Selective liver X receptor modulators (SLiMs): What use in human health?

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Review

Selective liver X receptor modulators (SLiMs): What use in human health?

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ABSTRACT

Liver X receptors (LXR) are members of the nuclear receptor family. As activated transcription factors, their putative association with human diseases makes them promising pharmacological targets because of the large potential to develop ligands. LXR are mainly considered as intracellular cholesterol "sensors" whose activation leads to decreased plasma cholesterol. They also modulate numerous physiological functions: fatty acid synthesis and metabolism, glucose homeostasis, steroidogenesis, immunity, and neurological homeostasis. LXR-deficiency in mouse results in several phenotypes mimicking pathological conditions in humans. This review will be focused on the various natural and synthetic LXR agonists and antagonists. Putative clinical targets including atherosclerosis, diabetes, Alzheimer's disease, skin disorders, and cancer will be covered.

Contents

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1. Introduction

Nuclear receptors are molecular regulators of gene transcription and intracellular function. Some of them are ligand-activated proteins that control various biological events varying from cell differentiation and development to lipid metabolism and energy homeostasis. Among the nuclear receptors, liver X receptors (LXR) α (Willy et al., 1995; NRIH3) and β (Shinar et al., 1994; Song et al., 1994; NRIH2) were discovered in the mid 90's. Although originally discovered as pivotal regulators of cholesterol homeostasis (Peet et al., 1998), the known roles of LXRs continue to grow with the study of many cell types and animal models. Thus far, there is evidence that LXR is involved in the following physiological functions: *de novo* synthesis of cholesterol (Wang et al., 2008a,b), excretion (reviewed in Repa and Mangelsdorf, 2000) and detoxification of bile acids (Barbier et al., 2009) or lipids (Volle et al., 2004), glucose homeostasis (Cha and Repa, 2007), immunity (reviewed in Zelcer and Tontonoz, 2006), skin development and homeostasis (Demerjian et al., 2009) and neurological functions (Koldamova and Lefterov, 2007) and reviewed in (Leoni and Caccia, 2011). LXRα was initially described as highly expressed in a restricted subset of tissues known to play an important role in lipid metabolism such as liver, small intestine, kidney, spleen and adipose tissue whereas LXRβ was found to be expressed more ubiquitously (www.nursa.org). Since their identification as orphan receptors, oxidized derivatives of cholesterol, known as oxysterols (for a review see Schroepfer, 2000), deorphanized both LXRs (Janowski et al., 1996; Janowski et al., 1999). Because LXR deficiency has been associated with various human-like diseases in mice, these receptors are promising pharmacological targets due to the enormous potential to develop ligands. The present review will thus be focused on the various known LXR ligands and their potential use in human health.

1.1. LXR structure

As members of the nuclear receptor superfamily, LXRs are composed of four independent domains (for an extensive review about LXR structure see (Viennois et al., 2011): (i) an amino-terminal domain (A/B domain) containing an activating function AF1, which permits the recruitment of ligand-independent co-activators; (ii) a DNA-Binding Domain (DBD) characterized by two zinc fingers; (iii) a hinge domain that permits the recruitment of co-repressors in absence of ligands; and (iv) a carboxy-terminal domain, containing a hydrophobic ligand-binding domain (LBD), which is required for dimerization, and a transactivation domain (AF-2), which recruits co-activators.

1.2. Mechanism of action

(Fig. 1) LXRα and LXRβ usually form obligatory heterodimers with retinoid X receptor, the receptor of *9-cis* retinoic acid (Willy et al., 1995; Willy and Mangelsdorf, 1997). Both also bind to a non-canonical responsive element on the renin promoter to regulate renin transcription (Morello et al., 2005). In this conformation LXRα functions as a cAMP activated factor (Tamura et al., 2000) while LXRβ seems to be inversely affected by cAMP (Morello et al., 2005). When bound to RXR in absence of ligand, acetylated LXR is located on LXR responsive element (LXRE) in the promoter of the target genes. The consensus LXRE sequence consists of two direct repeats of hexameric nucleotides, AGGTCA, separated by four or one nucleotide(s) (DR4 or DR1). The heterodimer interacts with either a co-repressors, nuclear receptor co-repressor (N-CoR), or silencing mediator for retinoic acid and thyroid hormone receptors (SMRT) (Hu et al., 2003), which block transcription by recruitment of histone deacetylase through the interaction with proteins such as stress activated MAP kinase interacting protein 3A (Sin3A) (Lazar, 2003). When the ligand of one of the two partners binds to the heterodimer, it leads to conformational changes that induce the release of the co-repressors, the recruitment of specific co-activators such as activating signal cointegrator-2 (ASC-2) (Lee et al., 2008) on the AF-2 domain (Svensson et al., 2003), the interaction with histone acetyl transferase leading to the transcription of the target genes (reviewed in Viennois et al., 2011).

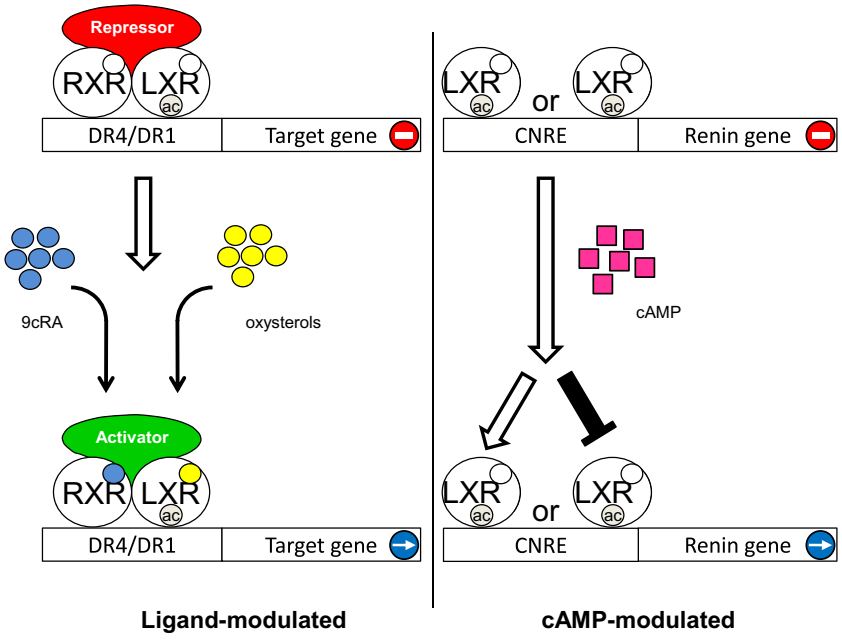

Fig. 1. Schematic view of LXR modulation of gene transcription. LXRαβ or LXRβ usually bind RXR, the receptor for 9-*cis* retinoic acid, on a DR4 or a DR1 element. In absence of ligand RXR/LXR heterodimer is silenced by corepressors. The binding of their respective ligands (9 cis RA and/or oxysterols) induces conformational changes that allow corepressor departure and coactivator recruitment. On the renin promoter, both LXR can bind as a monomer on a CNRE. Their transcriptional activity is modulated by cAMP. For more details, see text.

