Functional study of nuclear receptors and bile acids in the modulation of cholesterol homeostasis

Onsdag den 30 oktober, 2013, kl 10.00

av

Xiaoli Hu
MD

Huvudhandledare:
Professor Gösta Eggertsen
Karolinska Institutet
Department of Laboratory Medicine
Division of Clinical Chemistry

Bihandledare:
Professor Paolo Parini
Karolinska Institutet
Department of Laboratory Medicine
Division of Clinical Chemistry

Docent Mats Gåfvels
Karolinska Institutet
Department of Laboratory Medicine
Division of Clinical Chemistry

Fakultetsopponent:
Docent Uwe Tietge
University of Groningen
Department of Pediatrics

Betygsnämnd:
Docent Maria Norlin
University of Uppsala
Department of Pharmaceutical Biosciences

Docent Josefin Skogsberg
Karolinska Institutet
Department of Medical Biochemistry and Biophysics

Professor Allan Sirsjö
Örebro University
Department of Health and Medicine

Stockholm 2013
ABSTRACT

Cholesterol carries multiple biological functions in the body, and imbalanced cholesterol metabolism leads to atherosclerosis and cardiovascular diseases. The present thesis aims to extend the knowledge of cholesterol metabolic regulation mediated by nuclear receptor LXRs and bile acids, two major players in the homeostasis of body cholesterol.

In the first paper, we aim to understand how liver X receptor (LXR) regulates cholesterol metabolism in the intestine, in particular to compare the effects of the two isoforms, LXRα and LXRβ on dietary cholesterol absorption and serum lipoprotein profiles. We find that selective activation of LXRβ enhances dietary cholesterol absorption in mice, which is accompanied by increased apoB lipoprotein cholesterol in the circulation. We also find that LXRα and LXRβ compensate for each other in the transcriptional regulation of intestinal Abcg5, Abca1 and Npc1l1. Furthermore, the hepatic enzymes Cyp7a1 and Cyp8b1 are differently modulated upon systemic LXR isoform activation. Given the contribution of the hydrophobic bile acid profile in the intestine, these changes together with the net differences in biliary cholesterol output may partially explain the isoform mediated changes in cholesterol absorption. Our findings reinforce the non-redundant function of LXRα and LXRβ, and suggest that selective activation of LXRβ as anti-atherogenic therapy may lead to undesired metabolic adverse effects.

Bile acid synthesis represents the crucial elimination pathway for excess cholesterol. The negative feedback regulation by end-product hydrophobic bile acids has been well established, involving the activation of nuclear receptor FXR, and a subsequent upregulation of SHP and Fgf15 for the suppression of bile acid synthesis in mice (Fgf19 as human counterpart). However, the role of hydrophilic bile acids in such context has largely been ignored. By using a cholic acid (CA) deficient mouse model and different bile acid-modulating regimes, we define MCAs as FXR antagonistic bile acids, which counteract the FXR activation by hydrophobic bile acids. By modulating the enterohepatic circulation of bile acids, the positive feedback mechanism regulates bile acid homeostasis without employing the hormonal effect of Fgf15, although such an effect is likely to exist. This finding is of fundamental importance for the understating of bile acid metabolism in both humans and mice, as the Fgf15/19 negative feedback mechanism is believed to operate in both species.

Paper III explores the therapeutic potential of CA depletion on systemic cholesterol overloading by using second generation antisense oligonucleotides (ASOs). Several ASOs targeting Cyp8b1, the enzyme responsible for CA production, have been used in the study. In mice, we observe a significant reduction of the CA fraction in the biliary bile acid profile under ASO treatment. This reduction is accompanied by resistance to liver cholesterol accumulation and an athero-protective lipoprotein profile upon cholesterol overloading. The data suggest the feasibility of using second generation ASOs as therapeutic target for cholesterol homeostasis, although a careful systematic study is needed to address the clinical aspect in human subjects.