The human microbiome and how it affects health

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Lecture Outline

- Housekeeping
- Introduction
- Research Initiatives to Understand Microbiome
- Microbiota Development
- Questions
- BREAK
- Microbiota & Health
- Summary
- Future Learning
- Questions
Lecture Slides

Questions

• Time before break and at end of class

• No interruptions during lecture
Introduction: a little about me

• Neuroscientist
• Basic Researcher
• Contact: NafisaJadavji@cunet.Carleton.ca
Introduction: What are microbes?

- Microbes are small (non-visible to the naked eye) living creatures, we call germs, yeasts, and algae.

- They are also known as viruses, bacterial, lower fungi, and algae.
Introduction: Human Microbiome

Human microbiota consists of 10-100 trillion symbiotic microbial cells.

Different parts of the body (e.g. skin, vagina, gut) all have very different, distinct communities of microbes.
Human Microbiome

Blum, 2017
Introduction

This lecture will focus mainly on gut microbiome
Microbiome changes throughout life

F = Firmicutes
B = Bacteroidetes
A = Actinobacteria
P = Proteobacteria
O = Others

Upadhyaya & Banerjee 2015
Introduction

• Studies of diversity of human microbiome were started in 1680 by Antionie van Leewenhoek

• Microbiome is an essential organ

• Involved in basic biological processes, including development, and immune system function

• Provides specific molecules for reactions in the body

Wang et al., 2017
Introduction

• Variability in the gut microbiome
  • Microbiomes different from person to person

• Microbiota may play a significant role in health and disease

• Not all bacteria contribute to health benefits, some promote inflammation

Wang et al., 2017
Introduction

Possible ways through which microbiota impacts health and disease:

1. Changes energy extraction & nutrient harvest from food
   - Alters appetite signaling

2. Provides a physical barrier
   - Protects host against foreign pathogens

3. Essential in the development of the intestinal mucosa and immune system

Wang et al., 2017
National Institutes of Health
Human Microbiome Project, 2007

- Research initiative to improve understanding of the microbial flora involved in human health and disease

https://hmpdacc.org/
National Institutes of Health
Human Microbiome Project, 2007

Phase 1 (2007-14):

• perform preliminary characterization of the human microbiome
• explore the relationship between disease and changes in the human microbiome
• develop new technologies and tools for computational analysis
• study the ethical, legal, and social implications of human microbiome research
National Institutes of Health
Human Microbiome Project

- Phase 2 (2014-16)
  - Pregnancy and Preterm Birth
    - Understanding how the microbiome changes during the gestational period and influences the neonatal microbiome
  - Inflammatory Bowel Disease (IBD)
    - Understand the long term changes in the gut microbiome in adults with IBD
  - Type 2 Diabetes
    - Longitudinal analysis on the biological processes that occur in the microbiome of patients at risk
Some achievements of Human Microbiome Project……

• time-lapse "moving pictures" of the human microbiome
• identification of factors distinguishing the microbiota of healthy and diseased gut
Role of microbiota during development

Microbiota of mother may affect the health of her children

García-Mantrana et al., 2016
Development of microbiota

Dynamic interactions between microbes and the environment.

Example:

• Gastrointestinal (GI) track of human infant provides a brand new environment for microbial colonization
  • 20 minutes after birth, the microbiota of vaginally delivered infants resembles the microbiota of their mother’s vagina.
  • Infants born via Caesarean section (C-section) harbor microbial communities typically found on human skin.

Ursell et al., 2012
Microbiota development

Infant’s microbiota tracked over the first 2.5 years of life.

- Significant changes in the gut microbiota composition were apparent at 5 time points:
  - Starting breast milk
  - Onset of fever
  - Introduction of rice cereal
  - Introduction of formula and table foods
  - Antibiotic treatment

Ursell et al., 2012
Microbiota development

- When an infant begins to receive full adult diet → DNA in the microbiome associate with vitamin biosynthesis and polysaccharide digestion become enriched.

