Fremtidens sundhedsfremmende fødevarer – forskningsmæssige indsatsområder i Danmark

LIFE, University of Copenhagen Council for Strategic Research ActiFoods ApS

Peter Olesen
Needs and potentials

Pre/post natal window: metabolic imprinting
DIET/INF. NUTRITION

Development and maintenance of health
(metabolic homeostasis)
DIET & LIFESTYLE, Fct. Foods, Supplements

Compensate for metabolic and health decay
SPECIAL DIET & CLIN. NUTRITION, Fct. Foods, Supplements

Correction and treatment of non-healthy -> disease conditions
DRUGS

ALL FOOD IS FUNCTIONAL
POSITIVE & NEGATIVE EFFECTS
AND DIFFERENT FOR YOU AND ME

A population of nutritypes
Example of PPP needs and potentials

PRIVATE: Products and services

Pre/post natal window: metabolic imprinting
DIET/INF. NUTRITION

Development and maintenance of health (metabolic homeostasis)
DIET & LIFESTYLE, Fct.Foods

Compensate for metabolic and health decay
SPECIAL DIET & CLIN. NUTRITION

DIFFERENTIATION:
Who needs What and When

Correction and treatment of non-healthy -> disease conditions
DRUGS

PUBLIC: Recommendations; advice; incentives

HEALTH CLAIMS

HEALTH CLAIMS
Scientific Substantiation Hierarchy: 'Clinical Dogma'

Clinical efficacy: Randomized control trials (RCT) in humans

Metaanalysis of RCT's

Epidemiological a.o. observational (population) human studies

Other studies (animal, cells, etc.)
Food and health: the functional paradox

‘normal foods’

- Intrinsic health functionalities

‘functional foods’

- Modified/added functionalities

- **ALL FOOD IS FUNCTIONAL**
- **POSITIVE & NEGATIVE EFFECTS**
- **AND DIFFERENT FOR YOU AND ME**
Food and health: the documentation issue

Intrinsic health functionalities

**Isolated/enriched ingredients**

Whole foods matrix

Modified/added functionalities

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Observational studies

Clinical studies, RCT

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Major classes of health-related plant bioactives

- Flavanoids a.o. Phenolics*
- Carotenoids
- Plant sterols
- Glucosinolates in brassica’s
- Other sulphur compounds

*Most groups consist of many sub-categories, e.g. antocyanins, isoflavones, flavones, flavanones, flavan-3-ols and flavonols are sub-groups of flavonoids

EC can balance EFSA’s mass antioxidant rejection: ERNA

"Plant sterols" have been proven to lower/reduce blood cholesterol significantly. Blood cholesterol lowering has been proven to reduce the risk of (coronary) heart disease’

- Unilever PLC & Unilever NV -

"By actively lowering/reducing LDL-cholesterol (by up to 14% within 2 weeks, by blocking cholesterol absorption), plant stanol esters reduce the risk of (coronary) heart disease’

- McNeil Nutritionals / Benecol -
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Commonly proposed mechanisms of antioxidants a.o. plant bioactives in protection against chronic diseases

- Detoxification of cancer-causing agents (activation of Phase I/II detoxification enzymes
- Causing cancer cells to die (apoptosis / suppression of mitosis)
- Influencing cell-to-cell communication
- Modification of hormonal profile (e.g. steroid hormone levels)
- Modification of lipid profile
- Protection against DNA damages causing abnormal gene expression / increasing DNA repair
- Stimulation of the immune system
- Anti-inflammatory effects
- Reducing serum cholesterol
- Antimicrobial activity
Clinical efficacy a major shortcome

3-4 main categories of food bioactives known to have health-promoting (and disease prevention) functionalities, BUT.....

