METABOLISM

LRH-1 is a transcriptional regulator of glucokinase in the liver

Liver receptor homolog 1 (LRH-1; also known as NR5A2) is a transcriptional regulator of glucokinase in the liver and a key component of the hepatic glucose-sensing system, new data suggest.

LRH-1 is a member of the NR5A nuclear receptor superfamily and is a key player in bile acid homeostasis, cholesterol transport and steroidogenesis. Emerging evidence suggests that LRH-1 is a potential target for the prevention and treatment of hepatic steatosis. Nevertheless, the physiological role of LRH-1 in hepatic glucose and fatty acid metabolism is ill defined.

“We have been interested in the metabolic role of LRH-1 for a long while,” says senior author Kristina Schoonjans of École Polytechnique Fédérale de Lausanne, Switzerland. “On the basis of our initial observation that hepatic glycogen storage was delayed in mice with a conditional deletion of *Lrh1* in the liver (*Alb-Cre; Lrh1^{fl/fl}* mice), we hypothesized that LRH-1 could be important for hepatic postprandial glucose metabolism in a more general way. We have been using both *in vivo* and *in vitro* approaches to confirm this hypothesis.”

The investigators first assessed hepatic glucose fluxes in living *Alb-Cre; Lrh1^{fl/fl}* mice by using mass isotopomer distribution analysis. They found that

fluxes of glucokinase and glycogen synthase in *Alb-Cre; Lrh1^{fl/fl}* mice were reduced compared with those in wild-type mice (*Lrh1^{fl/fl}*). This finding indicated that glucokinase, which is the gatekeeper of liver glucose metabolism during the postprandial state, is a main target of LRH-1. Next, by carrying out chromatin immunoprecipitation assays and promoter studies, the researchers showed that LRH-1 directly controls the transcription of

glucokinase. Additional experiments, in which the researchers exposed the livers of *Alb-Cre; Lrh1^{fl/fl}* mice and *Lrh1^{fl/fl}* mice to acute and long-term glucose exposure, showed that glycogen synthesis is delayed and glycolysis and *de novo* lipogenesis are reduced in *Alb-Cre; Lrh1^{fl/fl}* mice. Lastly, the team aimed to understand how LRH-1 controls the activity of ChREBP (carbohydrate response element binding protein), a transcription factor involved in the control of glycolysis and *de novo* lipogenesis. The experiments showed that impaired glucokinase activity in *Alb-Cre; Lrh1^{fl/fl}* mice results in reduced ChREBP activity. Rescue experiments to correct glucokinase deficiency in *Alb-Cre; Lrh1^{fl/fl}* mice also revealed the indirect role of LRH-1 in controlling ChREBP transcriptional activity.

The researchers conclude that liver LRH-1 is a master transcriptional

regulator of glucokinase. “Our findings also underscore the role of its end product, glucose-6-phosphate, in triggering the activity of ChREBP,” says Schoonjans. “The role of LRH-1 therefore goes beyond the simple regulation of glucokinase; LRH-1 also controls the intrahepatic fate of its product glucose-6-phosphate by regulating postprandial glycogenesis, glycolysis and *de novo* lipogenesis.”

“LRH-1 is a potential target for the ... treatment of hepatic steatosis”

These insights could inform the development of strategies for the treatment of hepatic steatosis, but Schoonjans outlines the challenges ahead. “One of the future challenges will be to understand how we can modulate the activity of LRH-1 to curb excessive liver lipogenesis, which may ultimately interfere with normal liver function,” she explains. “The identification of molecules that could negatively affect the activity of the receptor as well as a better insight into the post-translational modifications that alter its activity will be of great value.”

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