Interactions Among Diet, Gut Microbiome, and the Brain: Implications for Mood and Behavior.

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Today’s Talk

• What is the microbiome?
• Factors that impact gut microbiome
• Gut microbiome interactions with brain
• Clinical associations
The Microbiome

• What is it?
  • Bacteria (Fungi, Archea, Virus) that live on and in our bodies.
  • considered commensal or symbiotic

• How big of a deal is this?
  • Sexy estimates ca 2014
    • 1:10 (10 trillion human cells and 100 trillion bacteria)
  • More recent (37.2 trillion cells, probably not due to obesity)
    • 1:3
    • 1:1

• Now referred to as an “organ”
Location Specific
Specificity Across GI Tract

INTESTINAL MICROFLORA
> 500 different species $10^{14}$ micro-organisms

- **Lactobacilli**: $10^2$ to $10^3$
- **Streptococci Lactobacilli**: $< 10^{4-5}$
- **Enterbacteria Enterococcus Faecalis Bacteroides Bifidobacteria Peptococcus Peptostreptococcus Ruminococcus Clostridia Lactobacilli**: $10^3$ to $10^7$
- **Colon**: $10^9$ to $10^{12}$

Liver
Gallbladder
Duodenum
Jejunum
Ileum
Caecum
Appendix
Rectum
Stomach
Regional diversity and function

**Stomach**
- **Host factors**
  - High pH
  - Oxygenated
- **Microbiota characteristics**
  - Sparse bacterial load ($10^2/g$)
  - Low-moderate diversity
  - Firmicutes, Actinobacteria predominate

**Duodenum**
- **Neutral pH**
- **Low O$_2$**
- **Bile**
- **Mucus**
- **Mono- and disaccharides**
- **Increased bacterial load ($10^9/g$)**
- **Low diversity**
- **Firmicutes, Proteobacteria predominate**

**Colon**
- **Neutral pH**
- **Low O$_2$**
- **Mucus**
- **Host-indigestible polysaccharides**
- **High bacterial load ($10^{12}/g$)**
- **High diversity**
- **Firmicutes, Bacteroidetes predominate**
**Good and Bad Bacterial Flora**

**GOOD**
- **BIFIDOBACTERIA**
  - The various strains help to regulate levels of other bacteria in the gut, modulate immune responses to invading pathogens, prevent tumour formation and produce vitamins.

**BAD**
- **CAMPYLOBACTER**
  - C. Jejuni and C. coli are the strains most commonly associated with human disease. Infection usually occurs through the ingestion of contaminated food.

**ESCHERICHIA COLI**
- Several types inhabit the human gut. They are involved in the production of vitamin K2 (essential for blood clotting) and help to keep bad bacteria in check. But some strains can lead to illness.

**LACTOBACILLI**
- Beneficial varieties produce vitamins and nutrients, boost immunity and protect against carcinogens.

**ENTEROCOCCUS FAECALIS**
- A common cause of post-surgical infections.

**CLOSTRIDIUM DIFFICILE**
- Most harmful following a course of antibiotics when it is able to proliferate.
• A large proportion of anaerobic bacteria
  • Difficult to culture
• Low-abundance/rare species
• What is the current tool(s) for measuring?
Microbiome Research
Metagenomics

Microbial community

Metagenomic reads

Reference sequences

Annotated reference sequences

Mapped reads

List of quantified genes
Gene 1: 5
Gene 2: 12
Gene 3: 3
Gene 4: 14
Gene n: 5
The Human Microbiome Project says the human body has 100 trillion microscopic life forms living in it.

Oooh I love carbs

Yuck carbs make me sick

You call this living?

Give us what we want to eat!
What we know

• Many of these findings are descriptive/associative
  • Complex system

• Diversity appears to be good as it associates with health
Dietary and Lifestyle Choices Impact Metabolism

Physical Activity 2000 vs. 1950 (Brownson, 2005)

- Time spent watching TV increased 61.4%
- Number of people walking to work dropped 71%
- Low physical activity occupations increased 83%
However, during 2007–2010, half of the total U.S. population consumed <1 cup of fruit and <1.5 cups of vegetables daily; 76% did not meet fruit intake recommendations, and 87% did not meet vegetable intake recommendations (2).
Environment has changed rapidly in last 150 years, what is the interaction with our microbiome?
Environmental, Dietary, and Behavioral Impacts on Microbiome

