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Review

Liver X Receptor: an oxysterol sensor and a major player in the control of lipogenesis

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ABSTRACT

De novo fatty acid biosynthesis is also called lipogenesis. It is a metabolic pathway that provides the cells with fatty acids required for major cellular processes such as energy storage, membrane structures and lipid signaling. In this article we will review the role of the Liver X Receptors (LXRs), nuclear receptors that sense oxysterols, in the transcriptional regulation of genes involved in lipogenesis.

Contents

Abbreviations: ABC, ATP-binding cassette; ACC, acetyl-CoA Carboxylase; ACL, ATP-citrate lyase; AF, transactivation function; AGPAT, 1-acylglycerol-3-phosphate acyltransferases; ASC-2, activating signal cointegrator-2; bHLH/LZ, basic-helix-loop-helix leucine zipper; CEPT1, choline/ethanolaminephosphotransferase 1; CERS, ceramide synthase; CDIPT, CDP-diacylglycerol-inositol 3-phosphatidyltransferase; CH25H, cholesterol 25 hydroxylase; CHPT1, choline phosphotransferase 1; ChoRE, carbohydrate response element; ChREBP, carbohydrate responsive element binding protein; CPT1, carnitine palmitoyl-transferase 1; DAG, diacylglycerol; DBD, DNA binding domain; DGAT, diacylglycerol acyltransferase; DNA, deoxyribonucleic acid; DOS, dioxidosqualene; ELOVL, elongation of very long chain fatty acid; FA, fatty acid; FACE, fatty acyl-CoA elongase; FASN, fatty acid synthase; FoxO, forkhead box-"Other"; FXR, farnesoid X receptor; GK, gluco kinase; GPAT, glycerol-3-phosphate acyltransferase; GSM, glucose sensing domain; GTF, general transcription factor; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDL, high density lipoprotein; HMGCR, 3-hydroxy-3-methylglutaryl CoA reductase; IR, insulin receptor; LBD, ligand binding domain; LCE, long chain fatty acyl elongase; LPA, lysophosphatidic acid; L-PK, liver pyruvate kinase; LXR, Liver X Receptor; LXRE, LXR responsive element; MD, malate dehydrogenase; ME, malic enzyme; MOS, monooxidosqualene; Mlx, Max like protein; NADPH, nicotinamide adenine dinucleotide phosphate; NAFLD, non alcoholic fatty liver disease; NCoR, nuclear receptor corepressor; NR, nuclear receptor; OAA, oxaloacetate; OSC, oxydosqualene cyclase; PC, phosphatityl-choline; PDK, phosphoinositide-dependent kinase; PI3K, phosphatidylinositol 3-kinase; PKB, protein kinase B; PKA, protein kinase A; PP2A, protein phosphatase 2A; PPARα, peroxysome proliferator activated receptor alpha; PUFA, polyunsaturated fatty acid; RIP140, receptor-interacting protein 140; RNA, ribonucleic acid; RXR, Retinoid X Receptor; SCD, stearoyl-CoA desaturase; SE, squalene epoxydase; SHP, short heterodimer partner; SIK2, serine/threonine kinase salt-inducible kinase 2; Sin3, stress-activated MAP kinase interacting protein 3; SIRT1, NAD-dependent deacetylase sirtuin-1; SMRT, silencing mediator of retinoid and thyroid receptors; SPTLC, serine palmitoyltransferase; SRE, sterol response element; SREBP, sterol regulatory element binding protein; SULT2B1, sulfotransferase 2B1; TFIID, transcription factor II D; TG, triacylglycerol; VLDL, very low density lipoproteins; X5P, xylulose-5-phosphate.

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1. Introduction

De novo lipogenesis is a key-process that leads to the synthesis of fatty acids (FAs). A very little amount of FAs remains unesterified as free FAs. Most FAs are used for the synthesis of complex lipids such as phospholipids, ceramides, cholesterol esters or triglycerides and thereby play a major role in membrane structure, cell signaling and energy storage.

The regulation of *de novo* lipogenesis is highly sensitive to hormonal, nutritional, environmental and/or genetic factors. It has been widely investigated in the context of the raising concerns about obesity and associated metabolic diseases such as hepatic steatosis or non alcoholic fatty liver disease (Ferre and Foufelle, 2010; Postic and Girard, 2008).

Since in mammals the liver is the major site for lipogenesis, most of the work reviewed here refers to the described regulation of hepatic fatty acid synthesis. We also examine the evidences for the role of the Liver X Receptors (LXR) as oxysterol sensors and their biological function. Finally, the specific roles of LXRs in the regulation of hepatic lipogenesis is presented.

2. Lipogenesis: *de novo* synthesis of fatty acids

The main enzymes involved in FA biosynthesis are indicated in Fig. 1A. Because lipogenesis is primarily associated with the synthesis of triacylglycerols (TG; Fig. 1B) for fatty acid storage these pathways will extensively described, even though alternative metabolic fate of *de novo* synthesized FAs and some of their role in signaling will also be presented.

2.1. Critical steps in fatty acid biosynthesis

De novo lipogenesis occurs when glucose supply is high. For instance, under fed conditions, higher animals preferentially burn carbohydrates to generate ATP while the excess of carbohydrate is converted into FAs. Therefore, FA synthesis is tightly linked to glucose catabolism (Postic and Girard, 2008). Indeed, the complete oxidation of glucose, also called glycolysis, leads to the synthesis of acetyl-CoA, which subsequently, can enter the citrate cycle in the mitochondria. Thus citrate, an intermediate compound of citrate cycle, is exported from mitochondria. This results in an increase of cytosolic citrate, which can next be converted into acetyl-CoA. This reaction is catalyzed by the ATP-citrate lyase (ACL).

Acetyl-CoA is then carboxylated into malonyl-CoA by the acetyl-CoA carboxylase (ACC) which is the first critical and rate-limiting enzyme in *de novo* FA synthesis. There are two isoforms of ACC: ACC1 and ACC2. ACC1 is cytosolic and mainly expressed in lipogenic tissues such as the liver and the adipose tissue whereas ACC2 is mitochondrial and predominantly expressed in oxidative tissues (Abu-Elheiga et al., 2000). These two isoforms are encoded by two distinct genes (Abu-Elheiga et al., 1995, 1997) and are known to play different roles: ACC1 is involved in *de novo* lipogenesis while ACC2 is rather implicated in the repression of mitochondrial β-oxydation providing the pool of malonyl-CoA which acts as allosteric inhibitor of carnitine palmitoyl-Transferase I (CPT1). During FA synthesis, such production of malonyl-CoA represents an important feedback loop on FA catabolism since CPT1 is involved in the entry of FAs in the mitochondria for oxidation (McGarry and Brown, 1997).

Transgenic mice lacking ACC1 are not viable (Abu-Elheiga et al., 2005). However, the liver-specific deletion of ACC1 leads to a reduction of lipogenesis and triglyceride accumulation without affecting FA oxidation (Mao et al., 2006). ACC2 knockout mice are leaner than wild-type mice, resistant to high fat/high carbohydrate diet induced obesity and more sensitive to insulin. This occurs as a result of an increased FA oxidation in the heart, the skeletal muscle and the liver (Abu-Elheiga et al., 2001, 2003).

Cytosolic malonyl-CoA can be used for FA biosynthesis. This reaction is catalyzed by the fatty acid synthase (FASN) that represents the second enzyme in *de novo* FA synthesis. Its major product is the sixteen carbon saturated FA: palmitic acid (C16:0). FASN uses the malonyl-CoA as a primer, acetyl-CoA as a carbon donor and the NADPH as a reducing equivalent (Chirala and Wakil, 2004). FASN consists of two multifunctional polypeptides forming a homodimeric complex of 260 kDa in the cytoplasm. Each homodimer is composed by three catalytic domains in the N-terminal section (β-ketoacyl synthase (KS), malonyl/acetyltransferase (MAT), and dehydrase (DH)) and are separated by a core region of around 600 residues from four C-terminal domains (enoyl reductase (ER), β-ketoacyl reductase (KR), acyl carrier protein (ACP) and thioesterase (TE)) (Chirala et al., 2001; Smith, 1994). Transgenic mice lacking *Fasn* die *in utero* (Chirala et al., 2003). Liver-specific deletion of *Fasn* does not protect against hepatic FA accumulation. Indeed, when fed a low fat/high cholesterol diet, the *Fasn* liver-specific knockout mice develop a fatty liver, which seems to occur as result of a defect in FA oxidation (Chakravarthy et al., 2005).

2.2. Fatty acid elongation and desaturation

The main product of FASN is palmitic acid (C16:0). It can either be elongated or desaturated. Elongation of FAs involves the addition of two carbons to a fatty acyl-CoA using malonyl-CoA as the carbon donor and NADPH as the reducting agent. Elongation of very long chain fatty acid (ELOVL) proteins are membrane-bound enzymes located in the endoplasmic reticulum. To date, in mammals seven ELOVL proteins (ELOVL1–7) have been identified. ELOVL6 (also known as long chain fatty acyl elongase (LCE) and fatty acyl-CoA elongase (FACE)) catalyzes the conversion of palmitate (C16:0) to stearate (C18:0). It was first discovered as an up-regulated gene in transgenic mice over-expressing the sterol regulatory element binding protein (SREBP)-1c and SREBP-2 (Moon et al., 2001). This discovery has been further confirmed in another study, which identified the gene coding for ELOVL6 as a gene under the control of SREBPs (Matsuzaka et al., 2002). ELOVL6 is expressed in the liver and is thought to catalyze the elongation of palmitic acid (C16:0) and palmitoleic acid (C16:1 n-7, see below) to form stearic acid (C18:0) and vaccenic acid (C18:1 n-7), respectively (Matsuzaka et al., 2002; Moon et al., 2001). It has been reported that ELOVL6 can also catalyze the elongation of FAs consisting of twelve or fourteen carbons (Matsuzaka et al., 2002; Moon et al., 2001). Mice lacking *Elovl6* have been created by Matsuzaka et al. (2007). They show a reduction of the hepatic content in stearic (C18:0) and oleic acid (C18:1 n-9). These mice are resistant to diet-induced insulin resistance. However, they do not show amelioration of obesity or

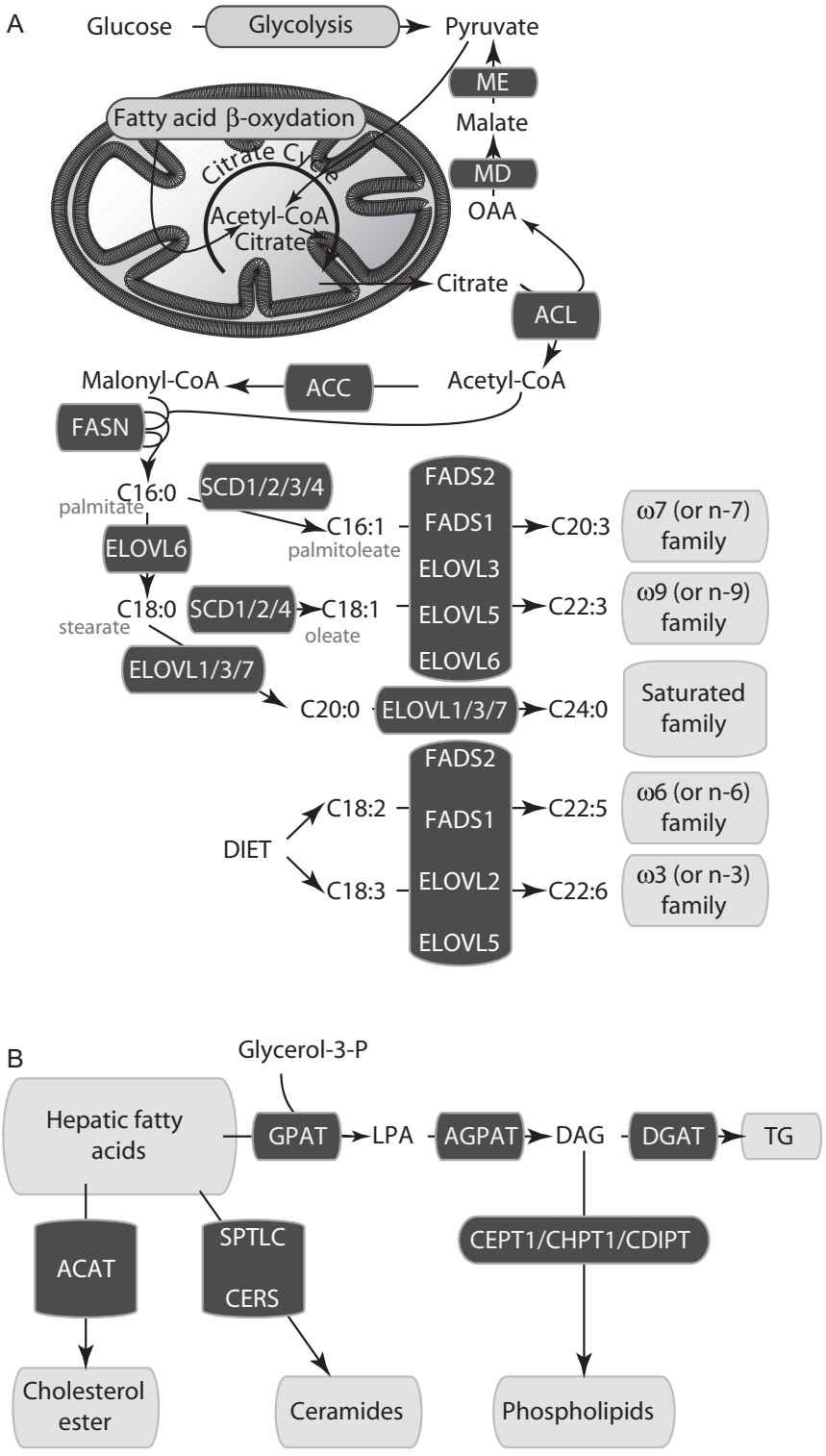

Fig. 1. *De novo* lipogenesis and triglyceride biosynthesis. (A) Acetyl-CoA, the precursor of palmitic acid biosynthesis is provided by the citrate cycle that uses glycolysis and pyruvate oxidative decarboxylation products or fatty acid β-oxidation. Mithochondrial acetyl-CoA is then condensed to form citrate and is exported to the cytosol. ATP citrate lyase (ACL) converts citrate to form oxaloacetate (OAA) and acetyl-CoA which is in turn carboxylated into malonyl-CoA by acetyl-CoA carboxylase (ACC). OAA is transformed into pyruvate through the action of two enzymes: malate dehydrogenase (MD) and malic enzyme (ME). The fatty acid synthase (FASN) leads to the synthesis of palmitate from the condensation of seven malonyl-CoAs. Palmitic acid (C16:0) can then be further elongated by elongation of very long chain fatty acids protein (ELOVL) 6 to form stearate (C18:0) or desaturated by stearoyl-CoA desaturase 1 (SCD1) to form palmitoleate (C16:1 n-7). Stearate can also be desaturated by SCD1 to form oleate (C18:1 n-9). Different of ELOVL and fatty acids (FAs) desaturase (FADS) can elongate and desaturate FAs including essential FAs supplied by the diet, to form the wide variety of FAs in the cell. (B) Triglyceride (TG) biosynthesis is supported by three enzymes Glycerol-3-phosphate acyltransferase (GPAT), 1-acylglycerol-3-phosphate O-acyltransferase (AGPAT) and diacylglycerol acyltransferase (DGAT) that catalyze the esterification of acyl-CoA on the first, second and third carbon of glycerol-3-phosphate respectively. GPAT and AGPAT products are lysophosphatidic acid (LPA) and diacylglycerol (DAG) respectively. FAs can also be incorporated into other complex lipids. Specific incorporation into various lipid classes is driven by rate-limiting enzymes in other pathways. Phospholipids are synthesized from DAG by several enzymes. Choline/ethanolaminephosphotransferase 1 (CEPT1) catalyzes the synthesis of phosphatidylcholine and phosphatidylethanolamine whereas choline phosphotransferase 1 (CHPT1) catalyzes the synthesis of phosphatidylcholine exclusively. CDP-diacylglycerol-inositol 3-phosphatidyltransferase (CDIPT) catalyzes the synthesis of phosphatidylinositol. FAs can also be incorporated into cholesterol by acetyl-CoA acetyltransferase to form a cholesteryl esters. Ceramides are synthesized by the incorporation of two FAs into serine and then sphinganine by serine palmitoyltransferase (SPTLC) and ceramide synthase (CERS) respectively.

hepatosteatosis. They also crossed *Elovl6*−/− mice with ob/ob mice and the pups showed a decreased hyperglycemia and improved insulin resistance compared to ob/ob pups.

