

## 1H. Liver X receptor-like receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

Donald P. McDonnell<sup>1</sup> and Rachid Safi<sup>1</sup>

1. Duke University, USA

### Abstract

Liver X and farnesoid X receptors (LXR and FXR, **nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [68]**) are members of a steroid analogue-activated nuclear receptor subfamily, which form heterodimers with members of the retinoid X receptor family. Endogenous ligands for LXRs include hydroxycholesterols (OHC), while FXRs appear to be activated by bile acids. In humans and primates, *NR1H5P* is a pseudogene. However, in other mammals, it encodes a functional nuclear hormone receptor that appears to be involved in cholesterol biosynthesis [71].

### Contents

This is a citation summary for 1H. Liver X receptor-like receptors in the [Guide to Pharmacology](#) database (GtoPdb). It exists purely as an adjunct to the database to facilitate the recognition of citations to and from the database by citation analyzers. Readers will almost certainly want to visit the relevant sections of the database which are given here under database links.

[GtoPdb](#) is an expert-driven guide to pharmacological targets and the substances that act on them. GtoPdb is a reference work which is most usefully represented as an on-line database. As in any publication this work should be appropriately cited, and the papers it cites should also be recognized. This document provides a citation for the relevant parts of the database, and also provides a reference list for the research cited by those parts.

Please note that the database version for the citations given in GtoPdb are to the most recent preceding version in which the family or its subfamilies and targets were substantially changed. The links below are to the current version. If you need to consult the cited version, rather than the most recent version, please contact the GtoPdb curators.

### Database links

#### 1H. Liver X receptor-like receptors

<http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=89>

#### Introduction to 1H. Liver X receptor-like receptors

<http://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=89>

#### Receptors

##### Farnesoid X receptor

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=603>

Farnesoid X receptor- $\beta$

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=604>

Liver X receptor- $\alpha$

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=602>

Liver X receptor- $\beta$

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=601>

## References

1. Alberti S, Schuster G, Parini P, Feltkamp D, Diczfalusy U, Rudling M, Angelin B, Björkhem I, Pettersson S and Gustafsson JA. (2001) Hepatic cholesterol metabolism and resistance to dietary cholesterol in LXRBeta-deficient mice. *J. Clin. Invest.* **107**: 565-73 [PMID:11238557]
2. Alberti S, Steffensen KR and Gustafsson JA. (2000) Structural characterisation of the mouse nuclear oxysterol receptor genes LXRA $\alpha$  and LXRB $\beta$ . *Gene* **243**: 93-103 [PMID:10675617]
