Journal of Cardiology 66 (2015) 1–8

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Review

Anti-inflammatory and immune-modulatory therapies for preventing atherosclerotic cardiovascular disease

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ARTICLE INFO

Article history:
Received 30 January 2015
Accepted 31 January 2015
Available online 2 March 2015

Keywords:
Inflammation
Vaccine
Regulatory T cell
Intestinal immunity

ABSTRACT

Atherosclerosis is believed to be a chronic inflammation of the arterial wall and various immune cells of innate and adaptive immunity involves in the pathogenesis of atherosclerosis. Based on this notion, several anti-inflammatory strategies for prevention of atherosclerosis have been examined mainly using animal models. Vaccination or mucosal immunization with athero-antigens comes under candidate therapeutic methods for antigen-specific prevention of atherosclerosis. Immune suppression mediated by regulatory T cells (Tregs) could be another method to regulate pathogenic chronic inflammation in atherogenesis. Inducible Tregs are reported to differentiate peripherally in the intestine and we have been interested in the oral tolerance, in which not only Tregs but also tolerogenic dendritic cells play crucial roles. We demonstrated that modulation of the intestinal immunity including oral tolerance could be a novel therapy against atherosclerosis. Further, downregulation of effector T cell response and/or Treg predominant condition was shown to induce atherosclerosis regression and inhibit the progression of aneurysm.

In clinical situations, none of the approaches to specifically and directly treat inflammation to prevent cardiovascular events or reduce atherosclerosis in human individuals were successful, although high-sensitive C-reactive protein is shown to have a strong relationship with recurrent events of cardiovascular diseases in several randomized clinical trials. Now two randomized placebo-controlled clinical trials evaluating anti-inflammatory agents are being conducted in the USA and Canada to clarify whether targeting the inflammation itself will reduce cardiovascular events and risks.

In this review, we present the current understanding of anti-inflammatory and immune-modulation therapies against atherosclerosis and discuss the future perspectives.

Contents

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http://dx.doi.org/10.1016/j.jjcc.2015.02.002
0914-5087/

Introduction

Cardiovascular disease (CVD), a leading cause of mortality in many developed and developing countries, is caused mainly by atherosclerosis. Clinical studies and animal experiments have established that high plasma concentrations of cholesterol, mainly transported by low-density lipoprotein (LDL), promote atherosclerotic CVD and statin-based lipid lowering therapy reduces CV events. However, some clinical trials revealed residual cardiovascular risks cannot be ignored even after the aggressive reduction of LDL cholesterol to target levels. Despite great advances in treating acute coronary syndrome with catheter-based therapies and controlling risk factors of CVD, there is still an enormous need for additional therapies as the recurrent rate of CV events remains at about 20% within 3 years even with optical medical treatment [1].

Atherosclerosis is considered not only a disorder of lipid accumulation in the arterial wall but also a chronic inflammatory disease that contains components of both innate and acquired immune systems [2–5]. Several immune responses are critical factors in the initiation and progression of atherosclerosis (Fig. 1). The first step preceding the atherosclerotic lesion formation is endothelial activation or dysfunction and LDL-cholesterol deposition in the arterial wall, which are mediated by coronary risk factors such as dyslipidemia, hypertension, diabetes mellitus, and smoking. Secondly, the accumulated LDL is oxidized and the resultant formation of oxidized LDL (OxLDL) has been suggested to be the critical event in deteriorating inflammation in vascular wall. Thirdly, not only monocytes but also various types of leukocytes adhere to the activated endothelium, migrate into the arterial wall via upregulated adhesion molecules, and produce pro-inflammatory cytokines or chemokines. Subsequently, monocyte-derived macrophages take up OxLDL via scavenger receptor leading to the formation of lipid-laden foam cells. Following such steps, the initial fatty streaks contain lipids and numerous immune cells such as macrophages, dendritic cells (DCs), and T lymphocytes. Progressed atherosclerotic lesions involve the migrated smooth muscle cells (SMCs), debris, apoptotic cells, and extracellular matrix such as collagen and proteoglycans [5]. B lymphocytes and their producing immunoglobulins including IgG and IgM are thought to be associated with atherogenesis. Finally, such indolent progressed atherosclerotic plaques may suddenly rupture and induce life-threatening coronary thrombosis presenting as an acute coronary syndrome. The notable features of unstable rupture-prone plaque are infiltration of many inflammatory cells, large lipid core, and thin fibrous cap [6,7].

