

Transcriptional control of intestinal cholesterol absorption

Sanja Levak-Frank Institute of Molecular Biology and Biochemistry, Centre of Molecular Medicine, Medical University of Graz

E-mail: sanja.levak-frank@meduni-graz.at; web: <http://user.meduni-graz.at/dagmar.kratky/sanja.html>

Cholesterol homeostasis is maintained by a series of regulatory pathways that control the synthesis of endogenous cholesterol, the absorption of dietary cholesterol, and the elimination of cholesterol and its catabolic end products, bile acids. Disturbances in cholesterol balance may lead to a high level of plasma cholesterol and the development of atherosclerosis and coronary heart disease [1].

Intestinal cholesterol absorption has been shown to be a major determinant of plasma cholesterol levels. Also, ezetimibe, a selective inhibitor of intestinal cholesterol uptake, has been effectively used in the treatment of hypercholesterolemia [1]. Although intestinal cholesterol absorption appears to be a multistep process, a recent study [2] has identified Niemann-Pick C1 like1 (NPC1L1) protein as a direct target for ezetimibe, indicating its key role in the intestinal cholesterol uptake. Since NPC1L1 is an integral part of complex processes of cholesterol homeostasis, it is speculated that it is highly regulated and that the regulation of its expression is harmonized with the modulation of other genes involved in cholesterol metabolism.

Transcriptional control of many genes implicated in cholesterol homeostasis can be attributed to two classes of transcription factors: sterol regulatory element-binding proteins (SREBPs), especially SREBP-2, which control the production of key enzymes in cholesterol biosynthesis [3], and the nuclear hormone receptor family, including liver X receptor (LXR), farnesoid X receptor (FXR) and peroxisome proliferator-activated receptor α (PPAR α) which control the expression of genes involved in cholesterol efflux, catabolism, and elimination [4]. The involvement of these transcription factors in the modulation of intestinal cholesterol absorption and the expression of NPC1L1 protein are still not fully understood. Recently, the expression of murine NPC1L1 was shown to be significantly decreased in response to feeding of a cholesterol-enriched diet [5]. In addition, the downregulation of NPC1L1 expression by LXR agonist was reported in both a human enterocyte cell line (CaCo-2) and mouse duodenum [6]. The PPAR α agonist – fenofibrate was also shown to reduce intestinal cholesterol absorption by inhibiting the expression of NPC1L1 in mouse intestine [7]. Taken together, these previous observations have indicated the

modulation of NPC1L1 expression by cholesterol and the involvement of several nuclear receptors in this regulation. However, the exact molecular mechanism by which cholesterol influences the express of intestinal NPC1L1 is still unclear.

The main aim of this project is to investigate the effect of cholesterol and LXR agonists on the expression and promoter activity of intestinal NPC1L1. For that purpose, the expression level of NPC1L1 will be investigated in cholesterol and/or LXR agonist treated CaCo-2 cells. In addition, nuclear extracts isolated from these cells will be hybridized to Nuclear Receptor/Protein Array (Panomics) in order to find novel nuclear factors that may play role in cholesterol-regulated expression of NPC1L1. The role of these novel nuclear factors intestinal cholesterol absorption will also be studied.

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