Have very interesting insights from a study on Hadza tribe that live in Tanzania

Schnorr, 2014; Nature Commun
Hunting and Gathering make up majority (>90%) of subsistence

*Schnorr, 2014; Nature Commun*
Hadza Tribe Microbiome

• Hadza have higher levels of microbial richness and biodiversity than Italian urban controls
• comparisons with two rural farming African groups illustrate other features unique to Hadza that can be linked to a foraging lifestyle
• Bifidobacterium and differences in microbial composition between the sexes that probably reflect sexual division of labor → although a number of studies have identified sex differences in microbiome
• Seasonal variation in microbiome (Smits, 2017)

Schnorr, 2014; Nature Commun
• Differences between rural and urban populations
• Urban more western looking
• Rural had increased diversity and proportions of bacteria involved in resistant starch and oligosaccharide degradation
Rural African gut microbiome correlates with feeding practices and parasites
Having a Parasite (Entamoeba)

• Enriches microbiome for Ruminococcaceae (uncl)
  • Also seen in Hadza
  • Part of the Termite gut microbiome
Changes across the lifespan

- **Pregnancy**
  - Sterile gastrointestinal track

- **Birth**
  - Cesarean delivery – *Bifidobacteria*, *Bacteroides Staphylococcus*, *Corynebacterium*, *Propionibacterium* spp.
  - Vaginal delivery – *Lactobacillus*, *Prevotella*, *Sneathia* spp., *Clostridium difficile*

- **Infancy (1 month)**
  - Enterobacteria

- **Infancy (6 months)**
  - Bifidobacteria
  - Bacteroides

- **Infancy (24 months)**
  - Firmicutes
  - Bacteroidetes
  - Diversity

- **Adulthood**
  - Firmicutes
  - Bacteroidetes
  - Diversity

- **Elderly**
  - Firmicutes
  - Bacteroidetes
Hospitalized Elderly with Higher Diversity have Longer Survival

**Figure 5.** Fecal microbiota biodiversity and survival in hospitalized patients. Survival distribution function of 76 hospitalized patients categorized according to values of Chao1 Index of biodiversity in fecal microbiota. Subjects with higher biodiversity (upper tertile of Chao1 Index, values ≥ 1105) have a statistically longer survival than patients with deeper dysbiosis after a 2-year follow-up.
Diet and Microbiome
Bacterial fermentation products

Carbohydrate

<table>
<thead>
<tr>
<th>SCFA (acetate, propionate, butyrate)</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gases ((\text{CO}_2, \text{H}_2, \text{CH}_4))</td>
<td>Ammonia BCFA</td>
</tr>
<tr>
<td>Biomass</td>
<td>Phenols/Indoles</td>
</tr>
<tr>
<td></td>
<td>Amines</td>
</tr>
<tr>
<td></td>
<td>Sulfides</td>
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</tbody>
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Amino Acids
Tryptophan
Tyrosine
Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes

Gary D. Wu,1* Jun Chen,2,3 Christian Hoffmann,4,5 Kyle Bittinger,4 Ying-Yu Chen,1 Sue A. Keilbaugh,2 Meenakshi Bewtra,1,2 Dan Knights,6 William A. Walters,7 Rob Knight,8,9 Rohini Sinha,4 Erin Gilroy,2 Kernika Gupta,10 Robert Baldassano,10 Lisa Nessel,2 Hongzhe Li,2,3 Frederic D. Bushman,4,1 James D. Lewis1,2,4*
Proportions of these bacteria associate with dietary intake
Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David¹,²*, Corinne F. Maurice¹, Rachel N. Carmody¹, David B. Gootenberg¹, Julie E. Button¹, Benjamin E. Wolfe¹, Alisha V. Ling³, A. Sloan Devlin⁴, Yug Varma⁴, Michael A. Fischbach⁴, Sudha B. Biddinger³, Rachel J. Dutton¹ & Peter J. Turnbaugh¹
Microbiome impacts metabolic response to “Western” diet

Backhed, 2006; PNAS
Microbiome and the Brain
Current Concepts

- Bidirectional relationship between brain and gut
- This is mediated by microbial communities
- This may be manifested through:
  - Developmental alterations in CNS
  - Vagal stimulation
  - Hormones
  - Changes in neurotransmitter precursors
GF mice show altered expression of anxiety and synaptic plasticity-related genes.

