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Review article

Role of inflammation in the pathogenesis of atherosclerosis and therapeutic interventions

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ABSTRACT

Rudolph Virchow (1821–1902) recognized inflammation in histological preparations of coronary arteries and proposed that inflammation plays a causal role in atherosclerosis. Despite this seminal observation, the main focus of research and drug development programs has been cholesterol alone, and inflammation received less attention over time. However, during the past several decades extensive observations supported the importance of inflammation in the development and destabilization of atherosclerosis. Studies in patients affected by rheumatological diseases suggested an interaction between chronic inflammation and atherosclerotic cardiovascular disease. Randomized clinical studies with lipid lowering agents suggested that part of the beneficial effect may have been related to reduction in inflammation. More recently, a few studies were designed to directly address the role of anti-inflammatory treatments in reducing risk of atherosclerotic heart disease beyond traditional risk factors. In this article, we review the pathophysiologic contribution of inflammation to atherosclerosis, biomarkers of inflammation and the evidence collected in observational studies regarding the role of chronic inflammation in the development of atherosclerotic heart disease. Finally, we discuss the most recent randomized clinical trials of anti-inflammatory agents directed at stemming atherosclerotic cardiovascular disease.

1. Introduction

For nearly a century, cholesterol has been considered the primary promoter of atherosclerosis development. First observed in arterial lesions of experimental rabbits in the early 1900s, cholesterol is now unequivocally recognized as a genetic and environmental driver of atherosclerotic disease [1]. Mechanistic understanding of the disease arose first from the 'response to injury' hypothesis put forward by Russell Ross, who postulated that endothelial injury induced proliferation and expansion of smooth muscle cells in the intimal space [2]. Although the observation that the atherosclerotic lesion is replete with inflammatory cells was made in the late 1800s, the contribution of immune cells to disease development began to be appreciated only in the last few decades [3]. The discovery of the contributions of the innate and adaptive immune system to atherogenesis has led to a refined understanding of lesion development that bridges both the cholesterol and injury hypotheses, and has led to a new line of inquiry for therapeutics to reduce vascular disease burden.

1.1. Retention and modification of lipoproteins

The initiating step in the development of atherosclerosis is the accumulation of low-density lipoproteins (LDL) that become sequestered in the subendothelial space by adhering to

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extracellular matrix proteins rich in proteoglycans (reviewed in Williams et al.) [4]. LDL can accumulate as a result of changes in endothelial permeability and paracellular transport between leaky cells or, as more recently described, through active receptor-mediated transcytosis across the cell membrane by transporters like SR-BI and Alk1 [5,6]. These recent studies have provided insight into a mechanism that was previously lacking with regards to how the endothelium enables the accumulation of large particles like LDL. Once in the sub-intimal space, LDL can undergo modification and become aggregated and/or oxidized. The aggregation of LDL results in large complexes ranging in size from 100 nm to 1.0 μm, which can undergo pinocytosis or phagocytosis by immune cells present in the subendothelial space [7]. The presence of reactive oxygen species and enzymes like lipoxygenases and myeloperoxidases modify both the phospholipid and protein components of LDL particles, rendering them substrates for scavenger receptor mediated uptake. Scavenger receptors present on innate immune phagocytes and antigen-presenting cells have evolved to recognize microbial and 'non-self' moieties, which are often in the form of oxidized phospholipids on bacteria [8]. Unlike native LDL uptake through the LDL receptor, scavenger receptor-mediated uptake is not subject to feedback inhibition by intracellular sterol levels, thus phagocytosis and/or receptor mediated uptake can continue unrestricted so long as there exists modified LDL in the extracellular milieu [9] (Fig. 1).

