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Review article

Immunotherapy for the prevention of atherosclerotic cardiovascular disease: Promise and possibilities

Jay Khambhati*, Marc Engels, Marc Allard-Ratick, Pratik B. Sandesara, Arshed A. Quyyumi, Laurence Sperling**

Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA

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ABSTRACT

Cardiovascular disease remains the leading cause of death worldwide with coronary atherosclerotic heart disease being the largest contributor. The mechanisms behind the presence and progression of atherosclerosis remain an area of intense scientific focus. Immune dysregulation and inflammation are key contributors to the development of an atherosclerotic plaque and its progression to acute coronary syndromes. Increased circulating levels of biomarkers of systemic inflammation including hsCRP are correlated with a higher cardiovascular risk. Targeting specific inflammatory pathways implicated in atherosclerotic plaque formation is an exciting area of ongoing research. Target specific therapies directed at pro-inflammatory cytokines such as IL-1β, IL-6, TNFα, and CCL2 have demonstrated slowing in the progression of atherosclerosis in animal models and improved cardiovascular outcomes in human subjects. Most notably, treatment with the monoclonal antibody canakinumab, which directly targets and neutralizes IL-1β, was recently shown to be associated with reduced risk of adverse cardiovascular events compared to placebo in a randomized, placebo-controlled trial. Several other therapies including colchicine, methotrexate and leukotriene inhibitors demonstrate the potential for lowering cardiovascular risk through immunomodulation, though further studies are needed. Understanding the role of inflammation in atherosclerosis and the development of targeted immunotherapies continues to be an evolving area of research that is rapidly becoming clinically relevant for the 21st century cardiac patient.

1. Introduction

Cardiovascular disease remains the leading cause of death in the United States and across the globe [1]. Primary and secondary prevention of adverse cardiovascular events remains a critical priority to alleviating morbidity and mortality. Underlying mechanisms behind the development of atherosclerosis are intrinsically tied to immune dysregulation through inflammatory mediators [2]. Multiple pathologic drivers such as pro-inflammatory cytokines, leukocyte recruitment, and inflammatory signaling drive atherogenesis in the vessel wall and systemic inflammation [3]. While excess cholesterol storage is no longer viewed as the singular criteria to develop atherosclerosis, hypercholesterolemia is a permissive factor enabling other risk factors to take effect [3]. Thus, current treatment recommendations to prevent atherosclerotic cardiovascular disease (ASCVD) are targeted to lipid lowering therapy, aspirin therapy, and modification of established risk factors with anti-hypertensives, smoking cessation, and blood glucose control.

Recently, extensive investigative efforts have further detailed the role of inflammation underlying atherosclerosis, establishing biomarkers and delineating mechanisms of immunomodulation [4]. Extensive evidence correlating inflammatory diseases and cardiovascular risk also argues for a common underlying inflammatory pathway. The inflammatory hypothesis of atherothrombosis argues for a dynamic state of immune dysregulation from multiple actors detectable by biomarkers and treatable by immunomodulatory drugs (Fig. 1). Targeting immune mechanisms underlying cardiovascular disease introduces a renewed paradigm to the primary prevention of ASCVD. In this review, treatment avenues that target inflammation are discussed.

* Corresponding author.
** Corresponding author. 1365 Clifton Road, NE Building A, Suite 2200, Atlanta, GA, 30322, USA.
E-mail addresses: jay.khambhati@emory.edu (J. Khambhati), lsperli@emory.edu (L. Sperling).

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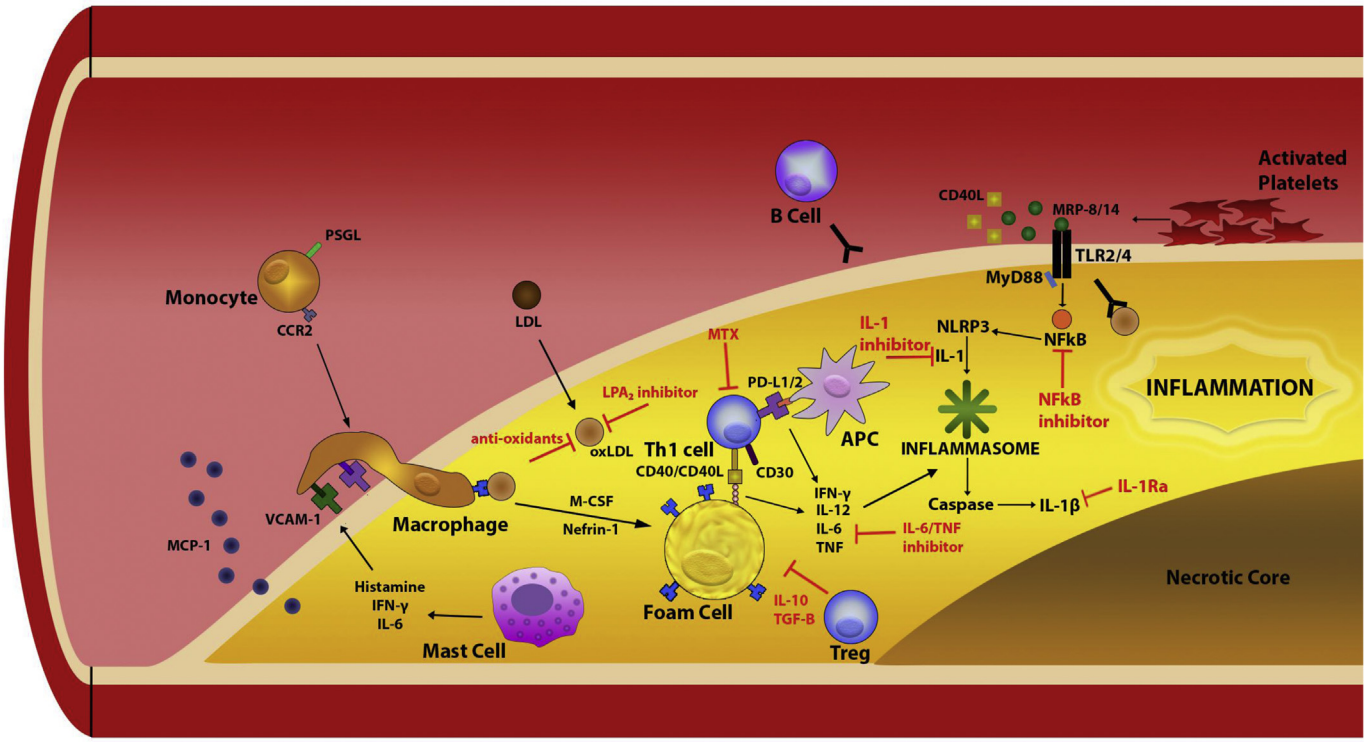

