Editorial

New function of Tip60 in controlling triacylglycerol synthesis

Takako Hattori

Department of Biochemistry & Molecular Dentistry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Correspondence to: Takako Hattori. Department of Biochemistry & Molecular Dentistry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 5-1 Shikata-cho, 2-chome, Kita-ku, Okayama 700-8525, Japan. Email: hattorit@cc.okayama-u.ac.jp; hattorit@md.okayama-u.ac.jp.

Provenance: This is an invited Editorial commissioned by the Executive Editor-in-Chief Dr. Hualin Sun (Jiangsu Key Laboratory of Neuroregeneration, Nantong University, Nantong, China).

Comments on: Li TY, Song L, Sun Y, *et al*. Tip60-mediated lipin1 acetylation and ER translocation determine triacylglycerol synthesis rate. Nat Commun 2018;9:1916.

Received: 16 August 2018; Accepted: 17 August 2018; Published: 04 September 2018.

doi: 10.21037/biotarget.2018.08.03

View this article at: http://dx.doi.org/10.21037/biotarget.2018.08.03

The HIV Tat-interactive protein, 60 kDa (Tip60) was originally identified as a cellular acetyltransferase belonging to the MYST (MOZ, Ybf2/Sas3, Sas2 and Tip60) family. Tip60 has been intensely investigated as tightly regulated transcriptional coregulator, acting in multiprotein complexes such as androgen receptor, a steroid receptor (1), or c-Myc and E2F1 to regulate cell cycle (2). Furthermore, it regulates multiple steps of DNA repair including activation of ataxia telangiectasia mutant (ATM) protein kinase (3), p53 directed apoptosis (4). Also, Sox9 dependent chondrocyte differentiation (5) usually involves recruitment of Tip60 acetyltransferase activities to chromatin. Recent studies accumulate evidence that Tip60 plays a key role as cytosolic mediator of the p38 signaling pathway controlling senescence (6), the insulin degrading enzyme pathway controlling amyloid-β protein process (7), and ER-stress inducing autophagy (8).

Triacylglycerol (TAG) is a major component of fatty acids. However, the signaling networks connecting fatty acids, TAG and lipid synthesis was largely unknown. There was some evidence for a connection of adipogenesis or generation of white adipose tissue with Tip60 (9,10), and the fact that Tip60 deficiency leads to embryonic lethality around the blastocyst stage (11) indicates an essential role of Tip60 in development. The acetyltransferase activity of Tip60 is controlled by phosphorylation at Ser 86 and 90. Ser 86 is phosphorylated by glycogen synthase kinase-3 (GSK3) (12).

Here Li *et al*. (13) have shown that mutation of Ser 86 attenuates acetyltransferase activity by almost 50 percent. In an elegant and stringently performed study they generated knock in mice by replacing the wild type Tip60 allele by Tip60-S86A. The homozygote mutant mice revealed 20–30% reduced body weight, small fat depots and reduced adipocyte size compared to wild type (WT) when subjected to high fat diet (HFD). The authors also found that depletion of Tip60 strongly impaired TAG synthesis, while phosphatidylcholine synthesis was not affected. Interestingly, adipogenic differentiation of mouse embryonic fibroblasts to adipocytes was similar in Tip60-S87A and WT mice. These data indicate that the decreased lipid deposition caused by Tip60 depletion was due to inhibition of TAG synthesis rather than inhibition of adipogenic differention.

In an elaborate survey the authors subsequently identified the steps of the TAG biosynthesis reaction controlled by Tip60. They report that lipin1 which catalyzes the conversion of phosphatidic acid (PA) to diacylglycerol (DAG) binds to Tip60, and is acetylated, while the Tip60-S86A mutant did not show acetylated lipin1. Mass-spec analysis revealed that PA, a substrate of lipin1, was elevated, and DAG, a product of lipin1 was decreased in extracts of white adipose tissue surrounding the epididymis (eWAT) of Tip60-S86A mice.

The next search of the authors was deacetylases responsible for lipin1 deacetylation. Unexpectedly, a class

I and II histone deacetylase (HDAC) inhibitor, trichostatin A (TSA), did not affect lipin1 acetylation, however, nicotinamide, a class III HDAC inhibitor, strongly increased lipin1 acetylation, indicating involvement of sirtuin(s), a nicotinamide-adenine-dinucleotide (NAD) dependent deacetylase. Among the sirtuin family, only sirtuin1 significantly deacetylates lipin1. Sirtuin1 deacetylates many transcription factors such as P53, FOXO3, PGC-1, LXR, and regulates apoptosis, stress response, homeostasis of sugar and lipid metabolism (14). Knockdown of sirtuin1 mRNA or EX527, a sirtuin1 inhibitor, increased the rate of DAG and TAG synthesis in 3T3-L1 adipocytes, most likely through increased levels of lipin1 acetylation. These data strongly suggest that sirtuin1 negatively regulates lipid synthesis.

Furthermore, in response to oleic acid (OA), Tip60 was found to translocate lipin1 from the cytosol to ER-associated membranes (microsomes) where DAG/TAG are generated. This was confirmed using MG419, a Tip60 inhibitor and by knock down of Tip60 in the cultured adipocytes, as well as in primary embryonic fibroblasts (MEF) from Tip60-S86A mutant mice, and after knockdown of sirtuin1, and EX527, a sirtuin1 inhibitor.

