# Update on the Role of the Gut Microbiome in Health and Disease

61st Annual NMAFP Family Medicine Seminar

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# Objectives

By the end of this presentation participants will be able to

1) List 3 ways that the gut microbiome contributes to the development of a healthy human
2) Describe 3 disease processes for which alteration of the gut microbiome may be therapeutic
3) Cite recent review articles linking the microbiota to health and disease

# Disclosures

None

# Definitions

MICROBIOME = the gene complement of a community

MICROBIOTA = a collection of microorganisms existing in the same place a the same time

Robinson CJ, Bohannan BJM, Young VB. Table 1. Microbial ecology definitions. "From Structure to Function: the Ecology of Host-Associated Microbial Communities." Microbiol. Mol. Biol. Rev, September 2010. 74(3): 453-476.

# Genes

Human genome 26 K (1)

3.3 million unique genes in the human gut

150 times the human genome (2)

1-Venter JC et al. The sequence of the human genome. Science. 2001; 291: 1304-1351.

2-Zhu B, Wang X, Li L. Human Gut microbiome: the second genome of human body. Protein Cell. 2010 Aug 1(8): 718-25.

# Human gut microbiota

- Bacteria
- Archaea (*Methanobrevibacter*)
- Viruses (5% of gut bacteria code for prophage proteins)
- Eukaryotes (e.g. fungi—*Candida*, *Malassezia*, *Saccharomyces;* helminths)

# What types of bacteria are found in the human gut?

Over 1,000 bacterial species characterized

Include

- Bacteriodaceae
- Clostridiaceae
- Prevotellaceae
- Bifidobacteriaceae
- Saccharomycetaceae
- Methanobacteriaceae

Rajilic-Stojanovic M, de Vos WM. The first 1000 cultured species of the human gastrointestinal microbiota. FEMS Microbiology Reviews. 38(5). 1 Sept 2014, 996-1047.

# Mycobiome

Fungal microbiome

5.1 million species of fungi

300 cause disease in humans

Predominant species in healthy humans:

- Saccharomyces
- Mallassezia
- Candida

Nash AK, et al. The gut mycobiome of the Human Microbiome Project healthy cohort. Microbiome. 2017. 5:153.

# What factors influence microbiome establishment?

- Delivery mode
- Breast feeding
- Geography
- Diet
- Early exposure to antibiotics

# Delivery mode

- Babies delivered vaginally appear to acquire *Lactobacillus*, *Prevotella* and *Sneathea* species from passage through the birth canal
- Babies born via c-section had bacterial communities found on the skin such as *Staphylococcus*, *Corynebacterium*, and *Propionibacterium*

Dominguez-Bello MG, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. 2010. Proc Natl Acad Sci USA, 107(26): 11971-11975.

# Why does this matter?

Higher rates of problems such as asthma, allergies, obesity, celiac disease and dental caries, among others, have been observed in children born by c-section.

# Breast feeding

Higher levels of E coli, C difficile, B fragilis and lactobacilli in exclusively formula-fed infants

“Term infants who were born vaginally at home and were breastfed exclusively seemed to have the most ‘beneficial’ gut microbiota, with the highest numbers of bifidobacteria and lowest numbers of C difficile and E coli.”

Penders J, et al. Factors influencing the composition of the intestinal microbiota in early infancy. August 2006. Pediatrics. 118 (2): 511-521.

# Human milk oligosaccharides

Digested by specific Bifidobacterium and Bacteriodes species

Prevent pathogen attachment to mucosa surfaces

Modulate epithelial and immune cell responses

Reduce risk for NEC

Sialic acid—brain development

Bode L. Human milk oligosaccharides: Every baby needs a sugar mama. Glycobiology. 2012 Sept 22(9):1147-82.

# Immune development

## Adaptive immunity—proinflammatory and regulatory T intestinal T cells

Ohnmacht C. et al. The microbiota regulates type 2 immunity through RORγT+ T cells. Science. 2015 Aug 28; 349 (6251): 989-93.

## Innate immunity—aged neutrophils are depleted by reduced microbiota and may promote tissue injury

Zhang D, et al. Neutrophil ageing is regulated by the microbiome. Nature. 2015 Sept 24; 525(7570): 528-32.

Both from Thomas S. et al. The Host Microbiome Regulates and Maintains Human Health: A Primer and Perspective for Non-Microbiologists. Cancer Res. 2017 April 15; 77(8): 1783-1812.

