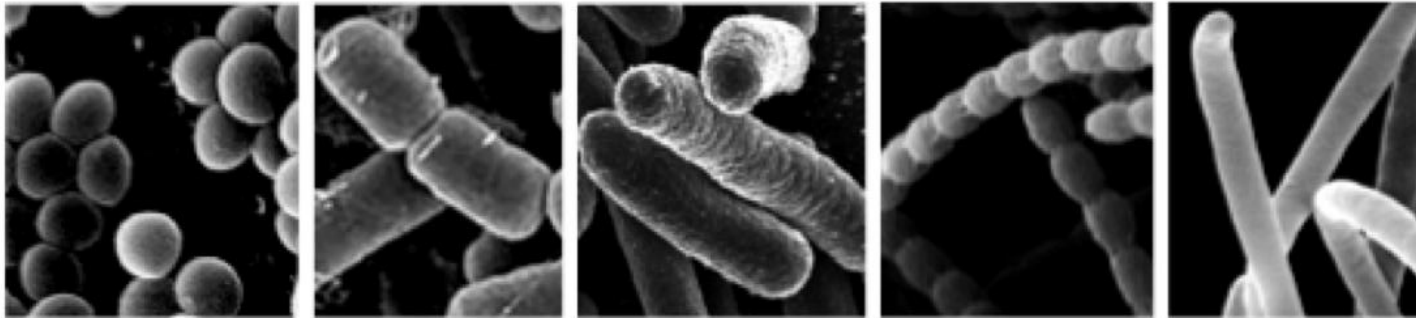


Chronic Diseases and Gut Flora, Correlation and Therapeutic Approaches



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University Hospital UKSH, Campus Kiel

Germany

Kuala Lumpur, July 2019

“Death is located in the gut”
(Hippocrates)

Physiologic Role of the Human Microbiome

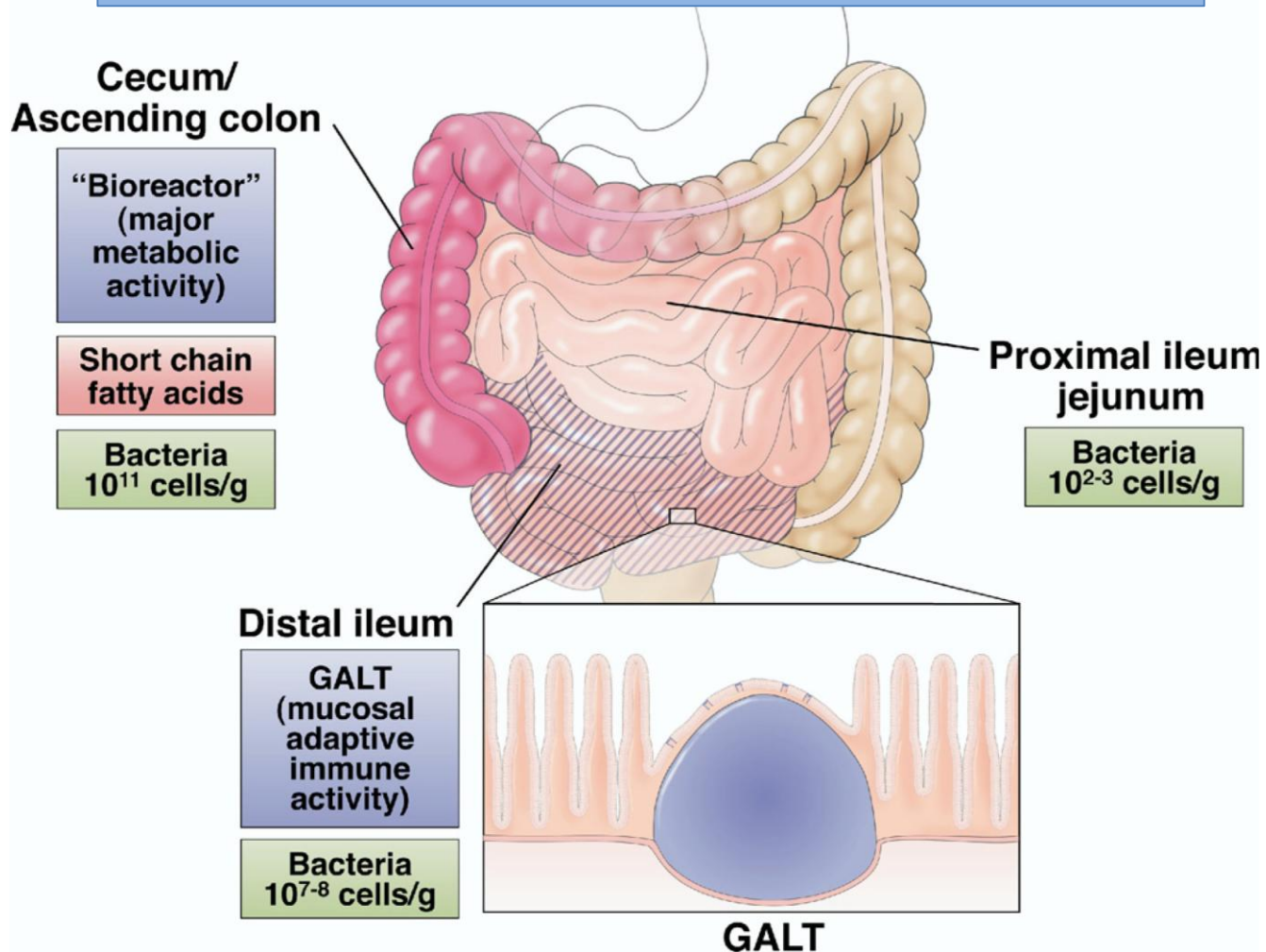


Figure 3. Preferred sites of commensal/probiotic interaction with the gut. Cecum/ascending colon is a "bioreactor" with the greatest amounts of bacteria, metabolic activity, and SCFA fermentation. Concentration of SCFA diminishes along the colon. The distal ileum is enriched in GALT (Peyer's patches) and is the dominant site of luminal sampling and mucosal adaptive immune activity.

