METABOLISM

Mechanisms of hepatic glucose production revealed

In patients with type 2 diabetes mellitus, insulin no longer regulates hepatic glucose production (HGP); however, the mechanism underlying this process has not been identified. Previous studies have suggested that insulin might regulate HGP either through direct effects mediated by the hepatic insulin receptor (IR), or through indirect effects that are mediated through extrahepatic targets of insulin action (such as the brain or adipose tissue). In new work published in *Nature Communications*, separate teams from the laboratories of Terry Unterman and Morris Birnbaum shed new light on how insulin regulates HGP.

Both research groups generated mouse models with liver-specific knockout of *IR* or double knockout of both *IR* and *FoxO1*, a major target of insulin action. *IR*-knockout mice were glucose intolerant and resistant to the effects of insulin on HGP; concomitant deletion of *FoxO1* reversed these metabolic abnormalities, despite the lack of insulin signalling in the liver.

Paul Titchenell (from Morris Birnbaum's laboratory) suggests that a primary role of liver insulin signalling in the control of glucose metabolism is inhibition of *FoxO1* activity. "Thus, in the absence of *FoxO1*, insulin signalling in the liver is dispensable for

the regulation of systemic glucose metabolism and insulin sensitivity," says Titchenell.

"These results demonstrate that IR-mediated suppression of *FoxO1* function is critical for the ability of insulin to regulate HGP," explains Terry Unterman. "At the same time, when *FoxO1* is disrupted in the liver, the extrahepatic effects of insulin are sufficient to maintain glucose homeostasis and regulate HGP through indirect (extrahepatic) mechanisms that do not require hepatic IR."

Unterman suggests that *FoxO1* could be targeted to treat patients with diabetes mellitus and hepatic insulin resistance.

"Future work will aim to identify the extrahepatic tissue responsible for the regulation of glucose production by insulin and the liver-specific signalling mechanisms for coordinating this response," says Titchenell. Identification of these pathways could lead to novel targets for treating metabolic disorders such as diabetes mellitus.

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Original articles Titchenell, P. M. *et al.* Hepatic insulin signalling is dispensable for suppression of glucose output by insulin *in vivo*. *Nat. Commun.* doi:10.1038/ncomms8078 | O-Sullivan, I. *et al.* *FoxO1* integrates direct and indirect effects of insulin on hepatic glucose production and glucose utilization. *Nat. Commun.* doi:10.1038/ncomms8079