Nutrigenomics:
The smart combination of genomics and molecular nutrition research to study metabolic health

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food

1- buy it with thought
2- cook it with care
3- use less wheat & meat
4- buy local foods
5- serve just enough
6- use what is left

don't waste it

U.S. Food Administration

1883
Challenge 1
What's healthy?
Challenge 2
Our “paleolithic” genes + modern diets

Paleolithic era
1.200.000 Generations between feast and famine

Modern Times
2-3 Generations in energy abundance

% Energy

Low-fat meat
Chicken
Eggs
Fish

Fruit
Vegetables (carrots)
Nuts
Honey

% Energy

Grain
Milk/-products
Isolated Carbohydrates
Isolated Fat/Oil
Alcohol

Meat
Chicken
Fish

Fruit
Vegetables
Beans

1.200.000 Generations between feast and famine
2-3 Generations in energy abundance
Challenge 3
We have a tsunami of health problems
Challenge 4
Complex diseases are too complex for 'mono-target' drug therapies
We are what we eat
We are what we eat
Our foods have large impact on our gene expression & phenotype

• (Micro & Macro) Nutrients
  – Mono & PU fatty acids
  – Vitamins (e.g. vitamin A & D), minerals (e.g. Zn)
• Microbiota (from foods)
  – Vegetarians / omni- /carnivores => different microbiota
  – “Raw” (e.g. “Sushi”) or fermented food consumption => food-specific microbiota
• Food components (bitter, toxic – or healthy?)
  – Secondary plant metabolites (e.g. resveratrol, glucosinolates, cafestol....)
  – MicroRNA (e.g. rice) => “nutrient”?
Phenotype plasticity

Phenotypic plasticity is the ability of an organism to change its phenotype in response to changes in the environment (e.g. nutrition).
1 Genotype => 5 nutritional phenotypes

Stuart Howell’s amazing weight loss journey from 24st 4.5lbs in January 2008 to 11st 13.5lbs in July 2010

155 kg

76 kg
Genome plasticity

Variations in RNA-dependent DNA methylation (e.g., regulation of de novo methylation, control of retrotransposable elements)

Abnormal methyl-transferases (e.g., ICF syndrome)

Abnormal methyl-binding factors (e.g., Rett syndrome)

Abnormal parental imprinting (e.g., Prader-Willi, Angelman, Beckwith-Wiedemann, Silver-Russel disorders)

Abnormal hypo-and/or hyper-methylation (e.g., Cancer, autoimmunity, neurological disorders, allergy, cardiovascular diseases, aging)

Abnormal histone modifications (e.g., imprinting disorders, neurological disorders, cancer)

Abnormal chromatin remodeling (e.g., Charge syndrome, neurological disorders, cancer)

Variations in deposition of RNA (e.g., hybrid dysgenesis, variations in pigmentation phenotypes, transgenerational cardiac hypertrophy)

Abnormal RNA editing (e.g., embryonic lethality, neurological disorders, longevity, cancer)

Structural inheritance (unknown epigenetic relevance)

Self-replication of sporadic or acquired prions (e.g., Transmissible Spongiform Encephalopathies, potentially other neurological disorders)

Protein
You are what you eat and have eaten: Received, Recorded, Remembered & Revealed
Nutrigenomics
Quantification of the nutritional genotype-phenotype
Why Nutrigenomics

- To understand nutrition & metabolic health/plasticity
- To comprehensively phenotype
- To validate FFQ
- To enable strategies to optimize personal health
- To provide scientific evidence for health claims of “functional” foods

- Mechanisms
- Biomarkers
- Nutritional Science 2.0
- Personal Nutrition
- Health claim support
How is gene regulation by dietary fat mediated?

