Biochimica et Biophysica Acta xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

The influence of dysfunctional signaling and lipid homeostasis in mediating the inflammatory responses during atherosclerosis

Melanie L. Buckley, Dipak P. Ramji *

Cardiff School of Biosciences, Cardiff University, Sir Martin Evans Building, Museum Avenue, Cardiff CF10 3AX, UK

ARTICLE INFO

Article history:
Received 22 January 2015
Received in revised form 25 March 2015
Accepted 8 April 2015
Available online xxxx

Keywords:
Atherosclerosis
Inflammation
Lipids
Lipoproteins
Cytokines
Signaling
Immune cells

ABSTRACT

Atherosclerosis, the underlying cause of myocardial infarction and thrombotic cerebrovascular events, is responsible for the majority of deaths in westernized societies. Mortality from this disease is also increasing at a marked rate in developing countries due to the acquisition of a westernized lifestyle accompanied with elevated rates of obesity and diabetes. Atherosclerosis is recognized as a chronic inflammatory disorder associated with lipid accumulation and the development of fibrotic plaques within the walls of medium and large arteries. A range of immune cells, such as macrophages and T-lymphocytes, through the action of various cytokines, such as interleukins-1 and -33, transforming growth factor-β and interferon-γ, orchestrates the inflammatory response in this disease. The disease is also characterized by marked dysfunction in lipid homeostasis and signaling pathways that control the inflammatory response. This review will discuss the molecular basis of atherosclerosis with particular emphasis on the roles of the immune cells and cytokines along with the dysfunctional lipid homeostasis and cell signaling associated with this disease.

1. Introduction

Coronary heart disease (CHD) is responsible for one in three deaths in westernized countries. An estimated 23.6 million people are expected to die globally from cardiovascular related pathologies by 2030 and the disease and its complications, which include stroke and myocardial infarction (MI), have been estimated to have total costs (both direct and indirect) of approximately $315.4 billion in 2010 [1]. Atherosclerosis, a chronic inflammatory disorder of the large and medium sized arteries, constitutes the major underlying cause of CHD [2]. Many risk factors for atherosclerosis have been identified and these are generally classified as modifiable and non-modifiable. The latter include age, gender, and genetic predisposition to hypercholesterolemia, hypertension, diabetes and systemic inflammation [2]. Modifiable risk factors include cigarette-smoking, diet rich in saturated fats, and a sedentary lifestyle [2]. It is now well accepted that atherosclerosis is initiated by a local immune response to lipid deposition within the arterial subendothelial compartment [2].

2. Lipid metabolism in atherosclerosis

Lipoprotein particles function as vehicles for the transport of insoluble lipids in the blood and are composed of a core region storing TAGs and cholesteryl esters (CEs), with a surrounding polar region consisting of phospholipids and apolipoproteins. Different forms of lipoproteins are involved in lipid trafficking and considerable exchange of various apolipoproteins occurs between them. For example, chylomicrons

Abbreviations: ABC, ATP-binding cassette transporter; ACAT-1, acyl-coenzyme A acyltransferase 1; AcLDL, acetylated LDL; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; ApoE, apolipoprotein E; CCL, CC-chemokine ligand; CD36, cluster of differentiation 36; CE, cholesteryl esters; CHD, coronary heart disease; CXCL, CXC-chemokine ligand; EC, endothelial cell; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; GF, growth factor; GM-CSF, granulocyte-macrophage colony stimulating factor; HDL, high-density lipoprotein; HF, heart failure; HL, hepatic lipase; HMG-CoA reductase, 3-hydroxy-3-methyl glutaryl coenzyme A reductase; IκB, inhibitor of κB; ICAM-1, intercellular adhesion molecule-1; IDL, intermediate-density lipoprotein; IDOL, inducible degrader of LDLR; IFN, interferon; IKK, IκB kinase; IL, interleukin; JNK, c-Jun N-terminal kinase; LDL, low-density lipoprotein; LDLR, LDL receptor; LOX, lipooxygenase; LOX1, lectin-like oxidized LDL receptor 1; LPL, lipoprotein lipase; LPS, lipopolysaccharide; LXR, liver X receptor; MAPK, mitogen-activated protein kinase; MARCO, macrophage receptor with collagenous structure; MCP-1, monocyte chemotactic protein-1; M-CSF, macrophage colony-stimulating factor; MHC, major histocompatibility complex; MI, myocardial infarction; mmLDL, minimally modified LDL; MMP, metalloproteinase; NEMO, NF-κB-essential modifier; NF-κB, nuclear factor kappa B; NK, natural killer; NLRP3, NOD-, LRR- and pyrin domain-containing 3; NOD, nucleotide-binding oligomerization domain; OxLDL, oxidized LDL; p90RSK, p90 ribosomal S6 kinase; PCSK9, proprotein convertase subtilisin/kexin type-9; PI3K, phosphoinositide 3-kinase; PRR, pattern-recognition receptor; PPAR, peroxisome proliferator-activated receptor; RCT, reverse cholesterol transport; ROS, reactive oxygen species; SMC, smooth muscle cell; SR, scavenger receptor; SREC1, scavenger receptor expressed by endothelial cells; SR-PSOX, scavenger receptor for phosphatidylserine and oxidized LDL; STAT, signal transducers and activators of transcription; TAG, triacylglycerol; TBK1, TANK-binding kinase 1; TGF, transforming growth factor; Th, T helper; TIMP, tissue inhibitors of metalloproteinase; TIR, Toll/IL-1 receptor; TLR, toll-like receptor; TNF, tumor necrosis factor; Tregs, regulatory T cells; TRIF, TIR-domain-containing adaptor protein inducing IFN-β; VLDL, very low-density lipoprotein; VSMC, vascular SMC

