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The Selective Alzheimer's Disease Indicator-1 Gene (*Seladin-1/DHCR24*) Is a Liver X Receptor Target Gene

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ABSTRACT

The nuclear hormone receptors liver X receptor α (LXRα) and LXRβ function as physiological receptors for oxidized cholesterol metabolites (oxysterols) and regulate several aspects of cholesterol and lipid metabolism. *Seladin-1* was originally identified as a gene whose expression was down-regulated in regions of the brain associated with Alzheimer's disease. Seladin-1 has been demonstrated to be neuroprotective and was later characterized as 3β-hydroxysterol-Δ24 reductase (DHCR24), a key enzyme in the cholesterologenic pathway. Seladin-1 has also been shown to regulate lipid raft formation. In a whole genome screen for direct LXRα target genes, we identified an LXRα occupancy site within the second intron of the *Seladin-1/DHCR24* gene. We characterized a novel LXR response element within the second intron of this gene that is able to confer LXR-specific ligand responsiveness to reporter gene in both HepG2 and human embryonic kidney 293 cells. Furthermore, we found that *Seladin-1/DHCR24* gene expression is significantly decreased in skin isolated from LXRβ-null mice. Our data suggest that *Seladin-1/DHCR24* is an LXR target gene and that LXR may regulate lipid raft formation.

Amyloid-β (Aβ) peptide accumulation in the central nervous system underlies the pathological process in Alzheimer's disease (AD), and these peptides are formed from proteolytic cleavage of the amyloid precursor protein (APP), an integral membrane protein. β-Secretase (BACE) and γ-secretase are the proteases responsible for cleaving the Aβ peptide from APP on the amino and carboxyl termini, respectively. The *Seladin-1* gene (*Selective Alzheimer's Disease Indicator-1*) was originally identified based on its selective down-regulation of expression in regions of the brain vulnerable to AD relative to normal brains (Greeve et al., 2000; Iivonen et al., 2002). In cell culture, increased Seladin-1 expression was protective against Aβ toxicity and oxidative stress-induced apoptosis (Greeve et al., 2000).

A link between cholesterol metabolism and AD has been recognized for some time (Puglielli et al., 2003). High plasma low-density lipoprotein (LDL) levels and the ε4 genotype of the major brain lipoprotein, apolipoprotein E, are associated with increased risk of development of AD (Kuo et al., 1998; Fernandes et al., 1999). Relative to age-matched controls, patients with AD have higher serum levels of LDL and reduced plasma levels of high-density lipoprotein (Kuo et al., 1998; Fernandes et al., 1999) In addition, LDL-lowering agents such as the statins have been shown to be associated with decreased risk of developing AD (Jick et al., 2000).

Seladin-1/DHCR24 encodes the 3β-hydroxysterol-Δ24 reductase (DHCR24) enzyme responsible for catalyzing the reduction of the Δ24 bond of sterol intermediates within the cholesterologenic pathway and is widely expressed (Waterham et al., 2001). DHCR24 is responsible for reducing the Δ24 double bond of desmosterol to produce cholesterol, and

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ABBREVIATIONS: Seladin-1, Selective Alzheimer's disease indicator-1; LXR, liver X receptor; LXRE, liver X receptor response element; Aβ, amyloid β protein; DHCR24, 3β-hydroxysterol-Δ24 reductase; RXR, retinoid X receptor; PCR, polymerase chain reaction; KO, knockout; WT, wild type; ChIP, chromatin immunoprecipitation; HEK, human embryonic kidney; EMSA, electrophoretic mobility shift assay; LDL, low-density lipoprotein; BACE, β-secretase; AD, Alzheimer's disease; APP, amyloid precursor protein; DRM, detergent-resistant membrane domain; GW3965, 3-[3-[*N*-(2-chloro-3-trifluoromethylbenzyl)-(2,2-diphenylethyl)amino]propyloxy]phenylacetic acid hydrochloride; T0901317, *N*-(2,2,2-trifluoroethyl)-*N*-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)-ethyl]phenyl]-benzenesulfonamide; 22R OHC, 22*R*-hydroxycholesterol.

deficiency in the *DHCR24* gene leads to desmosterolosis in humans, which is associated with elevated levels of plasma desmosterol and developmental abnormalities (Waterham et al., 2001). Seladin-1/DHCR24 has also been shown to be important in the formation of cholesterol-enriched lipid rafts or detergent-resistant membrane domains (DRMs) (Crameri et al., 2006). Because DRMs play an essential role in organization of integral membrane proteins required for cellular signaling pathways, the importance of Seladin-1/DHCR24 is clear (Simons and Toomre, 2000).

