System biology approaches in nutrition and health research

Ben van Ommen
Three challenges

- We do not eat enough
- We eat too much
- We eat the wrong things
Overall scheme of metabolic health & disease related processes

Caloric excess

- Adipose inflammation
- Visceral adiposity
- Insulin resistance
- Muscular inflexibility
- Myocardial infarctions
- Heart failure
- Cardiac dysfunction

Risk factors of the 'metabolic syndrome'

- High cholesterol
- High glucose
- Hypertension

Pathologies resulting from the 'metabolic syndrome'

- Dyslipidemia
- Glucose toxicity
- β-cell failure
- Atherosclerosis
- Stroke
- Retinopathy

Nakatsuji, Metabolism 2009
Many drugs interfere with these processes in “health care”
Experimental design

```
3 genetically differing mouse strains

- Lean male mice, 12-13 weeks old at start
- 9 weeks on high fat diet containing lard (24% w/w) to establish hallmarks of MetSyn (visceral adiposity, TG, glucose, insulin)
- matched into treatment groups of comparable body weight
- then intervention for 7 weeks
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The hepatic transcriptome: comparison between diets and fenofibrate

- Cholesterol biosynthesis
- Acute phase response
- Glycolysis/gluconeogenesis, respiration, FA biosynthesis
- FA beta-oxidation, peroxisome
- Immune response

79 significantly regulated GO categories
triglycerides

Fenofibrate

total adipose weight

cholesterol

liver weight
Fenofibrate reduces the amount of (visceral) adipose tissue, but...
The hepatic transcriptome: comparison between diets and T0901317 (LXR agonist, stimulates reverse cholesterol transport)
The LXR agonist stimulated cholesterol efflux but...

- Metabolically healthy
- Visceral adiposity
- Dyslipidemia
- Fatty liver
- LDL elevated
- Fenoibrate
- Rosiglitazone
- Pioglitazone
- Adipose IR
- Adipose inflammation
- Vioxx
- Systemic inflammation
- Hepatic IR
- Metformin
- Sitagliptin
- Adipose IR
- Muscle metabolic inflexibility
- Caloric excess
- Physical inactivity
- Hepatic inflammation
- Fibrosis
- Salicylate
- Endothelial inflammation
- IBD
- Glucose toxicity
- β-cell failure
- Hypertension
- Stroke
- Atherosclerosis
- Microvascular damage
- Retinopathy
- Nephropathy
- Brain disorders
- Cardiac dysfunction
- Heart failure
- Myocardial infarctions
- High cholesterol
- LXR agonist
- High glucose
- LXR agonist
- Hepatic IR
- Atorvastatin
- Glibenclamide
- Metabolically healthy
liver transcriptome

- FA beta-oxidation, peroxisome
- glycolysis/gluconeogenesis, respiration, FA biosynthesis
- cholesterol biosynthesis
- acute phase response
- immune response

79 significantly regulated GO categories
Survival as a function of HbA$_{1c}$ in people with type 2 diabetes: a retrospective cohort study

Figure 1: Adjusted hazard ratios for all-cause mortality by HbA$_{1c}$ deciles in people given oral combination and insulin-based therapies. Cox proportional hazards models were used, with the HbA$_{1c}$ base case scenario. Vertical error bars show 95% CIs, horizontal bars show HbA$_{1c}$ range. Red circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Metformin plus sulphonylureas (A); and insulin-based regimens (B).

Currie, Lancet 2010
The 5-year efficacy of diabetes type 2 treatment

Steven Kahn et al, NEJM 2006
There seems to be only one solution for diabetes type 2.
HUNDREDS OF YEARS OF MEDICAL PROGRESS, AND ALL YOU CAN TELL ME TO DO IS EAT LESS?
“the art of medicine consists of amusing the patient while nature cures the disease”

Voltaire
Systems flexibility is the key!

**Caloric excess**

- Visceral adiposity
  - Adipose inflammation
    - Systemic inflammation
    - Gut inflammation
      - IBD
      - Endothelial inflammation

- Fatty liver
  - Hepatic inflammation
    - Fibrosis
    - Ectopic lipid overload

- Dyslipidemia
  - LDL elevated
  - High cholesterol
  - High glucose

- Hepatic IR
  - Adipose IR
  - Adipose metabolic inflexibility