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2. Activator ligands

Traditional pharmacology states that a ligand can be either classified as agonist (full or partial), antagonist or inverse agonist, though this last type has never been described in either of the LXR. Due to the various diseases LXRα and/or LXRβ are associated with (see above), these nuclear receptors are promising pharmacological targets. This explains why numerous drug companies have been developing a large variety of natural or synthetic agonists. However, LXRα and LXRβ could be expressed in the same cells. It is thus important to have molecules that could selectively modulate each isoform. The other important point is the necessity to target this modulation specifically in the affected organ and make the ligand bio-available. Hence, the development of such *selective Liver X modulators* (SLiMs) will be the challenge in the future. This will prevent deleterious side effects. From previous studies, it appears that activating or inhibiting characteristics of LXR-ligands are dependent of the amino acid sequence of each LXR isoform, despite a clear homology. The cellular context should also be taken into account: for example, the sequence of the response elements within the promoter or the intracellular enzymes that could modify ligand activity. In general, SLIMs may apply a similar philosophy as that of Selective Estrogen Receptor Modulators (SERMs) such as raloxifen and tamoxifen.

2.1. Endogenous agonists: oxysterols and other sterols

Oxidized or hydroxylated metabolites of cholesterol known as oxysterols (Schroepfer, 2000) have been described to be the *bona fide* ligands for LXRs (Janowski et al., 1996). Two sources of oxysterols should be considered on mammals: (i) endogenous, by enzymatic or chemical synthesis; (ii) exogenous, by nutritional supply. The first screenings of LXR ligand have been performed by double hybrid experiments using the LXRα LBD associated with the DBD of GAL-4 (Janowski et al., 1996). Oxysterols showing the greatest induction factors were 22(*R*)-hydroxycholesterol, 20(*S*)-hydroxycholesterol, 24(*S*)-hydroxycholesterol, 7α-hydroxycholesterol and 27-hydroxycholesterol (Fig. 2). Besides, 24-cetocholesterol, 25-hydroxycholesterol and 24(*S*),25-epoxycholesterol have also been shown to be good LXRα and LXRβ activators (Lehmann et al., 1997) (Fig. 2). Interestingly, the nature of oxysterols depends on the site of synthesis: 22(*R*)-hydroxycholesterol in steroidogenic tissues, 24(*S*)-hydroxycholesterol (or cerebrosterol) in brain and plasma, 24(*S*),25-epoxycholesterol in liver, and 27-hydroxycholesterol in plasma and macrophages. In 1999, Janowski et al. (1999) synthesized and tested a series of related compounds. Their work revealed that position-specific monooxidation of the sterol side chain was requisite for LXR high-affinity binding and activation. Enhanced binding and activation could also be achieved through the use of 24-oxo ligands that act as hydrogen bond acceptors in the side chain. In addition, introduction of an oxygen on the sterol B-ring results in a ligand with LXRα selectivity. The ultimate demonstration that oxysterols were the true LXR ligands *in vivo* came from Russell's group (Chen et al., 2007): forced expression of cholesterol sulfotransferase, an enzyme that metabolizes oxysterol ligands, led to inactivation of LXR signaling in cell lines and cholesterol-fed mice. Also, genetic elimination of three oxysterol biosynthetic enzymes attenuated the response of some, but not all, LXR target genes in mouse liver.

Other cholesterol-derived molecules, such as follicular fluid meiosis activating sterol (FF-MAS), may also activate LXRα (Ruan et al., 1998). Likewise, desmosterol, a cholesterol precursor produced from zymosterol, could also activate LXR (Yang et al., 2006) (Fig. 3A).

Bile acid pathway-derived molecules have also been proposed as putative LXR ligands. Indeed, even though bile acids are the nuclear receptor FXR ligands (Makishima et al., 1999), cholestenoic

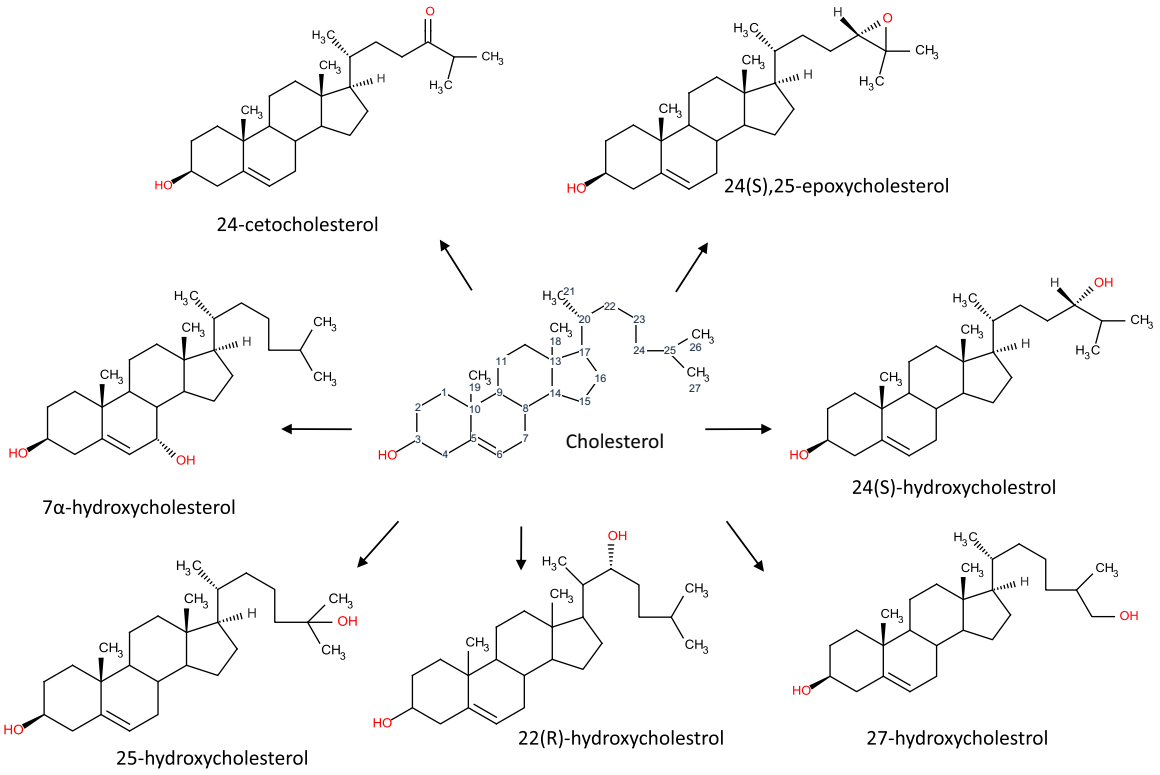

Fig. 2. Natural agonist ligands, the oxysterols. Cholesterol chemical structure is represented and carbon atoms are numbered. The name of each oxysterol depends on the hydroxyl group position.

