

Function of Peroxisomal ABC Proteins and Adrenoleukodystrophy

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So far, three ATP-binding cassette (ABC) proteins have been identified in mammalian peroxisomes, including ALDP (ABCD1), ALDRP (ABCD2), and PMP70 (ABCD3). We previously reported that PMP70 involved in metabolic transport of long-chain acyl-CoA into peroxisomes. In contrast, ALDP and ALDRP are thought to involve in the transport of very long-chain fatty acid (VLCFA) or VLCFA-CoA. In particular, mutations in the *ABCD1* gene is known to cause the neurodegenerative disorder X-linked adrenoleukodystrophy (X-ALD). The biochemical feature of X-ALD is the accumulation of pathognomonic amounts of saturated VLCFA in all tissues. Here, we chose nine arbitrary mutation of ALDP with naturally occurring missense mutations and examined intracellular behavior of their ALDPs. We found that mutant ALDPs (S606L, R617H and H667D) were degraded by proteasomes together with wild type ALDP. We also found fragmentation of mutant ALDP (R104C) on peroxisomes, which was not inhibited by proteasome inhibitors. In addition, mutant ALDP (Y174C), which has a mutation between transmembrane domain 2 and 3, did not exhibit peroxisomal localization. These results could provide us useful information on the putative function of particular domains within the ALDP and the quality control system of mutant peroxisomal ABC proteins including ALDP. Furthermore, we investigated how dysfunction of ALDP affect lipid metabolism using the ALDP-knockdown or -knockout glial cells. We found it decreased not only VLCFA β -oxidation but also perturbed cholesterol homeostasis. In addition, fatty acid elongation activity was increased. We also refer to our therapeutic approach for X-ALD.