3. Ananthanarayanan M, Li S, Balasubramanian N, Suchy FJ and Walsh MJ. (2004) Ligand-dependent activation of the farnesoid X-receptor directs arginine methylation of histone H3 by CARM1. *J. Biol. Chem.* **279**: 54348-57 [PMID:15471871]
4. Anisfeld AM, Kast-Woelbern HR, Lee H, Zhang Y, Lee FY and Edwards PA. (2005) Activation of the nuclear receptor FXR induces fibrinogen expression: a new role for bile acid signaling. *J. Lipid Res.* **46**: 458-68 [PMID:15604525]
5. Apfel R, Benbrook D, Lernhardt E, Ortiz MA, Salbert G and Pfahl M. (1994) A novel orphan receptor specific for a subset of thyroid hormone-responsive elements and its interaction with the retinoid/thyroid hormone receptor subfamily. *Mol. Cell. Biol.* **14**: 7025-35 [PMID:7935418]
6. AstraZeneca. AZ12260493.
7. AstraZeneca. AZD9291.
8. Bramlett KS, Houck KA, Borchert KM, Dowless MS, Kulanthaivel P, Zhang Y, Beyer TP, Schmidt R, Thomas JS, Michael LF, Barr R, Montrose C, Eacho PI, Cao G and Burris TP. (2003) A natural product ligand of the oxysterol receptor, liver X receptor. *J. Pharmacol. Exp. Ther.* **307**: 291-6 [PMID:12893846]
9. Brendel C, Schoonjans K, Botrugno OA, Treuter E and Auwerx J. (2002) The small heterodimer partner interacts with the liver X receptor alpha and represses its transcriptional activity. *Mol. Endocrinol.* **16**: 2065-76 [PMID:12198243]
10. Cao G, Beyer TP, Yang XP, Schmidt RJ, Zhang Y, Bensch WR, Kauffman RF, Gao H, Ryan TP, Liang Y, Eacho PI and Jiang XC. (2002) Phospholipid transfer protein is regulated by liver X receptors in vivo. *J. Biol. Chem.* **277**: 39561-5 [PMID:12177004]
11. Chao EY, Caravella JA, Watson MA, Campobasso N, Ghisletti S, Billin AN, Galardi C, Wang P, Laffitte BA and Iannone MA *et al.*. (2008) Structure-guided design of N-phenyl tertiary amines as transrepression-selective liver X receptor modulators with anti-inflammatory activity. *J. Med. Chem.* **51**: 5758-65 [PMID:18800767]
12. Chignard N, Mergey M, Barbu V, Finzi L, Tiret E, Paul A and Housset C. (2005) VPAC1 expression is regulated by FXR agonists in the human gallbladder epithelium. *Hepatology* **42**: 549-57 [PMID:16037943]
13. Claudel T, Sturm E, Duez H, Torra IP, Sirvent A, Kosykh V, Fruchart JC, Dallongeville J, Hum DW, Kuipers F and Staels B. (2002) Bile acid-activated nuclear receptor FXR suppresses apolipoprotein A-I transcription via a negative FXR response element. *J. Clin. Invest.* **109**: 961-71 [PMID:11927623]
14. Collins JL, Fivush AM, Watson MA, Galardi CM, Lewis MC, Moore LB, Parks DJ, Wilson JG, Tippin TK, Binz JG, Plunket KD, Morgan DG, Beaudet EJ, Whitney KD, Kliewer SA and Willson TM. (2002) Identification of a nonsteroidal liver X receptor agonist through parallel array synthesis of tertiary amines. *J. Med. Chem.* **45**: 1963-6 [PMID:11985463]
15. Costet P, Luo Y, Wang N and Tall AR. (2000) Sterol-dependent transactivation of the ABC1 promoter by the liver X receptor/retinoid X receptor. *J. Biol. Chem.* **275**: 28240-5 [PMID:10858438]
16. Cui J, Huang L, Zhao A, Lew JL, Yu J, Sahoo S, Meinke PT, Royo I, Pelaez F and Wright SD. (2003) Guggulsterone is a farnesoid X receptor antagonist in coactivator association assays but acts to enhance

