Interpreting Metabolic Profiles Using Unbiased Pathway Model
Motivation

- Individuals with the same apparent disease show remarkable variation in prognosis and treatment responsiveness
- Similar disease state can arise from diverse combinations of genetic and environmental factors
- Metabolomics represents a quantitative biologic information from patients
The experiment

- Oral Glucose Tolerance Test – OGTT
  - 25 individuals with normal glucose tolerance (NGT)
  - 25 individuals with impaired glucose tolerance (IGT)

- Blood samples were drawn fasting and 120 minutes after glucose ingestion

- Mass Spectrometry Analysis
The Naive Analysis

- Identification of significantly changed metabolites
- Pathway enrichment analysis

Enrichment solely in NGT for Bile Acid Biosynthesis
Shortcomings

- Sparseness of the metabolome coverage
- Most metabolites are implicated in multiple pathways
- Metabolic vs. Hierarchical regulation
- Physiologic perturbation only affects a subnetwork of metabolites that may not correspond to any of the preconceived pathway definitions
Building Metabolic Reaction Network and Finding Active Module Groups
Characterizing Active Modules of OGTT

- Enrichment for Glycerophospholipid Metabolism and Glycine, Serine and Threonine Metabolism

Using Shlomi et al. tissue specific predictions, AMGs showed enrichment for metabolites predicted to be active in kidney and liver

The pathways encompass very few of the AMG metabolites
Amino Acids involvement in Glucose Response

- A central cluster of highly interconnected standard and non-standard amino acids
### Table 1. Enrichment for enzymes and transporters in the NGT and IGT active module groups.

<table>
<thead>
<tr>
<th>Enzyme or Transporter Family</th>
<th>Enzyme or Transporter Family Member</th>
<th>System</th>
<th>Measured Substrates in Active Module Groups</th>
<th>Reaction</th>
<th>Tissue Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC6</td>
<td>SLC6A15†</td>
<td>NA</td>
<td>Val-L, Leu-L, Met-L, Ile-L</td>
<td>Facilitated</td>
<td>Brain</td>
</tr>
<tr>
<td>SLC3/SLC7</td>
<td>SLC7A1†</td>
<td>y+</td>
<td>Lys-L, Arg-L, Om-L, His-L</td>
<td>Facilitated</td>
<td>Ubiquitous except liver</td>
</tr>
<tr>
<td>SLC3/SLC7</td>
<td>SLC7A2†</td>
<td>y+</td>
<td>Lys-L, Arg-L, Om-L, His-L</td>
<td>Facilitated</td>
<td>Liver, skeletal muscle, pancreas</td>
</tr>
<tr>
<td>SLC3/SLC7</td>
<td>SLC7A3†</td>
<td>y+</td>
<td>Lys-L, Arg-L, Om-L, His-L</td>
<td>Facilitated</td>
<td>Thymus, ovary, testis, brain</td>
</tr>
<tr>
<td>SLC01</td>
<td>SLC01A2†</td>
<td>NA</td>
<td>taurochenodeoxycholate, glycocholate, glycochenodeoxycholate</td>
<td>Facilitated</td>
<td>Brain, kidney, liver, ciliary body</td>
</tr>
<tr>
<td>SLC01</td>
<td>SLC01B1†</td>
<td>NA</td>
<td>taurochenodeoxycholate, glycocholate, glycochenodeoxycholate</td>
<td>Facilitated</td>
<td>Liver</td>
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</table>
Amino Acids involvement in Glucose Response

- A central cluster of highly interconnected standard and non standard amino acids
A Role For the Osmoregulatory Transporter SLC6A12 in the Glucose Response

- The purpose of this coupling is to maintain cell osmolarity in face of the amino acid/glucose influx brought about by insulin
Comparison of NGT and IGT

- Glucose and/or insulin-stimulated changes appear to have been blunted in the IGT group
Changed Metabolites Cluster According to Transporter Activity
Limitations

- Measurements of additional metabolites may show other more convincing pathways
- Considering all significant changes equivalently
- Alteration in metabolic flux within the cell
- Significantly changed metabolites that are not closely linked are unlikely to appear in AMGs
**Summary**

- A different method for integrating high throughput data with metabolic model
- Identification of relationships among changed metabolites
- Highlighting the importance of specific solute carriers
- Comparison between NGT and IGT supported blunted glucose stimulated activities in IGT