

Transcription-based Identification of Insulin Resistance Subtypes

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We propose that expression patterns of small gene sets (gene expression signatures; GES) that reflect the insulin resistance state can be identified from large scale gene expression analysis of insulin resistant cells. Advantage of GESs is that they are not limited to genes known to play a role in insulin resistance, but are the minimal set of genes that best define the cell's response to the unique factors that contribute to insulin resistance.

3T3-L1 adipocytes were made 'insulin-resistant' using TNF α (3ng/ml, 72h), and insulin sensitivity restored by adding antidiabetic agents (10 μ M troglitazone; TGZ, 5mM aspirin; ASA) for the last 24h. TNF α reduced insulin-stimulated 2-deoxyglucose uptake by 37 \pm 6% compared with vehicle-treated adipocytes (p=0.003, n=6). Addition of TGZ/ASA reversed TNF α -impairment of insulin-stimulated glucose uptake by 28 \pm 4% (p=0.005, n=6). Whole genome microarrays were used to profile gene expression in insulin resistant *versus* insulin re-sensitised cells. Bayesian linear discriminant data analysis identified the optimal set of 11 genes that best defined the difference between the two cell states, and these genes constitute the insulin resistance-GES.

A human gene expression dataset was used to evaluate whether the *in vitro* derived GES could characterise insulin resistant phenotypes in humans. This profiling was undertaken on lymphocytes (San Antonio Family Heart Study) and measured the expression of 20,413 transcripts in 1,240 individuals from 42 extended family pedigrees using Illumina bead-based technology. Not only was the GES detected in the human dataset, but increased insulin resistance (Spearman's rho 0.138; p=0.0000012), obesity and dyslipidemia (p<0.001) were observed in subjects with a high GES score.

We developed a GES for insulin resistance mediated by a pro-inflammatory cytokine *in vitro*. Furthermore, the GES was able to identify individuals with a higher degree of insulin resistance *in vivo*. Application of this GES strategy provides the potential to categorise patients and optimise treatment regimes.