Centre for Environment and Toxicology, DHI

Links between gut, allergy and obesity?

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DHI

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Background

Background

Obesity:

Globally > 1 billion overweight, at least 300 million of them obese.

Obesity and overweight risk for chronic diseases, including type 2 diabetes, cardiovascular disease, hypertension and stroke, and certain forms of cancer.

Allergy:

Asthma prevalence in EU-children increased from 5% to over 20%.

Asthma and rhinoconjunctivitis symptoms cause a significant burden of disease.

The gut:

The adult human gut may contain up to 100 trillion microbial organisms.

The microbiota may serve various functions including promoting development of the human immune system, modulating inflammation, and affecting calorie extraction.

Background

Is there a link between the epidemics og obesity and allergic diseases?

Does the obesity induce decreased immune tolerance?

Is the a link between the modern lifestyle and lack of triggering of the immune system?

What can we do? Can treatment with pre- and probiotica prevent the epidemics of obesity and allergic diseases?

The Winter School

Seminars:

1. Allergy and Obesity, November 11th 2008
2. Inflammation in relation to allergy and obesity (December 9th 2008)
3. Gut microbiota and inflammation (January 13th 2009)
4. Pre- and probiotics (February 24th 2009)
5. Final meeting with summary of previous meetings and an overview of the relationship between the gut, obesity and allergy (March 10th 2009)

First winterschool

Time	Subject	Speaker
13.00-13.15	Introduction to the winter school	Anders Permin
13.15-13.45	Allergy: Prevalence; identification of focus areas within prevention	Lise Lotte Husemoen
13.45-14.00	Allergy: Risk factors and results from COPSAC	Klaus Bønnelykke
14.00-14.30	Coffee break	
14.30-15.20	Obesity: prevalence , causality and treatment	Søren Toubro
15.20-15.50	Recent status on the potential link between asthma, allergy and obesity	Betina Thuesen
15.50-16.00	Summing up and final discussion	Anders Permin

Conclusions - Husemoen

- Type 1 allergy (atopy) is characterised by a an IgE mediated immune response.
- Atopic diseases include asthma, hay fever, atopic dermatitis etc.
- The prevalence of allergies have increased during the last decades.
- The increase is related to affluence, westernisation and urbanisation.
- Environmental factors resulting in low allergen exposure may be responsible (the hygiene hypothesis).
- Lifestyle factors may also play a role (obesity, alcohol etc.)

Conclusions - Bønnelykke

- Childhood allergic diseases are highly heterogeneous
- Objective and detailed phenotyping is essential to understand the development of disease
- Genetics may be the key to improved understanding, diagnosis, prevention and treatment of disease

Conclusions – Søren Toubro

Environmental factors causing weight gain and obesity:

- Infections (Adenovirus)
- Drugs causing weight gain (antidepressiva)
- Meal size
- Smoking cessation
- Beverages (wine, beer)
- Lack of physical activities
- Birth weight
- Breast feeding

Conclusions - Betina Thuesen

- Insulin resistance is a risk factor for incident asthma symptoms in adults – the effect is independent of obesity
- Inflammatory pathways involved in insulin resistance may also contribute to the pathogenesis of asthma
- These inflammatory processes may be part of the underlying biological mechanism linking obesity to asthma

2nd winterschool – Inflammation in relation to allergy and obesity

Time	Subject	Speaker
13.00-13.20	Welcome & introduction to the Winter school and summary of 1. seminar	Lisbeth Valentin and Anders Permin
13.20-14.00	Inflammation in relation to rhinitis & asthma	Hans Jürgen Hoffmann
14.00-14.30	Coffee break and networking	
14.30-15.00	Interplay between the gut flora and the immune system in the development of chronic inflammation	Peter Olesen
15.00-15.30	Inflammation in relation to obesity	Jens Bruun
15.30-16.00	Summing up and final discussion	Lisbeth Valentin and Anders Permin

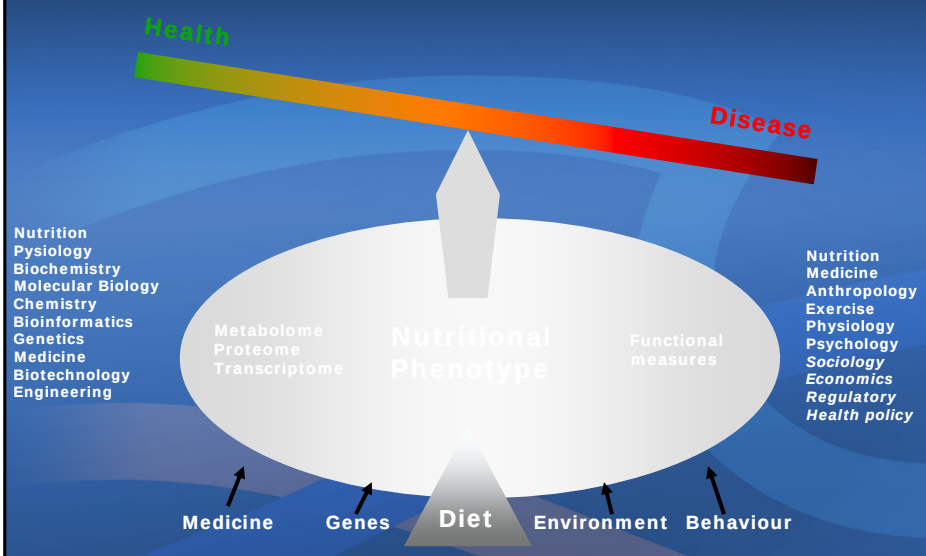
1. Signal/cytokine driven influence, due to obesity, on allergic or asthma related inflammation does not seem likely whereas obesity has a mechanically driven negative influence on asthma symptoms.