Palmitic (C16:0) and stearic (C18:0) acid can then be desaturated by the stearoyl-CoA desaturase 1 (SCD1 also known as Δ9 desaturase) into palmitoleic (C16:1 n-7) and oleic acid (C18:1 n-9), respectively (Ntambi, 1999). The entire coding sequences of the SCD encoding genes as well as their promoter regions have been characterized in different species. Four SCD isoforms have been identified in mice (Kaestner et al., 1989; Miyazaki et al., 2003; Ntambi et al., 1988; Zheng et al., 2001). *Scd1* is expressed in various tissues including the liver and the adipose tissue (Ntambi et al., 1988), *Scd2* is mainly expressed in the brain and neuronal tissues (Kaestner et al., 1989), *Scd3* is specifically expressed in harderian and preputial gland, and in the sebocytes (Zheng et al., 2001). The expression of the mouse *Scd4* appears to be restricted to the heart. In the liver, the ELOVL6 product stearic acid (C18:0) and palmitic acid (C16:0) can be desaturated to form oleic acid (C18:1 n-9) and palmitoleic acid (C16:1 n-7) respectively. These FAs are the major components of membrane phospholipids, triglycerides and cholesteryl esters. This reaction is catalyzed by SCD1. The rat liver SCD1 was the first desaturase purified (Strittmatter et al., 1974). SCD1 is a 40 kDa intrinsic membrane protein anchored in the endoplasmic reticulum. This iron-containing enzyme catalyzes the biosynthesis of monounsaturated FAs that requires acyl-CoA, NADH, NADH reductase, cytochrome b5, phospholipid, and oxygen. Global (Ntambi et al., 2002) and liver-specific (Miyazaki et al., 2007) *Scd1* knockout mice have been generated by Ntambi's group. Global Scd1 knockout mice are lean and show a defect in the synthesis of lipids including triglycerides. They are protected from diet-induced obesity and insulin resistance (Ntambi et al., 2002) and from obesity induced by leptin deficiency (Cohen et al., 2002). A decrease in lipogenesis combined with an increase in FA oxidation are reported to mediate the protective effects of SCD1 deficiency (Cohen et al., 2002; Dobrzyn et al., 2004; Ntambi et al., 2002). Study of the mice lacking *Scd1* in the liver shows that this enzymes protects from obesity and steatosis induced by a high carbohydrate/very low fat diet (Miyazaki et al., 2007).

2.3. Triglyceride biosynthesis

Long chain acyl-CoA produced by *de novo* lipogenesis can be esterified on glycerol in order to form glycerolipids (Fig. 1B). Three steps lead to the incorporation of three acyl-CoAs on glycerol-3-phosphate. The first esterification is catalyzed by glycerol-3-phosphate acyltransferase (GPAT) and consists in the esterification of an acyl-CoA on the first carbon of glycerol-3-phosphate to form lysophosphatidic acid (LPA), which in turn can be transformed either in phospholipid or in triglyceride. Four GPATs belonging to the same family of acyltransferase have been described and encoded by four different genes (Cao et al., 2006; Chen et al., 2008; Ganesh Bhat et al., 1999; Harada et al., 2007; Nagle et al., 2008; Wang et al., 2007). GPAT1 and GPAT2 are located in the outer membrane of the mitochondria (Lewin et al., 2004) whereas GPAT3 and GPAT4 are located in the endoplasmic reticulum (Gimeno and Cao, 2008). Unlike GPAT2 and GPAT3, GPAT1 and GPAT4 are highly expressed in the liver. GPAT1 plays an important role in triglyceride biosynthesis as illustrated by the decreased liver TGs and VLDL secretion as well as plasma TGs in mice lacking (Hammond et al., 2002; Hammond et al., 2005). These mice are also resistant to obesity and insulin resistance induced by high-fat diet (Neschen et al., 2005). They also show a 40% and 30% decrease in hepatic palmitic acid in triglycerides and phospholipids respectively (Hammond et al., 2002). This highlights the preference of GPAT1 for palmitate esterification at the sn-1 position of glycerol-3-phosphate. It has also been reported that *Gpat1* knock-down in Ob/Ob mice results in the diminution of hepatic triacylglycerol and diacylglycerol as well as plasma glycemia (Xu et al., 2006). *Gpat4* knockout mice are also protected from high fat/high carbohydrate diet-induced obesity and from obesity induced by leptin deficiency (Vergnes et al., 2006). It seems that GPAT4 is less specific than GPAT1 and that it is able to esterify both saturated and unsaturated FAs into glycerol 3-phosphate to produce lysophosphatidic acid (Chen et al., 2008).

The next step consists in the esterification of another acyl-CoA on the sn-2 position of the LPA glycerol backbone in order to form phosphatidic acid (PA). This reaction is catalyzed by 1-acylglycerol-3-phosphate acyltransferases (AGPATs) proteins. To date, there are ten proteins with suspected AGPAT activity (AGPAT1–10) (Agarwal et al., 2006, 2007; Leung, 2001; Li et al., 2003; Sukumaran et al., 2009; Tang et al., 2006; Ye et al., 2005). However, only AGPAT1 and AGPAT2 have a clearly demonstrated enzyme activity (Leung, 2001). Furthermore, it seems that AGPAT2 is the isoform involved in acylation of LPA in the formation of TG. First, AGPAT2 has the strongest activity in *in vitro* assays when compared to AGPAT3-5,9 (Agarwal et al., 2007; Lu et al., 2005). Second, 80% of transgenic pups lacking *Agpat2* die after three weeks of age (Cortes et al., 2009), confirming that AGPAT2 plays a crucial role and cannot be substituted by other AGPATs. The other *Agpat* mRNA levels were measured and only slight increases were observed in mice lacking *Agpat2*. Total AGPAT enzymatic activity was reduced by 90% in the liver of these mice, confirming that AGPAT2 is responsible for the majority of the activity in the liver (Cortes et al., 2009). Finally, the preferential acyl-CoA incorporated in LPA by AGPAT2 is oleyl-CoA (C18:1 n-9). Several other acyl donors are incorporated including C14:0, C16:0, and C18:2 acyl-CoAs, with lower incorporation of C18:0 and C20:4 acyl-CoAs (Eberhardt et al., 1997; Hollenback et al., 2006). This is in accordance with TG composition in which sn-2 position is mainly composed of monoenoic and dienoic acyl groups rather than polyenoic acyl group generally enriched in sn-2 position of phospholipids (Glosset, 1996).

In order to form a triglyceride by esterifying another acyl-CoA on the sn-3 of PA, this one has to be dephosphorylated. This dephosphorylation is catalyzed by a family of proteins called phosphatidate phosphatase-1 enzymes (also known as LIPIN). Three enzymes belong to this family: LIPIN1, LIPIN2 and LIPIN3 (Carman and Han, 2009).

The last step in the triglyceride synthesis is catalyzed by the diacylglycerol acyltransferase (DGAT). To date, two enzymes sharing a DGAT activity have been discovered: DGAT1 and DGAT2 (Coleman and Lee, 2004). These two proteins are encoded by separate genes (Cases et al., 1998, 2001; Lardizabal et al., 2001; Oelkers et al., 1998). Under basal condition DGAT2 localizes in the endoplasmic reticulum. When oleic acid is provided DGAT2 localizes near the surface of lipid droplets where it co-localizes with mitochondria (Stone et al., 2009). DGAT1 is located in the endoplasmic reticulum (Cao et al., 2007), but it has also been reported that it also co-localizes with lipid droplets in *S. cerevisiae* (Sorger and Daum, 2002). Overexpression of either *Dgat1* or *Dgat2* leads to increased amounts of TGs in transfected cells. In cells over-expressing *Dgat1* the TG accumulation occurs as small lipid droplets around the cell periphery whereas in *Dgat2* transfected cells TGs are located in large cytosolic lipids droplets (Stone et al., 2004). DGAT1 and DGAT2 are both expressed in a wide variety of tissues including the liver (Cases et al., 1998, 2001). DGAT2 seems to have a greater activity than DGAT1 as over-expression of *Dgat2* leads to more important TG accumulation than in *Dgat1* over-expressing cells (Stone et al., 2004). Furthermore, transgenic mice lacking *Dgat2* present a lethal neonatal lipopenia not compensated by the presence of DGAT1. Transgenic mice lacking *Dgat1* are viable but present a reduction in adiposity and a resistance to high fat diet-induced obesity (Smith et al., 2000).

2.4. Lipogenesis and fatty acid signaling

As opposed to essential FAs of the n-6 and n-3 series, FAs synthesized through *de novo* lipogenesis are saturated or unsaturated FAs of the n-7 and n-9 series. Through a combination of elongation and desaturation mammalian cells can synthesize a wide number of FAs (Guillou et al., 2010). Depending on chain length and unsaturation, these fatty acids may become substrates for enzymes catalyzing the incorporation of acyl chains into more complex lipids (Fig. 1B). The selective acyl-chain incorporation into various lipid classes has been known for a long time. The development of new methods in the field of lipid biochemistry (Brown and Murphy, 2009; Clark et al., 2011; Ivanova et al., 2009; Shevchenko and Simons, 2010) brings further insights into the analysis of specific lipids and allows to raise novel and major questions as to how this occurs and how the acyl chains may influence signaling (Chakravarthy et al., 2009; Clark et al., 2011).

In the recent years, original approaches based on the development of various transgenic mouse models, on cutting-edge lipidomic analysis and systems biology have led to the proposal that key-lipogenic enzymes not only provide fatty acid for storage as TGs but intermediate metabolic signals. This is consistent with the different phenotypes observed in mouse models lacking the various enzymes required for TG synthesis. Exploiting this signaling pathway represents the concept of "Lipoexpediency" that introduces possible lipogenic signals as involved in protecting the organism against deleterious effects of acute lipogenesis itself (Lodhi et al., 2011). Lipoexpediency in whole body homeostasis has been extensively discussed (Lodhi et al., 2011). Here, we focus on lipoexpediency occurring in the liver.

Free palmitoleic acid (C16:1 n-7) has been identified as a "lipokine" reported to have beneficial effects on insulin resistance. It has been reported that increased amounts of this lipokine were correlated with insulin sensitivity (Cao et al., 2008). Transgenic mice lacking *Elovl6* are protected against diet-induced insulin resistance without any amelioration of obesity or hepatosteatosis (Matsuzaka et al., 2007). This resistance was attributed to improved insulin signaling, a benefic effect suggested to be correlated with palmitoleic acid availability (Matsuzaka et al., 2007).

As detailed previously, transgenic mice lacking *Fasn* in the liver are not protected from lipid accumulation when fed a low fat/high carbohydrate diet. These mice also showed a decrease in peroxysome proliferator activated receptor alpha (PPARα) target genes expression and a phenotype similar to those observed with the transgenic mice lacking *Pparα* (Chakravarthy et al., 2005), a nuclear receptor that is a master regulator of genes involved in FA oxidation. Chakravarthy et al. (2009) demonstrated that phosphatityl-choline (PC) containing palmitic acid (C16:0) and oleic acid (C18:1 n-9), two fatty acids derived from FASN activity, is a relevant ligand for PPARα. Therefore, *de novo* lipogenesis produces an endogenous ligand that binds to and activates PPARα thereby preventing fat accumulation through the induction of FA oxidation.

While we have focused on hepatic FA synthesis and liver-related phenotype of transgenic mice, it should be stated here that lipogenesis occurs to a lower extent in various tissues. Moreover, it is not only a critical event in energy storage and signaling in the context of metabolic related diseases. It is also clear that FA metabolism is critical for many other cellular functions.

3. Oxysterols as ligands for LXRs

3.1. LXRs, class II nuclear receptors

The Liver X Receptors are transcription factors which belong to the nuclear receptor (NR) superfamily, which comprises 49 members in mouse and 48 in human. There are two isoforms of LXR: LXRα (NR1H3) and LXRβ (NR1H2). Both have been discovered in 1995 (Teboul et al., 1995; Willy et al., 1995). They are class II NRs and form obligate heterodimer with Retinoid X Receptors (RXRs) the receptors for 9-*cis* retinoic acid (Repa and Mangelsdorf, 2000). The heterodimer LXR/RXR binds to the DNA (Fig. 2), on LXR responsive element (LXRE) composed by two direct repeat of the consensus sequence (AGGTCA) separated by four nucleotides (DR4). While LXRα is highly expressed in liver, intestine, kidney, and adipose tissue, LXRβ expression is expressed in many tissues (Auboeuf et al., 1997; Repa and Mangelsdorf, 2000).

As other nuclear receptors, LXRs are organized in different functional domains. The poorly conserved amino-terminal domain (A/B) contains a ligand independent transactivation function (AF-1), which stimulates a basal transcription even in the absence of a ligand. The central domain or DNA binding domain (DBD) is highly conserved and contains two zinc finger motifs, which interact with DR4 binding sites in the promoter of target genes. And finally, LXR contains a well-conserved carboxy terminal ligand binding domain (LBD) that exhibits a ligand-dependent transactivation function (AF-2). Upon ligand binding, the LBD interacts with different coregulators (for a review see Viennois et al., 2011).

In the absence of the ligand LXR/RXR binds to the DNA in the promoter of target genes and interacts with corepressors such as nuclear receptor co-repressor (NCoR) or silencing mediator of retinoid and thyroid receptors (SMRT) (Hu et al., 2003). Corepressors recruit proteins with histone deacetylases activity (HDACs), recruited through the interaction with the stress-activated MAP kinase interacting protein 3 (Sin3) (Jones et al., 2001). The DNA environment is then in a non-transcription permissive state and the transcription machinery cannot interact with the initiation site of transcription. Upon ligand binding to the LBD there is a modification in the conformation of LXR (Glass and Rosenfeld, 2000) which leads to the release of co-repressors (Hu et al., 2003) and the recruitment of co-activators such as activating signal cointegrator-2 (ASC-2) (Lee et al., 2008) or receptor-interacting protein 140 (RIP140) (Herzog et al., 2007) on the helix 12 of the LBD (Svensson et al., 2003). The histones are then acylated, the chromatin gets in a transcription-permissive state and the transcription machinery can be recruited and initiate transcription. Upon binding to a response element, LXR becomes acylated. It has been shown (Li et al., 2007b) that after the transcription of the target gene has occurred, LXR is deacetylated by NAD-dependent deacetylase sirtuin-1 (SIRT1), which leads to the ubiquitination of LXR and its degradation by the proteasome. This action of SIRT1 improves the turnover of LXR through activation/degradation cycle and enhances LXR activity (Li et al., 2007b).

LXRs have first been considered as orphan receptors because their natural ligands were unknown. However, Mangelsdorf's group first showed that oxidative derivatives of cholesterol, the oxysterols, induce LXRα activity in a gene reporter system (Janowski et al., 1996).

3.2. Origins and synthesis of oxysterols

Oxysterols have been first discovered in 1913 by Lifschutz (1913) as autoxidation products of cholesterol. These compounds have early been described as modulators of cholesterol metabolism through their influence on the sequestration of SREBPs in the endoplasmic reticulum thereby limiting the expression of genes involved in cholesterol synthesis (see for review Brown and Jessup, 2009). They also directly regulate the degradation of 3-hydroxy-3-methylglutaryl CoA reductase (HMGCR), the rate-limiting enzyme in cholesterol synthesis (Brown and Jessup, 2009). Oxysterols are also activators of LXR (Janowski et al., 1996; Lehmann et al., 1997). Many different oxysterols are known, they all share a choles-

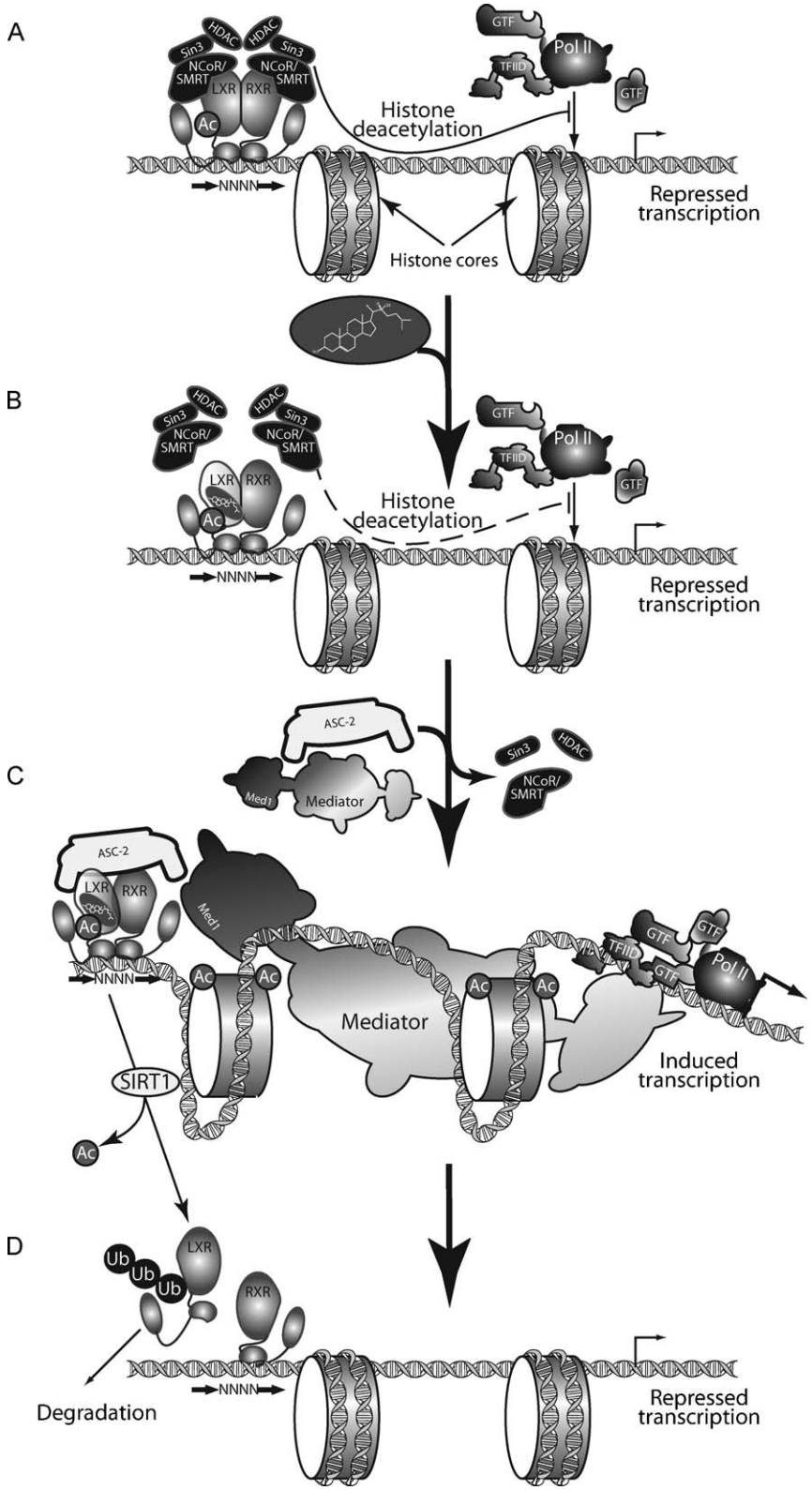

Fig. 2. Schematic representation of LXR activation. (A) In the absence of ligand, the Liver X Receptor (LXR)/Retinoid X Receptor (RXR) heterodimer is bound to a DR4 response element on the promoter of target genes. Co-repressors: nuclear receptor co-repressor (NCoR) or Silencing Mediator of Retinoid and Thyroid Receptors (SMRT), stress-activated MAP kinase interacting protein 3 (Sin3) and histone deacetylases (HDAC) are bound to the LXR/RXR heterodimer and keep the DNA in a non transcription-permissive state. (B) Upon binding of an agonist (for instance 22(R)-hydroxycholesterol) on the ligand binding domain (LBD) of LXR, there is a conformational change which leads to the departure of the co-repressors and recruitment of co-activators such as activating signal cointegrator-2 (ASC-2). (C) At the same time, several mechanisms including histone modifications and chromatin remodeling, allow RNA polymerase II and the transcriptional machinery including general transcription factor (GTF), transcription factor II D (TFIID), and the mediator complex, to increase the transcription of the target gene. (D) Next, NAD-dependent deacetylase sirtuin-1 (SIRT1) deacetylates LXR which leads to its ubiquitination and degradation by the proteasome. This mechanism seems to be important to start another transcription cycle of the target gene.

