Molecular mechanism of ABC proteins involved in lipid homeostasis

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We are trying to reveal the mechanism of ABC proteins involved in lipid homeostasis by comparing functions of various human ABC proteins.

ABCA1, a key player in HDL metabolism, mediates apoA-I-dependent free cholesterol and phospholipid efflux to form pre-β HDL. Purified ABCA1 shows robust ATPase activity when reconstituted in liposomes made of synthetic phosphatidylcholine (PC), suggesting that PC is the preferential substrate for ABCA1 (1).

ABCG1 is induced in macrophages in the LXR pathway coordinately with ABCA1 expression. Mass and TLC analyses revealed that ABCG1 and ABCA1 secrete several species of sphingomyelin and PC, and sphingomyelin is preferentially secreted by ABCG1, while PC is preferentially secreted by ABCA1 (2).

ABCB4 (MDR3 P-glycoprotein), secretes PC into the bile, has an amino acid sequence with 86% similarity to that of ABCB1 (MDR1). PC and cholesterol are secreted from HEK/ABCB4 cells, but not from HEK/ABCB1 cells, in the presence of taurocholate. Mass spectrometry revealed that HEK/ABCB4 cells preferentially secretes PC.

These results suggest that ABCA1, ABCG1, and ABCB4 mediate the lipid efflux in different mechanisms, in which different species of phospholipids are secreted to different acceptors. (1) Takahashi, K. et al. J Biol Chem, 281, 10760-10768 (2006), (2) Kobayashi, A. et al. J Lipid Res. 47, 1791-1802 (2006), (3) Morita, S.-y. et al. Hepatology, in press.