

Liver X receptors as potential targets for cancer therapeutics (Review)

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Abstract. Liver X receptors (LXRs) are important members of the nuclear receptor family that were originally determined to function in cholesterol transport and the regulation of immune responses. Synthetic LXR ligands have been developed to treat various diseases including diabetes, Alzheimer's disease and atherosclerosis. Previous studies have suggested that LXRs are also involved in numerous types of cancer and are therefore potential targets for cancer therapeutics. The present review summarizes LXR ligands and their mechanisms of action, the effects of LXRs in different types of cancer and their potential applications in clinical treatment. Together, the studies discussed in the present review indicate that LXRs may be potential targets for cancer therapeutics.

diabetes and metabolic diseases (1-3). Liver X receptors (LXRs) are important members of the NR family that were originally identified as major sensors of dietary cholesterol (4). Two LXRs, LXR α (NR1H3) and LXR β (NR1H2), were initially identified in a human liver cDNA library screen as orphan receptors (5-7). LXRs are involved in cholesterol synthesis and transport, glucose homeostasis, and the modulation of inflammatory and immune responses (8-10). LXRs exhibit the typical structure of the NR superfamily. LXR α and LXR β harbor four distinct domains: i) An N-terminal activation domain (AF-1); ii) a DNA-binding domain with two zinc fingers; iii) a hinge domain that binds co-repressors in the absence of ligand; and iv) a C-terminal domain that contains a hydrophobic ligand-binding domain and a transactivation domain (11,12).

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1. Introduction

The nuclear receptor (NR) superfamily consists of important ligand-inducible transcription factors that are involved in various physiological processes, including cell differentiation, embryonic development and metabolism (1,2). NR signaling serves important roles in a number of diseases including cancer,

2. LXR ligands and mechanism of action

LXRs were initially identified as orphan receptors. However, later studies identified oxysterols, or oxidized metabolites of cholesterol, as the endogenous ligands of LXR α and LXR β (13,14). Furthermore, 22(*R*)-hydroxycholesterol, 20(*S*)-hydroxycholesterol, 24-hydroxycholesterol, 7 α -hydroxycholesterol and 27-hydroxycholesterol also activate LXRs (13,15). Additionally, microbial and plant-derived sitosterol, sitostanol and acanthoic acid from *Rollinia* function as LXR agonists (16,17). Since the initial identification of endogenous LXR ligands, synthetic ligands have been developed by numerous pharmaceutical companies. T0901317 was the first synthetic LXR agonist to be developed, and is the most widely used in basic research. However, this compound may also activate two other NRs: Farnesoid X receptor and pregnane X receptor (18,19). A more selective synthetic agonist, GW3965, was identified in a screen of GlaxoSmithKline (Brentford, UK) compounds (20). However, neither of these agonists is used therapeutically owing to their temporary hypertriglyceridemic effects (20,21). More recently, promising synthetic ligands including 22(*E*)-ergost-22-ene-1 α , 2 β -diol and *N,N*-dimethyl-3 β -hydroxycholeamide have been developed with fewer side effects and greater potential for use in clinical testing (22,23).

In the absence of a ligand, LXRs form obligate heterodimers with the retinoid X receptor. These heterodimers bind to target gene promoters harboring the conserved LXR-response element, which consists of two direct repeats of AGGTCA separated by four nucleotides or one nucleotide.

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Table I. Effects of LXR in different types of cancer.

Ligand	Tumor type	Molecular mechanism	(Refs.)
LXR α and LXR β	Colon	Wnt signaling pathway, cell cycle arrest and pyroptosis	(25-29)
LXR α and LXR β	Prostate	AKT survival signaling, MAPK transduction pathways	(29-34)
LXR α and LXR β	Breast	EST, E2F family members	(35-39)
LXR β	Pancreatic	Inhibits cell proliferation, cell cycle arrest	(40,41)

LXR, liver X receptor; AKT, protein kinase B; MAPK, mitogen-activated protein kinase; EST, estrogen sulfotransferase; E2F, E2 factor.