* Corresponding author. Tel.: +44 2920876753; fax: +44 2920874116.
E-mail address: Ramji@Cardiff.ac.uk (D.P. Ramji).

http://dx.doi.org/10.1016/j.bbadis.2015.04.011

primarily facilitate the transport of dietary triacylglycerols (TAGs) from the intestine to peripheral tissues. The non-esterified fatty acids and 2-monoacyl glycerol produced by the digestion of TAGs within chylomicrons by lipoprotein lipase (LPL) are then taken up by the adipose tissue or skeletal muscle for utilization/storage [2]. The liver can acquire the resulting chylomicron remnants via specific receptors and metabolize them [3]. In contrast to chylomicrons, very low-density lipoproteins (VLDL) are involved in the transport of TAGs synthesized by the liver [2]. Intermediate-density lipoproteins (IDL) are formed following the digestion of TAGs in VLDL by LPL and hepatic lipase (HL) [2]. Further processing and hydrolysis of TAGs in IDL by HL results in the production of low-density lipoprotein (LDL) particles [2]. LDL functions to carry cholesterol from the liver to peripheral tissues. High plasma LDL levels is a major risk factor for atherosclerosis as identified from numerous epidemiological studies and clinical trials with statins, inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG-CoA reductase), a rate limiting step in the biosynthesis of cholesterol [2].

The LDL particles enter cells of peripheral tissues predominantly via receptor-mediated endocytosis involving its cognate receptor, LDLR (Fig. 1). The crucial involvement of LDL within atherosclerosis was discovered through studies on subjects with familial hypercholesterolemia; a condition that arises from mutations in the LDLR gene [4]. Heterozygous sufferers are relatively common (1 in 500) whereas homozygotes are less frequent (1 in a million) and exhibit six to ten times the levels of LDL within their plasma compared to non-sufferers, and are prone to MIs at an early age [4]. The clearance of plasma LDL by LDLR is critical for limiting atherosclerosis and it is therefore not surprising that considerable research and therapeutic approaches have been devoted on this receptor. For example, proprotein convertase subtilisin/kexin type-9 (PCSK9) is an emerging target for cholesterol-lowering therapies because this enzyme binds to LDLR and targets it for lysosomal degradation in cells [5]. Inducible degrader of LDLR (IDOL), an E3 ubiquitin lipase that mediates ubiquitination and subsequent degradation of LDLR, represents another promising target [6]. The pioneering work by Brown and Goldstein that demonstrated negative feedback regulation of transcription of LDLR and HMG-CoA reductase by the sterol regulatory element binding protein pathway [7] suggested that additional mechanisms mediate uncontrolled cellular uptake of LDL in atherosclerosis. Indeed, as discussed below in detail, LDL is subject to modification, particularly oxidation, and such modified LDL is taken up in an uncontrolled manner by scavenger receptors (SRs), such as A (SR-A) and cluster of differentiation 36 (CD36), by certain plaque-resident macrophages and smooth muscle cells (SMCs) [2] (Fig. 1).