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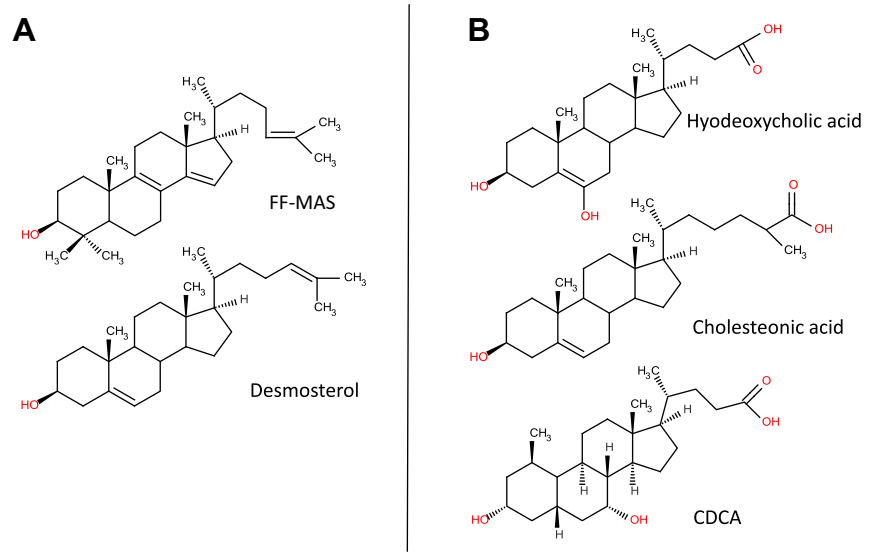

Fig. 3. Natural agonists, other cholesterol deriving sterols. (A) FF-MAS and demosterol chemical structure, molecules derived from cholesterol biosynthesis pathway, upstream cholesterol. FF-MAS, Follicular Fluid Meiosis Activating Sterol. (B) LXR agonists derived from Bile acids biosynthesis pathway. CDCA, chenodeoxycholic acid. Note that CDCA does not activate LXR.

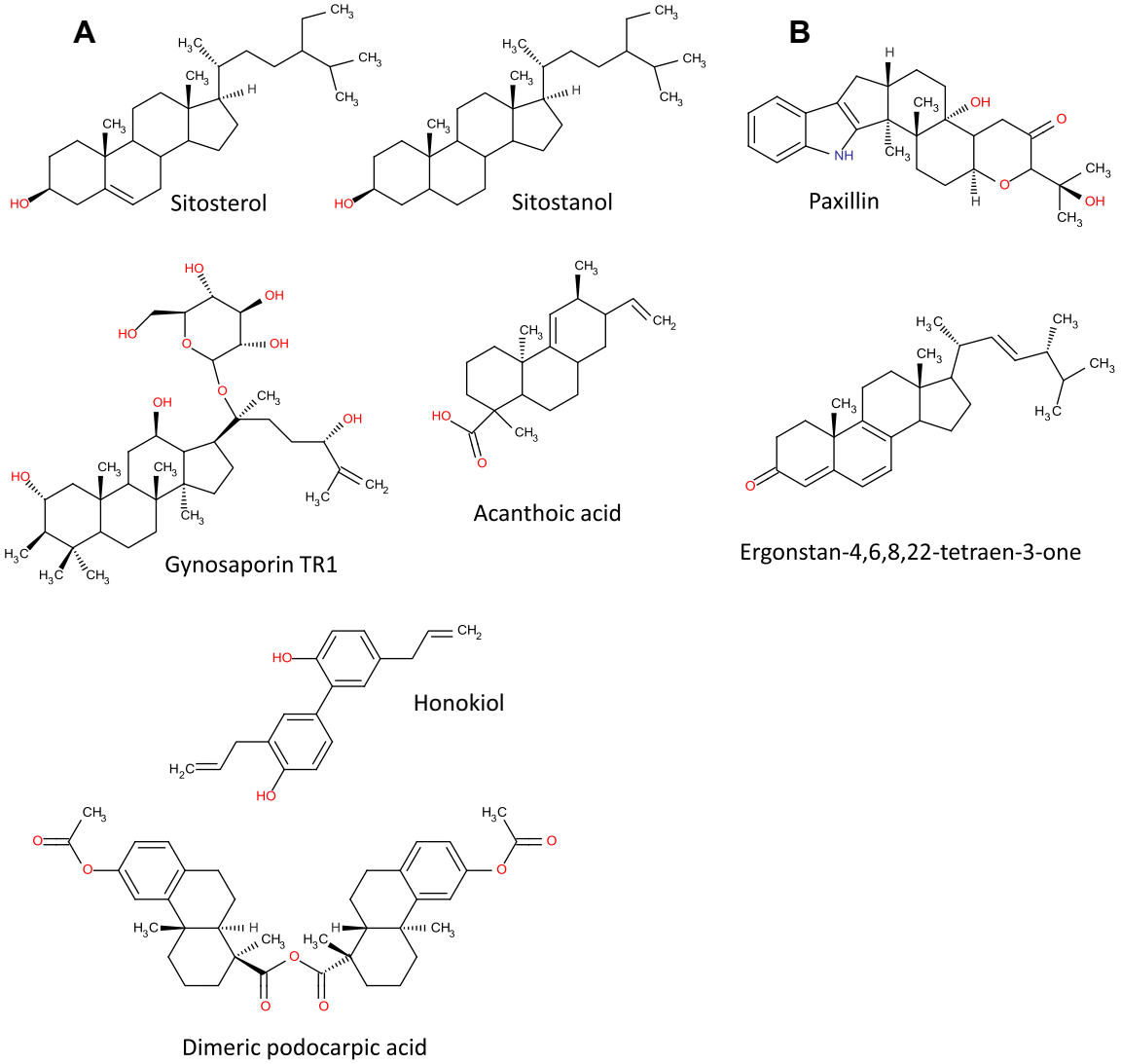

Fig. 4. LXR activators derived from plants (A) and fungi (B).

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acid, chenodeoxycholic acid (CDCA) precursor, is able to induce transcriptional activity of LXRα and β on gene reporter assay (Song and Liao, 2000). Likewise, the same group described 6α-hydroxylated bile acids (notably hyodeoxycholic acid) as selective activators of LXRα (Song et al., 2000) (Fig. 3B).

2.2. Ligands from microbial and plants

Over the last decade various plant sterols and stanols, which are structurally related to cholesterol, have been identified as LXR activators since they are the natural occurring equivalent of mammalian cholesterol (Fig. 4). Therefore, sitosterol and sitostanol, derived from the 4-desmethylsterol family, activated both LXRα and LXRβ and increased expression of ATP Binding Cassette A1, ABCA1 in Caco-2 cells (Plat et al., 2005). Gynosaponin TR1, isolated from the herbal medicine, *Gynostemma pentaphyllum*, an herbaceous vine of the *Cucurbitacea* family, demonstrated greater selectivity toward activation of the LXRα isoform than LXRβ in HEK293 cells (Huang et al., 2005). Acanthoic acid from *rollinia*, an exotic tropical fruit, selectively activates LXRα in HEK-293 cells (Jayasuriya et al., 2005) and both isoforms in macrophages lead to cholesterol efflux (Traves et al., 2007). Podocarpic acid is a natural activator derived from plant resins. This molecule gets its name from Podocarpus from which it was extracted. It has been reported that podocarpic acid is able to bind to LXRα and β. In hamster and mice models, it increases plasma HDL with concomitant decrease of plasma LDL (Singh et al., 2005). More recently, honokiol, extracted from the bark of *Magnolia abovata*, a native Japanese Magniola, has been showed to be an activator of the LXR/RXR heterodimer and its ABCA1 target gene in peritoneal macrophages, excluding foam cells (Kotani et al., 2010). However, it is not known whether honokiol directly binds RXR and/or LXRα. Besides plants, some fungal derivatives may also activate LXR (Fig. 4), such as Paxillin from *Penicillium paxilli* (Bramlett et al., 2003), or ergostan-4,6,8,22-tetraen-3-one, a ergostane derviate from *Tolypocladium niveum*, a Norwegian soil fungus (Ondeyka et al., 2005).

