The Microbiome, Diet and Health: Assessing Gaps in Science and Innovation Brussels, May 30, 2016

New foods and dietary guidelines must target the gut microbiota: the clinical prospective



Vall d'Hebron Institut de Recerca VHIR

Human Digestive System



2.

Gut Microbiota and Bowel Motor Function





FIG. 1. Gastrointestinal tract of conventional (above) and germ-free mice fed an aqueous carmine suspension via intragastric tube 6 hr prior to sacrifice. The small intestine of the germ-free animal contains a greater residual amount of dye than does its conventional counterpart. The distended cecum, characteristic of the germ-free mouse, is evident at the left.



Cecum

CV mouse

GF mouse

Abrams and Bishop, *J* Bacteriol 1966

IMPACT OF THE MICROBIOTA ON HOST ANATOMY AND PHYSIOLOGY

GERM FREE versus CONVENTIONAL MICROBIOTA

Reduced:

Organ weight (heart, liver, lungs)

Cardiac output

Oxygen consumption

Increased:

Food intake

Nutrition, Growth & Development

Reduced:

Mesenteric and systemic lymph nodes Mucosa-associated lymphoid tissue Serum immunoglobulin levels Increased: Susceptibility to infection



Wostmann, Annu Rev Nutr 1981

MICROBIOTA AND BEHAVIOR



Legacy of natural behaviour through the microbiome?

Diaz Heijtz et al. PNAS 2011

Brain-Gut Microbial interactions



Mayer et al, Gastroenterology 2014

Microbiota Impact on Human Metabolic Phenotype

The Hu

Numb

Fluid

All fluids Blood

Urine

Saliva

CSF

QUANTUM **COMPUTERS Choosing the** hardware **SUPERCONDUCTORS Going organic NUCLEAR** PROLIFERATION

4 March 2010 | www.nature.com/nature | £10

OUR OTHER **NED**

THE INTERNATIONAL WEEKLY JOURNAL OF S CIENCE

A gene catalogue of the human gut microbiome an Fluids % Microbial

origin

atabase

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8,2

4,8

NATUREJOBS Down on the farm

Ban laser uranium

enrichment?

Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk

Tang et al, NEJM 2013

Microbial metabolites of dietary lignans: potential for disease risk reduction

Hu Y, et al. A Prospective Investigation of the Association Between Urinary Excretion of Dietary Lignan Metabolites and Weight Change in US Women. Am J Epidemiol. 2015 Sep 15;182(6):503-11.

Struja T, et al. The association between urinary phytoestrogen excretion and components of the metabolic syndrome in NHANES. Eur J Nutr. 2014 Sep;53(6):1371-81.

Seibold P, et al. Enterolactone concentrations and prognosis after postmenopausal breast cancer: assessment of effect modification and meta-analysis. Int J Cancer. 2014 Aug 15;135(4):923-33.

Richard A, et al. Urinary phytoestrogens and depression in perimenopausal US women: NHANES 2005-2008. J Affect Disord. 2014 Mar;156:200-5.

Physiological Role of the Human Colon

Guarner & Malagelada, Lancet 2003

Fermentable substrates that reach the Human Colon

Substrate	Component	Amount (g day ⁻¹)
Carbohydrates	Resistant starch	5–35
	Non-digestible polysaccharides	10-25
	Oligosaccharides (e.g. fructo- or gluco-oligosaccharides, inulin)	2-8
	Monosaccharides (e.g. sugars, sugar alcohols)	2–5
	Mucins	3–5
	Synthetic carbohydrates (e.g. lactulose, polydextrose, modified cellulose)	Variable
Protein	Of dietary origin	1–12
	Of endogenous origin (e.g. pancreatic enzymes and other secretions)	4–8
	Desquamated epithelial cells	30-50
Other	Non-protein nitrogen (e.g. urea, nitrate)	~0.5
	Organic acids, lipids, bacterial recycling	Unknown

'Based on Refs [19,65-67].

Egert et al, Trends Microbiol 2006

Diet and Microbiota

Heinzmann et al, J Proteome Res 2012

Induction of the Immune System

Gut-Associated Lymphoid Tissue structures are strategically situated in relation to the greatest concentration of microbiota

- Peyer's patches: distal ileum (nos. 100-250)
- Isolated lymphoid follicles (ILFs): large bowel (nos. ~ 30 000)

Brandtzaeg, Immunological Investigations 2010

Decision making in the adaptive (acquired) immune system is instructed by the microbial impact on APCs and T cells

By Per Brandtzaeg in Guarner et al, Nature Clin Practice 2006

THE 'OLD FRIENDS' HYPOTHESIS

By Graham Rook in Guarner et al, Nature Clin Practice 2006

INVERSE RELATION BETWEEN THE INCIDENCE OF INFECTIOUS DISEASES AND IMMUNE DISORDERS

Bach JF, N Eng J Med 2002

Prevalence/abundance curves of individual bacteria in human groups with different degree of Westernization

Clemente et al, Science Advances 2015

Gut Microbiota Dysbiosis and Disease

Disorders linked to altered composition of the gut microbiota:

Nutrition-related disorders (obesity, type 2 diabetes and the metabolic syndrome)

Dysbiosis An imbalance of the normal structure and function of the microbiota

Tunctional bower alsoraers

- Systemic complications of decompensated liver disease
- Colo-rectal cancer
- Certain allergies
- Certain mental and neuro-developmental conditions, such as autism spectrum disorders

Common Traits of Dysbiosis

- Reduction of SCFA producing bacteria (butyrate producers such as Faecalibacterium, Roseburia, Lachnospiraceae, Eubacterium, Subdoligranulum).
- Increased mucus degradation potential by abnormal mucin degraders that displace Akkermansia.
- Reduced hydrogen and methane production potential combined with increased hydrogen sulphide formation potential. Hydrogen sulphide is toxic for the epithelium.
- Increase in abundance of bacteria with LPS endotoxins (Proteobacteria) that can drive inflammation.
- Increased potential to manage oxidative stress, i.e. microbes become able to proliferate in close vicinity to the epithelium.

Le Chatellier et al, Nature 2013

Diet and Long-Term Weight Gain

- Prospective observational study involving three separate cohorts that included 120,877 women and men who were free of chronic diseases and not obese at baseline.
- Follow-up period from 1986 to 2006.

Feeding the gut microbiota proved very beneficial!

Mozaffarian et al, NEJM 2011

Daily Serving, per 4-Year Period (lb)

NHS (women) NHS II (women)

Meta analysis for GI disease

PLos one

A Meta-Analysis of Probiotic Efficacy for Gastrointestinal Diseases

Marina L. Ritchie*, Tamara N. Romanuk

OPEN CACCESS Freely available online

April 2012 | Volume 7 | Issue 4 | e34938

Department of Biology, Dalhousie University, Halifax, Nova Scotia, Canada

In conclusion, our meta-analysis containing 74 studies, 84 trials and 10,351 patients shows that in general, probiotics are beneficial in treatment and prevention of GI diseases.

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Prevention and Treatment of Dysbiosis

Current strategies:

- Prebiotics and diet may increase diversity
- Screen probiotic organisms for properties and use them in disease
- Study the microbiota in disease and "replace" what is missing
- Study a clinically beneficial outcome (e.g. faecal transplant) and reverse engineer