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Action mechanisms of Liver X Receptors

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ABSTRACT

The two Liver X Receptors, LXRα and LXRβ, are nuclear receptors belonging to the superfamily of ligand-activated transcription factors. They share more than 78% homology in amino acid sequence, a common profile of oxysterol ligands and the same heterodimerization partner, Retinoid X Receptor. LXRs play crucial roles in several metabolic pathways: lipid metabolism, in particular in preventing cellular cholesterol accumulation; glucose homeostasis; inflammation; central nervous system functions and water transport. As with all nuclear receptors, the transcriptional activity of LXR is the result of an orchestration of numerous cellular factors including ligand bioavailability, presence of corepressors and coactivators and cellular context i.e., what other pathways are activated in the cell at the time the receptor recognizes its ligand. In this mini-review we summarize the factors regulating the transcriptional activity and the mechanisms of action of these two receptors.

1. Introduction

Liver X Receptors (LXRs) are nuclear receptors belonging to the family of ligand-activated transcription factors [1]. There are two isoforms with 78% amino acid identity in their DNA-binding domain and ligand-binding domain. LXRα (NR1H3), first discovered by Magnus Pfahl and called RLD1 [2,3], and LXRβ (NR1H2), also named RXR-interacting protein 15 (RIP15) [4], ubiquitously-expressed nuclear receptor (UNR) [5], steroid hormone-nuclear receptor (NER) [6] or orphan receptor-1 [7] because of its concomitant independent discovery by different laboratories. In humans, LXRα is located on chromosome 11p11.2 and LXRβ on chromosome 19q13.3.

2. Tissue distribution of LXRs

In adult rodents, the profiles of protein expression of the two LXR isoforms are different, LXRα being highly expressed in the liver, adipose tissue, intestine, kidney, and macrophages, and LXRβ expressed in epithelia active in transporting water such as pancreatic ductal epithelial cells [8], gallbladder and liver cholangiocytes [9,10] as well as in certain hypothalamic neurons [11], astrocytes and microglia [12].

During mouse development, starting from embryonic day 11.5, both LXRα and LXRβ mRNA are detected in the liver. LXRα maintains high expression throughout life while, hepatic LXRβ decreases during later embryonic development [13]. Between mouse embryo ages days 11.5 and 16.5, LXRα mRNA appears to be detectable in brown adipose tissue, thyroid gland, and intestine while LXRβ mRNA is strongly expressed in brain, retina, ganglia (vestibulocochlear, trigeminal, dorsal root), kidney, adrenal, thymus and thyroid gland [13]. In the brain, LXRβ protein expression is detectable as early as embryo age day 14.5 in the neurons of the cortical plate [14].

3. Ligands

The first identified natural ligands that can activate LXRs at physiological concentration are oxysterols, in particular 24(S)-hydroxycholesterol, 22(R)-hydroxycholesterol, 24(S),25-epoxycholesterol, 27-hydroxycholesterol [15] and its metabolite, cholestenoic acid [16]. Synthesis of 24(S)-hydroxycholesterol from cholesterol, the main mechanism of cholesterol removal from the brain [17], is catalyzed by cytochrome P450 46 A1 (CYP46A1). 22(R)-hydroxycholesterol is a naturally occurring oxysterol while 24(S),25-epoxycholesterol is made in cholesterol synthesis pathway from the cholesterol precursor squalene [18]. 27-Hydroxycholesterol is generated by a mitochondrial P450 enzyme, CYP27, involved in the alternative bile acid synthesis pathway [19]. The pattern of oxysterols that activates LXR, suggested that both anabolic and catabolic pathways in cholesterol metabolism may regulate LXR activity. Such a function of cholesterol metabolites was confirmed in *in vivo* experiments: (i). Knockout mice engineered to delete enzymes synthesizing 24(S)-HC, 25-HC and 27-HC are unable to induce LXR target genes in response to dietary cholesterol but remain responsive to a

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synthetic LXR agonist (T0901317) [20]; (ii). treatment of mice with inhibitors of cholesterol synthesis such as the archetypal statin, compactin, leads to a decrease in the synthesis of 24(S),25-epoxycholesterol, and to a decreased expression of LXR target genes [21,22]; (iii). bile duct ligation reduces hepatic oxysterol bioavailability and is associated with a down-regulation of LXR target genes, in rats [23]; (iv). adenovirus-mediated overexpression of cholesterol sulfotransferase, (SULT2A1) an enzyme capable of catabolizing oxysterols, prevents dietary induction of hepatic LXR target genes by dietary cholesterol but not by T0901317 [20].

In addition to oxysterols, D-glucose has been reported capable of binding to both LXRα and LXRβ and inducing LXR transcriptional activity [24]. This role of LXRs as glucose sensors is not well understood since only the transcription factor carbohydrate-responsive element binding protein (ChREBP), and not LXRs, has been shown to induce glucose-regulated genes in the liver [25].

Two non-steroidal synthetic compounds, GW3965 and T0901317 (29, 30) as well the phytosterol, β-sitosterol (28) have been identified as LXR agonists capable of activating both LXR isoforms. However, T0901317 is not specific for LXR since it can also activate the Farnesoid X Receptor (FXR) [26] and the Pregnane X Receptor (PXR) [27]. Therefore, at present GW3965 appears to be the most selective synthetic LXR ligand.

