LXRs: key regulators of intermediary metabolism in metabolic syndrome

Abstract

The prevalence of the metabolic syndrome (MetS) and its various manifestations as a significant health epidemic is currently affecting populations of developed and developing countries worldwide. It is characterized by a group of metabolic abnormalities including central adiposity, insulin resistance, high blood pressure, glucose intolerance and dyslipidemia. Individuals with MetS have the greater risk of developing major complications include fatty liver, type 2 diabetes mellitus and cardiovascular diseases. Nuclear receptors are master regulators of gene transcription, often regulating several different metabolic pathways. Among them LXRα/β play a key role in regulation of lipogenesis, cholesterol/glucose homoeostasis and inflammatory pathways, via the induction/repression of target genes. However, along with their established role in metabolic homeostasis and disease, lipogenesis and hypertriglyceridemia should be considered as the most important negative features of LXR activation. Given the importance of lipid and carbohydrate metabolism and inflammation in the development of metabolic disorders, this review focuses on the impact of the LXRs signaling on the risk of MetS and its related phenotypes with an emphasis on their potential therapeutic applications in treatment of MetS. Taken together, a growing body of evidences supports the notion that LXRs may represent potential drug targets for the treatment of MetS

Keywords: liver X receptor; metabolic syndrome; metabolic disorder

Background

Metabolic syndrome (MetS), also known as syndrome X or insulin resistance syndrome, refers to a group of metabolic abnormalities, including central obesity, dyslipidemia, insulin resistance, hyperglycemia and raised blood pressure (1). People who develop the MetS have a higher risk of developing diabetes and cardiovascular disease compared with people without MetS (2). The prevalence of the MetS is increasing throughout the world; however, its patterns vary among geographical regions and ethnicities and there has been an alarming increase in Asia (3). It is widely recognized, however, that developing strategies for decreasing the MetS incidence require careful examination of genetic and environmental contributions to the MetS and better understanding of its development and pathophysiology. The exact cause of MetS is not known but like many other multifactorial diseases the full expression of the syndrome depends on a complex interaction between genetic susceptibility and environmental factors related mainly to sedentary lifestyles and high-energy diets (4). Several large population-based studies have shown that the mutations and polymorphisms in the genes associated with insulin resistance, obesity favor dyslipidemia, hypertension, chronic inflammation, and autonomic imbalance may contribute in a polygenic manner in predisposing to components of the MetS (5-10). Identification of genes underlying susceptibility to the MetS is important in order to elucidate better the mechanisms of pathways leading to MetS and to identify new molecular based strategies for the treatment of the metabolic derived disorders. Some epidemiological and animal studies investigating LXR genes regarding to the risk of MetS and related parameters have indicated a potentially important regulatory role of LXRs in several metabolic signaling pathways involved in MetS and supported this hypothesis that drugs, which target LXRs, may offer benefits in the treatment of metabolic disorders (11-16).

Liver X receptors (LXRα and LXRβ)

Liver X receptors commonly known as LXRα and LXRβ (encoded by NR1H3 and NR1H2 genes respectively) are ligand-dependent transcription factors belonging to the family of nuclear receptors activated by oxysterols (17). Being as "cholesterol sensors", they sense elevated cellular cholesterol and work in a manner to decrease cholesterol level via the increased expression of target genes associated with reverse cholesterol transport, intestinal cholesterol absorption and cholesterol conversion to bile acid. LXRα encoded by NR1H3 gene located on chromosome 11p11.2, is expressed in tissues involved in lipid metabolism, including the liver, spleen, kidney, small intestine, adipose tissue, and macrophages, whereas LXRβ encoded by NR1H2 gene located on 19q13.33–q13.43 is expressed throughout the body (18).

