

## AUTOPHAGY REGULATES HEPATIC ACETYLOME

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**Abstract:** Liver acetylome is a set of protein acetylations whose level reflects cellular metabolic health and is directly linked to intracellular pathways. However, to date, little is known about the cellular pathways that maintain the hepatic acetylome levels. Here, we show that macroautophagy hereafter referred to as autophagy, an intracellular lysosomal degradative pathway, regulates the hepatic acetylome. Examination of total acetylome (nuclear, cytosolic, mitochondrial, membrane) in autophagy-deficient or autophagy-defective liver exhibited remarkably lower levels compared to normal liver. The lower hepatic acetylome was independent of the cellular injury that is commonly seen in autophagy-deficient conditions. In contrast, autophagy activation by fasting or rapamycin treatment increased the level of hepatic acetylome. Moreover, mechanistic studies showed that hepatic autophagy function is essential to maintaining levels of acetyl-CoA, a central intermediate metabolite needed for acetylation of proteins. Autophagy impairment significantly reduced hepatic acetyl-CoA production through transcriptional downregulation of key enzymes involved in the acetyl-CoA synthesis, including *AclY*, *AceCS1*, *AceCS2*, *Mcd*, and *Pdha1*. Notably, replenishing hepatic acetyl-CoA rescued the lowered hepatic acetylome and, interestingly, protected against liver injury in the autophagy-deficient liver. In conclusion, autophagy regulates the hepatic acetylome as an important mechanism for protecting livers against injury and causing liver damage. This work was supported in part by Louisiana Board of Regents grant R & D, RCS LEQSF (2021-24)-RD-A-17, TUSOM Endowment Fund, and BeHEARD Biotechne Award (to Khambu B).

**Key words:** *Hepatic Acetylome, autophagy, acetyl coenzyme-A, liver injury*