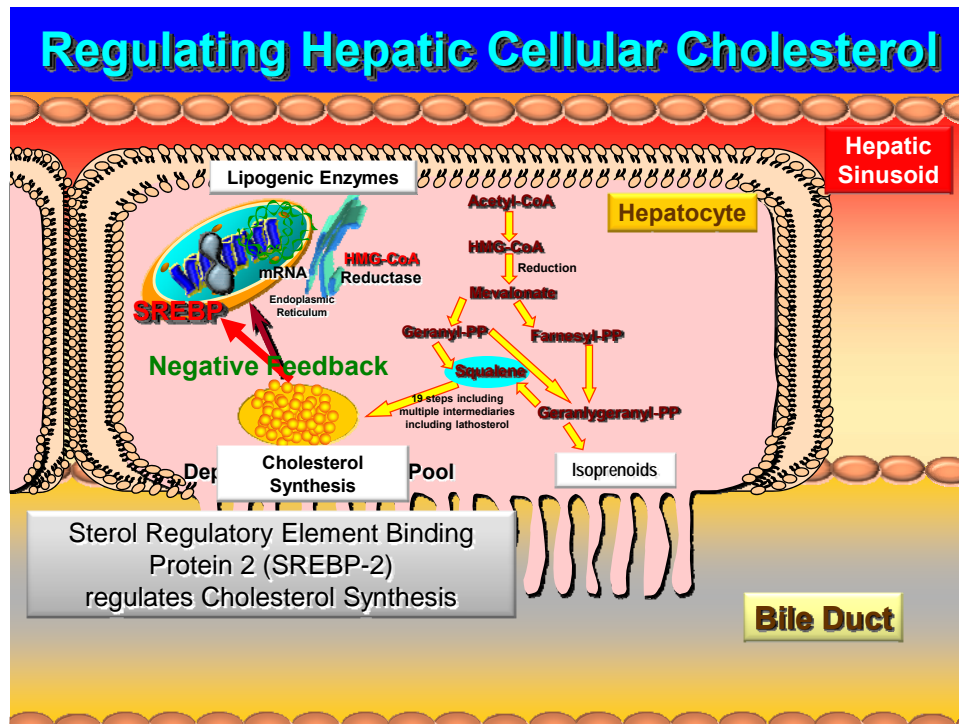


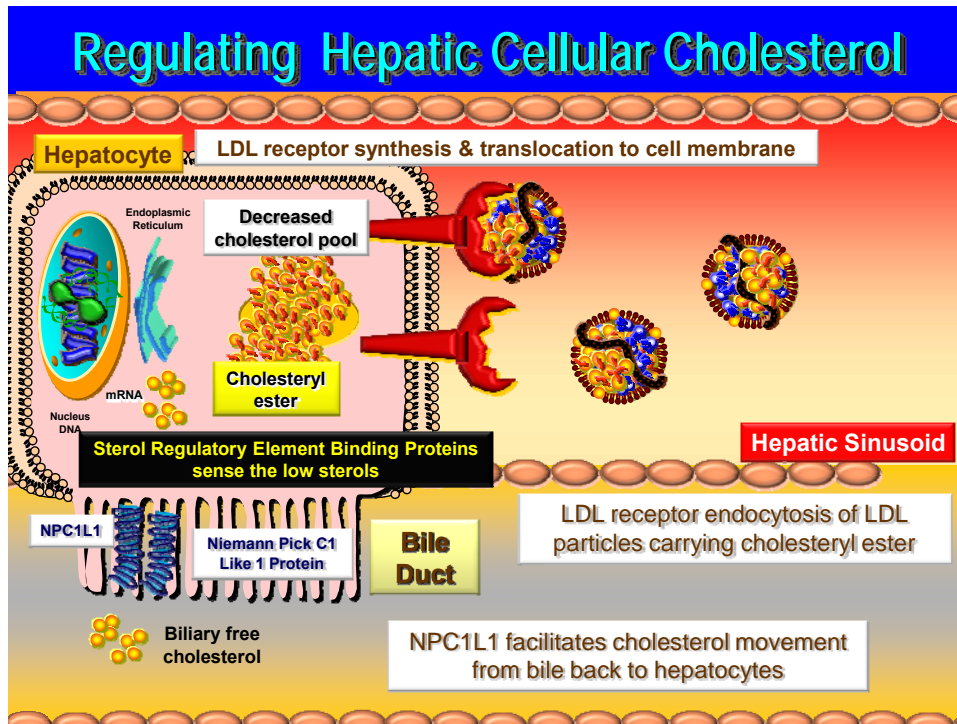
Nuclear Transcription Factors that Regulate Sterols
Thomas Dayspring MD, FACP

Under circumstances of cholesterol deficiency, Sterol Regulatory Element Binding Proteins (SREBPs) via binding to DNA nuclear response elements set off genomic production of proteins and enzymes that induce cholesterol synthesis, such as HMGCoA reductase.



