NPC1L1, A PHARMACOLOGICAL TARGET OF DYSLIPIDEMIA
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Intestinal absorption is an important process in the maintenance of cholesterol homeostasis in the body. Although the mechanism of cholesterol uptake from the intestinal lumen is poorly understood, the identification of ezetimibe (Zetia®) as a potent selective inhibitor of intestinal cholesterol absorption suggests that this process is mediated by a specific transport system. Through studies designed to understand the mechanism by which ezetimibe inhibits cholesterol absorption, Niemann-Pick C1-like 1 (NPC1L1) was identified as a crucial factor for intestinal cholesterol absorption (1), because NPC1L1-deficient mice exhibited reduction in the intestinal absorption of cholesterol, and the lower level of remaining cholesterol absorption was insensitive to ezetimibe treatment. These results, together with the finding that NPC1L1 is expressed on the apical membrane of the small intestine, particularly in the jejunum, where most sterol absorption takes place, suggest that NPC1L1 is involved in the intestinal absorption of cholesterol and is a target of ezetimibe.

NPC1L1 is reported to be negatively regulated by cellular cholesterol levels via SREBP2/HNF4α-mediated transcriptional regulations (2, 3) and, coordinately, treatment with HMG-CoA reductase inhibitors (statins) is generally known to increase the intestinal absorption of cholesterol. Based on these facts, ezetimibe has been believed to be useful especially in patients treated with statins. In fact, ezetimibe-dependent reduction in LDL cholesterol is shown to be more remarkable in patients treated with both of statins and ezetimibe than in patients treated with ezetimibe alone.

In addition, it is reported that low cholesterol absorption is associated with fewer recurrent cardiovascular events and with better survival in elderly patients (4). From these pieces of information, ezetimibe is believed to reduce the risk of cardiovascular events via the inhibition of intestinal cholesterol absorption mediated by NPC1L1. However, the benefit of ezetimibe is not yet supported by large clinical trials (5, 6); ezetimibe treatment couldn’t bring any benefit on the change of intima-media thickness in carotid arteries, in spite of the significant decrease in LDL cholesterol. Although the underlying mechanism remains to be clarified, we would like to discuss some possibilities, with recently identified novel functions of NPC1L1, such as vitamin E transport (7) and re-uptake of biliary-secreted cholesterol on the canalicular membrane of hepatocytes (8).

References:

Biography
1999 Graduated from Faculty of Pharmaceutical Sciences, The University of Tokyo
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