2.3. Synthetic agonists

The discovery of the hypocholesterolemia potency of LXR at the end of the 90's (Peet et al., 1998) motivated many pharmacological companies to develop LXR ligands (for an exhaustive review see Li et al., 2010). Among them, a non steroidal compound, T0901317 (Fig. 5) is the most commonly used synthetic ligand in fundamental research. However, this compound is not completely selective for LXR since it is able to activate PXR or FXR at high concentrations (Houck et al., 2004; Mitro et al.; 2007; Shenoy et al., 2004). T0901317 has also been found to be a very effective RORα and RORγ inhibitor (Kumar et al., 2010). A screening of GlaxoSmithKline (GSK) compounds has permitted the identification of the GW3965 (Fig. 5) as a strong agonist of LXRα and LXRβ. In contrast with T0901317, GW3965 is more selective for LXR (Mitro et al., 2007). Unfortunately, human therapeutic use of these molecules is impossible because of their temporary hypertriglyceridemic effects (Joseph et al., 2002a,b). More recently, GSK has also developed an intestinal-specific LXR agonist closely related to GW3965, GW6340, which specifically activates LXR target genes (ABCA1, G5 and G8) in small intestine without modification of hepatic target genes expression or hepatic triglyceride content (Yasuda et al., 2010).

A promising synthetic ligand was also identified by Makishima's group: (22E)-ergost-22-ene-1α,2β diol (YT-32) (Fig. 5), derived from ergosterol, shows strong LXR agonist activity (Kaneko et al., 2003). In mice, the oral administration of YT-32 leads to an intestinal accumulation of the ABCA1, ABCG5 and ABCG8 encoding genes, and a reduction of plasma cholesterol without any modification of expression of these genes in liver. This ligand is the first tissue-specific LXR agonist. To explain this specificity, Kaneko et al. suggested that YT-32 may reduce the intestinal absorption of cholesterol, by inducing expression of ABCG5 and G8, which could excrete the compound from the apical membranes of mucosal cells. A second hypothesis was that YT-32 is secreted into bile by ABCG5 and G8 before it has a chance to induce expression of lipogenic

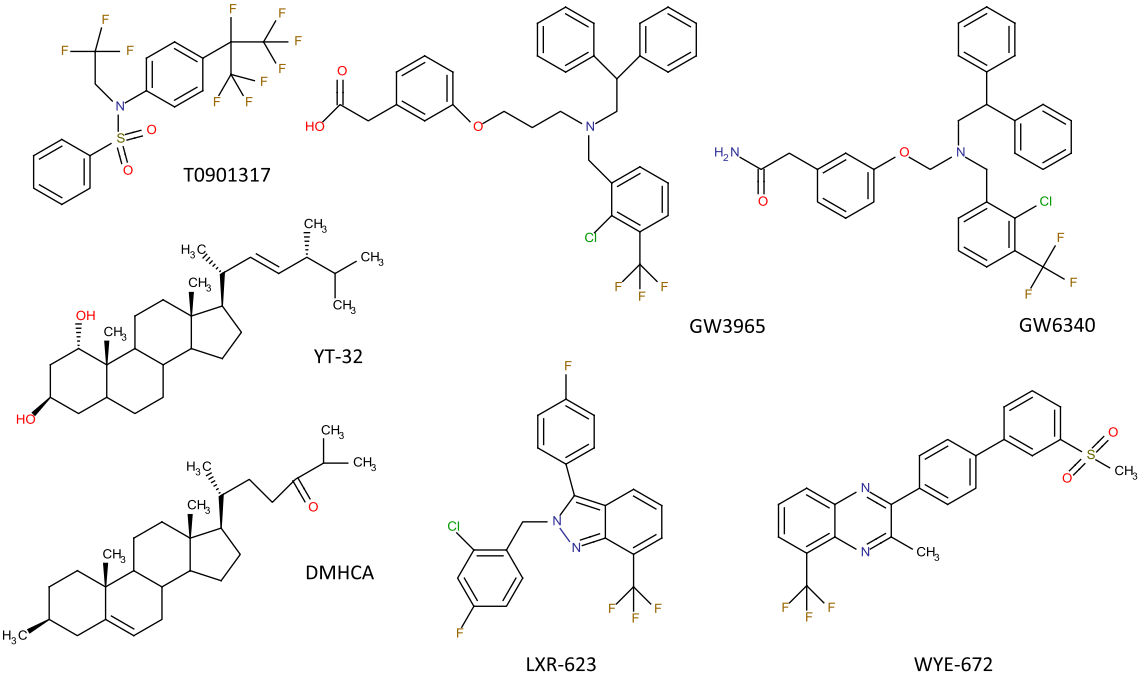

Fig. 5. Synthetic LXR agonists.

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genes in liver. A third explanation could be a tissue-specific agonist activity depending on co-factor recruitment as observed for selective estrogen receptor modulators.

In the same way as YT-32, DMHCA (N,N-Dimethyl-3β-hydroxycholenamide) (Fig. 5) is an LXR agonist that is able to stimulate cholesterol transport through upregulation of LXR target genes, including ABCA1, in liver, small intestine, and peritoneal macrophages (Quinet et al., 2004). DMHCA's binding affinity to both LXR isoforms was calculated by scintillation proximity assay at 100–200 nM (Janowski et al., 1999). Compared with known nonsteroidal LXR agonists, DMHCA exhibits only limited activity to increase hepatic Sterol-response element binding protein 1c (srebp-1c) and Fatty acid synthase (fas) mRNA and does not alter circulating plasma triglycerides (Quinet et al., 2004). A recent study shows that DMHCA significantly reduces cholesterol absorption and uptake in the duodenum and jejunum of the small intestine and, in turn, leads to a reduction of plasma cholesterol. Interestingly, this study reveals that DMHCA also suppresses endogenous cholesterol biosynthesis (Pfeifer et al., 2011).

