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## Liver X receptors in lipid signalling and membrane homeostasis

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### Abstract

Liver X receptors  $\alpha$  and  $\beta$  (LXR $\alpha$  and LXR $\beta$ ) are nuclear receptors with pivotal roles in the transcriptional control of lipid metabolism. Transcriptional activity of LXRs is induced in response to elevated cellular levels of cholesterol. LXRs bind to and regulate the expression of genes that encode proteins involved in cholesterol absorption, transport, efflux, excretion and conversion to bile acids. The coordinated, tissue-specific actions of the LXR pathway maintain systemic cholesterol homeostasis and regulate immune and inflammatory responses. LXRs also regulate fatty acid metabolism by controlling the lipogenic transcription factor sterol regulatory element-binding protein 1c and regulate genes that encode proteins involved in fatty acid elongation and desaturation. LXRs exert important effects on the metabolism of phospholipids, which, along with cholesterol, are major constituents of cellular membranes. LXR activation preferentially drives the incorporation of polyunsaturated fatty acids into phospholipids by inducing transcription of the remodelling enzyme lysophosphatidylcholine acyltransferase 3. The ability of the LXR pathway to couple cellular sterol levels with the saturation of fatty acids in membrane phospholipids has implications for several physiological processes, including lipoprotein production, dietary lipid absorption and intestinal stem cell proliferation. Understanding how LXRs regulate membrane composition and function might provide new therapeutic insight into diseases associated with dysregulated lipid metabolism, including atherosclerosis, diabetes mellitus and cancer.

The maintenance of cellular and systemic lipid levels is essential for physiological homeostasis. Perturbations of lipid metabolism are associated with several prevalent diseases, such as diabetes mellitus, atherosclerosis, cancer and neurodegenerative disease<sup>1,2</sup>. Control of lipid levels involves a carefully orchestrated balance between their endogenous biosynthesis, dietary uptake, metabolism and elimination from the body. Nuclear receptors are a class of ligand-activated transcription factors that have important roles in physiology<sup>3</sup>. Several nuclear receptors, including liver X receptors (LXRs; also known as oxysterols receptor LXR), farnesoid X receptors (FXRs) and peroxisome proliferator-activated

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#### Author contributions

B.W. and P.T. discussed the content, researched the data and contributed to writing the article and to reviewing and/or editing of the manuscript before submission.

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receptors (PPARs), respond to changes in cellular levels of endogenous lipid ligands by regulating the expression of genes that encode proteins involved in lipid metabolism<sup>1,4</sup>.

First cloned in the 1990s from mice, the LXR family consists of two isoforms, LXR $\alpha$  (encoded by *Nr1h3*) and LXR $\beta$  (encoded by *Nr1h2*)<sup>5,6</sup>. LXR $\alpha$  and LXR $\beta$  share extensive sequence homology but have distinct tissue distributions. LXR $\alpha$  is highly expressed in metabolically active tissues and cell types, including liver, intestine, adipose tissue and macrophages, whereas LXR $\beta$  is expressed ubiquitously<sup>7,8</sup>. LXRs form obligate heterodimers with the retinoid X receptor- $\alpha$  (RXR $\alpha$ ; also known as retinoic acid receptor RXR $\alpha$ ) and bind to a specific DNA recognition sequence known as an LXR response element (LXRE) (FIG. 1). LXREs contain variations of the repeated sequence AGGTCA, separated by four nucleotides<sup>6</sup>. In the absence of ligands, LXR–RXR complexes are believed to bind co-repressors, such as silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) or nuclear receptor co-repressor (NCoR), and repress target gene expression<sup>9,10</sup>. Ligands binding to LXRs induce a conformational change to the LXR–RXR complexes; this change causes the release of co-repressors and the recruitment of co-activators such as histone acetyltransferase p300 (also known as E1A-associated protein p300) and activating signal co-integrator 2 (ASC2; also known as NCOA6), resulting in the increased transcription of target genes<sup>11</sup>. A limited number of studies have suggested that LXRs act as monomers; however, these findings have not been widely replicated<sup>12,13</sup>. Further studies are needed to demonstrate that LXR regulates transcription by acting as a monomer under physiological conditions in vivo. LXRs are activated by endogenous ligands, including cholesterol derivatives such as oxysterols and 24(*S*),25-epoxycholesterol<sup>14–16</sup>, and by intermediate precursors in the cholesterol biosynthetic pathway, such as desmosterol<sup>17</sup>. Synthetic agonists, such as GW3965 and T0901317, have also been widely used as chemical tools to study LXR signalling pathways both in vitro and in vivo<sup>4</sup>.

This Review summarizes the roles of LXRs in cholesterol, fatty acid and phospholipid metabolism and their links to diseases related to lipid metabolism. We also discuss emerging strategies for targeting LXRs and their downstream pathways in the setting of metabolic diseases.

## LXRs in cholesterol metabolism

### Cholesterol excretion from the liver.

The discovery that LXRs were activated by oxysterols was the first clue that they might be involved in maintaining cholesterol homeostasis<sup>14</sup>. This idea was confirmed through the generation and analysis of *Lxra*-knockout mice. Mice lacking LXR $\alpha$  accumulate massive amounts of cholesterol in the liver when fed a high-cholesterol diet<sup>18</sup>. This early study also identified the gene encoding cytochrome P450 7A1 (*Cyp7a1*), the rate-limiting enzyme in the bile acid synthesis pathway, as the first direct target of LXRs (FIG. 2). The study showed that loss of LXR $\alpha$  in mice impairs the conversion of cholesterol into bile acids. Subsequent studies revealed that LXRs also stimulate biliary cholesterol excretion directly through their target genes *Abcg5* and *Abcg8* (REF.<sup>19</sup>). Mice lacking *Abcg5* and *Abcg8* fail to increase biliary cholesterol content in response to T0901317 treatment, suggesting that the expression

of *Abcg5* and *Abcg8* is required for LXR-dependent biliary sterol trafficking. The importance of LXRs, especially liver LXR $\alpha$ , in whole-body cholesterol homeostasis was reinforced by studies of hepatic-specific *Lxra*-knockout mice, which have impaired reverse cholesterol transport (RCT), cholesterol catabolism and cholesterol excretion<sup>20</sup>.

