S07-2 A cholesterol importer NPC1L1 modulates the protein secretion into bile

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For the maintenance of cholesterol homeostasis, intestinal absorption and biliary secretion have important roles as well as the biosynthesis and catabolism of cholesterol, and researches are in progress of the association of these steps with pathophysiology of dyslipidemias and gallstones. Recent studies revealed crucial roles of cholesterol transporters in the process, and Niemann-Pick C1-like 1 (NPC1L1) is thought to be responsible for the intestinal absorption and biliary reabsorption of cholesterol and is known as a pharmacological target of a cholesterol lowering drug ezetimibe. During a search for the proteins associated with NPC1L1, we found the molecular interaction between NPC1L1 and secretory proteins as Niemann-Pick C2 (NPC2) and Aminopeptidase N (APN/CD13). These interactions were not detected between rat orthologues but observed between human proteins, suggesting the association of the interactions with the function of highly-expressed NPC1L1 in the human liver. Results of transient transgenic experiments in the mouse liver using adenoviruses showed significant changes in the amount of NPC2 and APN in bile depending on the presence or absence of human NPC1L1. Since biliary NPC2 and APN are suggested to be involved in the gallstone formation, it is possible that human NPC1L1 controls the behavior of biliary cholesterol via the molecular interaction with these proteins in addition to its function as a cholesterol importer.