PI3Kγ within a nonhematopoietic cell type negatively regulates diet-induced thermogenesis and promotes obesity and insulin resistance

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AUTHOR SUMMARY

Obesity is the main cause of diabetes, a disease characterized by high blood sugar levels. Obese patients display chronic low-grade inflammation, and treatment with antiinflammatory drugs (high doses of salicylates, TNF-α-neutralizing antibodies infliximab, and recombinant IL-1Ra anakinra) can often improve glucose homeostasis in these patients (1). The lipid kinase PI3Kγ is an important signaling molecule that plays a major role in promoting inflammation. Previous studies have implicated PI3Kγ in the controlled secretion of the blood sugar-regulating hormone insulin, suggesting that reduced PI3Kγ activity may be a predisposing factor for glucose intolerance (2–4). In striking contrast to the results of these previous studies, results presented here and in a recent study by Kobayashi et al. (5) show that mice lacking PI3Kγ are dramatically protected from diet-induced glucose intolerance. The work by Kobayashi et al. (5) also suggested that inactivation of PI3Kγ reduces the sugar-lowering activity of insulin by directly affecting leukocytes (white blood cells): in other words, PI3Kγ activity within leukocytes was suggested to promote insulin resistance (5).

Using mice lacking the PI3Kγ gene (PI3Kγ−/− mice), we showed that resistance to diet-induced obesity is the main mechanism by which PI3Kγ inactivation protects mice from diet-induced insulin resistance, inflammation, and fat accumulation in liver cells (fatty liver). The impact of PI3Kγ gene deletion on diet-induced obesity was striking and comparable with the results typically obtained after weight loss surgery. We fed mice a high-fat diet (HFD) for 12 wk and observed a 20% reduction in body weight in PI3Kγ−/− mice compared with WT mice; this difference was largely attributable to a reduction in body fat.

We showed that diet-induced obesity, glucose intolerance, fatty liver, and metabolic inflammation depend on PI3Kγ activity in nonblood cells (nonhematopoietic cells). By contrast, PI3Kγ activity in blood cells (hematopoietic cells) did not affect glucose tolerance, fatty liver, or metabolic inflammation in mice, including mice that were overtly obese (weight ∼42 g). The work by Kobayashi et al. (5) reported that selective ablation of PI3Kγ activity in hematopoietic cells ameliorates glucose tolerance in morbidly obese ob/ob mice but not mice in which obesity was induced by HFD (5). We conclude that PI3Kγ activity in hematopoietic cells does not significantly contribute to glucose intolerance or the inflammation of fat tissues until mice develop morbid obesity. Thus, in mice, including overtly obese animals, the promotion of diet-induced obesity involving nonhematopoietic cells seems to be the main pathogenic role of PI3Kγ (Fig. PL4).

The molecular mechanisms by which PI3Kγ promotes diet-induced obesity remain to be identified. However, we showed that both PI3Kγ lipid kinase-dependent and -independent pathways (mediated by protein–protein interaction) potentially contribute to weight gain (Fig. PLB). PI3Kγ is an important enzyme in signaling pathways that are activated in obesity. On activation, PI3Kγ negatively regulates adaptive heat production (thermosogenesis) by an unknown mechanism operating within a nonhematopoietic cell type, and the mechanism possibly involves PI3Kγ lipid kinase-dependent and -independent scaffolding function.

A PI3Kγ lipid kinase-independent pathway was shown to repress PKA signaling, which is involved in lipid metab-
olism in the heart, where sympathetic activity is elevated by overfeeding. In this study, we showed that a PI3Kγ lipid kinase-independent pathway is a negative regulator of the PKA-mediated activation of hormone-sensitive lipase, an enzyme that breaks down fat molecules in white adipose tissue. An important factor involved in the resistance to obesity in mice lacking PI3Kγ lipid kinase activity may be the reduced ratio of two types of cell-signaling molecules or cytokines (i.e., IL-1Ra and IL-1β) in the white adipose tissue of these mice. Indeed, it has been reported that mice lacking IL-1 type I receptor maintained on a standard diet develop mature onset obesity, whereas mice that do not express IL-1Ra are resistant to diet-induced obesity because of a high metabolic rate. Furthermore, it was shown that the thermogenic effects of leptin, a central hormone that regulates energy intake and expenditure, can be blocked with IL-1Ra.

We conclude that PI3Kγ should be evaluated as a valuable target of drug therapy for obesity and its associated complications. An effective drug candidate targeting the PI3Kγ pathway should be able to efficiently inhibit PI3Kγ activity in non-hematopoietic cells, which are responsible for the obese phenotype of mice, compared with the lean phenotype of PI3Kγ+/− mice.