DRMs have been found to be disorganized in AD brains, and this is associated with abnormal proteolytic cleavage of APP (Ledesma et al., 2003). APP processing has been shown to be associated with lipid rafts (Ehehalt et al., 2003), and the rafts contribute to partitioning APP from BACE, thus limiting APP β-cleavage and subsequent production of Aβ (Abad-Rodriguez et al., 2004). Decreased levels of Seladin-1 seem to disturb normal lipid raft formation as a result of low membrane cholesterol levels, leading to altered APP-BACE compartmentalization (Crameri et al., 2006). This leads to increased APP β-cleavage and Aβ production both in cell culture and in *Seladin-1*-deficient mice (Crameri et al., 2006). A specific inhibitor of Seladin-1/DHCR24 has been shown to increase Aβ accumulation (Cecchi et al., 2008).

The liver X receptors (LXRα [(NR1H3) and LXRβ (NR1H2)] are nuclear hormone receptors that function as receptors for oxidized cholesterol metabolites and regulate several pathways involved in lipid and cholesterol metabolism (Michael et al., 2005; Zelcer and Tontonoz, 2006). LXRs have been shown to regulate cholesterol metabolism in the brain, and both LXRα and LXRβ are expressed in the brain, although LXRβ is expressed at considerably higher levels (Whitney et al., 2002). LXR ligands have been shown to modulate APP/Aβ processing in vitro (Koldamova et al., 2003; Sun et al., 2003; Brown et al., 2004) and decrease Aβ accumulation and AD pathology in mouse models of AD (Koldamova et al., 2005; Riddell et al., 2007; Zelcer et al., 2007). Based on these studies, many have suggested that LXR agonists may be useful to treat or prevent AD.

Here, we describe the identification and characterization of the *Seladin-1/DHCR24* gene as an LXR target gene. Our data suggest that LXR may play a role in Seladin-1/DHCR24-mediated regulation of lipid raft formation.

Materials and Methods

Plasmid Construction. Three copies of *DHCR24* LXRE and *NR1H3* LXRE were cloned into pTAL-Luc through MluI and BglII. LXRα and RXRα were cloned into pDEST14 (Invitrogen, Carlsbad, CA) using Gateway technology (Invitrogen) for electrophoretic mobility shift assay (EMSA). LXRα and LXRβ were cloned into pcDNA3.1 vector for overexpression analysis.

Cell Culture and Transfections. HepG2 cells were maintained and routinely propagated in minimal essential medium supplemented with 10% fetal bovine serum at 37°C under 5% CO_2 as described previously (Savkur et al., 2005; Stayrook et al., 2005). HEK293 cells were maintained in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum at 37°C under 5% CO_2. Twenty-four hours before transfection, HepG2 or HEK293 cells were plated in 96-well plates at a density of 15×10^3 cells/well. Each transfection contained 100 ng of the pTAL-Luc reporter, 50 ng of pGL4.73 reporter, and 100 ng of receptor as described in the figure legend using Lipofectamine 2000 (Invitrogen). Sixteen hours after transfection, cells were treated with LXR ligands. Twenty-four hours after treatment, the luciferase activity was measured using Dual-Glo Luciferase Assay System (Promega, Madison, WI). Three LXR agonists were used in the cotransfection: GW3965 (1 μM), T0901317 (1 μM), or 22*R*-hydroxycholesterol (22R OHC; 10 μM). All of these compounds were obtained from Sigma (St. Louis, MO).

EMSAs. LXRα and RXRα were expressed using coupled in vitro transcription and translation. EMSAs were performed using the [α-^{33}P]dCTP-labeled *DHCR24* LXRE oligonucleotide. Competition assays were performed using various amounts of the unlabeled *DHCR24* LXRE or *ABCA1* LXRE oligonucleotide as described previously (Burris et al., 1995).