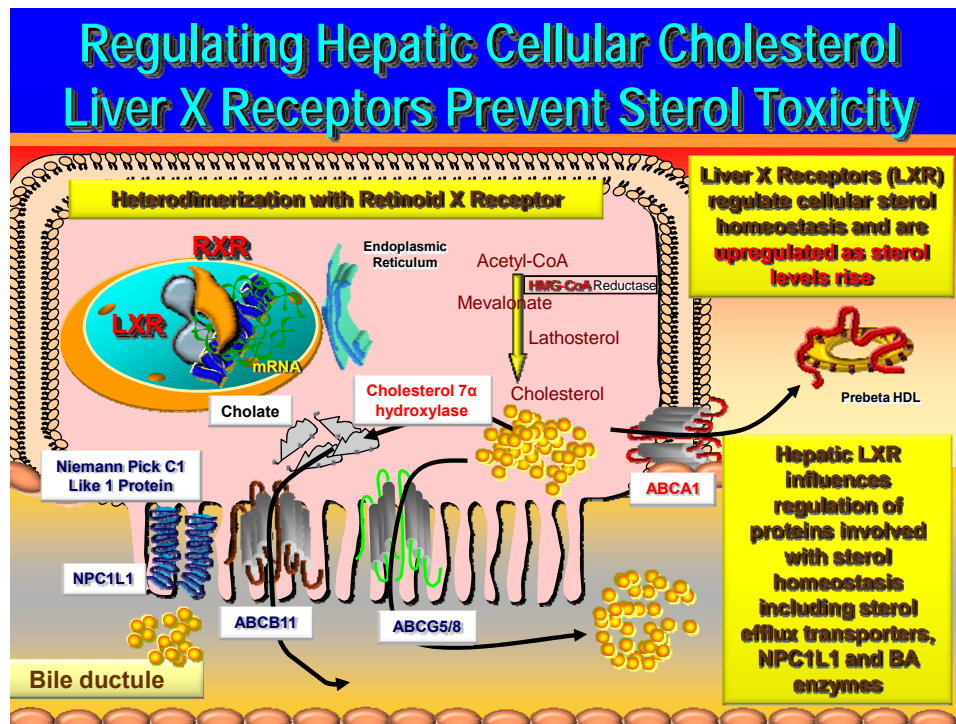
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SREBs also induce synthesis of LDL receptors which translocate to the surface of the cell and endocytose lipoproteins with apoE or apoB on their surface. These lipoproteins of course deliver sterols in this “indirect reverse cholesterol transport” process. Upregulation of the Niemann Pick C1 Like 1 protein NPC1L1 at the hepatobiliary interface is another source of cholesterol for the hepatocyte.



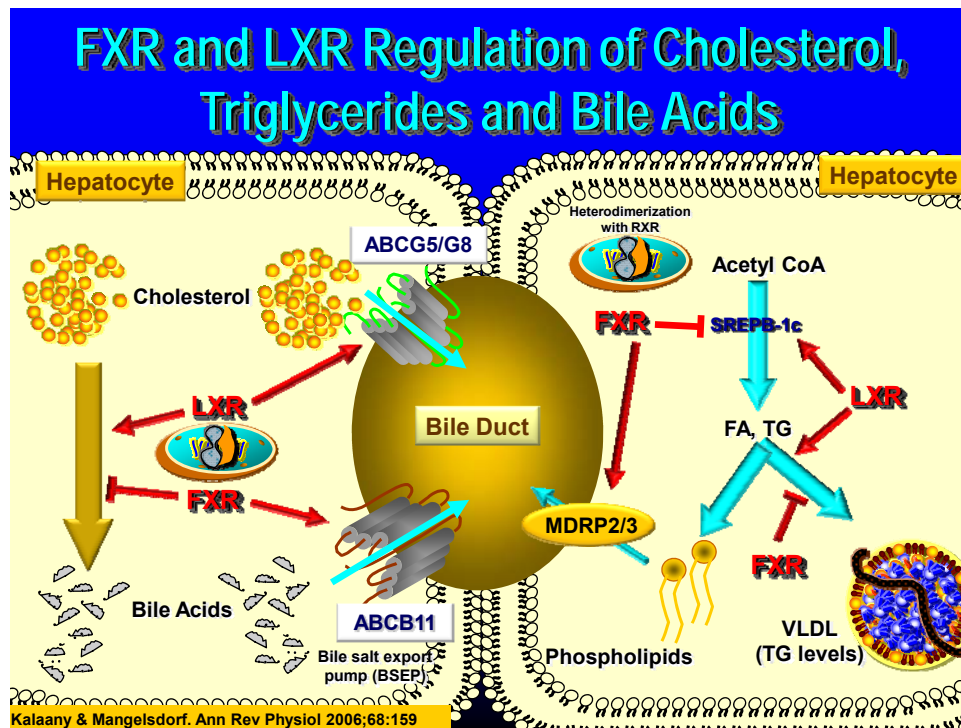
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Sterol cellular toxicity (crystallization) is prevented primarily by the liver X receptors (LXR) and the Farnesol or Farnesoid X receptors (FXR). The latter regulate bile acids. FXRs cross talk with the LXR via the short heterodimer protein (SHP). Under circumstances of hepatic sterol excess, LXRs induce the synthesis of several ATP binding cassette transporters namely ABCA1, ABCG5 and ABCG8 and ABCB11. All of these after synthesis translocate to various membrane areas and are involved with energy driven exportation of cholesterol (ABCA1, ABCG5, G8), non cholesterol sterols (ABCG5, G8) or bile acids (ABCB11). The LXR also by inducing cholesterol 7 alpha hydroxylase induce synthesis of bile acids with are excreted into the bile via the ABCB11 transporter. Suppression of HMGC_oA reductase would also help correct sterol toxicity as would suppression of the hepatobiliary and intestinal upregulation of the NPC1L1 protein.



