METABOLIC DISEASE

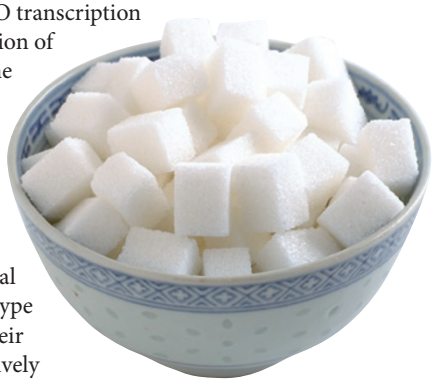
New role for HDACs in glucose homeostasis

Despite the many available classes of antidiabetic agents, achieving effective long-term blood sugar control is often challenging. Now, two papers have identified a novel mechanism that is involved in the regulation of glucose production by the liver, implicating class IIa histone deacetylases (HDACs) as promising therapeutic targets for the treatment of type 2 diabetes.

The liver is responsible for the production of glucose (gluconeogenesis), a process that is tightly regulated by the hormones insulin and glucagon, in response to nutrient availability. These hormones differentially regulate a complex signalling cascade, which ultimately leads to the regulation of the forkhead box protein O (FOXO) transcription factors that control gluconeogenic gene transcription. Part of this signalling cascade involves the LKB1 (also known as STK11)–AMP-activated protein kinase (AMPK) pathway that acts to suppress gluconeogenesis. Although numerous AMPK substrates have now been identified, it is likely that others exist. With this in mind, Shaw and colleagues set out to identify novel substrates of AMPK and its related family members that are involved in glucose homeostasis.

First, using a bioinformatics and proteomics screen for substrates of AMPK family kinases, they identified class IIa HDACs as direct targets of the AMPK pathway. Confirming this finding, deletion of LKB1 (an upstream AMPK activator) in mouse liver blocked basal phosphorylation of class IIa HDACs, whereas small molecule AMPK activation increased their phosphorylation.

Next, they investigated whether class IIa HDACs might be involved in the regulation of glucose production. Fasting and refeeding of mice respectively reduced and increased class IIa HDAC phosphorylation in the liver. These effects were shown to be hormonally regulated — injection of the fasting hormone glucagon reduced class IIa HDAC phosphorylation, inducing their nuclear translocation. Once in the nucleus, these HDACs associated with gluconeogenic gene promotors and recruited HDAC3 (a class I HDAC), causing the deacetylation and activation of FOXO transcription factors and induction of gluconeogenic gene transcription. Intriguingly, further studies showed that class IIa HDACs contribute to hyperglycaemia in several mouse models of type 2 diabetes, with their suppression effectively restoring glucose homeostasis.



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Meanwhile, Montminy and colleagues revealed that the same regulatory mechanism is present in *Drosophila melanogaster*. Their initial studies were focused on identifying the precise role of an AMPK-related kinase family member — salt inducible kinase 3 (SIK3) — in energy balance. They found SIK3 to be both nutritionally and hormonally activated. During feeding, SIK3 was activated by insulin, and this resulted in the phosphorylation and cytoplasmic sequestration of HDAC4, a class IIa HDAC. In response to starvation, however, SIK3 was inactivated, leading to dephosphorylation of HDAC4 and its translocation to the nucleus, causing deacetylation of FOXOs and activation of catabolic enzymes. Importantly, they tested whether this pathway was conserved in mammals. Indeed, in mouse hepatocytes, SIK2 (the mouse SIK3 homologue) mediated HDAC4 phosphorylation in response to insulin, whereas glucagon induced HDAC4 dephosphorylation through SIK2 inhibition, allowing gluconeogenic gene transcription.

Together, these studies have identified a novel role for class IIa HDACs in regulating liver glucose production. As many HDAC inhibitors are currently being developed as anticancer agents, it may be feasible to target this class of HDACs in the treatment of type 2 diabetes.

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ORIGINAL RESEARCH PAPER Mihaylova, M. M. *et al.* Class IIa histone deacetylases are hormone-activated regulators of FOXO and mammalian glucose homeostasis. *Cell* **145**, 607–621 (2011) | Wang, B. *et al.* A hormone-dependent module regulating energy balance. *Cell* **145**, 596–606 (2011)