Clinica Chimica Acta xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Clinica Chimica Acta

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

Invited critical review

Foam cells in atherosclerosis ☆

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ARTICLE INFO

Article history:
Received 25 April 2013
Received in revised form 4 June 2013
Accepted 6 June 2013
Available online xxxx

Keywords:
Macrophages
Foam cells
CD36
SR-A
ACAT1
nCEH
ABCA1
ABCG1
SR-BI

ABSTRACT

Atherosclerosis is a chronic disease characterized by the deposition of excessive cholesterol in the arterial intima. Macrophage foam cells play a critical role in the occurrence and development of atherosclerosis. The generation of these cells is associated with imbalance of cholesterol influx, esterification and efflux. CD36 and scavenger receptor class A (SR-A) are mainly responsible for uptake of lipoprotein-derived cholesterol by macrophages. Acyl coenzyme A:cholesterol acyltransferase-1 (ACAT1) and neutral cholesteryl ester hydrolase (nCEH) regulate cholesterol esterification. ATP-binding cassette transporters A1(ABCA1), ABCG1 and scavenger receptor BI (SR-BI) play crucial roles in macrophage cholesterol export. When inflow and esterification of cholesterol increase and/or its outflow decrease, the macrophages are ultimately transformed into lipid-laden foam cells, the prototypical cells in the atherosclerotic plaque. The aim of this review is to describe what is known about the mechanisms of cholesterol uptake, esterification and release in macrophages. An increased understanding of the process of macrophage foam cell formation will help to develop novel therapeutic interventions for atherosclerosis.

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Abbreviations: ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; SR-BI, scavenger receptor BI; SR-A, scavenger receptor class A; ACAT1, acyl coenzyme A:cholesterol acyltransferase-1; nCEH, neutral cholesteryl ester hydrolase; ox-LDL, oxidized low-density lipoprotein; HDL, high-density lipoprotein; apoA-I, apolipoprotein A-I; LDLR, low-density lipoprotein receptor; apoE, apolipoprotein E; CE, cholesterol ester; FC, free cholesterol; LXR, liver X receptor; RXR, retinoid X receptor; PPAR-γ, peroxisome proliferator-activated receptor-γ; ERK1/2, extracellular signal-regulated kinases 1 and 2; PPREs, PPAR response elements; PKB, protein kinase B; PKC, protein kinase C; TGF-β, transforming growth factor-β; MAPK, mitogen-activated protein kinase; RCT, reverse cholesterol transport; PI3K, phosphatidylinositol 3-kinase; AGE, advanced glycation end products.

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http://dx.doi.org/10.1016/j.cca.2013.06.006

Please cite this article as: Yu X, et al, Foam cells in atherosclerosis, Clin Chim Acta (2013), http://dx.doi.org/10.1016/j.cca.2013.06.006

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1. Introduction

Atherosclerotic diseases are the major causes of mortality and morbidity in the world. Formation of macrophage foam cells in the intima is a major hallmark of early stage atherosclerotic lesions. Uncontrolled uptake of oxidized low-density lipoprotein (ox-LDL), excessive cholesterol esterification and/or impaired cholesterol release result in accumulation of cholesterol ester (CE) stored as cytoplasmic lipid droplets and subsequently trigger the formation of foam cells. Scavenger receptors (SRs), CD36 and SR class A (SR-A) are the principal receptors responsible for the binding and uptake of ox-LDL in macrophages [1]. Acyl coenzyme A:cholesterol acyltransferase-1 (ACAT1) and neutral cholesteryl ester hydrolase (nCEH) play a critical role in cholesterol esterification [2]. ATP-binding cassette (ABC) transporter A1(ABCA1), ABCG1 and scavenger receptor-BI (SR-BI) mediate cholesterol export from macrophages [3]. This review focuses on the recent developments in our knowledge of the roles and regulation of these receptors, enzymes and transporters in the formation of macrophage foam cells.

2. Cholesterol uptake

Cholesterol uptake is a pathway by which extracellular modified LDL are ingested by macrophages via receptors-mediated phagocytosis and pinocytosis. SRs such as SR-A and CD36 have been implicated in this process. In vitro studies have shown that CD36 and SR-A account for 75% to 90% of ox-LDL internalization by macrophages, whereas other SRs cannot compensate for their absence [4]. Thus, CD36 and SR-A are the most important receptors responsible for the uptake of modified lipoproteins by macrophages.