# Autoimmune and Allergic Diseases

222 infants in Northern Europe birth to age 3

Early autoimmune disease more common in Finland and Estonia (2-6 x more allergy; 5-6 x more T1D)

Compared to Russia Karelia

Finnish and Estonian infants had more immune activation of the LPS from Bacteroides

Inhibits immune signaling and endotoxin tolerance

Vataren T et al. Variations in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans. Cell 5 May 2016. 165(4): 842-853.

# Host physiology

- Food digestion—2 catabolic pathways
- Saccharolytic—sugars to SCFAs
- Protein fermentation to SCFAs, ammonia, amines, thiols, phenols and indoles
- Intestinal mucosal surface barrier

Tang WHW. Kitai T.Hazen SL. Gut Microbiota in Cardiovascular Health and Disease. Circulation Research. 2017 March 30; 120: 1183-1196.

# Dysbiosis

Microbiota produce harm via

- Qualitative and quantitative changes in flora
- Changes in the metabolic activity of the flora
- Change in the flora distribution


- La Fata G, Weber P, Mohajeri MH. Probiotics and the Gut Immune System: Indirect Regulation. Probiotics & Antimicro. Prot. 31 August 2017.

# Dysbiosis associations

Inflammatory bowel disease

Multiple sclerosis

Type 1 and Type 2 diabetes

Allergies

Asthma

Autism

Cancer

Lloyd-Price J et al. The healthy human microbiome. Genome Med. 2016; 8:51.

# Diet

## Short term consumption of animal-based food increased bile-tolerant microbes

David LA et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014 Jan 23; 505(7484):559-63.

## Vegans, vegetarians and omnivores have different microbiomes

Zimmer J, et al. A vegan or vegetarian diet substantially alters the human colonic faecal microbiota. Eur J Clin Nutri. 2012 Jan; 66(1):53-60.

# Obesity pathophysiology

Gut microbiome, host genotype and lifestyle interaction

Turnbaugh PJ. An obesity-associate gut microbiome with increased capacity for energy harvest. 2006 Dec 21. Nature. 444(7122): 1027-31.

# Obesity-childhood abx

"Repeated exposures to broad-spectrum antibiotics ages 0 to 23 months is associated with early childhood obesity."

Baily et al. Association of Antibiotics in Infancy With Early Childhood Obesity. JAMA Pediatr. 2014; 168(11): 1063-1069.

# Objective 1 Summary

Mode of delivery, breastfeeding and early exposures affect the development of the microbiome .

The gut microbiome contributes to the development of a health human through modulation of the immune system, metabolism and intestinal mucosal surface dynamics.

# Objective 2

Describe 3 disease processes for which alteration of the gut microbiome may be therapeutic.

# Metabolic syndrome

Double-blind randomized controlled pilot study

20 men w/ metabolic syndrome randomized to single lean vegan-donor or autologous FMT.

+ detectable changes in intestinal microbiota

No change in TMAO production or inflammation

Smits LP et al. Effect of a Vegan Fecal Microgiota Transplantation on Carnitine- and Choline-Derived Trimethylamine-N-Oxide Production and Vascular Inflammation in Patients with Metabolic Syndrome. J Am Heart Assoc. 2018 Mar 26; 7(7).

# Prebiotics and T2DM

Daily supplementation of 10g of inulin, resistant starches or fructo-oligosaccharide-enriched inulin may benefit individuals with type 2 diabetes.

O'Connor S, Chouinard-Castonguay S, Gagnon C, Rudkowska I. Prebiotics in the management of components of the metabolic syndrome. Maturitas. 2017 Oct; 104: 11-18.

# Hypertension

- 2 rat models and a small cohort of patient
- Decreased microbial diversity
- Increased Firmicutes/Bacteriodetes ration
- Decreased acetate- and butyrate-producing bacteria
- Minocycline rebalanced the dysbiotic hypertension gut dysbiosis by reducing the F/B ratio

Yang T, et al. Gut dysbiosis is linked to hypertension. Hypertension, 2015 June; 65(6): 1331-40.