- transcription of bile salt export pump. *J. Biol. Chem.* **278**: 10214-20 [PMID:12525500]
17. Dalen KT, Ulven SM, Bamberg K, Gustafsson JA and Nebb HI. (2003) Expression of the insulin-responsive glucose transporter GLUT4 in adipocytes is dependent on liver X receptor alpha. *J. Biol. Chem.* **278**: 48283-91 [PMID:12970362]
  18. Deng R, Yang D, Yang J and Yan B. (2006) Oxysterol 22(R)-hydroxycholesterol induces the expression of the bile salt export pump through nuclear receptor farnesoid X receptor but not liver X receptor. *J. Pharmacol. Exp. Ther.* **317**: 317-25 [PMID:16371446]
  19. Downes M, Verdecia MA, Roecker AJ, Hughes R, Hogenesch JB, Kast-Woelbern HR, Bowman ME, Ferrer JL, Anisfeld AM, Edwards PA, Rosenfeld JM, Alvarez JG, Noel JP, Nicolaou KC and Evans RM. (2003) A chemical, genetic, and structural analysis of the nuclear bile acid receptor FXR. *Mol. Cell* **11**: 1079-92 [PMID:12718892]
  20. El-Gendy BEM, Goher SS, Hegazy LS, Arief MMH and Burris TP. (2018) Recent Advances in the Medicinal Chemistry of Liver X Receptors. *J. Med. Chem.* **61**: 10935-10956 [PMID:30004226]
  21. Flaveny CA, Griffett K, El-Gendy Bel-D, Kazantzis M, Sengupta M, Amelio AL, Chatterjee A, Walker J, Solt LA and Kamenecka TM *et al.*. (2015) Broad Anti-tumor Activity of a Small Molecule that Selectively Targets the Warburg Effect and Lipogenesis. *Cancer Cell* **28**: 42-56 [PMID:26120082]
  22. Forman BM, Goode E, Chen J, Oro AE, Bradley DJ, Perlmann T, Noonan DJ, Burka LT, McMorris T, Lamph WW, Evans RM and Weinberger C. (1995) Identification of a nuclear receptor that is activated by farnesol metabolites. *Cell* **81**: 687-93 [PMID:7774010]
  23. Frankenberg T, Rao A, Chen F, Haywood J, Shneider BL and Dawson PA. (2006) Regulation of the mouse organic solute transporter alpha-beta, Ostalpha-Ostbeta, by bile acids. *Am. J. Physiol. Gastrointest. Liver Physiol.* **290**: G912-22 [PMID:16357058]
  24. Fu X, Menke JG, Chen Y, Zhou G, MacNaul KL, Wright SD, Sparrow CP and Lund EG. (2001) 27-hydroxycholesterol is an endogenous ligand for liver X receptor in cholesterol-loaded cells. *J. Biol. Chem.* **276**: 38378-87 [PMID:11504730]
  25. Gerin I, Dolinsky VW, Shackman JG, Kennedy RT, Chiang SH, Burant CF, Steffensen KR, Gustafsson JA and MacDougald OA. (2005) LXRbeta is required for adipocyte growth, glucose homeostasis, and beta cell function. *J. Biol. Chem.* **280**: 23024-31 [PMID:15831500]
  26. Germain P, Staels B, Dacquet C, Spedding M and Laudet V. (2006) Overview of nomenclature of nuclear receptors. *Pharmacol. Rev.* **58**: 685-704 [PMID:17132848]
  27. Goodwin B, Jones SA, Price RR, Watson MA, McKee DD, Moore LB, Galardi C, Wilson JG, Lewis MC, Roth ME, Maloney PR, Willson TM and Kliewer SA. (2000) A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. *Mol. Cell* **6**: 517-26 [PMID:11030332]
  28. Griffett K, Solt LA, El-Gendy Bel-D, Kamenecka TM and Burris TP. (2013) A liver-selective LXR inverse agonist that suppresses hepatic steatosis. *ACS Chem. Biol.* **8**: 559-67 [PMID:23237488]
  29. Grober J, Zaghini I, Fujii H, Jones SA, Kliewer SA, Willson TM, Ono T and Besnard P. (1999) Identification of a bile acid-responsive element in the human ileal bile acid-binding protein gene. Involvement of the farnesoid X receptor/9-cis-retinoic acid receptor heterodimer. *J. Biol. Chem.* **274**: 29749-54 [PMID:10514450]
  30. Hoerer S, Schmid A, Heckel A, Budzinski RM and Nar H. (2003) Crystal structure of the human liver X receptor beta ligand-binding domain in complex with a synthetic agonist. *J. Mol. Biol.* **334**: 853-61 [PMID:14643652]
  31. Holt JA, Luo G, Billin AN, Bisi J, McNeill YY, Kozarsky KF, Donahee M, Wang DY, Mansfield TA, Kliewer SA, Goodwin B and Jones SA. (2003) Definition of a novel growth factor-dependent signal cascade for the suppression of bile acid biosynthesis. *Genes Dev.* **17**: 1581-91 [PMID:12815072]
  32. Hu X, Li S, Wu J, Xia C and Lala DS. (2003) Liver X receptors interact with corepressors to regulate gene expression. *Mol. Endocrinol.* **17**: 1019-26 [PMID:12663743]
  33. Hucke S, Herold M, Liebmann M, Freise N, Lindner M, Fleck AK, Zenker S, Thiebes S, Fernandez-Orth J and Buck D *et al.*. (2016) The farnesoid-X-receptor in myeloid cells controls CNS autoimmunity in an IL-10-dependent fashion. *Acta Neuropathol.* **132**: 413-31 [PMID:27383204]