Upon activation with endogenous LXR ligands, named the cholesterol-derived oxysterols, particularly 22(R)-hydroxycholesterol, 24(S),25-epoxycholesterol, 24(S)-hydroxycholesterol and 27-hydroxycholesterol (19) or by glucose (20), LXR-mediated gene regulation occurs through two mechanisms. One is a DNA-dependent pathway in which liganded LXR after the formation of heterodimer with retinoid X receptor and recruitment additional proteins, known as co-factors in the nucleus, is bounded to LXR response element of target genes involved essentially in lipid metabolism, lipogenesis and cholesterol/glucose homeostasis (21, 22). The other is an LXR response element–independent pathway that involves interference with other transcription factor pathways (23). Several co-regulators linked to metabolic processes, including PGC-1b, RIP140, GPS2, and ACS-2, have been shown to interact with LXRs and influence their transcriptional activity (24-26).

LXRs target genes involved in metabolic syndrome

LXR signaling depending on the nutritional state of the cell induces the expression of a variety of target genes involved in lipid and glucose metabolism. LXR has been shown to activate genes such as Sterol Regulatory Element-Binding Protein 1c (SREBP-1c) (27) (which serves as a trigger for down-stream transcriptional events), fatty acid synthase (FAS) (28), phosphoenolpyruvate carboxykinase (PEPCK) (29, 30)acetyl-CoA carboxylase (ACC) (which are involved in lipogenesis) and the ATP binding cassette transporters A (ABCA) (31) that are involved in cholesterol transport. Moreover, LXRs have been shown to mediate repression of inflammatory pathways through mechanisms collectively known as trans-repression. Then, it is reasonable to conclude that dysregulation of LXRs signaling may contribute in increased risk of the MetS.

Role of LXRs in regulation of metabolic functions

During the last decade, the physiological role of LXRs as key regulators of many target genes involved in cholesterol/glucose homoeostasis, inflammation, lipid uptake and efflux and lipoprotein metabolism in different tissues has been demonstrated.

In general, LXRs activators promote (i) the lipogenesis via the regulation of hepatic fatty acid biosynthesis in both an SREBP-1c-dependent, as well as an SREBP-1c-independent manner (32) and the cellular transmembrane transport of endogenous lipid substrates via the induction of ABCA1, ABCG1, ABCG5, ABCG4, and ABCG8, in human macrophages and intestine (33-35); (ii) the cholesterol homeostasis via inducing the transcription of genes that protect cells from cholesterol overload and also inducing the cholesterol trafficking from the endosome/lysosome to the plasma membrane through the activation of Niemann-Pick C (NPC) 1 and NPC2 expression in human macrophages (36). The activation of LXR results in bile acid synthesis and

metabolism/excretion, reverse cholesterol transport (RCT) and cholesterol absorption/excretion in the intestine; (iii) The inducing expression of the cholesterol transporters ABCA1 and ABCG1 and the regulation of acceptors in cholesterol efflux such as ApoE, ApoCI, ApoCII and ApoCIV expression in adipocytes and macrophages (37); (iv) The remodeling of lipoproteins through the control of modifying enzymes such as lipoprotein lipase (LPL) and phospholipid transfer protein (PLTP) in liver and macrophages (38); (v) The hepatic conversion of excess carbohydrate to lipids via regulation of carbohydrate response element-binding protein (ChREBP) as a glucose-sensitive transcription factor; (vi) The increasing insulin-mediated glucose uptake into adipose tissue and muscle via upregulation of the glucose transporter GLUT4 (39); and (vii) The regulation of inflammation and immunity via induction of classical inflammatory genes and various chemokines in response to bacterial, LPS, TNF-α, or IL-1β stimuli and inducing the expression of anti-inflammatory genes (39).

To support all these physiological roles of LXRs, analyzing gene expression in LXRα and LXRβ deficient mice and also LXRS agonists has confirmed the results (40-42). Therefore, LXRs play a central role in many pathways involved in the onset of the MetS, especially in HDL-cholesterol metabolism, fatty acid and carbohydrate metabolism in the liver, macrophages and intestine.

