

Cholesterol transport in endocrinology and metabolism

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Changes in the ‘accessible’ pool of plasma membrane cholesterol are linked with the regulation of endoplasmic reticulum sterol synthesis and metabolism by the Aster family of nonvesicular transporters. However, the relevance of such transport mechanisms for lipid homeostasis in vivo has not been defined. We reveal multiple physiological contexts that generate accessible plasma membrane cholesterol and engage the Aster pathway. In steroidogenic tissues, Asters are critical for delivering HDL cholesterol to cells for cortisol and estrogen synthesis. In the liver, Aster-dependent cholesterol transport during fasting facilitates cholesteryl ester formation, cholesterol movement into bile and very low-density lipoprotein production. During reverse cholesterol transport, high-density lipoprotein delivers excess cholesterol to the hepatocyte PM through SRB1. Finally, Aster-B and Aster-C are important for dietary cholesterol movement in the intestine. Enterocytes lacking Asters accumulate PM cholesterol and show endoplasmic reticulum cholesterol depletion. Aster-deficient mice have impaired cholesterol absorption and are protected against diet-induced hypercholesterolemia. These findings identify the Aster pathway as a physiologically important and pharmacologically tractable node in lipid transport.