


OhioHealth MS Center: *Hot Topics in MS*

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MS and the Microbiome

April 9, 2021

Daniel Smith, MD

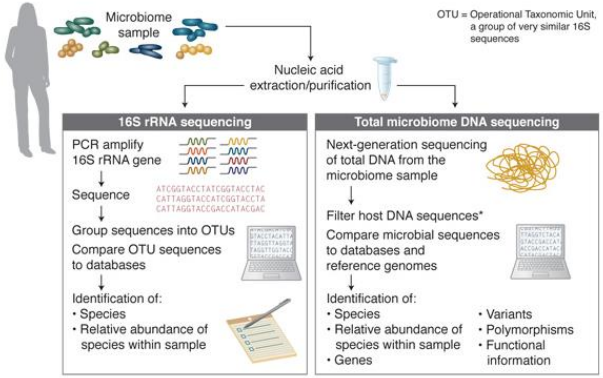
Disclosures

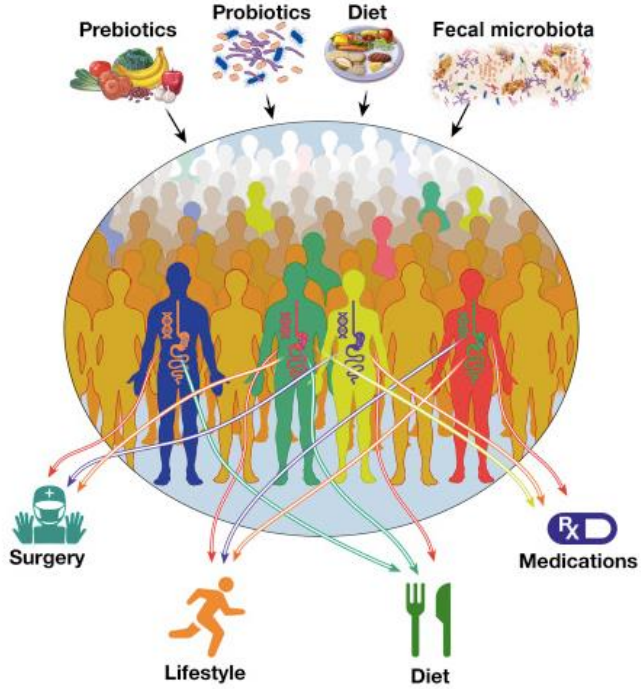
- I have no disclosures

Learning Objectives

- Gain an understanding/overview of the human microbiome
- Discuss the “gut-brain axis” and interactions with the immune system
- Review some of the evidence supporting a relationship between the microbiome and MS
- Review some of the potential treatment targets for modifying the microbiome

Imagine!





https://www.neb.com/tools-and-resources/feature-articles/addressing-challenges-in-microbiome-dna-analysis
Kashyap PC. *Mayo Clin Proc.* Dec 2017.

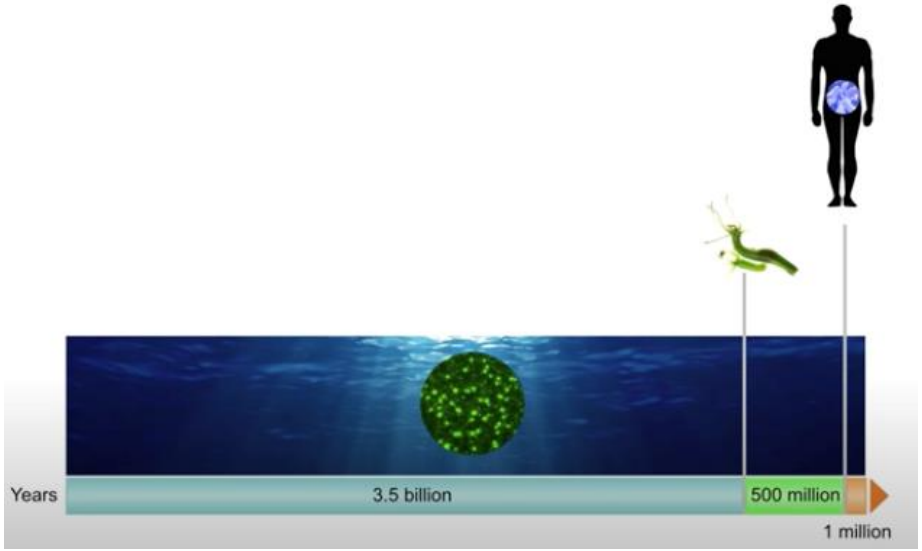
Today's Agenda

- Introduction
  - Microbiome: What it is, normal composition, how it is colonized
  - Gut-brain axis
  - Impact on neuro-development, aging, behavior
  - Interaction with immune system
    - GALT, innate, adaptive

- Studies in MS
  - Effect on blood-brain barrier, is a microbiome necessary?
  - signature microbiome in early MS, adult MS?
  - Causing EAE in mice from MS stool transfer, specific effects on immune system, effect on brain myelination

- Manipulation
  - Diet and lifestyle
  - Pro and prebiotics
  - Fecal transplant

How old is the microbiome?



Dr. Emeran Mayer,Ted Talk 2015

How vast is the microbiome?

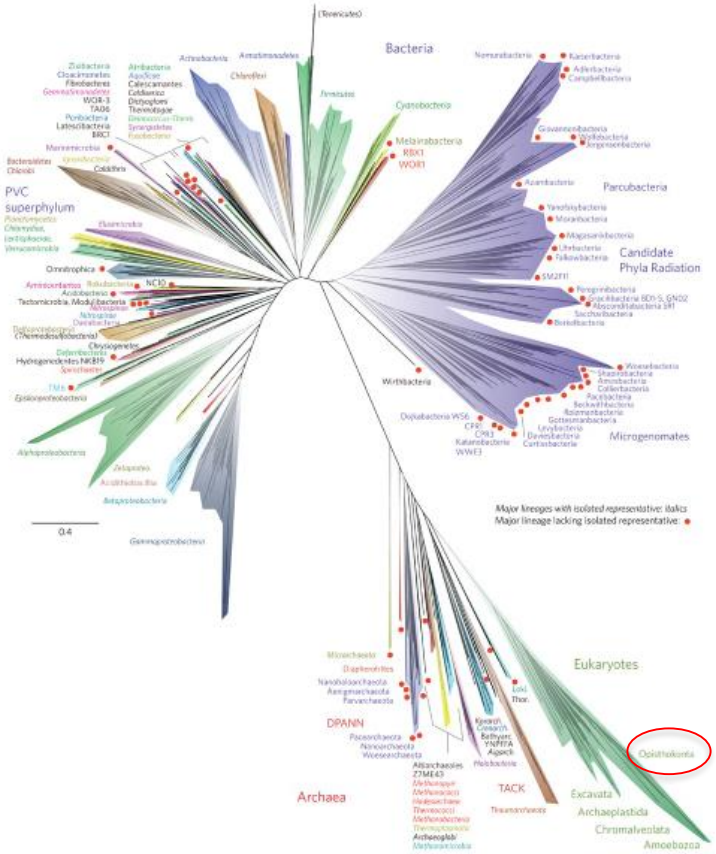
- Microbiota-trillions of organisms
  - More cells from microbes than ourselves
  - Total population of gut bacteria= 2 kg

- Microbiome- genetic material of microbiota
  - Humans are 99% microbial in terms of genetic material

Boziki MK et al. *Brain Sci*. Apr 2020
Cryan JF et al. *Lancet Neurol*. 2020

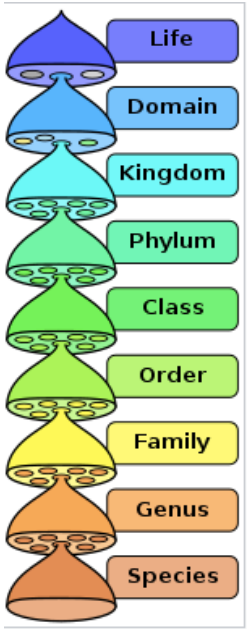
Figure: https://cosmosmagazine.com/biology/how-many-genes-in-the-human-microbiome/