Fig. 1. Inflammatory pathways in the atherosclerotic process.
Potential treatment targets are depicted in red. In response to certain inciting processes (e.g. endothelial shear stress or hypertension), the endothelium upregulates VCAM-1 and MCP-1, in part via cytokine release from mast cells. As a result, circulating PSGL+/CCR2+ monocytes are recruited into the intimal layer. These monocytes differentiate via Nefrin and M-CSF into macrophages, which internalize oxidized LDL and form foam cells. Th1 cells interact with foam cells via activated CD30 and CD40/CD40L and with APCs via PD-L1/2, thereby releasing pro-inflammatory cytokines such as IFN-gamma, IL-6, IL-12 and TNF. This is counteracted by anti-inflammatory effects of IL-10 and TGF-beta via Treg cells. Activated platelets release MRP-8/14, CD40L and IL-6, which activates TLR 2/4-MyD88 leading to downstream activation of the NFκB pathway. This activates NLRP3 and its associated inflammasome via IL-1 signaling, as well as via the cytokines released from activated Th1 cells. Inflammasome activation has many pro-inflammatory effects, such as activation of caspase, which contributes to foam cell apoptosis and cell necrosis. The resulting lipid-laden cellular debris accumulates in the necrotic core, which forms an atherosclerotic plaque. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2. Concept of inflammation in atherosclerotic vascular disease

Earlier concepts of the underlying mechanisms of atherosclerosis were largely based on the primary pathophysiologic importance of hypercholesterolemia in the inception of atherosclerotic cardiovascular disease (ASCVD). Atherosclerosis was believed to be a due to deposition of lipid debris in the arterial wall with concomitant proliferation of smooth muscle cells in the sub-intimal layer leading to formation of the atheromatous plaque. Progressive accumulation of a variety of cells and lipid was considered to result in plaque growth, plaque instability and eventually rupture, leading to an acute coronary syndrome. As insights into the contribution of endothelial dysfunction to the atherosclerotic process became evident, so did the realization of the role of inflammation as a key regulator of atherosclerosis progression [3,5,6].

Diabetes, smoking, hypertension, and the metabolic syndrome as well as autoimmune diseases are well known risk factors for ASCVD and are associated with a state of chronic inflammation [7–10]. Elevation of high sensitivity CRP (hsCRP), a systemic marker of inflammation, was shown to be a predictor of ASCVD events [11]. Although hsCRP is likely not directly involved in the atherosclerotic process, its increase points to a low level systemic inflammatory state. Together with smooth muscle cells, immune and inflammatory cell infiltration was long appreciated in atherosclerotic lesions [12,13]. Evidence of local adaptive and innate immune activation in atherosclerosis further solidified the concept of an active inflammatory process orchestrating atherosclerosis, supporting the inflammatory hypothesis of atherothrombosis [2,14].

3. Basic mechanisms of inflammation in atherosclerosis

3.1. Innate immunity in atherosclerosis

The innate immune system is heavily involved even in the earliest stages of atherosclerosis. The healthy vascular endothelium is relatively resistant to prolonged contact with leukocytes. Exposure to certain known cardiovascular risk factors (e.g. hypertension, hypercholesterolemia, diabetes mellitus, smoking, disruptions in laminar shear stress) stimulates the arterial endothelium to express adhesion molecules including vascular cell adhesion molecule-1 (VCAM-1) and chemokines such as monocyte chemoattractant protein-1 (MCP-1). These molecules recruit circulating monocytes and dendritic cells into the intimal layer. Upon stimulation by cytokines, such as monocyte-colony stimulating factor (M-CSF) monocytes differentiate into macrophages, the most common cell type in the atheromatous plaque [15,16]. Upon entry, these cells are retained in the atherosclerotic lesion due to paracrine signaling via netrin-1 [17,18]. Macrophages express scavenger receptors on their surface that permit internalization of LDL particles after oxidation. LDL oxidation is a necessary step for binding with macrophage scavenger receptors and therefore can catalyze foam-cell formation. Reactive oxygen species attack double bonds in unsaturated fatty-acids of cholesteryl esters that can generate crosslinks between free amino groups on Lys and Arg residues. These post-