**SREBP-1c regulates protein sulfhydration in metabolic disease**

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A metabolic imbalance between lipid synthesis and degradation can lead to hepatic lipid accumulation, a characteristic of patients with non-alcoholic fatty liver disease (NAFLD). Here, we report that high-fat-diet-induced sterol regulatory element-binding protein (SREBP)-1c, a key transcription factor that regulates lipid biosynthesis, impairs autophagic lipid catabolism via altered H2S signaling. SREBP-1c reduced cystathionine gamma-lyase (CSE) via miR-216a, which in turn decreased hepatic H2S levels and sulfhydration-dependent activation of Unc-51-like autophagy-activating kinase 1 (ULK1). Furthermore, Cys951Ser mutation of ULK1 decreased autolysosome formation and promoted hepatic lipid accumulation in mice, suggesting that the loss of ULK1 sulfhydration was directly associated with the pathogenesis of NAFLD. Moreover, silencing of CSE in SREBP-1c knockout mice increased liver triglycerides, confirming the connection between CSE, autophagy, and SREBP-1c. Overall, our results uncover a 2-fold mechanism for SREBP-1c-driven hepatic lipid accumulation through reciprocal activation and inhibition of hepatic lipid biosynthesis and degradation, respectively.