terol structure with an oxygen-containing functional group such as hydroxyl, keto or epoxyde group (for a review see Schroepfer, 2000). The oxygen-containing functional group can be added at the sterol ring or at the side chain of cholesterol. Oxysterols can be derived from non-enzymatic or from enzymatic oxidation of cholesterol or both.

There is a huge variety of oxysterols. Their origin has been reviewed by various authors (Brown and Jessup, 2009; Gill et al., 2008; Russell, 2000; Schroepfer, 2000). In addition, the specific impact of individual oxysterols on LXR may highly depend on genes and tissues. For instance, 5α,6α-epoxycholesterol was recently shown to exert both agonist or antagonist activities depending on LXR target genes and on cellular context (Berrodin et al., 2010). In the present manuscript we chose to focus on the formation of some oxysterols that have been described to occur through enzymatic pathways (Fig. 3). These oxysterols are 20(S)-hydroxycholesterol (Janowski et al., 1996), 22(R)-hydroxycholesterol (Janowski et al., 1996), 24(S)-hydroxycholesterol (Janowski et al., 1996; Lehmann et al., 1997), 25-hydroxycholesterol (Janowski et al., 1996), 27-hydroxycholesterol (Fu et al., 2001; Janowski et al., 1996) and 24(S),25 epoxycholesterol (Lehmann et al., 1997; Svensson et al., 2003) which are generally thought to be physiologically relevant LXR agonists in lipogenic tissues.

3.3. Biosynthesis of hydroxycholesterols

The formation of hydroxycholesterol is catalyzed by several enzymes (Fig. 3). CYP46A1 is a microsomal enzyme which catalyzes the reaction leading to the synthesis of 24(S)-hydroxycholesterol. This oxysterol is also called cerebrosol as it is found in large amounts in the brain (Bjorkhem, 2007). 27-Hydroxycholesterol is an intermediate in bile acid synthesis, it is produced by the mitochondrial enzyme CYP27A1 and it is the main oxysterol found in the circulation. Cholesterol 25 hydroxylase (CH25H) synthesizes the 25-hydroxycholesterol. Unlike other enzymes involved in oxysterol synthesis, which are cytochrome P450 members, CH25H is a di-iron enzyme located in the ER and the Golgi and found at low levels in most tissue (Russell, 2000). However, this oxysterol has also been

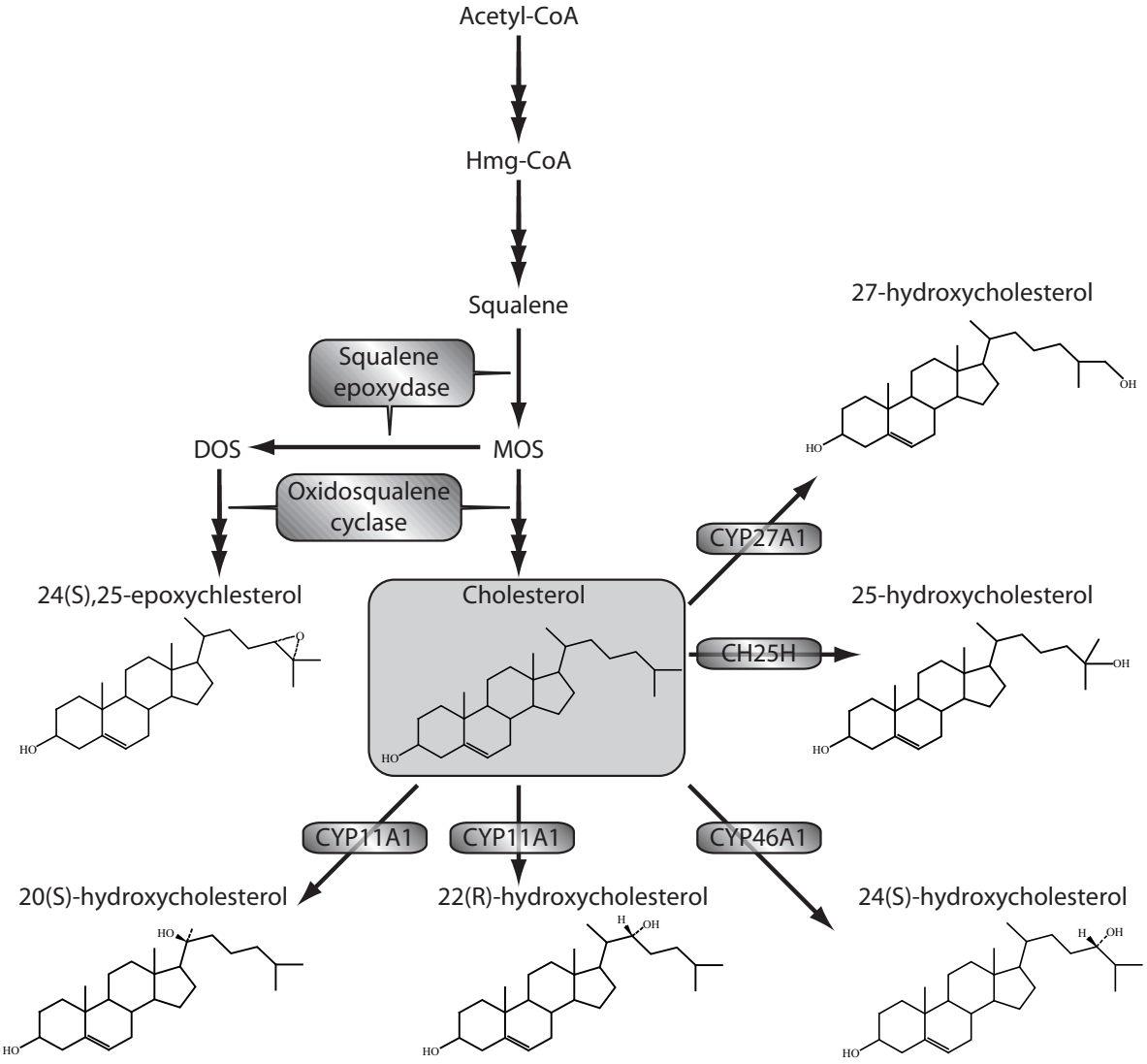

Fig. 3. Synthesis and structures of oxysterols with LXR agonist activity. 20(S)-hydroxycholesterol, 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, 25-hydroxycholesterol and 27-hydroxycholesterol are synthesized from cholesterol. Hydroxy groups are branched in different parts of the side chain of the cholesterol. The reactions that lead to their synthesis are catalyzed by CYP11A1 for both 20(S)-hydroxycholesterol and 22(R)-hydroxycholesterol and CYP46A1, CH25H and CYP27A1 for 24(S)-hydroxycholesterol, 25-hydroxycholesterol and 27-hydroxycholesterol respectively. 24(S),25-epoxycholesterol is synthesized in a "shunt pathway" which parallels and shares the same enzymes as the mevalonate pathway. Two enzymes are involved and control this pathway. Squalene epoxydase (SE) synthesizes monooxidosqualene (MOS) and dioxidosqualene (DOS). Oxydosqualene cyclase (OSC) catalyzes the first reaction of the pathway leading to the formation of cholesterol and 24(S),25-epoxycholesterol from MOS and DOS respectively. 24(S),25-epoxycholesterol have the same structure as cholesterol with an epoxy group branched on the carbons 24 and 25 of the side chain.

reported to appear through a non-enzymatic reaction (Smith, 1987) and through the activity of CYP3A (Honda et al., 2011). Finally, CYP11A1 catalyzes the formation of both 20(S)-hydroxycholesterol and 22(R)-hydroxycholesterol (Gill et al., 2008). However, these two compounds are intermediates in steroidogenesis and their synthesis mainly occurs in the adrenals (Gill et al., 2008).

Hydroxycholesterols have been reported in the mid 90s to activate LXR activity using gene reporter assays *in vitro*, for LXRα (Janowski et al., 1996) and for both isoforms (Lehmann et al., 1997). In 2007, Chen et al. (2007) brought another strong evidence *in vivo* for the activation of LXR by oxysterols. They showed that overexpression of the sulfotransferase SULT2B1 leads to an impaired LXR signaling both *in vitro* and *in vivo*. They also observed an impaired LXR activity in *Cyp46a1*, *Ch25h* and *Cyp27a1* triple knockout mice (Chen et al., 2007) demonstrating *in vivo* the role of oxysterols in the activation of LXRs. However, the expression of *Srebp-1c*, a LXR target gene, was still elevated in response to cholesterol feeding suggesting the presence of other endogenous ligands not synthesized by the deleted genes. Several studies showed that sulfated 25-hydroxycholesterol, the 25-hydroxycholesterol-3-sulfate is not only an inactivated oxysterol but has potent LXR antagonistic properties. Providing 25-hydroxycholesterol-3-sulfate to cell culture or over-expressing SULT2B1, the enzyme involved in generating 25-hydroxycholesterol-3-sulfate (Li et al., 2007a), leads to a decrease of LXR activity (Bai et al., 2010; Xu et al., 2010). Other sulfated oxysterols such as 5α,6α-epoxycholesterol-3-sulfates and 7-ketocholesterol-3sulfates are antagonistic ligands of Liver X Receptors (Song et al., 2001).

3.4. The mevalonate shunt pathway: another source of LXR ligands

24(S),25-epoxycholesterol is another activating ligand for LXRs. It has been discovered in 1981 by Nelson et al. (1981). As other oxysterols, 24(S),25-epoxycholesterol has the capacity to decrease cholesterol synthesis by reducing the activity of HMGCR (Dollis and Schuber, 1994; Saucier et al., 1985; Taylor et al., 1986), inducing its degradation (Song and DeBose-Boyd, 2004) as well as limiting the processing of SREBP-2 (Janowski et al., 2001; Wong et al., 2006) a transcription factor involved in cholesterol synthesis. Unlike previously mentioned hydroxycholesterols, 24(S),25-epoxycholesterol is not a cholesterol-derived oxysterol. Its established enzymatic biosynthesis occurs as a shunt in the mevalonate pathway which parallels the cholesterol biosynthesis pathway (Fig. 3). Therefore, 24(S),25-epoxycholesterol biosynthesis is under the same feedback control as cholesterol synthesis (Wong et al., 2007). This shunt pathway starts with the monooxidosqualene (MOS) which can be transformed into dioxidosqualene (DOS) by the squalene epoxydase (SE), also known as the squalene monooxygenase (SM). Remarkably, the degradation of this enzyme has very recently been reported to be under a proteasomal control regulated by cholesterol (Gill et al., 2011). The oxydosqualene cyclase (OSC) can then convert the cholesterol precursor, the MOS, and the 24(S),25-epoxycholesterol precursor, the DOS, into lanosterol and 24(S),25-epoxylanosterol respectively (Nelson et al., 1981). These two compounds are then transformed through several reactions to form either cholesterol or 24(S),25-epoxycholesterol (Panini et al., 1986). The enzymes involved in these reactions are shared by the two pathways. Several studies showed that this oxysterol activates LXR (Janowski et al., 1999; Lehmann et al., 1997). However, these studies relied on the addition of 24(S),25-epoxycholesterol to *in vitro* systems and cell culture. Later several approaches have also been used to modulate the amounts of endogenously produced 24(S),25-epoxycholesterol. Some of these approaches are based on the fact that OSC has a better affinity for DOS than for MOS (Boutaud et al., 1992). Statins, molecules used in therapy in order to decrease hypercholesterolemia and related cardiovascular diseases, are inhibitors of HMGCR an enzyme catalyzing the formation of mevalonate. Treatment of THP-1 macrophages with statins leads to the decreased synthesis of both 24(S),25-epoxycholesterol and cholesterol as well as the decrease of two typical LXR target genes: ABCA1 and ABCG1 (Wong et al., 2004). This impaired LXR response is rescued by adding exogenous 24(S),25-epoxycholesterol. These effects of statins seem to depend on the presence of cholesterol in the cells, since supplementing cells with cholesterol reverses the statin-mediated effects on LXR activity whereas depleting cellular cholesterol tends to strengthen the effect of statins (Wong et al., 2008b). Statins have also been used as a pretreatment in order to induce a burst on mevalonate pathway. This pretreatment on Chinese hamster ovary (CHO-7) cells leads to an increase of cholesterol synthesis paralleled with an increase of 24(S),25-epoxycholesterol synthesis and LXR signaling (Wong et al., 2008a). In both cases, increased or decreased mevalonate pathway flow, the 24(S),25-epoxycholesterol synthesis and cholesterol synthesis seem to parallel each other. The 24(S),25-epoxycholesterol appears as a compound that protects the cell against endogenous cholesterol (Wong et al., 2007). Other studies investigated the possibility of uncoupling 24(S),25-epoxycholesterol and cholesterol pathway to better elucidate the role of 24(S),25-epoxycholesterol. Because OSC shows a better affinity for DOS than for MOS, incomplete inhibition of this enzyme explains why the squalene epoxyde can be channeled into 24(S),25-epoxycholesterol pathways (Morand et al., 1997). Using partial inhibition of OSC allows to uncouple 24(S),25-epoxycholesterol synthesis from cholesterol synthesis as the MOS synthesized by SE accumulates and can be catalyzed once again by SE to form DOS. DOS will then be transformed into 24(S),25-epoxycholesterol. Indeed, OSC inhibitors was shown to induce a decrease of cholesterol synthesis as well as an increase of 24(S),25-epoxycholesterol synthesis and up-regulation of LXR activity in THP-1 human macrophages (Beyea et al., 2007; Wong et al., 2004), murine macrophage cell line (Wong et al., 2004) HepG2 (Morand et al., 1997), CHO-7 (Wong et al., 2008a). In 2007, Wong et al. (2008a) used another approach that evidenced the role of endogenous 24(S),25-epoxycholesterol. As a partial inhibition of OSC leads to increased synthesis of 24(S),25-epoxycholesterol, they overexpressed the gene coding for human OSC in CHO-7 cells. These cells are depleted from 24(S),25-epoxycholesterol and showed a decreased in LXR activity when compared to control cells. Interestingly, on the basis of experiments performed with statins in rat hepatoma cells it was also shown that a tonic activation of LXR by an oxysterol intermediate in the biosynthesis of cholesterol was required for the transcription of SREBP1c (DeBose-Boyd et al., 2001). All of these studies support the notion that cholesterol biosynthesis through its effect on 24(S),25-epoxycholesterol may influence LXR activity.