1.2. Recruitment of monocytes and their differentiation into macrophages

Numerous noxious stimuli (dyslipidemia, smoking, hypertension, abnormal blood rheology, viruses, etc) can cause endothelial damage [10,11]. The endothelium normally keeps a delicate balance of vasodilation, vasoconstriction and pro- and anti-coagulant activity. In the presence of damaging stimuli the endothelium responds by upregulating the transcriptional messenger NFkB and releasing a series of substances that enhance leukocyte adhesion on the endothelium E-selectin, vascular and inter-cellular adhesion molecules (VCAM-1 and ICAM-1), as well as endothelin and angiotensin II, and pro-coagulant factors. Rolling leukocytes adhere onto the endothelium and penetrate beneath the endothelial layer to reach the subintimal space. Modified lipoproteins are first taken up by tissue-resident dendritic cells and macrophages in the arterial intima [12]. Additionally, non-classical 'patrolling' monocytes can engulf oxLDL via scavenger receptor CD36 at very early stages of atherogenesis [13]. Immune cells further induce the expression of endothelial adhesion molecules (e.g. ICAM1) to recruit bone marrow derived monocytes into the intima. As they enter the subendothelial space, monocytes differentiate into macrophages and engulf modified LDL, where excess cholesterol is esterified for storage in lipid droplets, giving macrophages their foam-like appearance. Foam cells induce cytokine and chemokine production and the additional recruitment of circulating immune cells, setting off the sequelae of the inflammatory response. The activation of scavenger receptors, particularly CD36, by modified cholesterol engages innate immune responses downstream of the toll-like receptor pathway [14]. Most notably, cholesterol crystals induce the activation of the inflammasome in the cytoplasm of the macrophages in the arterial intima. The inflammasome is a protein complex that senses exogenous danger signals and cleaves pro-interleukin-1β (IL-1β) and IL-18 that are then secreted as activated cytokines. [15,16], IL-1α is also secreted in response to scavenger receptor activation by modified cholesterol, and has been postulated to play a more potent role in atherogenesis than IL-1β [17,18]. In the extracellular space, IL-1β, IL-1α and IL-18 interact with their cognate receptors and cause the release of reactive oxygen species, matrix degrading enzymes, activation and proliferation of T-cells and the further production of cytokines [19]. Of note, while some T-cells play a pro-atherogenic role such as T-helper-1 (Th1) cells, others have been shown to limit atherosclerosis progression [20]. For instance, regulatory T-lymphocytes (TREGs) secrete TGF-beta and IL-10, while T-helper 17 secrete IL-17 and they all help to stem atherosclerosis progression [21]. The signals downstream of IL-1-mediated inflammatory signaling make IL-1β one of the most potent drivers of atherosclerosis, and has thus been a recent focus of therapeutic developments. Of note, one of the major stimuli for IL-1β secretion is IL-1β itself.

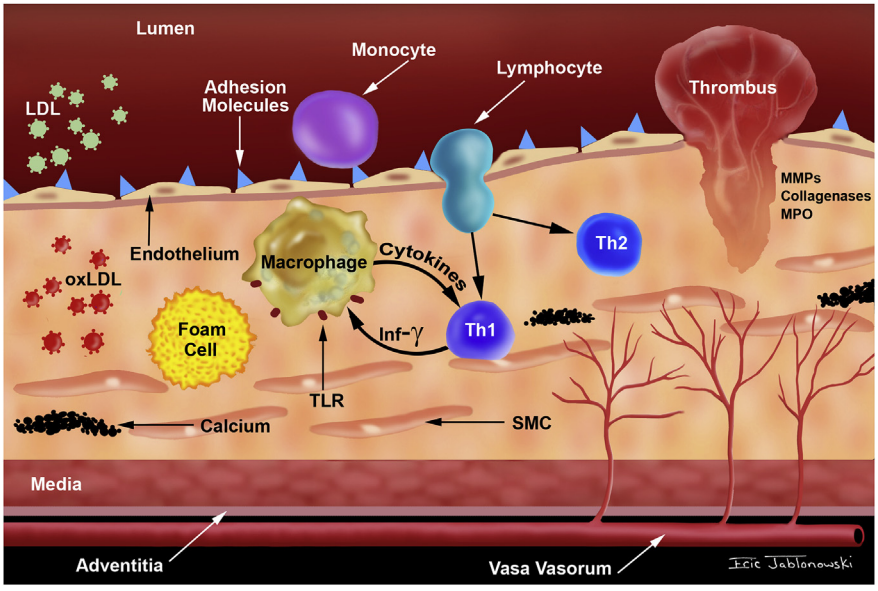

Fig. 1. Schematic and simplified representation of the multiple steps inherent with an atherosclerotic plaque formation and disruption.
Inf-Y; interferon gamma; MMPs: matrix metalloproteinases; MPO: myeloperoxidase; SMC: smooth muscle cells; Th1: lymphocyte T-helper 1; Th12: lymphocyte T-helper 2; TLR: toll like receptor (reproduced with permission from Raggi P, Alexopoulos N, McLean D, Lerakis S. Assessment of risk in the asymptomatic patient. In: Non-invasive cardiovascular imaging. A multimodality approach. (Editor: Garcia MJ. Lippincott, Williams&Williams, 2011).