Different Organ Compartments Harbor Different Strains of Bacteria

Table 1 The content and composition of microflora in different parts of the human digestive tract in health

Habitats of the digestive tract	The number of microorganism cells per 1 g of content		Dominant microflora
	Lumen microflora	Surface microflora	
Mouth	10^8 – 10^9	10^{11} – 10^{12}	<i>Streptococcus</i> (60–90 %), <i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>Propionibacterium</i> , <i>Bacteroides</i> , <i>Actinomyces</i>
Stomach	10^2 – 10^3	10^5 – 10^6	Acid resistant <i>Lactobacillus</i> , <i>Streptococcus</i> , <i>Staphylococcus</i>
Proximal small intestine	10^3 – 10^5	10^{10} – 10^{11}	<i>Streptococcus</i> , <i>Lactobacillus</i> , <i>Enterococcus</i> , <i>Bifidobacterium</i> , <i>Escherichia</i> ,
Distal small intestine	10^8 – 10^{10}	10^{10} – 10^{12}	<i>Lactobacillus</i> , <i>Escherichia</i> , <i>Enterococcus</i> , <i>Bacteroides</i> , <i>Bifidobacterium</i>
Colon	10^{11} – 10^{12}	10^{10} – 10^{12}	<i>Bifidobacterium</i> , <i>Lactobacillus</i> , <i>Propionibacterium</i> , <i>Bacteroides</i> – 90–95 %, <i>Escherichia</i> , <i>Enterococcus</i> – 5–10 %

Food nutrients impact on the diversity of the microbiome and correlate with healthy or unhealthy metabolism and disease prevention or chronic disease development, respectively

	Interaction with the gut microbiota	Gut microbiota changes	Health effects
Fibre or carbohydrates ^{16,72,78,80,81}	Principal carbon and energy source for colonic microorganisms; fermented to beneficial metabolites such as short-chain fatty acids	Increase in <i>Bifidobacterium</i> spp, Bacteroidetes, <i>Akkermansia muciniphila</i> , <i>Clostridium</i> spp, and <i>Prevotella</i> spp	Enhanced intestinal barrier integrity, insulin sensitivity, and intestinal motility; decreased inflammation; improved lipid metabolism; enhanced intestinal motility; and increased satiety
Proteins ^{16,82}	Major source of nitrogen for the gut microbiota, and essential for their assimilation of carbohydrates, gases, and putrefactive fermentation products	Increase in Bacteroidetes and a decrease in <i>Bifidobacterium</i> spp	Weight loss and increased risk of atherosclerosis and colonic diseases
Saturated fats ^{16,19,74,81-83}	Indirect modulation of the gut microbiota via bile acid metabolism	Increase in Firmicutes, Proteobacteria, and <i>Bilophila</i> spp, and a decrease in Bacteroidetes and <i>Bifidobacterium</i> spp	Increased endotoxaemia, bodyweight, and adiposity, and reduced insulin sensitivity
Unsaturated fats ^{16,19,74,81-83}	Indirect interaction with the gut microbiota via effects on bile acid secretion and composition	Increase in <i>Bifidobacterium</i> spp, <i>Lactobacillus</i> spp, and <i>Akkermansia muciniphila</i>	Decreased inflammation and adiposity
Polyphenols ⁸⁴⁻⁸⁶	Act as an energy substrate for some beneficial bacteria and inhibit the growth of pathogenic bacteria	Increase in <i>Bacteroides</i> spp, <i>Lactobacillus</i> spp, <i>Bifidobacterium</i> spp, and <i>Akkermansia muciniphila</i> , and a decrease in <i>Clostridium</i> spp	Reduced body-mass index, waist circumference, blood pressure, and blood glucose; and improved lipid metabolism

Table: Effects of the diet on the gut microbiota and host metabolism

MICROBIOLOGY

Fighting Obesity with Bacteria

Alan W. Walker and Julian Parkhill

The human large intestine harbors a complex community of microorganisms (microbiota) that affect many aspects of our physiology and health (1). Numerous lines of evidence, particularly from rodent models, have suggested that the intestinal microbiota may play a role in the development of obesity. On page 1079 of this issue, Ridaura *et al.* (2) demonstrate that the microbiota from lean or obese humans induces similar phenotypes in mice and, more remarkably, that the microbiota from lean donors can invade and reduce adiposity gain in the obese-recipient mice if the mice are fed an appropriate diet.

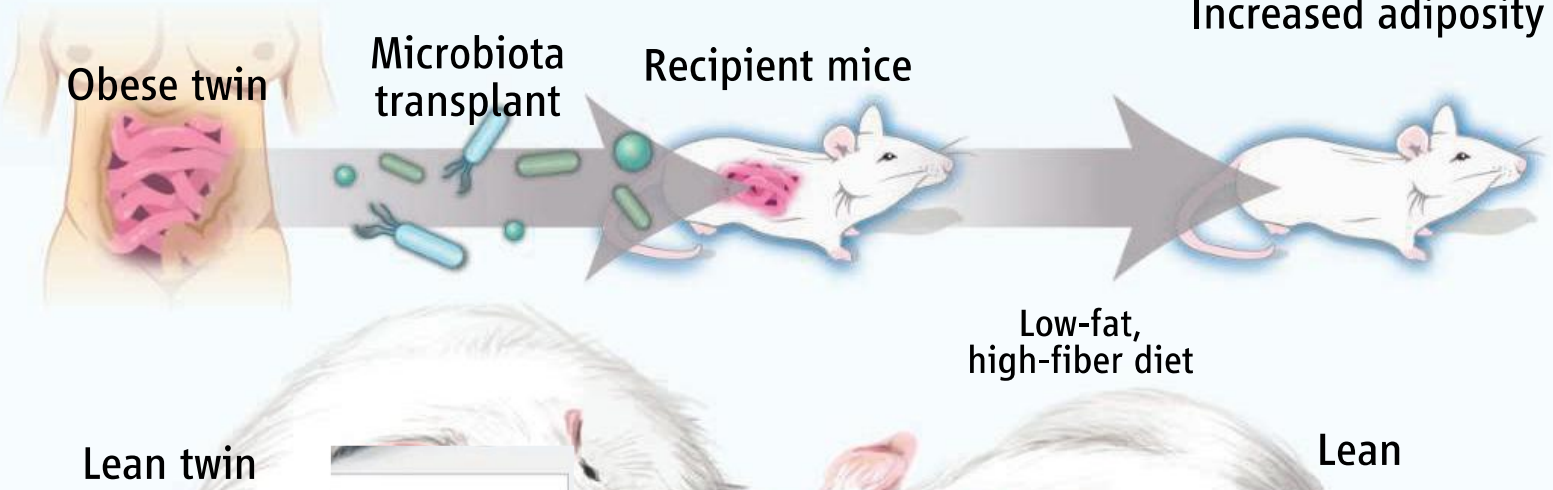
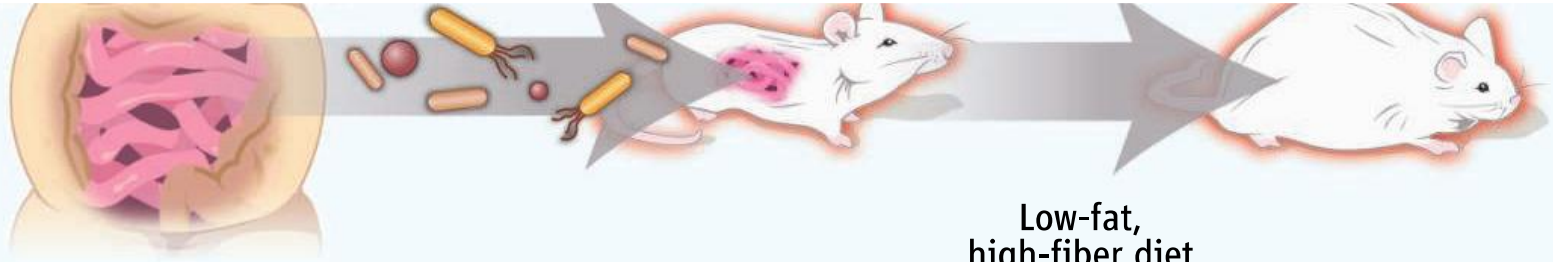
with reduced adiposity, did not reduce adiposity in the Ob^{ch} mice. This indicates that more complex bacterial interactions underlie protection against increased body mass and associated metabolic disturbance.