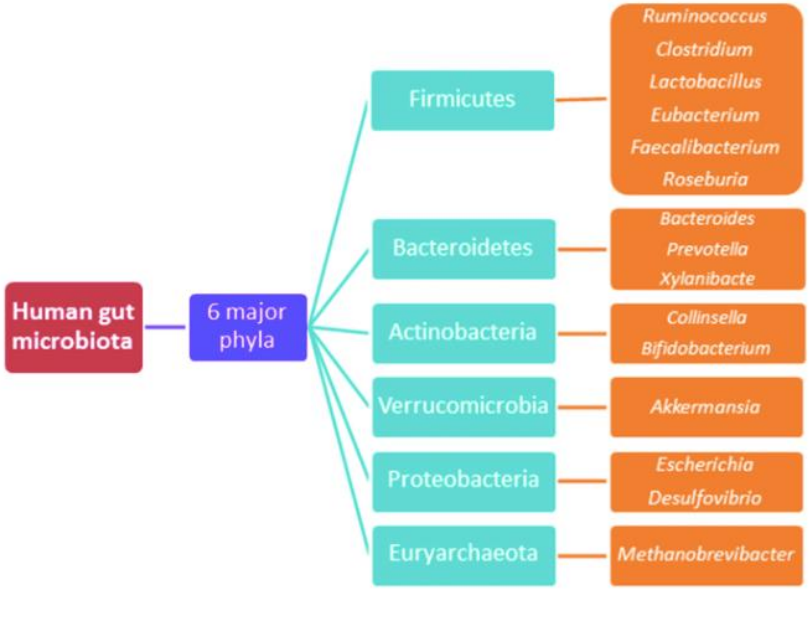
Complexity of the tree of life



Hug LA. *Nat Microbiol*. Apr 2016

Phyla of the Gut Microbiome



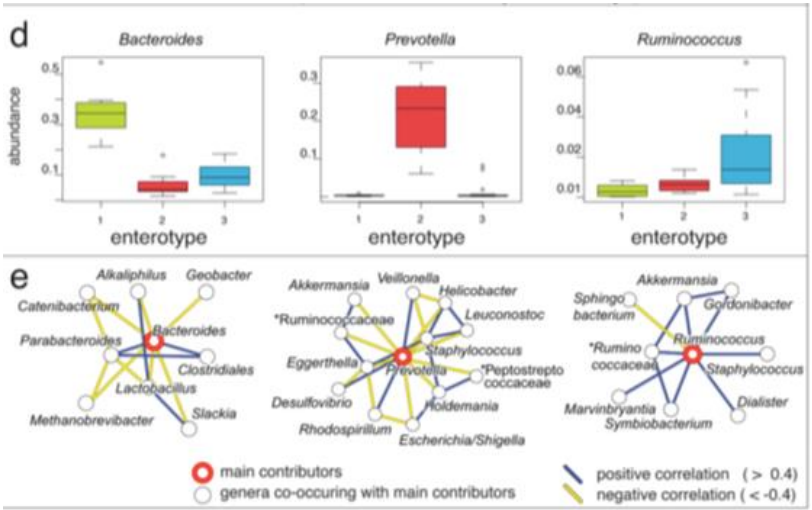


Bliss ES *Front Physiol*. 2018

Figure: https://en.wikipedia.org/wiki/Taxonomic_rank

What species make up our microbiome?

- Intestinal microbiota predominantly composed of *Prevotella* or *Bacteroides*; a third group has higher proportions of *Ruminococcus,* compared with the others
- Greater proportion of *Prevotella* in the human intestinal microbiota is a marker of residence in an agrarian culture, whereas a greater proportion of *Bacteroides* is associated with residence in more-industrialized regions
- Diet has also been associated with other types of microbes in the gut, such as archaea, fungi, and bacteriophage

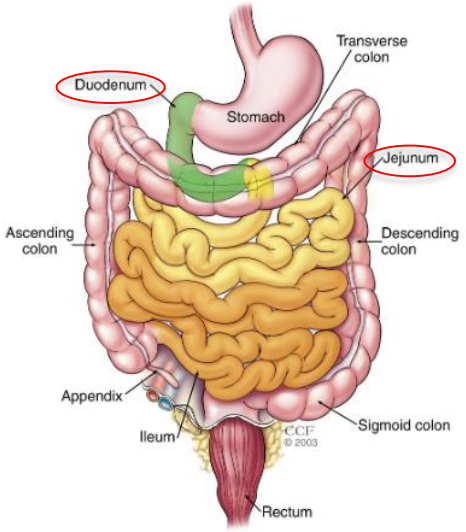


- 2172 species in humans! that are classified into 12 different phyla

Arumugam M Nature. 2011

Regional Specialization

- Is regional specialization with respect to the exact microbes that colonize each part of the gut. Cellular structure, pH of the mucosa accounts for the differences in types of bacteria found.
  - Duodenum= lactobaccili- Vit A and aryl hydrocarbon receptor ligands
  - Jejunum=lactobaccilli and streptococci
  - Cecum and appendix have most diversity and most microbes
  - Colon- most short-chain fatty acids (SCFA's)



Blum, H.E. Adv. Med. Sci. 2017
Boziki MK et al. *Brain Sci*. 2020
Mowat. Nat. Rev. Immunol. 2014
Figure: https://my.clevelandclinic.org/health/diseases/15850-small-bowel-obstruction
https://www.kenhub.com/en/library/anatomy/cecum-and-vermiform-appendix

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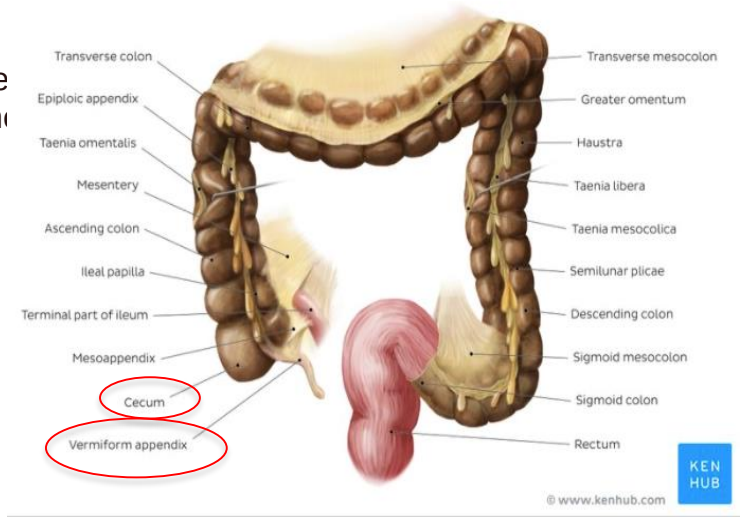


Blum, H.E. Adv. Med. Sci. 2017
Boziki MK et al. *Brain Sci*. 2020
Mowat. Nat. Rev. Immunol. 2014
Figure: https://my.clevelandclinic.org/health/diseases/15850-small-bowel-obstruction
https://www.kenhub.com/en/library/anatomy/cecum-and-vermiform-appendix

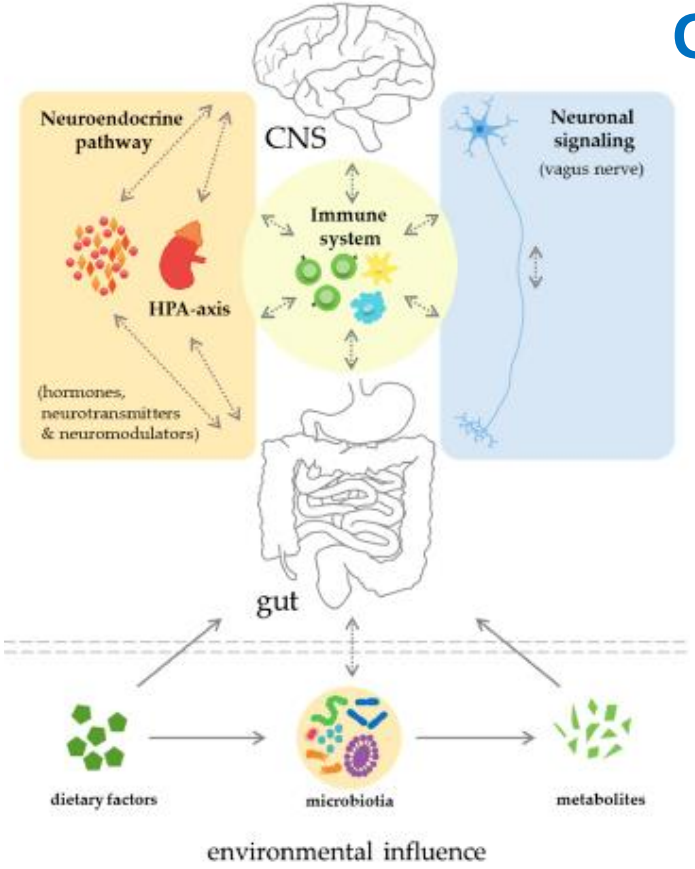
What influences colonization of the microbiome?

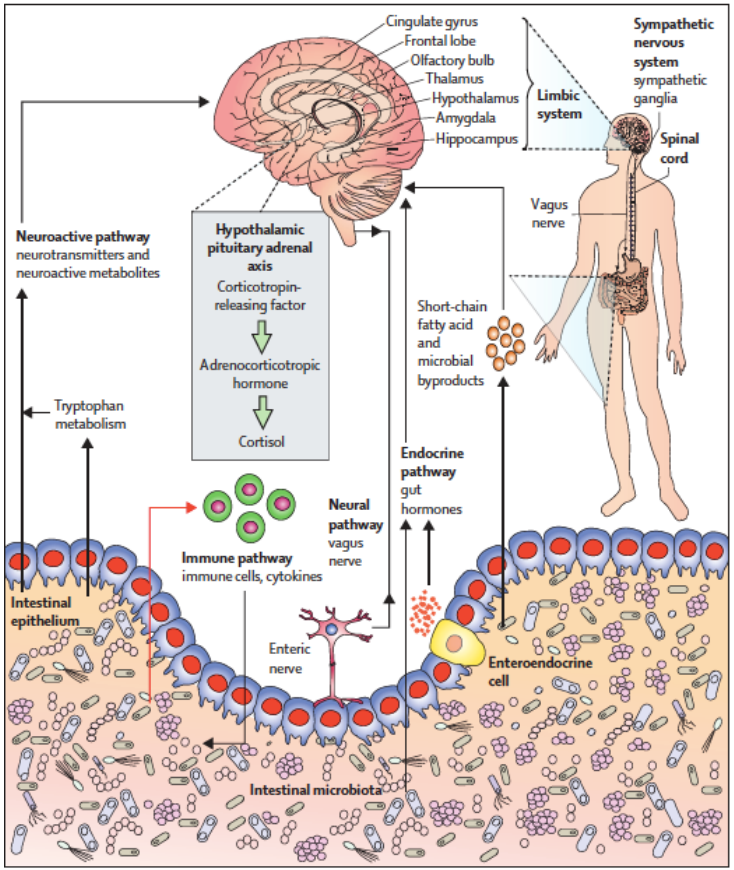
- Birth
  - Vaginal delivery
  - C-section
  - Intestine of an infant felt to be sterile environment, but quickly colonized after birth as typically able to find bacteria in meconium
- Breastfeeding/diet
- By the time a child is 3 years old, microbiome is similar composition to that of an adult
- Genetics?- one study showing monozygotic twins, small increase in *Christensenellaceae*, but small effect.
- Overall environment seems more important