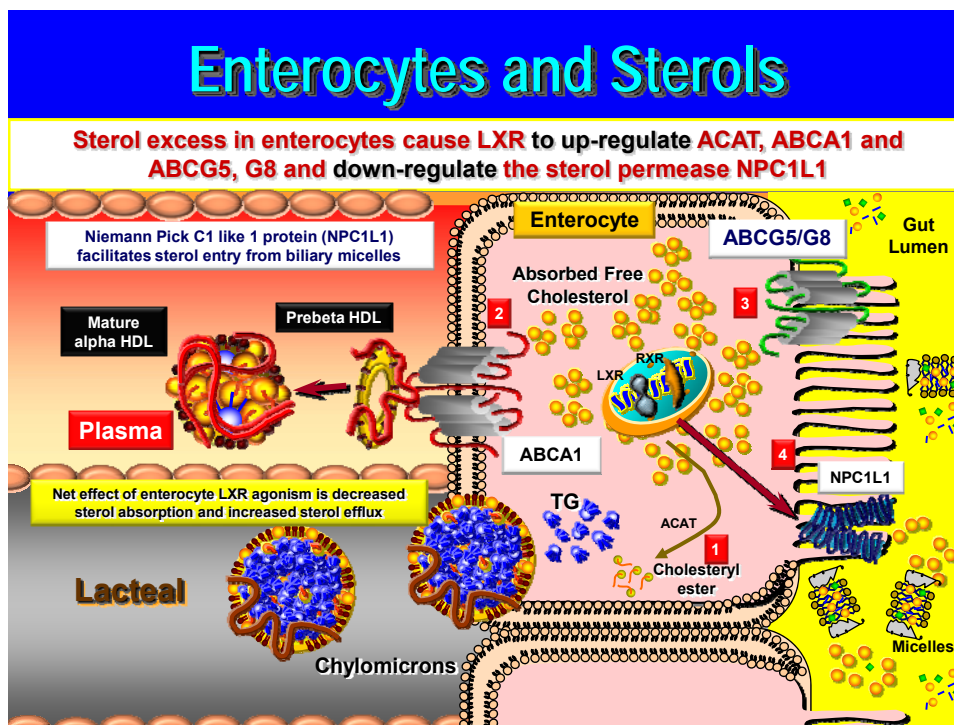
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This slide demonstrates the actions of LXR and FXR agonism. Like so many of the lipid nuclear transcription factors, the LXR and FXR heterodimerize with the RXR to facilitate attachment to the proper DNA response elements. FXR, or the bile acid toxicity nuclear transcription factor, suppress conversion of cholesterol to bile acids whereas LXR induces it. LXR upregulates the ABCG5, G8 transporter to efflux cholesterol and noncholesterol sterols into the bile whereas the FXR induces the ABCB11 (bile acid transporter) and the multidrug resistance proteins 2/3 (MDR2/3) to secrete phospholipids into bile. FXR inhibits SREBP 1c and TG synthesis whereas LXR (especially LXR isoform alpha) induces it. FXR inhibits SREBP 1c and TG synthesis whereas LXR (especially LXR isoform alpha) induces it.