3.5. Roles of LXR in vivo

With the identification of oxysterols as physiological ligands of LXRs the possible role for these receptors in cholesterol metabolism was suspected. Transgenic mice lacking LXRα (Peet et al., 1998), LXRβ (Repa et al., 2000a) or both (Repa et al., 2000a) have been created thereby providing great tools to better understand the importance and significance of individual LXR isoforms *in vivo*. Evidences from the first studies with mice lacking LXRs supported the hypothesis that LXRs are involved in the regulation of cholesterol disposal making it an attractive drug target for the treatment of cholesterol related diseases. Synthetic high affinity compounds capable of activating LXRs have been developed. T0901317 (Schultz et al., 2000) and the GW3965 (Collins et al., 2002) are the most frequently used compounds to target LXR in research. Unlike GW3965, TO901317 is not strictly selective for LXR (Houck et al., 2004; Mitro

et al., 2007; Shenoy et al., 2004) (for a review on the LXR-ligand see Viennois et al., 2011). When administered *in vivo*, these synthetic ligands regulate a set of genes involved in reverse cholesterol transport from peripheral tissues to the liver (Costet et al., 2000; Kennedy et al., 2001; Repa et al., 2000b). LXRs are also involved in the regulation of genes involved in cholesterol (Peet et al., 1998; Schultz et al., 2000), bile acid (Chiang et al., 2001; Peet et al., 1998) and steroid synthesis (Cummins et al., 2006; Mouzat et al., 2009; Robertson et al., 2005; Volle et al., 2007). However, LXRs are not only involved in the control of whole-body sterol homeostasis. They have been shown to be central receptors in the integration of both metabolic and inflammatory signaling (reviewed in Zelcer and Tontonoz, 2006). The studies performed with transgenic mice have also allowed to evidence that LXRs are particularly important in atherosclerosis (Calkin and Tontonoz, 2010; Lo Sasso et al., 2010b), thrombosis (Spyridon et al., 2011) macrophage signaling (A-Gonzalez et al., 2009; Hong et al., 2011), but also in immunity (Bensinger et al., 2008; Cui et al., 2011; Villablanca et al., 2010; Zelcer and Tontonoz, 2006), reproduction (El-Hajjaji et al., 2011; Viennois et al., 2011), cell proliferation (Bensinger et al., 2008; Lo Sasso et al., 2010a), cancer (Pommier et al., 2010; Villablanca et al., 2010), Alzheimer's disease (Adighibe et al., 2006; Infante et al., 2010; Koldamova et al., 2005; Zelcer et al., 2007), and skin biology (Hanley et al., 2000; Jiang et al., 2006; Komuves et al., 2002). All the findings listed above have made LXRs major drug targets (Viennois et al., 2011). But the role of LXR in the regulation of fatty acid synthesis prevents the use of current LXR synthetic agonists as therapeutic agents. However, one group has reported the beneficial effect of a phytosterol-derived LXR agonist on plasma cholesterol without hypertryglyceridemic effect (Kaneko et al., 2003). In addition, a recent report has evidenced the tissue specific activation of LXR that promotes macrophage reverse cholesterol transport *in vivo* (Yasuda et al., 2010).

4. The major role of LXR in liver lipogenesis

Early studies showed that the use of T0901317 *in vivo* leads to a massive hepatic steatosis and increased triglycerides enriched very low density lipoproteins (VLDLs) secretion (Grefhorst et al., 2002). Moreover, transgenic mice lacking LXRα showed decreased expression of genes involved in lipogenesis (*Srebp-1c*, *Fasn*, *Scd1*) (Peet et al., 1998). Therefore, LXR has early been suspected to be a major regulator of FA synthesis. A better understanding of the role of LXR in the control of hepatic lipogenesis is a major issue as increased FA synthesis has been shown to contribute to the progression of non alcoholic fatty liver disease (NAFLD) (Donnelly et al., 2005).

4.1. LXR a master regulator of lipogenesis

LXRs appear to be direct regulators of the expression of critical genes involved in lipogenesis in the liver. However, it must be said that a recent report highlight tissue-specific effect of LXR on lipogenesis (Korach-Andre et al., 2011). The work referred to in the following paragraphs mainly relate on the pro-lipogenic effect of LXR action in the liver.

LXRE have been described on the promoter of *Fasn* (Joseph et al., 2002), *Acc* (Talukdar and Hillgartner, 2006) and *Scd1* (Chu et al., 2006). LXRβ seems to play a weaker role in lipogenesis than LXRα since transgenic mice lacking LXRα but not LXRβ show reduced lipogenic genes expression pattern when compared to the wild-type mice fed a high cholesterol diet (Repa et al., 2000a). It has also been shown that LXRs control the expression of two transcription factors involved in lipogenesis: SREBP-1c (Repa et al., 2000a) and the carbohydrate responsive element binding protein (ChREBP) (Cha and Repa, 2007). Therefore LXRs play both a direct and an indirect role in the regulation of lipogenesis (Fig. 4).

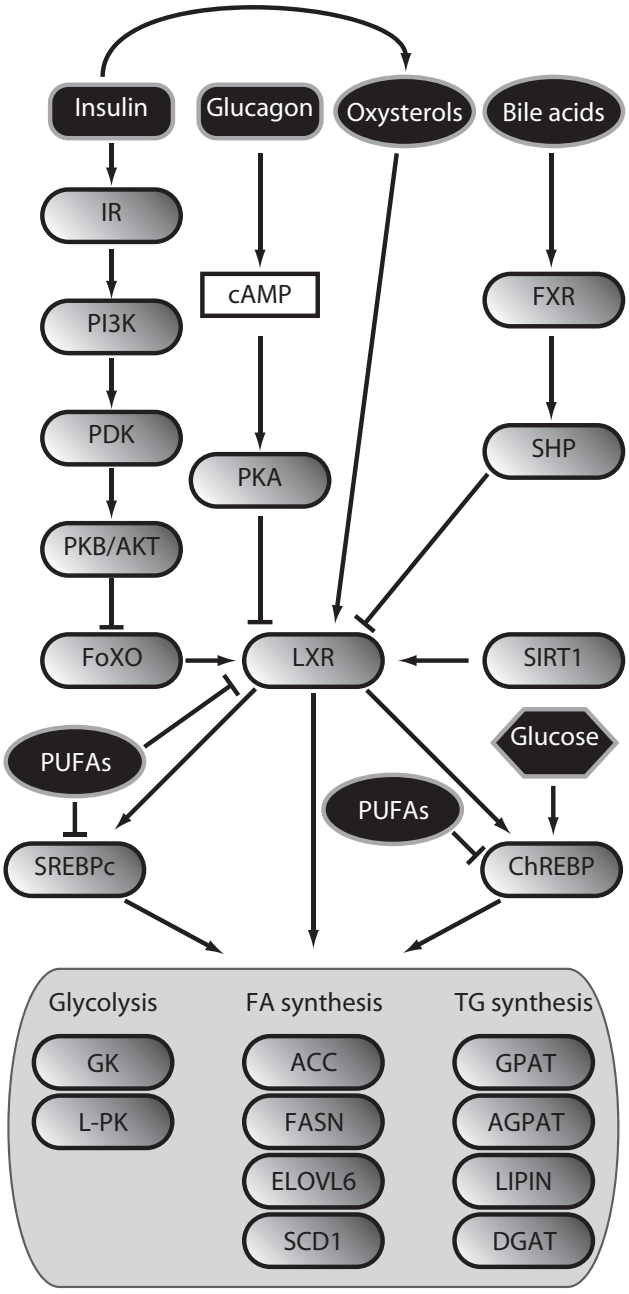

Fig. 4. Direct and indirect roles of LXR in the transcriptional control of hepatic lipogenesis by nutritional status. The genes coding for two lipogenic transcription factors: sterol regulatory element-binding protein 1c (SREBP-1c) and carbohydrate responsive element binding protein (ChREBP) are under the control of LXR. These three transcription factors regulate genes that are involved in glycolysis (GK, L-PK), fatty acid (FA) synthesis (ACC, FASN ELOVL6 and SCD1) and/or triglyceride (TG) synthesis (GPAT AGPAT, LIPIN and DGAT). The mechanisms are not fully described. ChREBP is activated by elevated glucose. Oxysterols are LXR ligands that can induce its activity. Other mechanisms can modify LXR activity. In the fed state, insulin regulates lipogenic genes including SREBP-1c however it seems that this regulation requires the presence of LXR. Insulin *via* the insulin receptor (IR), phosphatidylinositol 3-kinase (PI3 K) *phosphoinositide-dependent kinase* (PDK) protein kinase B (PKB/AKT) phosphorylates the Forkhead box O (FoxO) transcription factor and inhibits its inhibitory effect on LXR-dependant transcription of Srebp-1c. During fasting, glucagon level increases and, as a consequence, proteine kinase A (PKA), a mediator of glucagon/cAMP, represses the LXR induced expression of Srebp-1c. Bile acids also regulate LXR. Bile acids activate farnesoid X receptor (FXR) which in turn activates the small heterodimer partner (SHP) a nuclear receptor which lacks the DNA binding domain (DBD) common to most nuclear receptor. SHP is able to interact with LXR and represses the expression of LXR target gene. NAD-dependent deacetylase sirtuin-1 (SIRT1) is able to deacetylate LXR which leads to ubiquitination and degradation of LXR. This mechanism is important to "recycle" LXR and to enhance its transcriptional activity of its target genes. Polyunsaturated fatty acids (PUFAs) modulate the activity of LXR, ChREBP and SREBP-1c by distinct mechanism.

Two LXREs were identified in the promoter of *Srebp-1* (Chen et al., 2004) although usually most promoters of LXR target genes only have a single LXRE (Costet et al., 2000). SREBPs are transcription factors from the basic-helix-loop-helix leucine zipper (bHLH/LZ) transcription factor family and are located in the endoplasmic reticulum membrane as a precursor form. To influence transcription of their target genes, SREBPs must be proteolytically cleaved to release the NH2-terminal segment that can enter the nucleus (Wang et al., 1994). There are three SREBP isoforms in mammals which are designated SREBP-1a, SREBP-1c, and SREBP-2. SREBP-1a, and SREBP-1c are encoded by the same gene and differ only in their first exon (Shimomura et al., 1997; Yokoyama et al., 1993) whereas SREBP-2 is encoded by another gene (Hua et al., 1993; Miserez et al., 1997). SREBP-2 is involved in cholesterol synthesis, indeed expression of a dominant-positive truncated form of this protein leads to an increase of mRNA transcripts coding for enzymes involved in cholesterol synthesis and an increase of cholesterol synthesis (Horton et al., 1998). SREBP-1c plays a role in lipogenesis, as expression of a dominant-positive truncated form of SREBP-1c leads to triglycerides accumulation in the liver and an increase of lipogenic gene expression (Shimano et al., 1997, 1999). Transgenic mice expressing a dominant-positive truncated form of SREBP-1a show an increase in both cholesterol and triglycerides synthesis (Shimano et al., 1997), suggesting that SREBP-1a shares its effects with the two others SREBP isoforms. Truncated SREBP-1a has stronger effects on lipogenesis than truncated SREBP-1c (Shimano et al., 1997). However, SREBP-1a is expressed only at low levels in the livers of adult mice, rats, hamsters, and humans (Shimomura et al., 1997), which suggests that *in vivo* SREBP-1c is the main isoform involved in the control of lipogenesis in adults. The detailed mechanisms of SREBP-2 and SREBP-1a post-transcriptional activation in response to cellular sterol depletion is well-described (Brown and Goldstein, 2009; Goldstein et al., 2006). SREBP-1c cleavage does not occur in response to low cholesterol level. It is stimulated by insulin (Hegarty et al., 2005; Howell et al., 2009; Yabe et al., 2003) and by endoplasmic reticulum stress (Kammoun et al., 2009). However, it is clear that the LXR-SREBP-1c axis is very important for the effect of LXR on lipogenesis. Indeed, in mice with a liver-specific deletion of SREBP-1c a highly disminished response to LXR synthetic agonist and to fasting/refeeding was observed (Liang et al., 2002). The LXR-SREBP-1c axis is highly regulated. Interestingly, it has recently been reported that, in human, SREBP-1c regulates the expression of a MicroRNA that mediates a feedback loop on the auto-regulation (Laffitte et al., 2001) of LXRα expression (Ou et al., 2011).

Like SREBP-1c, ChREBP is also a bHLH/LZ transcription factor family that contributes to the regulation of lipogenesis (Denechaud et al., 2008b). It has been discovered in 2001 by Uyeda's group (Yamashita et al., 2001). The gene encoding for ChREBP is mainly expressed in liver, small intestine, kidney and white and brown adipose tissue (Iizuka et al., 2004). It acts as an heterodimer with Max like protein (Mlx) (Ma et al., 2006; Stoeckman et al., 2004). As SREBP-1c, ChREBP needs to be post-translationally modified and thus activated in order to exert its transcriptional activity in the nucleus. Under low concentration of glucose, ChREBP is phosphorylated and remains in the cytosol. Upon high carbohydrate feeding, ChREBP translocates into the nucleus. Even if ChREBP gene is under the transcriptional control of LXR it has been reported that only glucose induces its transcriptional activity (Denechaud et al., 2008a). To date, several activation mechanisms have been described. One requires dephosphorylation of ChREBP on its Ser-196 residue by the protein phosphatase 2A (PP2A) (Kabashima et al., 2003). This phosphatase is activated by xylulose-5-phosphate (X5P) (Kabashima et al., 2003), a metabolite of the pentose-phosphate pathway alimented by glucose. Another mechanism involves the glucose sensing domain (GSM), an evolutionary conserved domain located on the N-terminus part of ChREBP (Li et al., 2006). This GSM domain is reported to require glucose-6-phosphate (Li et al., 2010) to be activated. ChREBP activity in response to glucose also seems to involve its glycosylation (Sakiyama et al., 2010). Finally, a recent study has provided evidence for another molecular mechanism that regulates ChREBP activity. This mechanism involves the activity of p300, histone acetyltransferase (HAT) co-activator that coactivates glucose-mediated ChREBP induction of glycolytic and lipogenic gene expression by acetylating both histone and ChREBP itself (Bricambert et al., 2010). These authors have also identified the serine/threonine kinase salt-inducible kinase 2 (SIK2) as an upstream regulator of ChREBP through its effect on p300.

When activated, SREBP-1c and ChREBP translocate to the nucleus where they bind respectively to sterol response element (SRE) and carbohydrate response element (ChoRE) of their target genes and govern their expressions. SREs have been identified in the promoter of major genes involved in fatty acid synthesis: *Acc* (Lopez et al., 1996), *Fasn* (Latasa et al., 2000), *Elovl6* (Kumadaki et al., 2008), *Scd1* (Tabor et al., 1999). Similarly, ChoRE have been located on the promoters of *Acc* (O'Callaghan et al., 2001) and *Fasn* (Rufo et al., 2001). Moreover, SREBP-1c−/− mice and ChREBP−/− mice like LXRαβ−/− mice fed a standard diet show reduced expression of lipogenic genes (Cha and Repa, 2007; Iizuka et al., 2004; Liang et al., 2002; Repa et al., 2000a). LXR together with ChREBP and SREBP-1c belong to a network of nutrient sensing factors involved in the control of hepatic fatty acid synthesis.

4.2. Hormonal and nutritional regulation of LXR

Insulin signaling is essential to maintain glucose and lipid homeostasis in the fed state. It has been suggested that insulin activates LXR (Chen et al., 2004; Tobin et al., 2002). Furthermore, the lack of LXRs blunts the insulin induced expression of enzymes involved in fatty acid and cholesterol metabolism (Tobin et al., 2002). The use of a gene reporter assay showed that the induction of the expression of Srebp-1c by insulin requires the two LXREs in its promoter (Chen et al., 2004). It has also been suggested from experiments done in cell culture that a tonic activation of LXR by an endogenously produced sterol is required in order to maintain SREBP-1c expression (DeBose-Boyd et al., 2001). Brown and Goldstein's group also showed that insulin might lead to the synthesis of an endogenous ligand required for the activation of SREBP-1c by LXR (Chen et al., 2004). Another mechanism of LXR activation induced by insulin has been proposed. The hepatic over-expression of a constitutive active form of forkhead box-"Other" 1 transcription factor (FoxO1) leads to a decrease expression of *Srebp-1c* (Zhang et al., 2006). In the absence of any cellular stimulus FoxO transcription factors localize in the nucleus where they regulate transcription of their target genes. FoxOs are phosphorylated by the protein kinase B (PKB), a downstream target of insulin receptor, and are inactivated by relocalizing from the nucleus to the cytosol (Birkenkamp and Coffer, 2003). Zhang et al. (2006) postulated that constitutively active FoxO1 might impair LXR activity. Recently, it has been shown that active form of FoxO1 counteracts the binding of LXRα with the LXRE in the *Srebp-1c* promoter (Liu et al., 2010). This suppression of *Srebp-1c* expression by FoxO1 can be counteracted by the inactivation of FoxO1 by insulin (Liu et al., 2010).

During fasting, glucagon is secreted by the β-cells of the pancreatic islets in response to low blood glucose. In the liver, glucagon induces an increase of intracellular cAMP and induces downstream activation of the protein kinase A (PKA). This kinase is involved in several cellular mechanisms by phosphorylating its target proteins. PKA can phosphorylate LXR on its ligand binding domain and heterodimerization domain (Yamamoto et al., 2007). This leads to a decrease of LXR activity (Yamamoto et al., 2007). This finding is in accordance with an inhibition of lipogenesis induced by glucagon.