Ursell et al., 2012
Microbiota development study

• The infant microbiome educates the immune system and primes organ function.

• Infant microbiome development is perturbed by C-section, perinatal antibiotics, and formula feeding.

Mueller et al., 2015
Microbiota development study

• Perturbed infant microbiomes have been linked to increased risk of metabolic and immune diseases.

• Restoration of the microbiome in infants may decrease the risk of associated diseases.

Mueller et al., 2015
Human Microbiota and Health

Topics to cover:
- Autoimmune diseases
- Antibiotics
- Prebiotics/Probiotics
- Cancer
- Type 2 Diabetes & Obesity
- Brain Gut Axis

Athani et al., 2016
Human Microbiota and Chronic Diseases

Fig. 1. Human microbial symbiosis has a close relationship with diseases of different systems.

Abbreviations:
IBD: irritable bowel disease
ALD: alcoholic liver disease
NAFLD: non-alcoholic fatty liver disease

Wang et al., 2017
How bacteria rule over the body

Link to video: https://www.youtube.com/watch?v=VzPD009qTN4
Questions?
Break!
Inflammatory Bacteria

• Ulcerative colitis
  • Enterobacteriaceae
  • Bacteroides fragilis
Microbiota & Autoimmune diseases
Autoimmune diseases

- Dysfunction of microbiome may result in autoimmune diseases:
  - Diabetes
  - Rheumatoid arthritis
  - Muscular dystrophy
  - Multiple sclerosis
  - Fibromyalgia
  - Crohn’s disease

- Autoimmune diseases may be passed in families not by DNA inheritance but by inheriting the family’s microbiome
Autoimmune diseases

• Microbiome may influence susceptibility to infectious diseases and contribute to chronic illness of gastrointestinal (GI) system, like Crohn’s disease

• Disease-causing microbes accumulate over time, changing environment of microbiome → abnormal immune response
Infections
Clostridium difficile (C. difficile)

- An infection that causes serious diarrhoea to life-threatening inflammation of the colon, can be deadly

- Patients can receive faecal transplants from a donor with a health microbiome to “reset” their inner community

- Procedure that has been shown to rapidly cure the condition
Faecal transplants - *C. difficile*

Link to video from Johns Hopkins:
[https://www.youtube.com/watch?time_continue=54&v=-nDPjGAGEak](https://www.youtube.com/watch?time_continue=54&v=-nDPjGAGEak)
Impact of Antibiotics on Microbiota
Impact of Antibiotics on Microbiota

Millan et al., 2016

ABR = antibiotic resistance
Prebiotics & Probiotics
Prebiotics & Probiotics

• Prebiotics: fibre, substances useful for microbe, can thrive on

• Probiotics, microbes themselves that are though to be beneficial for health, such as *Lactobacillus* and *Bifidobacterium*

• Not clear what the benefits are for supplementation

• Probiotics good if you are taking antibiotics or have irritable bowel syndrome (IBS)
Probiotics Study

• Aim of study: to understand the impact of probiotics
• 6 weeks of probiotics administered to healthy adults
• *In vivo* mucosal responses of healthy adults to probiotics
• *Lactobacillus acidophilus*, *L. casei*, and *L. rhamnosus* each induced differential DNA networks and pathways in the human mucosa

van Baarlen et al., 2010
Protein–protein interaction network reflecting immune response-related transcriptome changes after consumption of *L. acidophilus*

Transcriptional information

Interaction map

Up-regulated genes are depicted in shades of red

Down-regulated genes are in shades of green

van Baarlen *et al.*, 2010
Table 2. Bacterial species that were significantly more abundant in the stool of healthy individuals compared to CRC patients.