   The appropriate inflammatory pressure will lead to development of disease.

2) Obesity facilitates sensitization to allergens and/or obesity aggravates allergic inflammation

3) It is important to understand the development of asthma and obesity better before recommendations for prevention can be described.

A complexity and multidisciplinary issue



ActiFoods

From: Steve Zeizel et al., 2005

Peter Olesen, Interplay between the gut flora and the immune system in the development of chronic inflammation

1) It is anticipated that the microbiota (incl. probiotics a.o. 'intruders') are constantly monitored by the immune system via dendritic cells and the response of the dendritic cells varies depending on whether they are presented to pathogens or beneficial bacteria/components.

   The dendritic cell is the most important cell type in maintenance of a healthy gut.

2) *Bifidobacteria* have beneficial effects in prevention of high-fat-diet induced diabetes in mice. Experimentally induced colitis in mice can be prevented by Polysaccharide A from *Bacteroides fragilis*.

Jens Bruun, Inflammation in relation to obesity

1) The weight of the adipose tissue is primarily a result of energy intake in relation to energy consumption, but increasing weight results in increased inflammation. Obesity results in insulin resistance.
2) BMI above 30 increases the risk of cardiovascular diseases and some types of cancer. Leptin has been used to treat obesity as well as surgery and diet. Adipose tissue is metabolically very active and secretes a number of signal molecules, and is characterized by low grade inflammation.

3RD meeting: Gut microbiota and inflammation

time	title	person
13-13.10	Welcome and summary	Anders Permin
13.10-13.35	Gut microbiota in humans	Tine Licht
13.35-14.10	The impact of the intestinal flora on rodent as models for human inflamatory disease	Axel Kornerup
14.10-14.40	Coffee & networking	
14.40-15.15	The immune system of the gut	Hanne Frøkiær
15.15-15.50	Response of the gut and the gut flora on pathogenic invasion	Karen Krogfeldt
15.50-16.00	Summing up and final discussion	Anders Permin

Conclusions from Hanne Frøkiær, KU Life: The immune system of the gut: Development, homeostasis, and response

Encounter with 'old friends' a prerequisite for a proper maturation of the immune system?

Commensal microbiota

Environmental bacteria

Helminths

Immunoregulatory conditioning (Homeostasis)

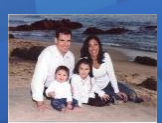
Prevention of excessive inflammation

Viral, bacterial, and protozoan infections or allergen exposure

Deviated Th1 or Th2 response

Modern hygiene

Lack of appropriate Microbial stimulation



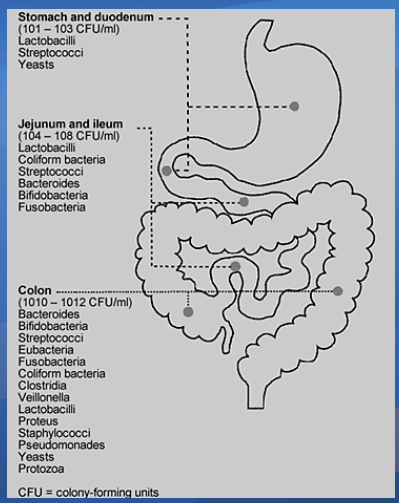
Genetically predisposition

Immune dysregulation:

Immune mediated diseases

(allergy, autoimmune diseases)

Tine Licht – the Intestinal microbiota

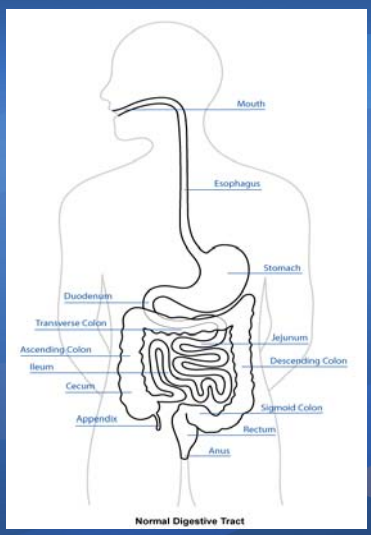


10^{14} bacteria
more than 500 different species

Most of these are not cultured

1

Tine Licht- Impact of gut microbes on host health



Immune system
- Maturation/maintenance
- Allergy
- IBD/IBS (Crohn's, Ulcerative Colitis)

