S-Adenosyl-*L*-Homocysteine Hydrolase, Key Enzyme of Methylation Metabolism, Regulates Phosphatidylcholine Synthesis and Triacylglycerol homeostasis in yeast: Implication for Homocysteine as a risk Factor of atherosclerosis

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S-adenosyl-*L*-methionine (AdoMet)-dependent methylation plays an important role in the regulation of biological processes. At least 50 AdoMet-dependent methyltransferases identified to date methylate a broad spectrum of cellular compounds including nucleic acids, proteins and lipids; and regulate many cellular processes including epigenetic control, protein synthesis and processing, as well as lipid metabolism.

S-adenosyl-*L*-homocysteine hydrolase (Sah1) offers a single way for degradation of *S*-adenosyl-*L*-homocysteine (AdoHcy), a product and potent competitive inhibitor of AdoMet-dependent methyltransferases. *De novo* phosphatidylcholine (PC) synthesis requires three AdoMet-dependent methylation steps and is a major AdoMet consumer. Here we show that down-regulation of *SAH1* expression in yeast leads to accumulation of AdoHcy and decreased *de novo* PC synthesis *in vivo*. Sah1p depletion leads as well to an increase in triacylglycerol (TG) levels, demonstrating that Sah1-regulated methylation has a major impact on cellular lipid homeostasis. TG accumulation is also observed in *cho2* and *opi3* mutants defective in methylation of phosphatidylethanol-amine to PC, confirming that PC *de novo* synthesis and TG synthesis are metabolically coupled through the efficiency of the phospholipid methylation reaction. Indeed, since both types of lipids share phosphatidic acid as a precursor, we find in cells with down-regulated Sah1 activity major transcriptional alterations of the *INO1* gene, which is dependent on the level of phosphatidic acid in the endoplasmic reticulum. Addition of homocysteine, by the reversal of the Sah1-catalyzed reaction, also leads to TG accumulation in yeast, providing an attractive model for the role of homocysteine as a risk factor of atherosclerosis in humans.