<table>
<thead>
<tr>
<th>Bacterial Species</th>
<th>Avg. Healthy (%)</th>
<th>Avg. CRC (%)</th>
<th>Fold Change</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroides finegoidii</td>
<td>0.74</td>
<td>0.29</td>
<td>2.5</td>
<td>0.0032</td>
</tr>
<tr>
<td>Bacteroides intestinalis</td>
<td>0.53</td>
<td>0.19</td>
<td>2.9</td>
<td>0.0063</td>
</tr>
<tr>
<td>Prevotella copri</td>
<td>4.09</td>
<td>0</td>
<td>40</td>
<td>0.0000</td>
</tr>
<tr>
<td>Prevotella aris</td>
<td>1.64</td>
<td>0</td>
<td>16</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ruminococcus obeum</td>
<td>0.62</td>
<td>0.34</td>
<td>1.8</td>
<td>0.0009</td>
</tr>
<tr>
<td>Dorea formicigenerans</td>
<td>0.24</td>
<td>0.08</td>
<td>2.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lachnospirae biformis</td>
<td>1.20</td>
<td>0.62</td>
<td>1.9</td>
<td>0.0002</td>
</tr>
<tr>
<td>Lachnospirae pectinoschiza</td>
<td>0.54</td>
<td>0.21</td>
<td>2.6</td>
<td>0.0005</td>
</tr>
<tr>
<td>Pseudobutyryrivibrio ruminis</td>
<td>0.39</td>
<td>0.12</td>
<td>3.2</td>
<td>0.0000</td>
</tr>
<tr>
<td>Bacteroides capillosus</td>
<td>0.23</td>
<td>0.10</td>
<td>2.2</td>
<td>0.0057</td>
</tr>
<tr>
<td>Ruminococcus albus</td>
<td>0.36</td>
<td>0.03</td>
<td>10.3</td>
<td>0.0008</td>
</tr>
<tr>
<td>Dialister invisus</td>
<td>3.45</td>
<td>0.07</td>
<td>48.7</td>
<td>0.0000</td>
</tr>
<tr>
<td>Dialister pneumosintes</td>
<td>0.48</td>
<td>0.01</td>
<td>52.6</td>
<td>0.0000</td>
</tr>
<tr>
<td>Megamonas hypermegale</td>
<td>0.24</td>
<td>&lt;0.01</td>
<td>44.5</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Abbreviation: CRC = Colorectal cancer

Weir et al., 2013
Table 3. Bacterial species significantly over-represented in CRC stool samples.

<table>
<thead>
<tr>
<th>Bacterial Species</th>
<th>Avg. Healthy (%)</th>
<th>Avg. CRC (%)</th>
<th>Fold Change</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidaminobacter unclassified</td>
<td>0.05</td>
<td>0.39</td>
<td>7.7</td>
<td>0.0045</td>
</tr>
<tr>
<td>Phascolarctobacterium unclassified</td>
<td>3.31</td>
<td>11.0</td>
<td>3.2</td>
<td>0.0000</td>
</tr>
<tr>
<td>Citrobacter farmeri</td>
<td>0.08</td>
<td>0.37</td>
<td>4.6</td>
<td>0.0050</td>
</tr>
<tr>
<td>Akkermansia muciniphila</td>
<td>3.54</td>
<td>12.8</td>
<td>3.6</td>
<td>0.0032</td>
</tr>
</tbody>
</table>

Weir et al., 2013
Type 2 Diabetes & Obesity
Type 2 Diabetes

- Prevalent metabolic disease worldwide
- Pancreas does not produce enough insulin, glucose metabolism

- Link between gut microbiome composition and development of type 2 diabetes is currently being uncovered
- Studies suggest, gut microbiome has lower diversity and resilience

Wang et al., 2017
Type 2 Diabetes & Human Microbiome Study

- gut microbiota was transferred from lean individual to an individual with metabolic syndrome (e.g. Type 2 diabetes)
  - insulin sensitivity of this recipient improved (peripheral tissues and hepatic tissue)
  - autologous transfer of gut microbiome was done, there was no change in the insulin sensitivity in these individuals
- role of gut microbiota in metabolic syndrome may be important

Upadhyaya & Banerjee 2015
Studying the microbiota in the laboratory
What are germ free mice?