Image source: https://www.nutraingredients-usa.com/Article/2020/02/12/Study-unlocks-how-gut-bacteria-may-protect-against-pathogenic-colonization

Boziki MK et al. *Brain Sci*. Apr 2020
Goodrich JK et al Cell, 2014

Gut-Brain Axis





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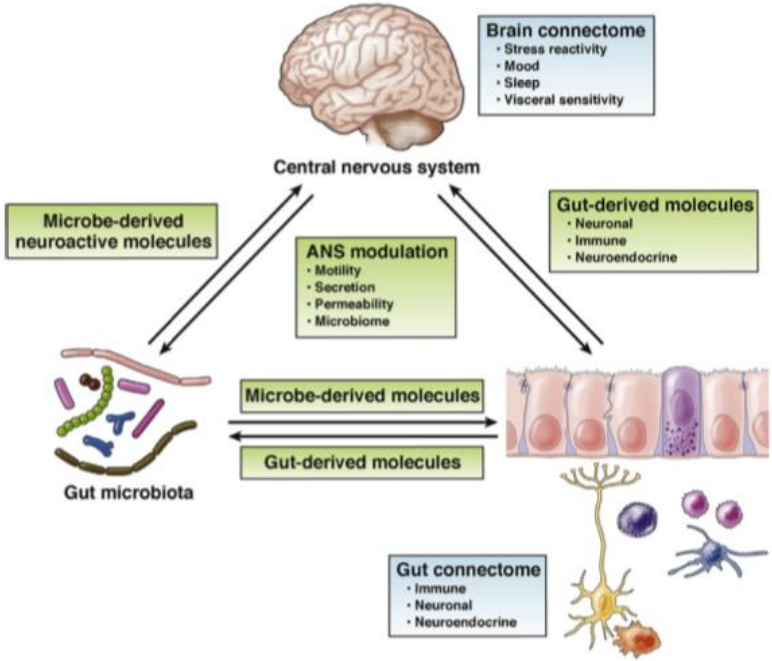
Fleck, A.K. Int. J. Mol. Sci. 2017
Boziki MK et al. *Brain Sci.* Apr 2020
Cryan JF et al. . *Lancet Neurol*. 02 2020

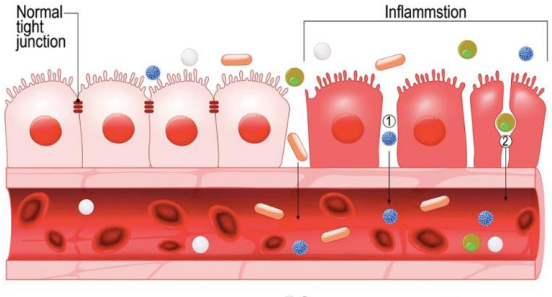
Microbiome Metabolites and Endothelial Dysfunction

- **SCFA's**: metabolites produced by microbes-have anti-inflammatory properties
- Inhibit histone deacetylases (HDACs) on T-regs and microglia
- Stimulate dendritic cells (DCs) towards the production of anti-inflammatory molecules, such as retinoic acid (RA) and transforming growth factor beta (TGF)



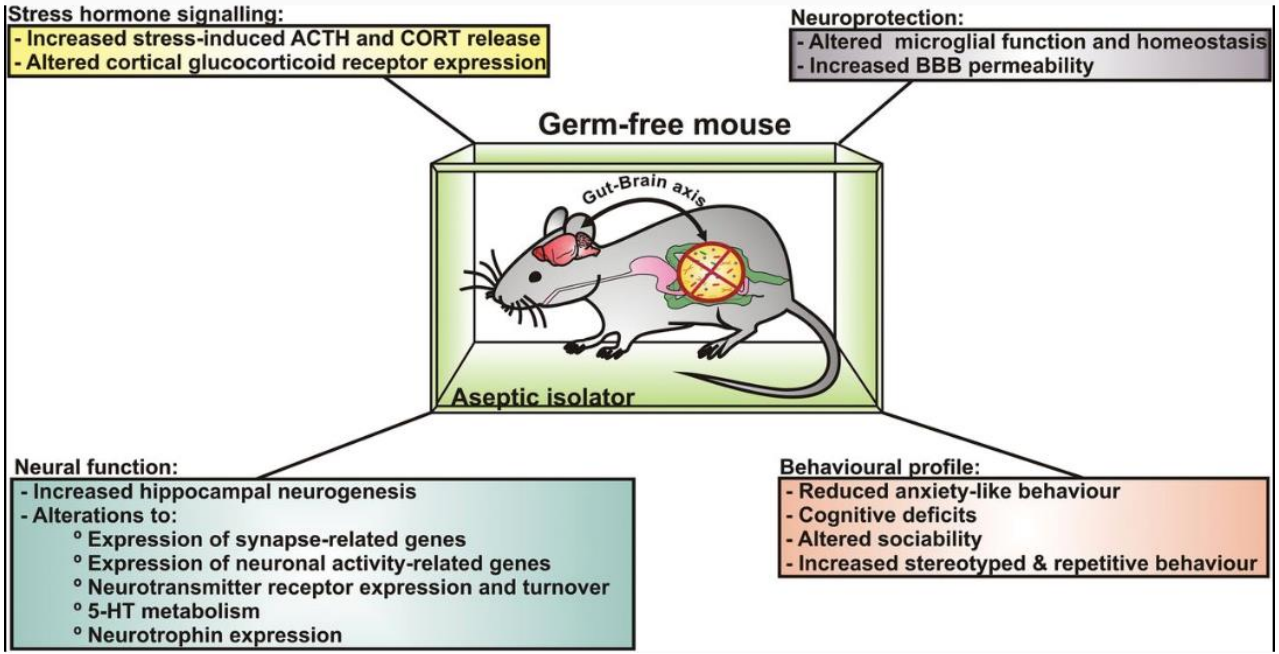
Role of intestinal barrier: "leaky gut"

- **Intestinal dysbiosis-** microbiome mediated process.
- May induce changes in mucus composition, enterocyte apoptosis and tight junction dysfunction through the translocation of associated structural components, as well as bacterial translocation to the lamina propria.
- May relate to chronic low grade inflammation and endotoxemia.



Martin CR, *Cell Mol Gastroenterol Hepatol*. 2018
Boziki MK et al. *Brain Sci*. Apr 2020
Figure: https://www.gastrosav.com/blog/leaky-gut-what-it-is-and-how-to-heal-it/

Impact on Neuro-behavior in Germ free Mice
Development/Aging (and everything in between)

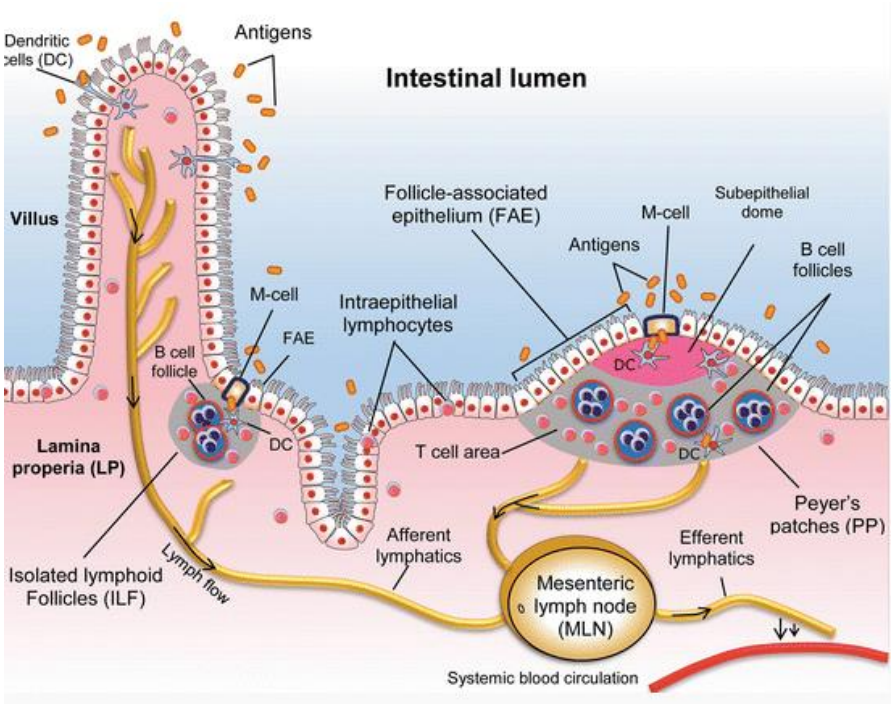


Luczynski P, *Int J Neuropsychopharmacol*. 08 2016

Microbiome and the Immune System

https://neurohacker.com/how-the-gut-microbiota-influences-our-immune-system

GALT (gut associated lymphatic tissue)