Essential fatty acids, also known as polyunsaturated fatty acids (PUFAs), of the n-3 and n-6 series can modulate lipids metabolism. Linoleic (C18:2 n-6) and α-linolenic acids (C18:3 n-3), the precursors of n-6 and n-3 fatty acid families respectively, cannot be synthesized in animals and must be provided by the diet. These precursors can be further desaturated and elongated to produce very long chain PUFAs such as arachidonic acid (C20:4 n-6) and docosahexaenoic acid (C22:6 n-3) (Guillou et al., 2010). It has been showed that the presence of PUFAs in the diet decrease the expression of genes coding for enzymes involved in lipogenesis such as *Fasn*, *Acc* and *Scd1* (Jump and Clarke, 1999). Whereas a deficiency in dietary PUFAs (Alwayn et al., 2004; Sekiya et al., 2003) or disruption of the very long chain PUFA synthesis pathway (Moon et al., 2009) leads to an increased lipogenesis and triglycerides accumulation in the liver. PUFAs repress the expression of SREBP-1c (Ou et al., 2001) and its post-transcriptional maturation (Hannah et al., 2001). Moreover, PUFAs also inhibit hepatic maturation of ChREBP (Dentin et al., 2005). PUFAs are also known to be able to bind to and activate certain nuclear receptors such as PPAR α (Gottlicher et al., 1992; Martin et al., 2007). It has also been showed that PUFAs bind to LXR and act as antagonists in *in vitro* settings and in cell culture (Ou et al., 2001; Svensson et al., 2003). Therefore PUFAs may not only repress lipogenic gene expression through SREBP-1c and ChREBP but also *via* LXR (Ou et al., 2001). However, this possibility is still very much debated since further studies performed in cell culture (Pawar et al., 2002, 2003) and *in vivo* (Pawar et al., 2003; Takeuchi et al., 2010) have provided results which are not consistent with such possibility. Beside the debated antagonistic effect of PUFAs on LXR activity, it has also been shown that certain PUFAs may repress transcription of *Srebp-1c* by reducing trans-activating capacity of LXR (Howell et al., 2009).

Other nutrient-sensing mechanisms that influence LXR-mediated promotion of fatty acid synthesis may involve the farnesoid X receptor (FXR, NR2H4) and the histone deacetylase SIRT1. FXR is activated by bile acids (Makishima et al., 1999). Upon activation, FXR induces the expression of the short heterodimer partner (SHP, NR0B2) (Goodwin et al., 2000), an atypical orphan nuclear receptor lacking a DNA-binding domain. It is known to act as a corepressor of many nuclear receptors. Brendel et al. (2002) showed that SHP interacts with the helix 12 of LXR and represses the expression of typical LXR target as well as reducing its activity in a gene reporter assay. SIRT1 acts in response to nutrient availability as a master switch in lipid and glucose homeostasis (Feige and Auwerx, 2007; Hou et al., 2008; Ponugoti et al., 2010). As described earlier, SIRT1 deacetylates LXR which leads to its ubiquitination and its degradation through the proteasome (Li et al., 2007b). This degradation is important for recycling LXR and maintaining its activity. Transgenic mice lacking *Sirt1* show similar characteristics as transgenic mice lacking LXR: decreased HDL-cholesterol and plasma triglycerides (Kalaany et al., 2005; Li et al., 2007b).

5. Conclusion

LXRs play an essential role in lipid homeostasis highlighted by its central position at the crossroad between cholesterol and fatty acid metabolism. It is a critical receptor in the control of various physiological functions that relates not only to metabolic and cardiovascular diseases such as obesity, atherosclerosis and diabetes, but also to other diseases such as dermatological and reproductive disorders, Alzheimer's disease and cancer. Therefore, LXRs show great potential as pharmacological targets and the development of selective LXR agonist without deleterious side effects such as those that occur as a consequence of elevated lipogenesis is a major challenge. Another challenge in the field is the development of highly sensitive biochemical approaches that will allow us to better understand the tissue-specific oxysterol metabolism. It is required to better delineate the role of the oxysterol-LXR axis in health and disease.

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References

A-Gonzalez, N., Bensinger, S.J., Hong, C., Beceiro, S., Bradley, M.N., Zelcer, N., Deniz, J., Ramirez, C., Diaz, M., Gallardo, G., de Galarreta, C.R., Salazar, J., Lopez, F., Edwards, P., Parks, J., Andujar, M., Tontonoz, P., Castrillo, A., 2009. Apoptotic cells promote their own clearance and immune tolerance through activation of the nuclear receptor LXR. Immunity 31, 245–258.

Abu-Elheiga, L., Almarza-Ortega, D.B., Baldini, A., Wakil, S.J., 1997. Human acetyl-CoA carboxylase 2. Molecular cloning, characterization, chromosomal mapping, and evidence for two isoforms. J. Biol. Chem. 272, 10669–10677.

Abu-Elheiga, L., Brinkley, W.R., Zhong, L., Chirala, S.S., Woldegiorgis, G., Wakil, S.J., 2000. The subcellular localization of acetyl-CoA carboxylase 2. Proc. Natl. Acad. Sci. U.S.A. 97, 1444–1449.

Abu-Elheiga, L., Jayakumar, A., Baldini, A., Chirala, S.S., Wakil, S.J., 1995. Human acetyl-CoA carboxylase: characterization, molecular cloning, and evidence for two isoforms. Proc. Natl. Acad. Sci. U.S.A. 92, 4011–4015.

Abu-Elheiga, L., Matzuk, M.M., Abo-Hashema, K.A., Wakil, S.J., 2001. Continuous fatty acid oxidation and reduced fat storage in mice lacking acetyl-CoA carboxylase 2. Science 291, 2613–2616.

Abu-Elheiga, L., Matzuk, M.M., Kordari, P., Oh, W., Shaikenov, T., Gu, Z., Wakil, S.J., 2005. Mutant mice lacking acetyl-CoA carboxylase 1 are embryonically lethal. Proc. Natl. Acad. Sci. U.S.A. 102, 12011–12016.

Abu-Elheiga, L., Oh, W., Kordari, P., Wakil, S.J., 2003. Acetyl-CoA carboxylase 2 mutant mice are protected against obesity and diabetes induced by high-fat/high-carbohydrate diets. Proc. Natl. Acad. Sci. U.S.A. 100, 10207–10212.

Adighibe, O., Arepalli, S., Duckworth, J., Hardy, J., Wavrant-De Vrieze, F., 2006. Genetic variability at the LXR gene (NR1H2) may contribute to the risk of Alzheimer's disease. Neurobiol. Aging 27, 1431–1434.

Agarwal, A.K., Barnes, R.I., Garg, A., 2006. Functional characterization of human 1-acylglycerol-3-phosphate acyltransferase isoform 8: cloning, tissue distribution, gene structure, and enzymatic activity. Arch. Biochem. Biophys. 449, 64–76.

Agarwal, A.K., Sukumaran, S., Bartz, R., Barnes, R.I., Garg, A., 2007. Functional characterization of human 1-acylglycerol-3-phosphate-O-acyltransferase isoform 9: cloning, tissue distribution, gene structure, and enzymatic activity. J. Endocrinol. 193, 445–457.

Alwayn, I.P., Javid, P.J., Gura, K.M., Nose, V., Ollero, M., Puder, M., 2004. Do polyunsaturated fatty acids ameliorate hepatic steatosis in obese mice by SREPB-1 suppression or by correcting essential fatty acid deficiency. Hepatology 39, 1176–1177, author reply 1177–1178.

Auboeuf, D., Rieusset, J., Fajas, L., Vallier, P., Frering, V., Riou, J.P., Staels, B., Auwerx, J., Laville, M., Vidal, H., 1997. Tissue distribution and quantification of the expression of mRNAs of peroxisome proliferator-activated receptors and liver X receptor-alpha in humans: no alteration in adipose tissue of obese and NIDDM patients. Diabetes 46, 1319–1327.

Bai, Q., Xu, L., Kakiyama, G., Runge-Morris, M.A., Hylemon, P.B., Yin, L., Pandak, W.M., Ren, S., 2010. Sulfation of 25-hydroxycholesterol by SULT2B1b decreases cellular lipids via the LXR/SREBP-1c signaling pathway in human aortic endothelial cells. Atherosclerosis 214, 350–356.

Bensinger, S.J., Bradley, M.N., Joseph, S.B., Zelcer, N., Janssen, E.M., Hausner, M.A., Shih, R., Parks, J.S., Edwards, P.A., Jamieson, B.D., Tontonoz, P., 2008. LXR signaling couples sterol metabolism to proliferation in the acquired immune response. Cell 134, 97–111.

Berrodin, T.J., Shen, Q., Quinet, E.M., Yudt, M.R., Freedman, L.P., Nagpal, S., 2010. Identification of 5alpha, 6alpha-epoxycholesterol as a novel modulator of liver X receptor activity. Mol. Pharmacol. 78, 1046–1058.

Beyea, M.M., Heslop, C.L., Sawyez, C.G., Edwards, J.Y., Markle, J.G., Hegele, R.A., Huff, M.W., 2007. Selective up-regulation of LXR-regulated genes ABCA1, ABCG1, and APOE in macrophages through increased endogenous synthesis of 24(S),25-epoxycholesterol. J. Biol. Chem. 282, 5207–5216.

Birkenkamp, K.U., Coffer, P.J., 2003. Regulation of cell survival and proliferation by the FOXO (Forkhead box, class O) subfamily of Forkhead transcription factors. Biochem. Soc. Trans. 31, 292–297.

Bjorkhem, I., 2007. Rediscovery of cerebrosterol. Lipids 42, 5–14.

Boutaud, O., Dolis, D., Schuber, F., 1992. Preferential cyclization of 2,3(S):22(S),23-dioxidosqualene by mammalian 2,3-oxidosqualene-lanosterol cyclase. Biochem. Biophys. Res. Commun. 188, 898–904.
Brendel, C., Schoonjans, K., Botrugno, O.A., Treuter, E., Auwerx, J., 2002. The small heterodimer partner interacts with the liver X receptor alpha and represses its transcriptional activity. Mol. Endocrinol. 16, 2065–2076.
Bricambert, J., Miranda, J., Benhamed, F., Girard, J., Postic, C., Dentin, R., 2010. Salt-inducible kinase 2 links transcriptional coactivator p300 phosphorylation to the prevention of ChREBP-dependent hepatic steatosis in mice. J. Clin. Invest. 120, 4316–4331.
Brown, A.J., Jessup, W., 2009. Oxysterols: sources, cellular storage and metabolism, and new insights into their roles in cholesterol homeostasis. Mol. Aspects Med. 30, 111–122.
Brown, H.A., Murphy, R.C., 2009. Working towards an exegesis for lipids in biology. Nat. Chem. Biol. 5, 602–606.
Brown, M.S., Goldstein, J.L., 2009. Cholesterol feedback: from Schoenheimer's bottle to Scap's MELADL. J. Lipid Res. 50 (Suppl.), S15–S27.
Calkin, A.C., Tontonoz, P., 2010. Liver X receptor signaling pathways and atherosclerosis. Arterioscler. Thromb. Vasc. Biol. 30, 1513–1518.
Cao, H., Gerhold, K., Mayers, J.R., Wiest, M.M., Watkins, S.M., Hotamisligil, G.S., 2008. Identification of a lipokine, a lipid hormone linking adipose tissue to systemic metabolism. Cell 134, 933–944.
Cao, J., Cheng, L., Shi, Y., 2007. Catalytic properties of MGAT3, a putative triacylglycerol synthase. J. Lipid Res. 48, 583–591.
Cao, J., Li, J.L., Li, D., Tobin, J.F., Gimeno, R.E., 2006. Molecular identification of microsomal acyl-CoA:glycerol-3-phosphate acyltransferase, a key enzyme in de novo triacylglycerol synthesis. Proc. Natl. Acad. Sci. U.S.A. 103, 19695–19700.
Carman, G.M., Han, G.S., 2009. Phosphatidic acid phosphatase, a key enzyme in the regulation of lipid synthesis. J. Biol. Chem. 284, 2593–2597.
Cases, S., Smith, S.J., Zheng, Y.W., Myers, H.M., Lear, S.R., Sande, E., Novak, S., Collins, C., Welch, C.B., Lusis, A.J., Erickson, S.K., Farese Jr., R.V., 1998. Identification of a gene encoding an acyl CoA:diacylglycerol acyltransferase, a key enzyme in triacylglycerol synthesis. Proc. Natl. Acad. Sci. U.S.A. 95, 13018–13023.
Cases, S., Stone, S.J., Zhou, P., Yen, E., Tow, B., Lardizabal, K.D., Voelker, T., Farese Jr., R.V., 2001. Cloning of DGAT2, a second mammalian diacylglycerol acyltransferase, and related family members. J. Biol. Chem. 276, 38870–38876.
Cha, J.Y., Repa, J.J., 2007. The liver X receptor (LXR) and hepatic lipogenesis. The carbohydrate-response element-binding protein is a target gene of LXR. J. Biol. Chem. 282, 743–751.
Chakravarthy, M.V., Lodhi, I.J., Yin, L., Malapaka, R.R., Xu, H.E., Turk, J., Semenkovich, C.F., 2009. Identification of a physiologically relevant endogenous ligand for PPARalpha in liver. Cell 138, 476–488.
Chakravarthy, M.V., Pan, Z., Zhu, Y., Tordjman, K., Schneider, J.G., Coleman, T., Turk, J., Semenkovich, C.F., 2005. "New" hepatic fat activates PPARalpha to maintain glucose, lipid, and cholesterol homeostasis. Cell Metab. 1, 309–322.
Chen, G., Liang, G., Ou, J., Goldstein, J.L., Brown, M.S., 2004. Central role for liver X receptor in insulin-mediated activation of Srebp-1c transcription and stimulation of fatty acid synthesis in liver. Proc. Natl. Acad. Sci. U.S.A. 101, 11245–11250.
Chen, W., Chen, G., Head, D.L., Mangelsdorf, D.J., Russell, D.W., 2007. Enzymatic reduction of oxysterols impairs LXR signaling in cultured cells and the livers of mice. Cell Metab. 5, 73–79.
Chen, Y.Q., Kuo, M.S., Li, S., Bui, H.H., Peake, D.A., Sanders, P.E., Thibodeaux, S.J., Chu, S., Qian, Y.W., Zhao, Y., Bredt, D.S., Moller, D.E., Konrad, R.J., Beigneux, A.P., Young, S.G., Cao, G., 2008. AGPAT6 is a novel microsomal glycerol-3-phosphate acyltransferase. J. Biol. Chem. 283, 10048–10057.
Chiang, J.Y., Kimmel, R., Stroup, D., 2001. Regulation of cholesterol 7alpha-hydroxylase gene (CYP7A1) transcription by the liver orphan receptor (LXRalpha). Gene 262, 257–265.
Chirala, S.S., Chang, H., Matzuk, M., Abu-Elheiga, L., Mao, J., Mahon, K., Finegold, M., Wakil, S.J., 2003. Fatty acid synthesis is essential in embryonic development: fatty acid synthase null mutants and most of the heterozygotes die in utero. Proc. Natl. Acad. Sci. U.S.A. 100, 6358–6363.
Chirala, S.S., Jayakumar, A., Gu, Z.W., Wakil, S.J., 2001. Human fatty acid synthase: role of interdomain in the formation of catalytically active synthase dimer. Proc. Natl. Acad. Sci. U.S.A. 98, 3104–3108.
Chirala, S.S., Wakil, S.J., 2004. Structure and function of animal fatty acid synthase. Lipids 39, 1045–1053.
Chu, K., Miyazaki, M., Man, W.C., Ntambi, J.M., 2006. Stearoyl-coenzyme A desaturase 1 deficiency protects against hypertriglyceridemia and increases plasma high-density lipoprotein cholesterol induced by liver X receptor activation. Mol. Cell. Biol. 26, 6786–6798.
Clark, J., Anderson, K.E., Juvin, V., Smith, T.S., Karpe, F., Wakelam, M.J., Stephens, L.R., Hawkins, P.T., 2011. Quantification of PtdInsP(3) molecular species in cells and tissues by mass spectrometry. Nat. Methods 8, 267–272.
Cohen, P., Miyazaki, M., Socci, N.D., Hagge-Greenberg, A., Liedtke, W., Soukas, A.A., Sharma, R., Hudgins, L.C., Ntambi, J.M., Friedman, J.M., 2002. Role for stearoyl-CoA desaturase-1 in leptin-mediated weight loss. Science 297, 240–243.
Coleman, R.A., Lee, D.P., 2004. Enzymes of triacylglycerol synthesis and their regulation. Prog. Lipid Res. 43, 134–176.
Collins, J.L., Fivush, A.M., Watson, M.A., Galardi, C.M., Lewis, M.C., Moore, L.B., Parks, D.J., Wilson, J.G., Tippin, T.K., Binz, J.G., Plunket, K.D., Morgan, D.G., Beaudet, E.J., Whitney, K.D., Kliewer, S.A., Willson, T.M., 2002. Identification of a nonsteroidal liver X receptor agonist through parallel array synthesis of tertiary amines. J. Med. Chem. 45, 1963–1966.
Cortes, V.A., Curtis, D.E., Sukumaran, S., Shao, X., Parameswara, V., Rashid, S., Smith, A.R., Ren, J., Esser, V., Hammer, R.E., Agarwal, A.K., Horton, J.D., Garg, A., 2009. Molecular mechanisms of hepatic steatosis and insulin resistance in the AGPAT2-deficient mouse model of congenital generalized lipodystrophy. Cell Metab. 9, 165–176.
Costet, P., Luo, Y., Wang, N., Tall, A.R., 2000. Sterol-dependent transactivation of the ABC1 promoter by the liver X receptor/retinoid X receptor. J. Biol. Chem. 275, 28240–28245.
Cui, G., Qin, X., Wu, L., Zhang, Y., Sheng, X., Yu, Q., Sheng, H., Xi, B., Zhang, J.Z., Zang, Y.Q., 2011. Liver X receptor (LXR) mediates negative regulation of mouse and human Th17 differentiation. J. Clin. Invest. 121, 658–670.
Cummins, C.L., Volle, D.H., Zhang, Y., McDonald, J.G., Sion, B., Lefrancois-Martinez, A.M., Caira, F., Veyssiere, G., Mangelsdorf, D.J., Lobaccaro, J.M., 2006. Liver X receptors regulate adrenal cholesterol balance. J. Clin. Invest. 116, 1902–1912.
DeBose-Boyd, R.A., Ou, J., Goldstein, J.L., Brown, M.S., 2001. Expression of sterol regulatory element-binding protein 1c (SREBP-1c) mRNA in rat hepatoma cells requires endogenous LXR ligands. Proc. Natl. Acad. Sci. U.S.A. 98, 1477–1482.
Denechaud, P.D., Bossard, P., Lobaccaro, J.M., Millatt, L., Staels, B., Girard, J., Postic, C., 2008a. ChREBP, but not LXRs, is required for the induction of glucose-regulated genes in mouse liver. J. Clin. Invest. 118, 956–964.
Denechaud, P.D., Girard, J., Postic, C., 2008b. Carbohydrate responsive element binding protein and lipid homeostasis. Curr. Opin. Lipidol. 19, 301–306.
Dentin, R., Benhamed, F., Pegorier, J.P., Foufelle, F., Viollet, B., Vaulont, S., Girard, J., Postic, C., 2005. Polyunsaturated fatty acids suppress glycolytic and lipogenic genes through the inhibition of ChREBP nuclear protein translocation. J. Clin. Invest. 115, 2843–2854.
Dobrzyn, P., Dobrzyn, A., Miyazaki, M., Cohen, P., Asilmaz, E., Hardie, D.G., Friedman, J.M., Ntambi, J.M., 2004. Stearoyl-CoA desaturase 1 deficiency increases fatty acid oxidation by activating AMP-activated protein kinase in liver. Proc. Natl. Acad. Sci. U.S.A. 101, 6409–6414.
Dollis, D., Schuber, F., 1994. Effects of a 2,3-oxidosqualene-lanosterol cyclase inhibitor 2,3:22,23-dioxidosqualene and 24,25-epoxycholesterol on the regulation of cholesterol biosynthesis in human hepatoma cell line HepG2. Biochem. Pharmacol. 48, 49–57.
Donnelly, K.L., Smith, C.I., Schwarzenberg, S.J., Jessurun, J., Boldt, M.D., Parks, E.J., 2005. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J. Clin. Invest. 115, 1343–1351.
Eberhardt, C., Gray, P.W., Tjoelker, L.W., 1997. Human lysophosphatidic acid acyltransferase. cDNA cloning, expression, and localization to chromosome 9q34.3. J. Biol. Chem. 272, 20299–20305.
El-Hajjaji, F.Z., Oumeddour, A., Pommier, A., Ouvrier, A., Viennois, E., Dufour, J., Caira, F., Drevet, J.R., Baron, S., Saez, F., Lobaccaro, J.M.A., 2011. Liver X receptors, lipids and their reproductive secrets in the male. BBA-Mol. Basis Dis. 1812, 974–981.
Feige, J.N., Auwerx, J., 2007. DisSIRTing on LXR and cholesterol metabolism. Cell Metab. 6, 343–345.
Ferre, P., Foufelle, F., 2010. Hepatic steatosis: a role for de novo lipogenesis and the transcription factor SREBP-1c. Diabetes Obes. Metab. 12 (Suppl. 2), 83–92.
Fu, X., Menke, J.G., Chen, Y., Zhou, G., MacNaul, K.L., Wright, S.D., Sparrow, C.P., Lund, E.G., 2001. 27-hydroxycholesterol is an endogenous ligand for liver X receptor in cholesterol-loaded cells. J. Biol. Chem. 276, 38378–38387.
Ganesh Bhat, B., Wang, P., Kim, J.H., Black, T.M., Lewin, T.M., Fiedorek Jr., F.T., Coleman, R.A., 1999. Rat sn-glycerol-3-phosphate acyltransferase: molecular cloning and characterization of the cDNA and expressed protein. Biochim. Biophys. Acta 1439, 415–423.
Gill, S., Chow, R., Brown, A.J., 2008. Sterol regulators of cholesterol homeostasis and beyond: the oxysterol hypothesis revisited and revised. Prog. Lipid Res. 47, 391–404.
Gill, S., Stevenson, J., Kristiana, I., Brown, A.J., 2011. Cholesterol-dependent degradation of squalene monooxygenase, a control point in cholesterol synthesis beyond HMG-CoA reductase. Cell Metab. 13, 260–273.
Gimeno, R.E., Cao, J., 2008. Thematic review series: glycerolipids. Mammalian glycerol-3-phosphate acyltransferases: new genes for an old activity. J. Lipid Res. 49, 2079–2088.
Glass, C.K., Rosenfeld, M.G., 2000. The coregulator exchange in transcriptional functions of nuclear receptors. Genes Dev. 14, 121–141.
Glosset, J.A., 1996. A branched metabolic pathway in animal cells converts 2-monoacylglycerol into sn-1-stearoyl-2-arachidonoyl phosphatidylinositol and other phosphoglycerides. In: Gross, R.W. (Ed.), Advances in Lipobiology, vol. 1. Elsevier, St. Louis, MO, pp. 61–100.
Goldstein, J.L., DeBose-Boyd, R.A., Brown, M.S., 2006. Protein sensors for membrane sterols. Cell 124, 35–46.
Goodwin, B., Jones, S.A., Price, R.R., Watson, M.A., McKee, D.D., Moore, L.B., Galardi, C., Wilson, J.G., Lewis, M.C., Roth, M.E., Maloney, P.R., Willson, T.M., Kliewer, S.A., 2000. A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. Mol. Cell 6, 517–526.
Gottlicher, M., Widmark, E., Li, Q., Gustafsson, J.A., 1992. Fatty acids activate a chimera of the clofibric acid-activated receptor and the glucocorticoid receptor. Proc. Natl. Acad. Sci. U.S.A. 89, 4653–4657.
Grefhorst, A., Elzinga, B.M., Voshol, P.J., Plosch, T., Kok, T., Bloks, V.W., van der Sluijs, F.H., Havekes, L.M., Romijn, J.A., Verkade, H.J., Kuipers, F., 2002. Stimulation of lipogenesis by pharmacological activation of the liver X receptor leads to production of large, triglyceride-rich very low density lipoprotein particles. J. Biol. Chem. 277, 34182–34190.
Guillou, H., Zadravec, D., Martin, P.G., Jacobsson, A., 2010. The key roles of elongases and desaturases in mammalian fatty acid metabolism: insights from transgenic mice. Prog. Lipid Res. 49, 186–199.
Hammond, L.E., Gallagher, P.A., Wang, S., Hiller, S., Kluckman, K.D., Posey-Marcos, E.L., Maeda, N., Coleman, R.A., 2002. Mitochondrial glycerol-3-phosphate