Reduced in germ-free mice
- Intestinal mucosal cell regeneration
- Digestive enzyme activity
- Mucosa-associated lymphoid tissue
- Lamina propria cellularity
- Muscle layer thickness
- Resistance to infection

Yoon et al., 2011
Type 2 Diabetes Study

• Adult germ-free mice

• Colonized with microbiota harvested from the cecum of obese (ob/ob) or lean donors

• ob/ob donor microbiota had a greater relative abundance of *Firmicutes* compared with the lean donor microbiota

• Mice ob/ob microbiota exhibited a significantly greater % increase in body fat over 2 weeks

Upadhyaya & Banerjee 2015
Type 2 Diabetes: dietary interventions

• Prebiotic/Probiotic interventions

  • Probiotics interventions, not all but specific species and strains of bacteria demonstrate benefit.

  • Probiotics like *Lactobacillus* or *Bifidobacterium* species for 4–12 weeks have demonstrated significant improvements in body fat and insulin sensitivity.

Upadhyaya & Banerjee 2015
Brain-Gut Axis

Influence on:
- motility
- secretion
- nutrient delivery
- microbial balance

Influence on:
- neurotransmitters
- stress/anxiety
- mood
- behaviour
Brain-Gut Axis

• Bidirectional communication between central and enteric nervous system

• Links cognitive centers of the brain with peripheral intestinal functions

• Enteric nervous system:
  • Mesh-like system of neurons
  • Govern gastrointestinal system
  • 2\textsuperscript{nd} brain
Brain-Gut Axis

- Regulate movement and sensation in gut
- Gut flora release molecules that can transmit information about state of the intestine to brain (via vagus nerve)
Vagus Nerve

Parasympathetic System

- Constricts pupils
- Stimulates flow of saliva
- Constricts bronchi
- Slows heartbeat
- Stimulates peristalsis and secretion
- Stimulates bile release
- Contracts bladder
Brain-Gut Axis

• Your gut and brain are also connected through chemicals called neurotransmitters.

• Neurotransmitters produced in the brain control feelings and emotions.

• For example, the neurotransmitter serotonin contributes to feelings of happiness and also helps control your body clock.
Brain-Gut Axis study

• Interestingly, many of these neurotransmitters are also produced by your gut cells and the trillions of microbes living there.

• A large proportion of serotonin is produced in the gut.
Brain-Gut Axis study

• Your gut microbes also produce a neurotransmitter called gamma-aminobutyric acid (GABA), which helps control feelings of fear and anxiety.

• Studies in laboratory mice have shown that certain probiotics can increase the production of GABA and reduce anxiety and depression-like behavior.
Interactions between body & gut microbiome
Complex interaction between body and gut

Athani et al., 2016
Precision Medicine & Microbiome

Fig. 1 Clinical data are combined with ‘omics’ data sets, including microbiome analysis, in precision medicine strategies to identify personalized treatment options for individuals presenting with a given disease.

Petrosino et al., 2018
Summary video

Link to video:
https://www.youtube.com/watch?v=1sISguPDIhY
Studies Presented in Lecture

-access through Carleton University Library


Free BadGut Lecture

Tuesday November 6\textsuperscript{th} 2018

https://www.badgut.org/events/lectures/

1-866-600-4875
Future Learning: Neuroscience

YouTube Channel: Neuro Transmissions
https://www.youtube.com/user/neurotransmissions

Alzheimer's disease blog (for non-scientists)
https://alzscience.wordpress.com/

List of Neuroscience Blogs:
http://www.prymd.com/blog/the-best-brain-blogs-neuroscience-for-the-non-scientific/
Questions?