### Reverse cholesterol transport.

Another important role of LXRs in maintaining cholesterol homeostasis is to promote RCT, a process by which excess cholesterol in peripheral tissues is transferred to HDL and transported to the liver for bile acid synthesis and excretion. The initial step in RCT is cellular cholesterol efflux, which involves the transfer of free cholesterol to apolipoprotein A1 (ApoA1) or pre- $\beta$  HDL. Cellular cholesterol efflux is mediated primarily by the ATP-binding cassette transporters ATP-binding cassette subfamily A member 1 (ABCA1) and ATP-binding cassette subfamily G member 1 (ABCG1), two of the earliest identified LXR-responsive factors<sup>21,22</sup>. Mutations in *ABCA1* in humans cause Tangier disease, a disorder characterized by severe reductions in plasma levels of HDL and increased cholesterol accumulation in peripheral tissues<sup>23,24</sup>. Structural analysis of membrane-bound ABCA1 revealed that two extracellular domains form a hydrophobic tunnel that probably facilitates the export of cholesterol<sup>25</sup>. ABCG1 was shown to localize to endosomes and to enable the transport of intracellular sterols away from the endoplasmic reticulum (ER)<sup>26</sup>. Several other LXR targets are also involved in the RCT pathway. For instance, ADP-ribosylation factor-like protein 7 (ARL7; also known as ARL4C), another LXR target, was shown to transport cholesterol between the perinuclear compartment and the plasma membrane<sup>27,28</sup>. Additionally, LXRs induce the expression of apolipoproteins (including ApoE, ApoC1, ApoC2, ApoC4 (REFS<sup>29,30</sup>) and ApoD<sup>31</sup>), as well as genes that encode proteins involved in lipoprotein remodelling (such as phospholipid transfer protein (PLTP)<sup>32</sup>, cholesteryl ester transfer protein (CETP)<sup>33</sup> and lipoprotein lipase (LPL))<sup>34</sup>. The net effect of LXR activation — the promotion of RCT from the peripheral tissues to the liver — probably results from the coordinated action of many, if not all, these factors.

### Cholesterol biosynthesis.

LXRs work hand in hand with the sterol regulatory element-binding protein 2 (SREBP2) pathway to maintain cellular and systemic sterol levels. Whereas LXRs facilitate elimination of excess cholesterol in response to high cellular levels of cholesterol, SREBP2 promotes cholesterol biosynthesis and uptake in response to low cholesterol levels in cells. Research over the past decade has revealed that these two key pathways engage in crosstalk on several levels. SREBP2 was shown to activate the transcription of ABCA1 by generating oxysterol ligands for LXRs<sup>35</sup>. Conversely, LXR activation in the liver inhibits cholesterol biosynthesis through the induction of the non-coding RNA LXR-induced sequence (*Lexis*)<sup>36</sup> and the E3 ubiquitin protein ligase RING finger protein 145 (RNF145)<sup>37</sup>. *Lexis* interacts with the ribonucleoprotein RNA-binding protein Raly (RALY), which acts as a cofactor in the transcription of genes that encode proteins involved in cholesterol biosynthesis. RNF145 is an ER membrane protein that ubiquitylates sterol regulatory element-binding protein cleavage-activating protein (SCAP) and inhibits its transport to the Golgi and the subsequent proteolytic processing of SREBP2 (REF.<sup>37</sup>).

### Cholesterol uptake.

A considerable body of evidence has demonstrated that high levels of LDL cholesterol are a dominant risk factor for atherosclerosis. The LDL receptor (LDLR), a cell surface protein, is essential for the uptake of LDL cholesterol and the maintenance of plasma levels of cholesterol<sup>38</sup>. Mutations in *LDLR* in humans or mice cause hypercholesterolaemia and accelerated atherosclerosis owing to reduced LDL clearance<sup>39–41</sup>. LDLR expression is regulated at both the transcriptional and post-translational levels. The primary transcription factor for LDLR is SREBP2. In response to low cholesterol levels, SREBP2 drives the transcription of genes encoding proteins involved in cholesterol biosynthesis and LDL cholesterol uptake<sup>42</sup>. In a counter-regulatory mechanism, LXRs induce the expression of inducible degrader of the LDLR (IDOL; also known as MYLIP), an E3 ubiquitin protein ligase that ubiquitylates and degrades LDLR and related proteins VLDL receptor (VLDLR) and apolipoprotein E receptor 2 (ApoER2; also known as LRP8), through clathrin-independent endocytosis and multivesicular-body-mediated lysosomal degradation<sup>43–45</sup>. Crystallography studies characterized the interactions between the ubiquitin-conjugated enzyme E2 D (UBE2D) family (UBE2D1–4) of E2 ligases and IDOL that drive ubiquitylation of LDLR<sup>46</sup>. Subsequent studies showed that the four-point-one, ezrin, radixin, moesin (FERM) domain of IDOL binds to a recognition sequence in the cytoplasmic tails of lipoprotein receptors and mediates their degradation<sup>47</sup>. Interestingly, the LXR–IDOL pathway appears to exert species-specific influences on LDLR expression and plasma levels of cholesterol<sup>48</sup>. In mice, LXR agonists or loss of IDOL has little effect on hepatic levels of LDLR protein and plasma levels of cholesterol. By contrast, LXR agonists reduce hepatic LDLR expression and raise plasma levels of LDL cholesterol in primates and humans, probably through an IDOL-dependent mechanism<sup>48,49</sup>. Genome-wide association studies identified an Asn342Ser polymorphism in the gene encoding IDOL (*MYLIP*) that is associated with plasma lipid levels in a Mexican population<sup>50</sup>. Individuals carrying the Ser342 allele had higher cholesterol and LDL levels than those carrying the Asn342 allele. Variation at the *MYLIP* locus is also linked with response to statin treatment<sup>51</sup>. These findings suggest that IDOL inhibition could be an alternative approach to lowering LDL cholesterol in humans.

### Sterol metabolism in the intestine.

As the gateway for cholesterol entry into the body, the intestine has a crucial role in maintaining whole-body cholesterol homeostasis. Dietary cholesterol absorption from the intestinal lumen is mediated by apical membrane Niemann–Pick C1-like protein 1 (NPC1L1; also known as NPC1-like intracellular cholesterol transporter 1)<sup>52</sup>. Cholesterol efflux from enterocytes to the circulation is mediated by basolateral membrane ABCA1 (REFS<sup>53–55</sup>). Cholesterol efflux from enterocytes into the lumen<sup>56,57</sup> and transintestinal cholesterol excretion are mediated by heterodimers of apical membrane ATP-binding cassette subfamily G members 5 and 8 (ABCG5 and ABCG8, respectively)<sup>58</sup>. LXRs regulate multiple aspects of intestinal cholesterol metabolism by controlling the expression of several target genes. For example, activation of LXRs in intestine promotes faecal cholesterol excretion by inducing expression of ABCG5 and ABCG8. Mutations in *ABCG5* and *ABCG8* result in sitosterolaemia, an autosomal recessive disorder characterized by increased plant sterol levels and accelerated atherosclerosis<sup>59,60</sup>. Similar to LXR activation

in other peripheral tissues, intestinal LXR activation leads to increased RCT and HDL production through the induction of ABCA1 expression<sup>53–55</sup>. Furthermore, LXR activation in the intestine also reduces cholesterol absorption, probably owing to increased ABCG5 and ABCG8 expression and cholesterol excretion from enterocytes<sup>55,61</sup>. Consistent with the effects of LXR activation in intestine, overexpression of ABCG5 and ABCG8 reduces cholesterol absorption<sup>62</sup>. The reduced cholesterol absorption upon LXR activation might also be due in part to reduced NPC1L1 expression<sup>55,61</sup>. The molecular mechanism by which LXR activation reduces NPC1L1 expression remains to be determined. It is unlikely to be a direct transcriptional effect, as LXRs are not known to function as ligand-dependent repressors<sup>63</sup>.