ChIP Analysis. ChIP/microarrays were performed from HuH7 as described previously (Stayrook et al., 2008). Putative LXREs within the region of the *Seladin-1/DHCR24* gene identified as LXR-bound were identified using nuclear hormone receptor scan (Sandelin and Wasserman, 2005).

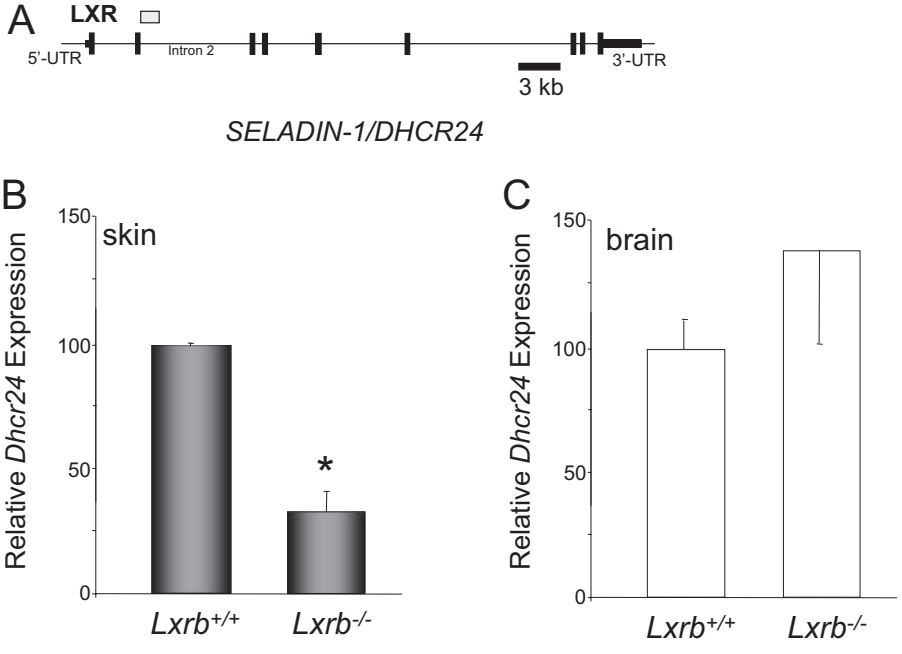

Fig. 1. Identification of *Seladin-1/DHCR24* as a putative LXR target gene. A, position of LXR occupancy within the *Seladin-1/DHCR24* gene as determined by ChIP-on-chip. The DHCR24 gene is represented by the line where large boxes indicate exons and narrow boxes represent untranslated regions. Intron 2, where the LXRE is located, is indicated. B, *Dhcr24* expression in LXRβ-null skin. The relative expression of *Dhcr24* was measured by real-time PCR in LXRβ WT ($lxrb^{+/+}$) and KO ($lxrb^{-/-}$) skin samples obtained from mice pups ($n = 8$). C, *Dhcr24* expression in LXRβ-null brain. The relative expression of *Dhcr24* was measured by real-time PCR in LXRβ WT ($lxrb^{+/+}$) and KO ($lxrb^{-/-}$) brain samples ($n = 8$). *, indicates $p < 0.05$ versus WT control as determined by Student's *t* test.

Analysis of Seladin-1/Dhcr24 Expression in LXRβ WT and KO Mice. Skin and whole brains from newborn (2–3 days old) LXRβ WT and KO mice (Deltagen, San Carlos, CA) were harvested. RNAs were isolated and purified using RNeasy column (Qiagen, Hilden, Germany). cDNA was made and subjected to Taqman assays according to the vendor's protocol using ABI 7900HT real-time PCR machine (Applied Biosystems, Foster City, CA). *Dhcr24* Taqman assay (Applied Biosystems) was performed to detect the expression level of *Dhcr24* in the skin samples from LXRβ WT and KO mice. The relative gene expression level was determined using ΔΔCt method.