2.1. CD36

CD36 is first identified as the platelet glycoprotein III b/IV, an 88 kDa heavily glycosylated transmembrane protein that belongs to SR class B family. It consists of an extracellular domain flanked by two transmembrane and two cytoplasmic domains. CD36 functions as a high-affinity receptor for ox-LDL. A domain located between amino acids 155 and 183 of CD36 involves in ox-LDL binding. Other ox-LDL binding sites have also been reported such as amino acids 28–93 and possibly 120–155. Binding of ox-LDL to CD36 leads to endocytosis through a lipid raft pathway that is distinct from the clathrin-mediated or caveolin internalization pathways. The pathogenic role of ox-LDL in atherosclerosis largely depends on CD36. A recent study revealed that plasma soluble CD36 correlates significantly with markers of atherosclerosis, insulin resistance and fatty liver in a nondiabetic healthy population [5]. Patients with acute coronary syndromes exhibit a significant increase in CD36 expression in circulating monocytes, which can be inhibited by a 6-month treatment of atorvastatin [6]. Small molecules with anti-CD36 activity have been shown to decrease postprandial hyperlipidemia and protect against atherosclerosis [7]. In addition, the 573A allele of CD36 has a protective effect against atherosclerosis development while the 591T allele is a cardiovascular risk factor [8]. On the other hand, Moore and colleagues reported that apoE$^{-/-}$ mice lacking CD36 or SR-A display increased aortic sinus atherosclerotic lesion area and abundant macrophage foam cells in the aortic intima despite reductions in peritoneal macrophage CE accumulation in vivo [9]. Moreover, clinical studies show that patients with CD36 deficiency are associated with severe and enhanced atherosclerotic diseases [10]. Therefore, the role of CD36 as a proatherogenic mediator of ox-LDL uptake in vivo needs to be reassessed.

CD36 is highly expressed in macrophages and its expression is regulated by multiple factors (Fig. 1). Recently, Inoue et al. reported that astaxanthin (ASX), an oxygenated carotenoid (xanthophyll), significantly increases CD36 levels in peritoneal macrophages by stimulating peroxisome proliferator-activated receptor-γ (PPARγ) [11]. On the other hand, curcumin, a potent antioxidant extracted from *Curcuma longa*, induces a PPARγ-independent CD36 overexpression through upregulating nuclear erythroid-related factor 2(Nrf2) [12]. Additionally, Gao et al. reported that palmitate increases CD36 expression in monocytes through the regulation of de novo ceramide synthesis [13]. Supplementation of the mushroom *Agaricus blazei* for 12 weeks markedly elevates CD36 expression and plaque vulnerability in apoE$^{-/-}$ mice,

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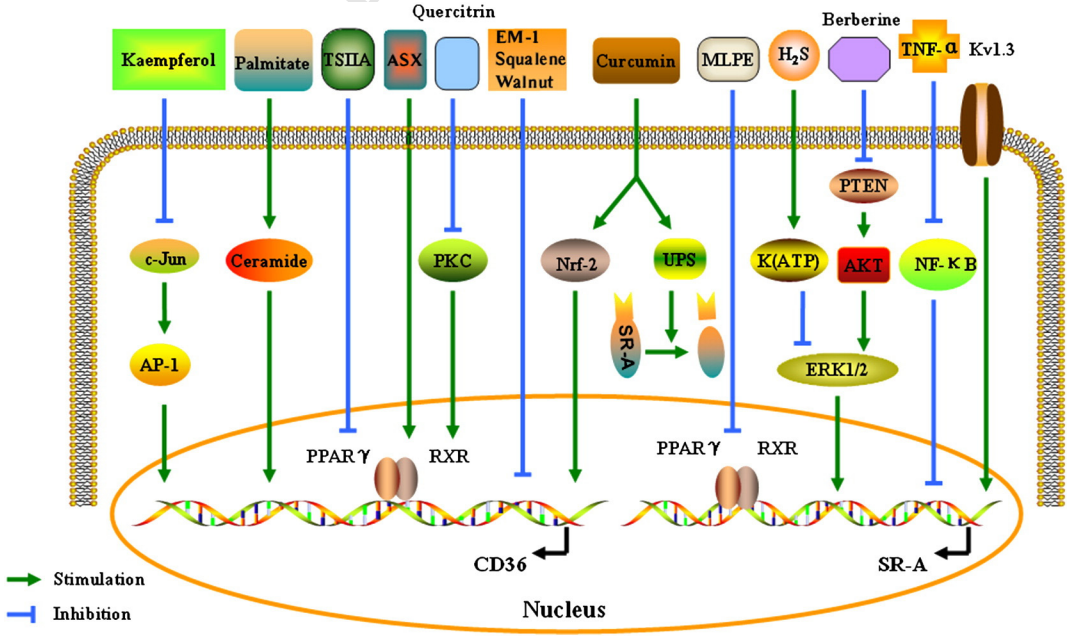

Fig. 1. Regulation of CD36 and SR-A expression in macrophages. CD36 expression is induced by ASX and inhibited by TSIIA and quercitrin via PPARγ pathway. Palmitate increases CD36 levels while kaempferol, EM-1, squalene and walnut reduce its levels. Curcumin also upregulates CD36 expression through promoting Nrf-2 nuclear translocation but decreases SR-A protein expression via UPS. Berberine, Kv1.3 and TNF-α enhance SR-A levels, whereas MLPE and H_2S diminish its levels. RXR: retinoid X receptor.

Please cite this article as: Yu X, et al, Foam cells in atherosclerosis, Clin Chim Acta (2013), http://dx.doi.org/10.1016/j.cca.2013.06.006

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