## LXRs in fatty acid metabolism

In addition to their importance in modulating cholesterol homeostasis, LXRs are also key regulators of de novo lipogenesis in the liver<sup>7,64,65</sup>. Administration of synthetic LXR agonists to mice increases hepatic and plasma levels of triglyceride owing to enhanced fatty acid biosynthesis and VLDL secretion<sup>64</sup>. The lipogenic activity of LXRs is due, in large measure, to the transcriptional induction of the gene encoding SREBP1c, a central transcription activator of fatty acid biosynthesis (FIG. 3). In addition, LXRs directly activate the transcription of several lipogenic genes via LXREs in their promoter regions, including those encoding fatty acid synthase (*Fasn*)<sup>65</sup> and stearoyl-coenzyme A desaturase 1 (*Scd1*; also known as acyl-coenzyme A desaturase 1)<sup>66</sup>. Furthermore, LXRs also modulate the expression of another lipogenic regulator, carbohydrate-response element-binding protein (ChREBP). This regulation probably contributes to the induction of certain lipogenic genes in SREBP1c-null livers upon T0901317 treatment<sup>67</sup>. Interestingly, LXRs are also important for the ability of other signals, such as insulin<sup>68,69</sup> and polyunsaturated fatty acids<sup>70–72</sup>, to regulate SREBP1c expression. Deletion of LXREs in the *Srebf1c* (which encodes SREBP1c) promoter disrupts its response to insulin<sup>68</sup>, and studies from the past 2 years have demonstrated that LXR $\alpha$  and CCAAT/enhancer-binding protein  $\beta$  (C/EBP $\beta$ ) form a complex that binds to the *Srebf1c* promoter and is activated by insulin<sup>69</sup>. Polyunsaturated fatty acids suppress SREBP1c expression and lipogenesis through inhibiting SREBP1 cleavage<sup>72</sup> and by competing with LXR ligands<sup>70</sup>.

In addition to modulating lipogenesis in the liver, LXRs also regulate fatty acid catabolism in other tissues. LXR agonists were shown to increase lipolysis and fatty acid  $\beta$ -oxidation in adipose tissues<sup>73,74</sup>. On a high-carbohydrate diet, LXR $\alpha$ -null mice exhibit higher energy expenditure and UCP1 expression in brown adipose tissue than wild-type mice<sup>75</sup>. Similarly, LXR $\alpha$ -null mice are resistant to high-fat and high-cholesterol diet-induced obesity owing to increased energy expenditure resulting from upregulation of UCPs in muscle and adipose tissues<sup>76</sup>. Other studies have delineated tissue-selective effects of LXR signalling pathways on lipogenesis in the setting of obesity<sup>77</sup>. As expected, LXR $\alpha$ -deficient and LXR $\beta$ -deficient *ob/ob* mice were protected from hepatic steatosis owing to impaired lipogenesis in the liver. Unexpectedly, however, loss of hepatic lipogenesis was accompanied by a reciprocal increase in lipogenesis and fat storage in adipose tissues. Moreover, *ob/ob* mice lacking LXRs were more insulin sensitive than *ob/ob* mice, despite having similar body weight, owing to enhanced adipose PPAR $\gamma$  and ChREBP $\beta$  activity.

## LXRs in phospholipid metabolism

Phospholipids are the major constituents of biological membranes. The fatty acyl composition of component phospholipids determines the biophysical properties of membranes and influences their function<sup>78,79</sup>. In mammalian cells, saturated and monounsaturated fatty acyl chains are predominantly linked at the *sn*-1 position of phospholipids, whereas polyunsaturated fatty acids are most often located at the *sn*-2 position<sup>78,79</sup>. This asymmetrical distribution of fatty acyl chains is established largely through a remodelling process of deacylation and reacylation — a pathway referred to as the Lands' cycle<sup>80,81</sup>. We and others showed that LXRs modulate membrane phospholipid composition through activation of lysophosphatidylcholine acyltransferase 3 (LPCAT3; also known as lysophospholipid acyltransferase 5), a phospholipid remodelling enzyme that catalyses the incorporation of polyunsaturated fatty acids at the *sn*-2 site of lysophospholipids<sup>82–84</sup>. The ability of LXR to alter phospholipid composition in response to changing cellular levels of sterol provides a mechanism to protect biological membranes against lipid stress. LXR activation increases LPCAT3 expression and the abundance of polyunsaturated phospholipids in cell membranes, thereby ameliorating ER stress induced by saturated free fatty acids in vitro or by hepatic lipid accumulation in vivo<sup>82</sup>.

### LXR-dependent phospholipid remodelling in the liver.

LXR activation promotes VLDL secretion in mouse liver through the transcriptional induction of *Srebf1c* and genes downstream of SREBP1c that encode proteins involved in lipogenesis, as well as PLTP, which transfers phospholipids into nascent VLDL to enable particle expansion<sup>85,86</sup>. Since phospholipids are a major component of lipoprotein particles, phospholipid availability is known to influence the production of lipoproteins<sup>87</sup>. Studies published in the past 3 years have demonstrated that LPCAT3 and phospholipid remodelling have unexpected roles in hepatic lipoprotein production<sup>88–91</sup>, suggesting that not only the quantity but also the composition of phospholipids is important for lipoprotein secretion. Mice lacking LPCAT3 in the liver show reduced plasma levels of triglycerides, VLDL lipidation and secretion, resulting in hepatic steatosis (FIG. 3). Mechanistic studies suggest that LPCAT3 activity and polyunsaturated phospholipids probably affect the fluidity and curvature of membrane surfaces, thereby reducing triglyceride mobilization to VLDL. Liver-specific *Lpcat3*-knockout mice secrete less VLDL from the liver in response to synthetic LXR agonist treatment than control mice, suggesting that induction of LPCAT3 activity is required for the ability of LXRs to promote hepatic VLDL production<sup>88</sup>. Subsequent studies revealed that LPCAT3 activity is also involved in the effects of LXRs on SREBP1c-dependent lipogenesis in the liver. Incorporation of polyunsaturated fatty acids into phospholipids by LPCAT3 promotes SREBP1c processing and lipogenesis<sup>92</sup>. Interestingly, polyunsaturated phospholipid levels are selectively increased in the ER of obese mice, which seems to be owing to elevated LPCAT3 activity. Inhibition of LPCAT3 activity in obese mice reduces SREBP1c pathway activity, blunts lipogenesis and ameliorates the development of fatty liver<sup>92</sup>.

