The Epigenetic Memory of Monocytes and Macrophages as a Novel Drug Target in Atherosclerosis

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ABSTRACT

Purpose: Atherosclerosis is characterized by a persistent inflammation of the arterial wall. Monocyte-derived macrophages are the most abundant immune cells in atherosclerotic plaques. After stimulation, monocytes can adopt a long-term proinflammatory phenotype. This nonspecific memory of innate immune cells is mediated by epigenetic reprogramming and has recently been termed "trained innate immunity." The goal of this study was to describe the potential role of trained immunity in the development of atherosclerosis and to discuss the potential clinical implications of this concept.

Methods: We performed a comprehensive literature search (PubMed) on the role of epigenetic programming of histones, and of trained immunity in particular, in atherogenesis.

Findings: In vitro studies demonstrate that modified LDL particles can induce a long-term proinflammatory phenotype in monocytes/macrophages by epigenetic reprogramming at the level of histone methylation. This scenario is associated with increased production of proatherogenic cytokines and chemokines and increased formation of foam cells.

Implications: Preclinical evidence suggests that trained innate immunity may contribute to vascular wall inflammation in patients with risk factors for atherosclerosis. Epigenetic reprogramming is regulated by enzymes that are amenable to pharmacologic modulation. Therefore, this mechanism could be used to develop novel pharmacologic targets for the prevention or treatment of atherosclerotic vascular disease. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮)

Key words: atherosclerosis, epigenetic modifications, inflammation, monocytes.

INTRODUCTION

Despite major advances in prevention and treatment, cardiovascular disease (CVD) is still the leading cause of death worldwide, leading to 17 million deaths per year.[1] CVD is caused by atherosclerosis, a chronic inflammatory disorder of the arterial vessel wall, which may result in vascular occlusion and subsequent cardiovascular events. Traditional risk factors such as smoking, dyslipoproteinemia, hypertension, diabetes, and obesity are major factors that contribute to the development of atherosclerosis, but vascular inflammation is now recognized as the major driver of initiation, progression, and rupture of the atherosclerotic plaque.[2] Novel imaging techniques, such as ^{18}F-fluorodeoxyglucose-positron emission tomography scanning, have found that inflammation of the arterial wall is an important mechanism contributing to the occurrence of cardiovascular events in various patient groups.[3] In the past decade, novel risk factors for CVD associated with vascular inflammation have been identified, including HIV infection[4] and rheumatoid arthritis.[5] Currently, large clinical trials are being performed in patients at risk for CVD; study drugs include anti-inflammatory agents, such as the interleukin (IL)-1 receptor antagonist anakinra, the anti–IL-1β antibody canakinumab,

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and methotrexate.[6] However, these drugs are nonspecific and can have serious adverse effects. Therefore, a better understanding of the inflammatory mechanisms in atherosclerosis is needed to identify novel drugs targets that can be used in the prevention and treatment of atherosclerosis.

In the present review, we postulate that stable epigenetic changes of monocytes and macrophages contribute to the persistent inflammation observed in atherosclerosis and that pharmacologic modulation of these epigenetic modifications might offer a novel treatment strategy for patients with risk factors for arterial wall inflammation.

MATERIALS AND METHODS

We performed a comprehensive literature search (PubMed) on the role of epigenetic reprogramming of histones, and of trained immunity in particular, in atherogenesis.

RESULTS

The Role of Monocytes and Macrophages in Atherosclerosis

Because the general pathophysiology of atherosclerosis has been extensively described in earlier reviews,[2,7,8] this point is only briefly discussed. Atherosclerotic plaque formation is initiated by an accumulation of apolipoprotein B100–containing lipoproteins in the arterial wall, mainly at those points where the laminar flow is disturbed and the endothelium is permeable for lipoproteins.[7] These lipoproteins are susceptible to oxidation or other modifications in the intimal layer, leading to activation of the overlying endothelium. Subsequently, the intimal layer is infiltrated with various immune cells, including monocytes. A pivotal role for monocytes in the initiation of atherosclerosis is demonstrated by the observation that atherosclerosis development is reduced in animal models by prevention of monocyte entry into the vascular wall.[9] Once in the intimal layer, monocytes mature into macrophages, which promotes the development of atherosclerosis by several mechanisms. First, by taking up modified lipoproteins via scavenger receptors, macrophages become cholesterol-laden foam cells. Clearance of cholesterol by macrophages may initially be viewed as beneficial, but the cholesterol-laden macrophages eventually lose their ability to emigrate out of the plaque. Van Gils et al[10] recently showed that loading of macrophages with cholesterol promotes the expression of netrin-1, a protein that blocks macrophage emigration out of the lesion by binding to its membrane-bound receptor. Eventually, foam cells die and induce the formation of a necrotic core, which is a key component of advanced plaques.[2,11] Second, macrophages produce various proinflammatory cytokines and chemokines after stimulation with oxidized LDL (oxLDL) particles or other proinflammatory stimuli in the plaque. Modified LDL particles act as damage-associated molecular patterns, which are recognized by membrane-bound and intracellular pattern recognition receptors on monocytes and macrophages.[12] For example, oxLDL stimulates secretion of IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-α (TNF-α) by signaling through CD36 and Toll-like receptor (TLR)-2, -4, and/or -6 pathways.[13–15] Moreover, intracellular and extracellular cholesterol crystals activate the NLRP3 inflammasome, thus inducing processing and release of IL-1β.[14] Thirdly, in the last stage of atherosclerotic plaque formation, macrophages can contribute to destabilization of plaques by the formation of proteases, including various matrix metalloproteinases.[16] Macrophages importantly contribute to the various phases of atherosclerosis via all of these mechanisms.

Interestingly, the number and phenotype of circulating monocytes are also associated with the development of atherosclerosis. In humans, the characteristics of circulating monocytes can predict future cardiovascular events.[17] In atherosclerosis-prone mouse models, several conditions, including myocardial infarction or abdominal sepsis, accelerate subsequent atherosclerosis by inducing monocytosis.[18,19] Similarly, hypercholesterolemia accelerates atherosclerosis by increasing the number of monocytes and switching the phenotype of circulating monocytes toward proinflammatory Ly-6C^{high} monocytes.[20–22] Two recent studies have shed some light on the mechanism of this hypercholesterolemia-induced shift toward proinflammatory monocytes and monocytosis:[22,23] bone marrow transplantation from hypercholesterolemic into normocholesterolemic mice results in a pronounced and persistent monocytosis and a shift toward more proinflammatory monocytes even in the normocholesterolemic acceptor environment, suggesting priming of hematopoietic stem and progenitor cells.

Although the role of monocytes and macrophages in atherosclerosis is well established, it is still unknown why the strong inflammatory response in the