mTORC1 Activates SREBP-1c and Uncouples Lipogenesis From Gluconeogenesis

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mTORC1 activates SREBP-1c and uncouples lipogenesis from gluconeogenesis

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Insulin resistance, which is defined as the inability of insulin to promote efficient glucose uptake by peripheral tissues, is a metabolic condition associated with obesity, type 2 diabetes, dyslipidemia, and cardiovascular diseases. Although important advances in our understanding of the molecular mechanisms involved in the development of insulin resistance have been made during the last decades (1), many questions remain. One of these questions relates to the fact that, in the liver of many insulin-resistant mouse models, insulin fails to suppress glucose production (gluconeogenesis) but continues to promote lipid synthesis (lipogenesis) (2). This selective hepatic insulin resistance contributes to hyperglycemia and hyperlipidemia and suggests that the insulin-signaling pathway must bifurcate upstream of lipogenesis and gluconeogenesis. In this issue of PNAS, Li et al. (3) identify a bifurcation point in the insulin-signaling pathway that could help resolve this important paradox.

The liver plays a central role in controlling metabolic homeostasis by serving as a key site for glucose and lipid metabolism. In insulin-sensitive hepatocytes, insulin binds to the insulin receptor, which in turn recruits the insulin receptor substrate (IRS) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates phosphoinositide 3-kinase (PI3K) and activates 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Nonetheless, it would be important to evaluate if SREBP-1c processing is affected by mTORC1 in primary hepatocytes. Alternatively, the possibility that mTORC1 could interfere directly with LXR action to regulate SREBP-1c mRNA expression must be considered, because activation of AMP-activated protein kinase, a kinase that negatively regulates mTORC1, was shown recently to affect SREBP-1c activation in a LXR-dependent fashion (15).

The identification of mTORC1 as an insulin-regulated component controlling lipogenesis, but not gluconeogenesis, provides a basis for understanding the selective nature of hepatic insulin resistance. The failure of insulin to suppress gluconeogenesis while lipogenesis remains active could be related to the differential sensitivity of these pathways to insulin, the mTORC1/SREBP-1c pathway being less affected by the reduction in PI3K-Akt signaling than the FoxO1/PEPCK pathway. One possible alternative to this mechanism is presented in Fig. 1C. An important characteristic of the mTORC1 signaling pathway is its high sensitivity to nutrients (8). In addition to being activated by insulin via the PI3K-Akt axis, mTORC1 is activated by amino acids in a way that depends on the Rag GTPases (16). Newgard et al. (17) have shown recently that obesity is associated with high circulating levels of many amino acids. This report also confirmed the conclusions of many others, showing that mTORC1 is highly active in the tissues of obese/insulin-resistant mouse models (18, 19). Interestingly, mTORC1 activation promotes insulin resistance by inducing a negative feedback loop in which S6K phosphorylates IRS and reduces its stability (18). mTORC1 also induces endoplasmic reticulum stress (20), a condition prevailing in the liver of obese mice that promotes both insulin resistance and SREBP-1c cleavage and activation (21).

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BIOCHEMISTRY
Correction for “mTORC1 activates SREBP-1c and uncouples lipogenesis from gluconeogenesis,” by Mathieu Laplante and David Sabatini, which appeared in issue 8, February 23, 2010, of Proc Natl Acad Sci USA (107:3281–3282; first published February 18, 2010; 10.1073/pnas.1000323107).

The authors note that, on page 3281, left column, second paragraph, the fourth sentence is incorrect in part. “In addition to promoting glucose uptake by allowing the translocation of the glucose transporter-4 to the plasma membrane, the activation of Akt by insulin stimulates the phosphorylation of the Forkhead box O1 (FoxO1), a transcription factor that controls gluconeogenesis (5)” should read “The activation of Akt by insulin stimulates the phosphorylation of the Forkhead box O1 (FoxO1), a transcription factor that controls gluconeogenesis (5).”

The authors also note that Fig. 1 appeared incorrectly. The corrected figure and its legend appear below.

Fig. 1. The control of lipogenesis and gluconeogenesis by the insulin-signaling pathway. (A and B) Signaling events observed in the liver of (A) insulin-sensitive or (B) insulin-resistant models. (C) A hypothetical model suggesting how mTORC1 activation could drive both lipogenesis and gluconeogenesis in obese/insulin resistant models. TSC1/2, tuberous sclerosis complex 1/2.

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