### LXR-dependent phospholipid remodelling in the intestine.

In the intestine, the phospholipid acyl chain composition of enterocyte membranes is critical for dietary lipid uptake<sup>90</sup>. Loss of LPCAT3 in the intestine results in a defect in the incorporation of linoleate and arachidonate into phospholipids, which leads to marked reduction in membrane fluidity and impairs passive fatty acid transport into enterocytes and chylomicron production (FIG. 4). LPCAT3 deficiency in the setting of a triglyceride-rich diet leads to the exacerbated production of gut hormones (such as glucagon-like peptide 1 (GLP1) and peptide YY (PYY)) and the cessation of food intake despite starvation, suggesting that LXR–LPCAT3 signalling functions in a gut–brain feedback loop that couples lipid absorption to food intake.

Research published in 2018 also uncovered an unexpected link between membrane phospholipid composition, cholesterol biosynthesis and intestinal stem cell homeostasis<sup>93</sup>. We found that LPCAT3 deficiency in the intestine increases the saturation of fatty acyl chains in membrane phospholipids and stimulates cholesterol biosynthesis, thereby driving intestinal stem cell proliferation (FIG. 4). Interestingly, cholesterol itself appears to act as a mitogen for intestinal stem cells. Increasing cellular cholesterol content, either by promoting endogenous synthesis or providing excess exogenous cholesterol, is sufficient to drive intestinal stem cell proliferation. Loss of LPCAT3 expression or overexpression of SREBP2 in *Apc*<sup>min</sup> mice markedly promoted intestinal tumour formation. Previous studies demonstrated that LXRs regulate cell apoptosis via AKT (also known as protein kinase B) survival signalling in lipid rafts<sup>94</sup>. Interestingly, polyunsaturated phospholipids inhibit cell proliferation through suppressing the binding of AKT to cell membranes<sup>95</sup>. LPCAT3 activity might mediate the effect of LXR activation on cell survival.

The mechanism whereby phospholipid remodelling is linked to cholesterol biosynthesis remains to be elucidated. It is important to note that the effects of phospholipid metabolism on SREBP1 and SREBP2 pathways appear to be tissue-specific as LPCAT3 deficiency selectively influences SREBP1c target genes in the liver, whereas it primarily affects SREBP2 target genes in the intestine. These studies highlight a mechanism whereby membrane phospholipid remodelling differentially influences SREBP maturation in response to cellular lipids.

## LXRs in metabolic diseases

### Atherosclerosis.

Atherosclerosis is initiated by subendothelial retention of cholesterol-rich, ApoB-containing lipoproteins in arteries<sup>96,97</sup>. Modified lipoproteins trigger a local inflammatory response in the arterial wall that activates endothelial cells and leads to the infiltration and accumulation of monocytes. These monocytes differentiate into tissue macrophages and phagocytose the modified lipoproteins through scavenger receptors and become lipid-laden foam cells<sup>98,99</sup>. Foam cells secrete pro-inflammatory mediators, including cytokines, chemokines and reactive oxygen species, which contribute to the unresolved inflammation and the progression of lesions into more advanced plaques. Considerable evidence points to LXR pathway activity as an important determinant of atherosclerosis susceptibility<sup>100–103</sup>. Loss of



LXRs markedly accelerates the initiation and progression of atherosclerosis in *Ldlr*<sup>-/-</sup> and *ApoE*<sup>-/-</sup> mouse models<sup>100</sup>. Conversely, chronic administration of synthetic LXR agonists reduces the size and abundance of atherosclerotic lesions in these models<sup>101,103</sup>. Several lines of evidence suggest that the anti-atherogenic effect of LXRs is due, in large measure, to their ability to promote cholesterol efflux from macrophages within lesions through the induction of ABCA1 and ABCG1 expression. LXR agonists fail to reduce atherosclerosis progression in irradiated *Ldlr*<sup>-/-</sup> mice transplanted with bone marrow from LXR-null mice<sup>104</sup>, confirming that expression of LXR in macrophages is essential for the anti-atherogenic effects of LXR agonists. Accordingly, transgenic overexpression of LXR $\alpha$  in macrophages suppresses atherosclerosis in *Ldlr*<sup>-/-</sup> mice<sup>105</sup>.

Inflammation also has a substantial role in atherosclerosis progression<sup>99,106,107</sup>. In addition to exerting beneficial effects on macrophage cholesterol efflux, LXR activation also affects atherogenesis through the repression of inflammatory gene expression<sup>101,108,109</sup>. How activation of LXRs inhibits inflammatory signalling is not well understood. One proposed mechanism postulated that LXRs can be modified by sumoylation when activated by agonist and that sumoylated LXR forms a complex with transcriptional co-repressors NCoR and/or SMRT on inflammatory gene promoters<sup>110-112</sup>. Conversely, excess cholesterol crystals in macrophages initiate pro-inflammatory signalling at atherosclerotic lesions<sup>113,114</sup>. Considering that LXR activation can efficiently remove intracellular cholesterol through efflux, their ability to regulate lipid metabolism through transcriptional activation probably contributes to repressed inflammation. Indeed, a study published in the past 2 years demonstrated that LXR agonists inhibit nuclear factor- $\kappa$ B (NF- $\kappa$ B) and mitogen-activated protein kinase (MAPK) signalling pathways downstream of Toll-like receptors through ABCA1-dependent changes in membrane lipid organization, suggesting that LXR transcriptional activation underlies dual biological functions in metabolism and inflammation<sup>115</sup>.

### Infection and immunity.

The LXR signalling pathway modulates the function of several types of immune cells<sup>116,117</sup>. In addition, extensive documentation reveals that LXR agonists repress inflammatory gene expression triggered by Toll-like receptors in macrophages and other immune cells<sup>108,118,119</sup>. The first in vivo evidence for a role of LXR signalling in immune responses came from studies of LXR-deficient mice. Mice lacking LXRs were susceptible to infection by the intracellular pathogen *Listeria monocytogenes* owing to accelerated macrophage apoptosis and defective bacterial clearance<sup>120</sup>. Subsequent work outlined a role for LXRs in phagocytosis and the maintenance of immune tolerance. The phagocytosis of apoptotic cells activates LXRs and initiates a positive feedback loop that promotes apoptotic cell clearance through tyrosine-protein kinase MER, which is critical for phagocytosis<sup>121</sup>. Furthermore, LXR-deficient mice exhibit defective phagocytosis of apoptotic cells in vivo and develop autoantibodies and autoimmune glomerulonephritis<sup>121</sup>.

