Liver one-carbon metabolism affects the integrated stress response and systemic metabolic control

T. Gantert,[1] A. Maida,[1] M. Warrier,[2] S.H. Zeisel[2] and A.J. Rose ,[1,3] [1]Molecular Metabolic Control, German Cancer Research Center, Heidelberg, 69120, Germany, [2]Nutrition Research Institute and Department of Nutrition, University of North Carolina, Kannapolis, NC 28081, USA and [3]Department of Biochemistry & Molecular Biology and Biomedicine Discovery Institute, Monash University, Clayton, VIC 3800, Australia.

Disruption of the liver one-carbon cycle is linked to systemic metabolism, fatty liver disease and liver cancer, both in model organisms such as rodents and humans. In particular, deletion of key genes of one-carbon metabolism, of which are abundantly expressed in the liver, leads to disturbed one-carbon metabolic balance, fatty liver, and spontaneous liver cancer development in rodents. Among these is the enzyme betaine-hydroxymethyl-transferase (BHMT), which catalyses the remethylation of homocysteine to methionine using the micro-nutrient betaine. Of note, despite being lean and hypermetabolic, germline BHMT knockout mice develop fatty liver disease and spontaneous liver cancer. Here using genetic loss of function as well as diet induced downregulation, we tested the precise role of liver-specific BHMT activity in liver and systemic metabolic control. To do this we engineered an adenovirus to re-express BHMT back into the liver. Importantly, the overexpression construct produced a correctly functioning protein as determined by native-PAGE and activity assays. Of note, in the BHMT knockout mice, restoration of BHMT completely reversed the altered levels of serum betaine and dimethylglycine, thereby demonstrating the efficacy of the approach *in vivo*. Furthermore, the disturbed liver betaine, S-adenosyl-methionine to S-adenosyl-homocysteine ratio, and phosphatidylcholine were reversed upon restoration of BHMT activity in the knockout mice. In order to test this in a physiological setting, we tested altered BHMT expression in a dietary model which promotes low BHMT expression. Both studies could demonstrate that BHMT expression correlates with altered indices of one-carbon metabolism and blunted activation of the integrated stress response, serum fibroblast growth factor 21 levels and the associated systemic metabolic remodelling. Taken together, liver one-carbon metabolism affects cellular/systemic signalling pathways and liver/systemic metabolic control, independent of potential developmental effects and in a liver-restricted fashion.