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 and activates the insulin receptor, which in turn recruits the insulin receptor substrate (IRS) and activates phosphoinositide 3-kinase (PI3K) (Fig. 1*A*). This sequence of events then induces Akt/protein kinase B activity, a kinase controlling many anabolic processes (4). 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). The phosphorylation of FoxO1 by Akt reduces its entry into the nucleus, the expression of key gluconeogenic genes, such as phosphoenolpyruvate carboxykinase (*PEPCK*), and the net glucose output from the liver. Another important anabolic role of insulin is to activate lipid synthesis. Insulin drives hepatic lipogenesis by inducing the sterol and regulatory element binding protein-1c (SREBP-1c), a basic helix–loop–helix transcription factor that controls the expression of genes required for cholesterol, fatty acids, triglycerides, and phospholipids synthesis (6). Insulin activates SREBP-1c by two mechanisms: (*i*) It increases the transcription of the *SREBP-1c* gene by an unknown mechanism, and (*ii*) it promotes the nuclear accumulation of SREBP-1c by favoring its cleavage from the membrane-bound SREBP-1c precursor (6).

The molecular mechanisms linking obesity to insulin resistance are complex, but it is widely accepted that both ectopic fat accumulation in nonadipose tissues and low-grade inflammation reduce the efficiency of insulin in activating its cellular targets (1). In the insulin-resistant state, the reduction in the ability of insulin to activate Akt triggers FoxO1 nuclear localization and the expression of gluconeogenic genes (Fig. 1*B*). The increase in hepatic glucose production and the associated reduction in glucose uptake from the liver and other peripheral tissues are the major driving forces leading to hyperglycemia. Paradoxically, high hepatic levels of *SREBP-1c* mRNA expression and nuclear accumulation have been observed in type 2 diabetic mouse models and are likely to contribute to the enhanced hepatic lipogenesis found in these animals (7). The molecular mechanisms underlying the selectivity of hepatic insulin resistance have not been characterized thus far.

Li et al. (3) show that the mammalian target of rapamycin complex 1 (mTORC1), a protein complex controlling protein synthesis and cell growth (8), is required for the insulin-stimulated induction of *SREBP-1c* expression. Using various pharmacological tools, Li et al. first show that inhibition of PI3K or Akt blocks the effect of insulin on the expression of both *SREBP-1c* and PEPCK, confirming that both lipogenesis and gluconeogenesis depend on the PI3K–Akt axis for their regulation. Interestingly, inhibition of mTORC1 by rapamycin dramatically reduces the expression of *SREBP-1c* in vitro and in vivo, whereas PEPCK remains unaffected. From a hierarchical perspective, these results place mTORC1 upstream of the lipogenic program but outside the gluconeogenic pathway (Fig. 1*A*). Last, Li et al. show that inhibition of the mTORC1 substrate S6 kinase (S6K) does not affect SREBP-1c expression, indicating that mTORC1 controls *SREBP-1c* expression through another effector.

On their own, these observations are consistent with other reports published during the last few years suggesting a potential link between mTORC1 and SREBP-1c–mediated lipid biosynthesis (9). Rapamycin was shown previously to block the expression of many SREBP-1c target genes including acetyl-CoA carboxylase, fatty acid synthase, and stearoyl-CoA desaturase-1 (10–12). Additionally, Porstmann et al. (13) recently observed in nonhepatic cells that under constitutive Akt activation, mTORC1 induces SREBP-1c activity by promoting its cleavage and its nuclear accumulation. Li et al. (3) used freshly isolated primary rat hepatocytes and performed in vivo experiments to show that *SREBP-1c* mRNA expression is tightly regulated by mTORC1 under physiological conditions. The identification of mTORC1 as the bifurcation point that separates hepatic lipogenesis from gluconeogenesis represents an important advance in our understanding of the molecular mechanisms linking hepatic insulin resistance to hyperglycemia and hyperlipidemia.

