Gene Expression Profiles for the Zucker Fatty Rat Versus Zucker Diabetic Fatty Rat are Highly Consistent with Those Observed in Human Patients

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Introduction

Zucker fatty (ZKR) rats and Zucker Diabetic Fatty (ZDF) rats are commonly used in research to model human obesity and Type II diabetes. Both strains are homozygous leptin receptor mutants – a monogenetic trait that stands in apparent stark contrast to the polygenetic traits responsible for these diseases in humans. Nevertheless, the symptoms exhibited by ZDF rats closely resemble those in humans, including hyperglycemia and the metabolic decompensation associated with glucose and lipid toxicities. Since the reliability of the ZDF rat for testing of compounds intended to treat Type II diabetes has been demonstrated, the objective of this poster was to map the pathways and associated gene based biomarkers which may have clinical relevance to the onset and treatment of diabetes.

This poster presents data generated by a 4 week study in which agematched ZKR and ZDF rats were subjected to weekly Oral Glucose Tolerance Tests (OGTT) at 11 to 14 weeks of age to assess the onset of frank diabetes. The phenotypic responses (serum glucose, triglycerides and cholesterol) of these two strains during this interval were as expected (data not presented). Total RNA isolated from liver specimens collected each week from both pre and post OGTT animals was analyzed for global gene expression using Affytmetrix Rat Genome 230 2.0 Arrays.

FIGURE 1: Gene expression profiles drived for either zucker or ZDF pre-diabetic and diabetic rats exhibited altered basal exprssion levels for many components of regulatory pathways implicated in Human type II Diabetes

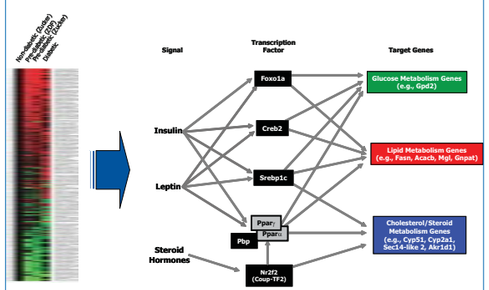


FIGURE 2: Probe sets for genes found in common between the Zucker-ZDF expression profiles and those identified in Human diabetes studies fall into several gene ontology categories, including lipid metabolism, immune/inflammatory response, and apoptosis

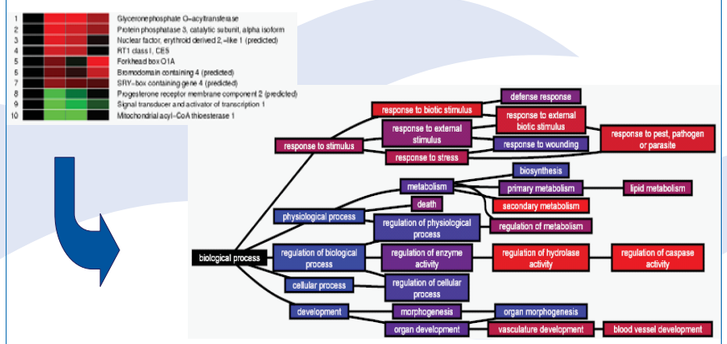
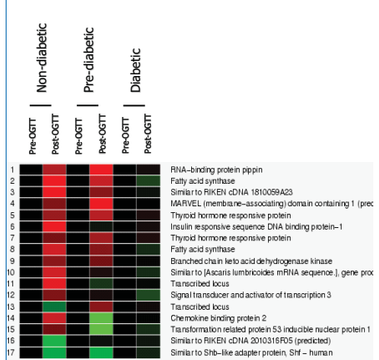


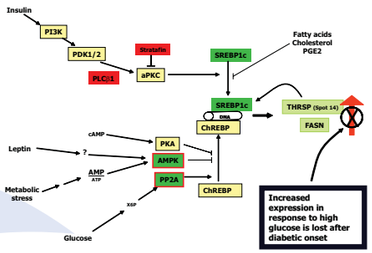
FIGURE 3: Gene Expression Profiles derived from animals before or after the administration of an oral glucose tolerance test (OGTT) identified a series of genes that consistently remain unresponsive to high glucose in pre-diabetic and/or diabetic animals



Several of these genes are well-known components of Insulin-responsive pathways:

- **Fatty Acid Synthase (FASN)**
- **Thyroid Hormone Responsive Protein (THRSP or Spot14)**
- **Signal Transducer and Activator of Transcription 3B (STAT3B)**
- **Insulin Responsive Sequence DNA Binding Protein-1 (IRE-BP1)**

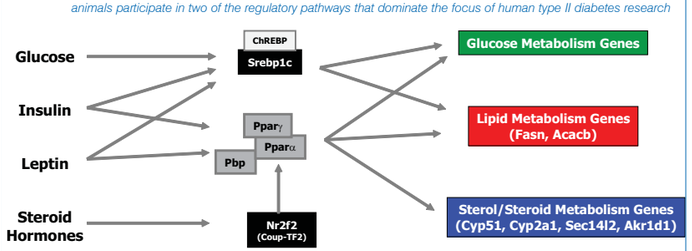
FINGURE 4: A number of genes in the data set participate in the pathway that regulates the response of FASN and THRSP to high glucose



Red and Green boxes indicate genes in the data set; Red = Increased expression, Green = Decreased expression

FIGURE 5: Filtering for similar gene expression profiles in hyperglycemic rats of both strains yielded a list of diabetes-relebant genes whose expression is consistently altered in pre- and/or post-diabetic animals

FIGURE 6: A number of the genes that consistently exhibit similar expression profiles in all hyperglycemic or diabetic animals participate in two of the regulatory pathways that dominate the focus of human type II diabetes research



As such, these profiles can serve as a consistent and reliable biomarker for the onset of type II diabetes and as mile posts to monitor the effects of pharmaceutical intervention

Results

As illustrated by Figure 1, the gene expression profiles derived for either ZKR or ZDF pre-diabetic and diabetic rats exhibited altered basal expression levels for many components of regulatory pathways implicated in Human type II Diabetes. Many of these genes exhibited sharp changes in expression between 12 and 13 weeks of age coinciding with the onset of frank diabetes in ZDF rats, but some also exhibited opposite changes in Zucker rats at the same time, suggestive of an age/maturation issue. A small subset of ZKR rats identified as pre-diabetic based on higher blood glucose values and comparisons of their genomic profiles with the non-diabetic ZKR rats, pre-diabetic ZDF rats and frankly diabetic ZDF rats lead to a much more focused data set with reduced potential confounding.

The major functional/ontology categories for genes found in common between the Zucker-ZDF expression profiles and those identified in human diabetes include: lipid metabolism, immune/inflammatory response, and apoptosis (Figure 2).

A subset of genes that are well-known components of insulin-responsive pathways were non-responsive to OGTT in pre-diabetic and/or diabetic rats (Figure 3) and pathway analysis revealed that a significant number of transcription factors in the regulatory pathway governing this response are present in the data (Figure 4).

In order to identify gene-based biomarkers common to both pre-diabetic/diabetic rodents and human type II diabetes patients, the data set was filtered for gene expression profiles that were similar for hyperglycemic rats of both strains. This yielded a list of diabetes-relevant genes in these rodent models (Figure 5).

Finally, the genes within these expression profiles were mapped relative to the regulatory pathways that dominate the focus of human type II diabetes research to identify possible gene-based biomarkers with clinical relevance in these models (Figure 6).

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