LXRs as potential drug targets for the metabolic syndrome

Owing to the fact that LXRs play a central role in cholesterol metabolism and are key regulators of lipogenesis and have an impact on systemic glucose homeostasis, understanding the mechanisms by which LXR signaling regulates diverse aspects of metabolism homeostasis has emerged new insights with respect to pharmacological manipulation of the LXR pathway for therapeutic intervention in human metabolism (43). The ability of LXRs to integrate metabolic

and inflammatory signaling has made them to appear attractive targets for drugs development. In addition to known endogenous oxysterols (oxidized derivatives of cholesterol) ligands for LXR activation which have similar affinities for both LXR isoforms, considerable efforts have been made to develop synthetic agonists' ligands to modulate activity of LXR-signaling pathways.

A number of synthetic LXR ligands have been developed that promote cholesterol efflux and inhibit inflammation in vivo and inhibit the development of atherosclerosis, metabolic disorders as well as inflammatory conditions in animal models, which suggests a broad spectrum of potential clinical applications (44). The nonsteroidal compounds T0901317and and GW3965 are two examples of such LXR activator that their beneficial outcome on cholesterol homeostasis has been proved in cell-base or in vivo in mice (45, 46). However, data from other in vivo studies revealed that the deleterious lipogenic effects of these first-generation synthetic ligands of LXR should be taken into account (27, 45, 46).

The lipogenic effects of LXRs has presented a major problem in strategies for development of LXR agonists and recent efforts have benefited from isoform-specific LXR ligands which is considered to be one of the most important options to develop LXR ligands with partial agonists property, exhibiting a LXR subtype-specificity which activate or block the receptor in a tissue specific manner (47). In other words, selective pharmacological activation of LXRβ may induce cholesterol-related effects of LXR but circumvent the lipogenic effects that are attributed to LXRα (48, 49). Recently, two synthetic LXR agonists, ATI-829, and DMHCA have been developed that selectively activate LXR target genes expression in certain tissues but have no impact on genes involved in liver lipogenesis (50). These data suggests that developing LXR modulators with no effect on hepatic lipogenic genes would lead to better therapeutic strategies.

Although a large body of studies have investigated to develop LXR agonists, the concept of undesirable lypogenic effect of LXR has prompted the development of LXR antagonists as an alternative approach for pharmacologically inhibition of LXR-driven lipogenesis and reduction in hepatic complications. Evidences from global loss of LXR activity studies suggests that LXR antagonist by improving insulin sensitivity in a tissue specific manner might have therapeutic utility for metabolic syndrome (51). Further studies will be necessary to find a suitable balance between desirable and adverse effects of both LXR agonists and antagonists on various aspects of metabolic syndrome and other metabolic related disease, before they could be considered as an ideal candidate for therapeutic purpose.

Conclusion

Given that the prevalence of MetS and its various manifestations is increasing globally and the consequences of this syndrome can include such outcomes as type 2 diabetes and cardiovascular diseases, the roles of LXRs as key regulators of intermediary metabolism have evoked interest in these receptors as targets for development of new ligands for the treatment of MetS. A number of synthetic LXR ligands have been designed that have beneficial outcome on cholesterol homeostasis with some undesirable lipogenic effects. With respect to this, further efforts are in progress to define possible approaches to avoid from such serious adverse effects, most importantly increasing plasma levels of triglyceride. One alternative approach is selective pharmacological activation of LXR subtype through the development of LXR ligands with partial agonist property or applying LXR antagonists repressing lipogenic gene expression in tissue specific manner. Finally, it must be noted that, most investigations revealing the beneficial outcome of LXR activation have been performed in animal model and have not been tested in humans. Thus, with considering the interspecies metabolic differences and genetic evolution, those

findings could be translated into human or further studies should be performed in human-based to verify such animal-based findings.