34. Hummasti S, Laffitte BA, Watson MA, Galardi C, Chao LC, Ramamurthy L, Moore JT and Tontonoz P. (2004) Liver X receptors are regulators of adipocyte gene expression but not differentiation: identification of apoD as a direct target. *J. Lipid Res.* **45**: 616-25 [PMID:14703507]
35. Huuskonen J, Fielding PE and Fielding CJ. (2004) Role of p160 coactivator complex in the activation of liver X receptor. *Arterioscler. Thromb. Vasc. Biol.* **24**: 703-8 [PMID:14764426]
36. Inagaki T, Choi M, Moschetta A, Peng L, Cummins CL, McDonald JG, Luo G, Jones SA, Goodwin B, Richardson JA, Gerard RD, Repa JJ, Mangelsdorf DJ and Kliewer SA. (2005) Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. *Cell Metab.* **2**: 217-25 [PMID:16213224]
37. Janowski BA, Grogan MJ, Jones SA, Wisely GB, Kliewer SA, Corey EJ and Mangelsdorf DJ. (1999) Structural requirements of ligands for the oxysterol liver X receptors LXRalpha and LXRbeta. *Proc. Natl. Acad. Sci. U.S.A.* **96**: 266-71 [PMID:9874807]
38. Janowski BA, Willy PJ, Devi TR, Falck JR and Mangelsdorf DJ. (1996) An oxysterol signalling pathway mediated by the nuclear receptor LXR alpha. *Nature* **383**: 728-31 [PMID:8878485]
39. Jaye MC, Krawiec JA, Campobasso N, Smallwood A, Qiu C, Lu Q, Kerrigan JJ, De Los Frailes Alvaro M, Laffitte B, Liu WS, Marino JP, Meyer CR, Nichols JA, Parks DJ, Perez P, Sarov-Blat L, Seepersaud SD, Steplewski KM, Thompson SK, Wang P, Watson MA, Webb CL, Haigh D, Caravella JA, Macphee CH, Willson TM and Collins JL. (2005) Discovery of substituted maleimides as liver X receptor agonists and determination of a ligand-bound crystal structure. *J. Med. Chem.* **48**: 5419-22 [PMID:16107141]
40. Joseph SB, Laffitte BA, Patel PH, Watson MA, Matsukuma KE, Walczak R, Collins JL, Osborne TF and Tontonoz P. (2002) Direct and indirect mechanisms for regulation of fatty acid synthase gene expression by liver X receptors. *J. Biol. Chem.* **277**: 11019-25 [PMID:11790787]
41. Jung D, Podvinec M, Meyer UA, Mangelsdorf DJ, Fried M, Meier PJ and Kullak-Ublick GA. (2002) Human organic anion transporting polypeptide 8 promoter is transactivated by the farnesoid X receptor/bile acid receptor. *Gastroenterology* **122**: 1954-66 [PMID:12055601]
42. Kalaany NY, Gauthier KC, Zavacki AM, Mammen PP, Kitazume T, Peterson JA, Horton JD, Garry DJ, Bianco AC and Mangelsdorf DJ. (2005) LXRs regulate the balance between fat storage and oxidation. *Cell Metab.* **1**: 231-44 [PMID:16054068]
43. Kanaya E, Shiraki T and Jingami H. (2004) The nuclear bile acid receptor FXR is activated by PGC-1alpha in a ligand-dependent manner. *Biochem. J.* **382**: 913-21 [PMID:15202934]
44. Kast HR, Nguyen CM, Sinal CJ, Jones SA, Laffitte BA, Reue K, Gonzalez FJ, Willson TM and Edwards PA. (2001) Farnesoid X-activated receptor induces apolipoprotein C-II transcription: a molecular mechanism linking plasma triglyceride levels to bile acids. *Mol. Endocrinol.* **15**: 1720-8 [PMID:11579204]
45. Kennedy MA, Venkateswaran A, Tarr PT, Xenarios I, Kudoh J, Shimizu N and Edwards PA. (2001) Characterization of the human ABCG1 gene: liver X receptor activates an internal promoter that produces a novel transcript encoding an alternative form of the protein. *J. Biol. Chem.* **276**: 39438-47 [PMID:11500512]
46. Kok T, Hulzebos CV, Wolters H, Havinga R, Agellon LB, Stellaard F, Shan B, Schwarz M and Kuipers F. (2003) Enterohepatic circulation of bile salts in farnesoid X receptor-deficient mice: efficient intestinal bile salt absorption in the absence of ileal bile acid-binding protein. *J. Biol. Chem.* **278**: 41930-7 [PMID:12917447]
47. Laffitte BA, Joseph SB, Chen M, Castrillo A, Repa J, Wilpitz D, Mangelsdorf D and Tontonoz P. (2003) The phospholipid transfer protein gene is a liver X receptor target expressed by macrophages in atherosclerotic lesions. *Mol. Cell. Biol.* **23**: 2182-91 [PMID:12612088]
48. Laffitte BA, Joseph SB, Walczak R, Pei L, Wilpitz DC, Collins JL and Tontonoz P. (2001) Autoregulation of the human liver X receptor alpha promoter. *Mol. Cell. Biol.* **21**: 7558-68 [PMID:11604492]
49. Laffitte BA, Repa JJ, Joseph SB, Wilpitz DC, Kast HR, Mangelsdorf DJ and Tontonoz P. (2001) LXRs control lipid-inducible expression of the apolipoprotein E gene in macrophages and adipocytes. *Proc. Natl. Acad. Sci. U.S.A.* **98**: 507-12 [PMID:11149950]
50. Landrier JF, Eloranta JJ, Vavricka SR and Kullak-Ublick GA. (2006) The nuclear receptor for bile acids,