Although this work sheds light on previously unresolved biological issues, it also generates many important questions. First, what is the molecular mechanism through which mTORC1 controls *SREBP-1c* mRNA expression? According to the results presented, mTORC1 controls *SREBP-1c* expression in an S6K-independent fashion. Is the other mTORC1 substrate, eukaryotic initiation factor 4E-binding protein 1, involved in the control of *SREBP-1c* expression? It is known that the stimulation of *SREBP-1c* by insulin requires the participation of liver X receptors (LXR) and one of the nuclear SREBP isoforms, producing a feed-forward stimulation (14). It is conceivable that mTORC1 may control *SREBP-1c* expression by modulating these factors. Indeed, previous reports indicate that mTORC1 induces the cleavage and the nuclear accumulation of SREBP-1c in epithelial cells expressing a constitutively activated form of Akt (13). The molecular mechanism linking mTORC1 and SREBP-1c processing has not been elucidated.

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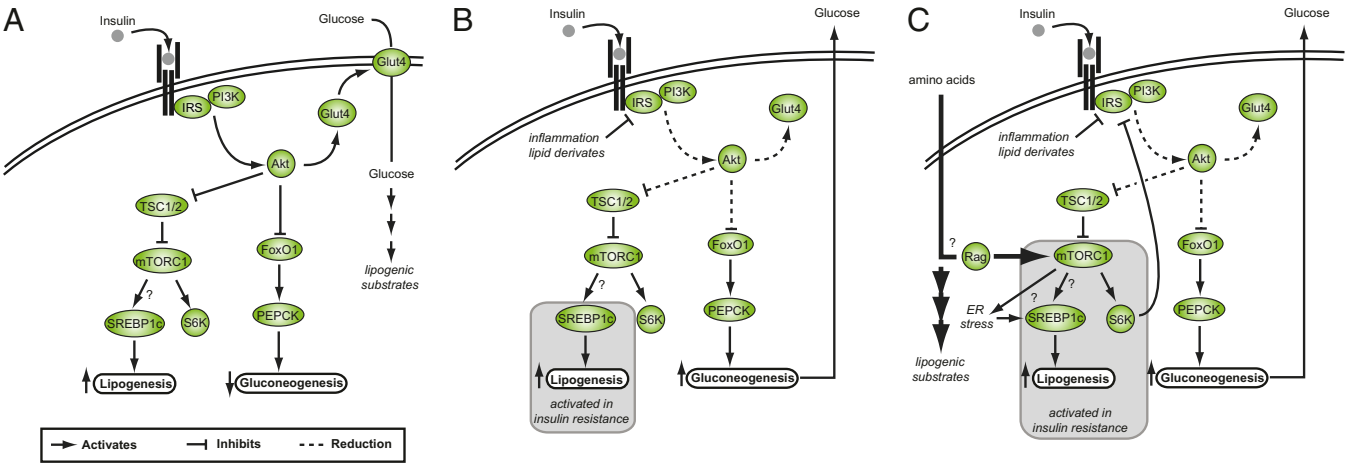

Fig. 1. The control of lipogenesis and gluconeogenesis by the insulin-signaling pathway. (*A* and *B*) Signaling events observed in the liver of (*A*) insulin-sensitive or (*B*) insulin-resistant models. (*C*) A hypothetical model suggesting how mTORC1 activation could drive both lipogenesis and gluconeogenesis in obese/insulin-resistant models. Glut4: glucose transporter-4; TSC1/2, tuberous sclerosis complex 1/2.

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. 1*C*. 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). Together, these findings suggest that, in obese/insulin-resistant models, overactivation of mTORC1 by amino acids could (*i*) further reduce insulin signaling through the degradation of IRS, (*ii*) promote FoxO1-mediated induction of the gluconeogenic program, and (*iii*) induce lipogenesis by positively regulating *SREBP-1c* (Fig. 1*C*). The use of genetically engineered mouse models targeting the mTORC1 pathway will facilitate the verification of this model and may help the development of new pharmacological tools to manage the metabolic defects linked to uncontrolled hepatic lipogenesis.

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