acyltransferase-deficient mice have reduced weight and liver triacylglycerol content and altered glycerolipid fatty acid composition. Mol. Cell. Biol. 22, 8204–8214.
Hammond, L.E., Neschen, S., Romanelli, A.J., Cline, G.W., Ilkayeva, O.R., Shulman, G.I., Muoio, D.M., Coleman, R.A., 2005. Mitochondrial glycerol-3-phosphate acyltransferase-1 is essential in liver for the metabolism of excess acyl-CoAs. J. Biol. Chem. 280, 25629–25636.
Hanley, K., Ng, D.C., He, S.S., Lau, P., Min, K., Elias, P.M., Bikle, D.D., Mangelsdorf, D.J., Williams, M.L., Feingold, K.R., 2000. Oxysterols induce differentiation in human keratinocytes and increase Ap-1-dependent involucrin transcription. J. Invest. Dermatol. 114, 545–553.
Hannah, V.C., Ou, J., Luong, A., Goldstein, J.L., Brown, M.S., 2001. Unsaturated fatty acids down-regulate srebp isoforms 1a and 1c by two mechanisms in HEK-293 cells. J. Biol. Chem. 276, 4365–4372.
Harada, N., Hara, S., Yoshida, M., Zenitani, T., Mawatari, K., Nakano, M., Takahashi, A., Hosaka, T., Yoshimoto, K., Nakaya, Y., 2007. Molecular cloning of a murine glycerol-3-phosphate acyltransferase-like protein 1 (xGPAT1). Mol. Cell. Biochem. 297, 41–51.
Hegarty, B.D., Bobard, A., Hainault, I., Ferre, P., Bossard, P., Foufelle, F., 2005. Distinct roles of insulin and liver X receptor in the induction and cleavage of sterol regulatory element-binding protein-1c. Proc. Natl. Acad. Sci. U.S.A. 102, 791–796.
Herzog, B., Hallberg, M., Seth, A., Woods, A., White, R., Parker, M.G., 2007. The nuclear receptor cofactor, receptor-interacting protein 140, is required for the regulation of hepatic lipid and glucose metabolism by liver X receptor. Mol. Endocrinol. 21, 2687–2697.
Hollenback, D., Bonham, L., Law, L., Rossnagle, E., Romero, L., Carew, H., Tompkins, C.K., Leung, D.W., Singer, J.W., White, T., 2006. Substrate specificity of lysophosphatidic acid acyltransferase beta – evidence from membrane and whole cell assays. J. Lipid Res. 47, 593–604.
Honda, A., Miyazaki, T., Ikegami, T., Iwamoto, J., Maeda, T., Hirayama, T., Saito, Y., Teramoto, T., Matsuzaki, Y., 2011. Cholesterol 25-hydroxylation activity of CYP3A. J. Lipid Res., in press.
Hong, C., Walczak, R., Dhamko, H., Bradley, M.N., Marathe, C., Boyadjian, R., Salazar, J.V., Tontonoz, P., 2011. Constitutive activation of LXR in macrophages regulates metabolic and inflammatory gene expression: identification of ARL7 as a direct target. J. Lipid Res. 52, 531–539.
Horton, J.D., Shimomura, I., Brown, M.S., Hammer, R.E., Goldstein, J.L., Shimano, H., 1998. Activation of cholesterol synthesis in preference to fatty acid synthesis in liver and adipose tissue of transgenic mice overproducing sterol regulatory element-binding protein-2. J. Clin. Invest. 101, 2331–2339.
Hou, X., Xu, S., Maitland-Toolan, K.A., Sato, K., Jiang, B., Ido, Y., Lan, F., Walsh, K., Wierzbicki, M., Verbeuren, T.J., Cohen, R.A., Zang, M., 2008. SIRT1 regulates hepatocyte lipid metabolism through activating AMP-activated protein kinase. J. Biol. Chem. 283, 20015–20026.
Houck, K.A., Borchert, K.M., Hepler, C.D., Thomas, J.S., Bramlett, K.S., Michael, L.F., Burris, T.P., 2004. T0901317 is a dual LXR/FXR agonist. Mol. Genet. Metab. 83, 184–187.
Howell III, G., Deng, X., Yellaturu, C., Park, E.A., Wilcox, H.G., Raghow, R., Elam, M.B., 2009. N-3 polyunsaturated fatty acids suppress insulin-induced SREBP-1c transcription via reduced trans-activating capacity of LXRalpha. Biochim. Biophys. Acta 1791, 1190–1196.
Hu, X., Li, S., Wu, J., Xia, C., Lala, D.S., 2003. Liver X receptors interact with corepressors to regulate gene expression. Mol. Endocrinol. 17, 1019–1026.
Hua, X., Yokoyama, C., Wu, J., Briggs, M.R., Brown, M.S., Goldstein, J.L., Wang, X., 1993. SREBP-2, a second basic-helix-loop-helix-leucine zipper protein that stimulates transcription by binding to a sterol regulatory element. Proc. Natl. Acad. Sci. U.S.A. 90, 11603–11607.
Iizuka, K., Bruick, R.K., Liang, G., Horton, J.D., Uyeda, K., 2004. Deficiency of carbohydrate response element-binding protein (ChREBP) reduces lipogenesis as well as glycolysis. Proc. Natl. Acad. Sci. U.S.A. 101, 7281–7286.
Infante, J., Rodriguez-Rodriguez, E., Mateo, I., Llorca, J., Vazquez-Higuera, J.L., Berciano, J., Combarros, O., 2010. Gene-gene interaction between heme oxygenase-1 and liver X receptor-beta and Alzheimer's disease risk. Neurobiol. Aging 31, 710–714.
Ivanova, P.T., Milne, S.B., Myers, D.S., Brown, H.A., 2009. Lipidomics: a mass spectrometry based systems level analysis of cellular lipids. Curr. Opin. Chem. Biol. 13, 526–531.
Janowski, B.A., Grogan, M.J., Jones, S.A., Wisely, G.B., Kliewer, S.A., Corey, E.J., Mangelsdorf, D.J., 1999. Structural requirements of ligands for the oxysterol liver X receptors LXRalpha and LXRbeta. Proc. Natl. Acad. Sci. U.S.A. 96, 266–271.
Janowski, B.A., Shan, B., Russell, D.W., 2001. The hypocholesterolemic agent LY295427 reverses suppression of sterol regulatory element-binding protein processing mediated by oxysterols. J. Biol. Chem. 276, 45408–45416.
Janowski, B.A., Willy, P.J., Devi, T.R., Falck, J.R., Mangelsdorf, D.J., 1996. An oxysterol signalling pathway mediated by the nuclear receptor LXR alpha. Nature 383, 728–731.
Jiang, Y.J., Lu, B., Kim, P., Elias, P.M., Feingold, K.R., 2006. Regulation of ABCA1 expression in human keratinocytes and murine epidermis. J. Lipid Res. 47, 2248–2258.
Jones, P.L., Sachs, L.M., Rouse, N., Wade, P.A., Shi, Y.B., 2001. Multiple N-CoR complexes contain distinct histone deacetylases. J. Biol. Chem. 276, 8807–8811.
Joseph, S.B., Laffitte, B.A., Patel, P.H., Watson, M.A., Matsukuma, K.E., Walczak, R., Collins, J.L., Osborne, T.F., Tontonoz, P., 2002. Direct and indirect mechanisms for regulation of fatty acid synthase gene expression by liver X receptors. J. Biol. Chem. 277, 11019–11025.
Jump, D.B., Clarke, S.D., 1999. Regulation of gene expression by dietary fat. Annu. Rev. Nutr. 19, 63–90.
Kabashima, T., Kawaguchi, T., Wadzinski, B.E., Uyeda, K., 2003. Xylulose 5-phosphate mediates glucose-induced lipogenesis by xylulose 5-phosphate-activated protein phosphatase in rat liver. Proc. Natl. Acad. Sci. U.S.A. 100, 5107–5112.
Kaestner, K.H., Ntambi, J.M., Kelly Jr., T.J., Lane, M.D., 1989. Differentiation-induced gene expression in 3T3-L1 preadipocytes. A second differentially expressed gene encoding stearoyl-CoA desaturase. J. Biol. Chem. 264, 14755–14761.
Kalaany, N.Y., Gauthier, K.C., Zavacki, A.M., Mammen, P.P., Kitazume, T., Peterson, J.A., Horton, J.D., Garry, D.J., Bianco, A.C., Mangelsdorf, D.J., 2005. LXRs regulate the balance between fat storage and oxidation. Cell Metab. 1, 231–244.
Kammoun, H.L., Chabanon, H., Hainault, I., Luquet, S., Magnan, C., Koike, T., Ferre, P., Foufelle, F., 2009. GRP78 expression inhibits insulin and ER stress-induced SREBP-1c activation and reduces hepatic steatosis in mice. J. Clin. Invest. 119, 1201–1215.
Kaneko, E., Matsuda, M., Yamada, Y., Tachibana, Y., Shimomura, I., Makishima, M., 2003. Induction of intestinal ATP-binding cassette transporters by a phytosterol-derived liver X receptor agonist. J. Biol. Chem. 278, 36091–36098.
Kennedy, M.A., Venkateswaran, A., Tarr, P.T., Xenarios, I., Kudoh, J., Shimizu, N., Edwards, P.A., 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, 39438–39447.
Koldamova, R.P., Lefterov, I.M., Staufenbiel, M., Wolfe, D., Huang, S., Glorioso, J.C., Walter, M., Roth, M.G., Lazo, J.S., 2005. The liver X receptor ligand T0901317 decreases amyloid beta production in vitro and in a mouse model of Alzheimer's disease. J. Biol. Chem. 280, 4079–4088.
Komuves, L.G., Schmuth, M., Fowler, A.J., Elias, P.M., Hanley, K., Man, M.Q., Moser, A.H., Lobaccaro, J.M., Williams, M.L., Mangelsdorf, D.J., Feingold, K.R., 2002. Oxysterol stimulation of epidermal differentiation is mediated by liver X receptor-beta in murine epidermis. J. Invest. Dermatol. 118, 25–34.
Korach-Andre, M., Archer, A., Gabbi, C., Barros, R.P., Pedrelli, M., Steffensen, K.R., Pettersson, A.T., Laurencikiene, J., Parini, P., Gustafsson, J.A., 2011. Liver-X Receptors regulate de novo lipogenesis in a tissue specific manner in C57Bl/6 female mice. Am. J. Physiol. Endocrinol. Metab. 301, 210–222.
Kumadaki, S., Matsuzaka, T., Kato, T., Yahagi, N., Yamamoto, T., Okada, S., Kobayashi, K., Takahashi, A., Yatoh, S., Suzuki, H., Yamada, N., Shimano, H., 2008. Mouse Elovl-6 promoter is an SREBP target. Biochem. Biophys. Res. Commun. 368, 261–266.
Laffitte, B.A., Joseph, S.B., Walczak, R., Pei, L., Wilpitz, D.C., Collins, J.L., Tontonoz, P., 2001. Autoregulation of the human liver X receptor alpha promoter. Mol. Cell. Biol. 21, 7558–7568.
Lardizabal, K.D., Mai, J.T., Wagner, N.W., Wyrick, A., Voelker, T., Hawkins, D.J., 2001. DGAT2 is a new diacylglycerol acyltransferase gene family: purification, cloning, and expression in insect cells of two polypeptides from Mortierella ramanniana with diacylglycerol acyltransferase activity. J. Biol. Chem. 276, 38862–38869.
Latasa, M.J., Moon, Y.S., Kim, K.H., Sul, H.S., 2000. Nutritional regulation of the fatty acid synthase promoter in vivo: sterol regulatory element binding protein functions through an upstream region containing a sterol regulatory element. Proc. Natl. Acad. Sci. U.S.A. 97, 10619–10624.
Lee, S., Lee, J., Lee, S.K., Lee, J.W., 2008. Activating signal cointegrator-2 is an essential adaptor to recruit histone H3 lysine 4 methyltransferases MLL3 and MLL4 to the liver X receptors. Mol. Endocrinol. 22, 1312–1319.
Lehmann, J.M., Kliewer, S.A., Moore, L.B., Smith-Oliver, T.A., Oliver, B.B., Su, J.L., Sundseth, S.S., Winegar, D.A., Blanchard, D.E., Spencer, T.A., Willson, T.M., 1997. Activation of the nuclear receptor LXR by oxysterols defines a new hormone response pathway. J. Biol. Chem. 272, 3137–3140.
Leung, D.W., 2001. The structure and functions of human lysophosphatidic acid acyltransferases. Front. Biosci. 6, D944–953.
Lewin, T.M., Schwerbrock, N.M., Lee, D.P., Coleman, R.A., 2004. Identification of a new glycerol-3-phosphate acyltransferase isoenzyme, mtGPAT2, in mitochondria. J. Biol. Chem. 279, 13488–13495.
Li, D., Yu, L., Wu, H., Shan, Y., Guo, J., Dang, Y., Wei, Y., Zhao, S., 2003. Cloning and identification of the human LPAAT-zeta gene, a novel member of the lysophosphatidic acid acyltransferase family. J. Hum. Genet. 48, 438–442.
Li, M.V., Chang, B., Imamura, M., Poungvarin, N., Chan, L., 2006. Glucose-dependent transcriptional regulation by an evolutionarily conserved glucose-sensing module. Diabetes 55, 1179–1189.
Li, M.V., Chen, W., Harmancey, R.N., Nuotio-Antar, A.M., Imamura, M., Saha, P., Taegtmeyer, H., Chan, L., 2010. Glucose-6-phosphate mediates activation of the carbohydrate responsive binding protein (ChREBP). Biochem. Biophys. Res. Commun. 395, 395–400.
Li, X., Pandak, W.M., Erickson, S.K., Ma, Y., Yin, L., Hylemon, P., Ren, S., 2007a. Biosynthesis of the regulatory oxysterol, 5-cholesten-3beta, 25-diol 3-sulfate, in hepatocytes. J. Lipid Res. 48, 2587–2596.
Li, X., Zhang, S., Blander, G., Tse, J.G., Krieger, M., Guarente, L., 2007b. SIRT1 deacetylates and positively regulates the nuclear receptor LXR. Mol. Cell 28, 91–106.
Liang, G., Yang, J., Horton, J.D., Hammer, R.E., Goldstein, J.L., Brown, M.S., 2002. Diminished hepatic response to fasting/refeeding and liver X receptor agonists in mice with selective deficiency of sterol regulatory element-binding protein-1c. J. Biol. Chem. 277, 9520–9528.
Lifschutz, I., 1913. Biochem. Zeitschrift 48.a.
Liu, X., Qiao, A., Ke, Y., Kong, X., Liang, J., Wang, R., Ouyang, X., Zuo, J., Chang, Y., Fang, F., 2010. FoxO1 represses LXRalpha-mediated transcriptional activity of SREBP-1c promoter in HepG2 cells. FEBS Lett. 584, 4330–4334.
Lo Sasso, G., Celli, N., Caboni, M., Murzilli, S., Salvatore, L., Morgano, A., Vacca, M., Pagliani, T., Parini, P., Moschetta, A., 2010a. Down-regulation of the LXR transcriptome provides the requisite cholesterol levels to proliferating hepatocytes. Hepatology 51, 1334–1344.