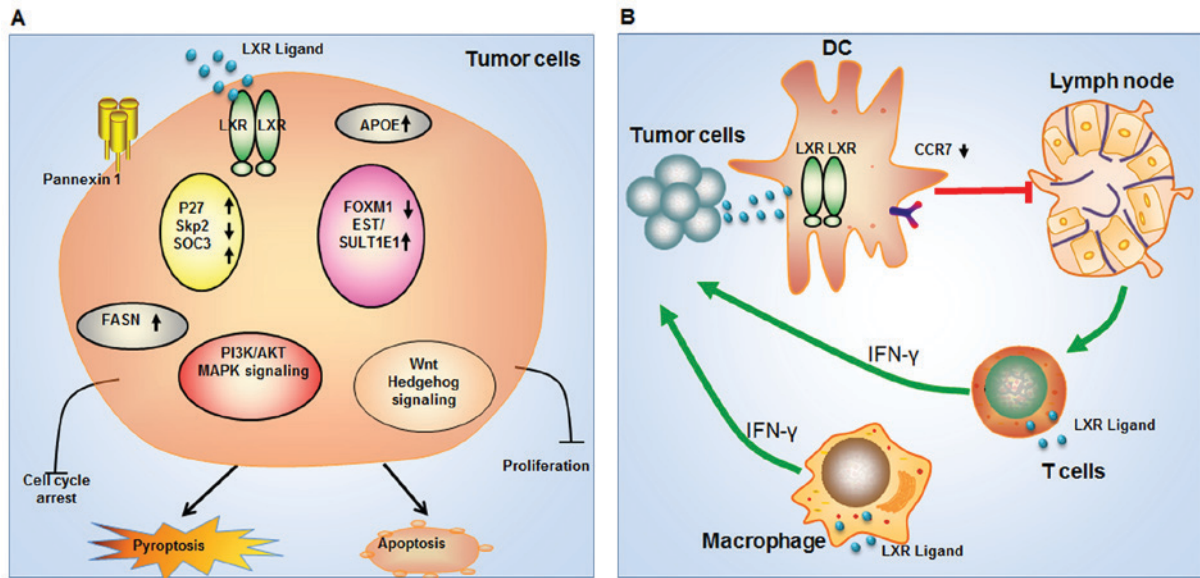


Figure 1. (A and B) Model of LXR agonist activation in various types of cancer and tumor immunity. LXR, liver X receptor; APOE, apolipoprotein E; p27, cyclin-dependent kinase inhibitor 1B; Skp2, S-phase kinase-associated protein 2; SOC3, suppressor of cytokine signaling 3; FOXM1, forkhead box M1; EST, estrogen sulfotransferase; SULT1E1, sulfotransferase family 1E member 1; FASN, fatty acid synthase; PI3K, phosphoinositide 3-kinase; MAPK, mitogen-activated protein kinase; IFN- γ , interferon- γ ; AKT, protein kinase B; CCR7, C-C chemokine receptor type 7; DC, dendritic cell.

The heterodimer forms a complex with NR co-repressor (NCoR) to block transcription (24). Upon ligand binding to the heterodimer, NCoR is released from the complex and co-activators are recruited, leading to chromatin remodeling and target gene transcription (12).

3. Effects of LXRs in different types of cancer

LXRs and colon cancer. LXR agonists suppress colon carcinogenesis by several mechanisms (Fig. 1A). Uno *et al* (25) demonstrated that LXR agonists block the activation of Wnt signaling by suppressing the transactivation activity of β -catenin. In HCT116 cells, LXR agonists decrease the mRNA expression of β -catenin target genes, including MYC proto-oncogene, matrix metalloproteinase 7 and bone morphogenetic protein 4. Notably, in colon cancer cells, LXR agonists inhibit endogenous β -catenin activity and cell proliferation without inducing apoptosis. Consistent with this result, LXR ligands induce pyroptosis, rather than apoptosis, in human and murine colon cancer cells. Pyroptosis is dependent on caspase-1 activation. More importantly, LXRs also serve non-genomic roles due to the differentially cytoplasmic localization of LXR β . LXR β is predominantly located in the

cytoplasm of colon cancer cells and induces pyroptosis when bound by ligand (26,27). Previously, a study revealed that LXR activation leads to cell cycle arrest in colon cancer cell lines. Furthermore, proliferation markers in the colon are significantly increased in LXR $\alpha\beta$ (-/-) mice compared with wild-type mice (28). Together, inhibition of the Wnt signaling pathway and cell cycle arrest serve important roles during LXR ligand-dependent inhibition of colon cancer cell proliferation (Table I). Ligand-mediated activation of LXR may suppress the growth of colon cancer (29).

LXRs and prostate cancer. Liao and colleagues were the first to report that the LXR agonist T0901317 inhibits the proliferation of human prostate LNCaP cells (30). T0901317 decreases the number of cells in S-phase and increases the expression of the cyclin-dependent kinase inhibitor p27 (Fig. 1A). LXR α expression levels are associated with the sensitivity to T0901317-mediated growth inhibition. Additionally, T0901317-treated nude mice exhibited decreased growth of xenograft LNCaP tumors. Additional studies revealed that protein kinase B survival signaling is downregulated following T0901317 treatment, and that T0901317 induces the apoptosis of LNCaP cells in a lipid raft-dependent manner *in vitro*

and *in vivo* (31). LXR agonists were demonstrated to inhibit cell proliferation and induce G1/S arrest through lipogenic activity (32). Furthermore, a prior study identified cross-talk between the androgen receptor and LXR, and determined that this interaction influences cellular cholesterol levels (33). The suppressor of cytokine signaling 3 pathway is also involved in LXR agonist-mediated prostate carcinogenesis (34) (Table I). Taken together, these results suggest that LXRs may be promising pharmacological targets for the treatment of prostate cancer.

