The recent explosion of research on orphan nuclear receptors has provided new insights into the regulation of lipid metabolism. A recurring theme that continues to emerge is the evolution of an elaborate, autoregulated system for sensing and metabolizing biologically active lipids. One branch of this system includes the oxysterol and bile acid receptors, which serve as sensors for sterol metabolism that regulate the transport and metabolism of cholesterol and bile acids. This review will focus on the five orphan nuclear receptors that thus far are known to govern cholesterol and bile acid homeostasis. These receptors include: the liver X receptors (LXRA and LXRB); farnesoid X receptor (FXR); liver receptor homologue-1 (LRH-1); and small heterodimer partner (SHP). Below we will summarize the discovery and molecular biology of these orphan receptors, their roles in regulating cholesterol and bile acid homeostasis, and their potential use as therapeutic targets for the treatment of lipid metabolism disorders.

The Nuclear Receptor Players

LXRs, the Oxysterol Receptors—The first human LXR was named because of its initial isolation from a liver cDNA library and its liver-enriched expression (reviewed in Ref. 1). The LXR subfamily consists of two members, LXRA (NR1H3) and LXRB (NR1H2). Both subtypes are expressed in the enterohepatic system, but each has a distinct pattern of expression in other tissues. Whereas LXRB is ubiquitously expressed, LXRA expression is restricted to tissues rich in lipid metabolism (Fig. 1). LXRA and LXRB form obligate heterodimers with the retinoid X receptor (RXR), which is bound and activated by 9-cis-retinoic acid. The RXR-LXR heterodimer preferentially binds to a DNA hormone response element (termed an LXRE) that consists of two hexanucleotide repeats separated by 4 nucleotides (i.e. DR4) (2, 3).

The first LXR activators were identified by screening organic tissue extracts and natural compound libraries. These activators consisted of a select group of oxysterols derived from tissue-specific cholesterol metabolism in the liver, brain, and gonads. The most potent LXR activators identified were 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, and 24(S),25-epoxycholesterol (4, 5). A binding assay based on scintillation proximity technology demonstrated that these compounds bind with high affinity ($K_d$ values of 0.1–0.4 mM) (6, 7). Since the identification of these natural ligands, extensive structure-activity relationship studies on LXR ligands have been performed and have yielded several synthetic LXR agonists, including a potent, high affinity ($K_d = 50$ nM), non-steroidal ligand (8, 9).

FXR, the Bile Acid Receptor—FXR (NR1H4) was first isolated from a rat liver cDNA library and structurally is most closely related to the insect edysone receptor and the LXR subfamily (10). Expression of FXR is restricted to the enterohepatic system, kidneys, and adrenals (Fig. 1). FXR forms an obligate heterodimer with RXR and binds to an inverted hexanucleotide repeat spaced by one nucleotide (i.e. IR1) (10).

The name FXR (farnesoid X receptor) derives from early studies that revealed supraphysiological concentrations of farnesol could activate some species of FXR (10). However, more recently, three independent groups identified bile acids as the endogenous ligands for FXR (11–13). Together, these researchers demonstrated that physiologic concentrations of biologically active bile acids can directly bind and transactivate FXR. The primary bile acid chenodeoxycholic acid was shown to be the most potent FXR ligand in vitro and in cells at an EC_{50} of 10–50 mM. FXR can also be activated by the secondary bile acids lithocholic acid and deoxycholic acid (11–13). Importantly, cholic acid and several conjugated bile acids also bind FXR in vitro, but because of their membrane impermeability they only transactivate FXR in cells that express a bile acid transporter, such as the sodium taurocholate cotransporter (NTCP) or the ileal bile acid transporter. Interestingly, this makes FXR the only known nuclear receptor that requires active transport of its endogenous ligands into its target cell. This requirement selectively limits the ligand-dependent activity of FXR to tissues (e.g. the ileum) that co-express a bile acid transporter (12). In addition to bile acids, a number of synthetic compounds are able to bind and activate FXR. These include the synthetic retinoid, TTPNB (14), and a novel, high affinity ($K_d = 50$ nM) non-steroidal agonist (15, 16).