Rochellys Diaz Heijtz et al. PNAS 2011;108:7:3047-3052
Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat

John R. Kelly a, b, Yuliya Borre a, Ciaran O'Brien a, c, Elaine Patterson a, c, Sahar El Aydi a, d, Jennifer Deane c, Paul J. Kennedy a, Sasja Beers a, Karen Scott a, Gerard Moloney a, Alan E. Hoban a, Lucinda Scott b, Patrick Fitzgerald a, Paul Ross c, Catherine Stanton c, Gerard Clarke a, b, John F. Cryan a, e, Timothy G. Dinan a, b, *
SCFA (Butyrate & Propionate) Increase Hormones that Reduce Food Intake

Lin, 2012; PLoS One
Hormonal response to microbiome and diet

Leptin

Ghrelin

Hooda, 2013; BJN
Humans

“Humans are a poor model of mouse physiology”
Consumption of Fermented Milk Product With Probiotic Modulates Brain Activity

KIRSTEN TILLISCH, JENNIFER LABUS, LISA KILPATRICK, ZHIGUO JIANG, JEAN STAINE, BAHAR EBRAT, DENIS GUYONNET, SOPHIE LEGRAIN-RASPAUD, BEATRICE TROTIN, BRUCE NALIBOFF, and EMERAN A. MAYER

- Supplementation with Fermented Milk Probiotic Product (FMPP)
- Reductions in negative affect
- Brain response to emotional faces task is reduced following FMPP (Tillisch, 2013; Gastroent)
- Structural alterations following FMPP (Tillish, 2017; Psychosom Med)

Figure 2. Regions showing reduced activity in response to an emotional faces attention task after FMPP intervention are shown, with significant regions demarcated.
Clinical Relevance – Bipolar Disorder

- All of the daily stool samples from the child with autism contained four organisms that earlier research had associated with autism. These included *Sarcina ventriculi*, *Barnesiella intestihominis*, *Clostridium bartlettii*, and *Clostridium bolteae*. By contrast, none of these bacteria appeared in the stool of the unaffected sibling.

Evans, 2017; J. Psy Res
Clinical Relevance – Autism Spectrum Disorder

Luna, 2017; Cell Mol Gastro Hepat
Changing the Diet

Individual's with microbiomes enhanced in B. adolescentis have increased Butyrate production in response to RS consumption.

Venkataraman, 2016; Microbiome
16s DNA sequencing

• Tells you who is there, but you have no idea what they are doing
• Can we start to understand function?
Regulation of TRP producing/sensing genes in bacteria

Stage 1. Transcription begins - polymerase pauses, translation begins, moving ribosome releases the paused polymerase.

Stage 2a. Adequate charged tRNA<sub>Trp</sub> - Peptide is synthesized and released, ribosome is released, anti-antiterminator and terminator form, transcription is terminated.

Stage 2b. Deficiency of charged tRNA<sub>Trp</sub> - Ribosome stalls at one of two Trp codons of trpL and the antiterminator forms, preventing formation of the terminator; the polymerase resumes transcription.

Yanofsky, 2007; RNA
Regulation of TRP producing/sensing genes in bacteria

Yanofsky, 2007; RNA
So far....

• Dietary RS supplementation
  • Alters community
  • Influences nutrients available to host
  • Reduces IL18, and increases prolactin
  • Decreases negative affect
  • Alters gene expression in tested species
Today’s Talk

- What is Microbiome
  - Definition
  - Locational Diversity
  - Gut
- Factors that impact Microbiome
  - Environment
  - Diet
  - Behavior
  - Sex
  - Life exposure/Adaptation
    - Mode of Birth
    - Germ Free as an extreme example
    - Changes in assisted living → links to frailty
- Gut microbiome and brain
  - Routes
    - Vagal stimulation
    - Neuroimmune
    - Hormonal
    - Metabolite
      - SCFA
      - Amino Acids
  - Brain to gut influence
- Clinical impacts
- Dietary intervention can influence microbiome and host-brain relationship
Thank you

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  • Sommer Pappas

• Collaborators
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  • Kevin Theis, PhD
  • Otto Muzik, PhD

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www.creme-lab.org