- PPARα
- PPARβ/δ
- PPARγ
- HNF4α
- RXRs
- LXR
- FXR
- SREBP1
- TLR4
- more
Nutrigenomics & molecular nutrition allows us to define the mechanistic framework.
Consumption of a High Monounsaturated Fat Diet Reduces Oxidative Phosphorylation Gene Expression in Peripheral Blood Mononuclear Cells of Abdominally Overweight Men and Women

Susan J. van Dijk, Edith J. M. Feskens, Marieke B. Bos, Lisette C. P. G. M. de Groot, Jeanne H. M. de Vries, Michael Müller, and Lydia A. Afman

Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands; and Netherlands Nutrigenomics Centre, TI Food and Nutrition, Wageningen, The Netherlands

Abstract

The Mediterranean (MED) diet is often considered health-promoting due to its high content of MUFA and polyphenols. These bioactive compounds can affect gene expression and accordingly may regulate pathways and proteins related to cardiovascular disease prevention. This study aimed to identify the effects of a MED-type diet, and the replacement of SFA with MUFA in a Western-type diet, on peripheral blood mononuclear cell (PBMC) gene expression and plasma proteins. Abdominally overweight men and women (waist: women ≥80 cm, men ≥94 cm) were allocated to an 8-wk, completely controlled SFA diet (19% daily energy as SFA), a MUFA diet (20% daily energy MUFA), or a MED diet (21% daily energy MUFA). Concentrations of 124 plasma proteins and PBMC whole-genome transcriptional profiles were assessed. Consumption of the MUFA and MED diets, compared with the SFA diet, decreased the expression of oxidative phosphorylation (OXPHOS) genes, plasma connective tissue growth factor, and apoB concentrations. Compared with the MED and SFA diets, the MUFA diet changed the expression of genes involved in B-cell receptor signaling and endocytosis signaling. Participants who consumed the MED diet had lower concentrations of proinflammatory proteins at 8 wk compared with baseline. We hypothesize that replacement of SFA with MUFA may improve health, thereby reducing metabolic stress and OXPHOS activity in PBMC. The MED diet may have additional antiatherogenic effects by lowering proinflammatory plasma proteins. J. Nutr. 142: 1219–1225, 2012.
Changes in the SFA, MUFA and MED groups in the expression of genes involved in oxidative phosphorylation, mitochondrial dysfunction, and ubiquinone biosynthesis

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Understanding Nutrition
How nutrients regulate our genes: via sensing molecular switches

J Clin Invest. 2004;114:94-103
J Biol Chem. 2006;28:934-44
Endocrinology. 2006;147:1508-16
Physiol Genomics. 2007;30:192-204
Endocrinology. 2007;148:2753-63
BMC Genomics 2007; 8:267
Arterioscler Thromb Vasc Biol. 2007;27:2420-7
PLOS ONE 2008;3(2):e1681
BMC Genomics 2008; 9:231
BMC Genomics 2008; 9:262
J Biol Chem. 2008;283:22620-7
Plos One 2009;4(8):e6796
HEPATOLOGY 2010;51:511-522
Am J Clin Nutr. 2009;90:1656-64
Mol Cell Biology 2009;29:6257-67
Am J Clin Nutr. 2010;91:208-17
BMC Genomics 2009
Physiol. Genomics 2009
Circulation 2010
Diabetes 2010
Cell Metabolism 2010
Nature 2011
Regulation of Cholesterol and Lipid Handling in Metabolic Organ Systems by Nuclear Receptors

**Serum**
- PPARγ
  - Decreased lipid concentration
- LXR
  - Increased reverse cholesterol transport

**Liver**
- LXR
  - Increased cholesterol catabolism, storage, and excretion
  - Increased fat synthesis
- FXR
  - Decreased synthesis of bile acids and fatty acids
  - Increased bile acid secretion
- PPARα
  - Increased fat oxidation
  - Increased fasting response

**Intestine**
- LXR
  - Decreased cholesterol absorption
- FXR
  - Increased bile salt recirculation
- PPARδ
  - Improved lipid handling

**Fat**
- PPARγ
  - Increased adipocyte differentiation and survival
  - Increased fat uptake and storage
- PPARδ
  - Increased fat oxidation
  - Increased energy expenditure

**Arterial macrophage**
- LXR
  - Increased cholesterol efflux
  - Decreased cytokine release
- PPARα
  - Increased oxidized LDL uptake
  - Increased LXR up-regulation
- PPARδ
  - Increased VLDL uptake

