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Review

Oxysterol signaling links cholesterol metabolism and inflammation via the liver X receptor in macrophages

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ABSTRACT

Sterols and fatty acids are common intermediary metabolites in all cells of the body. Oxidative modifications of these molecules can occur and result in the production of oxysterols and oxidized fatty acids. Significantly, these modified molecules not only participate in basic metabolic processes but they are also involved in signaling pathways. These two groups of molecules are known to regulate the activity of a special group of ligand-activated transcription factors, known as nuclear receptors. Oxysterols activate liver X receptor (LXR), while oxidized fatty acids regulate peroxisome proliferator-activated receptors (PPARs). These nuclear hormone receptors control the expression of their target genes upon ligand binding and via this effect many physiological as well as pathological processes. The role of the receptors and natural or synthetic activators have been studied extensively in the initiation, development and progression of atherosclerosis. Both the receptors themselves and their activators have been shown to exert anti-atherogenic effects. In this review we provide an overview of oxysterol-driven gene expression regulation. We introduce nuclear receptors, in particular LXR, how they become activated by oxysterols, how they work, what consequences of receptor activation on transcription regulation has and how these processes coordinate cholesterol metabolism and transport in macrophages. We place LXR into a network of transcription factors, enzymes and ligands. We also summarize data supporting the notion that LXR is also involved in the regulation

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Abbreviations: 9-HODE, 9-hydroxyoctadecadienoic acid; 13-HODE, 13-hydroxyoctadecadienoic acid; 22(R)-HC, 22(R)-hydroxycholesterol; 24(S),25-EC, 24(S),25-epoxycholesterol; 24(S)-HC, 24(S)-hydroxycholesterol; 25-HC, 25-hydroxycholesterol; 27-HC, 27-hydroxycholesterol; ABC, ATP-binding cassette; AEBP1, adipocyte enhancer-binding protein-1; AF-1, activation function domain 1; AF-2, activation function domain 2; apo, apolipoprotein; ASC-2, activating signal cointegrator-2; ATI-829, 3,6,24-trihydroxy-24,24-di(trifluoromethyl)-5β-cholane; CARM-1, coactivator-associated arginine methyltransferase-1; CFU-G, granulocyte colony forming units; CFU-GM, granulocyte-monocyte colony forming units; CFU-M, monocyte colony forming units; COX-2, cyclooxygenase-2; CTX, cerebrotendinous xanthomatosis; DBD, DNA binding domain; DC, dendritic cell; DMHCA, *N,N*-dimethyl-3β-hydroxycholenamide; ER, estrogen receptor; FXR, farnesoid X receptor; H3K4, histone H3 lysine 4; H3K4MT, histone H3 lysine 4 methyltransferase; HDL, high density lipoprotein; iDC, immature DC; IL, interleukin; iNOS, inducible nitric oxide synthase; IRF3, interferon regulatory factor 3-dependent; LBD, ligand binding domain; LDL, low density lipoprotein; LDLR, low density lipoprotein receptor; LPL, lipoprotein lipase; LPS, lipopolysaccharide; LXR, liver X receptor; LXREs, LXR-responsive elements; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MCP-3, monocyte chemoattractant protein-3; mDC, mature DC; mmLDL, minimally oxidized/modified; NCoR, nuclear receptor corepressor; NF-κB, nuclear factor κB; oxLDL, oxidized low density lipoprotein; PGJ_2, 15-deoxy-$\Delta^{12,14}$-PGJ_2; PLTP, phospholipid transfer protein; PPARγ, peroxisome proliferator-activated receptor; RAR, retinoic acid receptor; RXR, retinoid X receptor; SERM, selective estrogen receptor modulator; SMRT, silencing mediator of retinoic acid and thyroid hormone receptors; SR, scavenger receptor; SRC-1, steroid receptor coactivator-1; SREBP-1c, sterol regulatory element binding protein-1c; SULT, sulfotransferase; SUMO, small ubiquitin-related modifier; TLR, Toll-like receptor; TNF, tumor necrosis factor; TRRAP, transformation/transcription domain-associated protein; TZD, thiazolidinedione.

