Roadmap

- What is it?
- What prompted it?
- Goals
- Tools
- Methods
- Example
- Problems
- Cartoons!
What is it?

• Using genomics tools to research effects of food on metabolism and gene expression

• Working towards understanding
  – How regulation of homeostatic control is disturbed in a diet-related disease

• Nutrigenetics – To what extent an individual’s genotypes influences metabolic pathways
  • (Müller & Sander, 2003)
What prompted it?

- More information via new research procedures
  - New technology
  - New Methods (GWAS)
- Research began to indicate the importance of genetic predisposition
  - can be an important contributor to cardiovascular disease, diabetes type II, cancers
    - (Keating and Sanguinetti, 1996)
- Nutrients began to be seen as contributing factors
What are the goals?

• How nutrition influences metabolic pathways
  – Identification of transcription factors that function as nutrient sensors and the genes they target
  – Indicative biomarkers
    • Clinical diagnosis
  – Gene expression signatures
    • Clinical and research implications
• the identification of genotypes that are risk-factors for the development of diet related diseases
# Table 1 | Transcription-factor pathways mediating nutrient–gene interactions

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Compound</th>
<th>Transcription factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macronutrients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fats</td>
<td>Fatty acids</td>
<td>PPARs, SREBP1s, LXR, HNF4, ChREBP</td>
</tr>
<tr>
<td></td>
<td>Cholesterol</td>
<td>SREBP1s, LXR1s, FXR</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Glucose</td>
<td>USFs, SREBP1s, ChREBP</td>
</tr>
<tr>
<td>Proteins</td>
<td>Amino acids</td>
<td>C/EBP1s</td>
</tr>
<tr>
<td><strong>Micronutrients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamins</td>
<td>Vitamin A</td>
<td>RAR, RXR</td>
</tr>
<tr>
<td></td>
<td>Vitamin D</td>
<td>VDR</td>
</tr>
<tr>
<td></td>
<td>Vitamin E</td>
<td>PXR</td>
</tr>
<tr>
<td>Minerals</td>
<td>Calcium</td>
<td>Calcineurin/NF-ATs</td>
</tr>
<tr>
<td></td>
<td>Iron</td>
<td>IRP1, IRP2</td>
</tr>
<tr>
<td></td>
<td>Zinc</td>
<td>MTF1</td>
</tr>
<tr>
<td><strong>Other food components</strong></td>
<td>Flavonoids</td>
<td>ER, NFκB, AP1</td>
</tr>
<tr>
<td></td>
<td>Xenobiotics</td>
<td>CAR, PXR</td>
</tr>
</tbody>
</table>

AP1, activating protein1; CAR, constitutively active receptor; C/EBP, CAAT/enhancer binding protein; ChREBP, carbohydrate responsive element binding protein; ER, oestrogen receptor; FXR, farnesoid X receptor; HNF, hepatocyte nuclear factor; IRP, iron regulatory protein; LXR, liver X receptor; MTF1, metal-responsive transcription factors; NFκB, nuclear factor κB; NF-AT, nuclear factor of activated T cells; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; RAR, retinoic acid receptor; RXR, retinoid X receptor; SREBP, sterol-responsive-element binding protein; USF, upstream stimulatory factor; VDR, vitamin D receptor.

Muller and Sander, 2003
Methods

• Outlook: Systems biology
• Other fields
  – Genomics
  – Metabolomics – allows measuring of metabolites in blood or organs
  – Proteomics – study of proteins
  – Transcriptomics – study of RNA
• Model organisms
  – Drosophila
    • adipose-like tissues & lipid transport system
  – transgenic and knockout mouse models
Tools

- DNA microarray,
  - SNP arrays
- Gel electrophoresis
- Mass Spectrometry
- Proton Nuclear Magnetic Resonance
  - MRI scans
Example - Effect of Isoflavones on Breast & Prostate Cancer

• Human studies seem to indicate a correlation between soy isoflavone consumption and protection towards breast and prostate cancers

• Isoflavones – class of bioactive phytochemicals
  – potential role in the prevention of various chronic diseases

• Mechanisms

• Nutrigenetics
  – Individual variability in gut microflora composition and gene polymorphisms

![Isoflavones](image)
Isoflavones Mechanisms

• Breast Cancer - Estrogen Receptors
  – Estrogens are mediated by the binding of one of the two specific nuclear receptors which can induce gene transcription of estrogen-responsive target genes
    • ERa and ERb
  – Estrogens acting via ERa exert strong proliferation stimulatory effects; those interacting with ERb tend to reduce this stimulation.
    • More ERa during tumour progression

• Genistein correlated with downregulation of ERa and an upregulation of ERb mRNA and protein levels in breast cancer cells
  – A decrease in ERa protein expression in mammary tumours of rats after consumption of a soy extract
Isoflavones Mechanisms

• Prostate Cancer - Androgen Receptors
  – Genistein (isoflavone) exerts anti-androgenic effects and downregulates the expression and secretion of PSA
  – Numerous studies show a decrease in AR expression at mRNA and protein levels in prostate cells after exposure to isoflavone
    • Higher AR levels are correlated with higher risk or prostate cancer
  – Long-term soy protein consumption also lowered AR expression in prostate of men with high risk
Isoflavone Gene Interaction

• Known polymorphism
  – Phytoestrogen-gene interaction - CYP19 codes for the enzyme that catalyzes the irreversible conversion of androgens to estrogens.
  – 4 known haplotypes, 1 haplotype with T, 3 with C
  – The T allele of the CYP19 3’UTR T-C polymorphism is associated with higher mRNA levels and thus higher enzyme activity
    • This enzyme catalyzes androgens to become estrogen

• The TT genotype allows a specific nutrient-gene interaction which converts androgen receptors into estrogen receptors, decreasing the susceptibility to prostate cancer
Problems and Roadblocks

• Problems with Research
  – Control of intake
    • Diets are variable
    • Animal studies are more popular
  – Bioavailability
    • Uptake usually not measured
      – Critical to food studies
  – Biomarkers
    • Can’t rely on just one biomarker for a complex problem
  – Lack of knowledge of pathways
    • Lots of groundwork to be laid

• Roadblocks in advancement
  – Funding
  – Ethical Issues
    • Who will have access to this information?
      – Business v. Public Knowledge
    • “Functional Foods” efficacy?
    • What sort of behavior does this encourage?
"Four thousand packets of the new anti-obesity drug, please!"

"What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?"


