinical complications of the disease, plaque rupture [7]. It is therefore important that wherever possible key findings are analyzed in the human context.

2. Initial stages of atherosclerosis: key roles for chemokines

Atherosclerotic plaques tend to form particularly at the inner curvatures and branch points of arteries that are often associated with disturbed blood flow, and is augmented by other factors such as high plasma low-density lipoprotein (LDL) concentration,

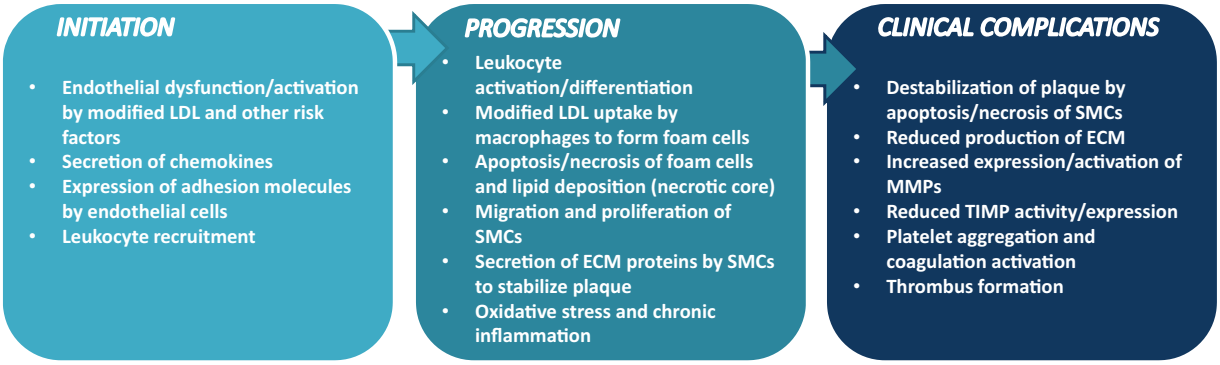

Fig. 1. *Pathogenesis of atherosclerosis.* The disease is initiated by the activation of the endothelium/endothelial cell (EC) dysfunction by accumulation of LDL, which subsequently gets modified (e.g. oxidized), together with other atherogenic factors. The activated ECs secrete a range of chemokines and increase the expression of adhesion proteins on their cell surface. This results in the recruitment and infiltration of immune cells such as monocytes. The monocytes differentiate into macrophages, which is accompanied by increased expression of pattern recognition receptors on their surface, which participate in the promotion of inflammation and uptake of modified LDL, leading to the formation of lipid laden foam cells. Continued accumulation of modified LDL together with disturbed cellular lipid homeostasis causes apoptosis/necrosis of foam cells resulting in lipid deposition (necrotic core) and amplification of the inflammatory response. Smooth muscle cells (SMCs) migrate from the media to the intima where they proliferate, uptake modified lipoproteins and secrete extracellular matrix (ECM) proteins that stabilizes the plaques (fibrous cap). Continued inflammation orchestrated by cytokines destabilizes such plaques via decreased production of ECM proteins (reduced synthesis together with apoptosis/necrosis of SMCs/SMC-derived foam cells), increased production/activities of ECM degrading matrix metalloproteinases (MMPs) and reduced expression/activities of inhibitors of these enzymes. Plaque rupture leads to platelet aggregation, coagulation and thrombus formation that ultimately results in the clinical complications associated with this disease. Cytokines affect all the different stages in the pathogenesis of atherosclerosis (see text for details). Abbreviations: ECM, extracellular matrix; LDL, low-density lipoprotein; MMP, matrix metalloproteinase; SMC, Smooth muscle cells; TIMP, tissue inhibitor of metalloproteinase.

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