# Hypertension

SCFA metabolites regulate blood pressure via olfactory signaling pathways in the kidneys

Increased atherosclerosis from microbiota generate TMAO

Increased sympathetic activity

Nitrate-nitrite-nitric oxide signaling pathway

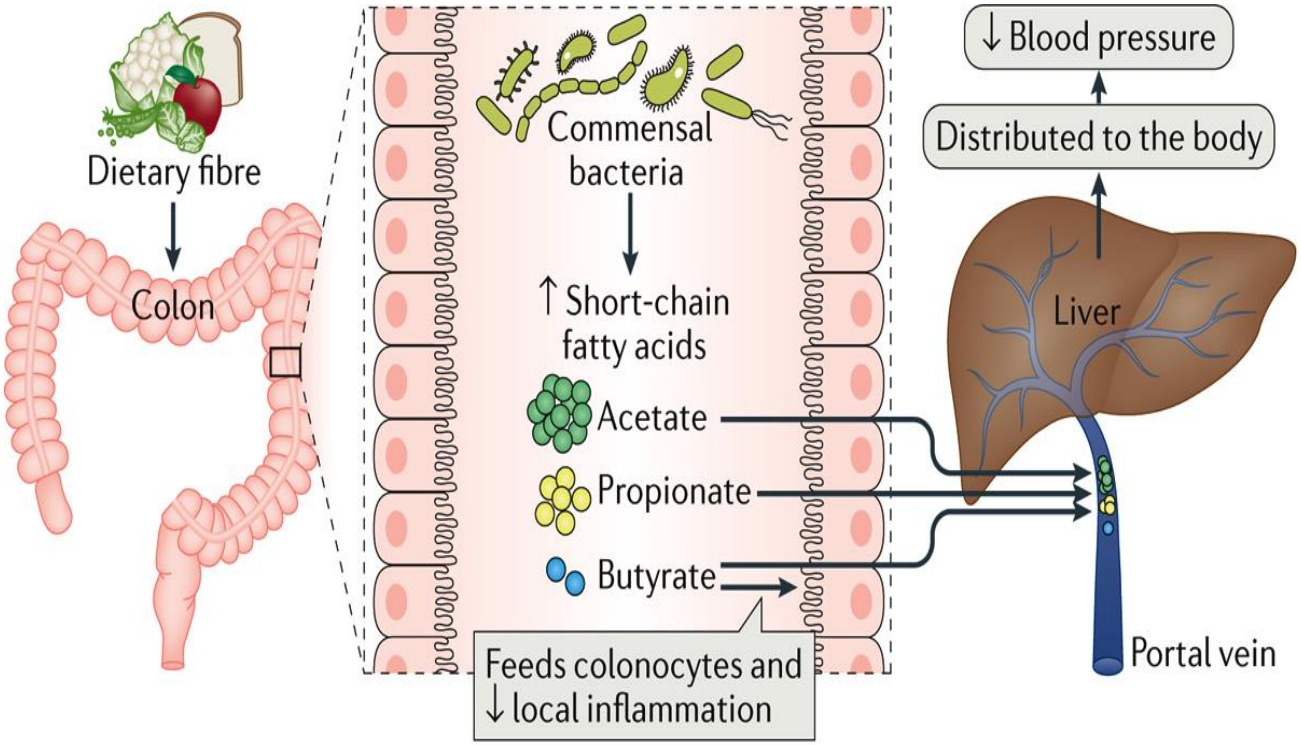
Khodor SA, Reichert B, Shatat IF. The Microbiome and Blood Pressure: Can Microbes Regulate Our Blood Pressure? Front Pediatr. 2017; 5: 138.

# Hypertension treatment?

“The meta-analysis of human studies supports that supplementation with probiotics reduces blood pressure.”

Robles-VeraI, et al. Antihypertensive Effects of Probiotics. Curr Hypertens Rep. 2017 April; 19(4): 26.