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List of abbreviations used: MetS; Metabolic syndrome, LXRs; liver X receptors, NR1H3; nuclear receptor subfamily 1 group H member 3, NR1H2; nuclear receptor subfamily 1 group H member 2, DNA; deoxyribonucleic acid, PGC-1b; Peroxisome proliferator-activated receptor gamma coactivator 1beta, RIP140; receptor-interacting protein 140, GPS2; G Protein Pathway Suppressor 2, ACS-2; Acetyl-coenzyme A synthetase 2, SREBP-1c; Sterol Regulatory Element-Binding Protein 1c, FAS; fatty acid synthase, PEPCK; phosphoenolpyruvate carboxykinase, ACC; acetyl-CoA carboxylase, ABCA; ATP binding cassette transporters A, NPC; Niemann-Pick C, RCT; reverse cholesterol transport, LPL; lipoprotein lipase, PLTP; phospholipid transfer protein, ChREBP, carbohydrate response element-binding protein, ATI-829; [3a,6a,24-trihydroxy-24, 24-di(trifluromethyl)-5b-cholane], DMHCA; [N,N-dimethyl-3b-hydroxy-cholenamide],

References

1. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2010 Jan 16;375(9710):181-3. PubMed PMID: 20109902.

2. Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? Diabetes care. 2004 Nov;27(11):2676-81. PubMed PMID: 15505004. Epub 2004/10/27. eng.

3. Juo SH, Lu MY, Bai RK, Liao YC, Trieu RB, Yu ML, et al. A common mitochondrial polymorphism 10398A>G is associated metabolic syndrome in a Chinese population. Mitochondrion. 2010 Apr;10(3):294-9. PubMed PMID: 20067846.

4. Grundy SM, Hansen B, Smith SC, Jr., Cleeman JI, Kahn RA, American Heart A, et al. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. Arteriosclerosis, thrombosis, and vascular biology. 2004 Feb;24(2):e19-24. PubMed PMID: 14766740.

5. Aguilera CM, Olza J, Gil A. Genetic susceptibility to obesity and metabolic syndrome in childhood. Nutricion hospitalaria. 2013 Sep;28 Suppl 5:44-55. PubMed PMID: 24010743.

6. Kristiansson K, Perola M, Tikkanen E, Kettunen J, Surakka I, Havulinna AS, et al. Genome-wide screen for metabolic syndrome susceptibility Loci reveals strong lipid gene contribution but no evidence for common genetic basis for clustering of metabolic syndrome traits. Circulation Cardiovascular genetics. 2012 Apr 1;5(2):242-9. PubMed PMID: 22399527. Pubmed Central PMCID: 3378651.

7. Gotoda T. [Genetic susceptibility to metabolic syndrome]. Nihon rinsho Japanese journal of clinical medicine. 2004 Jun;62(6):1037-44. PubMed PMID: 15206139.

8. Monda KL, North KE, Hunt SC, Rao DC, Province MA, Kraja AT. The genetics of obesity and the metabolic syndrome. Endocrine, metabolic & immune disorders drug targets. 2010 Jun;10(2):86-108. PubMed PMID: 20406164.

9. Rooki H, Ghayour-Mobarhan M, Pourhosseingholi MA, Azarpazhooh MR, Ebrahimi M, Ferns G, et al. Association of LXRalpha polymorphisms with obesity and obesity-related phenotypes in an Iranian population. Annals of human biology. 2014 May-Jun;41(3):214-9. PubMed PMID: 24180251.

10. Rooki H, Ghayour-Mobarhan M, Haerian MS, Ebrahimi M, Azimzadeh P, Heidari-Bakavoli A, et al. Lack of association between LXRalpha and LXRbeta gene polymorphisms and prevalence of metabolic syndrome: a case-control study of an Iranian population. Gene. 2013 Dec 15;532(2):288-93. PubMed PMID: 24100084.

11. Dahlman I, Nilsson M, Gu HF, Lecoeur C, Efendic S, Ostenson CG, et al. Functional and genetic analysis in type 2 diabetes of liver X receptor alleles--a cohort study. BMC medical genetics. 2009;10:27. PubMed PMID: 19292929. Pubmed Central PMCID: 2664799.

12. Dahlman I, Nilsson M, Jiao H, Hoffstedt J, Lindgren CM, Humphreys K, et al. Liver X receptor gene polymorphisms and adipose tissue expression levels in obesity. Pharmacogenetics and genomics. 2006 Dec;16(12):881-9. PubMed PMID: 17108812.