- Metabolically healthy

**Reversible processes**

- Microvascular damage
  - Retinopathy
  - Nephropathy
  - Brain disorders
  - Atherosclerosis

- Myocardial infarctions
  - Cardiac dysfunction
  - Heart failure

**Irreversible processes**

- β-cell failure
  - Hypertension
  - Stroke

- Glucose toxicity
  - Neuropathy
  - Nephropathy

- Myocardial infarctions
  - Cardiac dysfunction
  - Heart failure

**Risk factors**

- High cholesterol
  - High glucose

- Caloric excess

**Diabetes mellitus**

- Metabolically healthy
  - Reversible process
  - β-cell Pathology

- Irreversible process
  - β-cell
  - gluc

**Systems flexibility is the key!**
Each organ has its own characteristics in maintaining / loosing flexibility and this determines health→diabetes transition.
L-Carnitine Supplementation to Diet: A New Tool in Treatment of Nonalcoholic Steatohepatitis—A Randomized and Controlled Clinical Trial

Mariano Malaguarnera, AP1, Maria Pia Gargante, MD1, Cristina Russo, MD1, Tijana Antic, MD1, Marco Vacante, MD1, Michele Malaguarnera, MD2, Teresio Avitabile3, Giovanni Li Volti, AP2 and Fabio Galvano, AP2

WHAT IS NEW HERE

L-carnitine is effective in reducing total cholesterol, oxidized low-density lipoprotein cholesterol, and triglycerides, and in improving insulin resistance.

L-carnitine treatment and lifestyle changes, including weight loss and exercise, can represent therapeutic options in NASH.
The complex interactions between various nuclear receptors involved in lipid-carbohydrate-bile acid homeostasis determines fat accumulation in liver.
Metabolic pathway of choline.

Choline: an essential nutrient for public health

Why does fructose produce a fatty liver?
Nutrition and maintaining robustness?

The energy pulse and the control mechanisms

- Decreased flexibility
  - linked to ‘metabolic syndrome’
  - may result in damage

Energy pulse diagram:
- Oxidative stress
- Inflammatory stress
Nutrition and maintaining robustness?

The energy pulse and the control mechanisms

Optimal flexibility depends on
- optimal damage control phenotype
- micronutrient levels
- antioxidant status
- anti inflammatory elasticity

energy

Optimal flexibility depends on
- optimal damage control phenotype
- micronutrient levels
- antioxidant status
- anti inflammatory elasticity

time
The blind men 'see' the elephant-the many faces of fatty liver disease

It is oxidative stress, iron and free radicals

It is adipokines

Am sure...it is life style changes

It is IR

Visceral fat! Portal therory

It is inflammatory cytokines

World J Gastroenterol 2008 February 14; 14(6): 831-844

Madhusudana Girija Sanal
Each organ has its own characteristics in maintaining/loosing flexibility and this determines health→diabetes transition.
Many dietary ingredients optimize these processes

Omega 3/6 FA → Caloric restriction → Physical activity

- Visceral adiposity
- dyslipidemia

Visceral adiposity → Fatty liver

- Adipose inflammation
- ectopic lipid overload

Fatty liver → Hepatic IR

- High cholesterol
- LDL elevated

High cholesterol → Atherosclerosis

Atherosclerosis → Cardiac dysfunction

Cardiac dysfunction → Heart failure

Heart failure → Myocardial infections

Myocardial infections

Hepatic IR → Low glycemic index

- High glucose
- system insulin resistance

High glucose → Glucose toxicity

Glucose toxicity → β-cell failure

β-cell failure

- Hypertension
- Strokes

Hypertension → Nephropathy

Nephropathy → Retinopathy

Retinopathy

Brain disorders

Muscle metabolic inflexibility

Adipose IR

- Stannols, fibre
- polyphenols
- Soy ...

Stannols, fibre → Metabolically healthy

Metabolically healthy

Carnitine, Choline, ...

- Insulin resistance
- systemic inflammation

Insulin resistance → Microvascular damage

Microvascular damage → Stroke

Stroke

IBD

Caretonoids

- Systemic inflammation
- Adipose inflammation

Systemic inflammation → Gut inflammation

Gut inflammation → IBD

