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PPAR gamma Phosphorylation and Metabolic Disease

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Obesity induced in mice and humans activates the protein kinase Cdk5 (cyclin-dependent kinase 5) in adipose tissues. This results in phosphorylation of the nuclear receptor PPARγ (peroxisome proliferator-activated receptor γ), a dominant regulator of adipogenesis and fat cell gene expression, at serine 273. This modification of PPARγ does not alter its adipogenic capacity, but leads to dysregulation of a large number of genes whose expression is altered in obesity, including a reduction in the expression of the insulin-sensitizing adipokine, adiponectin. The phosphorylation of PPARγ by Cdk5 is blocked by anti-diabetic PPARγ ligands, such as rosiglitazone and MRL24. This inhibition works both in vivo and in vitro, and is completely independent of classical receptor transcriptional agonism. Similarly, inhibition of PPARγ phosphorylation in obese patients by rosiglitazone is very tightly associated with the anti-diabetic effects of this drug. All these findings strongly suggest that Cdk5-mediated phosphorylation of PPARγ may be involved in the pathogenesis of insulin-resistance, and present an opportunity for development of an improved generation of anti-diabetic drugs through PPARγ.

Using high throughput phosphorylation screening, we demonstrate that Gleevec blocks CDK5-mediated PPARγ phosphorylation devoid of classical agonism as a PPAR antagonist ligand. In high fat-fed mice, Gleevec improved insulin sensitivity without causing severe side effects associated with other PPAR-targeting drugs. Furthermore, Gleevec reduces lipogenic and gluconeogenic gene expression in liver and ameliorates inflammation in adipose tissues. Interestingly, Gleevec increases browning of white adipose tissue (WAT) and energy expenditure. Taken together, Gleevec exhibits greater beneficial effects on both glucose/lipid metabolism and energy homeostasis by blocking PPARγ phosphorylation. These data illustrate that Gleevec could be a novel therapeutic agent for use in insulin resistance and type 2 diabetes.

Phosphorylation of PPARγ at Ser273 by CDK5 in adipose tissue stimulates insulin resistance, but the underlying molecular mechanisms are unclear. We show that Thrap3 (thyroid hormone receptor-associated protein 3) can directly interact with PPARγ when it is phosphorylated at Ser273, and this interaction controls the diabetic gene programming mediated by the phosphorylation of PPARγ. Knockdown of Thrap3 restores most of the genes dysregulated by CDK5 action on PPARγ in cultured adipocytes. Importantly, reduced expression of Thrap3 in fat tissue by antisense oligonucleotides (ASOs) regulates a specific set of genes, including the key adipokines adiponectin and adipsin, and effectively improves hyperglycemia and insulin resistance in high-fat-fed mice without affecting body weight. These data indicate that Thrap3 plays a crucial role in controlling diabetic gene programming and may provide opportunities for the development of new therapeutics for obesity and type 2 diabetes.