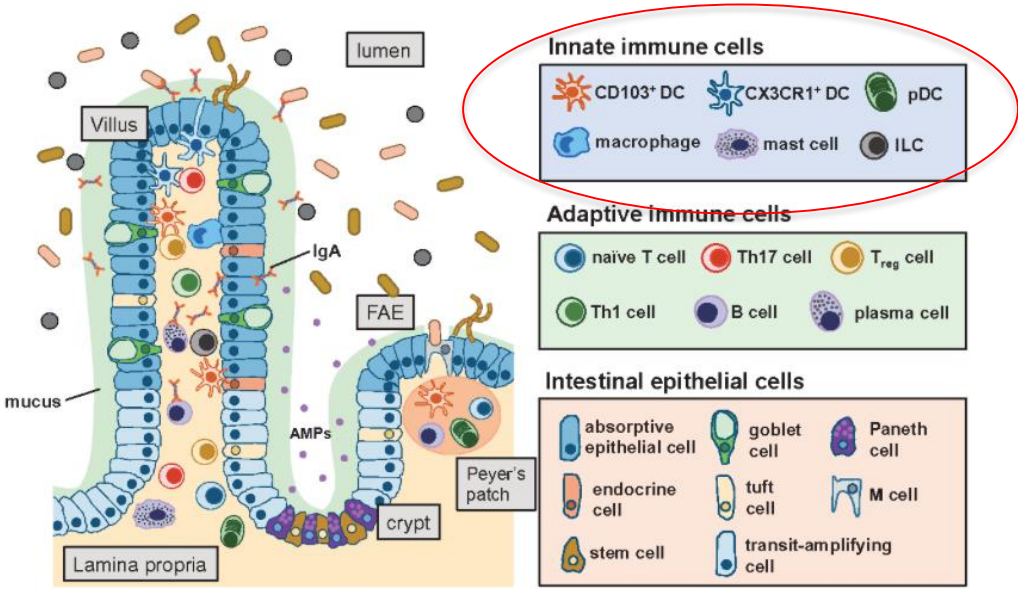
Zgair A., Wong J.C.M., Gershkovich P. (2016)

Microbiome and innate immune system

- **Mucosa-associated invariant T (MAIT) cells**- located in mucosal tissues (intestinal lamina propia)- produce pro-inflammatory cytokines (interleukin (IL)-17, interferon gamma (IFN), granzyme B, or tumor necrosis factor alpha (TNF).

- **Natural killer (NK)-cells** increase the expression of co-stimulatory molecules in response to microbial stimuli. NK cells are important for priming immune system attack: IL-4, IL-13, and IFN , as well as the promotion of chemokine (C-X-C motif) ligand 16 (CXCL16)

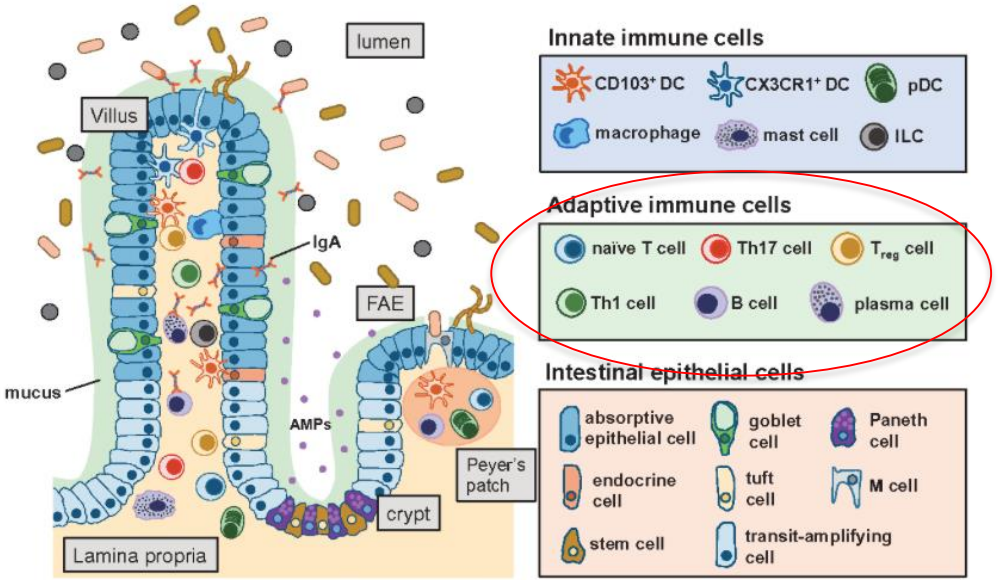
- **Dendritic cells and macrophages (classic APC's):** enhance the production of pro-IL-1 and its processing to bioactive IL-1 by caspase-1, thus discriminating between pathogenic and protective bacteria and dietary components



Boziki MK et al. *Brain Sci.* Apr 2020
Figure: Okumura R,. *Proc Jpn Acad Ser B Phys Biol Sci.* 2016.

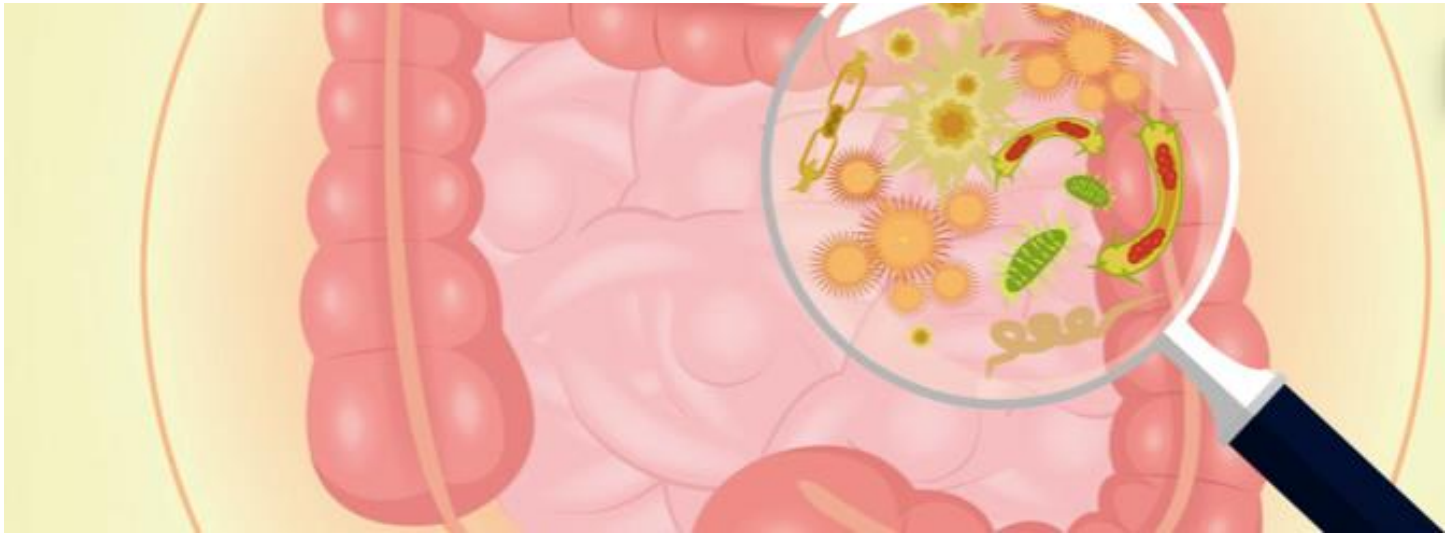
Microbiome and adaptive immune system

- **Th17 cells** are prevalent in intestine-important for defense. Secrete cytokines.
- **T regs** are 2-3 times higher in concentration in the intestine compared to other tissues.
- **T regs** are promoted by SCFA's. Important for regullation of mucosal immune response- controls expansion of T effector cells against normal flora. Also affect IgA levels in Peyer's patches.
- **B cells** class switch based on bacterial antigens.



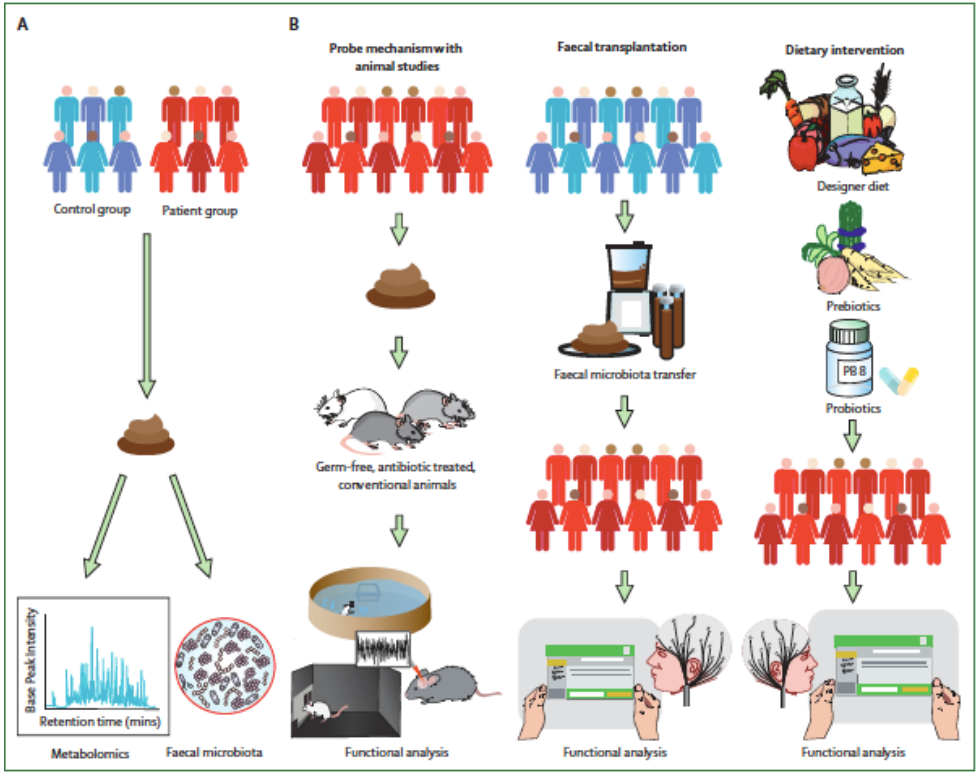
Boziki MK et al. *Brain Sci*. Apr 2020
Fleck, A.K. Int. J. Mol. Sci. 2017
Figure: Okumura R,. *Proc Jpn Acad Ser B Phys Biol Sci*. 2016.