LXRs couple cellular cholesterol homeostasis to immune cell function. Activation of LXR inhibits mitogen-driven T cell proliferation by altering cellular sterol content through ABCG1-mediated cholesterol trafficking, whereas loss of LXR $\beta$  expression promotes

lymphocyte proliferation, resulting in enhanced homeostatic and antigen-driven responses<sup>122</sup>. Furthermore, cholesterol accumulation in CD11c<sup>+</sup> immune cells and dendritic cells triggers the development of autoimmunity<sup>123,124</sup>. *Lxr $\beta$* <sup>-/-</sup> and *ApoE*<sup>-/-</sup> double-mutant or *Lxr $\beta$* <sup>-/-</sup> mice fed a high-cholesterol diet develop hypercholesterolaemia and autoantibodies. Mechanistically, cholesterol overload in lymphoid organs enhances antigen presentation and T cell priming and stimulates the production of the B cell growth factors BAFF (B cell activating factor; also known as TNFSF13B) and APRIL (a proliferation-inducing ligand; also known as TNFSF13)<sup>123</sup>. Similarly, loss of ABCA1 and ABCG1 in dendritic cells results in cholesterol enrichment and inflammasome activation, increased cell surface levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) and enhanced inflammatory cytokine production, leading to proliferation of T cells and B cells<sup>124</sup>.

### Alzheimer disease.

The brain is the most cholesterol-rich organ and contains ~25% of the cholesterol in the body<sup>125</sup>. Cholesterol is synthesized locally in the brain, and its metabolism is largely separated from peripheral cholesterol metabolism because of the blood-brain barrier. In the brain, cholesterol homeostasis is maintained through a balance between biosynthesis and clearance. Dysregulation of cholesterol homeostasis in the brain is associated with several neurodegenerative diseases, including Alzheimer disease, Parkinson disease and Huntington disease<sup>126</sup>. LXRs regulate cholesterol homeostasis in the brain. For instance, activation of LXRs by synthetic or endogenous ligands, including 24(*S*)-hydroxycholesterol, 22(*R*)-hydroxycholesterol, 24(*S*),25-epoxycholesterol and 27-hydroxycholesterol, induces the expression of ApoE (a primary apolipoprotein in the brain) and of its lipidating transporters ABCA1 or ABCG1 to promote cholesterol efflux<sup>127</sup>.

Given that the E4 isoform of ApoE, an LXR target, is a well-documented risk factor for late-onset Alzheimer disease, the potential involvement of LXRs in Alzheimer disease pathogenesis has been extensively investigated. Loss of LXRs and its target ABCA1 in a mouse model of Alzheimer disease led to a marked increase in amyloid- $\beta$  deposition and an Alzheimer-disease-like pathology<sup>128,129</sup>. Similarly, deficiency in another LXR target, IDOL, increased expression of LDLR in the brain, decreased levels of ApoE and soluble and insoluble amyloid- $\beta$ , reduced amyloid plaque burden and ameliorated neuroinflammation<sup>130</sup>. In agreement with these observations, LXR agonists increase clearance of amyloid- $\beta$  and improve memory in amyloid precursor protein (APP)-transgenic mice<sup>131</sup>. These studies demonstrate that LXRs and their target genes have important roles in the pathogenesis of Alzheimer disease and that pharmacological activation of LXRs might be a potential therapeutic approach for Alzheimer disease. The effect of LXRs on Alzheimer disease pathology is largely attributed to the induction of ABCA1 expression, which promotes cholesterol clearance and ApoE lipidation. ApoE, especially lipidated ApoE, interacts with amyloid- $\beta$  and facilitates its proteolytic clearance<sup>132</sup>. In addition, the repression of pro-inflammatory genes by LXR activation might also contribute to the slowing of Alzheimer disease progression<sup>132</sup>.

## Therapeutic targeting LXRs

Given the beneficial effects of LXR activation in animal models of metabolic diseases<sup>100,101</sup>, much effort has been expended to develop small-molecule agonists of LXRs. The first two widely studied agonists, GW3965 and T0901317, are potent pan-LXR agonists that induce the expression of target genes of both LXR $\alpha$  and LXR $\beta$  in vitro and in vivo. Although they are extensively used in research, they proved unsuitable for clinical trial because of undesirable adverse effects, including hepatic steatosis and hypertriglyceridaemia. To minimize the adverse effects of pan-LXR activation, several strategies have been explored. The lipogenic activity of LXRs is mainly mediated by the activation of SREBP1c by LXR $\alpha$  in the liver. The increased plasma levels of triglycerides induced by T0901317 treatment were largely eliminated in liver-specific *Lxra*-knockout mice, whereas its anti-atherogenic effects were preserved<sup>20</sup>, suggesting that LXR $\beta$  agonists might have fewer adverse effects than LXR $\alpha$  agonists.

The goal of identifying LXR $\beta$ -selective agonists has proved challenging owing to high homology in the ligand binding domains of LXR $\alpha$  and LXR $\beta$ <sup>133,134</sup>. Quinet and colleagues identified a synthetic oxysterol, *N, N*-dimethyl-3 $\beta$ -hydroxycholeamide (DMHCA), as a gene-selective LXR modulator that activates ABCA1 expression in liver, intestine and macrophages with limited effect on SREBP1c expression and serum levels of triglyceride<sup>135</sup>. Several partial agonists with considerable selectivity for LXR $\beta$  over LXR $\alpha$  were subsequently developed<sup>136–138</sup>. One such compound, LXR-623, lowered LDL cholesterol levels in primates and reduced the severity of atherosclerosis in mice without activating lipogenesis in the liver<sup>139</sup>. LXR-623 was the first LXR agonist to enter clinical trials (TABLE 1). Phase I studies suggested that LXR-623 activated the expression of ABCA1 and ABCG1 in healthy participants<sup>136</sup>. Unfortunately, the trial was terminated owing to unexpected adverse neurological effects<sup>136</sup>. Several other partial agonists, including CS-8080 and BMS-779788, were tested for safety and pharmacodynamics in healthy volunteers. The trial for CS-8080 was terminated owing to undisclosed safety concerns<sup>140</sup>. The phase I clinical trial for BMS-779788 was completed in July 2009, but the results were not published<sup>141</sup>. Another LXR $\beta$ -selective agonist, BMS-852927, was evaluated in patients with hypercholesterolaemia rather than healthy volunteers. Preclinical studies showed that BMS-852927 had favourable profiles in cynomolgus monkeys and mice with a wide therapeutic index<sup>49</sup>. Although BMS-852927 induced similar beneficial effects on the RCT pathway in patients with hypercholesterolaemia, it also caused adverse effects, including increased plasma and hepatic levels of triglyceride and increased plasma levels of LDL cholesterol, ApoB, ApoE and CETP as well as decreased circulating levels of neutrophils<sup>49</sup>. Despite these setbacks, efforts to identify LXR $\beta$ -selective agonists with fewer adverse effects are continuing<sup>142–144</sup>.

Another approach to theoretically avoid the lipogenic effects of LXR would be to develop tissue-selective agonists. As previously discussed, peripheral tissues and cell types, especially intestinal cells and macrophages, contribute to RCT and systemic cholesterol homeostasis. LXR activation in the intestine reduces cholesterol absorption, stimulates RCT and protects from atherosclerosis in the absence of hepatic steatosis, suggesting that intestine-specific activation of LXRs might be sufficient to achieve beneficial effects<sup>55</sup>.