Lo Sasso, G., Murzilli, S., Salvatore, L., D'Errico, I., Petruzzelli, M., Conca, P., Jiang, Z.Y., Calabresi, L., Parini, P., Moschetta, A., 2010b. Intestinal specific LXR activation stimulates reverse cholesterol transport and protects from atherosclerosis. Cell Metab. 12, 187–193.
Lodhi, I.J., Wei, X., Semenkovich, C.F., 2011. Lipoexpediency: de novo lipogenesis as a metabolic signal transmitter. Trends Endocrinol. Metab. 22, 1–8.
Lopez, J.M., Bennett, M.K., Sanchez, H.B., Rosenfeld, J.M., Osborne, T.F., 1996. Sterol regulation of acetyl coenzyme A carboxylase: a mechanism for coordinate control of cellular lipid. Proc. Natl. Acad. Sci. U.S.A. 93, 1049–1053.
Lu, B., Jiang, Y.J., Zhou, Y., Xu, F.Y., Hatch, G.M., Choy, P.C., 2005. Cloning and characterization of murine 1-acyl-sn-glycerol 3-phosphate acyltransferases and their regulation by PPARalpha in murine heart. Biochem. J. 385, 469–477.
Ma, L., Robinson, L.N., Towle, H.C., 2006. ChREBP*Mlx is the principal mediator of glucose-induced gene expression in the liver. J. Biol. Chem. 281, 28721–28730.
Makishima, M., Okamoto, A.Y., Repa, J.J., Tu, H., Learned, R.M., Luk, A., Hull, M.V., Lustig, K.D., Mangelsdorf, D.J., Shan, B., 1999. Identification of a nuclear receptor for bile acids. Science 284, 1362–1365.
Mao, J., DeMayo, F.J., Li, H., Abu-Elheiga, L., Gu, Z., Shaikenov, T.E., Kordari, P., Chirala, S.S., Heird, W.C., Wakil, S.J., 2006. Liver-specific deletion of acetyl-CoA carboxylase 1 reduces hepatic triglyceride accumulation without affecting glucose homeostasis. Proc. Natl. Acad. Sci. U.S.A. 103, 8552–8557.
Martin, P.G., Guillou, H., Lasserre, F., Dejean, S., Lan, A., Pascussi, J.M., Sancristobal, M., Legrand, P., Besse, P., Pineau, T., 2007. Novel aspects of PPARalpha-mediated regulation of lipid and xenobiotic metabolism revealed through a nutrigenomic study. Hepatology 45, 767–777.
Matsuzaka, T., Shimano, H., Yahagi, N., Kato, T., Atsumi, A., Yamamoto, T., Inoue, N., Ishikawa, M., Okada, S., Ishigaki, N., Iwasaki, H., Iwasaki, Y., Karasawa, T., Kumadaki, S., Matsui, T., Sekiya, M., Ohashi, K., Hasty, A.H., Nakagawa, Y., Takahashi, A., Suzuki, H., Yatoh, S., Sone, H., Toyoshima, H., Osuga, J., Yamada, N., 2007. Crucial role of a long-chain fatty acid elongase, Elovl6, in obesity-induced insulin resistance. Nat. Med. 13, 1193–1202.
Matsuzaka, T., Shimano, H., Yahagi, N., Yoshikawa, T., Amemiya-Kudo, M., Hasty, A.H., Okazaki, H., Tamura, Y., Iizuka, Y., Ohashi, K., Osuga, J., Takahashi, A., Yato, S., Sone, H., Ishibashi, S., Yamada, N., 2002. Cloning and characterization of a mammalian fatty acyl-CoA elongase as a lipogenic enzyme regulated by SREBPs. J. Lipid Res. 43, 911–920.
McGarry, J.D., Brown, N.F., 1997. The mitochondrial carnitine palmitoyltransferase system. From concept to molecular analysis. Eur. J. Biochem. 244, 1–14.
Miserez, A.R., Cao, G., Probst, L.C., Hobbs, H.H., 1997. Structure of the human gene encoding sterol regulatory element binding protein 2 (SREBF2). Genomics 40, 31–40.
Mitro, N., Vargas, L., Romeo, R., Koder, A., Saez, E., 2007. T0901317 is a potent PXR ligand: implications for the biology ascribed to LXR. FEBS Lett. 581, 1721–1726.
Miyazaki, M., Flowers, M.T., Sampath, H., Chu, K., Otzelberger, C., Liu, X., Ntambi, J.M., 2007. Hepatic stearoyl-CoA desaturase-1 deficiency protects mice from carbohydrate-induced adiposity and hepatic steatosis. Cell Metab. 6, 484–496.
Miyazaki, M., Jacobson, M.J., Man, W.C., Cohen, P., Asilmaz, E., Friedman, J.M., Ntambi, J.M., 2003. Identification and characterization of murine SCD4, a novel heart-specific stearoyl-CoA desaturase isoform regulated by leptin and dietary factors. J. Biol. Chem. 278, 33904–33911.
Moon, Y.A., Hammer, R.E., Horton, J.D., 2009. Deletion of ELOVL5 leads to fatty liver through activation of SREBP-1c in mice. J. Lipid Res. 50, 412–423.
Moon, Y.A., Shah, N.A., Mohapatra, S., Warrington, J.A., Horton, J.D., 2001. Identification of a mammalian long chain fatty acyl elongase regulated by sterol regulatory element-binding proteins. J. Biol. Chem. 276, 45358–45366.
Morand, O.H., Aebi, J.D., Dehmlow, H., Ji, Y.H., Gains, N., Lengsfeld, H., Himber, J., 1997. Ro 48-8.071, a new 2,3-oxidosqualene:lanosterol cyclase inhibitor lowering plasma cholesterol in hamsters, squirrel monkeys, and minipigs: comparison to simvastatin. J. Lipid Res. 38, 373–390.
Mouzat, K., Volat, F., Baron, S., Alves, G., Pommier, A.J., Volle, D.H., Marceau, G., DeHaze, A., Dechelotte, P., Duggavathi, R., Caira, F., Lobaccaro, J.M., 2009. Absence of nuclear receptors for oxysterols liver X receptor induces ovarian hyperstimulation syndrome in mice. Endocrinology 150, 3369–3375.
Nagle, C.A., Vergnes, L., Dejong, H., Wang, S., Lewin, T.M., Reue, K., Coleman, R.A., 2008. Identification of a novel sn-glycerol-3-phosphate acyltransferase isoform, GPAT4, as the enzyme deficient in Agpat6−/− mice. J. Lipid Res. 49, 823–831.
Nelson, J.A., Steckbeck, S.R., Spencer, T.A., 1981. Biosynthesis of 24,25-epoxycholesterol from squalene 2,3;22,23-dioxide. J. Biol. Chem. 256, 1067–1068.
Neschen, S., Morino, K., Hammond, L.E., Zhang, D., Liu, Z.X., Romanelli, A.J., Cline, G.W., Pongratz, R.L., Zhang, X.M., Choi, C.S., Coleman, R.A., Shulman, G.I., 2005. Prevention of hepatic steatosis and hepatic insulin resistance in mitochondrial acyl-CoA:glycerol-sn-3-phosphate acyltransferase 1 knockout mice. Cell Metab. 2, 55–65.
Ntambi, J.M., 1999. Regulation of stearoyl-CoA desaturase by polyunsaturated fatty acids and cholesterol. J. Lipid Res. 40, 1549–1558.
Ntambi, J.M., Buhrow, S.A., Kaestner, K.H., Christy, R.J., Sibley, E., Kelly Jr., T.J., Lane, M.D., 1988. Differentiation-induced gene expression in 3T3-L1 preadipocytes. Characterization of a differentially expressed gene encoding stearoyl-CoA desaturase. J. Biol. Chem. 263, 17291–17300.
Ntambi, J.M., Miyazaki, M., Stoehr, J.P., Lan, H., Kendziorski, C.M., Yandell, B.S., Song, Y., Cohen, P., Friedman, J.M., Attie, A.D., 2002. Loss of stearoyl-CoA desaturase-1 function protects mice against adiposity. Proc. Natl. Acad. Sci. U.S.A. 99, 11482–11486.
O'Callaghan, B.L., Koo, S.H., Wu, Y., Freake, H.C., Towle, H.C., 2001. Glucose regulation of the acetyl-CoA carboxylase promoter PI in rat hepatocytes. J. Biol. Chem. 276, 16033–16039.
Oelkers, P., Behari, A., Cromley, D., Billheimer, J.T., Sturley, S.L., 1998. Characterization of two human genes encoding acyl coenzyme A:cholesterol acyltransferase-related enzymes. J. Biol. Chem. 273, 26765–26771.
Ou, J., Tu, H., Shan, B., Luk, A., DeBose-Boyd, R.A., Bashmakov, Y., Goldstein, J.L., Brown, M.S., 2001. Unsaturated fatty acids inhibit transcription of the sterol regulatory element-binding protein-1c (SREBP-1c) gene by antagonizing ligand-dependent activation of the LXR. Proc. Natl. Acad. Sci. U.S.A. 98, 6027–6032.
Ou, Z., Wada, T., Gramignoli, R., Li, S., Strom, S.C., Huang, M., Xie, W., 2011. MicroRNA hsa-miR-613 targets the human LXR{alpha} gene and mediates a feedback loop of LXR{alpha} autoregulation. Mol. Endocrinol. 25, 584–596.
Panini, S.R., Sexton, R.C., Gupta, A.K., Parish, E.J., Chitrakorn, S., Rudney, H., 1986. Regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity and cholesterol biosynthesis by oxylanosterols. J. Lipid Res. 27, 1190–1204.
Pawar, A., Botolin, D., Mangelsdorf, D.J., Jump, D.B., 2003. The role of liver X receptor-alpha in the fatty acid regulation of hepatic gene expression. J. Biol. Chem. 278, 40736–40743.
Pawar, A., Xu, J., Jerks, E., Mangelsdorf, D.J., Jump, D.B., 2002. Fatty acid regulation of liver X receptors (LXR) and peroxisome proliferator-activated receptor alpha (PPARalpha) in HEK293 cells. J. Biol. Chem. 277, 39243–39250.
Peet, D.J., Turley, S.D., Ma, W., Janowski, B.A., Lobaccaro, J.M., Hammer, R.E., Mangelsdorf, D.J., 1998. Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXR alpha. Cell 93, 693–704.
Pommier, A.J., Alves, G., Viennois, E., Bernard, S., Communal, Y., Sion, B., Marceau, G., Damon, C., Mouzat, K., Caira, F., Baron, S., Lobaccaro, J.M., 2010. Liver X Receptor activation downregulates AKT survival signaling in lipid rafts and induces apoptosis of prostate cancer cells. Oncogene 29, 2712–2723.
Ponugoti, B., Kim, D.H., Xiao, Z., Smith, Z., Miao, J., Zang, M., Wu, S.Y., Chiang, C.M., Veenstra, T.D., Kemper, J.K., 2010. SIRT1 deacetylates and inhibits SREBP-1C activity in regulation of hepatic lipid metabolism. J. Biol. Chem. 285, 33959–33970.
Postic, C., Girard, J., 2008. Contribution of de novo fatty acid synthesis to hepatic steatosis and insulin resistance: lessons from genetically engineered mice. J. Clin. Invest. 118, 829–838.
Repa, J.J., Liang, G., Ou, J., Bashmakov, Y., Lobaccaro, J.M., Shimomura, I., Shan, B., Brown, M.S., Goldstein, J.L., Mangelsdorf, D.J., 2000a. Regulation of mouse sterol regulatory element-binding protein-1c gene (SREBP-1c) by oxysterol receptors, LXRalpha and LXRbeta. Genes Dev. 14, 2819–2830.
Repa, J.J., Mangelsdorf, D.J., 2000. The role of orphan nuclear receptors in the regulation of cholesterol homeostasis. Annu. Rev. Cell Dev. Biol. 16, 459–481.
Repa, J.J., Turley, S.D., Lobaccaro, J.A., Medina, J., Li, L., Lustig, K., Shan, B., Heyman, R.A., Dietschy, J.M., Mangelsdorf, D.J., 2000b. Regulation of absorption and ABC1-mediated efflux of cholesterol by RXR heterodimers. Science 289, 1524–1529.
Robertson, K.M., Schuster, G.U., Steffensen, K.R., Hovatta, O., Meaney, S., Hultenby, K., Johansson, L.C., Svechnikov, K., Soder, O., Gustafsson, J.A., 2005. The liver X receptor-{beta} is essential for maintaining cholesterol homeostasis in the testis. Endocrinology 146, 2519–2530.
Rufo, C., Teran-Garcia, M., Nakamura, M.T., Koo, S.H., Towle, H.C., Clarke, S.D., 2001. Involvement of a unique carbohydrate-responsive factor in the glucose regulation of rat liver fatty-acid synthase gene transcription. J. Biol. Chem. 276, 21969–21975.
Russell, D.W., 2000. Oxysterol biosynthetic enzymes. Biochim. Biophys. Acta 1529, 126–135.
Sakiyama, H., Fujiwara, N., Noguchi, T., Eguchi, H., Yoshihara, D., Uyeda, K., Suzuki, K., 2010. The role of O-linked GlcNAc modification on the glucose response of ChREBP. Biochem. Biophys. Res. Commun. 402, 784–789.
Saucier, S.E., Kandutsch, A.A., Taylor, F.R., Spencer, T.A., Phirwa, S., Gayen, A.K., 1985. Identification of regulatory oxysterols, 24(S), 25-epoxycholesterol and 25-hydroxycholesterol, in cultured fibroblasts. J. Biol. Chem. 260, 14571–14579.
Schroepfer Jr., G.J., 2000. Oxysterols: modulators of cholesterol metabolism and other processes. Physiol. Rev. 80, 361–554.
Schultz, J.R., Tu, H., Luk, A., Repa, J.J., Medina, J.C., Li, L., Schwendner, S., Wang, S., Thoolen, M., Mangelsdorf, D.J., Lustig, K.D., Shan, B., 2000. Role of LXRs in control of lipogenesis. Genes Dev. 14, 2831–2838.
Sekiya, M., Yahagi, N., Matsuzaka, T., Najima, Y., Nakakuki, M., Nagai, R., Ishibashi, S., Osuga, J., Yamada, N., Shimano, H., 2003. Polyunsaturated fatty acids ameliorate hepatic steatosis in obese mice by SREBP-1 suppression. Hepatology 38, 1529–1539.
Shenoy, S.D., Spencer, T.A., Mercer-Haines, N.A., Alipour, M., Gargano, M.D., Runge-Morris, M., Kocarek, T.A., 2004. CYP3A induction by liver X receptor ligands in primary cultured rat and mouse hepatocytes is mediated by the pregnane X receptor. Drug Metab. Dispos. 32, 66–71.
Shevchenko, A., Simons, K., 2010. Lipidomics: coming to grips with lipid diversity. Nat. Rev. Mol. Cell Biol. 11, 593–598.
Shimano, H., Horton, J.D., Shimomura, I., Hammer, R.E., Brown, M.S., Goldstein, J.L., 1997. Isoform 1c of sterol regulatory element binding protein is less active than isoform 1a in livers of transgenic mice and in cultured cells. J. Clin. Invest. 99, 846–854.
Shimano, H., Yahagi, N., Amemiya-Kudo, M., Hasty, A.H., Osuga, J., Tamura, Y., Shionoiri, F., Iizuka, Y., Ohashi, K., Harada, K., Gotoda, T., Ishibashi, S., Yamada, N., 1999. Sterol regulatory element-binding protein-1 as a key transcription factor for nutritional induction of lipogenic enzyme genes. J. Biol. Chem. 274, 35832–35839.

