NRN Nuclear Receptor News

Welcome to the Cholesterol Transport Issue

Welcome to the Cholesterol Transport issue of Nuclear Receptor News. The transport of excess cholesterol from the periphery into the liver and bile, followed by excretion in the feces, is defined as reverse cholesterol transport (RCT). This pathway has become increasingly popular as a target for therapeutic strategies aimed at achieving the regression of atherosclerosis. Many of the enzymes, transporter proteins and signaling pathways that influence the rate of RCT are transcriptional targets of nuclear receptors. In this newsletter, we will outline some of the salient features of RCT and how it is regulated by key NRs. A more detailed description of this process can be found in the "General Information" section of the Nuclear Receptor Resource (http://nrresource.org).

Nuclear Receptors and Cholesterol Transport

Cholesterol is the essential precursor of steroid hormones (progesterone, estrogen, testosterone, glucocorticoids and mineralocorticoids), bile acids and vitamin D and is also a vital constituent of cell membranes. Cholesterol can be derived from the diet as well as from endogenous biosynthesis, the latter being the major source in humans. In the process of reverse cholesterol transport (RCT), excess peripheral cholesterol is scavenged by tissue macrophages, which process cholesterol and transport it to the liver via HDL for excretion (See Figure 1; from references [1-8]). Atherosclerotic plaques contain macrophages that have ingested large amounts of cholesteryl ester, forming lipid droplets and gaining the appearance of a "foam cell". Besides endocytosis, lipoproteins could enter these cells through a receptor mediated pathway, such as scavenger receptor A (SR-A) and CD36. After macrophages ingested and metabolize lipoproteins, free cholesterol is released and transported to the ER by Niemann Pick type C (NPC) 1 and 2 proteins. Subsequently re-esterification of cholesterol is by acyl-CoA: cholesterol acyltransferase (ACAT) and stored as cholesteryl ester. Notably, the preferred acyl-CoA for this reaction is oleate, which is produced from stearate by the enzyme SCD-1 The storage form of cholesterol can be hydrolyzed by cholesteryl ester hydrolase (CEH) to release free cholesterol. In the presence of lipid acceptors in the blood stream, such as apoA-I or HDL, free cholesterol is transported out of cells, simultaneously with synthesis and secretion of apoE. The liver regulates de novo biosynthesis of cholesterol, the excretion of cholesterol into bile (directly or after conversion to bile acids) and the secretion of cholesterol into blood via VLDL. De novo synthesis of cholesterol in the liver is tightly regulated with HMG-CoA reductase being the rate limiting step. The conversion of free cholesterol to cholesterol esters is controlled by the same enzymes as described for macrophages.

In macrophages, control of the initial steps of RCT (cholesterol uptake and efflux) is manifested by a variety of NRs, in particular the PPARs and LXRs. Upon uptake of oxLDL by macrophages, oxysterols are synthesized, which allows activation of PPARγ and LXRα. Once activated, PPAR γ and LXR not only induce the expression of each other, but they also augment expression of many ABC transporters, as well as that of ApoE. The formation of esterified cholesterol is controlled, at least in part by the amount of oleate present, which is in turn controlled by SCD-1. In macrophages, the expression of this enzyme is controlled by FXR and its target gene SHP-1. PPARα and β/δ also controls the amount of CE present by affecting enzymes such as CPT-1 and ADRP and by regulating the expression of the transporter ABCA1.

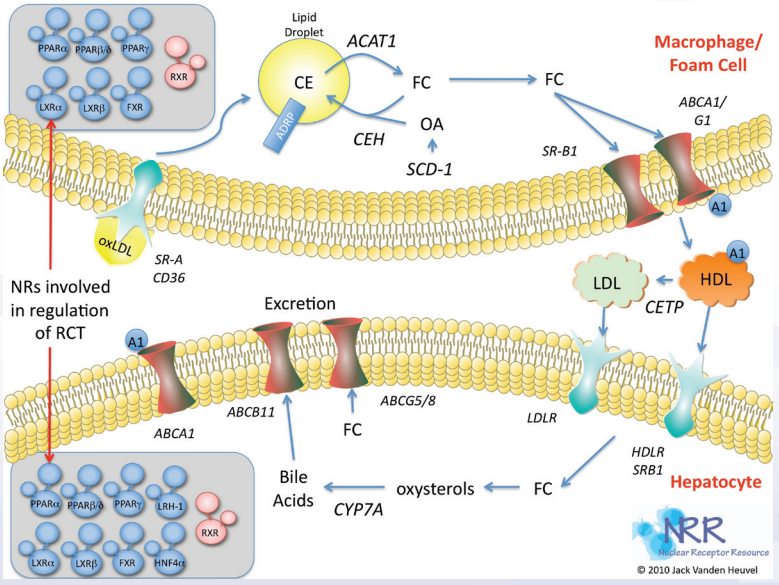

Figure 1. Reverse Cholesterol Transport. See text for details

Hepatic bile acid synthesis and secretion constitute the major route for elimination of cholesterol from the body. Oxysterols, natural ligands for LXRs, are generated when cholesterol levels are high. The classical pathway of bile acid synthesis is initiated by 7α-hydroxylation of cholesterol catalyzed by the cytochrome P450 cholesterol 7α hydroxylase (CYP7A1), which encodes the rate-limiting enzyme of this pathway . In rodents, LXRα stimulates the expression of CYP7A1. In contrast to observations in rats and mice, LXRα agonist treatment suppresses expression of CYP7A1 in primary human hepatocytes. This repression is, at least in part, due to the direct induction of small heterodimer partner (SHP), a gene that has a repressive effect on CYP7A1 via liver receptor homologue (LRH1; also called CPF in humans). These results suggest that different species may employ distinct molecular strategies to regulate cholesterol homeostasis. Taken together, these data shows that the complicated process of removing excess peripheral cholesterol, for subsequent elimination, an important process in the prevention and regression of atherosclerosis, is coordinated by the activity of nuclear receptors present in the macrophage and liver. This lays the groundwork for subsequent development of therapeutic or nutritional intervention.

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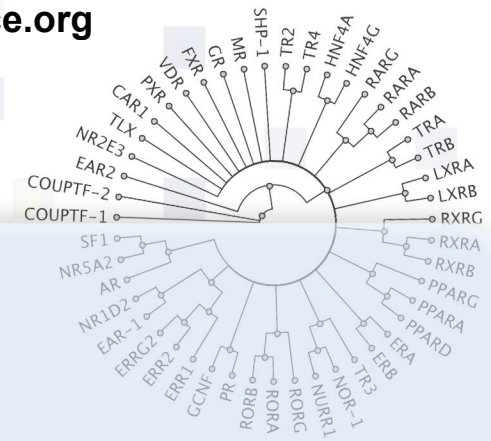

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INDIGO Launches New Cell-based Assay Systems; RXRα and CAR now available

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