Exploiting transcriptomic data in genome scale metabolic networks: new insight into obesity

Flash poster presentation
(Poster P5)
Obesity & Breast Cancer

Ilaria Granata (Poster P5)

Genome-scale Metabolic Network

High-throughput data collection:
- Transcriptomics, Metabolomics, Proteomics
- Physiological and pathological knowledge:
  - Mathematical constraints and objective functions

Constraint based modeling and simulation

Transcriptionally enriched pathways and metabolic hotspots

Compare specific networks and simulate flux capabilities:

NETTAB 2017 Workshop, Palermo, October 16-18, 2017
Ilaria Granata (P5)
Genome Scale Metabolic Model: iAdipocytes 1809 (Mardinoglu et al. 2013)

Transcriptomic Dataset:

Integrative Method:

Improving metabolic flux predictions using absolute gene expression data
Dave Lee1†, Kieran Smallbone1†, Warwick B Dunn1, Ettore Murabito1, Catherine L Winder1, Douglas B Kell1,2, Pedro Mendes1,3 and Neil Swainston1†

NETTAB 2017 Workshop, Palermo, October 16-18, 2017
Ilaria Granata (P5)
RESULTS

Gene expression

Reactions with changing fluxes

<table>
<thead>
<tr>
<th>Subsystem annotation of subtype specific dysregulated reactions</th>
<th>Basal-like</th>
<th>Her2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transport, endoplasmic reticular</td>
<td>Fatty acid activation (cytosolic)</td>
<td></td>
</tr>
<tr>
<td>Transport, extracellular</td>
<td>Transport, extracellular</td>
<td></td>
</tr>
<tr>
<td>Pool reactions</td>
<td>Transport, peroxisomal</td>
<td></td>
</tr>
<tr>
<td>Glycerophospholipid metabolism</td>
<td>Transport, endoplasmic reticular</td>
<td></td>
</tr>
<tr>
<td>Transport, mitochondrial</td>
<td>LB</td>
<td></td>
</tr>
<tr>
<td>Terpenoid backbone biosynthesis</td>
<td>Glycerophospholipid metabolism</td>
<td></td>
</tr>
<tr>
<td>Carnitine shuttle (cytosolic)</td>
<td>Transport, extracellular</td>
<td></td>
</tr>
<tr>
<td>Carnitine shuttle (endoplasmic reticular)</td>
<td>Transport, mitochondrial</td>
<td></td>
</tr>
<tr>
<td>Beta oxidation of even-chain fatty acids (peroxisomal)</td>
<td>LA</td>
<td></td>
</tr>
<tr>
<td>Formation and hydrolysis of cholesterol esters</td>
<td>Transport, extracellular</td>
<td></td>
</tr>
<tr>
<td>Tryptophan metabolism</td>
<td>Transport, extracellular</td>
<td></td>
</tr>
<tr>
<td>Tricarboxylic acid cycle and dicarboxylate metabolism</td>
<td>Transport, mitochondrial</td>
<td></td>
</tr>
<tr>
<td>Glycolysis / Gluconeogenesis</td>
<td>Transport, mitochondrial</td>
<td></td>
</tr>
<tr>
<td>Inositol phosphate metabolism</td>
<td>Transport, mitochondrial</td>
<td></td>
</tr>
<tr>
<td>Nucleotide metabolism</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NETTAB 2017 Workshop, Palermo, October 16-18, 2017
Ilaria Granata (P5)
RESULTS

In Luminal A subtype the reactions associated to cholesterol transport and esterification showed different rates between lean and obese subjects.
RESULTS

NETTAB 2017 Workshop, Palermo, October 16-18, 2017

Ilaria Granata (P5)
Acknowledgements

Mario Rosario Guarracino
Mara Sangiovanni
Enrico Troiano
Conclusions

• The integration of gene expression data into the adipocyte GEM allowed the identification of reactions and associated genes dysregulated in obese cancer patients.

• The knowledge at metabolic level overcomes the limit of looking at the gene expression alone without investigating the effect on cellular mechanisms.

• Intracellular cholesterol accumulation, inferred by flux rates in LumA obese women, is suggested to play an important role in development and progression of breast cancer.

• Further investigations are needed to unravel the differences in terms of mechanisms and outcomes of the obesity-BC subtypes association.