- FXR, transactivates human organic solute transporter-alpha and -beta genes. *Am. J. Physiol. Gastrointest. Liver Physiol.* **290**: G476-85 [PMID:16269519]
51. Lee FY, Kast-Woelbern HR, Chang J, Luo G, Jones SA, Fishbein MC and Edwards PA. (2005) Alpha-crystallin is a target gene of the farnesoid X-activated receptor in human livers. *J. Biol. Chem.* **280**: 31792-800 [PMID:16012168]
  52. Lehmann JM, Kliewer SA, Moore LB, Smith-Oliver TA, Oliver BB, Su JL, Sundseth SS, Winegar DA, Blanchard DE, Spencer TA and Willson TM. (1997) Activation of the nuclear receptor LXR by oxysterols defines a new hormone response pathway. *J. Biol. Chem.* **272**: 3137-40 [PMID:9013544]
  53. Li J, Pircher PC, Schulman IG and Westin SK. (2005) Regulation of complement C3 expression by the bile acid receptor FXR. *J. Biol. Chem.* **280**: 7427-34 [PMID:15590640]
  54. Li N, Wang X, Xu Y, Lin Y, Zhu N, Liu P, Lu D and Si S. (2017) Identification of a Novel Liver X Receptor Agonist that Regulates the Expression of Key Cholesterol Homeostasis Genes with Distinct Pharmacological Characteristics. *Mol. Pharmacol.* **91**: 264-276 [PMID:28087808]
  55. Lin J, Yang R, Tarr PT, Wu PH, Handschin C, Li S, Yang W, Pei L, Uldry M, Tontonoz P, Newgard CB and Spiegelman BM. (2005) Hyperlipidemic effects of dietary saturated fats mediated through PGC-1beta coactivation of SREBP. *Cell* **120**: 261-73 [PMID:15680331]
  56. Lo Sasso G, Murzilli S, Salvatore L, D'Errico I, Petruzzelli M, Conca P, Jiang ZY, Calabresi L, Parini P and Moschetta A. (2010) Intestinal specific LXR activation stimulates reverse cholesterol transport and protects from atherosclerosis. *Cell Metab.* **12**: 187-93 [PMID:20674863]
  57. Lu TT, Makishima M, Repa JJ, Schoonjans K, Kerr TA, Auwerx J and Mangelsdorf DJ. (2000) Molecular basis for feedback regulation of bile acid synthesis by nuclear receptors. *Mol. Cell* **6**: 507-15 [PMID:11030331]
  58. Lu TT, Repa JJ and Mangelsdorf DJ. (2001) Orphan nuclear receptors as eLiXIRs and FiXeRs of sterol metabolism. *J. Biol. Chem.* **276**: 37735-8 [PMID:11459853]
  59. Luo Y and Tall AR. (2000) Sterol upregulation of human CETP expression in vitro and in transgenic mice by an LXR element. *J. Clin. Invest.* **105**: 513-20 [PMID:10683381]
  60. Maisonneuve IM, Archer S and Glick SD. (1994) U50,488, a kappa opioid receptor agonist, attenuates cocaine-induced increases in extracellular dopamine in the nucleus accumbens of rats. *Neurosci Lett* **181**: 57-60 [PMID:7898771]
  61. Mak PA, Kast-Woelbern HR, Anisfeld AM and Edwards PA. (2002) Identification of PLTP as an LXR target gene and apoE as an FXR target gene reveals overlapping targets for the two nuclear receptors. *J. Lipid Res.* **43**: 2037-41 [PMID:12454263]
  62. Mak PA, Laffitte BA, Desrumaux C, Joseph SB, Curtiss LK, Mangelsdorf DJ, Tontonoz P and Edwards PA. (2002) Regulated expression of the apolipoprotein E/C-I/C-IV/C-II gene cluster in murine and human macrophages. A critical role for nuclear liver X receptors alpha and beta. *J. Biol. Chem.* **277**: 31900-8 [PMID:12032151]
  63. Makishima M, Okamoto AY, Repa JJ, Tu H, Learned RM, Luk A, Hull MV, Lustig KD, Mangelsdorf DJ and Shan B. (1999) Identification of a nuclear receptor for bile acids. *Science* **284**: 1362-5 [PMID:10334992]
  64. Maloney PR, Parks DJ, Haffner CD, Fivush AM, Chandra G, Plunket KD, Creech KL, Moore LB, Wilson JG, Lewis MC, Jones SA and Willson TM. (2000) Identification of a chemical tool for the orphan nuclear receptor FXR. *J. Med. Chem.* **43**: 2971-4 [PMID:10956205]
  65. Menke JG, Macnaul KL, Hayes NS, Baffic J, Chao YS, Elbrecht A, Kelly LJ, Lam MH, Schmidt A, Sahoo S, Wang J, Wright SD, Xin P, Zhou G, Moller DE and Sparrow CP. (2002) A novel liver X receptor agonist establishes species differences in the regulation of cholesterol 7alpha-hydroxylase (CYP7a). *Endocrinology* **143**: 2548-58 [PMID:12072387]
  66. Mi LZ, Devarakonda S, Harp JM, Han Q, Pellicciari R, Willson TM, Khorasanizadeh S and Rastinejad F. (2003) Structural basis for bile acid binding and activation of the nuclear receptor FXR. *Mol. Cell* **11**: 1093-100 [PMID:12718893]
  67. Mohan R. (2013) Liver x receptor (lrx) modulators for the treatment of dermal diseases, disorders and conditions Patent number: WO2013130892.

