High-density lipoprotein (HDL) cholesterol is widely recognized as the good plasma cholesterol for coronary heart disease and is believed to be responsible for cholesterol transport from peripheral tissues back to the liver, the central clearing house for cholesterol in the body. Interestingly, the liver is also a major site for HDL production, although the process of particle assembly is believed to occur intravascularly.1–4 ApoA-I is secreted by the liver in lipid-poor form and then interacts with ATP-binding cassette protein A1 (ABCA1) in liver and peripheral tissues to acquire phospholipids and cholesterol, forming a discoidal HDL intermediate sometimes referred to as pre–β-HDL. These particles are excellent substrates for the liver-derived plasma enzyme lecithin:cholesterol acyltransferase. Using the sn-2 fatty acids of the particle-associated phosphatidylcholine, lecithin:cholesterol acyltransferase catalyzes the esterification of cholesterol, which is partially derived from peripheral tissues. This reaction produces the cholesteryl esters (CE) that form the neutral lipid core of the mature spherical HDL particles. In addition to whole HDL particle uptake by the liver, the CE of mature HDL can also be removed by the liver through a process of selective CE uptake via scavenger receptor-class B type I (SR-BI). Both uptake mechanisms result in a directional flux of cholesterol from the plasma compartment to the liver. Some of the HDL-derived cholesterol becomes part of the hepatic pool that is used for bile acid formation (with subsequent secretion together with cholesterol into bile). Bile acid synthesis represents the primary pathway of cholesterol catabolism in the body. In addition, a portion of the hepatic pool of cholesterol is used for esterification by acyl-CoA:cholesterol o-acyltransferase 2 (ACAT2) with subsequent secretion of the CE in very low-density lipoprotein or storage in cytoplasm as CE-containing lipid droplets.5 CE solubility in membranes is limited; hence, ACAT2 functions to protect cell membranes from becoming overloaded with cholesterol.

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Because of the many intersecting pathways for cholesterol metabolism and disposal in the liver, the need for regulatory integration is critical. It was recently recognized that apoA-I synthesis is downregulated by bile acids (for review, see Claudel et al6), perhaps to limit the size of the cholesterol substrate pool obtained via uptake of plasma HDL. Dramatic examples of bile acid regulation of HDL and apoA-I include the reduction of plasma HDL concentrations in mice fed cholic acid–enriched diets7 and the elevated HDL found in farnesoid X receptor (FXR) knockout mice.8 Downregulation of apoA-I by FXR, which appears to be mediated in part through the atypical nuclear receptors liver receptor homolog-1 and small heterodimer partner,9 has been documented in human apoA-I transgenic mice and in human hepatocyte studies, and apoA-I promoter regions involved in this regulation have been mapped.8

The pregnane X receptor (PXR) is a xenobiotic nuclear receptor that is also sensitive to bile acids as ligands.10,11 A study in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology has examined the potential for PXR to regulate hepatic apoA-I and HDL formation in response to bile acids.12 Wild-type mice, mice in which the PXR gene had been disrupted (PXR-null), and mice expressing the native human PXR transgene in the livers of PXR-null mice (PXR transgenic)13 were fed cholic acid–enriched diets and compared for hepatic apoA-I mRNA and plasma apoA-I and HDL cholesterol concentrations. Dietary cholic acid reduced hepatic apoA-I mRNA in PXR-null mice to about the same extent as in wild-type mice, presumably because of the known inhibitory effects of bile acid–liganded FXR. However, this inhibition was less pronounced in the PXR transgenic mice. Furthermore, whereas plasma HDL cholesterol and apoA-I concentrations were significantly reduced by cholic acid in wild-type and PXR-null mice, they were completely normalized in the cholic acid–fed PXR transgenic mice. Hence, the cholic acid–induced decrease in HDL was antagonized when human PXR expression was abundant, an effect mediated either by overexpression of the PXR transgene by the albumin promoter or the known differences in ligand specificity between the mouse and human receptors (Figure).13,14

The authors also examined cholic acid effects on ABCA1, ABCG1, and SR-BI in the PXR-null and PXR-transgenic mice. Whereas cholic acid feeding increased SR-BI and ABCG1 mRNA abundance, an effect that may also contribute to the reduced HDL in these animals, the only specific effect of the human PXR transgene was to preserve ABCA1 mRNA abundance in the presence of dietary cholic acid. This may explain part of the normalization of plasma HDL cholesterol in the human PXR transgenic mice. Therefore, although a possible role of PXR in maintaining plasma HDL cholesterol was suggested by this study, further analyses are needed to both define the underlying transcriptional mechanisms involved and to identify the full spectrum of target genes.
Left, In wild-type mice fed a diet rich in cholic acid, the presence of hepatic FXR with its bile acid (BA) agonist in abundance induces a transcriptional down-regulation of apoA-I, resulting in a decrease in plasma HDL cholesterol concentrations. Right, In PXR-null mice expressing the transgene for human PXR and fed cholic acid, the bile acid agonist binds to PXR and interferes with the FXR-mediated downregulation of apoA-I (horizontal line) and independently trans-activates the apoA-I promoter (dotted arrow). In addition, PXR may directly or indirectly upregulate ABCA1 as well as other potential target genes involved in HDL metabolism. These PXR-mediated alterations in gene expression may antagonize the reduction in plasma HDL cholesterol and particle concentrations normally induced by bile acids.

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A Role for the Pregnane X Receptor in High-Density Lipoprotein Metabolism
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