LRH-1, a Tissue-specific Competence Factor—LRH-1 (NR5A2) is a monomeric orphan receptor that has been isolated by several groups and shown to be the mammalian homolog of the Drosophila fushi tarazu F1 receptor gene (17, 18). Expression of LRH-1 is limited to the liver, pancreas, intestine, and ovary. LRH-1 binds DNA as a monomer to an extended nuclear receptor half-site (Fig. 1). LRH-1 is the enterohepatic paralog of mammalian steroidalogenic factor-1 (SF-1), which has been shown to be essential for the development of the hypothalamic pituitary-adrenal and gonadal axes. SF-1 serves as a tissue-specific competence factor for transcription of steroidalogenic P450 enzymes (19). In similar fashion, LRH-1 is believed to serve as a tissue-specific competence factor for bile acid synthesis. To date, no ligands have been reported for LRH-1, but several target genes have been identified including a-fetoprotein (17), SHP (20), cholesterol ester transfer protein (CETP) (21), and a number of crucial bile acid-synthesizing enzymes, such as cholesterol 7a-hydroxylase (CYP7A1) (18) and sterol 12a-hydroxylase (CYP8B) (22, 23).

SHP, a Tissue-specific Repressor—SHP (NR0B2) was isolated by yeast two-hybrid techniques because of its ability to heterodimerize with several other nuclear receptors (24). Structurally, SHP is an atypical nuclear orphan receptor that has a ligand-binding domain but no DNA-binding domain. SHP is expressed in the liver, intestine, heart, pancreas, and adrenal glands (Fig. 1) (24). It shows greatest similarity to DAX1, another atypical nuclear orphan receptor without a DNA-binding domain that heterodimerizes with SF-1 and strongly represses SF-1 activity (25, 26). In a similar fashion, SHP has been shown to be a potent repressor of LRH-1 and its cognate target genes (discussed below). The current understanding of SHP action suggests that it may not have an endogenous ligand but rather it functions as a constitutive repressor (16, 24, 27–32).
Nuclear Receptor Control of Sterol Homeostasis

The Cholesterol Sensor: LXR—A number of studies over the past 3 years have elucidated the role of LXRs as the body’s key sensing apparatus for maintaining cholesterol homeostasis by regulating cholesterol catabolism, storage, absorption, and transport through the transcriptional control of the key target genes involved in these processes. This work has been facilitated by the use of mouse models to identify LXRs target genes (Table I) and by characterization of the phenotype of Lxr-null animals. The LXR regulatory pathways are summarized in Fig. 2 and discussed below.

The liver serves as the primary site for the elimination of cholesterol from the body (see Fig. 2). In the hepatocyte excess cholesterol has been shown to generate oxysterols (33), the signaling molecules that stimulate transcription of cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme in the classic bile acid biosynthesis pathway. Increased CYP7A1 catalyzes conversion of cholesterol into bile acids. In this pathway, bile acids serve as the direct end products of cholesterol catabolism and stimulate the excretion of excess cholesterol into the bile and feces (34, 35). LXRα has been shown to control this regulatory cascade by activating CYP7A1 transcription through an LXRE in the CYP7A1 promoter (5, 36). Physiological evidence for this process has been provided by the analysis of Lxrα-null mice, which fail to up-regulate CYP7A1 expression in response to cholesterol, and as a result, rapidly accumulate toxic levels of hepatic cholesterol. Although LXRβ is also expressed in the liver, its presence does not rescue the loss of LXRα in these mice (36). This conclusion has been confirmed by the generation of Lxrβ-null mice, which like wild-type animals are resistant to increased dietary cholesterol (37).2 Interestingly, the Lxrα/Lxrβ double knockout mice have a more severe liver phenotype than the Lxrα-null mice. Together these studies have provided unequivocal evidence that the LXRs serve as one of the body’s key sensors of dietary cholesterol and thereby regulate an important feed forward pathway in cholesterol catabolism.

Because the process of cholesterol catabolism is liver-specific, other tissues in the body must deal with elevated cholesterol by alternative means. There are two primary mechanisms by which these tissues deal with excess cholesterol: 1) esterification and storage of cholesterol within the cell; and 2) efflux of free cholesterol out of the cell and transport of this cholesterol back to the liver for further catabolic elimination. LXRs regulate the esterification and storage of cholesterol by an indirect means that involves the coordinate regulation of another important lipid metabolic pathway, fatty acid synthesis. Under high cholesterol conditions, LXRs up-regulate transcription of sterol regulatory element-binding protein 1c (SREBP-1c) (9, 38), the master regulator of genes involved in fatty acid synthesis (39). Increased SREBP-1c protein results in increased cleavage of this membrane-bound basic helix-loop-helix transcription factor and the transcription of a number of fatty acid-synthesizing enzymes, including steroyl-CoA desaturase-1. Steroyl-CoA desaturase-1 is an enzyme responsible for the Δ9-cis desaturation of steroyl-CoA and palmitoyl-

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2 J. M. Lobaccaro and D. J. Mangelsdorf, unpublished observation.