Owing to its poor absorption, YT-23, an oxidized derivative of the yeast sterol ergosterol, was shown to reduce cholesterol absorption by inducing ABCG5 and ABCG8 expression in enterocytes when orally delivered without causing hepatic steatosis or hypertriglyceridaemia<sup>145</sup>. Similarly, another study demonstrated that GW6340, an intestinal-specific LXR agonist, induced the expression of LXR target genes and promoted macrophage RCT in mice<sup>146</sup>. The development of tissue-selective LXR agonists that bypass their hepatic effects might provide a new avenue for LXR therapy in metabolic diseases.

A third strategy for modulating the LXR pathway without activating SREBP1c expression is to target one or more LXR-regulated gene products directly. ABC transporters, including ABCA1, ABCG1, ABCG5 and ABCG8, are major mediators of cholesterol trafficking in different tissues upon LXR activation. Activation of one or multiple ABC transporters might recapitulate some of the beneficial effects of LXR activation on cholesterol homeostasis, such as increasing RCT. Another candidate drug target for modulating the LXR pathway is IDOL. As described in this Review, induction of IDOL by LXR agonists reduces LDLR expression and LDL uptake in primates<sup>48</sup>. Finally, it might be possible to mimic some of the effects of the LXR pathway activity on membrane phospholipid composition through the development of small molecules that regulate LPCAT3 activity. Considering the important roles that LPCAT3 has in lipid metabolism (particularly in lipid absorption, VLDL secretion and high-fat-diet consumption) inhibitors of LPCAT3 activity might provide a new therapeutic approach for obesity and associated metabolic conditions.

## Conclusions

Our understanding of the LXR pathway in lipid homeostasis and metabolic diseases has advanced greatly over the past two decades. LXRs are now recognized to be fundamental to controlling the cellular and systemic homeostasis of major classes of lipids, including sterols, fatty acids and phospholipids. Given the diverse biological pathways affected by LXR-dependent transcription, the potential for harvesting the power of the LXR pathway for therapeutic ends remains great. Further basic and translational research will be needed to realize this potential and to develop novel strategies for manipulating LXRs and their targets in the setting of metabolic disease.

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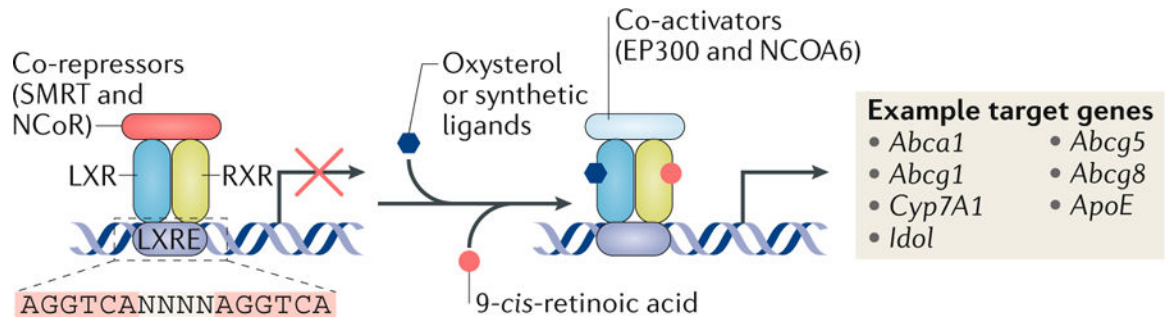
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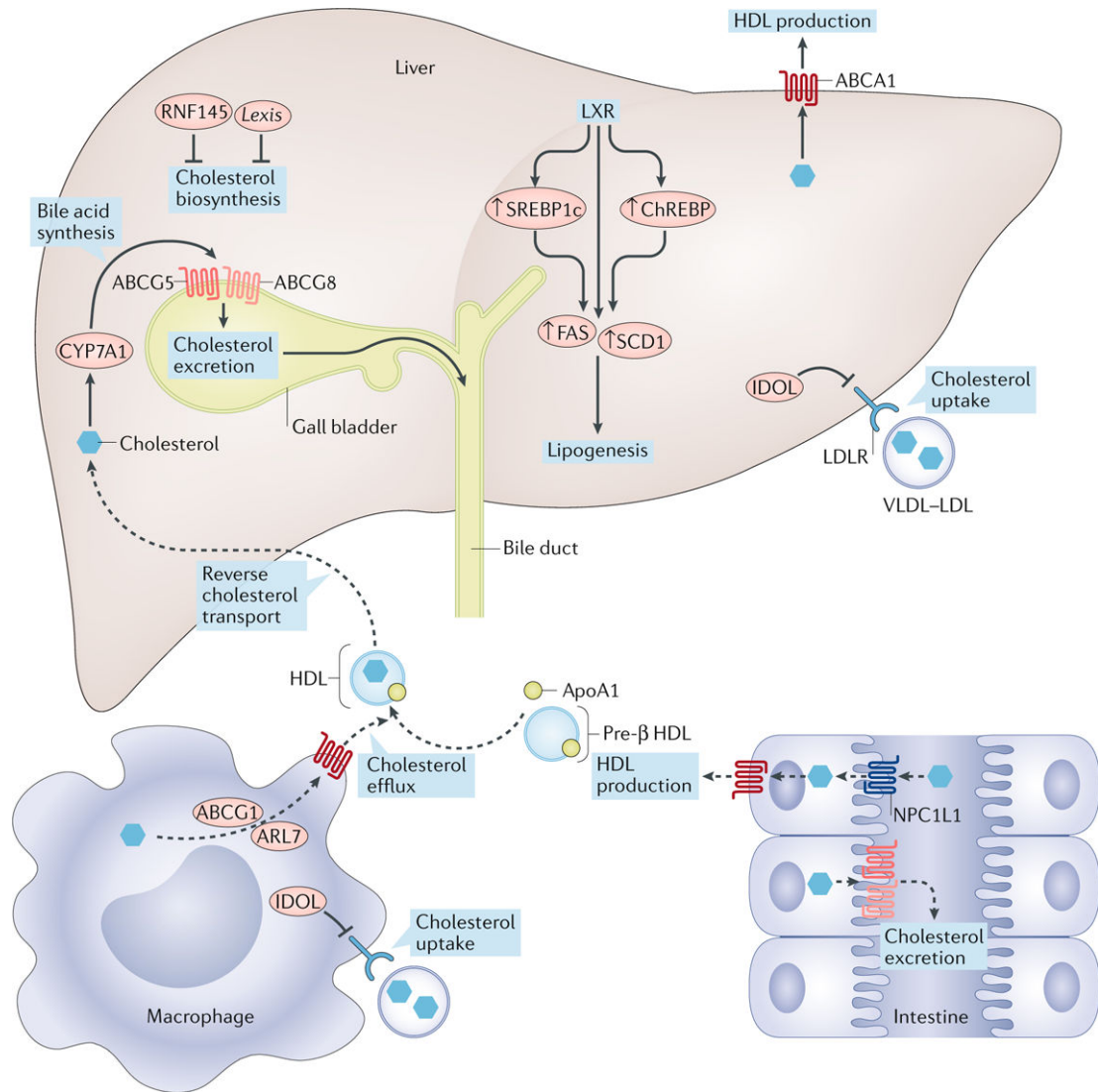
**Key points**

