A gene expression signature for insulin resistance

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Insulin resistance, a key factor in the pathogenesis of type 2 diaebtes, is a heterogeneous disorder caused by a range of genetic and environmental factors. This heterogeneity provides significant challenges to the development of effective therapeutic regimes for long-term management of type 2 diabetes. We used a novel strategy to identify a gene expression signature (GES) that reflects the overall state of insulin resistance in both cells and patients. The advantage of GESs is that they are the minimal set of genes that represent the integrated biological response of a cell/tissue to its environment. The insulin resistance GES was developed in 3T3-L1 adipocytes that were made 'insulin resistant' by treatment with the pro-inflammatory cytokine TNFα± and then reversed with a salicylate and a thiazolidinedione ('re-sensitized'). The GES consisted of five genes whose expression levels best discriminated between the insulin resistant and insulin re-sensitized states. The biological relevance of the cell culture-derived GES was assessed by determining relationships between expression levels of the GES genes and metabolic syndrome phenotypes in patients, where we identified individuals with a higher degree of insulin resistance based on their GES expression profile ($P < 0.001$).

Next we used the GES to screen a small molecule library to identify potential new therapeutic agents for type 2 diabetes. Insulin resistant cells were treated with 1200 compounds at a dose of 10 μM, and the expression of the GES genes was measured. Compounds were ranked on the basis of similarity of GES gene expression to the insulin re-sensitized cells, enabling the identification of a hit family of compounds including VVP808, which was then tested for anti-diabetic efficacy in diet induced obese (DIO) mice, db/db mice and STZ rats. VVP808 was administered by single daily oral gavage to animals for 12-40 days at a range of doses, and efficacy was assessed by measuring body weight, blood glucose, insulin and HbA1c concentrations, and by conducting hyperinsulinaemic-euglycaemic clamps. VVP808 reduced fasting blood glucose concentration (P=0.00004) and HbA1c levels (p=0.04) in db/db mice, and improved glucose tolerance in diet-induced obese (DIO) mice (P<0.05). In STZ diabetic rats, VVP808 (50 mg/kg/d for 12 days) had no effect on fasting blood glucose concentration. However, VVP808 significantly enhanced the glucose-lowering effects of exogenous insulin (0.5U/kg) in an insulin tolerance test (by 2.2-fold after 30 min (P=0.045) and by 2.4-fold after 60 min (P=0.038)). Data from hyperinsulinaemic-euglycaemic clamp studies in DIO mice showed that treatment with VVP808 (50 mg/kg/d for 14 days) increased the glucose infusion rate by 27% (P=0.005), and this was associated with a 23% decrease in endogenous glucose production (P=0.04). Therefore VVP808 is a novel insulin sensitizing agent that acts primarily on the liver to suppress endogenous glucose production.

The ability of the same GES to both stratify individuals according to their level of insulin resistance, and identify compounds with insulin sensitizing properties, demonstrates the potential of GES technology to target treatment of individuals according to their subtype(s) of insulin resistance, *i.e.*, a personalized medicine approach to type 2 diabetes.