Ridaura *et al.* also identified diet as an important factor in the transmission of microbiota and associated host phenotype. Lean twin-derived bacterial strains effectively colonized and ameliorated excess adiposity in Ob^{ch} mice when the recipients were fed a low-fat, high-fiber diet. This was not the case when the mice were fed a diet that was high in saturated fat but low in fiber.

Intestinal bacteria from lean humans can confer protection against fat gain in experimental mice.

The findings support some emerging hypotheses regarding potential mechanisms by which the microbiota can affect host weight gain. One of the main activities of the intestinal microbiota is to break down and ferment dietary fibers into short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. The host absorbs these acids, and humans obtain perhaps 5 to 10% of daily energy requirements from them (3). Ridaura *et al.* show that the microbiota in Ln mice produces greater amounts of SCFAs, particularly propionate and butyrate, and digests more of the plant fiber present in the mouse's

A





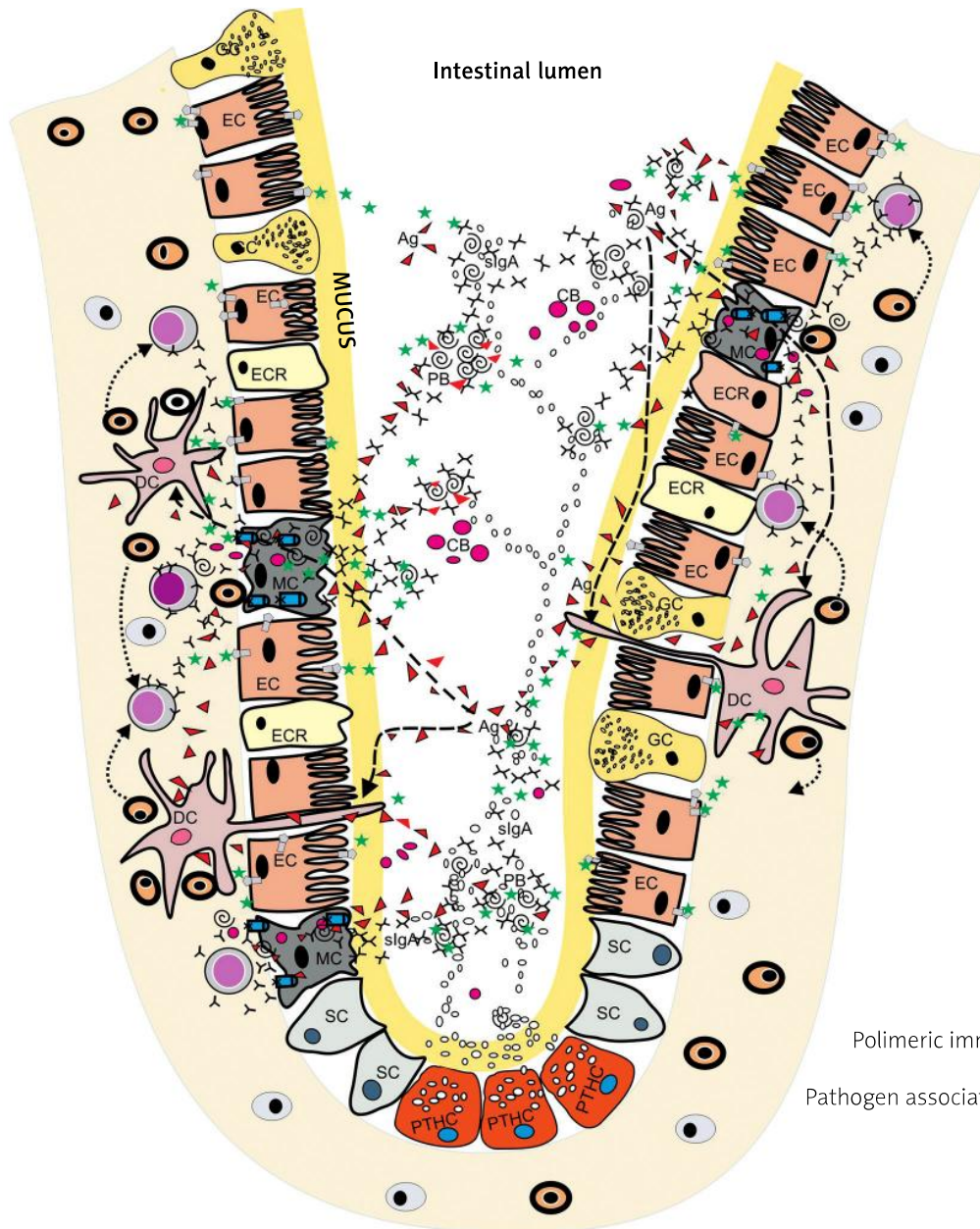
Low-fat, high-fiber diet



















Ineffective
microbiota
transmission

High-fat, low-fiber diet

Ineffective
microbiota
transmission

The Human Gut Constitutes the Biggest Immune Compartment of the Human Body



- Dendritic cells (DC) 
- Goblet cell (GC) 
- Plasma cell 
- M cell (MC) 
- Stem cell (SC) 
- Lymphocytes B 
- Lymphocytes T 
- Endocrine cell (ECR) 
- Enterocyte (EC) 
- Paneth cell (PTHC) 
- Antigen (Ag) 
- Toll-like receptor (TLR) 
- Immunoglobulin A (IgA) 
- Secretory IgA (sIgA) 
- Polimeric immunoglobulin A receptor (pIgR) 
- Pathogen associated molecular patterns (PAMP) 
- Comensal bacteria (CB) 
- Pathogenic bacteria (PB) 

What are Major Threats to the Human Microbiome?

Exposure to Nutrition and Environment



HHS Public Access

Author manuscript

Cell Metab. Author manuscript; available in PMC 2016 June 07.

Published in final edited form as:

Cell Metab. 2014 November 4; 20(5): 779–786. doi:10.1016/j.cmet.2014.07.003.

