

Glucose homeostasis regulation: reversible lysine acetylation of GAPDH

K.F. Howlett,² S. Bond,¹ K.R. Walder¹ and S.L. McGee,¹ ¹Metabolic Research Unit, School of Medicine, and ²Center for Physical Activity and Nutrition (C-PAN), School of Exercise and Nutrition Sciences, Deakin University, Geelong, VIC 3220, Australia.

Type 2 diabetes is characterised by persistent hyperglycaemia, of which altered liver metabolism is a key contributor through uncontrolled release of glucose. However, the molecular mechanism/s mediating this response in type 2 diabetes is not completely understood. Recent data in a number of organisms has shown that the majority of metabolic enzymes can be reversibly acetylated at lysine residues (Guarente, 2011). Acetylation of the glycolytic/gluconeogenic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH) controls glucose flux in *S. enterica*, with GAPDH acetylation favouring glucose consumption through glycolysis, and deacetylation of GAPDH favouring glucose production by gluconeogenesis (Wang *et al.*, 2010). Proteomic analysis has also shown that GAPDH is acetylated in human liver (Zhao *et al.*, 2010). While a number of acetylated lysine residues in GAPDH have been identified, their role in the control of glucose metabolism in mammalian liver is unknown. Therefore, the major aim of this project was to determine the role of GAPDH acetylation in regulating liver glucose flux, and whether this plays a role in type 2 diabetes.

Expression of an acetylation deficient GAPDH mutant in FAO hepatocytes increased basal glucose production compared with control cells expressing wild type GAPDH. The increase in basal glucose production was associated with reduced glycolysis and glucose oxidation. In response to insulin stimulation, the increase in glucose production in acetylation deficient GAPDH mutant FAO hepatocytes was suppressed, which suggests that insulin may regulate glucose production independently of lysine acetylation. However, in response to forskolin, an agent that increases cyclic AMP and mimics the action of hormones that increase glucose production, such as glucagon and adrenaline, the increase in basal glucose production in acetylation deficient GAPDH mutant in FAO hepatocytes was further enhanced. The potential role of GAPDH acetylation in diabetic mice that have elevated hepatic glucose production was also examined, and found to be reduced in the liver of diabetic *db/db* mice in the fed state compared to heterozygous littermates.

These data demonstrate that acetylation deficient GAPDH mutant hepatocytes have increased glucose production, and that diabetic *db/db* mice in the fed state have reduced liver GAPDH acetylation. These results suggest that altered lysine acetylation of GAPDH could contribute to the elevation of hepatic glucose output that is characteristic of type 2 diabetes, although the underlying mechanism/s mediating this response require further investigation.

Guarente L. (2011) *Cell Metabolism* **14**, 151-53.

Wang Q, Zhang Y, Yang C, Xiong H, Lin Y, Yao J, Li H, Xie L, Zhao W, Yao Y, Ning Z, Zeng R, Xiong Y, Guan K, Zhao S & Zhao G. (2010). *Science* **327** 1004-07.

Zhao S, Xu W, Jiang W, Yu W, Li Y, Zhang T, Yao J, Zhou L, Zeng Y, Li H, Li Y, Shi J, An W, Hancock S, He F, Qin L, Chin J, Yang P, Chen X, Lei Q, Xiong Y, Guan K. (2010) *Science* **327**, 1000-04.