

Centre for Environment and Toxicology, DHI

Links between gut, allergy and obesity?

Anders Permin, HoD, DVM, PhD



The consortium



THE EUROPEAN UNION

The European Regional
Development Fund

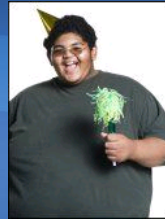


Investing in your future



DanORC

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 of obesity and allergic diseases?

Does the obesity induce decreased immune tolerance?

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

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

The Winter School



Why:

The idea for the winter school originates from a newly formed network where the potential for using probiotics to prevent development of allergy and obesity has been discussed.

The network hypothesizes that the function and reaction of the GI is central for development of the two diseases.

Purpose:

The purpose of the winter school is to get a common understanding of specific important issues and to identify needs for further research.

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)

The Winter School



Questions:

1. What is state-of-the-art within the field in question?
2. What are the hypotheses?
3. Which results have been achieved?
4. What are the most important areas to focus on?
5. What is the best way to use the results for prevention of allergy and/or obesity?

Programme for the 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 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

- All considered obesity measures were associated with incident asthma in adults
- 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

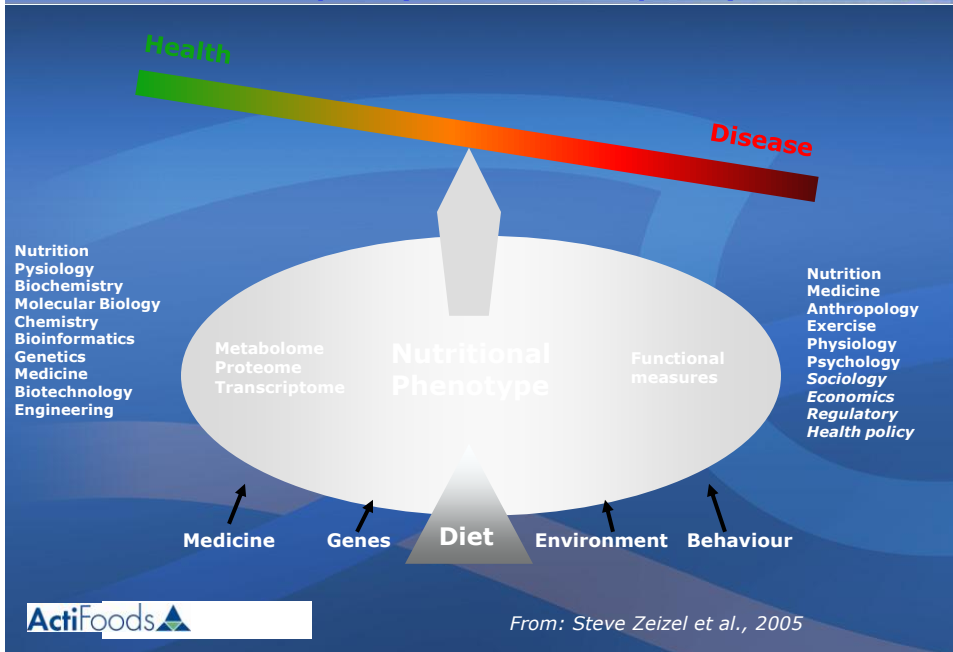


Time	Subject	Speaker
13.00-13.20	Welcome & introduction to the Winter school and summary of 1. seminar	Lisbeth Valentin and Anders Permin
13.20-14.00	Inflammation in relation to rhinitis & asthma	Hans Jürgen Hoffmann
14.00-14.30	Coffee break and networking	
14.30-15.00	Interplay between the gut flora 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





- 1) State of the art- In vitro and pre-clinical results look promising with probiotics, but clinical results are often inconclusive. Pre- and probiotics, fermented milk proteins and plant phenolics have been shown to have health-promoting functionalities, and as such potential for disease prevention.
- 2) Based upon in vitro and animal models, 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.
- 3) *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*.



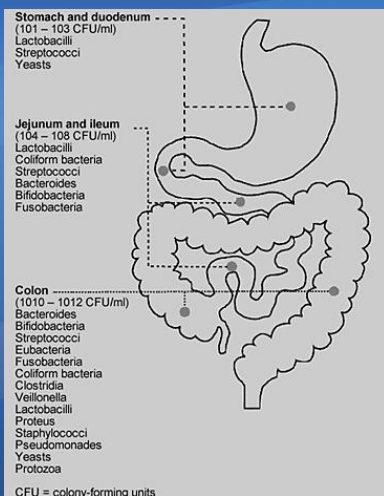
- 1) The weight of the adipose tissue is primarily a result of energy intake in relation to energy consumption, but increasing weight results in increased inflammation. Obesity results in insulin resistance.
- 2) BMI above 30 increases the risk of cardiovascular diseases and some types of cancer. Leptin 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



