AUTOPHAGY
2017, VOL. 13, NO. 10, 1790–1791
https://doi.org/10.1080/15548627.2017.1349581

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AUTOPHAGIC PUNCTUM

Local histone acetylation by ACSS2 promotes gene transcription for lysosomal biogenesis and autophagy

Xinjian Li[a], Xu Qian[a], and Zhimin Lu[a,b,c]

[a]Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [b]Department of Molecular and Cellular Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [c]Graduate School of Biomedical Sciences, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

ABSTRACT

Overcoming metabolic stress is a critical step in tumorigenesis. Acetyl coenzyme A (acetyl-CoA) converted from glucose or acetate is a substrate used for histone acetylation to regulate gene expression. However, how acetyl-CoA is produced under nutritional stress conditions is unclear. Herein we report that nutritional stress induces nuclear translocation of ACSS2 (acyl-CoA synthetase short-chain family member 2). This translocation is mediated by AMP-activated protein kinase (AMPK)-dependent ACSS2 Ser659 phosphorylation and subsequent exposure of the nuclear localization signal of ACSS2 to KPNA1/importin α5 for binding. In the nucleus, ACSS2 forms a complex with TFEB (transcription factor EB) and utilizes the acetate generated from histone deacetylation to locally produce acetyl-CoA for histone acetylation in the promoter regions of TFEB target genes. Knock-in of nuclear translocation-deficient or inactive ACSS2 mutants in glioblastoma cells abrogates glucose deprivation-induced lysosomal biogenesis and autophagy, reduces cell survival, inhibits brain tumorigenesis, and enhances the inhibitory effect of the glucose metabolism inhibitor 2-deoxy-D-glucose on tumor growth. These results reveal a novel biologic role for ACSS2 in recycling of nuclear acetate for histone acetylation to promote lysosomal and autophagy-related gene expression and counteract nutritional stress, highlighting the importance of ACSS2 in maintaining autophagy and lysosome-mediated cellular energy homeostasis during tumor development.

ARTICLE HISTORY
Received 14 June 2017
Revised 27 June 2017
Accepted 28 June 2017

KEYWORDS
acetyl-CoA; ACSS2; AMPK; autophagy; lysosomal biogenesis; nucleus; phosphorylation; TFEB; tumor development

In eukaryotic cells, histone acts as a spool around which DNA winds. Acetyl modification of histones can release the interaction between histones and DNA by neutralizing the positive charges of histones and subsequently loosening the structure of chromatin to enable gene expression. Histone acetylation is a reversible process in which histone acetyltransferases and histone deacetylases (HDACs) act as writers and erasers of acetylation, respectively. Under nutrient-sufficient conditions, acetyl-CoA can be generated by ACLY (ATP citrate lyase), the pyruvate dehydrogenase complex (PDC), and ACSS (acyl-CoA synthetase short-chain family member) from citrate, pyruvate, and acetate, respectively. However, it is still mysterious how cancer cells produce acetyl-CoA under nutrient-deficient conditions. Recently, a study reported in *Molecular Cell* by our group addressed this problem by proposing a model in which acetyl-CoA used for histone acetylation is produced by nuclear ACSS2 from acetate (Fig. 1). We observed that ACSS2 was translocated from the cytosol to the nucleus when glioblastoma (GBM) cells were deprived of glucose. Mechanistically, nuclear translocation of ACSS2 resulted from exposure of its nuclear localization signal to KPNA1/importin α5 in an AMPK phosphorylation-dependent manner.

In the nuclei of GBM cells, ACSS2 forms complexes with TFEB, a master regulator of lysosomal and autophagy-related genes, and locally produces acetyl-CoA for histone acetylation in the promoter regions of TFEB target genes. Chromatin immunoprecipitation (ChIP)-sequencing analyses revealed that binding targets of ACSS2 and TFEB as well as their de novo binding consensus motifs are highly overlapped under glucose-deprivation conditions. In addition, heat map analyses demonstrate a similar binding pattern around the transcription start site between *ACSS2* and *TFEB*. Furthermore, ChIP analyses of glucose-deprived GBM cells using the TFEB target genes as readouts indicate that ACSS2 binds to the promoter regions of TFEB target genes and that this binding is largely abrogated by expression of a nuclear translocation-deficient TFEB mutant. These results indicate that ACSS2 binds to the promoters of TFEB target genes in complexes with TFEB.

To determine the role of ACSS2 in nuclear acetyl-CoA production, we measured nuclear acetyl-CoA levels in GBM cells expressing wild-type ACSS2 or nuclear translocation-deficient or inactive ACSS2 mutants. We demonstrated that glucose deprivation largely decreases the nuclear acetyl-CoA levels and that this effect is further enhanced in cells expressing the nuclear translocation-deficient or inactive ACSS2 mutants. These results suggest that active nuclear ACSS2 is required to maintain the nuclear acetyl-CoA levels under glucose-deprivation conditions. ChIP analyses using antibodies against acetylated histones demonstrate that expression of the nuclear translocation-deficient or inactive ACSS2 mutant, or

CONTACT Zhimin Lu zhiminlu@mdanderson.org Department of Neuro-Oncology, Unit 1002, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA.
Punctum to: Li X, et al. Nucleus-translocated ACSS2 promotes gene transcription for lysosomal biogenesis and autophagy. Mol Cell 2017; 66(5):684-697.

