Abstract  
Atherosclerosis can be considered as both a chronic inflammatory disease and a lipid metabolism disorder. In- 
nate immunity pathways have long been suspected to con- 
tribute to the initiation and progression of atherosclerosis. 
This suggests that crosstalk between lipid metabolism and 
inmate immunity pathways plays an important role for 
the development and/or the prevention of atherosclerosis. 
However, it is not fully defined how innate immunity affects 
lipid metabolism. Macrophages play a central role in ath-
erogenesis through the accumulation of cholesterol and the 
production of inflammatory mediators and cytokines. Liver 
X receptors (LXRs) exert an important atheroprotective ef-
flect in the macrophage. In addition to regulating cholesterol 
metabolism, LXRs are also negative regulators of macro-
phage inflammatory gene responses. In this review, we will 
discuss the roles of LXRs in the macrophage as key factors 
that link innate immunity and lipid metabolism. — Shibata, N., 
and C. K. Glass. Regulation of macrophage function in inflam-

Supplementary key words  
liver X receptors • lipopolysaccharide • low density lipoprotein

Cardiovascular disease, including atherosclerosis, is the 
leading cause of morbidity and mortality in western socie-
ties. Atherosclerosis is a chronic inflammatory disease and 
a disorder of lipid metabolism. Although many epidemio-
logical studies have shown that high concentrations of 
LDL cholesterol are a major risk factor for atherosclero-
sis, innate immunity pathways have long been suspected to 
contribute to the initiation and progression of athero-
sclerosis. Atherosclerotic lesion progression has been shown 
to depend on chronic inflammation in the artery wall (1). 
After induction of hyperlipidemia, a rapid influx of mono-
cytes into the arterial intima occurs; if persistent, this influx 
generates the chronic inflammation characteristic of the 
atherosclerotic plaque (2). Many pro-inflammatory genes 
activated by pathogen engagement of innate immunity sig-
aling pathways are also induced in macrophages present 
in atherosclerotic lesions.

Macrophages play a central role in the atherogenic pro-
cess as modulators of both lipid metabolism and immune 
responses (1, 3). The accumulation of cholesterol-loaded 
macrophages in the arterial wall is the hallmark of the early 
atherosclerotic lesion (4, 5). In response to lipid loading, 
macrophages activate a compensatory pathway for cho-
sterol efflux mediated by the ATP binding cassette trans-
porters A1 and G1 (ABCA1 and ABCG1) (6, 7). In the face 
of systemic hypercholesterolemia, however, this homeostatic 
mechanism is overwhelmed, leading to the development of 
foam cells and the fatty streak lesion. In fact, combined 
deficiency of ABCA1 and ABCG1 promotes foam cell accu-
mulation and accelerates atherosclerosis in mice (8). Cho-
lesterol loading of macrophages stimulates the production 
of inflammatory mediators, such as cytokines and reactive 
oxyn species that recruit other cell types and contribute to 
the development of a complex lesion (9). Thus, pro-
cesses that interfere with the intracellular cholesterol bal-
ance would be expected to exacerbate lesion formation.

Liver X receptors (LXRs) are ligand-activated transcription 
 faktors that control cellular cholesterol and fatty acid 
homeostasis and have been established to exert athero-
protective effects in mouse models. In fact, the patho-
physiologic significance of the LXRs is illustrated by the 
observations that synthetic LXR ligands reduce athero-
sclerosis in animal models, whereas loss of macrophage 
LXRs expression dramatically accelerates the disease (10, 
11). Furthermore, overexpression of LXRα in macrophages 
has significant antiatherogenic properties (12). However, it 
remains unclear how these functions of LXRs are working 
under pathological conditions. In this review, we will pro-

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Abbreviations: ABCA1, ATP binding cassette transporter A1; 
ABCG1, ATP binding cassette transporter G1; iNOS, inducible nitric 
oxide synthase; IRF3, interferon regulatory factor 3; LBP, LPS binding 
protein; LPS, lipopolysaccharide; LXR, liver X receptor; MyD88, 
myeloid differentiation factor 88; NF-κB, nuclear factor κB; TLR, 
Toll-like receptor; TRIF, Toll/IL-1 receptor domain-containing adaptor 
inducing IFN-β; SR-A, scavenger receptor A; SRF/G1, scavenger recep-
tor expressed by endothelial cells I.

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provide a brief overview of the role of LXRs in the control of cholesterol metabolism during inflammation.

THE ROLE OF LXRs IN MACROPHAGE

Genomic and cDNA sequencing efforts have defined at least 48 nuclear receptors that are encoded by the human and mouse genomes (13). Several nuclear receptors have been identified to be expressed in macrophages, including receptors for steroid hormones, such as estrogen and glucocorticoid receptors, receptors for diverse products of lipid metabolism, such as peroxisome proliferator-activated receptors and LXRs (LXRα and LXRβ), and orphan receptors, such as Nurr77, Nurr1, and NOR-1. In the macrophage, several of these nuclear receptors have been demonstrated to inhibit inflammatory responses that are under the control of signal-dependent transcription factors, such as activator protein-1 and nuclear factor κB (NF-κB) (14–16).