Other activators of LXR include members of the Proton Pump Inhibitor (PPI) family, such as lansoprazole, pantoprazole and omeprazole [28]; a subset of natural bile acids which appear to be LXR-selective [16]; and N-acylthiadiazolines selective for LXRβ but with low potency [29].

4. Mechanism of action

LXRs regulate gene transcription through two different mechanisms of action: direct activation (Fig. 1 upper panels) and transrepression (Fig. 1 lower panels). In the first mechanism, LXRs form obligate heterodimers with the Retinoid X Receptor (RXR) [2] and bind to LXR-responsive elements (LXREs) consisting of a direct repeat of the core sequence 5′-AGGTCA-3′ separated by 4 nucleotides (DR4) [30] in the DNA of target genes. Inverted repeat of the same sequence with no space region (IR-0) or with 1 bp spacer (IR-1) may also mediate LXR transactivation [31,32].

In the absence of ligands, LXRs are in a non-active state, binding to cognate LXREs in complex with corepressors such as the Nuclear Receptor Corepressor (NCoR) or the Silencing Mediator of Retinoic Acid and Thyroid Hormone Receptor (SMRT) [33,34]. The binding of ligands induces a change in the conformation of LXRs that enables the release of corepressors, recruitment of coactivators [35] and in turn the direct activation of gene transcription. Several coactivators have been described for LXRs. These include: Peroxisome Proliferator Activated Receptor-γ (PPARγ) coativator-1α (PGC-1α) [36], the Steroid Receptor Coactivator-1 (SRC-1) [37] and the Activating Signal Cointegrator-2 (ASC-2) [38].

The second mechanism of action (Fig. 1), transrepression, plays a key role in regulating proinflammatory genes [39]. LXRβ exerts a strong inhibition of the transcription of NF-kB-regulated proinflammatory genes [40] that lack a direct binding site for LXRs. After ligand binding, LXRβ undergoes a specific SUMOylation by SUMO-2/3 that promotes interaction with GPS2, a subunit of the N-CoR complex. In this setting the dissociation of the N-CoR complex from NF-kB is prevented and in turn the transcription of pro-inflammatory genes is blocked [39].

5. Nuclear receptors influencing LXR activity

Two other nuclear receptors, PPARγ and Small Heterodimer Partner (SHP) influence the cellular actions of LXR. Indeed PPARγ, induces expression of LXRα in macrophages [41] while SHP, blocks the transcriptional activity of LXRα [42]. In the liver, SHP is one of the main effectors of the negative feedback regulation on CYP7A1,

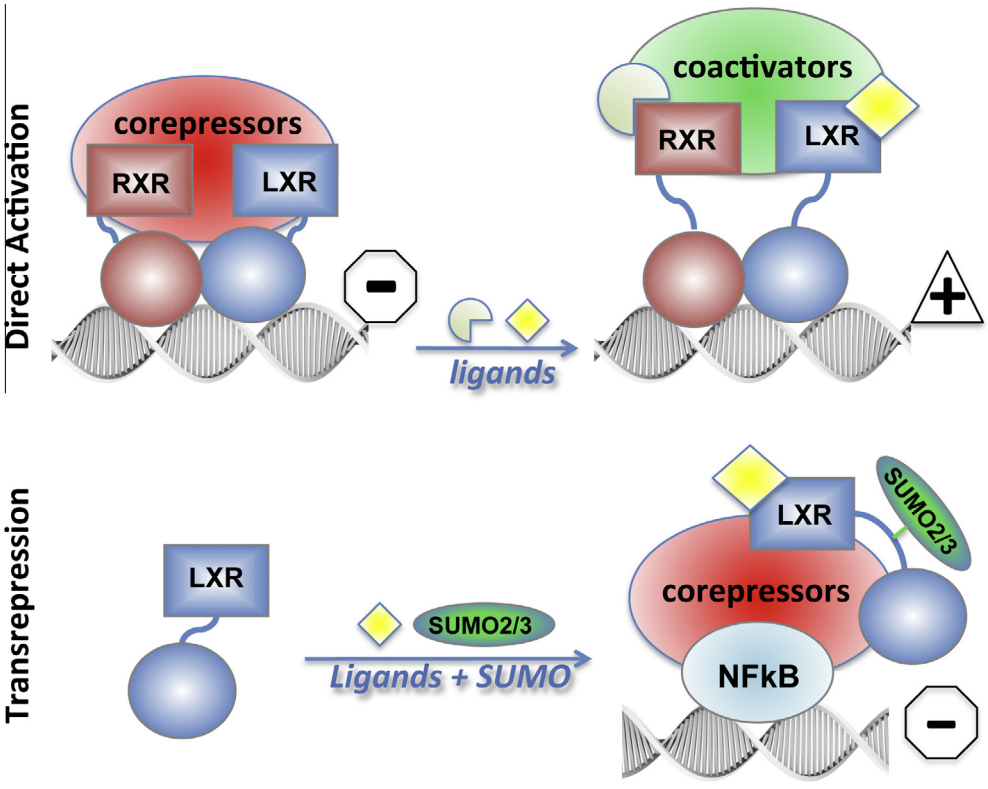

Fig. 1. LXRs influence gene expression by (i) directly promoting gene transcription after heterodimerization with RXR, binding with the ligands and interacting with coactivators and (ii) by transrepressing NF-kB regulated genes after SUMOylation and interaction with corepressors.

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