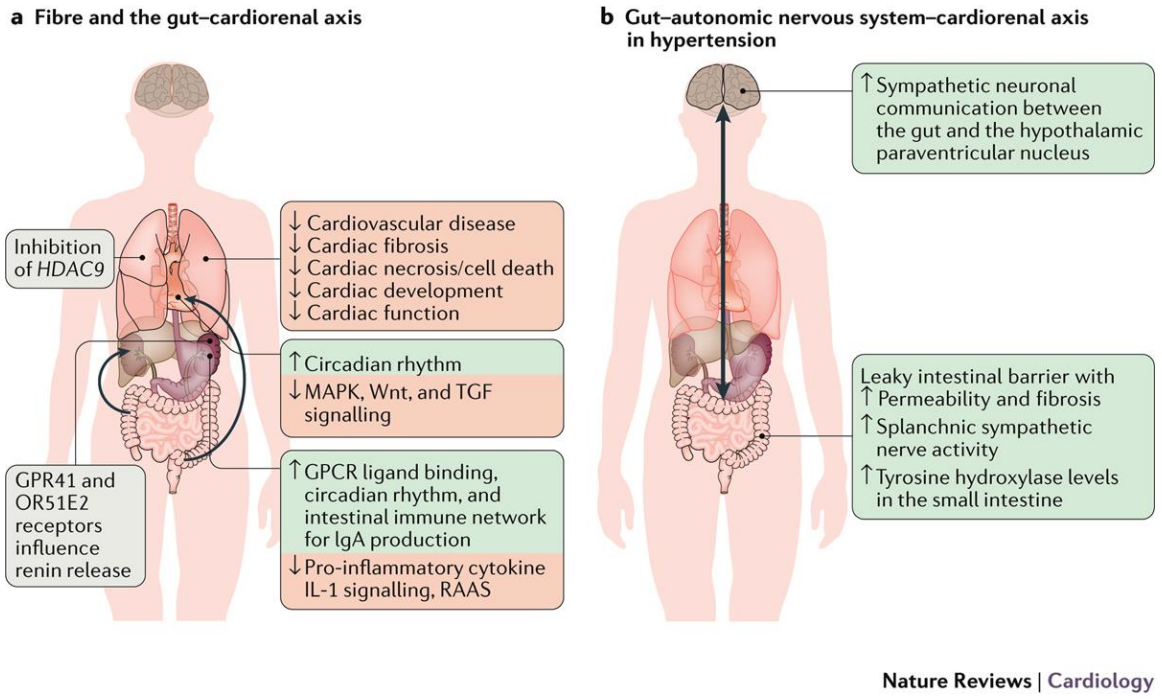
**Figure 1** Influence of diet on gut microbiota and blood pressure




Nature Reviews | Cardiology

Marques, F. Z. *et al.* (2017) Beyond gut feelings: how the gut microbiota regulates blood pressure
*Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2017.120

**Figure 2** Mechanisms of the gut–autonomic nervous system–cardiorenal axis that regulate blood pressure




Marques, F. Z. *et al.* (2017) Beyond gut feelings: how the gut microbiota regulates blood pressure *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2017.120

# SCFA-independent determinants

Trimethylamine N-oxide (TMAO) plasma levels in pts with chest pain predicted near- and long-term risks of MACE

Li, XS et al. Gut microbiota-dependent trimethylamine N-oxide in acute coronary syndromes: a prognostic marker for incident cardiovascular events beyond traditional risk factors. Eur Heart J. 2017 Mar 14; 38(11): 814-824.

# NAFLD

Mediterranean diet
Weight loss
Exercise most impacts liver fat

Romero-Gomez M et al. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol. 2017 Oct; 67(4): 829-846.

# GI disorders and emotions

FGID=functional GI disorders

Anxiety and depression are more common

Chronic stress stimulates the HPA axis by increasing release of adrenocorticotropic hormone from the hypothalamus