LXRs are transcriptional regulators of cholesterol absorption, transport, and elimination (17, 18). In macrophages, LXR signaling is critical for initiating the homeostatic response to cellular lipid loading (Fig. 1). Macrophage uptake of modified lipoproteins, such as oxidized LDL, leads to increased cellular concentration of oxysterols, the physiologic ligands for LXRs (19, 20). Activation of LXRs induces the expression of genes involved in cellular cholesterol trafficking, including Niemann Pick type C 1 and 2 proteins (21), and efflux, including ABCA1, ABCG1, and apolipoprotein E (17, 18). The end result of this transcriptional cascade is the transfer of excess cholesterol to extracellular acceptors, such as apolipoprotein AI and HDL. Recent studies have also revealed that the activation of LXRs by synthetic ligands in macrophages inhibits lipopolysaccharide (LPS)- or cytokine-induced expression of inflammatory genes, such as inducible nitric oxide synthase (iNOS), interleukin-1β, and monocyte chemotactic protein-1, by interfering with NF-κB signaling (Fig. 1).

![Fig. 1. Intersections of TLR and LXR signaling pathways in the macrophage. Upon activation by exogenous or endogenous ligands, TLRs regulate gene expression through MyD88- and TRIF-dependent signal transduction pathways that control the activities of NF-κB and IRF transcription factors. These factors induce the expression of inflammatory response genes, including genes that contribute to modifications of LDL (mLDL) that enhance recognition and uptake by scavenger receptors. TLR signaling also increases cholesterol biosynthesis and promotes cholesterol accumulation. Elevated cholesterol levels give rise to elevated oxysterols, which are activating ligands of LXRs. LXRs inhibit TLR signaling at the promoter level and induce genes that promote cholesterol efflux, including ABCA1 and ABCG1. LXR activation of these genes is inhibited by IRF3, which is activated by TLRs that couple to the TRIF signaling adaptor.](image-url)
microbial pathogens. In fact, the activation of macrophages findings link the development of atherosclerosis to a pro-
the development of atherosclerosis in mice (29). These phe peripheral administration of a ligand for TLR2 accelerated Chlamydia pneumoniae suggested that some bacterial or viral pathogens, such as (30). In accordance with these reports, several studies have in reduction in atherosclerosis in mouse models (28, 29).

cytogenetic properties, which lead to atherosclerosis results in an increased expression of pro-inflammatory cytokines (34). On the other hand, the delivery of LPS to HDL by LBP results in the attenuation of the immune response to infection (35). HDL-bound LPS is redistributed to LDL and VLDL (36) and transported to liver. Upon uptake by the liver, LPS is dephosphorylated/degraded and passed into the bile. Therefore, the uptake of LPS by HDL appears to serve as a first line of defense against the sustained activation of cellular immunity by LPS in the host.

LPS stimulation hepatic lipid synthesis and increases hepatic HMG-CoA reductase activity in mice (37). This increase of hepatic cholesterol production results in an increase in LDL cholesterol (38). Taken together, it is possible that the increase in HMG-CoA reductase provides cholesterol, which allows for the production of LDL and VLDL and elevations in plasma lipid levels. These studies suggest that increases in plasma lipid and lipoprotein levels may be beneficial during infection and inflammation.

The induction of sterol production by LPS occurs not only in the liver, but also in the macrophage (Fig. 1), although the responsible mechanisms are not fully established. Posokhova et al. (39) reported that the intraperitoneal injection of LPS in mice led to a dramatic increase of radiolabeled oleate incorporation into cholesteryl esters and triglycerides and radiolabeled acetate incorporation into cholesterol and fatty acids in peritoneal macrophages. In accordance with these findings, the LIPID MAPS Consortium revealed that the activation of TLR4 induced HMG-CoA reductase mRNA in bone-marrow-derived macrophage as well as several intermediates in the cholesterol biosynthetic pathway (These data can be found with LIPID MAPS Consortium online at http://www.lipidmaps.org/).

The acute-phase response at the whole-body level is characterized by increased plasma lipoprotein cholesterol levels and plasma LPS binding protein (LBP) levels. LBP is an acute-phase protein responsible for the binding and transport of LPS in circulation. Delivery of LPS by LBP to macrophages initiates signal transduction pathways that lead to the increased release of pro-inflammatory cytokines (34). On the other hand, the delivery of LPS to HDL by LBP in the attenuation of the immune response to infection (35). HDL-bound LPS is redistributed to LDL and VLDL (36) and transported to liver. Upon uptake by the liver, LPS is dephosphorylated/degraded and passed into the bile. Therefore, the uptake of LPS by HDL appears to serve as a first line of defense against the sustained activation of cellular immunity by LPS in the host.
Atherosclerosis can be considered to be a form of chronic inflammation resulting from interactions between modified lipoproteins, monocyte-derived macrophages, T-cells, and the normal cellular elements of the arterial wall. The induction of cholesterol accumulation in macrophage by LPS has been thought to be one of the “undesired” functions of inflammation. Numerous studies in the last few years reveal that oxysterol sensors, LXRs, are one of the key regulators of macrophage biology, including the promotion of reverse cholesterol transport and the limitation of inflammation. The antagonistic functions of TLRs and LXRs with respect to macrophage cholesterol homeostasis suggest that the activation of LXRs by undesired oxysterols may be thought to be a compensatory mechanism against the excess cholesterol accumulation and the excess toxic inflammatory response. Further studies are needed to elucidate the biological roles of LXRs during inflammation and the practical possibilities of targeting LXRs for therapeutic intervention.

REFERENCES