The first LXR agonist tested in human in a phase I clinical trial was a Wyeth's compound, the LXR-623 (Fig. 5): an orally bioavailable indazole highly selective for LXR (DiBlasio-Smith et al., 2008; Katz et al.; 2009). After administration of LXR-623 to healthy volunteers, LXR target genes involved in the reverse cholesterol transport were upregulated in the macrophages without any induction of triglyceride synthesis. Unfortunately, adverse effects were observed on the central nervous system, ending the trial. Pharmaceutical companies have focused their efforts on the identification of molecules specific of each LXR isoform. Wyeth group develop a phenylsulfone-substitued quinoxaline, WYE-672 (Fig. 5) as an oral and tissue active LXRβ isoform selective agonist (Hu et al., 2010). Recently, a novel synthetic steroidal LXR agonist, ATI-111 compound, has been described to significantly decrease cholesterol and triglyceride levels in plasma in LDLR−/− mice. This observation is correlated to an increased expression of ABCA1, ABCG1 and ABCG5/G8 in intestine and macrophages without modification of acetyl-coenzyme A carboxylase (ACC) and FAS expressions in liver and intestine (Peng et al., 2011).

3. Antagonists and inhibitors ligands

Given the hypocholesterolemia potency of LXR, pharmaceutical companies have focused their effort on the discovery of LXR activators rather than LXR antagonists. Thus, very few natural or synthetic antagonist compounds have been identified or developed. However, use of LXR-isoform antagonists could help in further deciphering the physiological roles of LXRα and LXRβ.

3.1. Natural antagonists

One of the most potent endogenous LXRα antagonists to date is 5α,6α-epoxycholesterol. This oxysterol, present in high quantities in food, has been detected in atherosclerotic plaques. This compound induces the recruitment of cofactor peptides to both LXRα and LXRβ. Radiolabeled ligand displacement assay demonstrated that 5α,6α-epoxycholesterol binds to LXRα. This molecule is able to antagonize LXR-mediated gene expression in different cell culture systems and notably in keratinocytes (Berrodin et al., 2010). Initially, it was only the sulfated form of this compound, 5α,6α-epoxycholesterol-3-sulfate which was described to antagonize LXR transactivation on a LXR reporter gene assay (Song et al., 2001). It has been demonstrated to disturb the recruitment of certain co-activators and to bind directly to LXR–LBD. In the same study the authors have described another sulfated oxysterol, 7-cetocholesterol-3-sulfate, as a LXR antagonist (Song et al., 2001) (Fig. 6).

Polyunsaturated fatty acids (PUFAs) are known to be PPARα and PPARδ agonists. Several PUFAs, especially arachidonic acid (Fig. 6), have a LXR–LBD-dependent antagonist effect on LXRα (Ou et al., 2001) and LXRβ (Yoshikawa et al., 2002). The physiological role of such antagonist activity has been found associated with the regulation of hepatic fatty acid elongase 5 (Qin et al., 2009). Indeed, PUFAs may feedback inhibit their own synthesis through repression of LXRα and blocking of *srebp1c* transcription, a master gene involved in fatty acid synthesis.

Herath et al. (2005) revealed, using a scintillation binding assay, that a new polyisoprenylated benzophenone named guttiferone I extract from *Garcinia humilis,* a small fruiting tree growing in Bolivia, is able to selectively bind LXRα (Herath et al., 2005) (Fig. 6). However, this compound is unable to provoke the recruitment of co-activators.

Riccardin is a compound deriving from the liverwort *Blasia pusilla*. Riccardin C is a natural antagonist of LXRβ and riccardin F is a natural antagonist of both LXR isoforms. Both compete with the endogenous or synthetic LXR ligand for LXR activation (Tamehiro et al., 2005) (Fig. 6).

A recent study highlights the LXRα antagonizing effect of naringenin (Fig. 6), a flavanone found in grapefruit, oranges and tomatoes (Goldwasser et al., 2010). Naringenin activates the ligand-binding domain of both PPARα and PPARδ while inhibiting LXRα in GAL4-fusion reporters. It inhibits LXRα association with the co-activator TRAP-222 in presence of T0901317. It also leads to an inhibition of LXRα target genes such as fas, abca1, abcg1, resulting in an increase of fatty acid oxidation in primary rat hepatocytes and a decrease of bile acid synthesis.

Whole leaf extract of *Parthenocissua tricuspidata* Virginia creeper from Japan, and *Euscaphis japonica,* a small Japanese tree, suppressed the transcriptional activity of LXRα as well as the expression of LXRα target genes (Kim et al., 2006). Furthermore, both extracts exerted repressive effects on adipocyte differentiation and on lipid metabolism *in vitro* without identification of the active compound.

3.2. Synthetic antagonists

The 22(*S*)-hydroxycholesterol is able to interfere with the binding of other oxysterols (Janowski et al., 1999) to LXR–LBD and to inhibit the lipogenic activity of T0901317 (Lehmann et al., 1997) (Fig. 6).

Motoshima et al. (Motoshima et al., 2009) focused on the creation of LXR antagonists using a multi-template approach based on thalidomide. They found that several thalidomide-related phthalimide derivatives, including PP2P (Fig. 6), possess LXR-antagonistic activity (Noguchi-Yachide et al., 2007). This is based on the agonist property of glucose on LXR. This group develops other phenethylphenyl phthalimide derivates (Motoshima et al., 2009). Likewise, GSK group identified GSK2033, a tertiary sulfonamide, as the first potent cell-active LXR antagonist described to date (Zuercher et al., 2010) (Fig. 6).

Finally, fibrates have been identified as PPARα ligand leading to inhibition of circulating triglycerides. Esterified-fibrates such as fenofibrate (Fig. 6) block LXRα activity by occupation of the ligand-binding pocket without induction of co-factor recruitment (Thomas et al., 2003).

4. From physiological function to pathology

LXR functions have been schematically associated with several various physiological fields from reproduction to energy

