

Regulation of Intracellular Cholesterol Distribution by the Na/K-ATPase

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Recent studies have ascribed many non-pumping functions to the Na/K-ATPase. We show here that graded knockdown of cellular Na/K-ATPase $\alpha 1$ subunit produces a parallel decrease in both caveolin-1 and cholesterol in light fractions of LLC-PK1 cell lysates. This observation is further substantiated by imaging analyses, showing redistribution of cholesterol from the plasma membrane to intracellular compartments in both $\alpha 1$ and caveolin-1 knockdown cells. Moreover, this regulation is confirmed in $\alpha 1^{+/-}$ mouse liver. Functionally, the knockdown-induced redistribution appears to affect the cholesterol sensing in the endoplasmic reticulum (ER) because it activates the sterol regulatory element binding protein (SREBP) pathway and increases expression of HMG-CoA reductase and low density lipoprotein (LDL) receptor in the liver. Consistently, we detect a modest increase in hepatic cholesterol as well as a reduction in the plasma cholesterol. Taken together, our new findings demonstrate a novel function of the Na/K-ATPase in control of the plasma membrane cholesterol distribution. Moreover, the data also suggest that the plasma membrane Na/K-ATPase/caveolin-1 interaction may represent an important sensing mechanism by which the cells regulate the SREBP pathway.

Supported by National Institutes of Health (HL-36573, HL-67963 and GM 78565) and UT predoctoral fellowships.