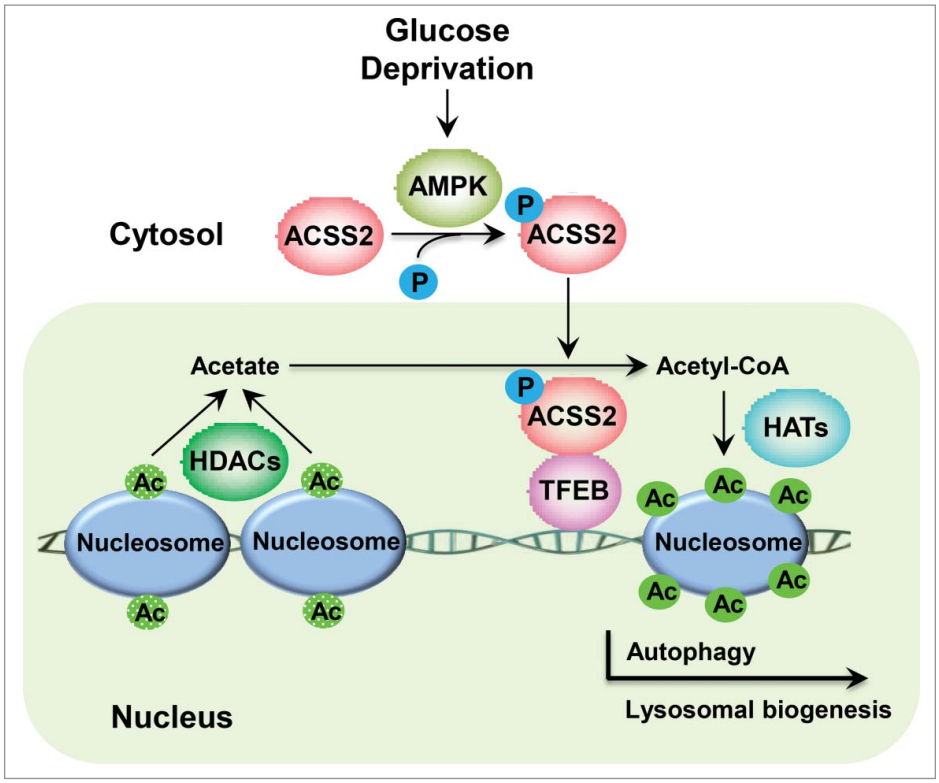

Figure 1. Model of ACSS2-mediated local histone acetylation. Glucose deprivation results in AMPK-dependent phosphorylation of ACSS2 and subsequent nuclear translocation of ACSS2. In the nucleus, ACSS2 uses acetate generated from HDAC-mediated histone deacetylation to locally produce acetyl-CoA to support histone acetyltransferase (HAT)-mediated histone acetylation in the promoter regions of TFEB target genes. P, phosphate group; Ac, acetyl-CoA.

pre-treatment of GBM cells with a HDAC inhibitor, abolish the glucose deprivation-induced histone acetylation in the promoter regions of TFEB target genes. These results suggest that ACSS2 utilizes the acetate generated from overall histone deacetylation to locally produce acetyl-CoA to support histone acetylation in the promoter regions of TFEB target genes.

Functional studies demonstrate that expression of the nuclear translocation-deficient or inactive ACSS2 mutants blocks glucose deprivation-induced expression of lysosomal and autophagy-related genes as well as lysosomal biogenesis and autophagy in GBM cells. In addition, survival of the cells expressing either mutant under glucose-deprivation conditions decreases dramatically. Studies using a xenografted brain tumor mouse model show that expression of the nuclear translocation-deficient or inactive ACSS2 mutants inhibits tumor growth and that this effect is enhanced by treatment with 2-deoxy-D-glucose, which is a compound that blocks glycolysis. Immunohistochemical staining of human astrocytoma and GBM tissue samples demonstrates that ACSS2 phosphorylation levels are positively correlated with AMPK activity and tumor aggressiveness. These results support an instrumental role for nuclear ACSS2 in tumorigenesis and tumor progression.

In summary, this study demonstrates that nuclear ACSS2 produces acetyl-CoA in TFEB-targeted gene promoter regions and enhances lysosomal biogenesis and autophagy to counteract the nutritional stress and maintain tumor cell survival and growth. These findings provide critical insights into epigenetic regulation of gene expression by the metabolic enzyme ACSS2 in cancer development and may lead to the development of promising strategies to treat human cancer by pharmacologically inhibiting ACSS2.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by National Institute of Neurological Disorders and Stroke grant 1R01 NS089754 (Z.L.) and National Cancer Institute grants 1R01CA204996 (Z.L.), 2R01 CA109035 (Z.L.), and 1R01 CA169603 (Z.L.).