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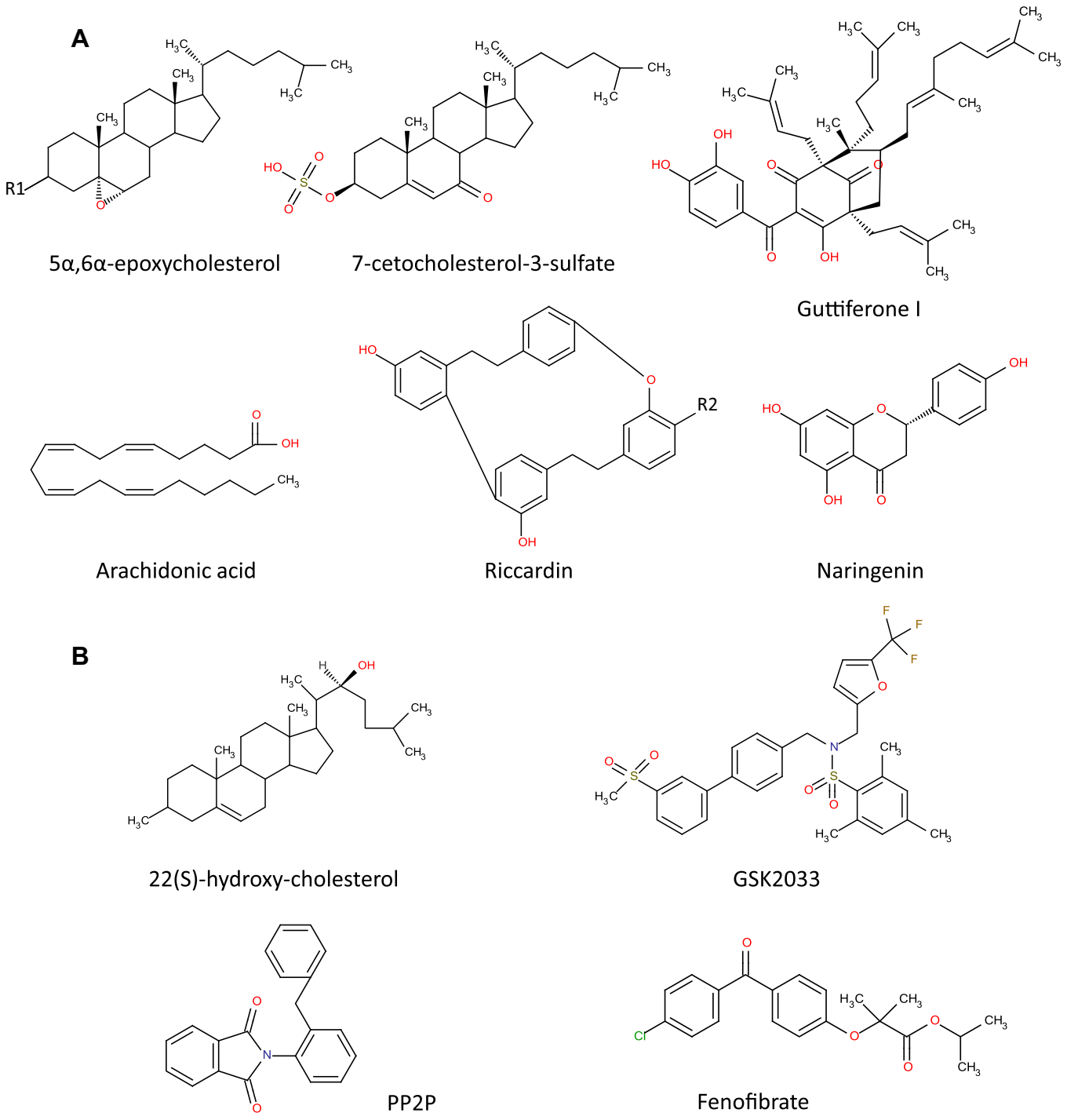

Fig. 6. Natural (A) or synthetic (B) LXR antagonists. (A) The R1 group is OH for 5α,6α-epoxycholesterol and H_2SO_4 for the 5α,6α-epoxycholesterol-3-sulfate, the compound initially described as LXR antagonist, R2 is OCH_3 for Riccardin F and OH for Riccardin C.

homeostasis, neuron physiology, immunity, skin development and apoptosis. Implication of LXR on these processes has been well documented (Cao et al., 2003; Cummins et al., 2006; El-Hajjaji et al., 2011; Joseph et al., 2004; Laffitte et al., 2003; Repa and Mangelsdorf, 2000; Schultz et al., 2000; Viennois et al., 2011; Volle and Lobaccaro, 2007). LXR−/− mouse analysis also pointed out that the lack of one or both isoform could be associated to the development of symptoms linked to human disease (Fig. 7). Hence, LXR are promising pharmacological targets.

4.1. LXR and cancer

4.1.1. LXR and hormone-dependant cancer

Breast and prostate cancers are the leading causes of cancer in women and men, respectively. They share many characteristics (Coffey, 2001). Incidence rates for both prostate and breast cancer are less than 10% compared to those observed in Occidental countries. As people migrate from Asia to the United States, the low rates observed in Asia begin to rise with time and subsequent generations toward those observed commonly in the general American

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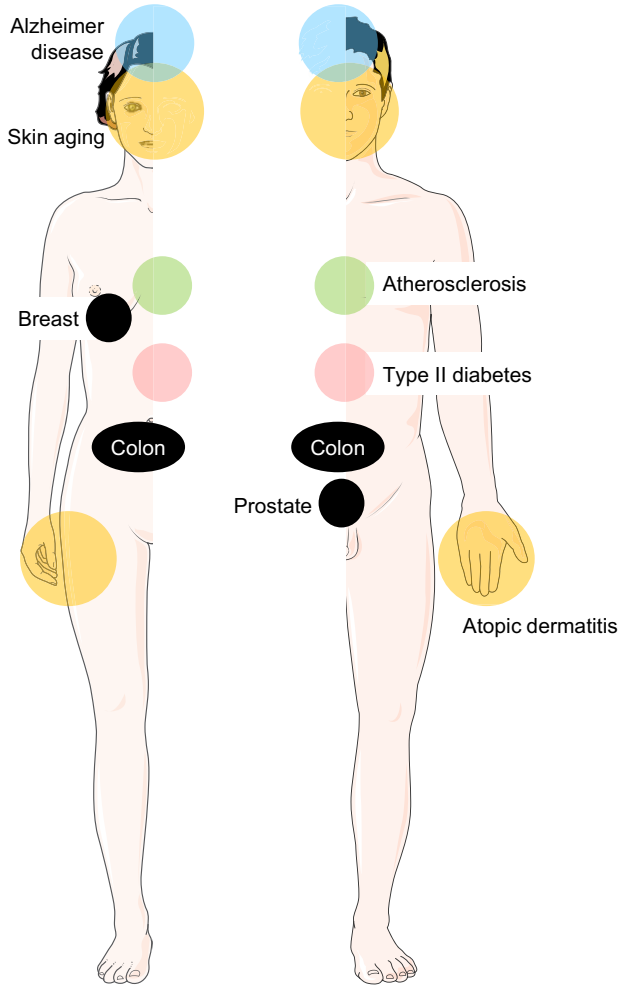

Fig. 7. Schematic representation of the diseases potentially targets of LXR ligands. Black circle, cancer.

population. Furthermore, as Asian countries adopt Western-style diets, their incidencies of prostate and breast cancer rise. In all of these situations, there is a close correlation between responses in the prostate and breast cancer rates. Moreover, the emergence of resistance is common, especially for locally advanced tumors and metastatic tumors (Rau et al., 2005).

4.1.1.1. LXRα and prostate cancer. As previously stated, prostate cancer is the most frequently diagnosed cancer and the second leading cause of cancer death in men (Gronberg, 2003). Among the various genetic and environmental risk factors, epidemiological analyses revealed a clear positive association between hypercholesterolemia and the development of prostate cancer (Bravi et al., 2006,Magura et al., 2008). Indeed, epidemiological studies have shown that Chinese populations, with initially low risk of prostate cancer, have an increased risk after migration to the United States. This environmental effect was mainly attributed to the deleterious impact of lipid consumption (Watanabe et al., 2000). Consistent with this hypothesis, a clinical study revealed that hypercholesterolemia increases prostate cancer risk while a statin treatment, inhibiting *de novo* cholesterol biosynthesis, is associated with lower risk of metastatic prostate cancer (Platz et al., 2006; Shannon et al., 2005). Even though LXR are key regulators of cholesterol homeostasis, their roles in prostate physiopathology remain little known. Fukushi's group first reports the control of proliferation by LXR on LNCaP human prostate carcinoma cell line (Fukuchi et al., 2004a,b). In their experiments, T0901317 decreases the number of cells in S-phase and induces the expression of ABCA1 (Fukuchi et al., 2004a,b). *In vitro* and *in vivo* analyses also revealed that modulation of LXR activity also triggers apoptosis in prostate cancer cells. This effect involves both increased cholesterol efflux by ABCA1 and the disruption of lipid-raft signaling activity (Pommier et al., 2010). Androgens also play a crucial role on prostate cancer development. Androgen ablation is also a common therapy for this type of cancer. Recently, androgens have been demonstrated to crosstalk with LXR in prostate cancer cell line LNCaP (Krycer and Brown, 2011). Hence LXR may also modulate prostate cancer development by decreasing the androgenic pathway.