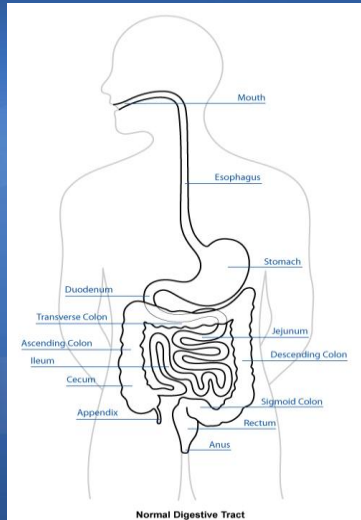
time	title	person
13-13.10	Welcome and summary	Anders Permin
13.10-13.35	Gut microbiota in humans	Tine Licht
13.35-14.10	The impact of the intestinal flora on rodent as models for human inflammatory disease	Axel Kornerup
14.10-14.40	Coffee & networking	
14.40-15.15	The immune system of the gut	Hanne 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

Tine Licht – the Intestinal microbiota



**10¹⁴ bacteria
more than 500 different
species**

**Most of these are not
cultured**



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: What is Axel's problem and what is the state of art?



Rodent breeders only standardize their animal according to specific infections

'Normal flora' is unstandardized

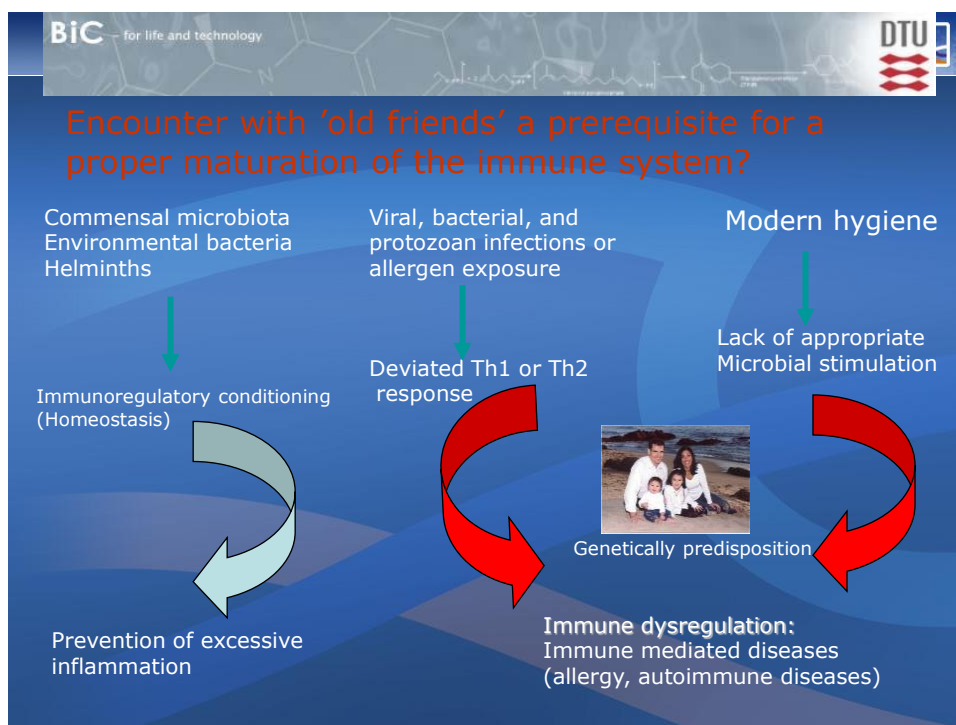
Many animal models have too little predictive validity

We need to put more efforts into improving animal models if we want to reduce the number of animals used and improve research

2

Karen Krogfeldt:

- **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**





Obesity

Intake of food, drinks

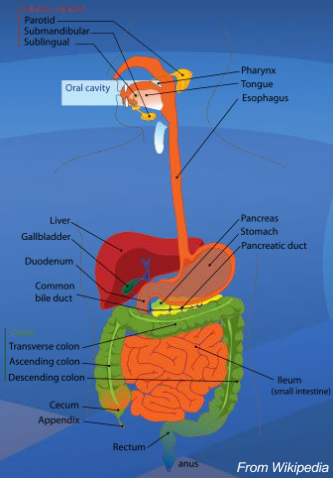
Lifestyle

Obesity leads to insulin resistance

Asthma

Gut Microbiota

Allergy



From Wikipedia