Interestingly, the authors described that reciprocal interaction of lipin1 with Tip60 and sirtuin1 was balanced in a status of acetylation and phosphorylation of lipin1. Without phosphorylation, lipin1 was strongly acetylated by Tip60 with enhanced association, but reduced association to sirtuin1. The binding of lipin1 with Tip60 or sirtuin1 was competitive. OA treatment promoted lipin1 interaction with Tip60 and attenuated its association with sirtuin1 in cultured adipocytes, leading to higher levels of acetylated lipin1. In conclusion, the competitive interaction of Tip60 and sirtuin1 with lipin1 is dynamically regulated by acetylation/deacetylation of lipin1.

Since Tip60 is highly conserved among the eukaryotes, the authors further estimated the role of Tip60 in TAG synthesis in yeast. Loss-of function of ESA1, the yeast homolog of Tip60, dramatically reduced the TAG content in cell extracts. Co-expression of ESA1 with each of the TAG biosynthetic enzymes from yeast in HEK293 cells induced twofold acetylation of PAH1, the yeast homologue of lipin1. Analogous to the results obtained with the Tip60 mouse mutants, reconstitution of yeast cell lysates from the PAH1-K496/801R mutant showed severely reduced TAG accumulation compared to the WT. These findings strongly suggest that PAH1 acetylation, most likely via the Tip60 homolog ESA1, plays a conserved role in TAG storage in eukaryotes.

This paper has provided fundamentally new insight into the Tip60-lipin1-sirtuin1 axis in fat synthesis and may open new possibilities for the treatment of obesity. Further new questions how the acetylation by Tip60 organize multiple cellular metabolic events will rise up.

Acknowledgments

The author thanks Drs. Satoshi Kubota, Takashi Nishida (Department of Biochemistry & Molecular Dentistry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan), Dr. Beniot de Crombrugghe (MD Anderson Cancer Center, University of Texas, TX, USA), and Dr. Klaus von der Mark (University of Erlangen-Nuremberg, Germany) for valuable discussion. This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan (#16K11476, 25462888), SHISEIKAI Scholarship Fund for basic researcher of medical science, Keiko Watanabe Award, Grant from Ryobi-Teien Memory Foundation, and Grant from The Foundation for Growth Science.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Culig Z, Santer FR. Androgen receptor co-activators in the regulation of cellular events in prostate cancer. World J Urol 2012;30:297-302.
2. Nagl NG Jr, Wang X, Patsialou A, et al. Distinct mammalian SWI/SNF chromatin remodeling complexes with opposing roles in cell-cycle control. EMBO J 2007;26:752-63.
3. Sun Y, Jiang X, Chen S, et al. A role for the Tip60 histone acetyltransferase in the acetylation and activation of ATM. Proc Natl Acad Sci U S A 2005;102:13182-7.
4. Sykes SM, Mellert HS, Holbert MA, et al. Acetylation of the p53 DNA-binding domain regulates apoptosis induction. Mol Cell 2006;24:841-51.
5. Hattori T, Coustry F, Stephens S, et al. Transcriptional regulation of chondrogenesis by coactivator Tip60 via chromatin association with Sox9 and Sox5. Nucleic Acids Res 2008;36:3011-24.

6. Zheng H, Seit-Nebi A, Han X, et al. A posttranslational modification cascade involving p38, Tip60, and PRAK mediates oncogene-induced senescence. Mol Cell 2013;50:699-710.
7. Buoso E, Biundo F, Lanni C, et al. AβPP intracellular C-terminal domain function is related to its degradation processes. J Alzheimers Dis 2012;30:393-405.
8. Nie T, Yang S, Ma H, et al. Regulation of ER stress-induced autophagy by GSK3β-TIP60-ULK1 pathway. Cell Death Dis 2016;7:e2563.
9. Gao Y, Hamers N, Rakhshandehroo M, et al. Allele compensation in tip60+/- mice rescues white adipose tissue function in vivo. PLoS One 2014;9:e98343.
10. Gao Y, Koppen A, Rakhshandehroo M, et al. Early adipogenesis is regulated through USP7-mediated deubiquitination of the histone acetyltransferase TIP60. Nat Commun 2013;4:2656.
11. Hu Y, Fisher JB, Koprowski S, et al. Homozygous disruption of the Tip60 gene causes early embryonic lethality. Dev Dyn 2009;238:2912-21.
12. Lin SY, Li TY, Liu Q, et al. GSK3-TIP60-ULK1 signaling pathway links growth factor deprivation to autophagy. Science 2012;336:477-81.
13. Li TY, Song L, Sun Y, et al. Tip60-mediated lipin1 acetylation and ER translocation determine triacylglycerol synthesis rate. Nat Commun 2018;9:1916.
14. Schwer B, Verdin E. Conserved metabolic regulatory functions of sirtuins. Cell Metab 2008;7:104-12.

doi: 10.21037/biotarget.2018.08.03
Cite this article as: Hattori T. New function of Tip60 in controlling triacylglycerol synthesis. Biotarget 2018;2:13.

