CHILDHOOD NUTRITION, UNDERNUTRITION & THE GUT MICROBIOTA

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The vertebrate gastrointestinal tract microbiota

• The microbial communities that inhabit the digestive tracts of vertebrates are especially impressive both in sheer number and complexity.

• The largest microbial populations are found in the digestive tracts of mammals, which can contain $10^{10}$ to $10^{13}$ cells/mL (e.g., in the rumen and large intestines),

• One of the most complex microbial ecosystems known

• These are the highest cell numbers recorded for any known microbial ecosystem (Whitman et al. 1998 *PNAS*)

• Human gut contains >500 bacterial species

• Humans contain ~1.5-2.5 kg of bacteria

• The microbes in our guts outnumber our own cells by 10:1
GUT MICROBIOTA COMPOSITION CHANGES WITH AGE

Figure from Ottman et al. (2012) Frontiers in Cellular and Infection Biology,

- Unborn
- Baby
- Toddler
- Adult
- Elderly

DNA
16S
Firmicutes
Bacteroidetes
Actinobacteria
Proteobacteria
Others

65 to 80 years
>100 years
DIETARY TRENDS IN EARLY LIFE

Figure adapted from: Bokulich et al. (2016) Sci Transl Med. 8:343
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Monozygotic twins have similar microbiota

Dicksved et al., (2008) ISME J

N ~40 P < 10^{-5}

HUMAN GENETICS

Tims et al., (2013) ISME J

Dicksved et al., (2008) ISME J
ADAPTATION OF MATERNAL GUT MICROBIOTA DURING PREGNANCY


First trimester  Third trimester

N=91 pregnant women
HUMAN MILK CONTAINS MICROBIAL SUBSTRATES

<table>
<thead>
<tr>
<th></th>
<th>Human milk</th>
<th>Cow's milk</th>
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<tbody>
<tr>
<td>Lactose</td>
<td>55-70 g/L</td>
<td>40-50 g/L</td>
</tr>
<tr>
<td>Total oligosaccharides</td>
<td>3.0-15.0 g/L</td>
<td>Traces</td>
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</tbody>
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CONFIDENTIAL AND PRIVILEGED
IMPACT OF DIET ON GUT MICROBIOTA

STUDY IN CHILDREN FROM WESTERN EUROPE AND RURAL BURKINA FASO

★ Children, aged 1–6 y, in rural village in Burkina Faso (BF)
★ Content of carbohydrate, fiber and nonanimal protein is very high
WHAT IS CAUSE & WHAT IS EFFECT?

Microbiome
- Probiotics
- Pathogens

Host physiology
- Health
- Disease

Nutrition
- Diet
- Prebiotics
Leptin is a hormone, which expression correlates with adipocyte lipid content. Leptin acts on receptors in the hypothalamus of the brain, where it inhibits appetite.

Obesity results in a pronounced shift in the relative abundance of the two dominant bacterial phyla in the mouse gut.

Ley R., et al., 2005

Leptin is a hormone is knocked out

Experiments with genetically modified mice

Obesity results in a pronounced shift in the relative abundance of the two dominant bacterial phyla in the mouse gut.

Ley R., et al., 2005
Difference in body fat gain between initially germ-free mice that receive a microbiota transplanted from either an obese donor (either a genetically obese donor \([ob/ob]\) or a diet-induced obese donor [“Western”]) or a lean donor (again, either a genetically lean donor \([+/+]\) or a diet-induced lean donor [“CHO”]).

*Turnbaugh et al., 2006, 2008.*
UNDERNUTRITION

★ Condition results from inadequate intake or assimilation of nutrients

★ It underlies more than one-third of all deaths worldwide in children younger than 5 years of age

★ Enteric infectious disease and undernutrition exacerbate and perpetuate each other by means of impaired innate and adaptive immune responses.

★ Together they produce an insidious condition called environmental enteropathy in which damaged gut mucosal architecture and function are associated with malabsorption, dysregulation of mucosal permeability, and inflammation.

★ This vicious cycle leaves approximately one-fifth of children in the world stunted
UNDERNUTRITION & THE GUT MICROBIOTA
Kwashiorkor is a form of severe undernutrition prevalent in regions confronting food insecurity and high burdens of infectious disease.

Over the past 60 years, there have been many ideas about the pathogenesis of kwashiorkor, including inadequate protein intake, the leaky gut syndrome (compromised gut epithelial barrier), and intestinal inflammation.

Smith et al. (2013) showed that the gut microbiota form a central factor in the cause of kwashiorkor.
RELATIVE ABUNDANCE OF ACTINOBACTERIA IN THE FECAL MICROBIOMES OF HEALTHY TWIN PAIRS AND TWIN PAIRS DISCORDANT FOR KWASHIORKOR

Children in twin pairs discordant for kwashiorkor were treated with a peanut-based, ready-to-use therapeutic food (RUTF).

TRANSPLANTATION OF FECAL MICROBIOTA FROM KWASHIORKOR AND HEALTHY INTO GF MICE FED MALAWIAN AND RUTF DIETS

GUT MICROBIOTA & CHILDREN WITH KWASHIORKOR

(a) Therapeutic intervention
- RUTF + antibiotics: Higher rates of weight gain and lower mortality than the RUTF-only group
- RUTF: Reduced mortality and increased weight gain

(b) Malawian twin pairs discordant for kwashiorkor
- 36 months
- Normal
- Gut microbiome with reduced overall gene content

(c) Control vs. Kwashiorkor mice
- Control microbiota
  - No change in weight
  - Change to RUTF: Rapid weight gain
  - Return to Malawian diet: Numerous changes remained
- Kwashiorkor mice
  - Loss of weight
  - Particularly rapid weight gain, change in microbiota
  - Changes not sustained

IN CONCLUSION

- Identified potential targets for kwashiorkor that are rooted in the microbiota.

- Specific microbes seem correlated with a positive response to RUTF, as well as signals that correlated with a lack of sustained improvement.

- This research provides a basis for understanding developmental patterns in healthy gut microbiota.

- Establishes robust preclinical models to improve nutritional and microbiota-based therapies for malnutrition.