13. Legry V, Bokor S, Beghin L, Galfo M, Gonzalez-Gross M, Molnar D, et al. Associations between common genetic polymorphisms in the liver X receptor alpha and its target genes with

the serum HDL-cholesterol concentration in adolescents of the HELENA Study. Atherosclerosis. 2011 May;216(1):166-9. PubMed PMID: 21316679. Epub 2011/02/15. eng.

14. Legry V, Cottel D, Ferrieres J, Chinetti G, Deroide T, Staels B, et al. Association between liver X receptor alpha gene polymorphisms and risk of metabolic syndrome in French populations. International journal of obesity (2005). 2008 Mar;32(3):421-8. PubMed PMID: 18209740. Epub 2008/01/23. eng.

15. Mouzat K, Mercier E, Polge A, Evrard A, Baron S, Balducchi JP, et al. A common polymorphism in NR1H2 (LXRbeta) is associated with preeclampsia. BMC medical genetics. 2011;12:145. PubMed PMID: 22029530. Pubmed Central PMCID: PMC3214159. Epub 2011/10/28. eng.

16. Solaas K, Legry V, Retterstol K, Berg PR, Holven KB, Ferrieres J, et al. Suggestive evidence of associations between liver X receptor beta polymorphisms with type 2 diabetes mellitus and obesity in three cohort studies: HUNT2 (Norway), MONICA (France) and HELENA (Europe). BMC medical genetics. 2010;11:144. PubMed PMID: 20939869. Pubmed Central PMCID: PMC2958901. Epub 2010/10/14. eng.

17. Janowski BA, Willy PJ, Devi TR, Falck JR, Mangelsdorf DJ. An oxysterol signalling pathway mediated by the nuclear receptor LXR alpha. Nature. 1996 Oct 24;383(6602):728-31. PubMed PMID: 8878485.

18. Willy PJ, Umesono K, Ong ES, Evans RM, Heyman RA, Mangelsdorf DJ. LXR, a nuclear receptor that defines a distinct retinoid response pathway. Genes & development. 1995 May 1;9(9):1033-45. PubMed PMID: 7744246. Epub 1995/05/01. eng.

19. Lehmann JM, Kliewer SA, Moore LB, Smith-Oliver TA, Oliver BB, Su JL, et al. Activation of the nuclear receptor LXR by oxysterols defines a new hormone response pathway. The Journal of biological chemistry. 1997 Feb 7;272(6):3137-40. PubMed PMID: 9013544.

20. Mitro N, Mak PA, Vargas L, Godio C, Hampton E, Molteni V, et al. The nuclear receptor LXR is a glucose sensor. Nature. 2007 Jan 11;445(7124):219-23. PubMed PMID: 17187055. Epub 2006/12/26. eng.

21. Beaven SW, Tontonoz P. Nuclear receptors in lipid metabolism: targeting the heart of dyslipidemia. Annual review of medicine. 2006;57:313-29. PubMed PMID: 16409152.

22. Peet DJ, Janowski BA, Mangelsdorf DJ. The LXRs: a new class of oxysterol receptors. Current opinion in genetics & development. 1998 Oct;8(5):571-5. PubMed PMID: 9794827.

23. Terasaka N, Hiroshima A, Ariga A, Honzumi S, Koieyama T, Inaba T, et al. Liver X receptor agonists inhibit tissue factor expression in macrophages. The FEBS journal. 2005 Mar;272(6):1546-56. PubMed PMID: 15752369.

24. Lin J, Yang R, Tarr PT, Wu PH, Handschin C, Li S, et al. Hyperlipidemic effects of dietary saturated fats mediated through PGC-1beta coactivation of SREBP. Cell. 2005 Jan 28;120(2):261-73. PubMed PMID: 15680331. Epub 2005/02/01. eng.

25. Jakobsson T, Venteclef N, Toresson G, Damdimopoulos AE, Ehrlund A, Lou X, et al. GPS2 is required for cholesterol efflux by triggering histone demethylation, LXR recruitment, and coregulator assembly at the ABCG1 locus. Molecular cell. 2009 May 14;34(4):510-8. PubMed PMID: 19481530. Epub 2009/06/02. eng.