4.1.1.2. LXR and breast cancer. Several studies have described LXR activity on modulation of breast cancer cell line proliferation and apoptosis. In several estrogen dependent breast cancer cell lines, Vedin et al. demonstrated that T0901317 treatment decreases the number of proliferating cells independently of their lipogenic activity (Vedin et al., 2009). In estrogen independent cell lines, this effect is abolished suggesting a crucial role of estrogen on this LXR effect. *In vivo*, LXR activation increases estrogen catabolism leading to estrogen deprivation. In this way, LXR inhibits estrogen-dependent breast cancer growth (Gong et al., 2007). Among the other female cancers, studies enlighten the anti-proliferative effects of LXR-ligand on ovarian cancer models (Rough et al., 2010).

4.1.2. LXR and colon cancer

Several studies have described a correlation between colon cancer and LXR modulation. Uno et al. pointed that LXR ligand activation decreases the expression of several endogenous β-catenin target genes such as myc, bmp4 and mmp7 in colon cancer cells. This correlates with a reduction of cell proliferation without modification of apoptosis (Uno et al., 2009). In a recent review, Chuu (2011) hypothesized that LXR could be a biomarker or a therapeutic target in colon cancers. Phytosterol-rich diets were reported to decrease incidence of several cancer and β-sitosterol were shown to suppress proliferation of HT-29 colon cancer cells. Since β-sitosterol is an efficient LXR agonist, phytosterols may possibly suppress tumor growth partially through activation of LXR signaling (Chuu, 2011). A case-control study that associates soy (containing phytosterols) consumption and colon cancer onset supports this hypothesis (Spector et al., 2003).

4.2. LXR and skin disorders

Both LXRα and LXRβ are expressed in human keratinocytes and fetal rat epidermis and LXRβ is predominantly expressed in mouse epidermis (Hanley et al., 2000; Komuves et al., 2002). Studies on LXR−/− mice pointed out that epidermal differentiation is regulated by LXRβ and that oxysterols can induce differentiation and inhibit proliferation through LXRβ activation (Komuves et al., 2002). Cholesterol homeostasis is essential for cutaneous barrier function. A study demonstrated that an increase in cholesterol stimulates both ABCA1 (Jiang et al., 2006) and ABCG1 (Jiang et al., 2010) expression, whereas inhibition of cholesterol synthesis by statins decreases ABCA1 and ABCG1 expression in cultured human keratinocytes. After acute permeability disruption, ABCA1 expression decreases keratinocyte cholesterol efflux to make more cholesterol available for regeneration of the barrier (Jiang et al., 2006). Topical treatment of murine skin with LXR activators also increases ABCG1 expression in murine epidermis (Jiang et al., 2010). In case of skin-aging resulting from photo-aging and normal chronological skin aging, an *in vivo* study showed that LXR agonists reverse aging associated syndrome in a photo-aging animal model. Moreover, LXRβ−/− mice could represent a great model of chronologically aged human skin (Chang et al., 2008). Furthermore, LXR

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ligands reverse clinical symptoms of atopic dermatitis, an inflammatory, chronically relapsing and non-contagious skin disorder (Chang et al., 2008; Hatano et al., 2010).

Interestingly, Sticozzi et al. made a connection between cigarette smoke and LXR activity on the skin (Sticozzi et al., 2010). They showed an increase of ABCA1 expression on human keratinocytes, HaCaT cell line, after cigarette smoke exposure. This is the first study describing the negative potential effect of cigarette smoke on cholesterol skin content (Sticozzi et al., 2010). Finally, locally administrated LXR agonists may be potentially useful in the treatment of skin conditions such as dermatitis or aging.

4.3. LXR and Alzheimer's disease

The link between cholesterol and Alzheimer's disease (AD), an age-related dementia disorder, has been well established by two groups after they treated their patients with statins (Jick et al., 2000; Wolozin et al., 2000). Koldamova et al. evaluated the effect of the synthetic LXR ligand T0901317 on ABCA1 expression in the brain of APP transgenic mouse model of AD. T0901317 significantly enhanced ABCA1 expression and downregulated the production of Aβ peptide, whose deposit leads to neuronal degeneration, suggesting that ABCA1 plays a protective role in AD progression (Koldamova et al., 2005). Likewise, the loss of *lxr*α or *lxr*β in APP23 transgenic mice increases Aβ deposit (Zelcer et al., 2007) while activation of LXR by T0901317 causes a significant reduction of memory deficits observed in APP23 model fed a high fat diet (Fitz et al., 2010). Recently, it has been demonstrated that beneficial effects, like memory recovery, of LXR agonists in an APP/presenilin1 (whose mutations are the most common cause of familial early-onset Alzheimer's disease) model of amyloidogenesis, is mediated by ABCA1 (Donkin et al., 2010). Zelcer et al. (2007) showed that LXR activation decreases the inflammatory response likely involved in AD. Likewise, seladin-1/DHCR24, a selective AD marker, is a LXR target gene (Wang et al., 2008a,b). At last, T0901317 significantly decreases amyloid pathology caused by a high-cholesterol diet and improves cognitive performance (Fitz et al., 2010).

Altogether, these data suggest that LXR may be promising pharmacological targets for the treatment of AD and other neurological disorders involving the disruption of cholesterol homeostasis. It is worthwhile to note that two single-nucleotide polymorphisms in LXRβ have been associated with AD (Adighibe et al., 2006; Infante et al., 2010), further suggesting that LXR is involved in this neurodegenerative disease in human. Leoni and Caccia (Leoni and Caccia, 2011) showed that 24(*S*)-hydroxycholesterol, a LXR-ligand (see above) is reduced in plasma and in cerebrospinal fluid of patients with neurodegenerative disease, while 27-hydroxycholesterol is increased. This study highlights the potential use of LXR endogenous ligand not only as a pharmacological compound to treat symptoms, but also as a biomarker of certain diseases.

