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Review

Oxysterol generation and liver X receptor-dependent reverse cholesterol transport: Not all roads lead to Rome

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ABSTRACT

Cell cholesterol metabolism is a tightly regulated process, dependent in part on activation of nuclear liver X receptors (LXRs) to increase expression of genes mediating removal of excess cholesterol from cells in the reverse cholesterol transport pathway. LXRs are thought to be activated predominantly by oxysterols generated enzymatically from cholesterol in different cell organelles. Defects resulting in slowed release of cholesterol from late endosomes and lysosomes or reduction in sterol-27-hydroxylase activity lead to specific blocks in oxysterol production and impaired LXR-dependent gene activation. This block does not appear to be compensated by oxysterol production in other cell compartments. The purpose of this review is to summarize current knowledge about oxysterol-dependent activation by LXR of genes involved in reverse cholesterol transport, and what these defects of cell cholesterol homeostasis can teach us about the critical pathways of oxysterol generation for expression of LXR-dependent genes.

Contents

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1. Introduction

Overaccumulation of cholesterol in arterial wall macrophages and smooth muscle cells is the biochemical hallmark of atherosclerosis, manifested clinically as ischemic vascular disease (Katsuda et al., 1992). The fact that cholesterol escapes catabolism in most cells requires that a mechanism be in place for its removal. Cholesterol removal from non-hepatic cells and its delivery back to the liver for excretion is mediated by multiple steps collectively termed 'reverse cholesterol transport' (RCT)[1] (Francis, 2010). This coordinated pathway involves activation of nuclear liver X receptors on the promoter regions of several genes, including those encoding cholesterol metabolizing enzymes, membrane lipid transporters, apolipoproteins, and lipid transfer proteins (Tontonoz and Mangelsdorf, 2003).

Liver X receptors or LXRs are thought to be activated predominantly by binding of oxysterols, intermediate cholesterol metabolites whose formation is increased co-ordinately with increasing cell cholesterol content. LXRs thus serve a critical role as cholesterol sensors, and are themselves dependent on cholesterol transport pathways and oxysterol generation for this activity. The purpose of this review is to highlight the important interplay between sites of oxysterol generation, LXR activation, the RCT pathway, and the importance of intracellular cholesterol trafficking pathways in the context of cellular responses to cholesterol overload.

1.1. Liver X receptors

Liver X receptors are members of the nuclear hormone receptor superfamily that bind both steroidal and non-steroidal ligands (Edwards et al., 2002; Francis et al., 2003). The LXR subfamily is further divided into two isoforms, α and β, which respond similarly to oxysterol and nonoxysterol ligands (Ulven et al., 2005). Manglesdorf and colleagues demonstrated that LXRα and LXRβ partner with retinoid X receptor (RXR) to form obligate heterodimers for gene activation (Willy and Mangelsdorf, 1997; Willy et al., 1995). Without a ligand, the LXR–RXR heterodimer, bound to LXR response elements (LXREs) in the promoter region of target genes, interacts with corepressors and remains inactive (Hu et al., 2003). When bound by its ligands, LXR undergoes a conformational change (Glass and Rosenfeld, 2000) whereby the corepressors are released and coactivators are recruited, leading to gene activation (Herzog et al., 2007; Lee et al., 2008; Svensson et al., 2003).

In addition to genes involved in RCT, LXRs regulate a diverse array of genes involved in fatty acid synthesis (Repa et al., 2000), triglyceride metabolism by lipoprotein lipase (Zhang et al., 2001), de novo cholesterol synthesis (Wang et al., 2008), degradation of the LDL receptor (Zelcer et al., 2009) and bile acid detoxification (Barbier et al., 2009). LXR activation is also thought to play a protective role against Alzheimer's disease (Adighibe et al., 2006; Donkin et al., 2010; Infante et al., 2010; Koldamova et al., 2005), and may have varying effects on cancer development (Pommier et al., 2010; Villablanca et al., 2010). In addition, LXR can upregulate its own expression (Laffitte et al., 2001a,b; Whitney et al., 2001). LXR isoforms are also important regulators of inflammation, acting as anti-inflammatory transcription factors during innate and adaptive immune responses (Tint and Salen, 1982). The physiological ligand for LXR in these pathways also appears to be oxysterols.

1.2. LXR-dependent regulation of reverse cholesterol transport genes

Genes regulated by oxysterol-dependent activation of LXRs in the reverse cholesterol transport pathway include the ATP-binding cassette transporters ABCA1, ABCG1, ABCG5 and ABCG8, as well as apolipoprotein E, cholesteryl ester transfer protein, phospholipid transfer protein, scavenger receptor BI, and cholesterol 7α-hydroxylase. Their roles in RCT are described briefly here.

1.2.1. ABCA1

ABCA1 is an integral membrane transporter that facilitates the movement of cell phospholipids and cholesterol onto exchangeable apolipoproteins (apos), in particular apoA-I, to initiate the formation of HDL particles (Oram and Heinecke, 2005). The identification of an LXRE region in the ABCA1 gene was first described in 2000 (Costet et al., 2000; Schwartz et al., 2000). Additionally, Repa et al. demonstrated that loss of LXR resulted in the inability of oxysterols or synthetic LXR agonists to upregulate ABCA1 expression, establishing the essential role of LXRs in cholesterol efflux via ABCA1. Mice deficient in LXR exhibit characteristics similar to mice lacking ABCA1, developing enlarged spleens and accumulating foam cells in several tissues (Schuster et al., 2002; Tangirala et al., 2002). Based on its critical role in initial HDL formation, ABCA1 is a primary target for the development of pharmaceutical agonists of LXR to increase HDL therapeutically.

1.2.2. ABCG1

Another ABC transporter, ABCG1, is believed to promote additional efflux of cellular cholesterol to preformed HDL particles (Cavelier et al., 2006; Klucken et al., 2000; Lund-Katz and Phillips, 2010; Rothblat et al., 1999). The induction of ABCA1 and ABCG1 expression by cholesterol loading and synthetic LXR agonists, in various cell types and tissues including macrophages (Venkateswaran et al., 2000) and placenta (Aye et al., 2010; Jiang et al., 2010; Venkateswaran et al., 2000), suggest a coordinated role of these two transporters in managing cellular cholesterol overload. LXRE sequences in the promoter region of the ABCG1 gene have been identified (Sabol et al., 2005).

1.2.3. ABCG5 and G8

Other members of the ABC transporter family, ABCG5 and ABCG8, export sterols into the intestinal lumen and promote biliary cholesterol secretion in the liver under the influence of LXRs (Brown and Yu, 2009; Repa et al., 2002; Yu et al., 2003). Both genes have been demonstrated to be target genes of the LXR/RXR heterodimer, despite not containing a classic LXR response element (Repa et al., 2002).

1.2.4. ApoE

ApoE on the surface of plasma lipoproteins, including chylomicron and VLDL remnants and some HDL particles, facilitates their uptake by the liver. ApoE is also a key mediator of cellular lipid efflux and uptake in the brain, and of cholesterol efflux from macrophages (Curtiss and Boisvert, 2000; Liang et al., 2004).

[1] *Abbreviations used:* RCT, reverse cholesterol transport; ABC, ATP-binding cassette; OHC, hydroxycholesterol; NPC, Niemann-Pick type C; StAR, steroidogenic acute regulatory protein; LAL, lysosomal acid lipase; CTX, cerebrotendinous xanthomatosis.