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**Table I**

| Nuclear receptor | Target gene | Regulation of expression | Function | Ref. |
|------------------|-------------|--------------------------|----------|-----|
| LXR              | CYP7A1      | Bile acid synthesis      | 5, 36    |
| SREBP-1c         |             | Lipogenesis              | 9, 38    |
| ABCA1            |             | Cholesterol efflux       | 8, 41    |
| ABCG1           |             | Cholesterol transport    | 43       |
| ABCG5/G8        |             | Sphingolipid efflux      | 40       |
| CETP             |             | Cholesterol ester transfer | 49     |
| SHP              |             | HDL particle formation   | 44       |
| LXR              | SHP         | Transcriptional repressor | 16, 30   |
| CYP8B1           |             | Bile acid synthesis      | 22, 23   |
| SHP              |             | Transcriptional repressor | 16, 30   |
| CETP             |             | Bile acid efflux         | 11, 59   |
| SHP              |             | HDL particle formation   | 62, 63   |
| LXR              | CYP7A1      | Bile acid synthesis      | 16, 18, 30 |
| LXR              | CYP8B1      | Bile acid synthesis      | 16, 20, 30 |
| CETP             |             | Cholesterol ester transfer | 49    |
| SHP              |             | Bile acid synthesis      | 11, 16, 30 |
| SHP              |             | Reexpression             | 16, 30   |

* LXR response elements have not yet been mapped.
* Phospholipid transfer protein.
* Repression by SHP is inferred from LRH-1 regulation studies.

**Fig. 1.** Characterization of enterohepatic nuclear orphan receptors involved in sterol metabolism. Tissue expression of each receptor in the adult mouse is shown using northern blot analysis (cytochrome P450, shown as a comparative control). The mode of DNA binding, response element, and ligands are also listed.

**Fig. 2.** Model of nuclear receptor control of sterol metabolism. In the macrophage, intestine, and hepatocyte, LXRs increase storage, efflux, and transport of cholesterol to decrease intracellular cholesterol levels. In the hepatocyte, LXRs govern forward regulation of cholesterol catabolism into bile acids. Feedback repression, efflux, and enterohepatic recirculation of bile acids are regulated by FXR. See text for details. Yellow boxes represent LXR target genes and green boxes represent FXR target genes.

CoA, converting them to oleoyl-CoA and palmitoleoyl-CoA, respectively. Increased oleoyl-CoA, the preferred substrate for acyl-CoA:cholesterol acyltransferase, enables increased esterification of cholesterol for storage under high cholesterol conditions. Furthermore, increased fatty acid synthesis yields phospholipids that are required for lipoprotein transport of excess cholesterol and for main-
taining plasma membrane integrity by providing the correct phospholipid/cholesterol ratio. Lipid metabolism studies in Lxr-null mice have confirmed the essential role of LXRs in this pathway (9, 36–38).

When the amount of cholesterol exceeds the storage capacity of the cell, the increased cholesterol load is alleviated by effluxing the excess cholesterol back into the serum, where it is transported to the liver by a process that is termed reverse cholesterol transport. Cellular efflux of free cholesterol and phospholipids is a component of membrane ATP-binding cassette (ABC) transporters that deliver cholesterol to high density lipoproteins (HDL) that serve as the primary serum transporter of cholesterol back to the liver. This process is especially important in the enterocyte and macrophage, both of which can be exposed to large surges in sterols because of unsaturable uptake of free cholesterol from the diet and serum.

Several recent studies have now shown that LXRs prevent the overaccumulation of sterols in the intestine and macrophage by the induction of multiple ABC transporters and acceptor proteins involved in this pathway (8, 40–44). In the macrophage, activation of the RXR-LXR heterodimer by dietary cholesterol or oxysterols or RXR/LXR agonists stimulates transcription of ABCA1 and ABCG1 (8, 43). ABCA1 is the protein mutated in Tangier disease, a rare autosomal recessive disorder characterized by low circulating levels of HDL and the appearance of cholesterol-engorged macrophages and reticuloendothelial cells (45). ABCA1 is responsible for the cellular efflux of free cholesterol and phospholipids to apolipoprotein acceptors. In vitro and in vivo studies have shown that ABCA1 is a direct target of the RXR-LXR heterodimer and that LXRs are required for cholesterol-induced regulation of the ABCA1 and ABCG1 promoters (41, 46, 47). ABCG1 is another transporter expressed in macrophages that has been suggested to play a role in cellular efflux of cholesterol and phospholipids (42). In addition, LXRs also increase the availability of HDL acceptor particles through transcriptional up-regulation of ApoE, which contributes to the formation of HDL particles (44, 48).

