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THE MOLECULAR BASIS OF LIPID ALTERATIONS IN YEAST MODELS OF HYPERHOMOCYSTEINEMIA

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Hyperhomocysteinemia (HHcy) is a common pathological condition that is characterized by high levels of homocysteine (Hcy) in the blood. HHcy is associated with a number of diverse diseases of modern society including cardiovascular and neurological diseases as well as fatty liver and even cancer. The mechanisms underlying the development of Hcy-triggered pathologies are not understood. In HHcy Hcy is converted to *S*-adenosyl-*L*-homocysteine (AdoHcy) by Sah1/AHCY and evidence suggests that AdoHcy is indeed a more sensitive marker of HHcy. AdoHcy acts as strong product inhibitor of *S*-adenosyl-*L*-methionine (AdoMet)-dependent methyltransferases. Notably, about 50% of AdoMet in mammals is used for phospholipid methylation.

Yeast mutants lacking Sah1 or wild type cells supplemented with Hcy accumulate AdoHcy. These cells also accumulate TG and display an increased fatty acid content and altered composition of their glycerolipids. To discriminate between Hcy and AdoHcy-induced lipid defects we have cloned and expressed an alternative, irreversible bacterial pathway for AdoHcy catabolism. Its expression in *sah1* mutants or in wild type cells supplemented with Hcy restores wild-type AdoHcy levels and also fully suppresses alterations in lipid metabolism. AdoHcy accumulation not only impairs phospholipid methylation, but also leads to an up-regulation of fatty acid *de novo* synthesis at the level of the FAS complex. These data demonstrate that impaired catabolism of AdoHcy affects multiple key steps in lipid metabolism; additional roles for Hcy – independent of its conversion to AdoHcy, for instance in oxidative stress responses – cannot be excluded.

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