68. Moore DD, Kato S, Xie W, Mangelsdorf DJ, Schmidt DR, Xiao R and Kliewer SA. (2006) International Union of Pharmacology. LXII. The NR1H and NR1I receptors: constitutive androstane receptor, pregnane X receptor, farnesoid X receptor alpha, farnesoid X receptor beta, liver X receptor alpha, liver X receptor beta, and vitamin D receptor. *Pharmacol. Rev.* **58**: 742-59 [PMID:17132852]
69. Nomura S, Endo-Umeda K, Aoyama A, Makishima M, Hashimoto Y and Ishikawa M. (2015) Styrylphenylphthalimides as Novel Transrepression-Selective Liver X Receptor (LXR) Modulators. *ACS Med Chem Lett* **6**: 902-7 [PMID:26288691]
70. Oberkofler H, Schraml E, Krempler F and Patsch W. (2003) Potentiation of liver X receptor transcriptional activity by peroxisome-proliferator-activated receptor gamma co-activator 1 alpha. *Biochem. J.* **371**: 89-96 [PMID:12470296]
71. Otte K, Kranz H, Kober I, Thompson P, Hoefler M, Haubold B, Rimmel B, Voss H, Kaiser C, Albers M, Cheruvallath Z, Jackson D, Casari G, Koegl M, Pääbo S, Mous J, Kremoser C and Deuschle U. (2003) Identification of farnesoid X receptor beta as a novel mammalian nuclear receptor sensing lanosterol. *Mol. Cell. Biol.* **23**: 864-72 [PMID:12529392]
72. Parks DJ, Blanchard SG, Bledsoe RK, Chandra G, Consler TG, Kliewer SA, Stimmel JB, Willson TM, Zavacki AM, Moore DD and Lehmann JM. (1999) Bile acids: natural ligands for an orphan nuclear receptor. *Science* **284**: 1365-8 [PMID:10334993]
73. Peet DJ, Turley SD, Ma W, Janowski BA, Lobaccaro JM, Hammer RE and Mangelsdorf DJ. (1998) Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXR alpha. *Cell* **93**: 693-704 [PMID:9630215]
74. Pellicciari R, Fiorucci S, Camaioni E, Clerici C, Costantino G, Maloney PR, Morelli A, Parks DJ and Willson TM. (2002) 6alpha-ethyl-chenodeoxycholic acid (6-ECDC), a potent and selective FXR agonist endowed with anticholestatic activity. *J. Med. Chem.* **45**: 3569-72 [PMID:12166927]
75. Pineda Torra I, Freedman LP and Garabedian MJ. (2004) Identification of DRIP205 as a coactivator for the Farnesoid X receptor. *J. Biol. Chem.* **279**: 36184-91 [PMID:15187081]
76. Pircher PC, Kitto JL, Petrowski ML, Tangirala RK, Bischoff ED, Schulman IG and Westin SK. (2003) Farnesoid X receptor regulates bile acid-amino acid conjugation. *J. Biol. Chem.* **278**: 27703-11 [PMID:12754200]
77. Repa JJ, Berge KE, Pomajzl C, Richardson JA, Hobbs H and Mangelsdorf DJ. (2002) Regulation of ATP-binding cassette sterol transporters ABCG5 and ABCG8 by the liver X receptors alpha and beta. *J. Biol. Chem.* **277**: 18793-800 [PMID:11901146]
78. Repa JJ, Liang G, Ou J, Bashmakov Y, Lobaccaro JM, Shimomura I, Shan B, Brown MS, Goldstein JL and Mangelsdorf DJ. (2000) Regulation of mouse sterol regulatory element-binding protein-1c gene (SREBP-1c) by oxysterol receptors, LXRalpha and LXRbeta. *Genes Dev.* **14**: 2819-30 [PMID:11090130]
79. Repa JJ, Turley SD, Lobaccaro JA, Medina J, Li L, Lustig K, Shan B, Heyman RA, Dietschy JM and Mangelsdorf DJ. (2000) Regulation of absorption and ABC1-mediated efflux of cholesterol by RXR heterodimers. *Science* **289**: 1524-9 [PMID:10968783]
80. Rizzo G, Renga B, Antonelli E, Passeri D, Pellicciari R and Fiorucci S. (2005) The methyl transferase PRMT1 functions as co-activator of farnesoid X receptor (FXR)/9-cis retinoid X receptor and regulates transcription of FXR responsive genes. *Mol. Pharmacol.* **68**: 551-8 [PMID:15911693]
81. Savkur RS, Thomas JS, Bramlett KS, Gao Y, Michael LF and Burris TP. (2005) Ligand-dependent coactivation of the human bile acid receptor FXR by the peroxisome proliferator-activated receptor gamma coactivator-1alpha. *J. Pharmacol. Exp. Ther.* **312**: 170-8 [PMID:15329387]
82. Schote AB, Turner JD, Schiltz J and Muller CP. (2007) Nuclear receptors in human immune cells: expression and correlations. *Mol. Immunol.* **44**: 1436-45 [PMID:16837048]
83. Schultz JR, Tu H, Luk A, Repa JJ, Medina JC, Li L, Schwendner S, Wang S, Thoolen M, Mangelsdorf DJ, Lustig KD and Shan B. (2000) Role of LXRs in control of lipogenesis. *Genes Dev.* **14**: 2831-8 [PMID:11090131]
84. Schuster GU, Parini P, Wang L, Alberti S, Steffensen KR, Hansson GK, Angelin B and Gustafsson JA. (2002) Accumulation of foam cells in liver X receptor-deficient mice. *Circulation* **106**: 1147-53

