Impact of Lipoproteins on Atherobiology
Emerging Insights

Ma Feng, BSc[a,b], Fabiana Rached, MD, PhD[c], Anatol Kontush, PhD[a,b], M. John Chapman, PhD, DSc[d,*]

KEYWORDS

• LDL • HDL • Dyslipidemia • CETP • Monocyte-derived macrophage

KEY POINTS

- Modified low-density lipoproteins constitute a key driver of plaque inflammation through their interaction with monocyte-derived macrophages in the arterial intima.
- Inflammatory cytokines are central actors in amplifying the inflammatory response.
- High-density lipoprotein may inhibit the modification of both low-density lipoprotein lipids and proteins by virtue of their antioxidative biological activities.
- High-density lipoproteins are frequently dysfunctional in dyslipidemic states involving subnormal high-density lipoprotein cholesterol levels.
- Markedly elevated high-density lipoprotein cholesterol levels seem to be deleterious; under such conditions, high-density lipoprotein particles may display defective biological activities consistent with increased cardiovascular risk.

INTRODUCTION

Despite extensive basic and clinical research and prevention strategies involving efficacious therapies, atherosclerotic cardiovascular disease (ASCVD) and its clinical manifestations, such as myocardial infarction, ischemic stroke, and peripheral vascular disease, represent the leading cause of morbidity and mortality throughout the world.[1] Moreover, ASCVD constitutes a major economic burden to society; indeed, the global cost of CVD is expected to exceed US$1 billion dollars by 2030.

Atherobiology encompasses the complex processes that underlie the initiation, formation, and progression of the arterial atherosclerotic plaque, processes that can ultimately be expressed as a thrombotic event, the consequence of the formation of an occlusive or partially occlusive thrombus at the surface of an eroded or ruptured lesion.[2–4]

The key factors that act in a multiplicative and interactive manner to initiate atherosclerotic plaque formation at sites of predilection in the arterial tree are multiple, and include not only dyslipidemia, but also smoking, hypertension, hemodynamic factors, oxidative stress, and diabetic hyperglycemia, the latter possibly involving advanced glycation end products, and others.[2–5] Among these modifiable risk factors, dyslipidemia is prominent, and implies marked imbalance between elevated circulating levels of cholesterol in the form of apolipoprotein (apo)-B–containing, lipoproteins (including very low-density lipoprotein, intermediate density lipoproteins,

Disclosure: The authors have nothing to disclose.

[a] National Institute for Health and Medical Research (INSERM), INSERM UMR 1166 ICAN, University of Pierre and Marie Curie – Paris 6, 91 Boulevard de l'Hôpital, Paris 75013, France; [b] AP-HP, Groupe Hospitalier Pitié-Salpêtrière, 91 Boulevard de l'Hôpital, Paris 75013, France; [c] Heart Institute (InCor), Medical School, University of Sao Paulo, and Albert Einstein Hospital, 44, Avenida Doutor Eneas Carvalho de Aguiar, Sao Paulo 05403-000, Brazil; [d] National Institute for Health and Medical Research (INSERM) and University of Pierre and Marie Curie – Paris 6, Pitié-Salpêtrière University Hospital, 91 Boulevard de l'Hôpital, Paris 75013, France
* Corresponding author. NSFA, 13 Avenue des Arts, Saint Maur 94100, France.
E-mail address: john.chapman@upmc.fr

Cardiol Clin 36 (2018) 193–201
https://doi.org/10.1016/j.ccl.2017.10.001

low-density lipoproteins [LDL] and lipoprotein [a]), versus subnormal levels of cholesterol transported in the form of high-density lipoproteins (HDL) containing apoAI.[2,5–7]

It has long been recognized that elevated levels of plasma apoB-containing particles are atherogenic, and indeed this concept has been consolidated with recent evidence attesting to the causality of LDL in the pathophysiology of ASCVD from genetic, Mendelian randomization, epidemiologic, and interventional studies.[8] By contrast, the potential atheroprotectivity of elevated levels of HDL has been brought into question by recent prospective population cohort studies.[9–11] Indeed, a reassessment of the relationship between cardiovascular risk and circulating concentrations of HDL on the one hand, and the functionality of HDL particles on the other, is ongoing. This article updates emerging insights into the atherobiology of apoB-containing particles on the one hand, and apoAI-containing HDL on the other.