Results

We used ChIP-on-chip technology to identify LXRα occupancy sites within the genome. As described previously, we overexpressed Flag-tagged LXRα in hepatoma (HuH7) cells and identified regions within the genome with significant LXR occupancy (Stayrook et al., 2008). LXRα occupancy regions were screened for putative LXREs using algorithms described previously (Sandelin and Wasserman, 2005; Varga and Su, 2007). LXRα occupancy regions were then queried against the human genome database, and 1304 unique genes were identified with a LXRα occupancy region within 1 kilobase of a gene. These data were then compared with microarray data obtained from the livers of mice treated with an LXR-directed antisense oligonucleotide that significantly reduced LXR expression (Hu et al., 2005). Thus, we identified genes that were significantly altered by LXR depletion that also demonstrated LXRα occupancy and contained a defined LXRE. Fifty-seven genes were identified and included the known LXR target genes such as *ABCA1* and *NR1H3*. The *Seladin-1/DHCR24* gene was identified in this fashion, and based on the relationship of this gene to cholesterol biosynthesis, lipid raft formation, and AD pathology, we decided to examine the LXR regulation of this gene further.

The LXR occupancy site detected by ChIP-on-chip is a ~1.5-kilobase region within the second intron of the *Seladin-1/DHCR24* gene (Fig. 1A). As indicated above, we noted a decrease in *Seladin-1/DHCR24* gene expression in mice treated with an LXR antisense oligonucleotide. We also examined the expression of this gene in LXR-null mice. Cholesterol is a component of the lipid barrier of the skin, and skin cells have a very active cholesterol biosynthetic pathway (Feingold, 2007). The LXRs are expressed in skin, with LXRβ being the predominant subtype (Schmuth et al., 2008). Thus, we used cultured skin samples isolated from WT and LXRβ KO mice as a model to examine the LXR requirement for *Seladin-1/Dhcr24* expression. As illustrated in Fig. 1B, *Seladin-1/Dhcr24* gene expression was reduced ~75% in LXRβ-null skin confirming the importance of this receptor in maintaining the correct level of expression of *Seladin-1/Dhcr24*. We also examined *Seladin-1/Dhcr24* gene expression in brains isolated from WT and LXRβ null mice because we believed there may be a link between LXR regulation of *Seladin-1/Dhcr24* gene expression and the beneficial effects of LXR agonists in rodent models of AD. It is curious that there was no detectable difference in *Seladin-1/Dhcr24* gene expression between WT and LXRβ-null mice in the brain (Fig. 2C). These data suggest that although LXRβ is required to maintain normal levels of *Seladin-1/Dhcr24* expression in the skin, it is not required in the brain. Thus, there seems to be tissue specificity with respect to the requirement of LXRβ for maintenance of the normal level of expression of *Seladin-1/Dhcr24*.

We identified a putative LXRE within the LXR occupancy site identified by ChIP-on-chip using nuclear hormone receptor scan (Sandelin and Wasserman, 2005). A single putative LXRE with a DR4 configuration was identified and is compared with other DR4 LXREs from the well characterized LXREs from the *ABCA1* and *NR1H3* genes in Fig. 2A. Figure 2B shows the results of an electrophoretic mobility shift

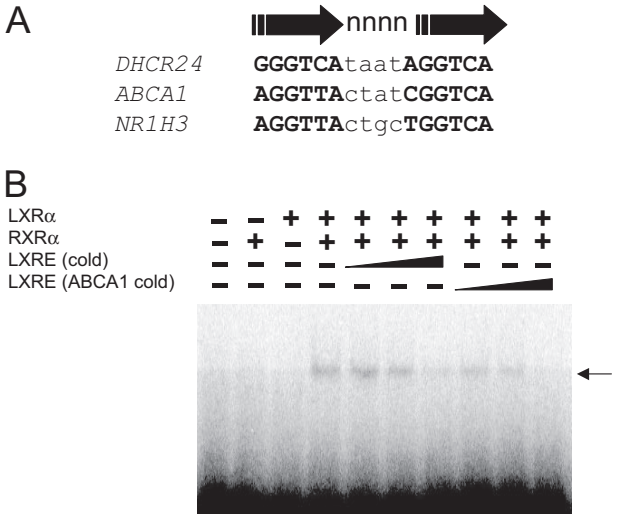

Fig. 2. Identification of the *Seladin-1/DHCR24* LXRE. A, comparison of the sequence of the putative *Seladin-1/DHCR24* LXRE to the LXREs of the *NR1H3* (LXRα gene) and *ABCA1* genes. B, electrophoretic mobility shift assay illustrating the ability of LXRα/RXRα to bind to the *Seladin-1/DHCR24* LXRE. Titration of unlabeled LXRE was at the following molar excess; 1×, 10×, and 100×.