- Liver X receptors (LXRs) are ligand-activated nuclear receptors that modulate lipid homeostasis.
- Cellular and systemic cholesterol homeostasis is maintained by LXRs through the regulation of cholesterol absorption, cellular uptake, excretion, reverse transport and biosynthesis in multiple tissues and cell types.
- LXR activation increases lipogenesis through the control of sterol regulatory element-binding protein 1c and its target genes in liver.
- LXRs modulate membrane phospholipid composition through inducing the expression of lysophosphatidylcholine acyltransferase 3, an enzyme that has important roles in lipid metabolism in liver and intestine.
- The lipogenic activity of hepatic LXR $\alpha$  is a major limitation for the development of LXR agonists as therapeutics for atherosclerosis or Alzheimer disease.
- Further basic and translational research is needed to develop novel strategies for manipulating LXRs and their targets in the setting of metabolic disease.



**Fig. 1 | LXR are lipid-responsive transcription factors.**

Liver X receptors (LXRs) and retinoid X receptors (RXRs) form heterodimers and bind to LXR response elements (LXREs) in the regulatory regions of their target genes. The target regions consist of variations of the repeated sequence AGGTCA, separated by four nucleotides (N). In the absence of ligands, the LXR–RXR complex binds co-repressors and suppresses gene expression. When LXRs are activated by oxysterols or synthetic ligands and/or RXR is activated by its ligands, such as 9-*cis*-retinoic acid, the co-repressors are replaced by co-activators, thereby activating the expression of target genes involved in lipid metabolism. ASC2, activating signal co-integrator 2; EP300, histone acetyltransferase p300; NCoR, nuclear receptor co-repressor; SMRT, silencing mediator of retinoic acid and thyroid hormone receptor.



**Fig. 2 | LXR signalling pathways in cholesterol and fatty acid metabolism.**

Liver X receptor (LXR) activation modulates cholesterol and fatty acid metabolism in a tissue-specific manner. LXR targets are shown in red. In the liver, LXR agonism promotes the conversion of cholesterol into bile acids via cytochrome P450 7A1 (CYP7A1) and biliary cholesterol excretion through ATP-binding cassette subfamily G members 5 and 8 (ABCG5 and ABCG8, respectively). LXR inhibits cholesterol uptake in the liver and macrophages through inducing the expression of inducible degrader of the LDL receptor (IDOL) and the degradation of LDL receptor (LDLR). LXR activation suppresses cholesterol biosynthesis in liver by inducing the transcription of non-coding RNA LXR-induced sequence (*Lexis*) and E3 ubiquitin protein ligase RING finger protein 145 (RNF145). LXR activation promotes fatty acid biosynthesis by inducing the expression of sterol regulatory element-binding protein 1c (SREBP1c), carbohydrate-response element-binding protein (ChREBP) and their targets, fatty acid synthase (FASN) and stearoyl-coenzyme A desaturase 1 (SCD1). In peripheral cells such as macrophages, LXRs increase expression of ATP-binding cassette subfamily A member 1 (ABCA1), ABCG1 and ADP-

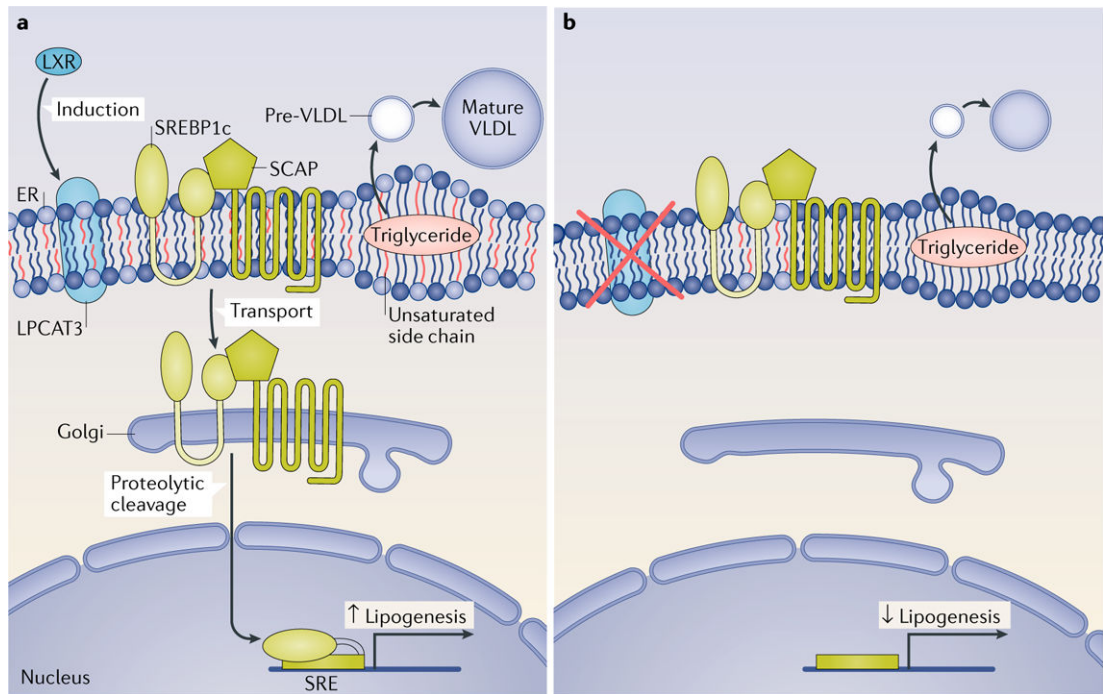
ribosylation factor-like protein 7 (ARL7), thereby promoting cholesterol movement to the plasma membrane and cholesterol efflux to apolipoprotein A1 (ApoA1) or pre- $\beta$  HDL. In the intestine, LXR activation increases HDL formation via basolateral ABCA1 and promotes cholesterol efflux and trans-intestinal cholesterol excretion through ABCG5 and ABCG8. LXR also inhibits cholesterol absorption by indirectly inhibiting Niemann–Pick C1-like protein 1 (NPC1L1). The dashed arrows indicate reduced cholesterol uptake.