FOCUS ON THE ATHEROBIOLOGY OF APOLIPOPROTEIN B–CONTAINING LIPOPROTEINS

Circulating lipoproteins, and particularly elevated levels of LDL as occurs in familial hypercholesterolemia for example, play key roles as initiating factors in atherogenesis but equally drive plaque progression.[2–8] On a mechanistic basis, substantial evidence attests to the penetration of the endothelial layer by atherogenic lipoproteins at sites of activation such as arterial branch points, and to the potential for retention within the arterial intima of all forms of such apoB100-containing particles (LDL, very low-density lipoprotein, very low-density lipoprotein remnants, and lipoprotein [a]).[12] Lipoprotein retention occurs by both particle trapping in the extracellular matrix network and by electrostatic interaction.[12] Upon retention, LDL may be modified by aggregation, lipolysis, oxidation, or proteolysis. Modified LDL, frequently containing oxidized lipids, acts as a chronic stimulator of the innate and adaptive immune response. As a consequence, both endothelial cells and smooth muscle cells are activated to express surface adhesion molecules, (eg, vascular cell adhesion molecule–1, intercellular adhesion molecule–1), chemoattractants (eg, monocyte chemoattractant protein-1), and growth factors (eg, macrophage colony-stimulating factor and granulocyte-macrophage colony-stimulating factor), which bind to receptors on circulating monocytes and stimulate their homing and migration into the intima, with subsequent differentiation into macrophages or dendritic cells.[4] Modified LDLs are taken up by intimal monocyte-derived macrophages through scavenger receptor or other pathways.[13] Macrophage foam cells filled with droplets of lipoprotein-derived cholesteryl esters (CEs) result, classically displaying a proinflammatory phenotype, an essential element not only in the early fatty streak lesion, but also in determining the progression of the lesion (**Fig. 1**).

It has now emerged that the transformation of the monocyte-macrophage to the M1 or inflammatory phenotype, together with the ultimate fate of this cell, are key determinants of the ensuing intraplaque inflammatory response.[4,13,14] Typically, the chronic inflammatory response becomes maladaptive, resulting in failure to resolve inflammation. Macrophage-derived foam cells lose mobility owing to their lipid load and are unable to exit the arterial wall. In addition, defective efferocytosis leads to an increased inflammatory response, necrotic core expansion subsequent to the accumulation of cellular debris and cholesterol, and plaque progression. Macrophage necrosis amplifies this inflammatory response in a self-perpetuating cycle. At the center of this scenario is the macrophage NLRP3 inflammasome that, under the impact of inflammatory cytokines released from several cell types, including T-helper type 1, T-helper type 2, T-regulatory lymphocytes, and mast cells, drives the production and secretion of a spectrum of factors favoring plaque progression and instability; these include matrix-degrading enzymes, reactive oxygen species, proinflammatory eicosanoids, cytokines (including interleukin-1 beta) and lipids. Importantly, it is currently believed that it is the binding of modified LDL to pattern recognition receptors such as Toll-like receptors on macrophages, which constitutes the primary trigger for secretion of these proinflammatory factors.[4,5,12–14] For further insight into these complex cellular pathways, the reader is referred to the comprehensive review by Libby and colleagues.[15]

It is of immediate relevance that the reduction in cardiovascular outcomes seen recently in the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) trial, in which cananikumab, a human monoclonal antibody to interleukin-1 beta, was used to attenuate residual inflammation in statin-treated patients with elevated levels of highly sensitive C-reactive protein (>2 mg/dL) and incident ASCVD, attests to the key role of inflammation in plaque formation and progression, and ultimately in plaque stability and instability.[16]

Nonetheless, it is noteworthy that modified LDL is the primary ligand in macrophage foam cell formation and, as such, is the primum movens in driving inflammatory cell recruitment, foam cell formation, cellular apoptosis and necrosis, smooth muscle cell proliferation and extracellular matrix