Human microbiome and health benefits of exposure to microbial diversity the environment

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The vertebrate ecosystem

Vertebrates evolved about 500 million years ago

Complex communities of microbial partners.... Microbiota

Complex adaptive immune system

Manage or “farm”

Pathogens

Development
- Most organs, including brain
- Sex hormone reuptake from gut

Regulate
- Immune system
- Metabolism
- Diurnal rhythms
- Gut-brain axis

Metabolites
? 20-30 % of small molecules in blood, reaching every cell in the body

Organisms with which humans co-evolved: the “Old Friends”

**Microbiota**
from mother and family and environment

**Natural environment.**
Spores, organisms (and their genes)

**Immune system at birth**
- hardware
- software
- needs DATA

**Immunoregulation**
- Do not attack “forbidden targets”
  (self, allergens, gut contents)
- Increase **repertoire of tolerated microbiota**
- Turn off redundant inflammation
  (cardiovascular & metabolic disease, depression)

**Attack**
*Repertoire*: biodiversity drives a wide range of “memory” cells that can rapidly recognise pathogens

**DATA**

**Epigenetic**
- Development
- Repertoire
## System failures in high-income urban settings

### All have distorted microbiota

**Metabolic dysregulation**
- Obesity

**Chronic unnecessary inflammation**
- Depression
- Cancer (colon and breast)

**Forbidden targets**
- Autoimmunity
- Asthma, other allergies
- Inflammatory bowel disease

### Risk increased by antibiotics

- Shao *et al* (2017) *Front Endocrinol* **8**:170

- Cao *et al* (2017) Apr 4 *Gut*

- Rosser & Mauri (2016) *J Autoimmun* **74**:85
Perinatal (pregnancy or early life) antibiotic exposure and obesity

Dose–response meta-analysis of the association between antibiotic exposure in early life and childhood obesity

The gut microbiota (the symbiotic bacteria that live in the gut) can influence **weight gain**

Mice with gut microbiota

Transfer gut microbiota

Genetically **normal**, identical *germ-free* mice

Give **same** diet to all mice

Genetically obese

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The gut microbiota (the symbiotic bacteria that live in the gut) can influence weight gain.

Indentical germ-free mice

Transfer gut microbiota

Give same diet to all mice

Gut microbiota from depressed humans induces “depression” in the rat and mouse

Antibiotics to deplete rat\(^1\) microbiota or use germ-free mice\(^2\)

microbiota from depressed human

microbiota from happy human

\(^1\) Kelly et al (2016) *J Psychiatr Res* **82**:109  
Gut microbiota in people from high- versus low-income countries

60% of bacterial genera in the microbiota make spores (= 30% of the total intestinal bacteria)

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Environmental microbes and allergies

**Epidemiology**
- Aichbhaumik et al (2008) CEA **38**:1787
- Sozanska et al (2013) JACI **133**:1347
- Song et al (2013) Elife **2**:e00458
- Lynch et al (2014) JACI **134**:593

**Mechanisms**
- Treg (regulatory T lymphocytes), earlier maturation of Th1, IL-10, DCreg

**Identification of candidate organisms**
- Ege et al (2012) Allergy **67**:1565
- Hanski et al (2012) PNAS **109**:8334
- Karvonen et al (2014) Allergy
- Lynch et al (2014) JACI

**Test in animal models**
- Debarry et al (2007) JACI. **119**:1514
- Vogel et al (2008) JACI **122**:307
- Conrad et al (2009) JEM **206**:2869
- Hagner et al (2013) Allergy **68**:322

- Farms
- Cowsheds
- Dogs *in the home*
- Rural versus urban
- Microbe-rich house dust

**Environment**
- Plants
- Soil
- Animals
- Outside air

**Rural versus urban**
Effects in the airways of the microbiota we breathe

Microbiota of the air (up to $10^{10}$ in 24hrs)

- Allergen
- Various inflammatory signals
  - attract and activate cells of immune system

Bacterial components
- Including LPS
  - Regulatory mechanisms
    - Including A20

Allergic response

Exposure to dust in a traditional farming environment causes:
- Decreased expression of markers of inflammation
- & increased expression of A20 \textbf{in blood cells}  

Environmental microbial biodiversity & chronic inflammatory disorders in Russia, Finland & Estonia

4-fold higher prevalence of childhood atopy
6-fold higher prevalence of Type 1 diabetes
- in Finnish Karelia than in Russian Karelia

House dust dominated by gram-negative bacteria

High Bacteroides in infant gut microbiota

7-fold more clones of animal-associated species

House dust dominated by gram-positive bacteria

Low Bacteroides in infant gut microbiota

Fails to block mouse model of Type 1 diabetes
Fails to drive immunoregulation

Blocks mouse model of Type 1 diabetes
Drives immunoregulation

Loss of ~80% of flying insect biomass in 27 years

Not attributable to changes in climate or vegetation

agricultural chemicals, pesticides, antibiotics

industrial pollution

Healthy human microbiota
- High biodiversity

Development and function of all organs

Well regulated - immune system.
- metabolism
Chronic inflammatory disorders rare

Data to immune & metabolic systems

organisms, spores, genes

Microbiota of natural environment
- High biodiversity

Health of ecosystems, & yields of plants, crops

Sustainable agriculture
Good crop health & yields
Distorted human microbiota - Lower biodiversity

Development and function of all organs

Less data to immune & metabolic systems

Failure to regulate the immune & metabolic systems: autoimmunity, allergies, inflammatory bowel disease, some cancers, psychiatric disorders, diabetes, obesity, cardiovascular disease

Non-sustainable agriculture
Reduced crop health & yields
 Reduced input to human immune system and to human microbiota

Microbiota of natural environment - Lower biodiversity

Health of ecosystems, & yields of plants, crops