Triggers increased cortisol release from the adrenal cortex

Alters the mesolimbic brain reward system

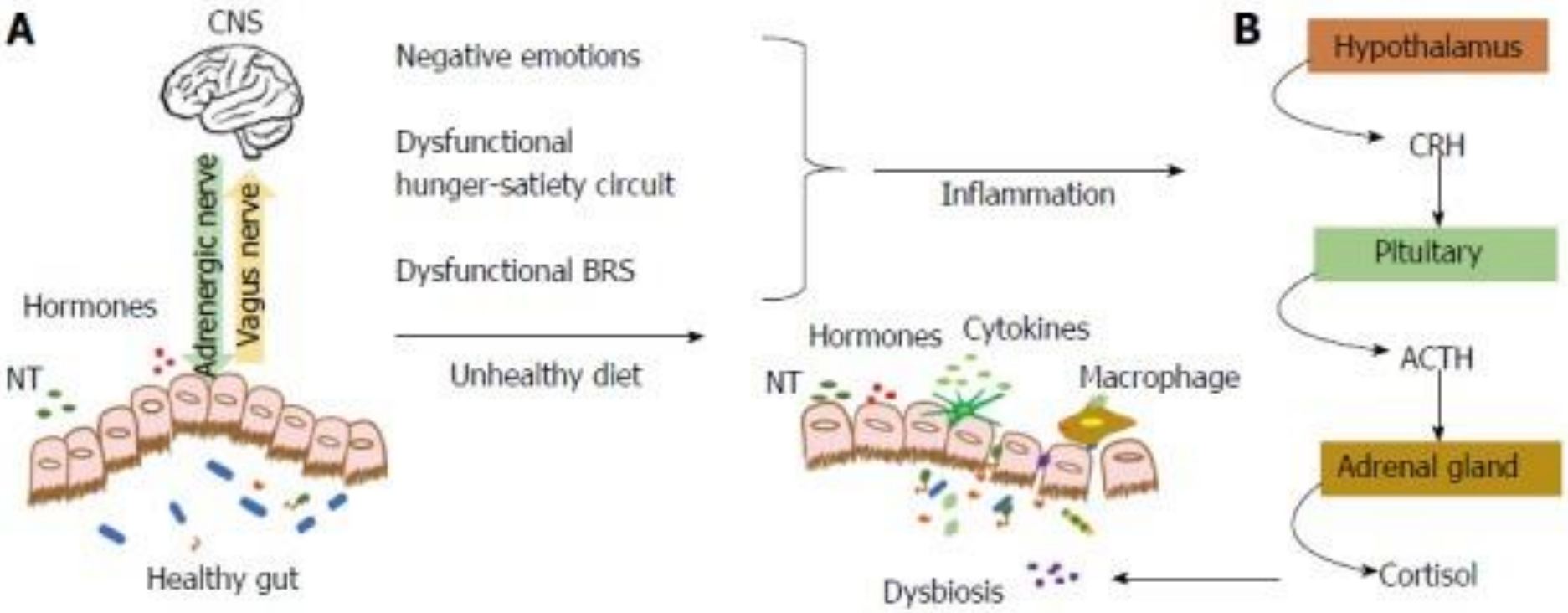



Figure 1 from Panduro A, Rivera-Iniquez, Sepulveda-Villegas M, Roman S. Genes, emotions and gut microbiota: The next frontier for the gastroenterologist. World J Gastroenterol 2017 May 7; 23(17): 3030-3042.

# Fecal microbial transplantation

$4^{th}$ and $16^{th}$ century China

C difficile, IBD, metabolic syndrome

Roux-en-Y gastric bypass surgery may work due to altered composition of gut microbiota

Challenges: regulation, safety, efficacy

De Groot PF, Frissen MN, de Clercq, Nieuwdorp M. Fecal microbiota transplantation in metabolic syndrome: History, present and future.

Gut Microbes. 2017; 8(3): 253-267.