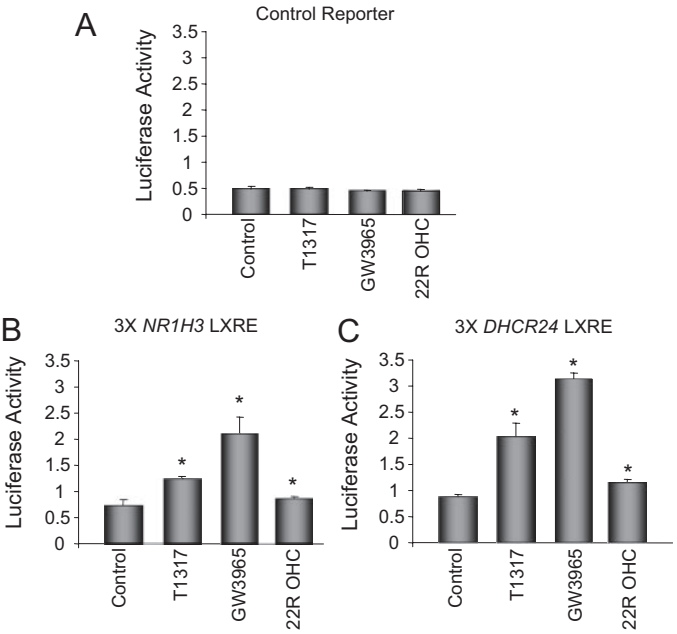

Fig. 3. Analysis of the transcriptional activity of the *Seladin-1/DHCR24* LXRE in HepG2 cells. A, cells transfected with a control reporter containing no LXREs are not responsive to LXR ligands. B, cells transfected with a control reporter containing three copies of an LXRE from the *NR1H3* gene show responsiveness to all three LXR agonists. C, cells transfected with a reporter vector containing three copies of the *Seladin-1/DHCR24* LXRE upstream of luciferase display LXR agonist-dependent transcriptional activation. *, $p < 0.05$ versus WT control as determined by Student's *t* test.

assay in which the binding of the LXRα/RXRα heterodimer to the *DHCR24* LXRE is demonstrated. Neither LXRα nor RXRα alone bound to the element, indicating that only the heterodimer binds to the element as expected. Binding of the heterodimer to the radiolabeled *DHCR24* element was dose-dependently reduced by the addition of unlabeled *DHCR24* or *ABCA1* LXRE oligonucleotides (1×, 10×, or 100× molar excess) (Fig. 2B).

To examine the ability of the *DHCR24* LXRE to mediate transcriptional activation by LXR, we cloned three copies of this LXRE upstream of a luciferase reporter and transfected this reporter into HepG2 cells that were treated with LXR agonists (T0901317, GW3965, or 22R OHC). As shown in Fig. 3A, the LXR ligands did not alter transcription of a control reporter lacking LXREs within the promoter. As a positive control, a luciferase reporter containing three copies of the LXRE derived from the LXR target gene *NR1H3* in the promoter was transfected into HepG2 cells and treated with the LXR ligands. All three LXR ligands induced transcription with the two synthetic LXR ligands, T0901317 and GW3965, displaying greater efficacy than the natural oxysterol ligand, 22R OHC (Fig. 3B). The reporter gene containing the *DHCR24* LXRE showed similar results with the LXR agonists, inducing transcription with a rank order of efficacy identical with that of the *NR1H3* reporter construct (Fig. 3B). These data indicate that the *DHCR24* LXRE can mediate transcriptional activation by ligand-bound LXR.

