**PTP1B Inhibitors for Type 2 Diabetes Treatment**

**Introduction**

People with diabetes have difficulty regulating their blood sugar, leading to damage of heart, kidney, nerves, and other tissues. Normally, insulin binds to its surface receptor to trigger removal of sugar from the blood. In type II diabetes, insulin no longer sufficiently triggers sugar removal from the blood. Protein tyrosine phosphatase-1B (PTP1B) affects regulation of blood sugar, because it dephosphorylates the insulin receptor and reduces its activity. Studying PTP1B can help us understand whether inhibitors of this phosphatase could slow dephosphorylation of the insulin receptor, improving the blood sugar regulation in Type II diabetics.

**What is Diabetes?**

Following a meal, blood sugar levels rise. In response to this, the pancreas produces insulin, which increases glucose uptake by fat and muscle (Fig 1). The insulin receptors of muscle and fat cells need to be signaled at an appropriate level in order to control cells’ glucose absorption process (Fig 2).

**Type I Diabetes:** Pancreas does not produce any insulin usually due to damage. Without insulin cells cannot absorb glucose. Interventions are insulin dependent.

**Type II Diabetes:** Insulin is made, however body does not respond to insulin as well as others without diabetes (insulin resistance). Therefore, blood sugar levels remain high for extended periods (Fig 2 & Fig 7). Interventions include diet, exercise, and blood sugar control medications.

**Dephosphorylation by PTP1B**

PTP1B affects blood sugar regulation by dephosphorylating the insulin receptor and reducing its activity. Structurally, PTP1B has a highly positive binding pocket which binds to the highly negative phosphate groups on the phosphorylated insulin receptor. A loop in PTP1B called the WPD loop then closes over the phosphate as PTP1B removes it from the insulin receptor. Blocking PTP1B using a drug with LZP25, an inhibiting compound, could increase insulin effectiveness by leaving the phosphorylation groups on the insulin receptor longer.

**LZP25**

- The PTP1B inhibiting compound LZP25 has a polar negative charge which can bind to the PTP1B active site pocket
- LZP25 prevents a part of the enzyme active site from closing, inhibiting PTP1B
- Inhibited PTP1B in the insulin pathway would increase insulin receptor activity and better regulate blood sugar

**Proof of Principle**

Figure 7 (Ma et al.) shows the PTP1B inhibitor (CCF06240) improves blood glucose response in mice with a diabetes-like condition. In an oral glucose tolerance test (oGTT), normal mice (---), glucose rises a little but returns to normal after one hour. In the Insulin Resistance Model (IRM) mice (---), glucose becomes very high and never comes back to normal, even after 2 hours. Treatment with the inhibitor CCF06240 shows improved glucose response with levels back to control mice. This inhibitor as effective in this test as rosiglitazone, which is one of the existing major drugs prescribed to people with Type II diabetes.

**Protein Model**

- Alpha helices are colored turquoise
- Beta sheets are colored magenta
- Non-motive potions are colored orange
- H-bonds are colored ivory
- Struts are colored light grey and are magnetic:
  - Amino acids SER 216, ALA 217, ILE 219, GLN 262, GLN 266, are displayed because they form the binding sites for compound LZP25.
  - WPD loop of PTP1B (Amino Acids 179-187) which closes during removal of the phosphate group, is in medium purple.
  - Amino acid TYR 46's hydrophobic bond with the phenyl ring of LZP25 (in the PDB known as LZQ322) is highlighted in yellow because it forms a 4th docking site for LZP25.

**Conclusions**

- If PTP1B is inhibited in the insulin pathway by a potential drug based on LZP25, people who have type 2 diabetes could better regulate their blood sugar.
- If the insulin receptor would signal appropriately, the blood sugar would improve, preventing problems with the heart, kidney, nerves, and brain.
- In other research a PTP1b inhibitor has been tested on mice, and this treatment of blood sugar control appears to improve blood clearance of glucose.

**References**

1. Primary Citation: Skaja Liu, Li Fan, Zheng Li Wu, Xiao Yu, Ting Ruan, Andrea M. Gunawan, Ya-Qiu Long, and Zhang-Yin Zhang. (2008). Targeting Inactive Enzyme Conformation: Aryl Halides as a New Class of PTP1B Inhibitors. JACS Articles 130, 17975-17984

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