- Carnitine, Choline, ...
- Quercetin, Se, Zn, ...

Carnitine, Choline, ...

Many dietary ingredients optimize these processes
But what if you are healthy…?

› How can we quantify the state of your “organ health”?

› Are there “hidden (i.e. genetic) predispositions”?

Challenge the system!
Effect of “inflammation status optimizing” diet on inflammation in healthy mice

Verschuren et al, J Nutrition, 2011
Fibrinogen in a human intervention study with the same “inflammation status optimizing” diet after a standardized postprandial challenge

Bakker et al, AJCN 2010; Pellis et al, Metabolomics, 2011
Plasma metabolomics and proteomics profiling after a postprandial challenge reveal subtle diet effects on human metabolic status

Linette Pellis · Marjan J. van Erk · Ben van Ommen · Gertrud C. M. Bakker · Henk F. J. Hendriks · Nicole H. P. Cuconau · Robert Kleemann · Eugene P. van Someren · Ivana Bobeldijk · Carina M. Rubingh · Suzan Wopereis

Metabolomics

Received: 31 March 2011 / Accepted: 12 May 2011
## Processes involved in phenotypic flexibility, in relation to diet, health consequences and quantification methods

<table>
<thead>
<tr>
<th>Physiological function</th>
<th>Adaptation process</th>
<th>Dietary ingredients affect this process</th>
<th>Consequences of mal-functioning</th>
<th>Challenge test</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic flexibility</td>
<td>liver metabolic flexibility</td>
<td>lipids, glucose, carnitine, choline, fructose, ...</td>
<td>fatty liver, high cholesterol, high glucose, high triglycerides</td>
<td>OGTT, OLTT, OPTT</td>
<td>lipoprotein profile, plasma metabolome, turn-over of liver specific metabolites</td>
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<tr>
<td>Appropriate response to temporary macronutrient overload</td>
<td>adipose lipogenesis, lipolysis switch</td>
<td>availability of energy</td>
<td>improper function of adipose tissue, ectopic storage of lipids</td>
<td>OLTT</td>
<td>adipose tissue transcriptome, FFA availability, impaired switching from oxidation of fat to glucose by RQ</td>
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<td></td>
<td>muscle carbohydrate / lipid switch mitochondrial efficiency</td>
<td>availability of energy</td>
<td>muscle insulin resistance</td>
<td>OLTT, OGTT</td>
<td>CK, respiratory quotient MRI fat distribution</td>
</tr>
<tr>
<td>Appropriate storage of excess energy in adipose tissue</td>
<td>adipose tissue flexibility in storing and releasing lipids as required for whole body energy metabolism</td>
<td>(saturated) fatty acids, excess dietary energy resveratrol, etc.</td>
<td>lipid accumulation in muscle tissues low grade inflammation, insulin resistance</td>
<td>OGTT, OLTT, delta respiratory exchange ratio</td>
<td>MRI fat distribution, palmitoylate (16:1,n-7)</td>
</tr>
<tr>
<td>Immune response Optimal inflammatory tone against/ repair of tissue damage</td>
<td>inflammatory dynamics, appropriate hepatic acute phase response</td>
<td>excess dietary energy surplus of saturated fatty acids deficiencies for retinol, vitamin C, essential nutrients like fatty acids &amp; minerals (Se)</td>
<td>chronic (low-grade) inflammation, that has a potential role in cancer, CVD, diabetes, arthritis, ...</td>
<td>inflammation challenge test, OLTT ETEC ET infusion</td>
<td>Muscle &amp; adipose tissue expression of inflammatory mRNAs, plasma / tissue conc. of essential nutrients PBMC transcriptome Plasma and tissue concentrations of cytokines and other inflammatory markers</td>
</tr>
<tr>
<td>Processes involved in phenotypic flexibility, in relation to diet, health consequences and quantification methods (continued)</td>
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<td><strong>Anti-oxidant defense capacity</strong></td>
<td>oxidative stress adaptation</td>
<td>Plant polyphenols</td>
<td>Chronic increased oxidative stress, lack of oxidative stress response when needed</td>