We next examined the ability of the *DHCR24* LXRE to mediate LXR-induced transcription in another cell line. HEK293 cells were transfected with the *DHCR24* or *NR1H3* LXRE luciferase reporters along with expression vectors for LXRα or LXRβ. Cells transfected with a control reporter lacking an LXRE and an expression vector for LXRα displayed no responsiveness to LXR ligands (Fig. 4A). Cells transfected with the *DHCR24* LXRE reporter and no LXR expression vector showed some responsiveness to LXR ligands, consistent with previous reports that HEK293 cells express some LXR (Yoshikawa et al., 2003) (Fig. 4B). Overexpression of either LXRα (Fig. 4C) or LXRβ (Fig. 4D) resulted in an increase in basal transcription and significant responsiveness to all three LXR agonists was noted, which confirms the ability of the *DHCR24* LXRE to mediate LXR-dependent transcriptional activation.

Discussion

The *Seladin-1* gene was originally identified based on its reduced expression in the brains of individuals affected by AD (Iivonen et al., 2002). This gene was later shown to encode DHCR24, an enzyme critical for the final step in cholesterol biosynthesis (Waterham et al., 2001). Seladin-1/Dhcr24 has been shown to modulate membrane cholesterol levels and lipid raft formation (Crameri et al., 2006). Lipid rafts, cholesterol-rich microenvironments on the cell surface, are important in the localization of many membrane-associated proteins and are responsible for creating areas of enriched components of signaling or enzymatic pathways (Simons and Toomre, 2000). In a whole genome

