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Commentary

sLRP1ng Up Glucose: LRP1 Regulates Hepatic Insulin Responses

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The "metabolic syndrome" is composed of an inter-related group of risk factors including dyslipidemia, obesity, elevated blood pressure, fatty liver, and elevated blood glucose levels. A common feature in these conditions is the dysregulation of metabolic processes. In this issue of *eBioMedicine*, Joachim Herz and colleagues demonstrate that loss of the LDL Receptor-Related Protein (LRP1) in the liver primes mice for a range of metabolic dysfunctions. These findings suggest that physiological actions of LRP1 normally serve to protect against development of the metabolic syndrome (Ding et al., 2016).

LRP1 was first identified by Herz et al. in 1988 on the basis of its sequence homology with the LDL receptor (Herz et al., 1988). Consequently, much of the research into LRP1 function has been focused on lipid metabolism and its effects on atherosclerosis. In the liver, LRP1 clears the remnants of triglyceride-rich lipoproteins (chylomicrons and very low-density lipoproteins), after they have delivered their payload of triglyceride to peripheral tissues. In the endothelium, LRP1 has been linked to the intracellular transport of a range of cell-surface receptors, and this action has also been proposed to protect against the development and progression of atherosclerosis. Recently, a proteomics study identified LRP1 as a component of the glucose transporter regulatory vesicles in isolated adipocytes (Jedrychowski et al., 2010), suggesting that LRP1 may have a novel role regulating glucose metabolism. Based on this finding, Ding et al. hypothesized that liver-specific deletion of LRP1 in mice would reveal its importance in systemic glucose metabolism.

The authors challenged control and liver-specific LRP1-deficient mice with a high-fat diet (60% of the calories derived from fat). Liver-specific LRP1 knockout mice had a marked loss of metabolic control relative to liter-mate controls. The knockout mice were obese, they had higher fasting glucose levels and reduced glucose clearance, and they had fatty liver. These phenotypes were linked with decreased VLDL secretion, and attenuated responses to insulin. Interestingly, when the authors probed hepatic insulin signaling they observed that the chow-fed LRP1 knockout mice had more profound perturbations in insulin signaling than the high-fat diet-fed mice, despite maintaining whole body glucose and insulin responses.

The authors probed this latter observation further by performing a hyperinsulinemic-euglycemic clamp studies on mice administered a short-term high-fat diet to avoid the confounding factor of obesity. This experiment demonstrated that loss of hepatic LRP1 was sufficient to uncouple insulin's feedback on the gluconeogenesis pathway, suggesting that the dietary fat somehow primes the LRP1-deficient liver for insulin resistance.

The authors used primary hepatocytes to interrogate the molecular mechanisms responsible for the interaction between dietary fat and LRP1. Previous work demonstrated that insulin stimulated the transport of LRP1 to the cell surface in a variety of cell types, and that this translocation is essential for the internalization of the insulin receptor in neurons. Ding et al. confirmed that LRP1 is required for normal cell surface localization of the insulin receptor in hepatocytes; however, loss of LRP1 in did not affect insulin receptor internalization in the presence or absence of fatty acids. Although the authors were unable to pinpoint precisely how LRP1 interacts with dietary fats to affect insulin signaling, they did observe that palmitate, but not oleate or linoleate, was able to attenuate the cell-surface localization of LRP1 in response to insulin. Future studies based on this finding should be able to tease out the interaction between saturated fatty acids, LRP1, and insulin receptor signaling.

Ding et al. also revealed the potential for LRP1 to regulate the trafficking of the glucose transporter GLUT2 to the cell surface. Glucose is transported across the plasma membrane by three members of a family of transmembrane receptors. All cells have low-level expression of a high-affinity transporter, GLUT1, which is proposed to maintain basal glucose uptake. Adipose and muscle cells express GLUT4, another high-affinity transporter that is translocated to the cell surface in response to post-prandial hyperglycemia. Hepatocytes express GLUT2, a low-affinity high-capacity bidirectional transporter that is proposed to be the dominant means of glucose transport in liver (Efeyan et al., 2015; Thorens, 2015). This functionality allows the liver to take up glucose after feeding and release gluconeogenesis-derived *de novo* glucose while fasting. GLUT2 levels are thought to be regulated primarily through a transcriptional mechanism; however, studies in the intestine suggest that GLUT2 translocation from the basolateral to the apical membrane may facilitate uptake from the lumen in response to feeding (Kellett and Helliwell, 2000; Leturque et al., 2009).

Ding et al. demonstrated that loss of LRP1 reduced the cell-surface localization of GLUT2 in primary hepatocytes in the presence

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of insulin. This finding suggests an additional level of regulation by which hepatocytes respond to hyperglycemia. The model proposed by Ding et al. is consistent with previous reports that mice lacking hepatic GLUT2 have a reduced capacity to clear glucose from the bloodstream but maintain output of newly synthesized glucose from the liver while fasting (Seyer et al., 2013). Similarly, deletion of hepatic LRP1 reduced the clearance of a bolus of glucose but did not affect hepatic glucose output.

Our understanding of the biological functions of the lipoprotein receptor superfamily has advanced a great deal since the original identification of the LDL receptor. Structurally related proteins of the LDLR superfamily, including LRP-1, have now been implicated in a range of cellular processes. The studies of Ding et al., build on this progress by implicating LRP-1 in glucose transporter trafficking and hepatic metabolism *in vivo*. In the future it will be important to better define exactly how LRP-1 affects the cellular movement of GLUT2 and perhaps other membrane proteins. The question of whether the LRP-1 pathway could be targeted for therapeutic benefit in the setting of the metabolic syndrome also remains to be addressed.

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