<td>OGTT, OLTT</td>
<td>uric acid, PBMC gene expression, lipid hydroperoxides, 8-iso-PGF2, MDA, 8-OHdG, total thiols, glutathione</td>
</tr>
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<td><strong>Vascul. flexibility, blood pressure regulation, blood coagulation</strong></td>
<td>blood pressure adaptation, flexible microvasculature</td>
<td>Salt, omega-3 fatty acids,</td>
<td>Arterial stiffness, hypertension, vascular insulin sensitivity</td>
<td>Exercise challenge, tilt test, OGTT</td>
<td>Blood pressure, imaging, plasma metabolomics</td>
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<td><strong>Optimal DNA maintenance</strong></td>
<td>DNA damage response to maintain genome integrity and DNA methylation patterns</td>
<td>Calorie restriction improves genome stability. B-vitamins (e.g. folic acid, vitamin B12, choline, betaine) are important for DNA damage repair and methylation pattern</td>
<td>Accumulation of gene and chromos mutations, Shortening and dysfunction of telomeres, increased risk for senescence and cancer</td>
<td>In vitro caloric restriction / excess and essential micronutrient deficiency / excess</td>
<td>Chromatin plasticity, DNA methylation, telomere length, gamma-H2AX phosphorylation, micronuclei, promoter DNA hypomethylation; gene expression, Folic acid, B12, methyl malonic acid</td>
</tr>
<tr>
<td><strong>Maintenance of intestinal function</strong></td>
<td>Adaptation of intestinal microbiota, intestinal integrity &amp; permeability</td>
<td>Probiotics, fibres</td>
<td>Leakage from gut, suboptimal digestion with diarrhea or constipation, inflammation</td>
<td>OLTT, challenge with ETEC (enterotoxigenic Escherichia coli)</td>
<td>CRP, LPS</td>
</tr>
<tr>
<td><strong>Optimal concentration and mental performance</strong></td>
<td>training</td>
<td>n-3 PUFAs B-vitamins</td>
<td>Alzheimer’s disease, reduced cognitive function</td>
<td>Examination</td>
<td>MRI of the brain, ERP (evoked response potential)</td>
</tr>
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<td><strong>Adequate stress response</strong></td>
<td>HPA axis</td>
<td></td>
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<td>Psychological stress test</td>
<td>Cortisol, …</td>
</tr>
</tbody>
</table>
Diet

Inflammation

Stress / Negative emotions

Autonomous nervous Systemic activity
Oxidative stress
NF-kB activation
Metabolic response To food

From: Kiecolt-Glaser, Psychosomatic Med. 2010
Reciprocal regulation of the neural and innate immune systems

Michael R. Irwin and Steven W. Cole
Two major and connected projects start January 2012 to explore and exploit the concept of phenotypic flexibility.

**Food Industry Consortium (4M€)**
- Development of phenotypic flexibility method in relation to nutrition and health

**NutriTech (6M€)**
- Human Intervention study
- Technology analysis evaluation
- Human Intervention Studies as Proof of Principle
- Cohort Validation of methods & Mechanistic research

**Integration**

**TNO**
- Wageningen Un
- TU Munich
- Imperial Coll London
- Un Coll Dublin
- Un Oslo
- Un Varna
- Un Cordoba
- NuGO
- ISS
- IMDEA
- TUFTS
- CSIRO
- Un Alberta
- Un Toronto
- IARC
- ILSI
- Un Auckland
- 4 SME

Others in the process of joining:
TNO
Nestlé
Danisco
Friesland Campina
Abbott
DSM
ILSI

**NutriTech**

**Time**
- M0
- M12
- M24
- M36
- M48
Gene + environment = phenotype, an example

- regulatory element
- the gen(om)e
- the phenotype
- the environment
- calories
- nutrients
Biomedical biomarkers? Homeostatic values? No!

Biomarkers of resilience, robustness, elasticity (stress tests, challenge tests)

- Use ALL relevant parameters (nutrigenomics)
Food is about maintaining flexibility
Pharma is about correcting deviations

So ...

Study flexibility processes and biomarkers in food

Study disease processes and biomarkers in pharma
We are not the same
Exploit inter individual differences
(at least look for subgroups)