[PMID:12196343]

85. Seol W, Choi HS and Moore DD. (1995) Isolation of proteins that interact specifically with the retinoid X receptor: two novel orphan receptors. *Mol. Endocrinol.* **9**: 72-85 [PMID:7760852]
86. Shinar DM, Endo N, Rutledge SJ, Vogel R, Rodan GA and Schmidt A. (1994) NER, a new member of the gene family encoding the human steroid hormone nuclear receptor. *Gene* **147**: 273-6 [PMID:7926814]
87. Sinal CJ, Tohkin M, Miyata M, Ward JM, Lambert G and Gonzalez FJ. (2000) Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. *Cell* **102**: 731-44 [PMID:11030617]
88. Song C, Kokontis JM, Hiipakka RA and Liao S. (1994) Ubiquitous receptor: a receptor that modulates gene activation by retinoic acid and thyroid hormone receptors. *Proc. Natl. Acad. Sci. U.S.A.* **91**: 10809-13 [PMID:7971966]
89. Sparrow CP, Baffic J, Lam MH, Lund EG, Adams AD, Fu X, Hayes N, Jones AB, Macnaul KL, Ondeyka J, Singh S, Wang J, Zhou G, Moller DE, Wright SD and Menke JG. (2002) A potent synthetic LXR agonist is more effective than cholesterol loading at inducing ABCA1 mRNA and stimulating cholesterol efflux. *J. Biol. Chem.* **277**: 10021-7 [PMID:11790770]
90. Svensson S, Ostberg T, Jacobsson M, Norström C, Stefansson K, Hallén D, Johansson IC, Zachrisson K, Ogg D and Jendeborg L. (2003) Crystal structure of the heterodimeric complex of LXRalpha and RXRbeta ligand-binding domains in a fully agonistic conformation. *EMBO J.* **22**: 4625-33 [PMID:12970175]
91. Theofilopoulos S, Wang Y, Kitambi SS, Sacchetti P, Sousa KM, Bodin K, Kirk J, Saltó C, Gustafsson M and Toledo EM *et al.*. (2013) Brain endogenous liver X receptor ligands selectively promote midbrain neurogenesis. *Nat. Chem. Biol.* **9**: 126-33 [PMID:23292650]
92. Tully DC, Rucker PV, Chianelli D, Williams J, Vidal A, Alper PB, Mutnick D, Bursulaya B, Schmeits J and Wu X *et al.*. (2017) Discovery of Tropifexor (LJN452), a Highly Potent Non-bile Acid FXR Agonist for the Treatment of Cholestatic Liver Diseases and Nonalcoholic Steatohepatitis (NASH). *J. Med. Chem.* **60**: 9960-9973 [PMID:29148806]
93. Unno A, Takada I, Takezawa S, Oishi H, Baba A, Shimizu T, Tokita A, Yanagisawa J and Kato S. (2005) TRRAP as a hepatic coactivator of LXR and FXR function. *Biochem. Biophys. Res. Commun.* **327**: 933-8 [PMID:15649435]
94. Urizar NL, Liverman AB, Dodds DT, Silva FV, Ordentlich P, Yan Y, Gonzalez FJ, Heyman RA, Mangelsdorf DJ and Moore DD. (2002) A natural product that lowers cholesterol as an antagonist ligand for FXR. *Science* **296**: 1703-6 [PMID:11988537]
95. Venkateswaran A, Repa JJ, Lobaccaro JM, Bronson A, Mangelsdorf DJ and Edwards PA. (2000) Human white/murine ABC8 mRNA levels are highly induced in lipid-loaded macrophages. A transcriptional role for specific oxysterols. *J. Biol. Chem.* **275**: 14700-7 [PMID:10799558]
96. Walczak R, Joseph SB, Laffitte BA, Castrillo A, Pei L and Tontonoz P. (2004) Transcription of the vascular endothelial growth factor gene in macrophages is regulated by liver X receptors. *J. Biol. Chem.* **279**: 9905-11 [PMID:14699103]
97. Wang H, Chen J, Hollister K, Sowers LC and Forman BM. (1999) Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. *Mol. Cell* **3**: 543-53 [PMID:10360171]
98. Willy PJ, Umesono K, Ong ES, Evans RM, Heyman RA and Mangelsdorf DJ. (1995) LXR, a nuclear receptor that defines a distinct retinoid response pathway. *Genes Dev.* **9**: 1033-45 [PMID:7744246]
99. Wu J, Xia C, Meier J, Li S, Hu X and Lala DS. (2002) The hypolipidemic natural product guggulsterone acts as an antagonist of the bile acid receptor. *Mol. Endocrinol.* **16**: 1590-7 [PMID:12089353]
100. Xu P, Li D, Tang X, Bao X, Huang J, Tang Y, Yang Y, Xu H and Fan X. (2013) LXR agonists: new potential therapeutic drug for neurodegenerative diseases. *Mol. Neurobiol.* **48**: 715-28 [PMID:23625315]
101. Yang C, McDonald JG, Patel A, Zhang Y, Umetani M, Xu F, Westover EJ, Covey DF, Mangelsdorf DJ and Cohen JC *et al.*. (2006) Sterol intermediates from cholesterol biosynthetic pathway as liver X receptor ligands. *J. Biol. Chem.* **281**: 27816-26 [PMID:16857673]
102. Zelcer N, Hong C, Boyadjian R and Tontonoz P. (2009) LXR regulates cholesterol uptake through Idol-dependent ubiquitination of the LDL receptor. *Science* **325**: 100-4 [PMID:19520913]
103. Zhang Y, Castellani LW, Sinal CJ, Gonzalez FJ and Edwards PA. (2004) Peroxisome proliferator-activated

