Almost always, obesity is an obligate prerequisite for the development of type 2 diabetes mellitus. Loss of a well-known lipid phosphatase appears to prevent insulin-resistant diabetes in mice by removal of a positive regulator of adiposity.

In recent years, a substantial amount of attention has been directed toward understanding type 2 diabetes mellitus (T2DM), both because of the disease's profound impact on health care as well as the intrinsically fascinating problem of how an efficient homeostatic mechanism can be so considerably disrupted by lifestyle changes. T2DM, formerly known as adult-onset diabetes, is the most common cause of hyperglycemia, which is believed to result when increasing resistance to the actions of the hormone insulin is accompanied by the failure of the pancreatic β cell to keep pace with the augmented needs for insulin secretion. Thus, a reasonable strategy to alleviate the symptoms of T2DM would be to enhance insulin's action in classical target tissues such as muscle and fat, and this is precisely the mechanism used by the commonly prescribed thiazolidinedione class of drugs. However, this action of thiazolidinediones was discovered by chance, and current efforts to develop novel therapeutics are guided by more rational approaches. Since it is generally believed that it is easier to develop an inhibitor drug than an activator one, a logical focus is pathways that antagonize or terminate insulin signaling. As shown in Figure 1, phosphorylation of both proteins and phospholipids is essential to insulin signaling, making the prospect of inhibiting the enzymes that remove the critical phosphates an attractive strategy for drug development. In the current issue of Nature Medicine, Sleeman et al. describe mice deficient in the lipid phosphatase SH2 domain containing inositol 5-phosphatase 2 (SHIP2), identifying this protein as an important negative regulator of insulin action and adiposity (Sleeman et al., 2005).

The best-studied example of improved hormone action by reduction in phosphatase activity is provided by the enhanced insulin sensitivity phenotype of mice deficient for protein tyrosine phosphatase 1B (PT1B), the enzyme that dephosphorylates the insulin receptor (Elchebly et al., 1999). Likewise, tissues lacking the 3′ phosphoinositide phosphatase, Pten (phosphatase and tension homolog deleted n chromosome 10), show improved insulin responsiveness (Komazawa et al., 2004; Stiles et al., 2004; Wijesekara et al., 2005). Another enzyme that degrades phosphoinositol 3,4,5 trisphosphate (PIP3) is SHIP2, which removes the 5′ phosphate (Figure 1). Sleeman et al. revisit the metabolic consequences of loss of SHIP2 in the mouse (Sleeman et al., 2005). An earlier publication reported that SHIP2 knockout mice displayed marked insulin responsiveness and death at an early age due to hypoglycemia, though this result has been tempered by the authors' recent discovery that a neighboring gene was also inadvertently deleted (Clement et al., 2001). Sleeman et al. find a much milder phenotype in which increased insulin sensitivity is obvious only when mice are placed on a high-fat diet, a manipulation that increases fat cell mass and promotes insulin resistance. More importantly, SHIP2 appears to play a critical role in the control of weight gain, and it is only through the prevention of obesity that the absence of SHIP2 enhances the metabolic actions of insulin. This important distinction emphasizes the close relationship between body size and composition on the one hand and the efficiency of insulin action on the other. In fact, even in experimental model systems, discerning whether alterations in insulin responsiveness are direct or a consequence of leanness is often a challenge. For example, two recent publications describing mouse knockout experiments emphasize the importance of the genes studied to optimal insulin signaling but do not establish definitively whether the gene products normally antagonize peripheral insulin signaling or expansion of adipose stores (Hirosumi et al., 2002; Um et al., 2004). Sleeman et al. address this issue directly and favor the idea that, in the SHIP2-deficient mice, improved insulin responsiveness results from reduced adiposity. Nonetheless, due to efficient compensatory mechanisms, it is sometimes difficult in the mouse to assess insulin responsiveness, and many scientists now regard the euglycemic hyperglycemic clamp as the most reliable measure. Glucose levels are notoriously unreliable, and though Sleeman et al. see no statistically significant differences in serum insulin when the animals are on a chow diet, the absolute values are 2-fold different. A decrease in circulating insulin is a reasonable indication...
of increased insulin responsiveness, suggesting that SHIP2-null mice might have improved insulin action even on a chow diet. In fact, activation of the PIP$_3$-dependent protein kinase Akt/PKB in chow-fed SHIP2$^{-/-}$ mice is significantly more efficient under the same conditions. Even it were possible to detect enhanced insulin sensitivity in these animals, this would not prove a direct effect of SHIP2 on peripheral metabolism, as the chow-fed mice also show a reduction in fat pad size (Sleeman et al., 2005).

An exciting and unsuspected issue raised by these data is the mechanism by which loss of SHIP2 protects against obesity. On a high-fat diet, SHIP2$^{-/-}$ mice demonstrate an increased metabolic rate, suggesting but certainly not proving a central site of action. There is accumulating evidence that the protection from obesity afforded by loss of PTP1B is due, at least in part, to neural expression of the phosphatase, and there is substantial support for the idea that PIP$_3$ is an important intermediary signaling molecule in the hypothalamic pathway controlling satiety and energy expenditure (Barsh and Schwartz, 2002; Figure 1). “Total body” knockouts often are associated with ambiguity regarding the primary responsible organ, but brain- and muscle-specific SHIP2 ablation should provide very intriguing results.

Another point to be taken from these experiments is the physiological roles played by different pathways for turnover of inositol phosphoinositides. As noted above and shown in the figure, Pten removes the 3’ phosphate from PIP$_3$, producing PI4,5P$_2$, whereas SHIP2 converts PIP$_3$ to PI3,4P$_2$, itself an important signaling lipid. For example, PIP$_3$ and PI3,4P$_2$ each bind to Akt/PKB, the most important target downstream of phosphoinositide 3’ kinase, with approximately equal affinity. There is no doubt that the consequences of loss of Pten are much more dramatic than that of SHIP2, but it is unlikely that the roles of the two phosphatases differ only by degree or tissue distribution. Pten is usually associated with the suppression of growth, but careful experiments also indicate a role in metabolism (Komazawa et al., 2004; Stiles et al., 2004; Wijesekara et al., 2005). Unfortunately, the abnormalities in the brain-specific Pten knockouts are so severe that it is impossible to evaluate the contribution of Pten to control of appetite or energy expenditure (Groszer et al., 2001). As is generally the case, future resolution of these issues will be through a combination of physiological and biochemical experiments. For the time being, SHIP2 represents an intriguing drug target as well as a tantalizing link between the regulation of obesity and insulin action.

Figure 1. Cartoon depicting PI3 kinase signaling pathways in brain and peripheral tissues
A very abbreviated version of the signaling pathway involving SHIP2 is shown. The upper panel represents peripheral tissues, whereas the lower panel refers to specialized cells of the hypothalamus. In both cases, SHIP2 and Pten degrade PIP$_3$ to PI3,4P$_2$ and PI4,5P$_2$, respectively, which negatively regulate PI 3’ kinase Department of Medicine and Howardsignaling and reduce Akt activity. Thus, in the periphery, blockade of SHIP2 would increase the activity of this pathway and augment insulin’s ability to suppress hepatic glucose output or increase glucose uptake into muscle. In hypothalamus, it has been suggested that there is a PI 3’ kinase-dependent pathway that signals satiety in response to leptin and possibly insulin. Loss of SHIP2 in these cells would sensitize these pathways and may explain the resistance to obesity in the SHIP2$^{-/-}$ mice.

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Selected reading


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