Shimomura, I., Shimano, H., Horton, J.D., Goldstein, J.L., Brown, M.S., 1997. Differential expression of exons 1a and 1c in mRNAs for sterol regulatory element binding protein-1 in human and mouse organs and cultured cells. J. Clin. Invest. 99, 838–845.
Smith, L.L., 1987. Cholesterol autoxidation 1981–1986. Chem. Phys. Lipids 44, 87–125.
Smith, S., 1994. The animal fatty acid synthase: one gene, one polypeptide, seven enzymes. FASEB J. 8, 1248–1259.
Smith, S.J., Cases, S., Jensen, D.R., Chen, H.C., Sande, E., Tow, B., Sanan, D.A., Raber, J., Eckel, R.H., Farese Jr., R.V., 2000. Obesity resistance and multiple mechanisms of triglyceride synthesis in mice lacking Dgat. Nat. Genet. 25, 87–90.
Song, B.L., DeBose-Boyd, R.A., 2004. Ubiquitination of 3-hydroxy-3-methylglutaryl-CoA reductase in permeabilized cells mediated by cytosolic E1 and a putative membrane-bound ubiquitin ligase. J. Biol. Chem. 279, 28798–28806.
Song, C., Hiipakka, R.A., Liao, S., 2001. Auto-oxidized cholesterol sulfates are antagonistic ligands of liver X receptors: implications for the development and treatment of atherosclerosis. Steroids 66, 473–479.
Sorger, D., Daum, G., 2002. Synthesis of triacylglycerols by the acyl-coenzyme A:diacyl-glycerol acyltransferase Dga1p in lipid particles of the yeast Saccharomyces cerevisiae. J. Bacteriol. 184, 519–524.
Spyridon, M., Moraes, L.A., Jones, C.I., Sage, T., Sasikumar, P., Bucci, G., Gibbins, J.M., 2011. LXR as a novel antithrombotic target. Blood 117, 5751–5761.
Stoeckman, A.K., Ma, L., Towle, H.C., 2004. Mlx is the functional heteromeric partner of the carbohydrate response element-binding protein in glucose regulation of lipogenic enzyme genes. J. Biol. Chem. 279, 15662–15669.
Stone, S.J., Levin, M.C., Zhou, P., Han, J., Walther, T.C., Farese Jr., R.V., 2009. The endoplasmic reticulum enzyme DGAT2 is found in mitochondria-associated membranes and has a mitochondrial targeting signal that promotes its association with mitochondria. J. Biol. Chem. 284, 5352–5361.
Stone, S.J., Myers, H.M., Watkins, S.M., Brown, B.E., Feingold, K.R., Elias, P.M., Farese Jr., R.V., 2004. Lipopenia and skin barrier abnormalities in DGAT2-deficient mice. J. Biol. Chem. 279, 11767–11776.
Strittmatter, P., Spatz, L., Corcoran, D., Rogers, M.J., Setlow, B., Redline, R., 1974. Purification and properties of rat liver microsomal stearyl coenzyme A desaturase. Proc. Natl. Acad. Sci. U.S.A. 71, 4565–4569.
Sukumaran, S., Barnes, R.I., Garg, A., Agarwal, A.K., 2009. Functional characterization of the human 1-acylglycerol-3-phosphate-O-acyltransferase isoform 10/glycerol-3-phosphate acyltransferase isoform 3. J. Mol. Endocrinol. 42, 469–478.
Svensson, S., Ostberg, T., Jacobsson, M., Norstrom, C., Stefansson, K., Hallen, D., Johansson, I.C., Zachrisson, K., Ogg, D., Jendeberg, L., 2003. Crystal structure of the heterodimeric complex of LXRalpha and RXRbeta ligand-binding domains in a fully agonistic conformation. EMBO J. 22, 4625–4633.
Tabor, D.E., Kim, J.B., Spiegelman, B.M., Edwards, P.A., 1999. Identification of conserved cis-elements and transcription factors required for sterol-regulated transcription of stearoyl-CoA desaturase 1 and 2. J. Biol. Chem. 274, 20603–20610.
Takeuchi, Y., Yahagi, N., Izumida, Y., Nishi, M., Kubota, M., Teraoka, Y., Yamamoto, T., Matsuzaka, T., Nakagawa, Y., Sekiya, M., Iizuka, Y., Ohashi, K., Osuga, J., Gotoda, T., Ishibashi, S., Itaka, K., Kataoka, K., Nagai, R., Yamada, N., Kadowaki, T., Shimano, H., 2010. Polyunsaturated fatty acids selectively suppress sterol regulatory element-binding protein-1 through proteolytic processing and autoloop regulatory circuit. J. Biol. Chem. 285, 11681–11691.
Talukdar, S., Hillgartner, F.B., 2006. The mechanism mediating the activation of acetyl-coenzyme A carboxylase-alpha gene transcription by the liver X receptor agonist T0-901317. J. Lipid Res. 47, 2451–2461.
Tang, W., Yuan, J., Chen, X., Gu, X., Luo, K., Li, J., Wan, B., Wang, Y., Yu, L., 2006. Identification of a novel human lysophosphatidic acid acyltransferase, LPAAT-theta, which activates mTOR pathway. J. Biochem. Mol. Biol. 39, 626–635.
Taylor, F.R., Kandutsch, A.A., Gayen, A.K., Nelson, J.A., Nelson, S.S., Phirwa, S., Spencer, T.A., 1986. 24,25-Epoxysterol metabolism in cultured mammalian cells and repression of 3-hydroxy-3-methylglutaryl-CoA reductase. J. Biol. Chem. 261, 15039–15044.
Teboul, M., Enmark, E., Li, Q., Wikstrom, A.C., Pelto-Huikko, M., Gustafsson, J.A., 1995. OR-1, a member of the nuclear receptor superfamily that interacts with the 9-cis-retinoic acid receptor. Proc. Natl. Acad. Sci. U.S.A. 92, 2096–2100.
Tobin, K.A., Ulven, S.M., Schuster, G.U., Steineger, H.H., Andresen, S.M., Gustafsson, J.A., Nebb, H.I., 2002. Liver X receptors as insulin-mediating factors in fatty acid and cholesterol biosynthesis. J. Biol. Chem. 277, 10691–10697.
Vergnes, L., Beigneux, A.P., Davis, R., Watkins, S.M., Young, S.G., Reue, K., 2006. Agpat6 deficiency causes subdermal lipodystrophy and resistance to obesity. J. Lipid Res. 47, 745–754.
Viennois, E., Pommier, A.J., Mouzat, K., Oumeddour, A., El Hajjaji, F.Z., Dufour, J., Caira, F., Volle, D.H., Baron, S., Lobaccaro, J.M., 2011. Targeting liver X receptors in human health: deadlock or promising trail? Expert Opin. Ther. Targets 15, 219–232.
Villablanca, E.J., Raccosta, L., Zhou, D., Fontana, R., Maggioni, D., Negro, A., Sanvito, F., Ponzoni, M., Valentinis, B., Bregni, M., Prinetti, A., Steffensen, K.R., Sonnino, S., Gustafsson, J.A., Doglioni, C., Bordignon, C., Traversari, C., Russo, V., 2010. Tumor-mediated liver X receptor-alpha activation inhibits CC chemokine receptor-7 expression on dendritic cells and dampens antitumor responses. Nat. Med. 16, 98–105.
Volle, D.H., Mouzat, K., Duggavathi, R., Siddeek, B., Dechelotte, P., Sion, B., Veyssiere, G., Benahmed, M., Lobaccaro, J.M., 2007. Multiple roles of the nuclear receptors for oxysterols liver X receptor to maintain male fertility. Mol. Endocrinol. 21, 1014–1027.
Wang, S., Lee, D.P., Gong, N., Schwerbrock, N.M., Mashek, D.G., Gonzalez-Baro, M.R., Stapleton, C., Li, L.O., Lewin, T.M., Coleman, R.A., 2007. Cloning and functional characterization of a novel mitochondrial N-ethylmaleimide-sensitive glycerol-3-phosphate acyltransferase (GPAT2). Arch. Biochem. Biophys. 465, 347–358.
Wang, X., Sato, R., Brown, M.S., Hua, X., Goldstein, J.L., 1994. SREBP-1, a membrane-bound transcription factor released by sterol-regulated proteolysis. Cell 77, 53–62.
Willy, P.J., Umesono, K., Ong, E.S., Evans, R.M., Heyman, R.A., Mangelsdorf, D.J., 1995. LXR, a nuclear receptor that defines a distinct retinoid response pathway. Genes Dev. 9, 1033–1045.
Wong, J., Quinn, C.M., Brown, A.J., 2004. Statins inhibit synthesis of an oxysterol ligand for the liver X receptor in human macrophages with consequences for cholesterol flux. Arterioscler. Thromb. Vasc. Biol. 24, 2365–2371.
Wong, J., Quinn, C.M., Brown, A.J., 2006. SREBP-2 positively regulates transcription of the cholesterol efflux gene, ABCA1, by generating oxysterol ligands for LXR. Biochem. J. 400, 485–491.
Wong, J., Quinn, C.M., Brown, A.J., 2007. Synthesis of the oxysterol, 24(S), 25-epoxycholesterol, parallels cholesterol production and may protect against cellular accumulation of newly-synthesized cholesterol. Lipids Health Dis. 6, 10.
Wong, J., Quinn, C.M., Gelissen, I.C., Brown, A.J., 2008a. Endogenous 24(S),25-epoxycholesterol fine-tunes acute control of cellular cholesterol homeostasis. J. Biol. Chem. 283, 700–707.
Wong, J., Quinn, C.M., Gelissen, I.C., Jessup, W., Brown, A.J., 2008b. The effect of statins on ABCA1 and ABCG1 expression in human macrophages is influenced by cellular cholesterol levels and extent of differentiation. Atherosclerosis 196, 180–189.
Xu, H., Wilcox, D., Nguyen, P., Voorbach, M., Suhar, T., Morgan, S.J., An, W.F., Ge, L., Green, J., Wu, Z., Gimeno, R.E., Reilly, R., Jacobson, P.B., Collins, C.A., Landschulz, K., Surowy, T., 2006. Hepatic knockdown of mitochondrial GPAT1 in ob/ob mice improves metabolic profile. Biochem. Biophys. Res. Commun. 349, 439–448.
Xu, L., Bai, Q., Rodriguez-Agudo, D., Hylemon, P.B., Heuman, D.M., Pandak, W.M., Ren, S., 2010. Regulation of hepatocyte lipid metabolism and inflammatory response by 25-hydroxycholesterol and 25-hydroxycholesterol-3-sulfate. Lipids 45, 821–832.
Yabe, D., Komuro, R., Liang, G., Goldstein, J.L., Brown, M.S., 2003. Liver-specific mRNA for Insig-2 down-regulated by insulin: implications for fatty acid synthesis. Proc. Natl. Acad. Sci. U.S.A. 100, 3155–3160.
Yamamoto, T., Shimano, H., Inoue, N., Nakagawa, Y., Matsuzaka, T., Takahashi, A., Yahagi, N., Sone, H., Suzuki, H., Toyoshima, H., Yamada, N., 2007. Protein kinase A suppresses sterol regulatory element-binding protein-1C expression via phosphorylation of liver X receptor in the liver. J. Biol. Chem. 282, 11687–11695.
Yamashita, H., Takenoshita, M., Sakurai, M., Bruick, R.K., Henzel, W.J., Shillinglaw, W., Arnot, D., Uyeda, K., 2001. A glucose-responsive transcription factor that regulates carbohydrate metabolism in the liver. Proc. Natl. Acad. Sci. U.S.A. 98, 9116–9121.
Yasuda, T., Grillot, D., Billheimer, J.T., Briand, F., Delerive, P., Huet, S., Rader, D.J., 2010. Tissue-specific liver X receptor activation promotes macrophage reverse cholesterol transport in vivo. Arterioscler. Thromb. Vasc. Biol. 30, 781–786.
Ye, G.M., Chen, C., Huang, S., Han, D.D., Guo, J.H., Wan, B., Yu, L., 2005. Cloning and characterization a novel human 1-acyl-sn-glycerol-3-phosphate acyltransferase gene AGPAT7. DNA Seq. 16, 386–390.
Yokoyama, C., Wang, X., Briggs, M.R., Admon, A., Wu, J., Hua, X., Goldstein, J.L., Brown, M.S., 1993. SREBP-1, a basic-helix-loop-helix-leucine zipper protein that controls transcription of the low density lipoprotein receptor gene. Cell 75, 187–197.
Zelcer, N., Khanlou, N., Clare, R., Jiang, Q., Reed-Geaghan, E.G., Landreth, G.E., Vinters, H.V., Tontonoz, P., 2007. Attenuation of neuroinflammation and Alzheimer's disease pathology by liver X receptors. Proc. Natl. Acad. Sci. U.S.A. 104, 10601–10606.
Zelcer, N., Tontonoz, P., 2006. Liver X receptors as integrators of metabolic and inflammatory signaling. J. Clin. Invest. 116, 607–614.
Zhang, W., Patil, S., Chauhan, B., Guo, S., Powell, D.R., Le, J., Klotsas, A., Matika, R., Xiao, X., Franks, R., Heidenreich, K.A., Sajan, M.P., Farese, R.V., Stolz, D.B., Tso, P., Koo, S.H., Montminy, M., Unterman, T.G., 2006. FoxO1 regulates multiple metabolic pathways in the liver: effects on gluconeogenic, glycolytic, and lipogenic gene expression. J. Biol. Chem. 281, 10105–10117.
Zheng, Y., Prouty, S.M., Harmon, A., Sundberg, J.P., Stenn, K.S., Parimoo, S., 2001. Scd3-a novel gene of the stearoyl-CoA desaturase family with restricted expression in skin. Genomics 71, 182–191.