Regulation of Cholesterol and Lipid Handling in Metabolic Organ Systems by Nuclear Receptors
Comparison PPAR target pathways

intestine / liver
A major role for PPARα in intestinal fatty acid sensing

Physiol Genomics. 2007;30(2):192-204
Intestinal PPAR target genes are largely regulated by dietary PUFAS/MUFAs

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<tr>
<th>6h after oral gavage</th>
<th>OA 18:1</th>
<th>EPA 20:5</th>
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Response to different doses of dietary fat
Dose-dependent effects of dietary fat on development of obesity in relation to intestinal differential gene expression in C57BL/6J mice

![Graph showing weight gain in kilograms for different dietary fat percentages. The graph indicates weight gain for 10 E%, 20 E%, 30 E%, and 45 E% diets. The abbreviations 'a', 'ab', 'bc', and 'c' indicate statistical significance between groups.](image-url)
Robust & concentration dependent effects in small intestine
Differentially regulated intestinal genes by high fat diet

Number of differentially expressed genes

- non-Dose-dependent
- Dose-dependent (%)

Dose-dependent (%)

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Number of differentially expressed genes

- non-Dose-dependent
- Dose-dependent (%)

Dose-dependent (%)
Cellular localization and specific lipid metabolism-related function of fat-dose dependently regulated genes

PLOS one 2011
The intestinal tube model for lipid absorption

4 cm

C1  C2  C3  C4  C5  C6  C7  C8  C9  C10

10% FAT

45% FAT
Saturated fat affects obesity and gut microbiota composition

De Wit et al AJPhysiol 2012 online
Diet-induced changes in gut microbiota composition
Lipid metabolism-related gene expression in the distal small intestine after 8 weeks of diet intervention
You are what you eat

Influence of dietary protein on the metabolic phenotype in the gut-liver axis

Macronutrient composition of the diet

GI-tract

Gut peptides
Nutrients
Bacterial derived components

Liver

Protein turnover
Amino acid metabolism
Glycogenogenesis
Glyconeogenesis
Glycolysis
Lipogenesis, oxidation

Peripheral blood
Objectives

• Investigating the effect of a high protein diet on hepatic lipid accumulation.

• Unravel mechanisms which are responsible for the reduced liver fat.
Design & diets

Run-in: control diet

Acute effect of a high fat / high protein diet

Long term diet effect on the development of liver steatosis

<table>
<thead>
<tr>
<th>Experimental diets</th>
<th>Carbohydrate (en%)</th>
<th>Fat (en%)</th>
<th>Protein (en%)</th>
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<td><strong>Two low fat diet – normal or high protein</strong></td>
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Body composition and food intake

A

Cumulative food intake (kJ)

11 weeks

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B

Body weight (g)

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C

Epididymal adipose tissue (g)

1 week

<table>
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12 weeks

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D

Leptin (ng/mL)

1 week

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12 weeks

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Less liver fat / hepatic steatosis

Enrichment map for HP vs. NP feeding to identify biological functions

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<th>Energy &amp; oxidative metabolism</th>
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Conclusion

• Prevention of NAFLD by HP diet by enhanced lipid secretion and differential use of ingested energy.
• Sufficient protein in the diet modulates lipid handling in the mouse small intestine, prevents obesity and hepatic steatosis.
Very personal conclusions
How to keep our metabolic flexibility/health

• Identify chronic (non-resolving) stress using systems “perturbation” tests & deep genomics-based phenotyping

• Solve it!
  – Less Inflammation
  – Less Metabolic Stress (less sat. fat, highly processed / lipogenic foods)
  – More Exercise (muscle & other organs) with a “challenging” lifestyle & food pattern
  – Eat less from time to time
Nicole de Wit
Mark Boekschoten
Jessica Schwarz
Susan van Dijk
Lydia Afman
Sander Kersten
Guido Hooiveld
Philip de Groot
Mohammad Ohid Ullah

Michiel Kleerebezem
Christian Trautwein
Folkert Kuipers
Ben van Ommen
Hannelore Daniel
Bart Staels
Edith Feskens

...