Starving our Microbial Self: The Deleterious Consequences of a Diet Deficient in Microbiota-Accessible Carbohydrates

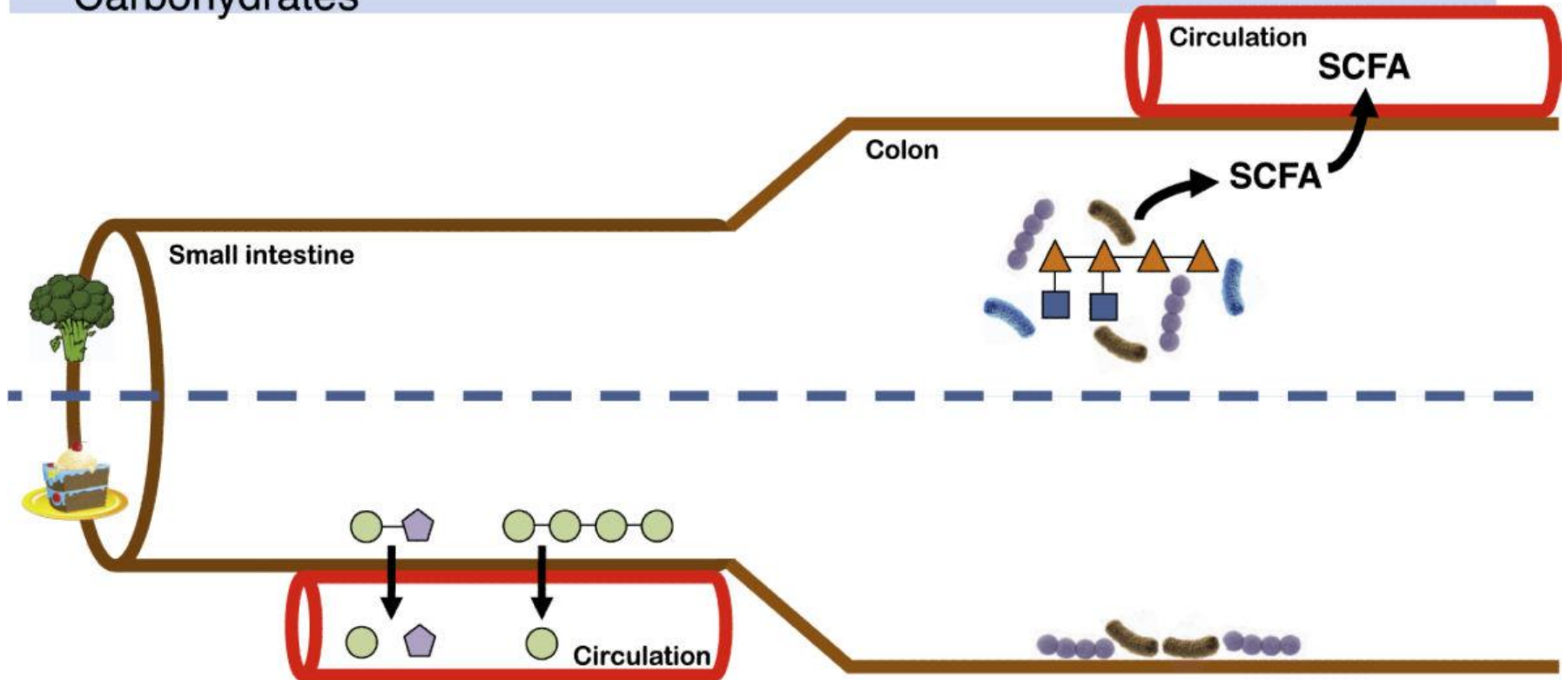
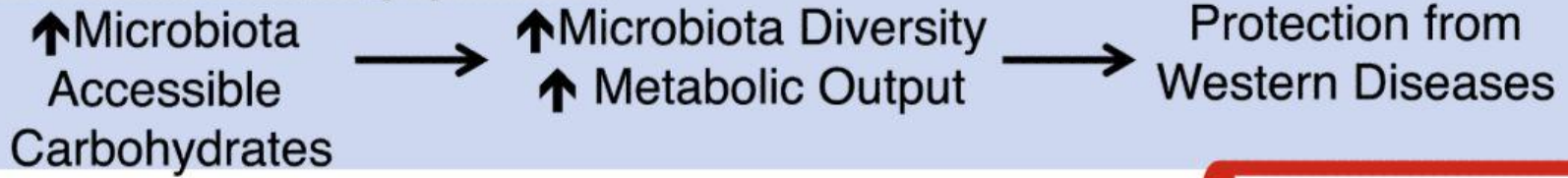
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Abstract

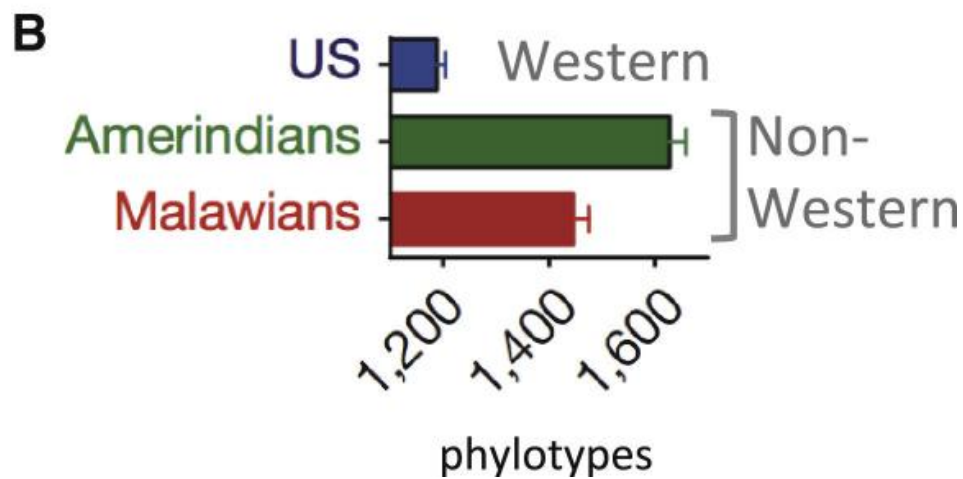
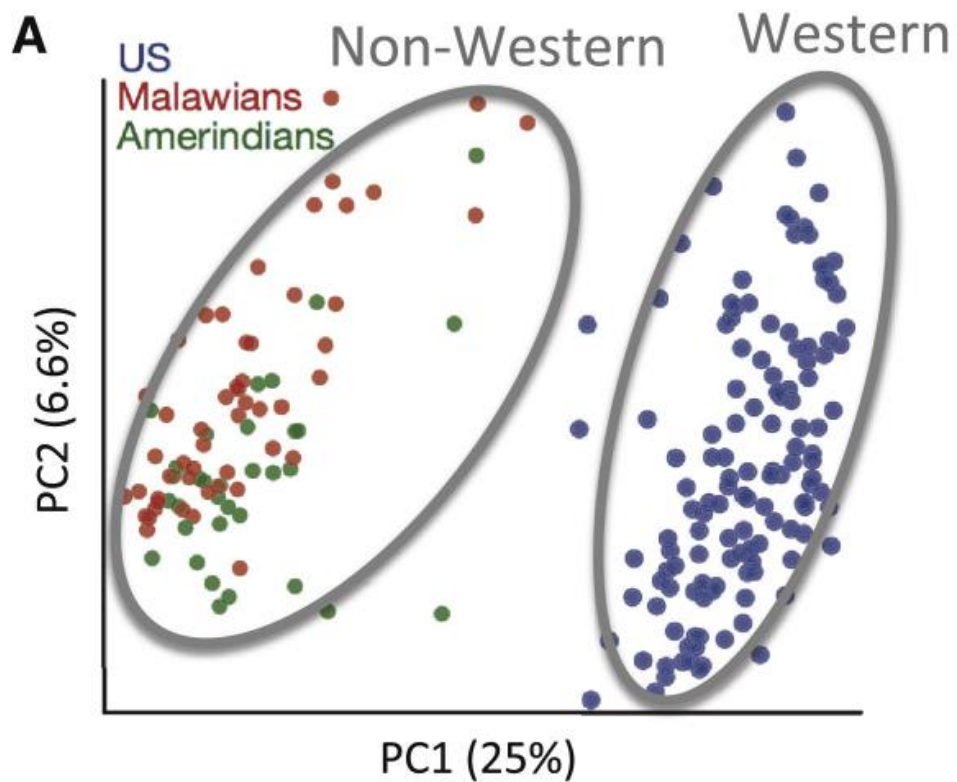
The gut microbiota of a healthy person may not be equivalent to a healthy microbiota. It is possible that the Western microbiota is actually dysbiotic and predisposes individuals to a variety of diseases. The asymmetric plasticity between the relatively stable human genome and the more malleable gut microbiome suggests that incompatibilities between the two could rapidly arise. The Western lifestyle, which includes a diet low in microbiota-accessible carbohydrates (MACs), has selected for a microbiota with altered membership and functionality compared to those of groups living traditional lifestyles. Interactions between resident microbes and host leading to immune dysregulation may explain several diseases that share inflammation as a common basis. The low-MAC Western diet results in poor production of gut microbiota-generated short-chain fatty acids (SCFAs), which attenuate inflammation through a variety of mechanisms in mouse models. Studies focused on modern and traditional societies, combined with animal models, are needed to characterize the connection between diet, microbiota composition, and function. Differentiating between an optimal microbiota, one that increases disease risk, and one that is causative or potentiates disease will be required to further understand both the etiology and possible treatments for health problems related to microbiota dysbiosis.

