J Inherit Metab Dis (2017) 40:469
DOI 10.1007/s10545-017-0062-2

HIGHLIGHTS

News and views

Sander M. Houten[1]

Published online: 26 June 2017

Acyl-CoA esters can act as acylating agents that target lysine residues in proteins

Lysine acetylation is an important posttranslational modification of proteins and plays a role in many biological pathways, such as epigenetic regulation of gene expression. In addition, lysine in protein can be acylated with a variety of other molecules, including propionyl, butyryl, and malonyl groups. While sirtuins are now known to be nicotinamide adenine dinucleotide $(NAD)^+$-dependent protein deacylases that catalyze the removal of these modifications, the identification of specific acyltransferases that perform the acylation reaction has been challenging. Indeed, there is evidence that acyl-CoAs are reactive molecules that can chemically (nonenzymatically) modify proteins. In inborn errors of acyl-CoA metabolism, aberrant protein acylation is a frequent observation, but it is currently unknown whether it plays a role in pathophysiology (Pougovkina et al. 2014; Tan et al. 2014). Wagner et al. now show that short-chain dicarboxylate-CoAs, such as succinyl-, glutaryl- and 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), are inherently unstable and form a highly reactive anhydride after ring closure (Wagner et al. 2017). As a consequence, the proteome of liver mitochondria isolated from HMG-CoA lyase knockout (KO) mice is heavily HMGylated and that of glutaryl-CoA dehydrogenase KO mice is heavily glutarylated. Wagner et al. further demonstrate that many protein sites are uniquely modified by either HMG-CoA or glutaryl-CoA, but some pathways, such as the tricarboxylic acid cycle, are commonly modified (Wagner et al. 2017). Given that these modifications affect the activity of many enzymes, protein acylation has been proposed as a biological regulatory mechanism that controls metabolism. Alternatively, many acylation events may be collateral damage of metabolic processes, requiring a repair mechanism that is in turn provided by the sirtuins. Regardless, this new work further establishes evidence that aberrant protein acylation may be a recurring theme in the pathophysiology of inborn errors of metabolism.

Conflict of interest Sander M. Houten declares that he has no conflict of interest.

References

Pougovkina O, te Brinke H, Wanders RJ, Houten SM, de Boer VC (2014) Aberrant protein acylation is a common observation in inborn errors of acyl-CoA metabolism. J Inherit Metab Dis 37:709–714

Tan M, Peng C, Anderson KA et al (2014) Lysine glutarylation is a protein posttranslational modification regulated by SIRT5. Cell Metab 19:605–617

Wagner GR, Bhatt DP, O'Connell TM et al (2017) A class of reactive acyl-CoA species reveals the non-enzymatic origins of protein acylation. Cell Metab 25(823–837):e828

✉ Sander M. Houten
Sander.houten@mssm.edu

[1] Department of Genetics and Genomic Sciences, Icahn Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, Box 1498, New York, NY 10029, USA