26. Kim GH, Park K, Yeom SY, Lee KJ, Kim G, Ko J, et al. Characterization of ASC-2 as an antiatherogenic transcriptional coactivator of liver X receptors in macrophages. Molecular

endocrinology (Baltimore, Md). 2009 Jul;23(7):966-74. PubMed PMID: 19342446. Pubmed Central PMCID: PMC2703598. Epub 2009/04/04. eng.

27. Schultz JR, Tu H, Luk A, Repa JJ, Medina JC, Li L, et al. Role of LXRs in control of lipogenesis. Genes & development. 2000 Nov 15;14(22):2831-8. PubMed PMID: 11090131. Pubmed Central PMCID: PMC317060. Epub 2000/11/23. eng.

28. Joseph SB, Laffitte BA, Patel PH, Watson MA, Matsukuma KE, Walczak R, et al. Direct and indirect mechanisms for regulation of fatty acid synthase gene expression by liver X receptors. The Journal of biological chemistry. 2002 Mar 29;277(13):11019-25. PubMed PMID: 11790787. Epub 2002/01/16. eng.

29. Laffitte BA, Chao LC, Li J, Walczak R, Hummasti S, Joseph SB, et al. Activation of liver X receptor improves glucose tolerance through coordinate regulation of glucose metabolism in liver and adipose tissue. Proceedings of the National Academy of Sciences of the United States of America. 2003 Apr 29;100(9):5419-24. PubMed PMID: 12697904. Pubmed Central PMCID: PMC154360. Epub 2003/04/17. eng.

30. Cao G, Liang Y, Broderick CL, Oldham BA, Beyer TP, Schmidt RJ, et al. Antidiabetic action of a liver x receptor agonist mediated by inhibition of hepatic gluconeogenesis. The Journal of biological chemistry. 2003 Jan 10;278(2):1131-6. PubMed PMID: 12414791. Epub 2002/11/05. eng.

31. Repa JJ, Berge KE, Pomajzl C, Richardson JA, Hobbs H, Mangelsdorf DJ. Regulation of ATP-binding cassette sterol transporters ABCG5 and ABCG8 by the liver X receptors alpha and beta. The Journal of biological chemistry. 2002 May 24;277(21):18793-800. PubMed PMID: 11901146. Epub 2002/03/20. eng.

32. Liang G, Yang J, Horton JD, Hammer RE, Goldstein JL, Brown MS. Diminished hepatic response to fasting/refeeding and liver X receptor agonists in mice with selective deficiency of sterol regulatory element-binding protein-1c. The Journal of biological chemistry. 2002 Mar 15;277(11):9520-8. PubMed PMID: 11782483.

33. Costet P, Luo Y, Wang N, Tall AR. Sterol-dependent transactivation of the ABC1 promoter by the liver X receptor/retinoid X receptor. The Journal of biological chemistry. 2000 Sep 8;275(36):28240-5. PubMed PMID: 10858438. Epub 2000/06/20. eng.

34. Venkateswaran A, Laffitte BA, Joseph SB, Mak PA, Wilpitz DC, Edwards PA, et al. Control of cellular cholesterol efflux by the nuclear oxysterol receptor LXR alpha. Proceedings of the National Academy of Sciences of the United States of America. 2000 Oct 24;97(22):12097-102. PubMed PMID: 11035776. Pubmed Central PMCID: 17300.

35. Repa JJ, Turley SD, Lobaccaro JA, Medina J, Li L, Lustig K, et al. Regulation of absorption and ABC1-mediated efflux of cholesterol by RXR heterodimers. Science. 2000 Sep 1;289(5484):1524-9. PubMed PMID: 10968783.

36. Rigamonti E, Helin L, Lestavel S, Mutka AL, Lepore M, Fontaine C, et al. Liver X receptor activation controls intracellular cholesterol trafficking and esterification in human macrophages. Circulation research. 2005 Sep 30;97(7):682-9. PubMed PMID: 16141411.