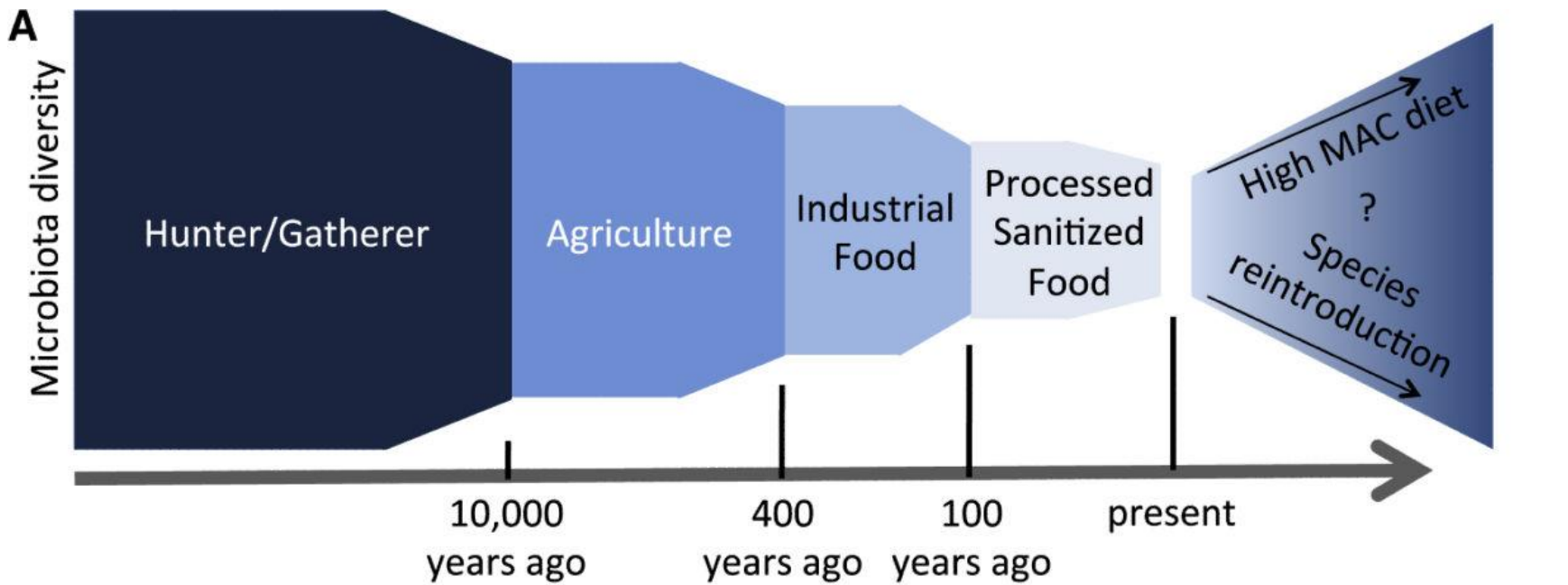
Scenario 1: traditional populations



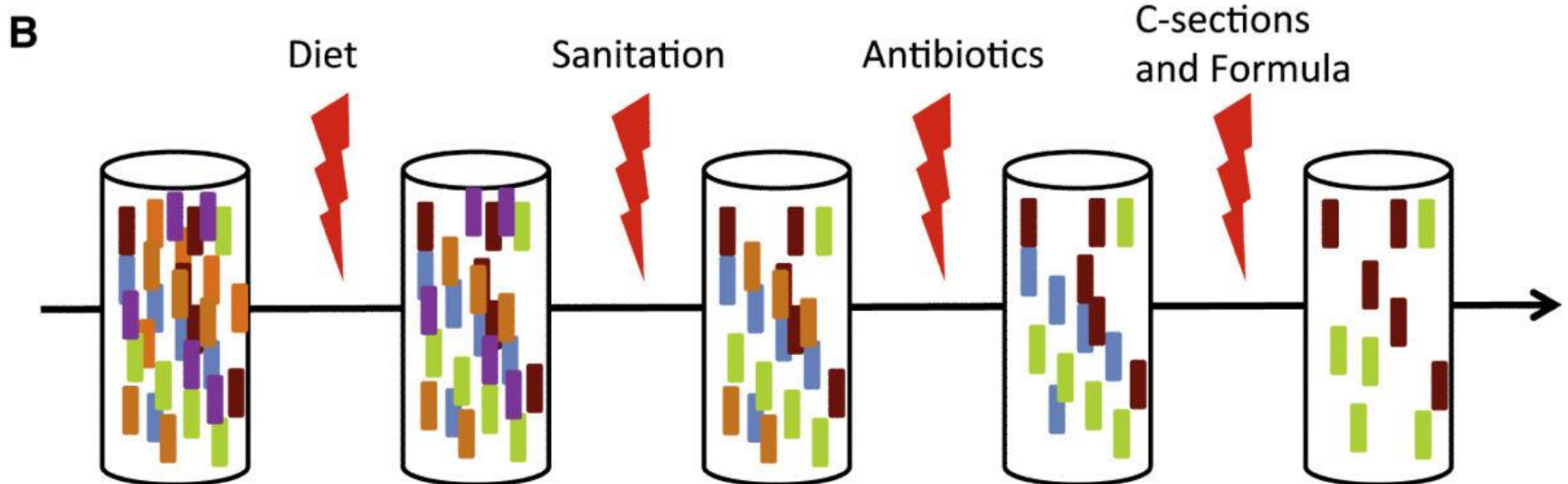
Scenario 2: industrialized populations







HFCS = high fructose corn syrup

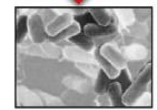
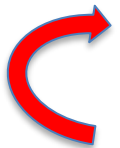


