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SMILE Is an Insulin-Inducible Transcriptional Corepressor of Hepatic Gluconeogenic Gene Programs

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COMMENTARY

Insulin is the major hormone that regulates hepatic glucose metabolism by repressing gluconeogenic enzyme-encoding genes, and the counteracting glucagon/protein kinase (PKA)–inducible coactivating peroxisome proliferator–activated receptor γ coactivator-1α (PGC-1α) signaling pathway is also well characterized in hepatic glucose metabolism (1–3). Until now, however, the regulation of the insulin/protein kinase B (PKB)/Akt–inducible corepressor signaling pathway has remained largely unknown. Previously, it was believed that insulin suppression of gluconeogenesis was largely mediated through PKB activity via direct phosphorylation and dephosphorylation mechanisms (4). However, in this issue of *Diabetes*, Lee et al. (5) dissect the role of the small heterodimer partner–interacting leucine zipper protein (SMILE) in insulin-mediated hepatic glucose metabolism. SMILE is a member of the CREB/ATF family of basic-region leucine zipper (bZIP) transcription factors and has been reported to function as a corepressor of nuclear receptor superfamily genes, including estrogen-related receptor γ (ERRγ), glucocorticoid receptor (GR), hepatocyte nuclear factor 4α (HNF4α), and cAMP-responsive element–binding protein H (CREBH) (6–8). In fact, ERRγ, GR, HNF4α, and CREBH have all been implicated in upregulating gluconeogenic gene expression (9–12).

Lee et al. (5) show that SMILE is an insulin-inducible corepressor that suppresses hepatic gluconeogenesis by opposing the action of PGC-1α. The hepatic expression of SMILE is tightly regulated by nutritional status and is elevated in response to feeding. On the other hand, refeeding fails to increase SMILE gene expression in insulin-resistant mouse models (*db/db* and high-fat diet [HFD]–fed mice). Additionally, liver-specific insulin receptor knockout (LIRKO) or PKB β-deficient ($PKB\beta^{-/-}$) mice fail to upregulate *SMILE*, suggesting that the insulin/PKB pathway plays a major role in regulating SMILE expression. Also, enforced *SMILE* expression could downregulate hepatic gluconeogenic genes and counter hyperglycemia and glucose intolerance in both *db/db* and HFD-fed mice. It was also shown that SMILE competes with PGC-1α for dimerization with HNF4α, attenuating binding to, and transactivation of, gluconeogenic gene promoters, ultimately reducing hepatic glucose production (5).

It is well known that the action of insulin in suppressing gluconeogenesis is rapid due to dynamic phosphorylation and dephosphorylation of its downstream signal pathway components. Here, Lee et al. (5) demonstrate that the delayed effect of insulin regulation on gluconeogenesis very likely depends on the induction of the SMILE corepressor. Interestingly, in early insulin response, *SMILE* knockdown did not affect insulin-mediated repression, while at later time points, insulin-mediated repression of gluconeogenic gene expression (or hepatic glucose output) was significantly relieved by *SMILE* knockdown. This proposed mechanism was then tested in vivo to validate a critical role for SMILE in hepatic glucose metabolism, showing that ablation of SMILE significantly elevated blood glucose levels. In contrast, overexpression of SMILE improved fasting blood glucose levels and glucose/pyruvate tolerance in *db/db* and HFD-fed mice. Thus, this work represents a comprehensive examination of the mechanisms whereby insulin action of delayed response may be achieved through SMILE in the regulation of hepatic glucose metabolism.

Insulin is known to increase lipogenic gene expression through the sterol regulatory element–binding transcription factor-1c (SREBP-1c), which Lee et al. (5) show to upregulate *SMILE*. However, previous studies by this same group also showed that SMILE downregulates liver X receptor α (LXRα)–mediated hepatic lipogenic gene expression (13). To explain this paradox, it will be important to assess the physiological relevance of SMILE on the expression of

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See accompanying article, p. 62.

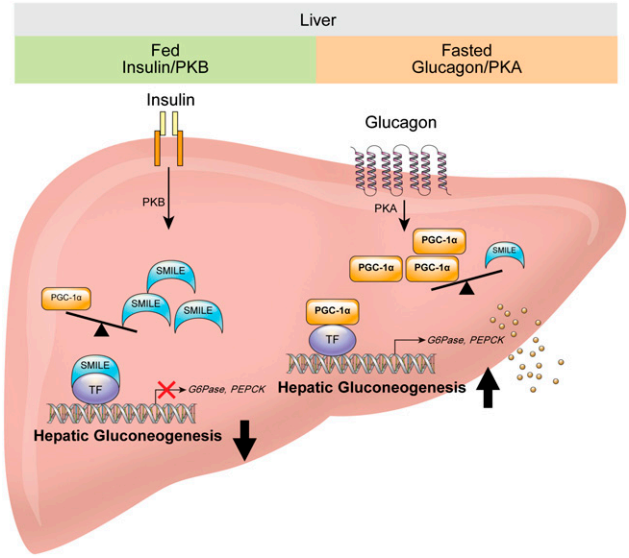

Figure 1—Gluconeogenic gene expression is regulated by corepressors and coactivators during fed and fasting states, respectively. During the fed state, insulin induction of SMILE increases the formation of SMILE transcription factor (TF) duplexes, resulting in the repression of gluconeogenic genes such as *G6Pase* and *PEPCK*. Conversely, during fasting, glucagon upregulates PGC-1α, which binds to TFs, resulting in the induction of gluconeogenic gene expression. TFs are HNF4α, FOXO1, GR, ERRγ, and CREBH, for example.

gluconeogenic and lipogenic enzyme genes. In addition, assessment of the effects of SMILE activity on the cellular physiology of specific tissues will require *SMILE* tissue-specific knockout mouse models.

A previous report demonstrated that hepatic gluconeogenesis is also decreased due to the inhibition of HNF4α activity by DAX-1, which itself is an insulin-inducible corepressor of nuclear receptors (11), suggesting a redundancy of insulin-inducible corepressor-mediated inhibition of hepatic gluconeogenesis. Consequently, the relative contribution of these two nuclear receptors in mediating insulin-dependent regulation of hepatic gluconeogenesis should also be assessed in the future.

It was previously reported that hepatic SMILE expression can be induced by curcumin and ursodeoxycholic acid (UDCA) in an AMPK-dependent fashion (8,13), suggesting that the pharmacological activation of SMILE expression might also be used as a new therapeutic strategy to treat hyperglycemia. To that end, however, assessment of altered SMILE expression or activity in patients with diabetes will be necessary for developing antihyperglycemia drugs.

Overall, the study by Lee et al. (5) purports that SMILE counteracts the stimulatory effect of PGC-1α on hepatic gluconeogenesis while also playing an important role in insulin-signaling effects on hepatic glucose metabolism. Under fasting conditions, the PKA/PGC-1α pathway increases hepatic gluconeogenesis, while in the fed condition, the PKB/SMILE pathway silences PGC-1α–induced hepatic gluconeogenesis (Fig. 1). In addition to HNF4α, other transcription factors interacting with SMILE, including ERRγ, GR, CREBH, and/or FOXO1 (6–8), might mediate the inhibitory effects of insulin on gluconeogenic gene expression (9,11,12). To summarize, the article by Lee et al. (5) demonstrates that the nuclear orphan receptor SMILE plays a large role in the homeostatic regulation of hepatic gluconeogenesis and that correction of its aberrant activity (possibly via pharmacological agents) represents a promising avenue for the therapy of metabolic disease.

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