EBioMedicine 35 (2018) 27–28

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

Histone deacetylase 11 as a key regulator of metabolism and obesity

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ARTICLE INFO

Article history:
Received 2 August 2018
Accepted 6 August 2018
Available online 17 August 2018

ABSTRACT

In this thought commentary, I highlight the discoveries made by Seto and colleagues related to HDAC11 and obesity. I discuss how their reported work fills a gap in the HDAC field and comment on the clinical implications of their findings. Overall, selective inhibition of HDAC11 could be a novel potential therapeutic avenue for both obesity and diabesity, the diabetes caused by obesity. Future studies to further dissect this mechanistic link between HDAC11 and metabolic programs will pave the way for designing mechanism-based combination therapeutic strategies for these two life style diseases.

Histone or lysine deacetylase (HDAC/KDAC) enzymes target histone and non-histone proteins, removing acetyl or acyl groups from their lysine residues to regulate a variety of processes including transcription, cell death and metabolism. Unconventional roles for HDACs in genome maintenance via functioning in DNA replication and DNA repair have also been demonstrated [1]. Altered HDAC expression, their aberrant functions, and numerous HDAC targets are implicated in many human diseases. HDACs are therefore attractive therapeutic targets in cancers as well as in metabolic disorders, cardiovascular, neurological and inflammatory diseases. So far, four HDAC inhibitors—Vorinostat, Romidepsin, Panobinostat, and Belinostat—are approved by the United States Food and Drug Administration (FDA) for certain hematological cancers. Several clinical trials are currently underway testing the therapeutic benefits of inhibiting HDACs for many cancers and various other human diseases. These FDA-approved HDAC inhibitors broadly target both 'good' as well as 'bad' HDACs, causing adverse side effects including cardiac or gastrointestinal toxicity and thrombocytopenia in patients. Therefore, it has become important to study and understand the fundamental functions of individual HDACs in various organs and cellular processes, in order to use isotype-specific or selective HDAC inhibition as a targeted strategy for treating specific diseases.

Mammalian HDACs are divided into four classes: class I HDACs include HDAC1, 2, 3 and 8; class IIa and IIb HDACs include HDAC 4,5,6,7,9,10; class III HDACs or Sirtuins are classified as Sirt1–7; and class IV consist of HDAC11 [2]. While Sirtuins require nicotinamide adenine dinucleotide (NAD^+) for their catalytic activity, the class I, II and IV family HDACs are Zn^{2+}-dependent enzymes that differ in their cellular localization, expression and catalytic domains. Amongst HDACs, HDAC11 is relatively new, being discovered in 2002. Nevertheless, several interesting studies have uncovered functions for HDAC11 in immune response, neutrophil and T cell development, and in tumor biology [3].

The role of HDACs in the pathophysiology of metabolic disorders is an emerging field of investigation. Liver-specific deletion of HDAC3 favors lipid accumulation and causes hepatomegaly [4, 5]. MS-275, a class I HDAC inhibitor, was shown to promote browning of the white adipose tissue to counteract high-fat diet induced obesity [6]. SIRT1 regulates glucose and lipid homeostasis in the liver [7] and *Sirt3-null* mice exhibit metabolic syndrome when fed with a high-fat diet [8]. Unlike class I-III family HDACs, the contributions of HDAC11, if any, in obesity was not known. Recently published in EBioMedicine, using a knockout (KO) mouse model, Sun et al. demonstrate that HDAC11 regulates metabolism and obesity—findings with high clinical relevance [9]. They show that HDAC11 KO mice are resistant to high-fat diet-induced obesity. Deletion of HDAC11 decreases liver damage and enhances glucose tolerance, uncovering important contribution(s) of HDAC11 in livers. Their work provides insights into the mechanism by which HDAC11 deficiency reduces hypercholesterolemia and hepatosteatosis, while increasing insulin sensitivity and glucose tolerance. These findings have direct implications to diabetes, a rampant worldwide metabolic disease. They report that loss of HDAC11 increases energy expenditure via promoting thermogenic capacity, contributing to an elevated expression of uncoupling protein-1, which can facilitate the clearance of metabolic stores. In addition, they show that deletion of HDAC11 elevates oxygen consumption and adiponectin signaling that promotes lipid metabolism. These important results therefore reveal HDAC11 functions in metabolic programs, opening up avenues for its therapeutic targeting in metabolic disorders.

Obesity is a major challenge for patients and physicians alike today. About 60% of adults are obese or overweight in the United States alone,

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.06.025.

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https://doi.org/10.1016/j.ebiom.2018.08.008

and it is associated with a range of co-morbidities including type 2 diabetes, cardiovascular disease and certain cancers. Diabesity—a term for type 2 diabetes caused by obesity—is a major health concern worldwide that is fast approaching alarming epidemic proportions. Complications from diabetes include renal failure, myocardial infarction, stroke and blindness, that together cause high morbidity and mortality. Lifestyle-changing treatments of obesity often provide temporary results, because of the body's adaptation and weight regain. Pharmacotherapy for obesity is not used broadly, as anti-obesity drugs vary in their efficacy and display side effects. Metformin—the common drug for type 2 diabetes—increases SIRT1 activity while inhibiting or decreasing Class II HDACs and histone methyl transferases [10]. Given this effect on multiple epigenetic regulators, there is a high degree of ambiguity regarding the long-term effects of metformin on the epigenome. Therefore, the promising and intriguing results of Sun et al. using an HDAC11 KO mouse model provides the rationale for the design and testing of HDAC11-selective inhibitor(s) for obesity and diabetes. Future studies identifying the targets of HDAC11 would shed light on its precise molecular mode-of-action in the diseased states of the liver, and also set the stage for potential mechanism-based combination therapies. Their work therefore lays a strong foundation for a treatment strategy that could improve the lives of millions of individuals afflicted with these life-threatening life-style diseases in the United States and worldwide.

Declaration

The author declares no conflict of interest.

Role of the funding Source

This commentary was supported by NIH/NCI R01 grant (R01-CA188520) to SB.

References

[1] Bhaskara S, et al. Deletion of histone deacetylase 3 reveals critical roles in S phase progression and DNA damage control. Mol Cell 2008;30:61–72.
[2] Haberland M, Montgomery RL, Olson EN. The many roles of histone deacetylases in development and physiology: implications for disease and therapy. Nat Rev Genet 2009;10:32–42.
[3] Yanginlar C, Logie C. HDAC11 is a regulator of diverse immune functions. Biochim Biophys Acta 2018;1861:54–9.
[4] Sun Z, et al. Hepatic Hdac3 promotes gluconeogenesis by repressing lipid synthesis and sequestration. Nat Med 2012;18:934–42.
[5] Knutson SK, et al. Liver-specific deletion of histone deacetylase 3 disrupts metabolic transcriptional networks. EMBO J 2008;27:1017–28.
[6] Ferrari A, et al. Attenuation of diet-induced obesity and induction of white fat browning with a chemical inhibitor of histone deacetylases. Int J Obes 2017;41:289–98.
[7] Li X. SIRT1 and energy metabolism. Acta Biochim Biophys Sin Shanghai 2013;45:51–60.
[8] Hirschey MD, et al. SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. Mol Cell 2011;44:177–90.
[9] Sun L, et al. Programming and regulation of metabolic homeostasis by HDAC11. EBioMedicine 2018;33:157–68.
[10] Bridgeman SC, Ellison GC, Melton PE, Newsholme P, Mamotte CDS. Epigenetic effects of metformin: from molecular mechanisms to clinical implications. Diabetes Obes Metab 2018;20:1553–62.