The bacterial translocation process leading to metabolic disease

Microbiota



Microbiota eubiosis



Microbiota dysbiosis

Pesticide
Herbicide
Heavy metals
HFCS / AGEs

Bacterial Translocation

Intestinal immune defense

Bacteroidetes/
Firmicutes
/Actinobacteria

AMP

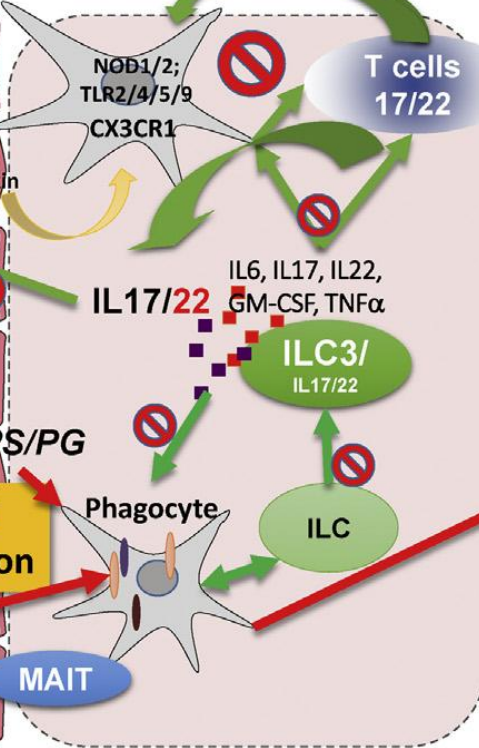
Mucosal dysbiosis

LPS/PG
xenobiotics,
antigens,
radicals...

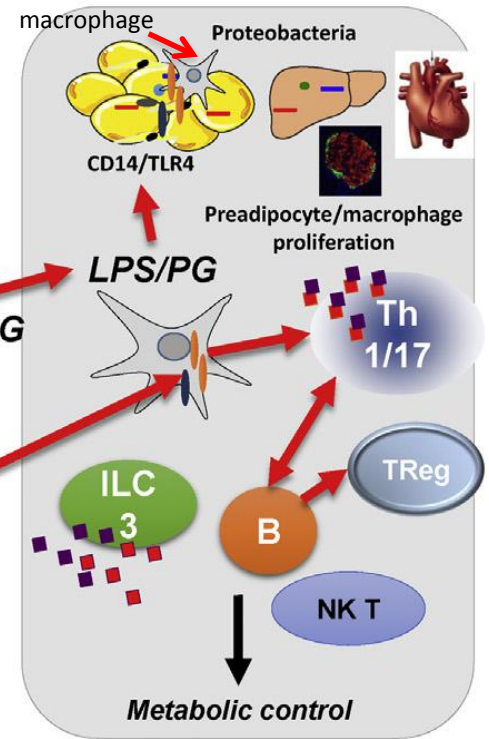
Firmicutes
/Proteobacteria

Bacterial translocation

Phagocyte



Target tissue inflammation

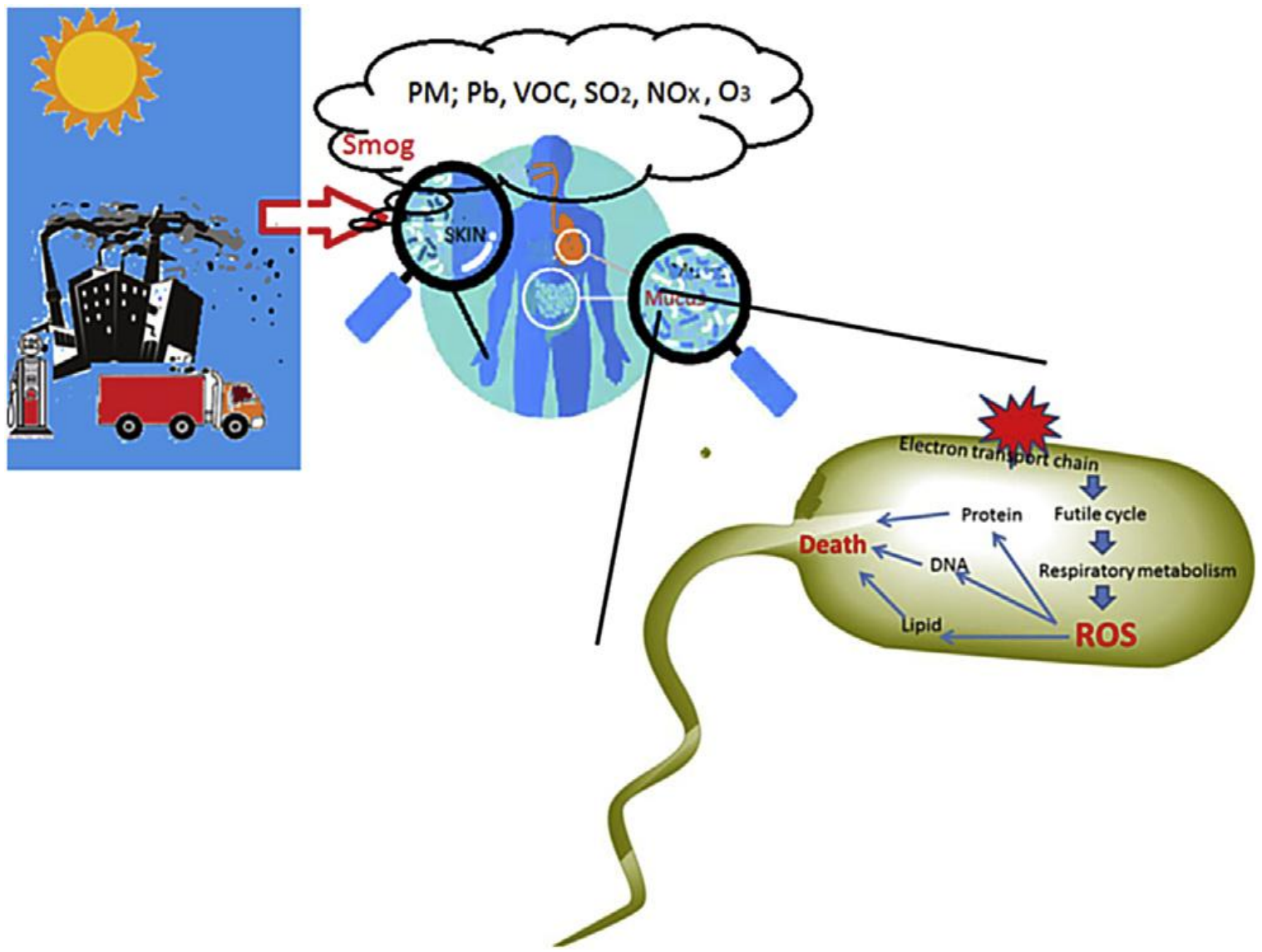


ENVIRONMENT



Figure 1. Smoke haze from peat fires shrouds the centre of the provincial capital of Palangkaraya, Central Kalimantan, October 2015 (photo source: Suzanne Turnock and Outrop). (Online version in colour.)

