The use of molecular nutrition and nutrigenomics research to understand metabolic plasticity and health

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Institute of Food Research

TGAC

The Genome Analysis Centre™

BBSRC

Greater Norwich Development Partnership

University of East Anglia
You are what you eat, have eaten, host & how you lived
2 Meals/day, work as long as possible & embrace challenges

Walter Breuning (1896 – 2011, aged 114 years, 205 days)

(But Breuning was also a lifelong cigar smoker, but quit in 1999 when he was 103 because it became too expensive)
Genes and Nutrition => Phenotype
It is not that easy
Our “paleolithic” genes + modern diets

Real Foods with 'challenges'

- Low-fat meat
- Chicken
- Eggs
- Fish
- Fruits
- Vegetables (carrots)
- Nuts
- Honey

Processed foods: Less 'challenges'

- Grain
- Milk/-products
- Isolated Carbs
- Isolated Fat/Oil
- Alcohol
- Meat
- Chicken
- Fish
- Fruits
- Vegetables
- Beans

Paleolithic era

1,200,000 Generations between feast en famine

Modern Times

3-4 Generations in energy abundance

100 % Energy

50

0

100 % Energy

50

0

1.200.000 Generations between feast en famine

3-4 Generations in energy abundance

Our "paleolithic" genes + modern diets

Real Foods with 'challenges'

Processed foods: Less 'challenges'
Nutrigenomics based quantitative analysis of the nutrition-related genotype-phenotype relationship
Why using Nutrigenomics and Systems Nutrition

- To define the mechanistic framework of nutrition (evidence-based nutrition);
- To stratify cohorts (participants) for intervention studies by using individual Omics-data (e.g. genotype, epigenome, microbiome, ‘metabotype’);
- To quantify the nutritional needs for optimized fitness at different life stages (“personalized” health);
- To improve early diagnostics of immuno-metabolic disorders;
- To support the development of “smart healthy food patterns” for modern mankind (healthy, tasty, sustainable, affordable);
- To enable the transition of nutritional science to nutritional science 2.0.
‘No pain, no gain’
The molecular basis of adaptation
Expression heatmapping of PPAR target genes & inflammatory genes in human PBMCs after MUFA consumption

Expression changes are indicated as individual signal-log-ratios (SLR) for all subjects (n=32) after SFA and MUFA consumption

Afman et al
'Heatmap'ping genes changing in PBMCs from an "old" profile to a "younger" profile upon CR

Afman et al
Gene expression analysis of biopsies from human skeletal muscles from young and elderly subjects

Partial Least Squares Discriminant Analysis
What do we know about the mechanisms?
Healthy food (pattern) s have a large impact on our gene expression & phenotype

• (Micro & Macro) Nutrients
  – High in Mono & (N-3) polyunsaturated fatty acids
  – Sufficient high-quality protein (optimal macro-nutrient ratio)
  – Vitamins (e.g. vitamin A & D) , minerals (e.g. Zn)
• Microbiota (from foods)
  – Vegetarians / omnivores / carnivores => different microbiota
  – “Raw” or fermented food (e.g. diary, cheese) consumption => food-borne microbiota
  – Dietary diversity => microbiota diversity & genetic richness
• Plant food components
  – Fibers or secondary plant metabolites (e.g. resveratrol, glucosinolates)
    e.g. bitter, “toxic” = “healthy”
• Less foods/calories & diet-related stress (caloric restriction)
  – “Chromatin exercise” & other epigenetic mechanisms
  – “Cell exercise” (e.g. via autophagy)
Understanding Nutrition: Identifying the mechanisms involved in the regulation of chromatin activity and gene transcription

Impact on metabolic capacity & health of organs & the epigenetic memory

Transgenic mice (e.g. k.o. for NRF2, HIF1, AHR, PPARs etc)

How can we use our genomes in a more optimal way with healthy nutrition & lifestyles?
PPARα

a master regulator in hepatic lipid metabolism
Context-dependent gene regulation by the nutrient-sensing transcription factor PPARα
A systems view on the GUT
Dietary impact on the activation of the AhR essential for the gut immune system

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HF-Chow HF-LF Chow-LF

Diet low in AhR ligands

a. Homeostasis

- Balanced diet
- Macrophage or DC
- Dimeric IgA
- Plasma cell
- Microorganism
- Cryptopatch or isolated lymphoid follicle
- Gut homing
- M cell
- IEC
- Gut lumen
- Paneth cell
- α-defensins

b. Absence of AhR ligands

- Diet low in AhR ligands
- Decreased number of IELs
- Reduced lymphoid tissue organization
- Reduced lymphoid follicles
- Decreased immune surveillance
Chronic overload of organs leads to metabolic diseases

- Saturated fat (but not or to a less extent unsaturated fat) stimulates obesity and the development of fatty liver disease and affects gut microbiota composition & diversity by an enhanced overflow of dietary fat to the distal intestine.
- Unsaturated fats are more effectively taken up by the small intestine, likely by more efficiently activating nutrient sensing systems (PPARs) and thereby contributing to the prevention of organ overload & the development of early pathology (e.g. NASH).
Synthesis of short chain fatty acids (SCFAs) by commensal bacteria and regulation of immunity by SCFAs.
Role of dietary fibres on gut function

INULIN, FOS, GuarGum, NAXUS (Arabinoxylan), Resistant Starch, Ctrl (Starch)
Role of dietary fibres in the colon

• Differential regulation of genes involved in metabolic, energy-generating and oxidative processes & those involved in adhesion dynamics and signalling by dietary fibres.

• Strongly linked to Clostridium cluster XIVa bacteria (butyrate producers) & likely governed by the transcription factor PPARgamma (MolCelBiol 2013).

• Because of different fermentation behaviour fibres will have a diverse location-specific impact.

• So not ‘one fibre fits all’: Diverse food patterns are recommended to keep our guts flexible and healthy!
FAHA: Food and Immuno-Metabolic Health Alliance

Network analysis & Systems integration (TGAG/UEA/IFR)

Plant Foods (JIC/IFR/UEA)

Human Nutrition (UEA/IFR/NNUH)

Molecular Nutrition (UEA/IFR/JIC)

Gut-Food-Microbe Interaction (IFR/UEA)

Stem cells & organ memory (IFR/UEA)

The impact of the gut for systemic diseases (UEA/NNUH/IFR)

Human Gut (Patho)biology (NNUH/UEA/IFR)

Gut Mucosal Immunity (IFR/UEA)

Food-borne pathogens in the gut (IFR/UEA)

Norfolk and Norwich University Hospitals NHS Foundation Trust
Gradients regulate organ capacity and plasticity

- Nutrients
- Bioactives
- Metabolism

SCFAs
Microbiota
Immunity