# Objective 2

Metabolic syndrome

T2DM

Hypertension

heart disease

NAFLD

anxiety

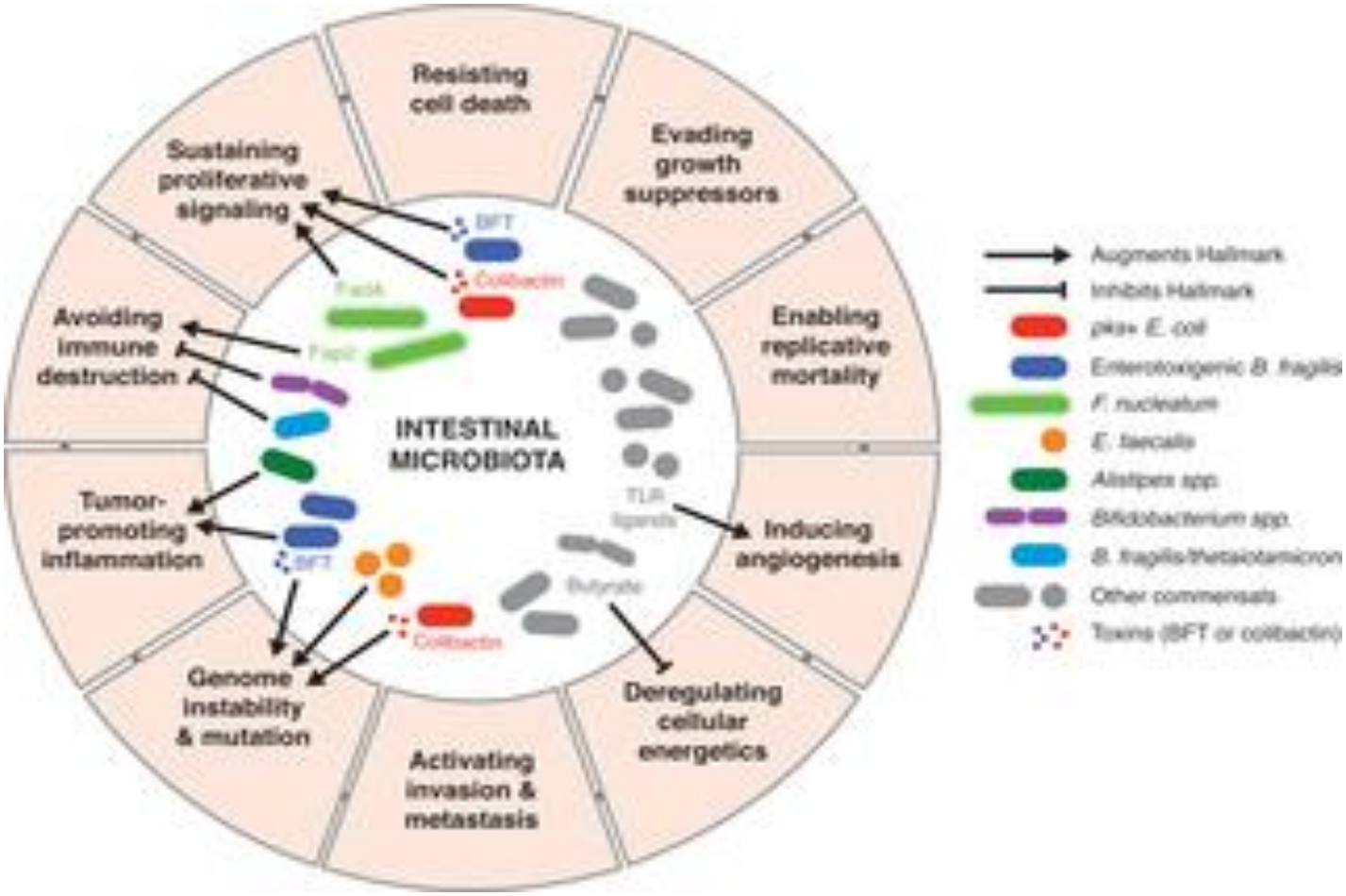
C dificile

# The microbiome and the hallmarks of cancer

Butyrate—anticancer effect by starving cancer cells which use glucose

Butyrate is a histone deactylase inhibitor—promotes apoptosis and inhibits cellular proliferation through epigenetic mechanisms

Donohoe DR et al. A gnotobiotic mouse model demonstrates that dietary fiber protects against colorectal cancer tumorigenesis in a microbiota- and butyrate-dependent manner. Cancer Discovery. American Association for Cancer Research; 2014; 4: 1387-1397.


Resisting cell death
Evading growth suppressors
Enabling replicative mortality
Inducing angiogenesis
Deregulating cellular energetics
Activating invasion & metastasis
Genome instability & mutation
Tumor-promoting inflammation
Avoiding immune destruction
Sustaining proliferative signaling
INTESTINAL MICROBIOTA
BFT
Colibactin
FadA
Fap2
TLR ligands
Butyrate
Augments Hallmark
Inhibits Hallmark
pks+ E. coli
Enterotoxigenic B. fragilis
F. nucleatum
E. faecalis
Alistipes spp.
Bifidobacterium spp.
B. fragilis/thetaiotaomicron
Other commensals
Toxins (BFT or colibactin)

# From

Fulbright LE, Ellerman M, and Arthur JC. The microbiome and the hallmarks of cancer. PLoS Pathog. 2017 Sept; 13(9): e1006480.

# CVD and gut microbial metabolites

"Elevated TMAO and its precursors were associated with increased risks of MACE and all-cause mortality independently of traditional risk factors."

Heianza Y, et al. Gut Microbiota Metabolites and Risk of Major Adverse Cardiovascular Disease Events and Death: A Systematic Review and Meta-Analysis of Prospective Studies." J Am Heart Assoc. 2017 Jun 29; 6(7).

# Cardiovascular disease

Unstable cardiac plaques “associated with reduced fecal levels of the genus Rosburiam and ….may thus be fostering inflammation by producing more proinflammatory molecules.”

Mechanism linking gut microbiota to severity of MI

TMAO (trimethylamine N-oxide) elevations associated with adverse cardiac risk and outcomes

Tang et al.