<table>
<thead>
<tr>
<th>Probiotics &amp; Prebiotics</th>
<th>(Fermented) Milk Peptides</th>
<th>Resveratrol a.o. Plant Phenolics</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI stability</td>
<td>Anti-hypertensive</td>
<td>Anti-oxidant</td>
</tr>
<tr>
<td>Inflammatory gut diseases</td>
<td>Anti-arrhythmic</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Anti-cholesterolaemic</td>
<td>Anti-diabetic</td>
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<td>Anti-infective</td>
<td>Anti-atherosclerotic</td>
<td>Anti-obesigenic</td>
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<tr>
<td>Immune stimulating</td>
<td>Anti-inflammatory</td>
<td>Liver protecting</td>
</tr>
<tr>
<td>Anti-allergic</td>
<td>Satiating (anti-obesigenic)</td>
<td>Energy (endurance)</td>
</tr>
<tr>
<td>Satiating (anti-obesigenic)</td>
<td></td>
<td>Anti-carcinogenic</td>
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</tbody>
</table>

COMMON FEATURES:
- small, additive, multiple/multifactorial effects

COMMON CHALLENGE:
- impressive laboratory and pre-clinical data – BUT human clinical trials often inconclusive
FOOD – GUT – BRAIN: immune response, metabolic syndrome and complications

**Defence**

**Stress**

- Metabolic
- Oxidative
- Mental
- Inflammatory

**Imbalance**

**Barrier Function**

- Probiotics
- Prebiotics
- Other bioactives
- Infection
- High fat diet
- Env./stress
- Gut microbiota

**Phys.**
**Env.**
**Genes**
**Diet**

**Defence**
**Imbalance**

**Systemic inflammation & MS**

- Adipocytes
- Fatty liver
- Atherosclerosis
- Ins.res. T2DM
- CVD etc

**Cognitive performance**
- Alzheimer's
- Autism

**Oxid.**
**ROS**

**STRESS**

**ActiFoods**
Nutrition relates to health optimizing, so needs to target the homeostasis of overarching processes instead of the disease process.
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A PARADIGM SHIFT: From focus on disease to maintenance of health?

..........coming soon in a university close to you!
HEALTH = not just the ‘absence of disease’, but the organism’s ability to maintain metabolic homeostasis (balance)

- Metabolic
- Oxidative
- Mental
- Inflammatory

Reversible stress condition, e.g. increasing oxidative and/or inflammatory load

Irreversible stress condition, leading to chronic inflammation and metabolic syndrome

Clinical complications: Cardiovascular, obesity, insulin resistance, T2-diabetes, atherosclerosis, fatty liver, mental/cogn. etc.

HEALTH – ability to counteract the reversible stress condition ~ ‘metabolic plasticity’

DISEASE – irreversible progress into metabolic syndrome and, potentially, clinical complications
HEALTH = not just the ‘absence of disease’, but the organism’s ability to maintain metabolic homeostasis (balance)

Reversible stress condition, e.g. increasing oxidative and/or inflammatory load

Irreversible stress condition, leading to chronic inflammation and metabolic syndrome

Clinical complications: Cardiovascular, obesity, insulin resistance, T2-diabetes, atherosclerosis, fatty liver, mental/cogn. etc.

RESEARCH DIRECTION: Under experimental conditions, use weak stress challenges and investigate the effect of ingested health compounds (plant/food bioactives) to revert to homeostatic healthy condition. Parallel omics analyses (transcriptomics / proteomics / metabolomics) will confirm which genes / pathways / compounds are involved in maintenance of health...→ biomarkers of health
Measuring Human health and risk: the importance of systems biology

Biomarkers
Pathways
System Knowledge

Informatics

Measurement
Analysis
Interpretation

OMICS
DATA WAREHOUSE
NUTRITYPES

Tissue
Cell
Organism

mRNA
proteins
metabolites
physiology
psychology

ActiFoods

Courtesy of TNO–Quality of Life
OUTLOOK: potentials in omic’s

- **NUTRITYPES** (genes-envir.)
  - Coming out of Nutrigenomics

- Based upon increasing power of omics/system biology approaches, new research may help companies and organizations to navigate and position their NPD and strategic actions in the Food/Nutrition/Health landscape
- Targets, positions, and requirements for effective Priv/Publ innovation

- **SENSOTYPES** (perc.-pref.)
  - LT objective with select partners

- **LIFE-TYPES** (age-activity)
  - Consolidate data, PPP initiative
A human gut microbial gene catalogue established by metagenomic sequencing