- receptor-gamma coactivator 1alpha (PGC-1alpha) regulates triglyceride metabolism by activation of the nuclear receptor FXR. *Genes Dev.* **18**: 157-69 [PMID:14729567]
104. Zhang Y, Kast-Woelbern HR and Edwards PA. (2003) Natural structural variants of the nuclear receptor farnesoid X receptor affect transcriptional activation. *J. Biol. Chem.* **278**: 104-10 [PMID:12393883]
  105. Zhang Y, Repa JJ, Gauthier K and Mangelsdorf DJ. (2001) Regulation of lipoprotein lipase by the oxysterol receptors, LXRAalpha and LXRBeta. *J. Biol. Chem.* **276**: 43018-24 [PMID:11562371]
  106. Zollner G, Wagner M, Moustafa T, Fickert P, Silbert D, Gumhold J, Fuchsbichler A, Halilbasic E, Denk H, Marschall HU and Trauner M. (2006) Coordinated induction of bile acid detoxification and alternative elimination in mice: role of FXR-regulated organic solute transporter-alpha/beta in the adaptive response to bile acids. *Am. J. Physiol. Gastrointest. Liver Physiol.* **290**: G923-32 [PMID:16357057]
  107. Zuercher WJ, Buckholz RG, Campobasso N, Collins JL, Galardi CM, Gampe RT, Hyatt SM, Merrihew SL, Moore JT and Oplinger JA *et al.*. (2010) Discovery of tertiary sulfonamides as potent liver X receptor antagonists. *J. Med. Chem.* **53**: 3412-6 [PMID:20345102]