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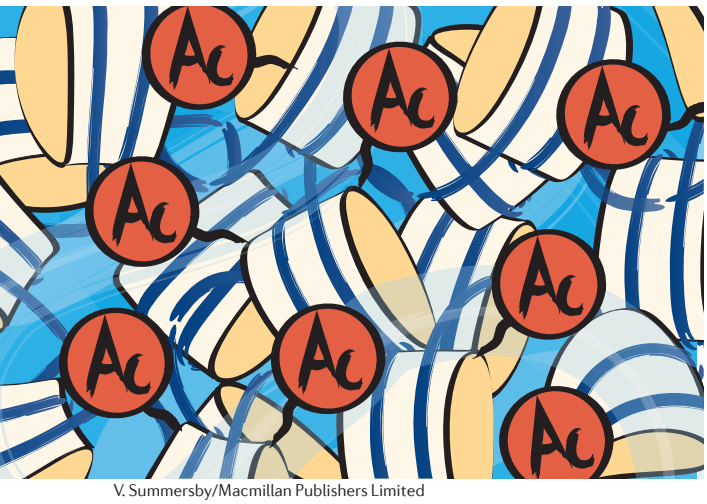
GENE EXPRESSION

ACSS2 boosts local histone acetylation

> ACSS2 and TFEB are required as a complex for the activation of lysosomal and autophagy genes

Acetyl coenzyme A (acetyl-CoA) is the acetyl donor for Lys acetylation reactions in mammalian cells. Histone Lys acetylation promotes transcription and is regulated by the metabolic state of the cell, but it is unclear how it is maintained during metabolic stress when sources of acetyl-CoA, such as glucose and acetate, are limited. Metabolic stress is common in tumours, in which acetyl-CoA levels are maintained by acyl-CoA synthetase short-chain family member 2 (ACSS2), which generates acetyl-CoA from acetate. Li *et al.* now show that ACSS2 binds to the promoter regions of lysosomal and autophagy genes to locally produce acetyl-CoA to support histone acetylation and gene expression.

The authors monitored ACSS2 subcellular localization in human glioblastoma cells and observed that cytosolic ACSS2 translocated into the nucleus when the cells were deprived of glucose. Nuclear translocation was induced by phosphorylation of Ser 659 of ACSS2 by AMP-activated protein kinase (AMPK) and was mediated by importin 5.



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Once in the nucleus, ACSS2 interacted with transcription factor EB (TFEB) — a master regulator of lysosomal and autophagy genes. Lysosomal degradation and autophagy provide cancer cells with alternative sources of nutrients. Glucose deprivation induced the expression of lysosomal and autophagy genes, and this was largely abrogated by knock-in of ACSS2 mutants.

Chromatin immunoprecipitation (ChIP) showed that in conditions of glucose deprivation, TFEB and ACSS2 bind in a mutually dependent manner to the promoters of TFEB-target genes. Furthermore, ChIP followed by high-throughput sequencing revealed that lysosomal and autophagy genes were globally enriched for ACSS2 binding. These results indicated that ACSS2 and TFEB are required as a complex for the activation of lysosomal and autophagy genes following glucose deprivation.

Glucose deprivation in human glioblastoma cells resulted in a large reduction of nuclear acetyl-CoA levels, which were further reduced by ACSS2 deactivation. However, ChIP using antibodies against acetylated histones showed that following glucose deprivation, histone acetylation was induced rather than reduced at the promoter regions of lysosomal and autophagy genes. This effect was blocked by deactivating ACSS2 or by pretreatment with a histone deacetylase inhibitor and was restored by the addition of acetyl-CoA to the medium.

These results suggest that ACSS2 utilizes the acetate that is generated by histone deacetylation to locally produce acetyl-CoA to support histone acetylation and the expression of lysosomal and autophagy genes. In support of this model, glucose deprivation induced lysosomal biogenesis and autophagy in an ACSS2-dependent manner, and this was required for cell survival. Furthermore, ACSS2 depletion or deactivation reduced TFEB-target gene expression and tumour growth in nude mice, especially following inhibition of glycolysis. Finally, immunohistochemistry analysis of human astrocytoma and glioblastoma samples revealed a direct correlation between phosphorylated ACSS2 levels and tumour aggressiveness.

Interestingly, a study by Mews *et al.* reports a connection between ACSS2-mediated acetyl-CoA metabolism and neuronal plasticity in mice. These authors found that in differentiating neurons and in the hippocampus, ACSS2 is recruited together with the acetyltransferase CREB-binding protein (CBP) to the promoter regions of neuronal genes, where it supports histone acetylation and gene expression. This results in hippocampus-mediated long-term memory consolidation.

In summary, nuclear ACSS2 can form complexes with transcription activators at the promoter regions of different sets of genes to locally support histone acetylation and activate gene expression programmes.

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ORIGINAL ARTICLES Li, X. *et al.* Nucleus-translocated ACSS2 promotes gene transcription for lysosomal biogenesis and autophagy. *Mol. Cell* http://dx.doi.org/10.1016/j.molcel.2017.04.026 (2017) | Mews, P. *et al.* Acetyl-CoA synthetase regulates histone acetylation and hippocampal memory. *Nature* http://dx.doi.org/10.1038/nature22405 (2017)

FURTHER READING Sabari, B. R. *et al.* Metabolic regulation of gene expression through histone acylations. *Nat. Rev. Mol. Cell Biol.* **18**, 90–101 (2017)