Studies looking the Microbiome and MS



https://multiplesclerosisnewstoday.com/news-posts/2019/11/27/investigators-narrow-in-on-a-microrna-for-treating-multiple-sclerosis/

Overview of Methods to Study Impact on Microbiome on Neurological Disorders



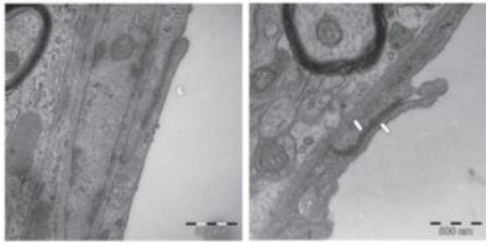
Cryan JF *Lancet Neurol*. 02 2020

The gut microbiota influences blood-brain barrier permeability in mice

Viorica Braniste[1,†,*], **Maha Al-Asmakh**[1,*], **Czeslawa Kowal**[2,*], **Farhana Anuar**[1], **Afrouz Abbaspour**[1], **Miklós Tóth**[3], **Agata Korecka**[1], **Nadja Bakocevic**[4], **Lai Guan Ng**[4], **Parag Kundu**[5], **Balázs Gulyás**[3,5], **Christer Halldin**[3,5], **Kjell Hultenby**[6], **Harriet Nilsson**[7], **Hans Hebert**[7], **Bruce T. Volpe**[8], **Betty Diamond**[2,‡], and **Sven Pettersson**[1,5,9,†,‡]

[1]Department of Microbiology, Tumor and Cell Biology, Karolinska Institute, 17177 Stockholm, Sweden.

- The blood brain barrier begins to develop during the early period of intrauterine life and is formed by capillary endothelial cells sealed by tight junctions, astrocytes, and pericytes
- Lack of gut microbiota is associated with increased BBB permeability and altered expression of tight junction proteins.
- Fecal transfer from mice with pathogen-free gut flora into germ-free mice or treatment of germ-free mice with bacteria that produce short chain fatty acids (SCFA) decreased the permeability of the BBB



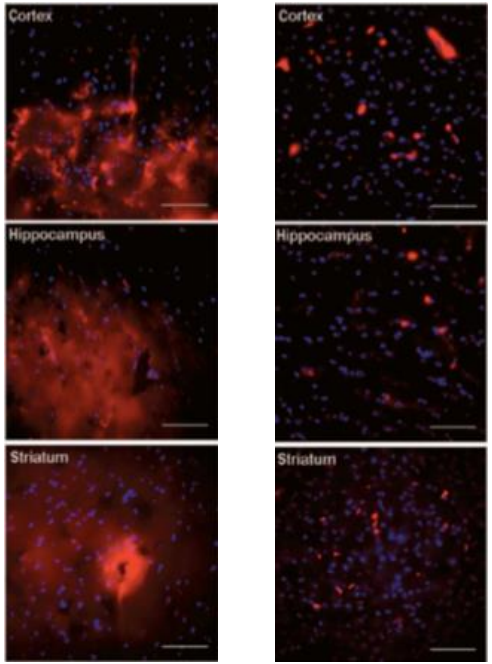
Disrupted BBB-tight-junction

Take home:

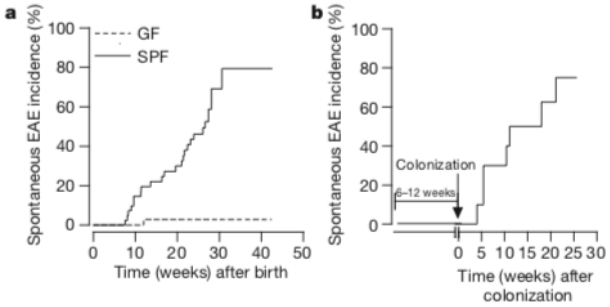
Effect of microbiome on gates to nervous system

Germ free with leakage across BBB

Fecal transplant restoring without leakage outside vessels

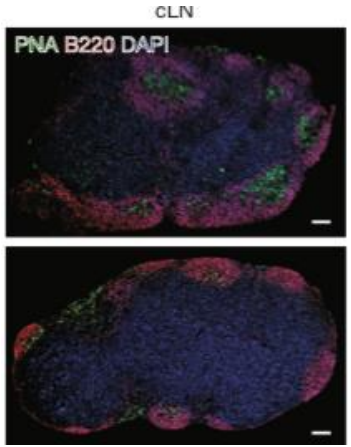


Braniste V. Sci Transl Med 2014



Microbiome required for the development of spontaneous EAE (germ free mice did not get EAE)

Recolonization led to EAE



Germ free mice (below) with poorly formed germinal centers

LETTER
doi:10.1038/nature10554

Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination

Kerstin Berer[1], Marsilius Mues[1], Michail Koutrolos[1], Zakeya Al Rasbi[1], Marina Boziki[1], Caroline Johner[2], Hartmut Wekerle[1] & Gurumoorthy Krishnamoorthy[1]

Question: what happens to T/B cell profiles in mice who are “germ free?” How important is a microbiome for the immune system?

Deficit of TH17-like cells in germ- free mice which was most pronounced in T cells intimately connected to the intestinal wall, lamina propria T cells and in Peyer’s patch but not in mesenteric lymph node populations.

T cells required but not sufficient. Needs B cells also. B cell recruitment impaired in germ free mice. When repopulated, get more antibodies

Author hypothesis:
Propose a two-phase scenario that starts out in the GALT with expanding and activating CNS autoreactive T cells, which then recruit autoantibody-producing B cells.

Take home:

To get EAE, need a microbiome.

Mice with no microbiome had deficit of Th-17 cells.

Mice with no microbiome had impaired B cells.

Berer K, Nature, 2011

european journal of neurology
the official journal of the european academy of neurology

Original Article

Gut microbiota in early pediatric multiple sclerosis: a case–control study

H. Tremlett, D. W. Fadrosh, A. A. Faruqi, F. Zhu, J. Hart, S. Roalstad, J. Graves ... See all authors

- **Question: is there characteristic bacterial composition in stool of children with MS? Is this specific to MS?**

- Pediatric MS is unique: opportunity to study the disease when only a few years of life have gone by

Design:

- Case-controlled, cross-sectional, observational 2011-2013
- 18 children <18 yrs (12 +/- 4.7 yrs), MS onset within 2 years
- 9/18 exposed to DMT's (GA, IFN, NTZ)

- First stool of day was collected on ice and shipped to USCF

- DNA extracted 16s RNA

Results:

- MS: significantly increased relative abundance of *Desulfovibrionaceae* (family) (*Bilophila, Desulfovibrio and Christensenellaceae* (genus)

- Significantly decreased relative abundance of *Lachnospiraceae and Ruminococcaceae*

- Subtle taxonomic changes

- β-diversity significantly differed by immunomodulatory drug exposure

- Microbial genes predicted as enriched in MS vs. controls included those involved in glutathione metabolism (important agent in endogenous antioxidant defense system)- loss of balance has been implicated in MS

Limitations:

- Cross-sectional study design, small sample size, single-center study
- Use of immunomodulatory drugs or systemic corticosteroids was included and potential effects of this not controlled for
- Asthma and eczema were allowed in the control population
- Stool samples collected at home

Take home:

In this small pediatric study, were some unique signatures. Small numbers and more studies needed.

Tremlett H, Eur J Neurol 2016

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Review article

The multiple sclerosis gut microbiota: A systematic review

Ali Mirza[a], Jessica D. Forbes[b,e,f], Feng Zhu[a], Charles N. Bernstein[b], Gary Van Domselaar[c,d], Morag Graham[c,d], Emmanuelle Waubant[g], Helen Tremlett[a,*]

[a] Djavad Mowafaghian Centre for Brain Health, Faculty of Medicine (Neurology), University of British Columbia, Vancouver, BC, Canada
[b] Department of Internal Medicine, University of Manitoba, University of Manitoba IBD Clinical and Research Centre, Winnipeg, MB, Canada
[c] National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB, Canada
[d] Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, MB, Canada
[e] University of California San Francisco, San Francisco, CA, United States
[f] Department of Laboratory Medicine & Pathobiology, University of Toronto, ON, Canada

Question: Is there a “signature microbiome” of MS?

- Systematic Review 2008-2018
- In general, no large differences could be deduced between cases and controls
- Two of seven studies reported a difference in beta-diversity (P≤0.002).
- At the taxa-level, ≥2 studies observed: lower relative abundance of *Prevotella, Faecalibacterium prausnitzii, Bacteroides coprophilus, Bacteroides fragilis*, and higher *Methanobrevibacter and Akkermansia muciniphila* in MS cases versus controls.
- In general, studies were small in size to assess for confonders (only 286 cases).

