A nutrigenomic strategy to assess the physiological properties of dairy products

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The importance of species and life cycle in evaluating the nutritional properties of milk

Nutritional and immunomodulatory properties of milk during growth

Physiological properties of bovine milk in human adults?
Toward a nutritional systems biology of dairy products

- DNA 
  - Genomics
  - Genetics
  - Epigenomics
- RNA 
  - Transcriptomics
- Proteins 
  - Proteomics
- Metabolites 
  - Metabolomics

Phenotype • Systems Biology
(living organism)

Information ("bit") • Bioinformatics

DNA → Genomics → Phenotype
RNA → Transcriptomics
Proteins → Proteomics
Metabolites → Metabolomics
Life cycle management of the product ‘milk’

Nutrient composition

Biological in vitro assays

Animal models

Human studies

Nutritional biology of milk
• Academic research
• Life cycle management (dairy industry)

Product development (dairy industry)

Dairy ingredients

Milk transformation
• Technology
• Microbiology

Feeding strategy
1. Postprandial blood cell transcriptomics in healthy individuals having ingested dairy products

Agroscope Liebefeld-Posieux (ALP), Berne, Switzerland
• MF Sagaya
• G Vergères

Laboratory for Human Nutrition, ETH Zurich, Switzerland
• RF Hurrell
Study design

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<tr>
<th>Wash-out</th>
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<th>540 g Yogurt</th>
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Kinetic analysis of the differentially expressed genes

Method

- ANOVA analysis of differential gene expression analysis
- Ratio 0h (D4) vs 0h (D8); 2h vs 0h (D4); 4h vs 0h (D4); 6h vs 0h (D4)

Number of differentially expressed genes identified in the milk group (FDR 12.5%)

- Repeated measures 67 genes
- Linear contrast 379 genes
- Quadratic contrast 0 genes
Correlation between the postprandial blood cell transcriptomes after milk and yogurt ingestion

Differentially expressed genes: 379 (milk); 362 (yogurt)
Overlap between both set of genes: 11%
Correlation between the two set of data: $\rho=0.79$
Transcription factor analysis

Bioactive nutrients in dairy products

Signal 1 → TF1 → Gene1
Signal 2 → TF2 → Gene2
Signal 3 → TF3 → Gene3
Signal 4 → TFm → GeneX
Similar profiles for DNA recognition motifs in the sets of genes changing after milk and yogurt ingestion

Clover analysis of DNA recognition motifs in the set of genes in the milk & yogurt group
DNA sequences were screened against a pre-compiled non-redundant library of 123 motifs
Common postprandial pathways changed after the ingestion of milk and yogurt

Up-regulation between 2h and 6h of metabolic pathways
- Protein synthesis
- Oxidative phosphorylation

Down-regulation between 2h and 6h of immune-regulatory pathways
- Apoptosis
- Inflammatory response
Regulation of mitochondrial genes after the ingestion of dairy products

Nutrients

Feeding malnourished patients for 1 month restores mitochondrial complex I activity
Briet et al, Am J Clin Nutr 2004

Energy

➢ Mitochondrial genes as early markers for clinical nutrition?
Regulation of the TLR signaling pathway after the ingestion of dairy products

Genes down-regulated between 2h and 6h
- TLR2
- TLR4
- TLR6
- TLR8
- CD14
- TOLLR
- IRAK1/2
- IRAK1
- MEK3/MA2K
- NF-kB
- IL-6
- IL-8

Genes up-regulated
- TRAF6
TLRs as molecular bridges between nutrition, metabolism and immunity

Taken from Wolowczuk et al. Clin Dev Immunol 2008: ID 639803
Regulation of the TLR pathway after dairy ingestion

Microbial components

Saturated fat activates TLRs

- Role in the development of chronic inflammatory diseases?

Postprandial down-regulation of inflammatory genes between 2h and 6h after dairy ingestion:

- TLR2, TLR4, TLR6, CD14

Adapted from Akida and Takeru International Immunology 2005 17:1
Regulation of inflammatory genes after the ingestion of dairy products

- Postprandial metabolic stress of dairy products compared to other products (e.g. saturated fat)?
Relevance of postprandial inflammation to the development of chronic inflammatory diseases?
The selfish milk drinker

Vorbach et al 2006
BioEssays 28:606
Apoptosis and inflammation are key biological processes in mammary gland development.

MAPK (Mitogen-Activated Protein Kinase) pathways play a pivotal role in the regulation of apoptosis and inflammation, which are crucial for mammary gland development.
Bovine milk in adult diet: more than macronutrients?

117 bovine milk proteins with homologous human genes

Gene set enrichment analysis (GSEA) algorithm
- The 117 proteins tend to be clustered towards the top of the list that contains the most differentially expressed genes
- P value is 0.0024
2. Impact of technological and microbial transformation on the nutritional properties of milk

Tools to assess the impact of milk transformation on its nutritional properties?
NutriChip - A technological platform for nutrition analysis to promote healthy food

Collaborators at Agroscope
- Katrin Bolanz
- Flurina Schwander
- Guy Vergères
- Charlotte Egger
- Portmann Reto
- Paolo Silacci
- Linda Corino
- Magali Chollet
- Group Nutrition

http://www.nano-tera.ch/projects/403.php
Goals of the NutriChip project

To evaluate the anti-inflammatory properties of milk and dairy products in vitro and in human nutrition intervention studies.

To develop the NutriChip, a microfluidic analytical platform mimicking the human gastrointestinal tract for screening dairy products for anti-inflammatory properties.
Biological workflow of the NutriChip project

Selection of panel of dairy products

In vitro digestion

Screening of digested products in vitro in epithelial/monocytic co-culture Transwell system

Anti-inflammatory properties of selected dairy product

Human intervention trials (obese & healthy; postprandial & long-term)

Selected dairy product & high fat diet

Inflammatory & metabolic profiling, nutrikinetics
3. Milk as a strategic dietary vector for modulation of the gut microflora

Fermented dairy products as a strategic vector for delivering regulators of human metabolism?
Analysis of the blood cell transcriptome of mice co-inoculated with *E. coli* and *L. gasseri*

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Faculty of Biotechnology, University of Ljubljana, Domžale, Slovenia
- **B Hacin**
- I Rogelj
- BB Matijašić
Study design and blood cell analysis

The blood cell transcriptome as a source of biomarker for probiotic research?
Biological pathways differentially regulated following bacterial challenges in mice

- Most of the significant pathways are found in the *E. coli* group and involve activation of the immune response
- Co-incubation or pre-incubation with *L. gasseri* coincides with a reduction of the statistical significance of all pathways
Berne, the birth place of dairy transcriptomics?