LXRs and breast cancer. Estrogen metabolism serves an important role in breast cancer and LXR controls estrogen homeostasis (35) (Table I). Estrogen sulfotransferase (EST) is a transcriptional target of LXR. In *in vitro* and *in vivo* breast cancer models, LXR inhibits estrogen-dependent cancer cell proliferation by regulating the hepatic expression of EST. These results suggest that LXR inhibits breast cancer growth through a novel mechanism involving the regulation of estrogen homeostasis (35). However, LXR agonists were demonstrated to decrease the proliferation of several breast cancer cell lines independent of lipid biosynthesis (36). LXR agonists decrease the proliferation of cells in S-phase and induce G₁ arrest and apoptosis in MCF-7 cells (37,38). Microarray analysis of gene expression revealed that LXR ligands target a set of common responsive genes, including those regulated by E2 factor family members (39).

LXRs and pancreatic cancer. Pancreatic cancer is one of the most fatal types of cancer; the 5-year survival rate of patients with pancreatic ductal adenocarcinoma (PDAC) is only 5%. LXR agonists inhibit cell proliferation, cell-cycle arrest and colony formation in pancreatic cancer cell lines and regulate multiple gene networks involved in cell-cycle arrest and growth factor signaling (40) (Fig. 1A). However, LXR agonists do not induce apoptosis in PDAC cells (40). Further study is required to clarify the types of cell death induced by LXR agonists. Notably, a prior study revealed that the LXR agonist 22(R)-dihydroxycholesterol (Oxy16) inhibits pancreatic cancer cell-induced paracrine Hedgehog signaling (Table I). However, this inhibition is independent of LXR activation (41).

4. LXRs and tumor immunity

It has been reported that LXRs are involved in innate and adaptive immune responses in various diseases (42,43). LXR $\alpha\beta$ ^(-/-) mice are highly susceptible to intracellular bacterial infection, suggesting that LXR-dependent gene expression serves an important role in innate immunity (42). A-Gonzalez *et al* (44) revealed that LXR signaling promotes apoptotic cell clearance by macrophages and the maintenance of immune tolerance. LXR signaling is also involved in the regulation of other types of immune cell (Fig. 1B). LXR activation inhibits lymphocyte proliferation, and loss of LXR expression confers a proliferative advantage on lymphocytes (45). LXR agonists induce interferon- γ expression in macrophages and T-cells, and increase the survival rate and the tumor-free population of mice inoculated with tumor cells (46,47). However, further studies are required to clarify whether these effects are conserved in other model systems. In Th17 cells, ectopic expression of

LXR negatively regulates differentiation, whereas loss of LXR expression promotes differentiation (48). The role of LXR in dendritic cells (DCs) and tumor immunity is controversial. Villablanca *et al* (49) reported that LXR ligands released from tumor cells inhibit C-C chemokine receptor type 7 (CCR7) expression on maturing DCs. In mice, abrogating LXR agonist release from tumor cells controls tumor growth by recovering DC migration to the tumor area (49). However, another study revealed that treatment with LXR agonists increased CCR7 mRNA expression in an immature DC line (50). Additional investigations are required to determine the underlying molecular mechanism of the potentially opposing roles of LXR.

The antitumor effects of LXR agonists are also evident in the tumor microenvironment. LXR agonists impair the compartmentation of vascular endothelial growth factor receptor-2 in lipid rafts and decrease tumor growth by inhibiting angiogenesis (51). Furthermore, LXR β agonist treatment induces apolipoprotein E secretion by stromal and tumor cells and blocks tumor growth, angiogenesis and metastasis (52). However, further studies are required in order to investigate whether other types of cell in the tumor microenvironment are influenced by LXR β agonists.

5. Conclusion

LXR ligands have been developed to treat various diseases, including diabetes, Alzheimer's disease, atherosclerosis and cancer. In spite of progress, a number of fundamental questions remain with respect to cancer therapeutics. A number of natural and synthetic LXR ligands have been identified. T0901317 and GW3965 are the most widely used agonists for mechanistic and functional studies of LXR activity. However, T0901317 has been reported to increase triacylglycerol levels in the plasma and liver and was therefore suggested to be a poor candidate for clinical application (29). New synthetic agonists, including LXR-623, were developed to minimize the side effects on plasma triacylglycerol levels for clinical testing. The development of novel agonists, particularly for cancer treatment, may accelerate basic and clinical applications. The expression profiles of the two LXRs in clinical samples are unknown, and whether these expression profiles are associated with disease subtype, pathological parameters or disease outcomes requires clarification. Endogenous ligands in tumor and stromal cells must also be identified. Taken together, these results suggest that LXRs may be potential targets for cancer therapeutics.

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