

## Abstract

Mitochondrial function depends on the coordinated expression of the nuclear and the mitochondrial genomes. In contrast to our wide knowledge of the molecular mechanisms involved in the transcription of nuclear-encoded mitochondrial proteins (NEMPs), the regulators of the translation process are largely unknown. Recently, we discovered that the cytosolic protein Clustered mitochondria homolog (CLUH) is a RNA-binding protein which specifically binds to mRNAs of several NEMPs. Depletion of CLUH in different cellular systems revealed that CLUH regulates the expression of its target mRNAs. This finding raises the questions of the molecular mechanism behind the reduced expression and the physiological significance of the interaction between CLUH and its target mRNAs. To answer these questions, CLUH deficiency was previously modeled in the mouse. Full-body *Cluh* knock out (KO) mice die shortly after birth due to an inability to shift mitochondrial metabolism from anabolism to catabolism to survive post-birth starvation. The liver seems to be one of the main organs in which CLUH function is essential. Consistently, liver-specific *Cluh* KO mice fail to adapt their metabolism in response to starvation. Proteomic and transcriptomic analysis of *Cluh*-deficient livers revealed the coherent downregulation of hundreds of mRNAs and proteins belonging to interconnected metabolic pathways involved in oxidative phosphorylation, amino acid degradation, TCA cycle, fatty acid oxidation, and ketogenesis. Remarkably, all downregulated mRNAs encoded for NEMPs and partially overlapped with previously identified CLUH-targets in HeLa cells, suggesting that without CLUH its target transcripts may become unstable. Indeed, I demonstrated that the half-lives of the target transcripts are decreased in *Cluh*-deficient MEFs. Moreover, in all organisms so far analyzed homologs of CLUH are crucial to maintain mitochondrial distribution. Loss of CLUH *in vitro* and *in vivo* reproduced the highly conserved mitochondrial clustering phenotype. The identification of interaction partners of CLUH revealed the molecular reason for this phenotype. CLUH interacts with astrin, a negative regulator of mTOR complex 1 (mTORC1) upon stress. Depletion of CLUH leads to hyperactivation of mTORC1 upon starvation due to an impairment of mTORC1 inhibition. This causes a defect in autophagy resulting in the inhibited removal of dysfunctional mitochondria and their subsequent accumulation close to the nucleus. In conclusion, I showed that CLUH is essential to increase mitochondrial fitness upon nutrient deprivation by regulating the expression of specific NEMPs important for the metabolic switch from glycolysis towards catabolism and by shutting off mTORC1 signaling to induce autophagic flux.