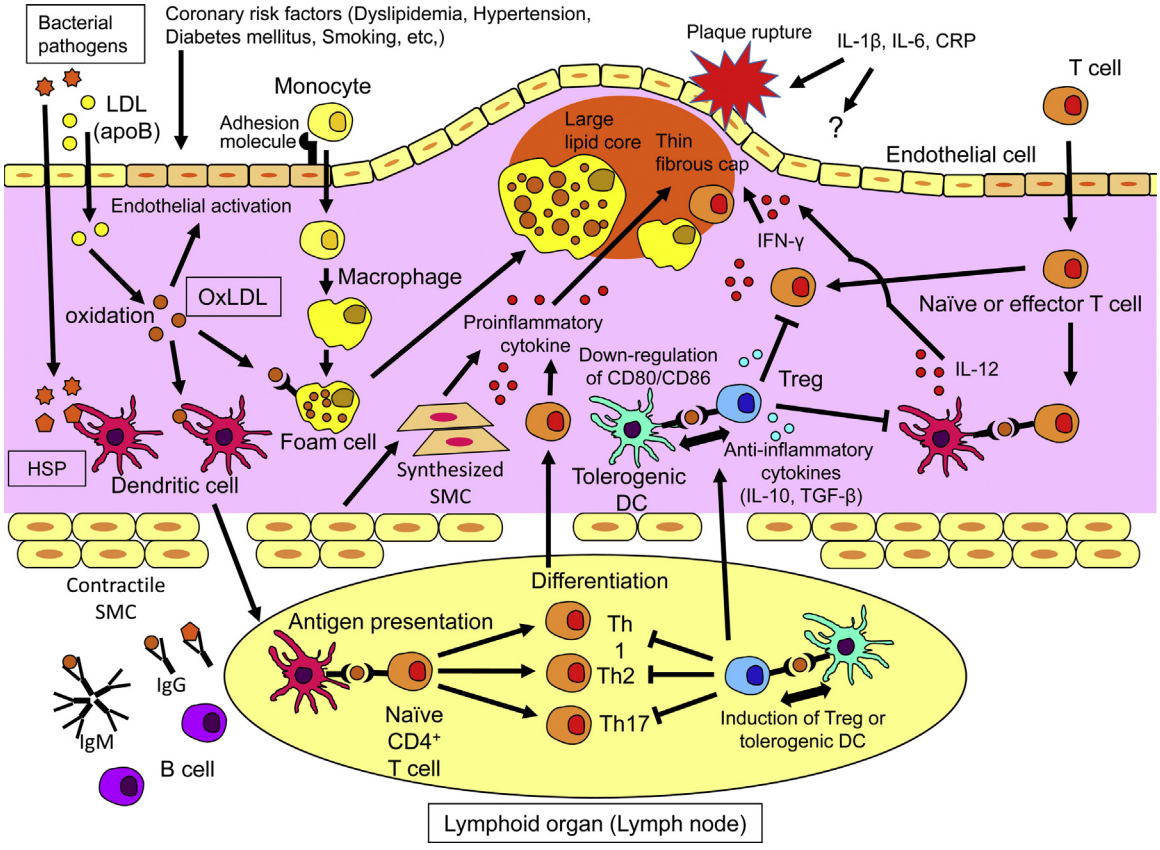

Fig. 1. Role of inflammatory cells and immune responses in atherogenesis. Low-density lipoprotein (LDL) is deposited in the subendothelial space, and the accumulated LDL is oxidized to OxLDL (oxidized LDL) that activates the endothelium. Coronary risk factors also activate the endothelium and induce the adhesion molecules. Monocytes migrate into the subendothelial space using the adhesion molecules, differentiate into macrophages, take up OxLDL, and change to foam cells. The protein components of the OxLDL particle are processed and presented as antigens to T cells by macrophages and dendritic cells (DCs). Other self and foreign antigens may also trigger similar immune reactions. T cells differentiate into effector T cells (Th1, Th2, and Th17) and release cytokines and chemokines, and stimulate the migration of smooth muscle cell (SMC) and other inflammatory reactions. Migrated SMCs change their phenotype from contractile SMCs to synthesized ones that produce cytokines. Synthesized SMCs and foam cells contribute to form the atherosclerotic plaques including the lipid core and fibrous cap formation. Proatherogenic cytokines including IFN-γ secreted by Th1, and IL-12 secreted by DCs and macrophages deteriorate the lesion formation, might be associated with destabilizing the plaque, and induce the plaque rupture. Regulatory T cells (Tregs) suppress effector T cell activation, the differentiation of naïve T cell into effector T cells, and downregulate antigen presentation of DCs via secretion of anti-inflammatory cytokines including interleukin (IL)-10 and transforming growth factor (TGF)-β. Tolerogenic DCs, characterized by downregulated expressions of CD80/CD86, maintain the tolerance to self-antigens by inducing Tregs or by inhibiting effector T cells. Immunoglobulins produced by B cells are also thought to play a role in atherogenesis. apo B, apolipoprotein B; CRP, C-reactive protein; HSP, heat shock protein; IFN, interferon; Ig, immunoglobulin.