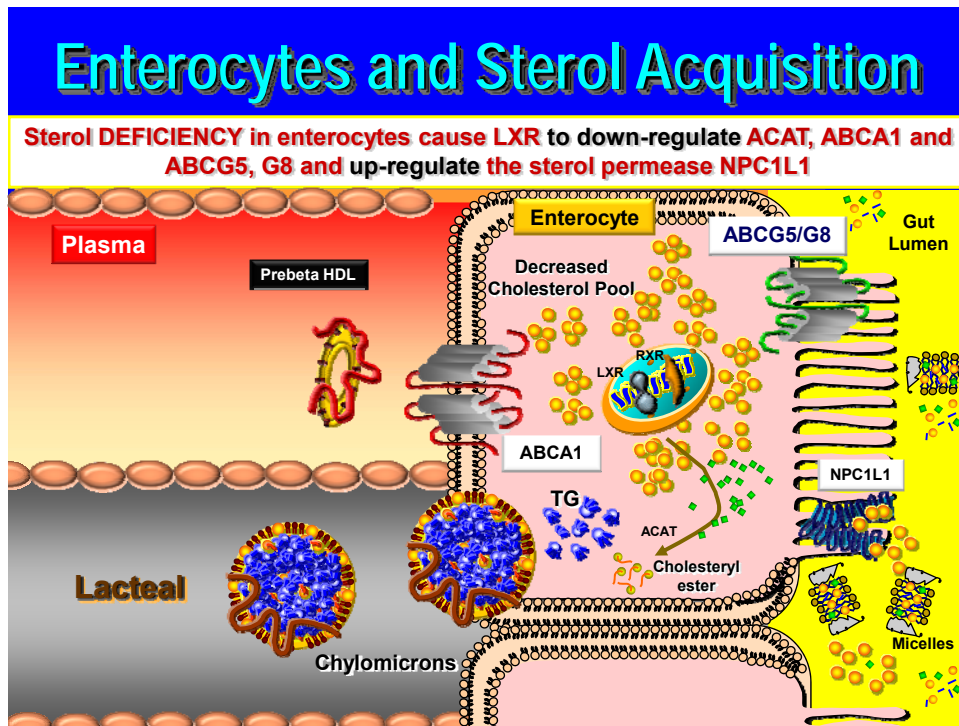
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Nuclear transcription factors also control enterocyte handling (absorption and excretion) of sterols. The Niemann Pick C1 Like 1 protein (NPC1L1) attaches to and delipidates sterols from the biliary micelles. Once in the enterocyte LXR induces acylcholesterol acyltransferase (ACAT) to change cholesterol into cholesteryl ester (CE). ACAT cannot esterify noncholesterol sterols. CE joins with enterocyte formed TG and apolipoprotein B48 in the genesis of chylomicrons which are secreted into lacteals. The LXR also upregulates enterocyte ABCA1 which exports unesterified (free) cholesterol into unlipidated apoA-I or prebeta HDL species. Upwards of 20-30% of total HDL-C is acquired intestinally. Excess cholesterol and all noncholesterol sterols can be excreted back to the intestinal lumen via the ABC5 and ABCG8 half transporters (sometimes called sterolin). Under conditions of sterol excess the NPC1L1 protein can be down regulated.



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Enterocyte sterol deficiency will cause a suppression of the LXR: ACAT, ABCA1, ABCG5,G8 expression is down regulated. There will also be down regulation of the NPC1L1 protein. This will decrease chylomicron cholesterol content, HDL cholesterol content and sterol excretion into the gut lumen. It will also cause the retention of noncholesterol sterols. All of these changes can be seen in persons using statins, which likely explains what used to be termed statin tachyphylaxis and why statins increase noncholesterol sterol levels.



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In summary sterols enter via the NPC1L1 protein and cholesterol but not noncholesterol sterols are esterified by ACAT2. The CE, and any noncholesterol sterols not excreted by ABCG5,G8 joins with intestinally resynthesized TG, apoB48 into chylomicron formation. After secretion into lacteals, where the chylomicrons acquire several other surface apolipoproteins from lymphatic HDLs, they enter the venous and ultimately the arterial circulation where they are exposed to lipoprotein lipase (LPL) at muscular and adipocyte vascular endothelium. Lipolysis of chylomicrons releases phospholipids, fatty acids and surface apoA-I. Unlipidated apoA-I and prebeta HDLs can attach to enterocyte ABCA1 and acquire additional unesterified cholesterol. All of the proteins in blue in the slide are under the influence of LXR.