Excess intracellular cholesterol is toxic and there are essentially two main routes for its removal; either through enzymatic-driven conversion to a more soluble transportable form or through reverse cholesterol transport (RCT) [2,8]. Cholesterol is enzymatically modified through a number of processes such as hydroxylation and esterification within the endoplasmic reticulum (ER) to produce oxysterols and sterol esters respectively [2,8–10]. Esterification of cholesterol reduces the solubility of the molecule and promotes storage within cytoplasmic lipid droplets [2,8–10]. RCT is the primary pathway for the removal of excess cholesterol and involves lipid transporters such as ATP-binding cassette transporter (ABC)-A1 and –G1 that mediate the transfer of cholesterol from peripheral cells to selected extracellular acceptors such as high-density lipoproteins (HDL) and associated apolipoproteins [2,8–10] (Fig. 1). The cholesterol is then delivered to the liver for conversion to bile salts in preparation for excretion [2,8–10]. Homeostatic mechanisms exist to prevent lipid overload and many act by stimulating cholesterol efflux and modulating the inflammatory response. For example, the production of oxysterols and desmosterol activates liver X receptors (LXRs) leading to induced expression of ABC-A1 and -G1 [11,12], and thereby RCT. In addition, macrophage cholesterol loading induces autophagy, a process by which double-membrane vacuoles sequesters intracellular contents and targets them for degradation via fusion with secondary lysosomes, leading to RCT [13]. Furthermore, peroxisome proliferator-activated receptors (PPARs) play an important role in the control of cholesterol homeostasis [14,15].

The involvement of HDL particles within atherosclerosis has received a great level of attention [16,17]. Sufferers of Tangier disease contain mutations within the gene for ABC-A1 and are associated with drastically low levels of HDL, localized accumulation of CEs within different tissues of the body and development of premature atherosclerosis [18]. The relationship between reduced HDL levels and incidences of CHD have long been established as one of the major risk factors for the

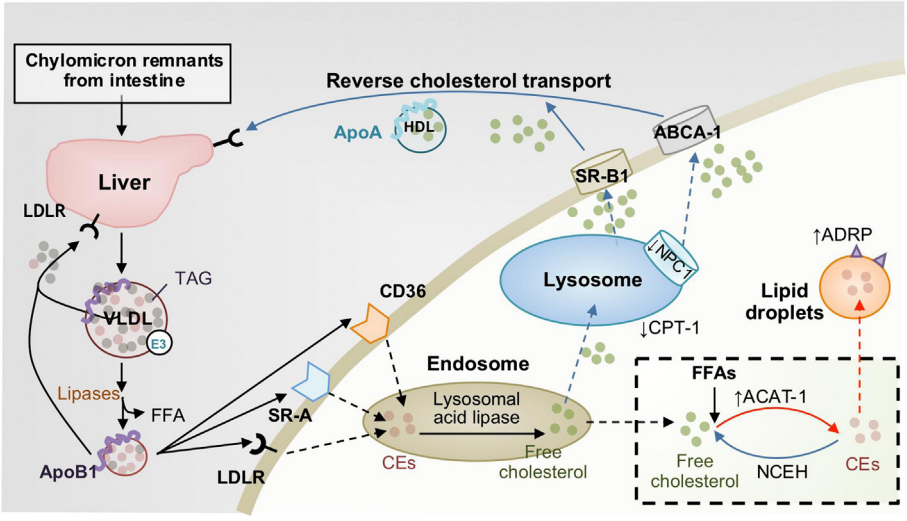

Fig. 1. Overview of cholesterol metabolism. Dietary lipids are absorbed in the intestine and transported by chylomicrons to peripheral tissues. Following lipolysis by lipases, chylomicron remnants deliver dietary lipids to the liver. Liver-derived VLDLs containing ApoB and ApoE (E3) mediate the transport of endogenously synthesized lipids. VLDLs are then hydrolyzed to intermediate density lipoproteins and on to LDLs. ApoB facilitates LDL binding to its cognate receptor (LDLR), which are then internalized and degraded in the lysosomes. The uptake of LDL by LDLR is under negative feedback regulation. Scavenger receptors such as SR-A and CD36 predominantly facilitate the excessive, uncontrolled uptake of modified LDL particles into macrophages during the disease. Lysosomal acid lipases hydrolyze cholesteryl esters (CEs) to free cholesterol and free fatty acids (FFAs). The free cholesterol is either trafficked out of the cells for reverse cholesterol transport through ABC transporters, such as ABCA-1 and SR-B1, or re-esterified to CEs for storage by the action of acyl-coenzyme A acyltransferase 1 (ACAT-1) within the endoplasmic reticulum, and then stored as lipid droplets [regulated by adipocyte differentiation-related protein (ADRP)]. The accumulation of CEs depends on the FFA availability [regulated by carnitine palmitoyltransferase 1 (CPT-1)] and hydrolysis of CEs [modulated by neutral cholesterol ester hydrolase (NCEH)]. NPC-1 and -2 regulate the intracellular trafficking of cholesterol.

Please cite this article as: M.L. Buckley, D.P. Ramji, The influence of dysfunctional signaling and lipid homeostasis in mediating the inflammatory responses during atherosclerosis, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2015.04.011