After free cholesterol is accepted by the HDL particle, it is esterified by lecithin-cholesterol acyltransferase. The HDL particle then has two fates. Through LXR up-regulation of CETP, HDL can exchange cholesterol esters for triglycerides carried by other lipoproteins (49). Alternatively, HDL can deliver cholesterol esters to the liver for excretion and cholesterol absorption discussed above (50).

Similar to the macrophage, in the small intestine increased dietary and/or secreted biliary cholesterol activates LXR and increases transcription of at least three ABC transporters, ABCA1, ABCG5, and ABCG8. In the enterocyte, these transporters are hypothesized to increase cholesterol efflux into the intestinal lumen and thereby prevent net sterol absorption. In vitro studies have shown that both LXR agonists and RXR agonists (i.e., rexinoids) strongly up-regulate the ABC transporters in enterocytes and inhibit cholesterol absorption (8). Consistent with these findings, one of the studies performed in Abca1-null mice showed a significant elevation in cholesterol absorption (51).

Subtraction cloning from mice treated with an LXR agonist has recently led to the identification of two new ABC half-transporters, ABCG5 and ABCG8 (40). Mutations in these transporters, which are expressed exclusively in the liver and intestine, are responsible for sitosterolemia, a rare genetic disorder characterized by hyperabsorption of cholesterol and toxic plant sterols (40, 52). Experiments in Lxr-null mice have confirmed that these transporters are transcriptional targets of LXR action.3 Taken together, these studies have established the role of at least four ABC transporters as essential downstream mediators of the RXR/LXR signaling cascade.

The Bile Acid Sensor: FXR—The ability of bile acids to both activate and repress transcription of genes involved in bile acid metabolism has been recognized for many years (see Table I). Similar to the pathways that regulate cholesterol homeostasis, bile acid–induced gene expression and uptake. As the bile acid receptor, FXR is the key factor that maintains bile acid homeostasis by modulating the expression of these genes (summarized in Fig. 2).

The best understood process in bile acid homeostasis is that which governs feedback repression of synthesis. When the bile acid pool size is increased, transcription of CYP7A1 is repressed (34, 35). Preliminary studies had identified a conserved “bile acid response element” in the CYP7A1 promoter of all species, a region later identified as an LRH-1 binding site (18, 53). On the CYP7A1 promoter, LRH-1 serves as a competence factor required for liver-specific expression of CYP7A1 (18, 30). Bile acid–mediated repression of CYP7A1 and other genes occurs through FXR- and bile acid–induced expression of SHP, the major FXR target gene in the liver (16, 30). Increased SHP protein forms an inactivating heterodimeric complex with LRH-1, turning off transcription of CYP7A1 and other LRH-1 target genes, including sterol 22-hydroxylase (CYP8B1) and SHP itself. The ability of SHP to repress its own transcription provides an elegant mechanism by which the bile acid sensor turns itself on and off (16, 30).

Although the Shp- and Lrh-1-null mice have not yet been characterized, in vivo evidence supporting this mechanism has come from studies in Fxr-null mice. In wild-type mice treated with rexinoids and/or FXR agonists, transcriptional repression of CYP7A1 is coincident with a diacemic induction of SHP (16, 30). In contrast, Fxr-null mice fail to up-regulate SHP expression and consequently fail to repress transcription of CYP7A1 (54). Furthermore, analysis of Cyp7a1- and Cyp27a1-null mice, where bile acid pool sizes are significantly diminished, has shown that SHP levels are severely reduced. Consequently, SHP target genes are derepressed. As would be predicted, restoration of the bile acid pool by feeding bile acids restores SHP expression and appropriately down-regulates SHP target genes (30, 55).