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of inflammatory processes. Finally, the *in vivo* consequences of LXR activation or deletion are discussed.

Contents

1. Oxidized lipids as signaling molecules

Fatty acids and cholesterol are key metabolites in animals and humans. Fatty acids are stored as triglycerides and serve as an important source of energy. The production and degradation of fatty acids are strictly regulated at multiple levels. The activation of phospholipases and lipoxygenases acting on phospholipids and fatty acids results in the production of lipid hydroperoxides. It has been also documented that lipid oxidation, peroxidation may be induced by non-enzymatic steps as well (Spiteller, 2005). Cholesterol accounts for 99% of all sterols in mammals and plays multiple important biological roles. It is a major constituent of cell membranes where it is required to establish proper membrane permeability and fluidity. Importantly it is a precursor of numerous signaling molecules. Oxysterols have very short half-lives if compared to cholesterol. As a consequence they are present in very low concentrations. While fatty acids and cholesterol are synthesized in large amounts their oxidative derivatives are surprisingly rare. This might explain why these oxidized sterols, oxysterols and oxidized fatty acids have evolved to serve as physiological mediators in numerous signaling pathways (Björkhem, 2002). This way the metabolic state of a cell can provide a signal to gene and protein activation.

For example oxidized fatty acids are known to bind to and activate G-protein-coupled receptors. G2A is a receptor for 9-hydroxyoctadecadienoic acid (9-HODE) and other oxidized free fatty acid derivatives of linoleic and arachidonic acids (Obinata et al., 2005). More importantly, oxidized fatty acids have been shown to activate another group of receptors, peroxisome proliferator-activated receptors (PPARs) of the nuclear receptor superfamily. These proteins are ligand-activated transcription factors that regulate the expression of genes and gene networks. However, the first endogenous ligand for PPARγ was suggested to be a prostanoid, 15-deoxy-$\Delta^{12,14}$-PGJ_2 (PGJ_2) (Forman et al., 1995; Kliewer et al., 1995). The amount of this compound appears to be too low in tissues to result in PPARγ activation (Powell, 2003) if compared to other PPARγ activator molecules identified later and which are derived from unsaturated fatty acids (Kliewer et al., 1997; Krey et al., 1997). In macrophages, and more recently in other tissues, it has been shown that oxidized fatty acids, like 9-HODE and 13-hydroxyoctadecadienoic acid (13-HODE), are both present in oxidized low density protein (oxLDL), and are biologically relevant agonists of PPARγ (Nagy et al., 1998; Marx et al., 1999; Schild et al., 2002).

A striking similarity exists in the case of oxysterols. Oxysterols are ligands for another nuclear receptor, the liver X receptor (LXR) (Janowski et al., 1996, 1999; Lehmann et al., 1997; Peet et al., 1998). This receptor has been extensively studied in the last few years principally by the Mangelsdorf and Tontonoz laboratories among others. This receptor appears to be involved in many cholesterol and bile acid related biological and pathological processes. More relevantly for the purposes of this review, it orchestrates cholesterol metabolism in macrophages and contributes to the regulation of the enterohepatic circulation of cholesterol (Repa et al., 2000a).

Therefore the common feature of PPARγ and LXR is that both are activated by oxidized lipid molecules. In addition they have been implicated in many similar biological processes ranging from regulating lipid metabolism to inflammation suggesting further that there are overlaps or at least similarities between oxidized fatty acid and oxysterol signaling. To add further credence to this notion recently, a hierarchical, unsupervised clustering of nuclear receptor tissue expression and distribution profiles grouped PPARγ and LXR together along with the glucocorticoid receptor and apart from retinoid or other PPAR receptors (Bookout et al., 2006), suggesting the existence of a certain physiological linkage between the two pathways. Moreover, these two receptors have been linked to the development of pathological conditions in which lipid abnormalities and inflammation coexist as well. An extensive accumulation of lipid molecules including oxysterols and fatty acids in the sub-endothelial re-