37. Mak PA, Laffitte BA, Desrumaux C, Joseph SB, Curtiss LK, Mangelsdorf DJ, et al. 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. The Journal of biological chemistry. 2002 Aug 30;277(35):31900-8. PubMed PMID: 12032151.

38. Zhang Y, Repa JJ, Gauthier K, Mangelsdorf DJ. Regulation of lipoprotein lipase by the oxysterol receptors, LXRalpha and LXRbeta. The Journal of biological chemistry. 2001 Nov 16;276(46):43018-24. PubMed PMID: 11562371.

39. Faulds MH, Zhao C, Dahlman-Wright K. Molecular biology and functional genomics of liver X receptors (LXR) in relationship to metabolic diseases. Current opinion in pharmacology. 2010 Dec;10(6):692-7. PubMed PMID: 20829110.

40. Hong C, Bradley MN, Rong X, Wang X, Wagner A, Grijalva V, et al. LXRα is uniquely required for maximal reverse cholesterol transport and atheroprotection in ApoE-deficient mice. Journal of Lipid Research. 2012;53(6):1126-1133.

41. Ulven SM, Dalen KT, Gustafsson JA, Nebb HI. Tissue-specific autoregulation of the LXRalpha gene facilitates induction of apoE in mouse adipose tissue. Journal of lipid research. 2004 Nov;45(11):2052-62. PubMed PMID: 15292368.

42. Xu P, Li D, Tang X, Bao X, Huang J, Tang Y, et al. LXR agonists: new potential therapeutic drug for neurodegenerative diseases. Molecular neurobiology. 2013 Dec;48(3):715-28. PubMed PMID: 23625315. Epub 2013/04/30. eng.

43. Cannon MV, van Gilst WH, de Boer RA. Emerging role of liver X receptors in cardiac pathophysiology and heart failure. Basic research in cardiology. 2016 Jan;111(1):3. PubMed PMID: 26611207

44. Bradley MN, Hong C, Chen M, Joseph SB, Wilpitz DC, Wang X, et al. Ligand activation of LXR beta reverses atherosclerosis and cellular cholesterol overload in mice lacking LXR alpha and apoE. The Journal of clinical investigation. 2007 Aug;117(8):2337-46. PubMed PMID: 17657314. Pubmed Central PMCID: 1924496.

45. Kugimiya A, Takagi J, Uesugi M. [Role of LXRs in control of lipogenesis]. Tanpakushitsu kakusan koso Protein, nucleic acid, enzyme. 2007 Oct;52(13 Suppl):1814-5. PubMed PMID: 18051439.

46. Tontonoz P, Mangelsdorf DJ. Liver X receptor signaling pathways in cardiovascular disease. Molecular endocrinology (Baltimore, Md). 2003 Jun;17(6):985-93. PubMed PMID: 12690094.

47. Hong C, Tontonoz P. Liver X receptors in lipid metabolism: opportunities for drug discovery. Nature reviews Drug discovery. 2014 Jun;13(6):433-44. PubMed PMID: 24833295.

48. Lund EG, Peterson LB, Adams AD, Lam MH, Burton CA, Chin J, et al. Different roles of liver X receptor alpha and beta in lipid metabolism: effects of an alpha-selective and a dual agonist in mice deficient in each subtype. Biochem Pharmacol 2006;71:453-6.

49. Quinet EM, Savio DA, Halpern AR, Chen L, Schuster GU, Gustafsson JA, et al. Liver X receptor (LXR)-beta regulation in LXRalpha-deficient mice: implications for therapeutic targeting. Mol Pharmacol 2006;70:1340-9.

50. Fievet C, Staels B. Liver X receptor modulators: effects on lipid metabolism and potential use in the treatment of atherosclerosis. Biochem Pharmacol. 2009 Apr 15;77(8):1316-27. PubMed PMID: 19101522.

51. Beaven SW, Matveyenko A, Wroblewski K, Chao L, Wilpitz D, Hsu TW, et al. Reciprocal regulation of hepatic and adipose lipogenesis by liver X receptors in obesity and insulin resistance. Cell metabolism. 2013 Jul 02;18(1):106-17. PubMed PMID: 23823481.