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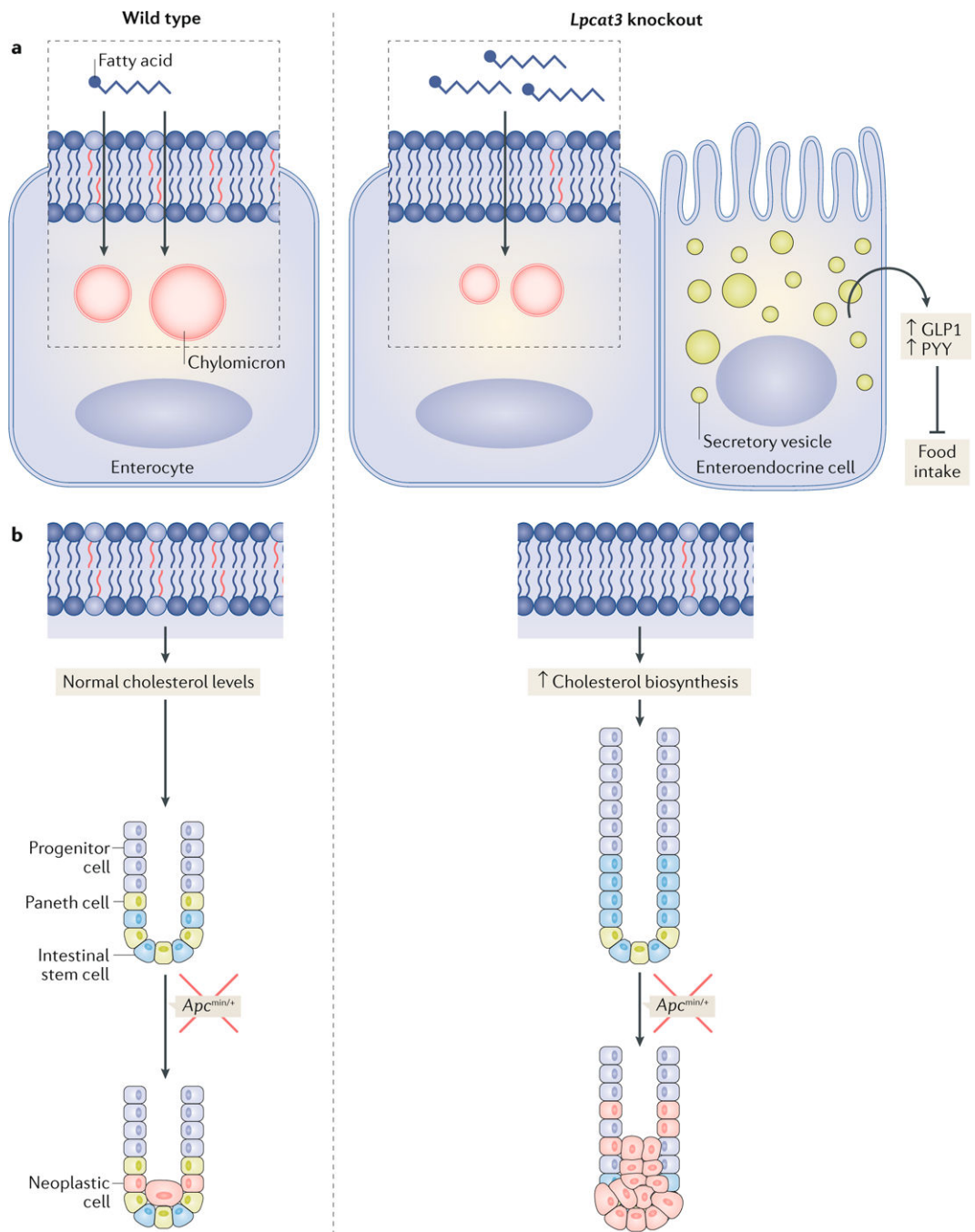
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**Fig. 3 | Roles of LXR-dependent phospholipid remodelling in liver.**

**a** | The effects of liver X receptor (LXR) activation. LXR activation promotes the incorporation of polyunsaturated fatty acids into phospholipids through the induction of lysophosphatidylcholine acyltransferase 3 (LPCAT3) expression. Polyunsaturated phospholipids facilitate sterol regulatory element-binding protein 1c (SREBP1c) transport from the endoplasmic reticulum (ER) to the Golgi and its proteolytic cleavage, thereby promoting lipogenesis. LXR agonists and LPCAT3 activation also promote VLDL secretion. Increased abundance of polyunsaturated phospholipids creates a dynamic membrane environment that facilitates the transfer of triglyceride to nascent apolipoprotein B (ApoB)-containing lipoprotein particles, leading to the efficient lipidation of ApoB-containing lipoproteins. **b** | Consequences of LPCAT3 deficiency. Loss of LPCAT3 expression reduces the composition of polyunsaturated phospholipids in the ER membrane and impairs the translocation of SREBP1c from the ER to the Golgi and its proteolytic cleavage. SCAP, sterol regulatory element-binding protein cleavage-activating protein; SRE, sterol response element.





**Fig. 4 | LPCAT3 and phospholipid remodelling in lipid absorption and intestinal homeostasis.** **a** | Lysophosphatidylcholine acyltransferase 3 (LPCAT3) activity regulates lipid absorption in the small intestine. Loss of LPCAT3 in the intestine reduces polyunsaturated phospholipid content and membrane fluidity, resulting in impaired passive fatty acid transport into enterocytes and chylomicron production. When challenged with a triglyceride-rich diet, LPCAT3-deficient mice produce more gut hormones (glucagon-like peptide 1 (GLP1) or peptide YY (PYY)), leading to the inhibition of food intake. **b** | Loss of LPCAT3 increases membrane saturation and stimulates cholesterol biosynthesis, thereby driving the

proliferation of intestinal stem cells and progenitor cells. Consequently, LPCAT3 deficiency and cholesterol biosynthesis enhance tumour formation in *Apc*<sup>min/+</sup> mice.

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Table 1 |

LXR agonists tested in clinical trials for metabolic diseases

Compound	Activity	Clinical trial	Outcomes	Refs
LXR-623	Partial LXR $\alpha$ -LXR $\beta$ agonist	NCT00366522 (phase I in healthy adults) NCT00385489 (phase I in healthy Japanese adults) NCT00379860 (phase I in healthy adults)	Completed, no results reported Completed, no results reported Terminated owing to central nervous system-related adverse effects	136,147 148 149
CS-8080	Unknown	NCT00613431 (phase I in healthy volunteers)	Completed, no results reported	150
BMS-779788	Unknown	NCT00796575 (phase I in healthy volunteers)	Terminated owing to undisclosed safety concerns	140
BMS-852927	Unknown	NCT01651273 (phase I in patients with hypercholesterolaemia)	Completed, no results reported Terminated owing to increased plasma and hepatic levels of triglyceride, increased plasma levels of LDL cholesterol, ApoB, ApoE and CETP and decreased circulating levels of neutrophils	141 49,151

ApoB, apolipoprotein B; ApoE, apolipoprotein E; CETP, cholesteryl ester transfer protein; LXR, liver X receptor.