Alpha/beta/gamma diversity-

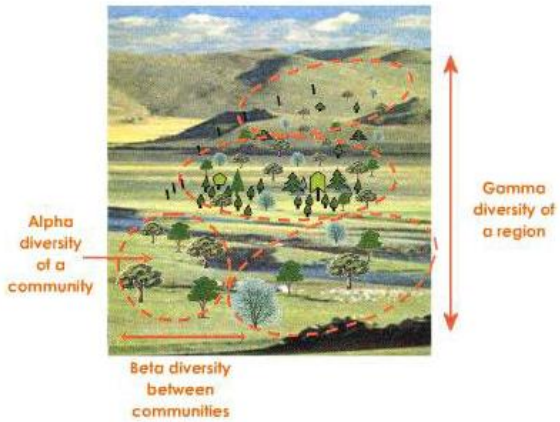


Figure: https://eco-intelligent.com/2016/10/14/alpha-beta-gamma-diversity/

Take home:

Some suggestions of signatures, but no big differences, small numbers. More studies needed.

Hot Topics in MS

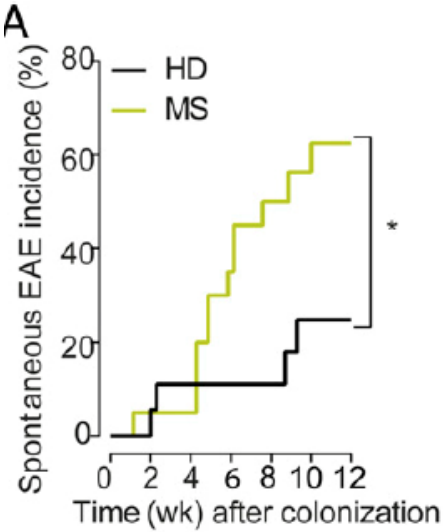
Mirza A. *Mult Scler Relat Disord*. Jan 2020

Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice

Kerstin Berer[a,1], Lisa Ann Gerdes[b,1], Egle Cekanaviciute[c], Xiaoming Jia[c], Liang Xiao[d], Zhongkui Xia[d], Chuan Liu[d], Luisa Klotz[e], Uta Stauffer[f], Sergio E. Baranzini[c,g], Tania Kümpfel[b], Reinhard Hohlfeld[b,h], Gurumoorthy Krishnamoorthy[a,i,2], and Hartmut Wekerle[a,h,2]

Question: link between microbiome in MS pts and EAE?

- Transplanted the microbiota from patients with multiple sclerosis into two different models of experimental autoimmune encephalomyelitis
- 34 monozygotic twins discordant for MS (tried to minimize variables)
- Transplanted fecal samples from selected twin pairs to germ-free mice (expressing a myelin autoantigen specific T cell receptor) to assess functional differences in the human intestinal microbiota of MS and healthy twins. Was a higher rate of EAE in these mice.
- Immune cells from mouse recipients of MS-twin samples produced less IL-10 than immune cells from mice colonized with healthy-twin samples



Take home:

Stool from MS patients more likely to cause autoimmunity (EAE) in mice.

Berer K Proc Natl Acad Sci USA 2017

Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models

Egle Cekanaviciute[a,1,2], Bryan B. Yoo[b,1], Tessel F. Runia[a,3], Justine W. Debelius[c], Sneha Singh[a], Charlotte A. Nelson[a], Rachel Kanner[a], Yadira Bencosme[d], Yun Kyung Lee[b,4], Stephen L. Hauser[a], Elizabeth Crabtree-Hartman[a], Ilana Katz Sand[d], Mar Gacias[d], Yunjiao Zhu[d], Patrizia Casaccia[d,e], Bruce A. C. Cree[a], Rob Knight[c], Sarkis K. Mazmanian[b], and Sergio E. Baranzini[a,5]

Question: can stool from MS patients induce cell type/cytokine changes?

- 71 MS patients not undergoing treatment and 71 healthy controls
- No major changes seen but *Akkermansia muciniphila* and *Acinetobacter calcoaceticus*, both increased in MS patients, induced proinflammatory responses in human peripheral blood mononuclear cells and in monocolonized mice
- Interestingly, *Acinetobacter* encode peptides that mimic the amino acid sequences of myelin basic protein (MBP) and MOG
- *Parabacteroides distasonis*, which was reduced in MS patients, stimulated antiinflammatory IL-10–expressing human $CD4^+CD25^+$ T cells and $IL\text{-}10^+FoxP3^+$ Tregs in mice.
- Author hypothesis:
  - MS patients have impaired Treg differentiation in response to autologous (self) bacteria. Thus, the initial exposure to *P. distasonis* or other “beneficial” bacteria found in healthy subjects may contribute to expanding regulatory T lymphocyte precursor populations, thus promoting antiinflammatory responses upon subsequent exposure to the same bacteria.
- Finally, microbiota transplants from MS patients into germ-free mice resulted in more severe symptoms of experimental autoimmune encephalomyelitis and reduced proportions of $IL\text{-}10^+$ Tregs compared with mice “humanized” with microbiota from healthy controls.

Take home:

Stool from MS patients more likely to cause autoimmunity (EAE) in mice, showed differences in cell numbers (Th-1) and cytokines (IL-10).

Exposure to “beneficial bacteria” may promote more T regs and more self-tolerance

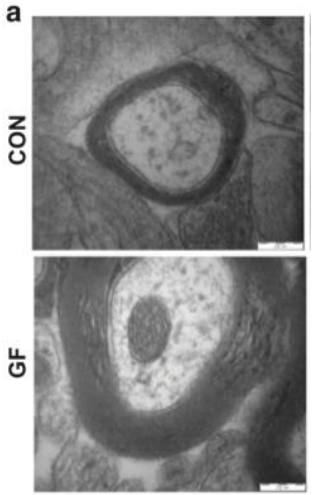
Cekanaviciute E, Proc Natl Acad Sci USA 2017

ORIGINAL ARTICLE

Regulation of prefrontal cortex myelination by the microbiota

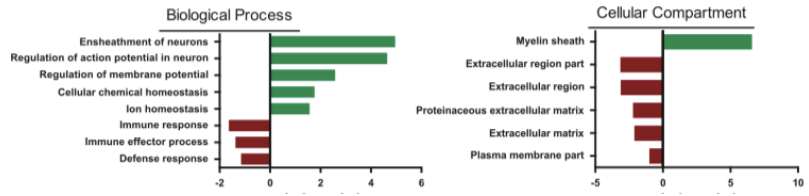
AE Hoban[1,2], RM Stilling[1,2], FJ Ryan[1,3], F Shanahan[1], TG Dinan[1,4], MJ Claesson[1,3], G Clarke[1,4,5,6] and JF Cryan[1,2,5,6]

Question:
Does microbiome affect brain structure?



Prefrontal cortex- central neuronal circuit underlying emotional regulation, and also facilitates memory storage, behavioral flexibility and attention.

- Normal and germ free mice
- Sequenced genes that were activated in prefrontal cortex (transcriptome). 236 genes were found to be different between groups.



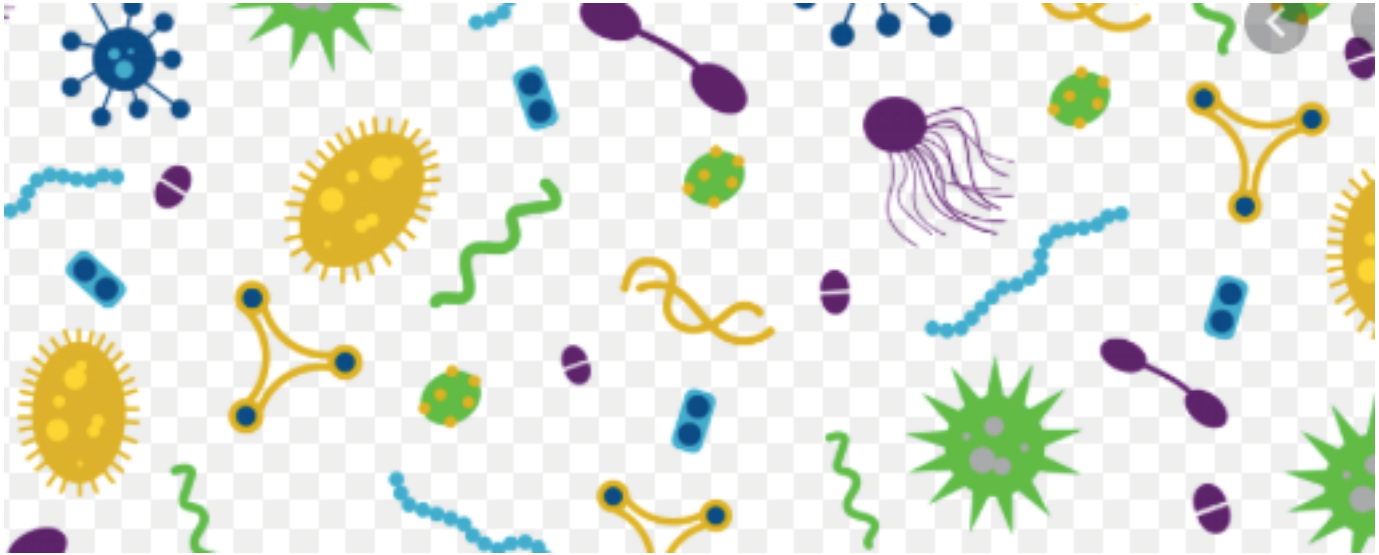
- These were genes involved in myelination→ germ free seemed to have hypermyelination (negative effect).
- Questions: how does microbiome affect this? Vagus nerve→ the nucleus tractus solitarius has an extensive network of projections, including the parabrachial nucleus, which further projects to the PFC
- Microbe byproducts may affect cytokine levels (which influence oligodendrocytes)

Take home:

appropriate myelination relies on microbiome affecting gene regulation/myelination at key points in neurodevelopment

Hoban AE. Transl Psychiatry 2016

Modulating the Microbiome



https://microbiome.ucdavis.edu

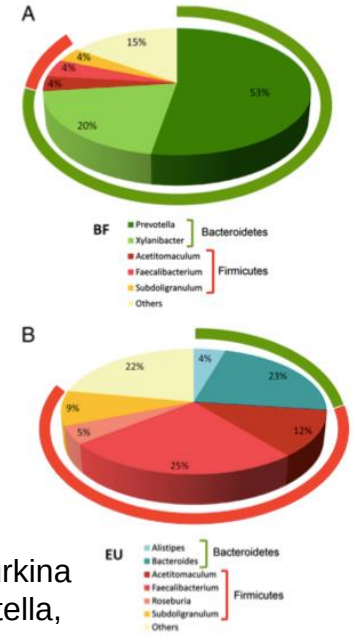
Effect of diet on microbiome?

Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

Carlotta De Filippo[a], Duccio Cavalieri[a], Monica Di Paola[b], Matteo Ramazzotti[c], Jean Baptiste Poullet[d], Sebastien Massart[d], Silvia Collini[b], Giuseppe Pieraccini[e], and Paolo Lionetti[f,1]

[a]Department of Preclinical and Clinical Pharmacology, University of Florence, 50139 Firenze, Italy; [b]Department of Pediatrics, Meyer Children Hospital University of Florence, 50139 Firenze, Italy; [c]Department of Biochemical Sciences, University of Florence, 50134 Firenze, Italy; [d]DNA Vision Agrifood S.A. 4000 Liege, Belgium; and [e]Centro Interdipartimentale di Spettrometria di Massa, University of Florence, 50139 Firenze, Italy

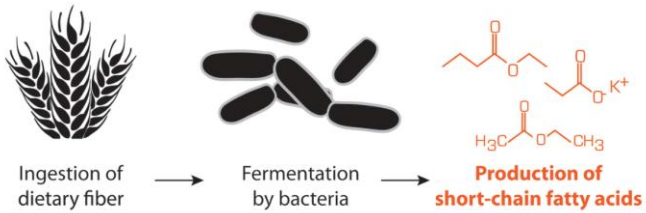
Edited* by Daniel L. Hartl, Harvard University, Cambridge, MA, and approved June 30, 2010 (received for review April 29, 2010)



Difference globally (De Filippo)-Burkina Faso had greater amounts of Prevotella, lower amounts of Bacteroides, overall greater microbial richness, and produced higher levels of short-chain fatty acids than the microbiota of European children

…and on the metabolome

- Metabolome: “the total number of metabolites present within an organism, cell, or tissue.”
- Although diet affects the composition and/or richness of the intestinal microbiota, perhaps more important are its effects on the microbial metabolome (down-stream effects).
- Fruits, vegetables: complex carbohydrates and polysaccharides, collectively termed glycans, which leads to production of short-chain fatty acids through fermentation

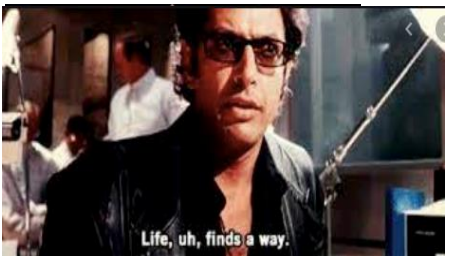


Sonnenburg JLScience. 2005
De Filippo CProc Natl Acad Sci U S A. 2010
Albenberg LG & Wu. Gastroenterology (2014)
Figure: https://www.thinkbiome.com/postbiotics

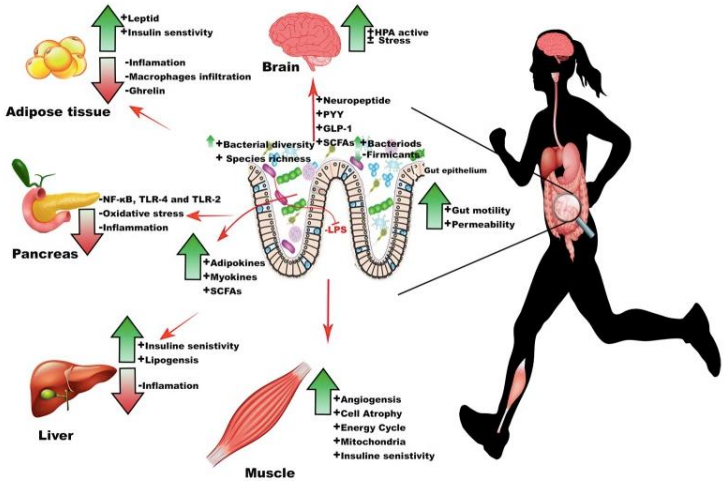
Other ways to Impact Microbiome

Impact of diet on functional metabolism of microbiome

Studies in Japanese populations have shown that following consumption of seaweeds, genes that encode enzymes that metabolize marine red algae are transferred from marine-associated bacteria to specific bacterial taxa in the intestinal microbiome[1]



Exercise[3]



Original Article

MOLECULAR METABOLISM

Gut microbiota and glucometabolic alterations in response to recurrent partial sleep deprivation in normal-weight young individuals

Christian Benedict [1], Heike Vogel [2,3], Wenke Jonas [2,3], Anni Woting [4], Michael Blaut [4], Annette Schürmann [2,3], Jonathan Cedernaes [1,*]

Sleep

Microbiota composition analysis revelaed that after two days of PSD vs. after two days of NS, had subtle changes in microbiome composition. Also a change in fasting and postprandial insulin levels[2].

Exposures

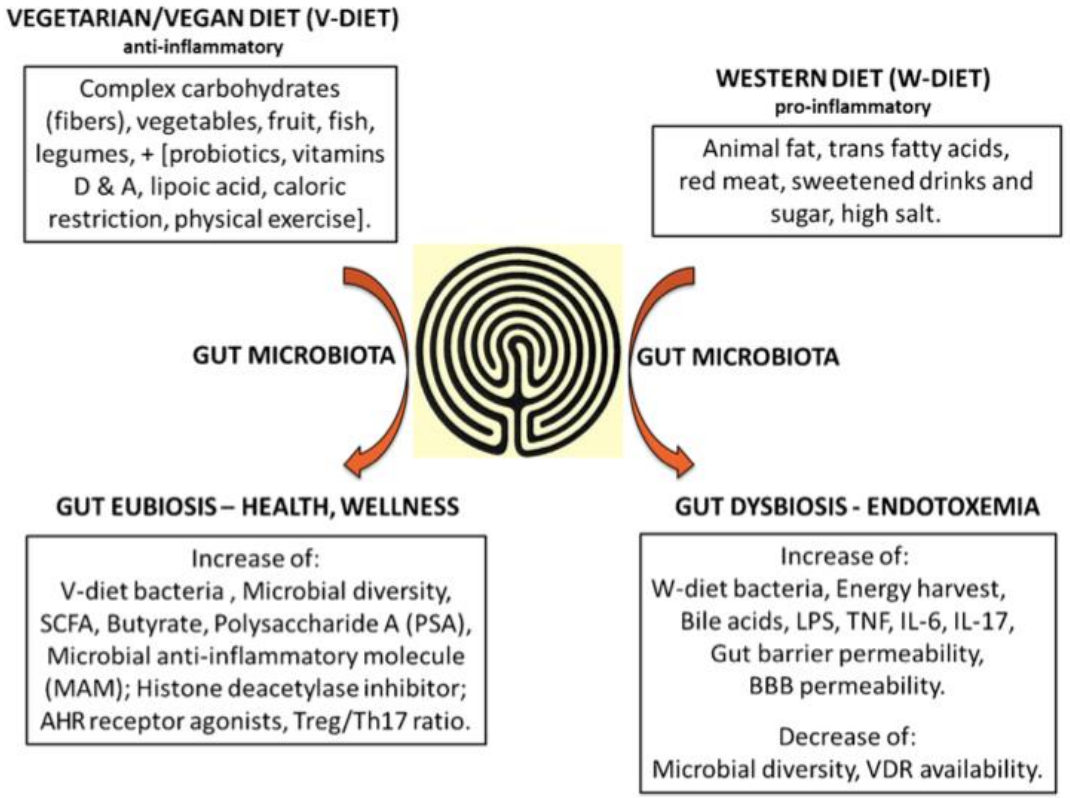
In one study, the skin microbiome of couples living together has a closer resemblance if the couple has a dog, but, intriguingly, a small child did not provide the same trend, so couples with a child but no dog were not significantly more similar to one another than couples without a child[4].

1. Hehemann JH, Nature. 2010
2. Benedict C Mol. Metab, 2016.
3. Sohail MU, *Rev Diabet Stud*. 2019.
4. Song SJ. eLife 2, e00458 (2013).