Junjie Qin1*, Ruiqiang Li1*, Jeroen Raes2,3, Manimozhiyan Arumugam2, Chaysavanh Manichanh3, Trine Nielsen4, Nicolas Pons5, Florence Levenez5, Takuji Yamada6, Daniel R. Mende2, Junhua Li1,7, Junming Xu1, Shaochuan Li1, Dongfang Li1,8, Jianjun Cao1, Bo Wang1, Huising Liang1, Huising Zheng1, Yinlong Xie1,7, Julien Tap6, Patricia Lapage6, Marcelo Bertalan9, Jean-Michel Batto6, Torben Hansen1, Denis Le Paslier10, Allan Linneberg11, H. Bjørn Nielsen11, Eric Pelletier10, Pierre Renault6, Thomas Sicheritz-Ponten9, Keith Turner12, Hongmei Zhu1, Chang Yu1, Shengting Li1, Min Jian1, Yan Zhou1, Yingrui Li1, Xiuqing Zhang1, Songgang Li1, Nan Qin1, Huanming Yang1, Jian Wang1, Søren Brunak9, Joel Doré6, Francisco Guarner5, Karsten Kristiansen11, Oluf Pedersen4,14, Julian Parkhill12, Jean Weissenbach10, MetaHIT Consortium†, Peer Bork2, S. Dusko Ehrlich6 & Jun Wang1,13

To understand the impact of gut microbes on human health and well-being it is crucial to assess their genetic potential. Here we describe the Illumina-based metagenomic sequencing, assembly and characterization of 3.3 million non-redundant microbial genes, derived from 576.7 gigabases of sequence, from faecal samples of 124 European individuals. The gene set, ~150 times larger than the human gene complement, contains an overwhelming majority of the prevalent (more frequent) microbial genes of the cohort and probably includes a large proportion of the prevalent human intestinal microbial genes. The genes are largely shared among individuals of the cohort. Over 99% of the genes are bacterial, indicating that the entire cohort harbours between 1,000 and 1,150 prevalent bacterial species and each individual at least 160 such species, which are also largely shared. We define and describe the minimal gut metagenome and the minimal gut bacterial genome in terms of functions present in all individuals and most bacteria, respectively.
**MetaHIT**

MetaHIT står for Metagenomics of the Human Intestinal Tract.

Projektet er financieret af EU og har et samlet budget på 150 mio. kr. Der er 13 partnere (universiteter og virksomheder), herunder DTU, KU, Steno Diabetes Center og SDU.

MetaHIT startede i 2008 og løber i 4 år og indgår i konsortium med The Human Microbiome Project i USA.

[www.metahit.eu](http://www.metahit.eu)
**Metabolic imprinting and the pre-/postnatal window**

- Risk for transmission of obesity and obesity-related microbiota?

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**Gut health linked to excessive weight gain during pregnancy**

By Stephen Daniells, 10-Mar-2010

Related topics: Probiotics, Research, Prebiotics and probiotics, Gut health, Maternal & infant health, Weight management

The link between gut microflora populations and weight may also extend to pregnancy, with a new study revealing that women who gain excessive weight during pregnancy have different microfloral profiles.

A study with 50 pregnant women revealed that women who experienced excessive weight gain during pregnancy had more *Escherichia coli* bacteria in their gut, and fewer *Bifidobacteria* than women with normal weight gain during pregnancy, according to findings published in the *British Journal of Nutrition.*

<table>
<thead>
<tr>
<th></th>
<th>Normal-weight (n34)</th>
<th>Overweight (n16)</th>
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<tbody>
<tr>
<td>Bifidobacteria</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Bacteroides</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>E. coli</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Staphylococci</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Folic acid</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>TAG</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Anti-inflammatory and cardioprotective effects of n-3 polyunsaturated fatty acids and plant sterols in hyperlipidemic individuals

Michelle A. Micalef, Manohar L. Garg

A Nutraceuticals Research Group, School of Biomedical Sciences, Faculty of Health, University of Newcastle, Callaghan, NSW, Australia
b Hunter Medical Research Institute, John Hunter Hospital, New Lambton, NSW, Australia

ARTICLE INFO

ABSTRACT

Background: Risk factors of cardiovascular disease such as lipid aberrations, hypertension, abdominal adiposity and elevations in systemic inflammation, are prominent aetiologies in hyperlipidemia.