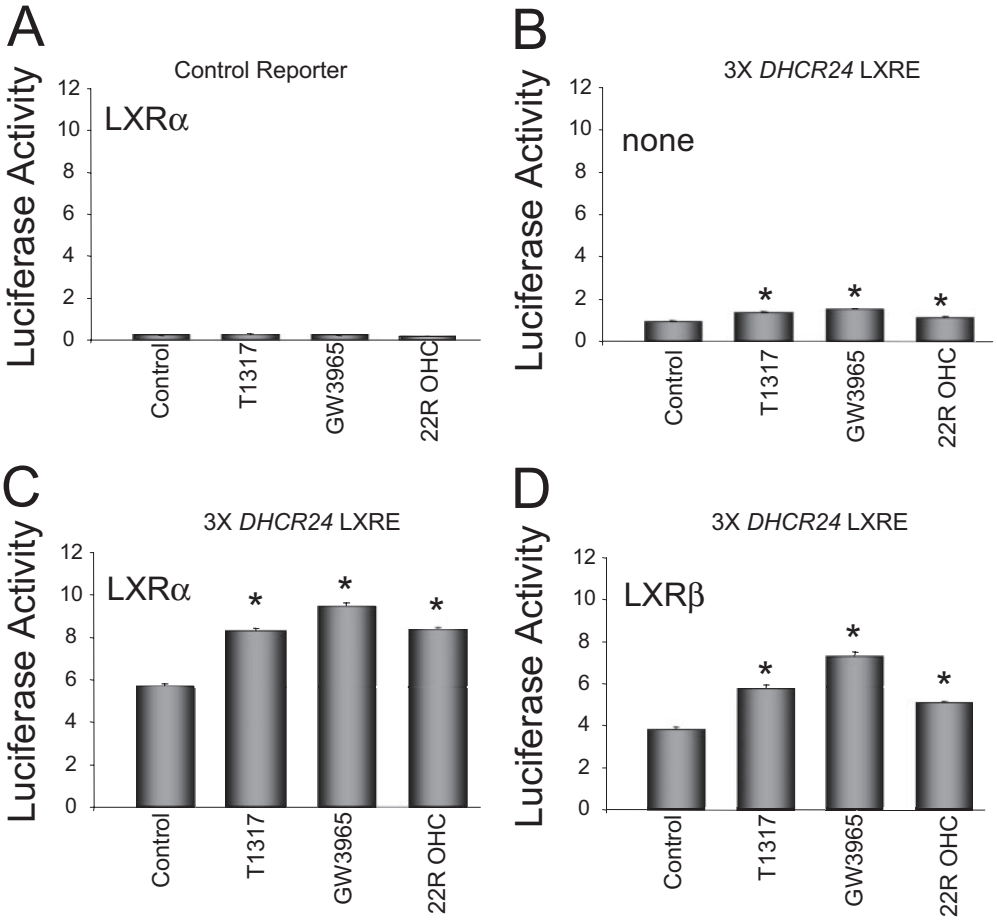

Fig. 4. Analysis of transcriptional activity of the *Seladin-1/DHCR24* LXRE in HEK293 cells overexpressing either LXRα or LXRβ. A, cells, overexpressing LXRα, transfected with a control reporter containing no LXREs are not responsive to LXR ligands. B, cells transfected with a reporter vector containing three copies of the *Seladin-1/DHCR24* LXRE upstream of luciferase display LXR agonist-dependent transcriptional activation. C, cells, overexpressing LXRα, transfected with a reporter vector containing three copies of the *Seladin-1/DHCR24* LXRE upstream of luciferase display increased LXR agonist-dependent transcriptional activation. D, cells, overexpressing LXRβ, transfected with a reporter vector containing three copies of the *Seladin-1/DHCR24* LXRE upstream of luciferase display increased LXR agonist-dependent transcriptional activation.

screen for LXR binding sites, we discovered that this gene contained a functional LXRE. We also found that *Seladin-1/Dhcr24* gene expression is disrupted in LXRβ-null mice, indicating that LXR is important to maintain normal expression of this gene in skin. Although we originally identified this gene as an LXR target gene in human hepatoma cells and mouse liver and skin, the ubiquitous expression of both LXR and *Seladin-1/Dhcr24* indicates that LXR regulation of this gene may be important in many but apparently not all tissues, as revealed by the brain expression data (Fig. 2C). Thus, LXR-mediated regulation of *Seladin-1/DHCR24* gene expression suggests that this oxysterol receptor may play a role in the modulation of lipid raft formation in many tissues throughout the organism.

The importance of lipid rafts in the regulation of enzymatic activity associated with the plasma membrane is especially apparent in processing of APP, where the rafts have been shown to play a role in segregation of APP from BACE in both Chinese hamster ovary and cultured neurons (Abad-Rodriguez et al., 2004). Because lipid rafts are disorganized in AD brains potentially because of low plasma cholesterol content (Ledesma et al., 2003), it has been suggested that this leads to aberrant APP processing and Aβ peptide accumulation and, thus, to AD (Abad-Rodriguez et al., 2004). These data are consistent with the proposed role of Seladin-1/DHCR24 in AD, in which expression levels of this gene are low in AD brains (presumably leading to low plasma cholesterol levels and aberrant APP processing) (Greeve et al., 2000). Increasing Seladin-1/DHCR24 expression seems to confer resistance to neurodegeneration in several models (Greeve et al., 2000; Crameri et al., 2006; Cecchi et al., 2008; Kuehnle et al., 2008). It has been proposed that pharmacological enhancement of Seladin-1 activity may be an effective Aβ-lowering approach to the treatment of AD (Crameri et al., 2006). Thus, the results we show here are intriguing because previous studies have indicated that LXR agonists are effective in reducing Aβ peptide accumulation and AD pathology in rodent models (Koldamova et al., 2003, 2005; Sun et al., 2003; Brown et al., 2004; Riddell et al., 2007; Zelcer et al., 2007). Previous studies have attributed the protective effects of LXR agonists to increased ABCA1 expression (Koldamova et al., 2003, 2005; Sun et al., 2003). However, no abnormal Aβ accumulation has been noted in *Abca1*-null mice (Burns et al., 2006), and no premature AD has been noted in patients with Tangier disease (mutated *ABCA1* gene), suggesting that other mechanisms may also be mediating the protective effects of LXR agonists.

We were intrigued by the observation that expression of *Seladin-1/Dhcr24* was not altered in the brains of LXRβ-null mice. It is unlikely that LXRα would be playing a compensatory role because LXRβ is the predominant form of LXR in the brain (Whitney et al., 2002). This is, in fact, consistent with the lack of AD-like pathology in LXR-null animals, which suggests that LXR would not be required for maintenance of *Seladin1/Dhcr24* expression in the brain as we have observed. However, it is possible that pharmacological activation of LXR may increase *Seladin1/Dhcr24* expression in the brain, leading to improved AD pathology in animal models of the disease.

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