4.4. LXR and atherosclerosis

The LXR signaling pathway clearly displays anti-atherogenic properties, both by reducing cholesterol levels and by anti-inflammatory properties. Studies in various models of atherosclerosis such as LDLR−/− or APOE−/− mice have now clearly established that treatment with LXR agonist leads to a regression of atherosclerosis *in vivo*. Joseph et al. initially demonstrated that GW3965 treatment inhibited atherosclerotic lesions in APOE−/− or in LDLR−/− mice fed a high-cholesterol diet (Joseph et al., 2002a,b). LXR is also involved in the stimulation of macrophages transcription of ABC transporters resulting in release of cholesterol from the cells. This prevents the transformation of macrophages into foam cells in response to lipid loading. Moschetta's group (Lo Sasso et al., 2010) demonstrated that genetic intestinal-specific LXR activation led to decreased intestinal cholesterol absorption, improved lipoprotein profile, and increased reverse cholesterol transport *in vivo* in the absence of hepatic steatosis thus protecting LDLR−/− mice from atherosclerosis. Lo Sasso et al. identified the intestines as a key player in the LXR-driven protective environment against cardiovascular disease (Lo Sasso et al., 2010). The athero-protective role of LXR may also be mediated by the inhibition of platelet function and thrombus formation (Spyridon et al., 2011): LXRβ is present in human platelets and its ligand activation inhibits platelet aggregation, suggesting the anti-thrombotic role LXRβ.

Using a pharmacological approach with GW6340, Yasuda et al. (2010) showed that intestinal-specific LXR activation promotes macrophage reverse cholesterol transport. ABCA1, ABCG5 and ABCG8 were significantly upregulated in the small intestine, but not in the liver. Two independent mechanisms could account for these observations: increased intestinal HDL production and promotion of intestinal excretion of HDL-derived cholesterol (Yasuda et al., 2010). These data demonstrate that activation of LXR in intestine and macrophages efficiently prevents atherosclerosis. Likewise, and in contrast with T0901317, LXR-623 treatment is not associated with increased hepatic lipogenesis. In non-human primates with normal lipid levels, LXR-623 significantly reduces total and LDL-cholesterol in a time and dose-dependent manner. LXR-623 is also associated with increased expression of the target genes ABCA1/G1 in peripheral blood cells (Quinet et al., 2009). These observations suggest that LXR-623 is a promising pharmacological ligand in atherosclerosis. However, as discussed above, the first clinical trial with this synthetic LXR ligand showed adverse effects (Katz et al., 2009). In the rabbit model of atherosclerosis, LXR-623 and simvastatin, which inhibits endogenous synthesis of cholesterol, reduce the progression of atherosclerosis and induce plaque regression (Giannarelli et al., 2011). A novel LXR therapeutic approach could involve combination therapy for synergistic anti-atherotic effects.

Stein and Matter recently compiled data concerning the protective role of SIRT1 in atherosclerosis (Stein and Matter, 2011). SIRT1 directly deacetylates LXRα, regulating its transcriptional activity. In SIRT1−/− macrophages, cholesterol efflux is lower than in SIRT+/+ macrophages (Li et al., 2007). This study highlights the potential use of activators or inhibitors of LXR co-factors as a new way to modulate LXR.

Human genetics also illuminate LXR as putative pharmacological targets. Analysis of LXR gene sequences in patients with coronary heart disease identified three mutations in the LBD of LXRα (Dave et al., 2009). These mutations create conformational changes that may prevent activation of LXRα by its natural ligands.

4.5. LXR and inflammation

Besides the anti-inflammatory impact of LXR in Alzheimer's disease, dermatitis or atherosclerosis, LXR has also a suppressive role in numerous inflammatory diseases such as, stroke, lung inflammation or rheumatoid arthritis.

Stroke or cerebrovascular accident causes irreversible neuronal injury. It can be due to ischemia (caused by thrombosis or arterial embolism) or hemorrhages. Recently, anti-inflammatory agents have shown to restraint inflammation during a stroke, enhancing neurogenesis and tissue repair. Previously in this review, we discussed about the anti-inflammatory role of LXR and their functional amelioration in Alzheimer's disease. Interestingly, Sironi et al. demonstrated that LXR activation with a single dose of GW3965 blocks ischemia-induced brain damage two hours after the induction of ischemia in rat model (Sironi et al., 2008). In another study, it has been shown that GW3965 or T0901317 improves stoke outcome in rats after ischemic occlusion. This

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neuroprotection is correlated with a decrease of proinflammatory factors in brain, like *cox-2*, *iNos* or NF-kB (Morales et al., 2008).

Using a pre-clinical rat model of endotoxin-induced lung inflammation it has also been shown that LXR activation leads to a suppression of lung inflammatory response (Birrell et al., 2007). In a mouse model of carrageenan-induced pleuristy, LXR activation induces a significant reduction of numerous parameters of inflammation such as cytokine, iNOS formation in lung, lipid peroxidation and apoptosis (Crisafulli et al., 2010).

GW3965 prophylaxis significantly reduced arthritis incidence and attenuated the clinical and histological severity in collagen-induced arthritis mice. Moreover, GW3965 prophylaxis also significantly attenuated inflammatory mediator production in joint sections and serum pro-inflammatory cytokine levels in a dose-dependent manner (Park et al., 2010).

It can be noted that oxysterols may act as EBI2 (*Epstein–Barr virus-induced gene 2*, an orphan G-protein-coupled receptor) ligands and have an important role on adaptative immune response. By this way, oxysterols act as chemoattractant for immune cells, directing cell migration (Hannedouche et al., 2011; Liu et al., 2011).

Altogether, LXR agonists play various anti-inflammatory roles on different tissues like brain, lung immune cells. One way by which LXR exert its anti-inflammatory effect is by SUMOylation. Especially, LXR ligands inhibited STAT1-mediated inflammatory responses in IFNγ-stimulated brain astrocytes. Ligand-dependent SUMOylations of LXRs are required for inhibitory action on STAT1, as STAT1 complexed with SUMOylated LXR become unable to bind to promoter regions of target genes, resulting in transcriptional failure (Lee et al., 2009 #136).

4.6. LXR and diabetes

Diabetes mellitus type 2 is a metabolic disorder whose main risk factor is obesity. It is characterized by high blood glucose in the context of insulin resistance (Misra and Khurana, 2008). Treatment of diabetic rodents or mouse models of diet-induced obesity with LXR agonists improves glucose tolerance (Cao et al., 2003; Laffitte et al., 2003). However, *in vitro* experiments showed that the lipogenic effect of LXR agonists in the skeletal muscle of patients with type 2 diabetes is increased compared to healthy control patients (Kase et al., 2005). This study shows that LXR activation may promote triglyceride accumulation in the presence of high glucose concentration in skeletal muscle cells probably via induction lipogenic enzymes expression (Kase et al., 2005). This may prove to be problematic effect of LXR activation in muscle. Genetic linkage analyses suggest role of LXR in obesity (Dahlman et al., 2006) or pancreatic β-cell dysfunction (Ketterer et al., 2011).

5. Conclusion

This review enlightened the potential applications of LXR ligands as therapeutic agents in various pathologies. Thus far, few studies have addressed the effect of such agonists in human because of their adverse effects on lipogenesis. The first clinical trial in human was the use of LXR-623 against atherosclerosis in healthy patients. This compound does not activate the lipogenic enzymes in liver and acts specifically in macrophages. Unfortunately, this trial was rapidly aborted because of the adverse side effects of this compound on the central nervous system. Nonetheless, the way has been opened for the use of LXR agonists in human. The goal is to be able to activate LXR specifically in the target tissue. It is precisely the concept of develop new SLiMs that could activate or inhibit LXRα or LXRβ depending on the tissue. Future studies will be necessary to determine whether manipulations of these pathways have utility in the treatment of the human diseases described above.

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