# Gut hypothesis of heart failure

- Decreased cardiac output and elevated congestion
- Intestinal mucosal ischemia and edema
- Increased bacterial translocation
- Increased circulating endotoxins and inflammatory cytokines
- Increased circulating TMAO
- Adverse ventricular remodeling

Tang et al.

# Heart failure treatment

DASH

Mediterranean

Decrease oxidative stress, homocysteine and inflammation

Modulate microbiome

Higher antioxidants and nitric oxide bioavailability

Conor P Kerley. A Review of Plant-based Diets to Prevent and Treat Heart Failure. Card Fail Rev. 2018 May; 4(1): 54-61.

# Gut biodiversity

Increased gut biodiversity is associated with less Western disease

Decreased gut biodiversity is associated with many diseases.

Justin and Erica Sonnenburg. The Good Gut: Taking Control of Your Weight, Your Mood and Your Long Term Health. 2015. Penguin Press.

# Recommendations for fiber intake

Males 19-50 years of age, 38 g/day

Females 19-50 years of age, 25 g/day

Pregnant female, 28 g/day

2015-2020 Dietary Guidelines for Americans:

“Choose fiber-rich fruits, vegetables and whole grains often.”

“The recommended dietary fiber intake is 14 grams per 1,000 calories consumed.”

# A healthy eating pattern includes:

A variety of vegetables from all of the subgroups—dark green, red and orange, legumes (beans and peas), starchy, and other.

Fruits, especially whole fruits

Grains, at least half of which are whole grains

# Healthy diet pattern

Anthropomorphic, dietary, physical activity and lifestyle evaluation—120 participants

Adherence to Mediterranean diet associated with lower E coli, higher bifidobacteria: E coli, increased acetate, higher defecation freq, and more GI symptoms.

Fast food associated with suppressed lactobacilli and butyrate-producing bacteria

Mitsou EK, et al. Adherence to the Mediterranean diet is associated with the gut microbiota pattern and gastrointestinal characteristics in an adult population.

Br J Nutr. 2017 Jun; 117(12):1645-1655.

# Exercise

Enriched biodiversity

Improved Bacteroides-Firmicutes ration

Stimulate bacteria protective against GI disorders and colon CA (SCFAs)

Reduced inflammation

Improve cognitive decline associated with HFD

Improve gut mucosa—increased Lactic acid bacteria

# Exercise

Low intensity-reduced stool transit and contact time

Endurance-increased toxicity due to decreased blood flow

Prolonged-increased intestinal permeability

# Exercise

Improved B:F with calorie restricted diet

Improved energy homeostasis and regulation

Juvenile exercise—increased lean body mass, positively impact brain function

Monda V et al. Exercise Modifies the Gut Microbiota with Positive Health Effects. Oxid Med Cell Longev. 2017; 2017: 3831972.

# Sleep

SF (sleep fragmentation) –higher LPS-binding protein

Gut microbiota altered within 2 weeks

IH (intermittent hypoxia)—6 weeks of IH followed by 6 weeks of normoxia did not fully normalize gut microbial alteration

Farre N et al. Sleep Apnea Morbidity: A Consequence of Microbial-Immune Cross Talk? Chest. 14 March 2018. https://doi.org/10.1016/j.chest.2018.03/001

# Obstructive sleep apnea

OSA modeled in rats by inflating a tracheal balloon during sleep

Normal chow diet-OSA did not affect blood pressure

High fat diet—BP increased

High fat diet + OSA associated with decreased butyrate producing bacteria

Transplant of dysbiotic cecal contents from hypertensive OSA rats on high fat diet caused HTN similar to the donor

Durgan DJ, et al. Role of the Gut Microbiome in Obstructive Sleep Apnea-Induced Hypertension. Hypertension. 2016 Feb; 67(2): 469-474.

# Gut-brain axis

Evidence links gut microbiota to

Autism

ADHD

Schizophrenia

Depression

Parkinson's disease

Cenit MC, Sainz Y, Codoner-Franch P. Table 2. Influence of gut microbiota on neuropsychiatric disorders. 14 Aug 2017. World J Gastroenterol. 23 (30): 5486-5498.

# Objective 3

Recent review articles detail the connections between the microbiome and microbiota to cancer, CVD, heart failure, Mediterranean diet, exercise, dysfunctional sleep, and brain function.

# Conclusion

The human gut microbiome is linked to most chronic diseases plaguing our nation

What can be done to improve health and reduce disease burden?

Thank you!