Conclusion: We have demonstrated, for the first time that dietary intervention with n-3 PUFA and plant sterols reduces systemic inflammation in hyperlipidemic individuals. Furthermore, our results suggest that reducing inflammation provides a potential mechanism by which the combination of n-3 PUFA and plant sterols are cardioprotective.
Combined effects of n-3 PUFAs (omega-3) and plant sterols - a human intervention study

- Cardiovascular risk factors tend to cluster in hyperlipidemias
- Interventions targeted at multiple risk factors likely to be beneficial
- Cardioprotective effects would be expected

**HYPOTHESIS**

60 hyperlipidemias*

male n= 27; female n= 33
aged 35-70 years
NSW – Australia

-Plasma chol. > 6 mmol/L
-Plasma triacylglycerol > 1.5 mmol/L

**Exclusion criteria**

- No previous CVD
- No DB / chr. infl. disease
- No hypertension (< 140/95 mmHg)
- No liver or renal disease
- No anti.infl. or hypolipidemic drugs
- Not consuming sterol-enriched food or fish oil supplements
- No more than 2 fatty fish meals/week

**DESIGN**

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>SO</td>
<td>Sunola oil 4 g</td>
</tr>
<tr>
<td>FO</td>
<td>Tuna oil 4 g</td>
</tr>
<tr>
<td>SOP</td>
<td>Sunola oil 4 g, Plant sterols 2g</td>
</tr>
<tr>
<td>FOP</td>
<td>Tuna oil 4 g, Plant sterols 2g</td>
</tr>
</tbody>
</table>

*Careful compliance controls: tracking all materials + plasma FA composition analyses
Synergistic effects on key biomarkers

Fig. 1. Effect of dietary intervention with 4 g sunola oil/d (SO), 4 g fish oil/d (FO), SO and 2 g plant sterols/d (SOP), or FO and 2 g plant sterols/d (FOP) on selected inflammatory markers: (A) CRP, (B) TNF-α, (C) IL-6, (D) LTB4, (E) adiponectin, and (F) leptin. Bars represent percentage change from baseline (means ± S.E.M.), following 3 weeks of dietary supplementation. Statistical analyses were performed using paired samples t-test: *P < 0.05, †P < 0.01, ††P < 0.001 vs. baseline. Between-group differences were analysed using two-way ANOVA. Where significance was found, Tukey’s HSD post hoc analysis was used for multiple comparisons. Bars without a common letter differ, P < 0.05.
SUMMARY:

- High-sensitivity C-reactive protein (hs-CRP) .......... ↓ 39 % (P=0.009)
- Tumor necrosis factor-α (TNF-α) ........................... ↓ 10 % (P=0.02)
- Interleukin-6 (IL-6) ................................................. ↓ 11 % (P=0.009)
- Leukotriene B₄ (LTB₄) .................................................. ↓ 30 % (P=0.01)
- Adiponectin .............................................................. ↑ 30 % (P=0.05)

Overall CVD risk (calculated) reduced by 22.6% (P=0.006)

*Micallef & Garg 2009 Atherosclerosis 204: 476-82*
Commercial value of the nutritype concept

Added value, product differentiation and personalization will go hand-in-hand in the Food and Nutrition industry.

- Nutritype definitions will be a major knowledge base for the industry in order to embark on NPD in the move from mass marketing towards personalized nutrition.

- Which they otherwise would be resistant to due to the ‘unsurmountable’ task of moving directly to individualized products with no fit to existing business models.
KONKLUSION - forsknings prioriteringer

- Sundhed i fokus, ikke sygdom
  - reversibel stress balance
  - effekt af bioaktiver under eksperimental stress påvirkning

- Omics tilgang til identifikation og dokumentation
  - konsolidering af mange sub-biomarkører
  - erkendelse og definition af nutritypes
  - metagenomics – DK godt med

- Pre-/postnatale vindue, metabolisk imprinting

- Kombination af bioaktiver og ’rigtige’ RCT’s

- Store satsninger i internationalt samarbejde
Tak for ordet...