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Review

Nuclear receptor mediated mechanisms of macrophage cholesterol metabolism

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ABSTRACT

Macrophages comprise a family of multi-faceted phagocytic effector cells that differentiate "*in situ*" from circulating monocytes to exert various functions including clearance of foreign pathogens as well as debris derived from host cells. Macrophages also possess the ability to engulf and metabolize lipids and this way connect lipid metabolism and inflammation. The molecular link between these processes is provided by certain members of the nuclear receptor family. For instance, peroxisome proliferator activated receptors (PPAR) and liver X receptors (LXR) are able to sense the dynamically changing lipid environment and translate it to gene expression changes in order to modulate the cellular phenotype. Atherosclerosis embodies both sides of this coin: it is a disease in which macrophages with altered cholesterol metabolism keep the arteries in a chronically inflamed state. A large body of publications has accumulated during the past few decades describing the role of nuclear receptors in the regulation of macrophage cholesterol homeostasis, their contribution to the formation of atherosclerotic plaques and their crosstalk with inflammatory pathways. This review will summarize the most recent findings from this field narrowly focusing on the contribution of various nuclear receptors to macrophage cholesterol metabolism.

Contents

Abbreviations: ABC, ATP-binding cassette transporter; ACAT1, acyl-CoA:cholesterol acyltransferase-1; Apo, apolipoprotein; ATRA, all-trans-retinoic acid; ChIP, chromatin immunoprecipitation; CPT, 1 carnitine palmitoyl transferase 1; FAS, fatty acid synthase; FXR, farnesoid X receptor; GR, glucocorticoid receptor; GRO-Seq, Global Run on Sequencing; HDL, high density lipoprotein; IDOL, inducible degrader of the LDLR; LDL, low density lipoprotein; LDLR, LDL receptor; LPS, lipopolysaccharide; LXR, liver X receptor; NOR-1, Neuron-derived Orphan Receptor; NPC, Niemann Pick type C; Nurr, 1 Nuclear receptor related 1; Nur77, Nuclear receptor related 77; oxLDL, oxidized LDL; PPAR, peroxisome proliferator activated receptor; PXR, pregnane X receptor; RAR, retinoic acid receptor; RXR, retinoid X receptor; TTNPB, 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid; VLDL, very low density lipoprotein.

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1. Introduction

In their pioneering work Brown and Goldstein described that macrophages of patients with familial hypercholesterolemia – whose cells lack the receptor for low-density lipoprotein (LDL) – are able to accumulate cholesteryl-esters suggesting that macrophage uptake of LDL involves another group of receptors distinct from the LDL receptor (LDLR) (reviewed in (Brown and Goldstein, 1983)). It was later recognized that the LDLR independent uptake of LDL by macrophages within the atherosclerotic lesions requires LDL to first undergo chemical or enzymatic alteration, which in humans is now proven to be an oxidative modification *in vivo* (Quinn et al., 1987). Last but not least, the notion that the uptake of oxLDL initiates a positive feedback in foam cells by inducing the expression of the CD36 scavenger receptor gave rise to the hypothesis that an oxLDL driven intracellular mechanism should be accountable for the generation of foam cells and the development of atherosclerosis (Han et al., 1997). These above results pointed to a highly relevant question: what are the molecular links that connect the derivatives of oxLDL and the enhanced lipid uptake by atherosclerotic macrophages? The groundbreaking results of the last 15 years in this field of study revealed that lipid activated nuclear receptors are not only involved in regulating macrophage lipid uptake but play critical roles in the regulation of lipid intracellular trafficking as well as efflux. The current review will focus on how nuclear receptors regulate receptor mediated cholesterol uptake, cellular storage, transport and efflux, as well as production of apolipoproteins and lipoprotein remodeling enzymes.

1.1. Macrophage biology

Macrophages play central roles in host defense in both innate and adaptive immunity. They are also linked to the pathology of many disease processes. Macrophages are professional phagocytes that reside in nearly every tissue and are responsible for clearance of pathogens, dying cells and oxidized lipid molecules. Macrophages – with the exception of microglia (Ginhoux et al., 2010) – are derived from multipotent hematopoietic stem cells (Friedman, 2002) characterized by long term repopulating capacity. Monocytes differentiate from common myeloid progenitors through monoblasts to circulating monocytes maturing to various tissue-specific macrophages. During activation macrophages become equipped with a plethora of features by which they are able to sense, engulf and eliminate foreign invaders and toxic host-derived particules. The activation of macrophages is stimulated by signaling pathways of cytokines and growth factors that lead to the activation of specific transcription factors. Macrophages also take part in tissue repair and the resolution phase of inflammation.

It is now evident that activated macrophages can be classified into classically (M1) and alternatively (M2) activated subtypes (Gordon and Martinez, 2010). M1 macrophages develop in response to Th1 cell derived cytokines such as IFNγ, or microbial lipopolysaccharide (LPS). These cells produce inflammatory cytokines, reactive oxygen species and perform cytotoxic functions to eradicate foreign invaders. However, if not kept under tight control at the resolution phase of inflammation, these cells can be very harmful to the host cells and tissues and can contribute to the pathogenesis of certain metabolic disorders such as atherosclerosis and obesity induced insulin resistance (Olefsky and Glass, 2010). M2 macrophages, on the other hand, develop upon stimulation with IL-4 or IL-13 cytokines, are linked to Th2 responses and involved in anti-inflammatory processes (Gordon and Martinez, 2010).

The macrophage population in chronic disorders such as atherosclerosis (foam cells) is very likely of a mixed M1/M2 phenotype (Olefsky and Glass, 2010). Nuclear receptors are widely expressed in macrophages and are intimately implicated in regulating their metabolic and immune homeostasis (reviewed in (Rigamonti et al., 2008)).

1.2. Atherosclerosis and macrophage cholesterol homeostasis

Various cell types are involved in the development of atherosclerosis including endothelial cells, monocytes/macrophages, T cells and smooth muscle cells (Ross, 1999). At the initial stage of atherosclerosis, cholesterol, cholesteryl-ester and phospholipid containing LDL is accumulated and oxidized in the subendothelial layer of arterial walls (Tabas et al., 2007). oxLDL causes endothelial cell activation which leads to the recruitment of blood derived monocytes to the subendothelial layer (Mestas and Ley, 2008). These monocytes then differentiate into macrophages and take up oxidized and native LDL via scavenger receptors such as CD36 and SR-A, as well as LDLR (Suzuki et al., 1997; Nozaki et al., 1995; Fogelman et al., 1988). Further uptake of modified LDL by macrophages leads to foam cell formation and early atherosclerotic lesions (Moore and Tabas, 2011). Activated T cell and macrophage derived cytokines and growth factors induce smooth muscle cell migration and proliferation as well as extracellular matrix production leading the development of fibrous plaques (Lusis, 2000).