In addition to bile acid synthesis, FXR regulates transport and prevents overaccumulation of bile acids in the hepatocyte. The two principal transporters governing bile acid levels in the hepatocyte are the sodium taurocholate cotransporter polypeptide (NTCP) and the bile salt export pump (BSEP). NTCP is responsible for bile acid uptake into the hepatocyte, and its expression is down-regulated by FXR (54). Simultaneously, FXR up-regulates transcription of BSEP and increases bile acid efflux into the bile (54, 56). In the intestine, bile acids up-regulate transcription of the ileal bile acid–binding protein (IBABP) (11, 57–60). This protein is believed to assist in decreasing the effective free concentration of bile acids to limit their toxicity and recirculation. Recent studies have identified IBABP as a direct target gene of FXR (11, 59).

Definitive evidence that FXR serves as the bile acid sensor has come from analysis of the Fxr-null mice (54). In addition to being unable to down-regulate bile acid synthesis, Fxr-null mice fail to regulate appropriately BSEP, NTCP, and IBABP. As a result, Fxr-null mice develop cholestasis and severe liver damage.

Therapeutic Potential of Nuclear Orphan Receptors eLiXiRs—The model in Fig. 2 summarizes the regulation of cholesterol and bile acid metabolism by nuclear receptors. Given the importance of other nuclear hormone receptors as drug targets, the biology illustrated in Fig. 2 suggests the potential to develop a new series of therapeutic targets for the treatment of cholesterol and bile acid metabolism disorders. First line treatments for hypercholesterolemia currently entail the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (or “statins”). Although statins have been very effective, they are not able to prevent full progression of atherosclerosis, and some patients are non-responsive to statin treatment.

The identification of LXR as a cholesterol sensor that governs transport, absorption, and catabolism of sterols provides new possibilities for intervention in the treatment of hypercholesterolemia. Ideally, an LXR drug (i.e., an eLXiR) would have three potent antiatherogenic effects: 1) increased catabolism of free and cholesterol esters through up-regulation of CYP7A1; 2) inhibition of dietary cholesterol absorption by up-regulating intestinal transporters (ABCA1, ABCG5, and ABCG8); and 3) increased cholesterol transport from peripheral tissues through up-regulation of efflux transporters (ABCA1 and ABCG1) and apolipoproteins (ApoE). One potential problem with an LXR agonist is its ability to also up-regulate fatty acid synthesis, resulting in hypertriglyceridemia. The future design of LXR agonists would have to dissociate this process from the beneficial effects on cholesterol metabolism. One possibility might be to design specific agonists for LXRα and LXRβ. Studies of LXRα

3 J. J. Repa, H. H. Hobbs, and D. J. Mangelsdorf, unpublished observation.
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and LXRs single and double knock out mice have provided evidence that the LXRs have overlapping but distinct roles. LXR subtype-specific agonists would be useful in identifying these pathways and would aid in the design of drugs that have selective activities.

FixER—Although it is clear that FXR mediates repression of bile acid synthesis, it is less clear whether it would be therapeutically useful to inhibit this process with an FXR drug (i.e. a FixER). For example, a FXR antagonist would increase conversion of cholesterol into bile acids and lower hepatic cholesterol levels, which would be therapeutically desirable. Indeed, transgenic studies overexpressing CYP7A1 have shown to lower serum cholesterol levels (61). On the other hand, when the FXR-RXR heterodimer is activated by an agonist, bile acid synthesis and dietary cholesterol absorption are repressed (8). Furthermore, FixR-null mice on a low fat diet have elevated serum triglycerides and cholesterol levels, in particular elevated very low density lipoprotein and low density lipoprotein. In addition, phospholipid transfer protein, a serum protein that is believed to help form HDL, has been shown to decrease overexpressing CYP7A1 have been shown to lower serum cholesterol levels (8). Furthermore, FixR-null mice on a low fat diet have elevated serum triglycerides and cholesterol levels, in particular elevated very low density lipoprotein and low density lipoprotein. In addition, phospholipid transfer protein, a serum protein that is believed to help form HDL, has been shown to decrease.

Specific agonists would be useful in identifying these pathways and designing pharmaceutical drugs. Whether specific phamacophores designed for binding to these pockets will have therapeutic utility remains to be seen.

Summary

With the recent characterizations of several nuclear orphan receptors, an emerging theme has developed placing these receptors as master regulators of lipid metabolism. The identification of the oxysterol receptors (LXRs) and a bile acid receptor (FXR) has opened up new and exciting fields of research in cholesterol and bile acid metabolism. Understanding the physiological pathways that these receptors regulate and designing pharmaceutical drugs for these receptors may provide alternative treatments for cholesterol and bile acid disorders.

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Orphan Nuclear Receptors as eLiXiRs and FiXeRs of Sterol Metabolism
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