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DIABETES

LMPTP inhibitors — potential treatment for type 2 diabetes?

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New research has identified low molecular weight phosphotyrosine protein phosphatase (LMPTP) — a class II protein tyrosine phosphatase (PTP) encoded by *ACPI* — as a crucial promoter of insulin resistance and diabetes mellitus induced by high-fat diet. These effects are caused by LMPTP affecting insulin signalling in the liver.

When activated by insulin, the insulin receptor autophosphorylates and induces several signalling cascades, including the phosphoinositide 3-kinase (PI3K)–AKT pathway. Data suggest that PTPs inactivate the insulin receptor and thus terminate insulin signalling by dephosphorylating the receptor and its substrates. A promising strategy for treating insulin resistance is to use pharmaceuticals that target PTPs to sensitize the cellular responses to insulin.

“Most research in the field has been focused on a class I PTP, PTP1B, but, for several reasons, we decided to investigate the role of

LMPTP in diabetes mellitus,” says lead author Stephanie Stanford. “Firstly, human genetics studies have shown that polymorphisms in *ACPI* that induce high-activity LMPTP predispose to the metabolic syndrome. In addition, data show that knockdown of LMPTP expression in obese mice using antisense oligonucleotides improves glucose tolerance.”

The team used global and tissue-specific genetic deletion of LMPTP deletion to define the tissue responsible for its mechanism of action. Once they had found that the action of LMPTP was in the liver, Stanford and colleagues treated mice fed on a high-fat diet with a novel LMPTP inhibitor to determine the role of LMPTP in obesity-induced diabetes mellitus. They assessed the phosphorylation of insulin receptor and downstream signalling mediators in obese mice lacking LMPTP in the liver and obese mice treated with the LMPTP inhibitor.

Stanford and colleagues found that, by affecting insulin signalling in the liver, LMPTP has a pivotal role in the development of insulin resistance in obesity. Genetic deletion and pharmacological inhibition of LMPTP in obese mice improved glucose tolerance without affecting body weight.

“We think that LMPTP could be a promising candidate therapeutic target for type 2 diabetes mellitus and so definitely warrants further investigation,” concludes Stanford. “Our long-term goal is to advance an LMPTP inhibitor to clinical trials in humans. In this study we did not observe evident adverse effects in mice treated with our LMPTP inhibitor but our next step is to rigorously determine if this compound is safe for use.”

Alan Morris

ORIGINAL ARTICLE Stanford, S. M. *et al.* Diabetes reversal by inhibition of the low-molecular-weight tyrosine phosphatase. *Nat. Chem. Biol.* <http://dx.doi.org/10.1038/nchembio.2344> (2017)