Competitive exclusion of pathogens
- Colonization resistance
- Competition for nutrients
- Competition for adhesion sites
- Production of SCFA and antipathogenic substances (Lactic Acid Bacteria)

Host nutrition utilization
- Growth promotion
- Obesity

Cancer

Cardiovascular diseases

2

Axel Kornerup: Animal models

1. Rodent breeders only standardize their animal according to specific infections
2. 'Normal flora' is unstandardized
3. Many animal models have too little predictive validity
4. We need to put more efforts into improving animal models if we want to reduce the number of animals used and improve research

Conclusions from Karen Krogfelt, SSI
Response of the gut and the gut flora on pathogenic invasion

- Intestinal flora: complex organ (>500 species) enrolled in crucial tropho-metabolic and immunological functions
- Balance between different bacterial species, and between bacteria and the host, influences the human health
- Unbalanced gutflora is involved in the pathogenesis of many gastro-intestinal (and not only) diseases

4th winterschool – The role of the gastrointestinal tract for development of allergy and obesity

Time	title	person
13.00	Welcome	Anders Permin
13.15	Pro- and prebiotics in relation to allergy and obesity	Arthur Ouwehand, Danisco
13.55	Prebiotic components in food and their relation to human health	Helle Nygaard Lærke, AAU
14.25	Coffee	
14.55	Pre- and probiotics for compromized newborns	Per Sangild, KU
15.25	Biomarkers as a tool in research in general and specifically in relation to pre and probiotics	Lars Hellgren, DTU
15.55	Final discussion	

Conclusions from Arthur Ouwehand, Danisco Innovations/University of Turku: Pro- and prebiotics in relation to allergy and obesity

Weight management

1. Current data on the relation between microbiota and weight management is based on:
   - Animal studies (with genetically obese animals)
   - Small human populations
   - Particular sub-populations
2. Will probiotics work? If they work, they probably have a limited influence

Allergy

1. Current information suggests a causal relation between microbiota composition and allergy
2. Probiotics do not seem to treat atopic dermatitis
3. Selected probiotic strains may contribute to primary prevention of atopic dermatitis

Conclusions from Helle Nygaard Lærke, University of Århus
Prebiotic components in food and their relation to human health

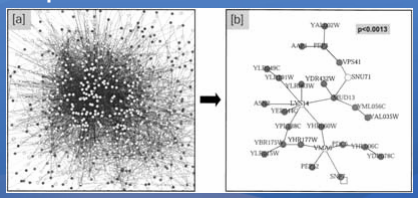
1. Only few dietary sources qualify as prebiotics according to Gibson/Roberfroids definition
2. Prebiotics can influence the 'quality' and/or activity of the gut microflora
3. Diet and microflora can affect systemic inflammatory status (e.g.TNF-α) i animal models
4. Systemic TNF-α is overexpressed in obesity and type-2 diabetes and linked to insulin sensitivity

Conclusions from Per Sangild, KU Life
Pre- and probiotics for compromized newborns

1) Intense studies on time/dose/strains have shown to be "A deep soup!"
2) It is established that pre- and probiotics help gut microbiota & immunity
3) Future studies should focus on biological mechanisms of pre- and probiotic action
4) More combined cell, animal and human studies should be performed in the future

Conclusions from Lars Hellgreen, DTU, Dep. Systems Biology
Biomarkers as a tool in general research

1. The open source software platform “Cytoscape” can be used to construct networks of correlating biomolecules.
2. Data from different “-omics” analyses can be pooled and used to visualize correlations



Shannon P. et.al. Genome Res. 2003;13:2498-2504

www.cytoscape.org

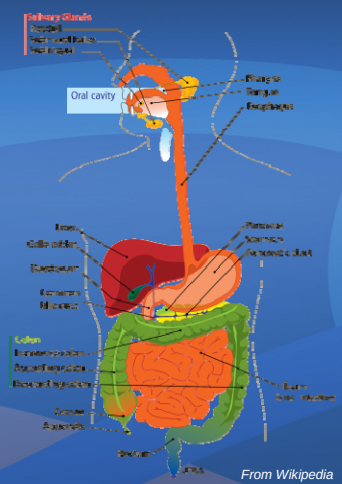
Final Meeting 10/3 2009

Obesity

Intake of food, drinks

Lifestyle

Obesity leeds to insulin resistance



From Wikipedia

Asthma

Gut Microbiota

Allergy