Figure: Jurassic Park

Diet

- No clear diet has emerged as a recommended approach, but this scheme serves as a general approach.
- In general, want to avoid dysbiosis-> alterations in intestinal wall, contaminants through wall, low grade chronic inflammation
- Implications for systemic immunity, perhaps crossing BBB and contributing to MS



Boziki MK et al. *Brain Sci*. Apr 2020
Riccio P. *Neurotherapeutics*. 01 2018

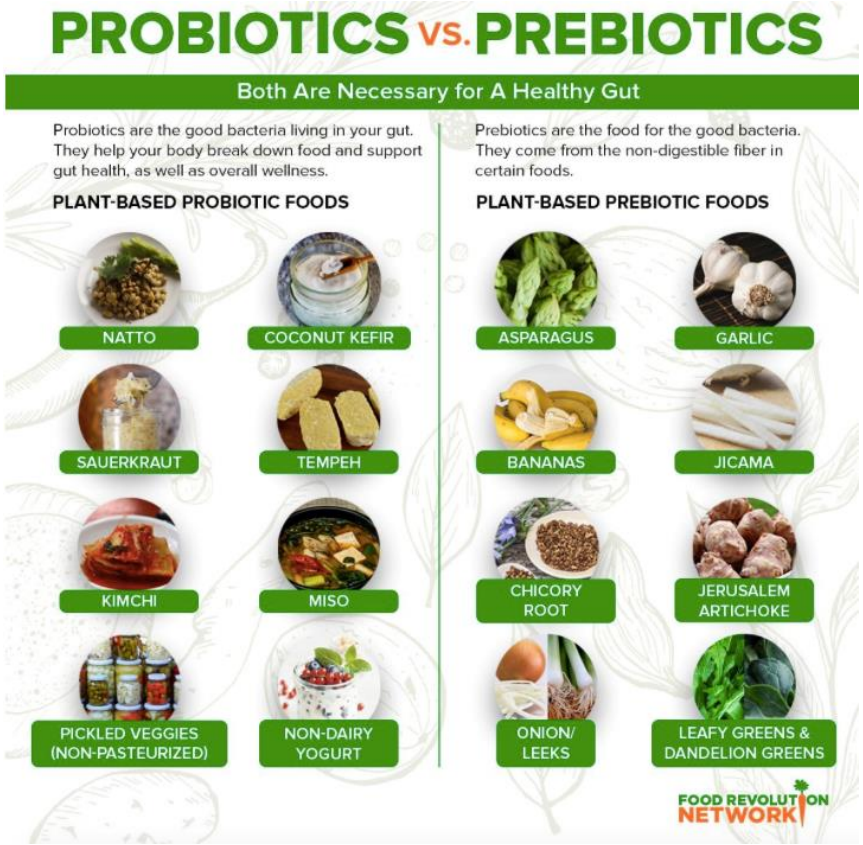


Figure: https://foodrevolution.org/blog/probiotics-and-prebiotics/

HHS Public Access
Author manuscript
Ann Neurol. Author manuscript; available in PMC 2018 October 11.

Published in final edited form as:
Ann Neurol. 2018 June ; 83(6): 1147–1161. doi:10.1002/ana.25244.

A probiotic modulates the microbiome and immunity in multiple sclerosis

- **Can microbiota be targeted for RRMS with probiotics?**

- Pilot study of 9 patients: Multispecies probiotic (containing Lactobacillus species, Bifidobacterium species, and Streptococcus species administered twice daily for 2 months reversed microbiota changes and was shown to have anti-inflammatory properties (induced an anti-inflammatory peripheral immune response characterized by decreased frequency of inflammatory monocytes).

- Significant increase in abundance of lactobacillus, known to be reduced in patients with multiple sclerosis; significant decrease in abundance of akkermansia, dorea, and blautia associated with dysbiosis, suggesting that such a microbiota targeted strategy is worth pursuing.

ELSEVIER
Volume 36, Issue 5, October 2017, Pages 1245-1249

Randomized Control Trials

Clinical and metabolic response to probiotic supplementation in patients with multiple sclerosis: A randomized, double-blind, placebo-controlled trial

Ebrahim Kouchaki [a, b], Omid Reza Tamtaji [b], Mahmoud Salami [b], Fereshteh Bahmani [c], Reza Daneshvar Kakhaki [a], Elmira Akbari [b], Maryam Tajabadi-Ebrahimi [d], Parvaneh Jafari [a], Zatollah Asemi [c]

- Double-blind, randomized , placebo-controlled

- 25 women with multiple sclerosis (mean age 34) treated for 12 weeks with probiotic containing Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum, and Lactobacillus fermentum; control group: five men and 25 women (mean age 33¯8 years who took placebo

- Significant increase in depression scores on BDI, multiple sclerosis scores on EDSS, diet scores on DHQ, and scores on DASS

- Significant changes in concentrations of high-sensitivity C-reactive protein, plasma nitric oxide metabolites, and malondialdehyde; significantly increased quantitative insulin sensitivity check index and HDL cholesterol; significantly decreased serum insulin homoeostasis model of assessment-estimated insulin resistance, β-cell function, and total and HDL cholesterol in patients with multiple sclerosis compared with placebo

JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION
https://doi.org/10.1080/07315724.2017.1347074
Taylor & Francis
Taylor & Francis Group

The Effects of Probiotic Supplementation on Gene Expression Related to Inflammation, Insulin, and Lipids in Patients With Multiple Sclerosis: A Randomized, Double-Blind, Placebo-Controlled Trial

Omid Reza Tamtaji, MSc[a], Ebrahim Kouchaki, MD[a,b], Mahmoud Salami, MD[a], Esmat Aghadavod, PhD[a], Elmira Akbari, MSc[c], Maryam Tajabadi-Ebrahimi, PhD[d], and Zatollah Asemi, PhD[c]

- Double-blind, ramdonimzed placebo-controlled

- 40 patients with multiple sclerosis aged 18- 55 years,treated for 12 weeks with probiotic containing L acidophilus, L casei, B bifidum, and L fermentum, and 20 received a starch placebo

- Significantly reduced expression of IL-8, TNFα, and mRNA from peripheral blood mononuclear cells; no change in IL-1, LDL-receptor, or PPAR-γ expression in patients with multiple sclerosis compared with controls

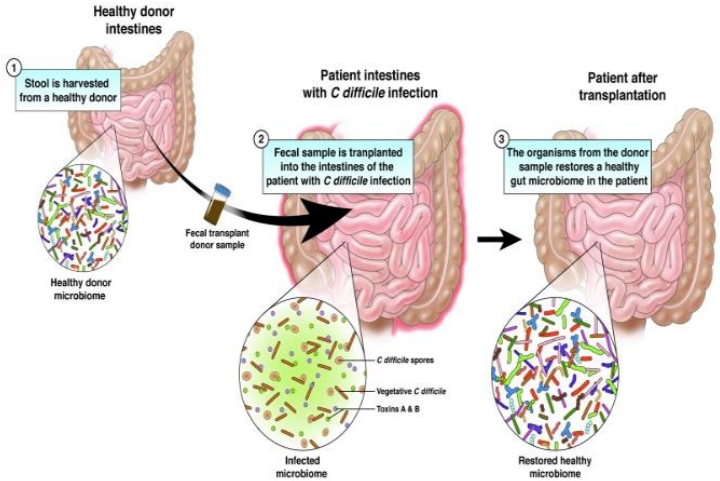
Tankou SK, Ann Neurol 2018
Kouchaki E, Clin Nutr 2017
Tamtaji OR. J Am Coll Nutr 2017

Fecal microbiota transplantation (FMT)

- Originally described in 4th century Chinese medicine for patients with severe food poisoning
- 16th century Ming dynasty, fermented fecal mixture, “yellow soup” used for remedies and at times to induce vomiting

- Used for C.diff colitis 1958- in 2013 had first randomized trial

- Usually given via colonoscope or enema, duodenal infusions, oral capsules



- **Phase 1b trial: 30 capsules (supplied by OpenBiome),** followed by monthly doses of 10 capsules for five months.
- Will measure safety, short chain fatty acid profiles, T cell profiles
- MRI,PET, microglial cells
- H.Weiner ACTRIMS 2020

- **Fecal Microbiota Transplantation (FMT) of FMP30 in Relapsing-Remitting Multiple Sclerosis (MS-BIOME)-** UCSF
- ClinicalTrials.gov Identifier: NCT03594487
- Active, not recruiting
- Estimated completion June 2021
- Measuring safety, changes in microbiome, immunonologic data

- **Fecal Microbiota Transplantation After Autologous HSCT in Patients With Multiple Sclerosis (St. Petersburg)**
- ClinicalTrials.gov Identifier: NCT04203017

- **Oral FMT (Fecal Microbial Transplant) in Subjects With Multiple Sclerosis- Griffin Hospital- Yale-** 15 pts
- ClinicalTrials.gov Identifier: NCT04096443

Wang JW *J Formos Med Assoc*. Mar 2019
Figure: https://gastro.org/practice-guidance/gi-patient-center/topic/fecal-microbiota-transplantation-fmt/

Themes/Limitations/Questions for Future

- Intersection of microbiology, gastroenterology, immunology, endocrinology and neurology
- Five way communication (microbes, intestinal network, endocrine system, immune system, brain)

Limitations:

- EAE is not MS-many studies in mice
- Human studies small numbers
- Hard to get good control populations (microbiome easily affected by medications)
- Getting stool samples before clinical symptoms
- Because system is complex, many confounding variables

Future:

- New advances will allow for new studies (sequencing, metabolomics)
- This field highlights importance of experimental models
- Important for looking at shapshots in time-pre-clinical phase/treatment phase
- Understanding brain gut connection at important times like birth and aging
- Personalized medicine
- How can microbiome be modified (diet/antibiotics/probiotics/prebiotics/fecal transplant)?
- Which bacteria to target? Single species (microbial network analysis)
- If bacteria are targeted, are the effects temporary or permanent?

Thank you!

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