Smog induces oxidative stress and microbiota disruption



Premature Mortality by Country Domestic and Transboundary Contributions

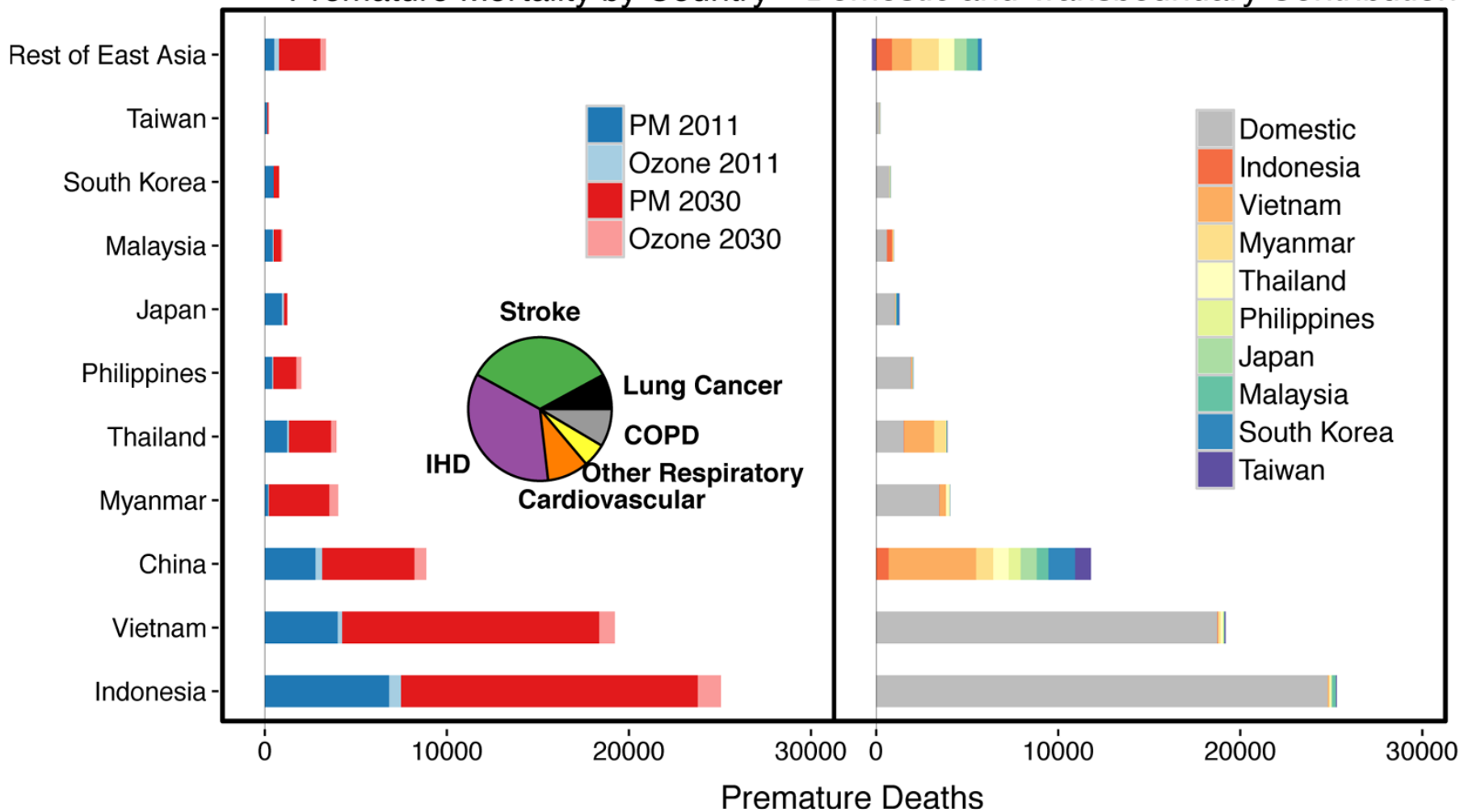
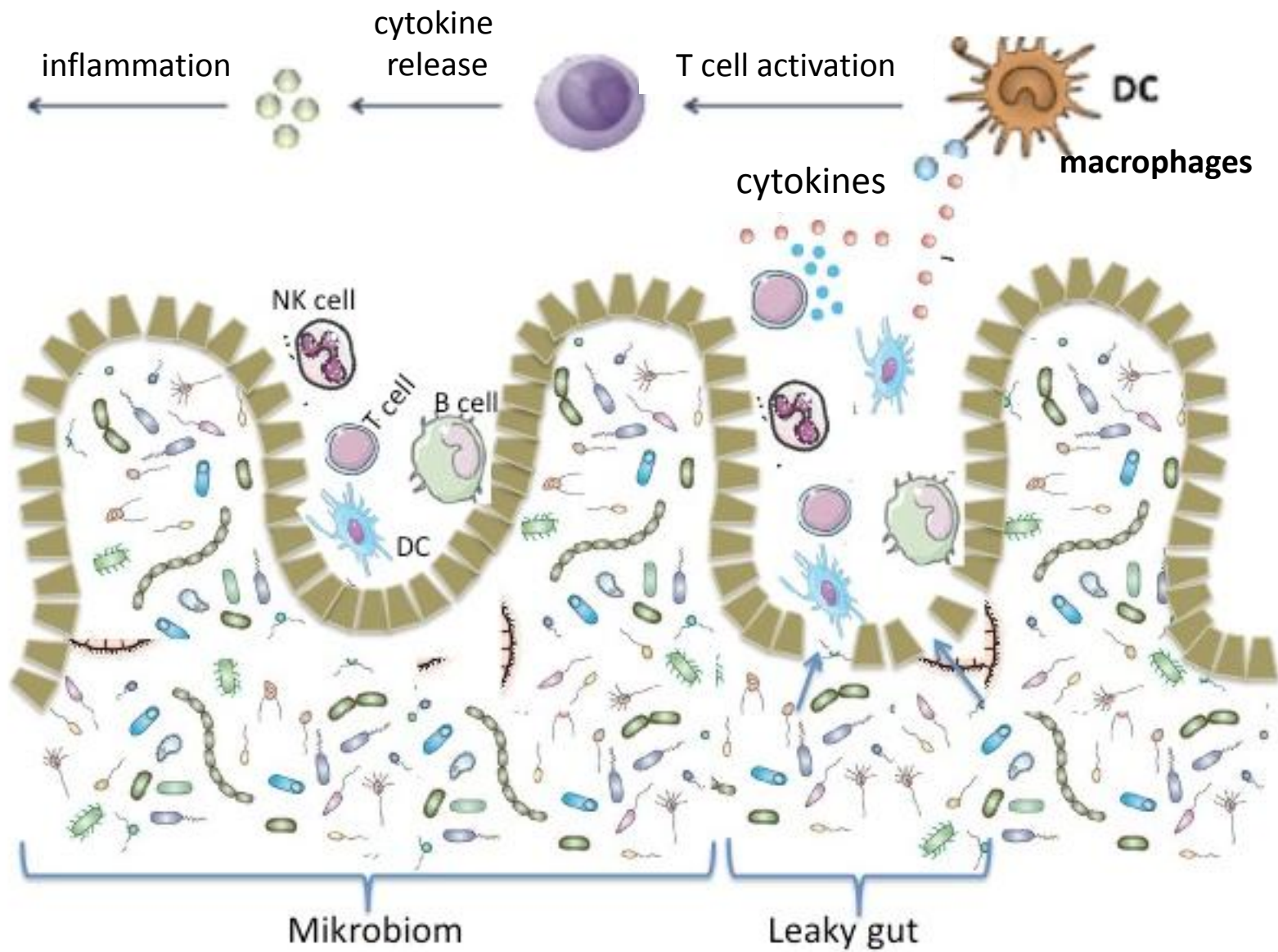
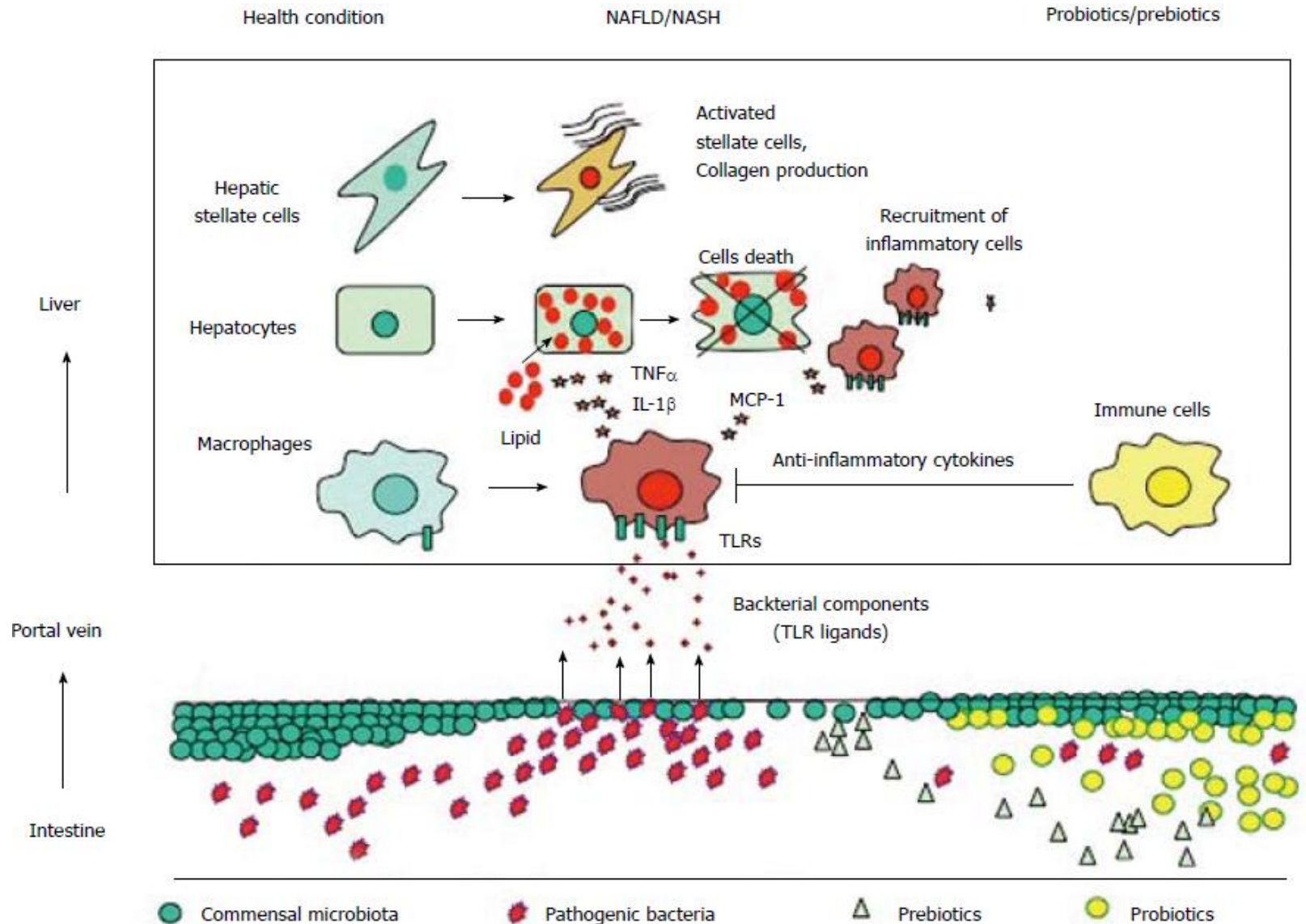


Figure 4. Coal-related mortality due to emissions in Southeast Asia (countries in [Table 1](#)). The left panel shows the premature deaths in individual countries. Premature deaths due to 2011 emissions are shown in blue, and increases between 2011 and projected 2030 emissions are shown in red (population-normalized results are shown in [Table S4](#)). Deaths due to PM_{2.5} and ozone are shown separately. The fraction of PM_{2.5}-related mortality by cause is shown in the pie chart as an average for the whole region in 2030 (IHD ≡ ischemic heart disease, COPD ≡ chronic obstructive pulmonary disease). All ozone-related mortality is from respiratory diseases. The right panel shows the 2030 coal-related mortality in each country broken down by contributions from domestic and transboundary sources (see [SI Figure S5](#) for the domestic and transboundary contributions in 2011). Source countries responsible for transboundary pollution are identified in the legend. As computed here, mortality in China and Rest of East Asia (not included in [Table 1](#)) is solely from transboundary pollution. The mortality totals in the right panel are the sums of the contributions from the national simulations with vs without coal emissions for the individual countries in [Table 1](#); because of chemical and CRF nonlinearities they may be greater than the mortality totals in the left panels.



Microbiome Dysbiosis and Steatotic Liver Development



Antibiotics in early life and obesity

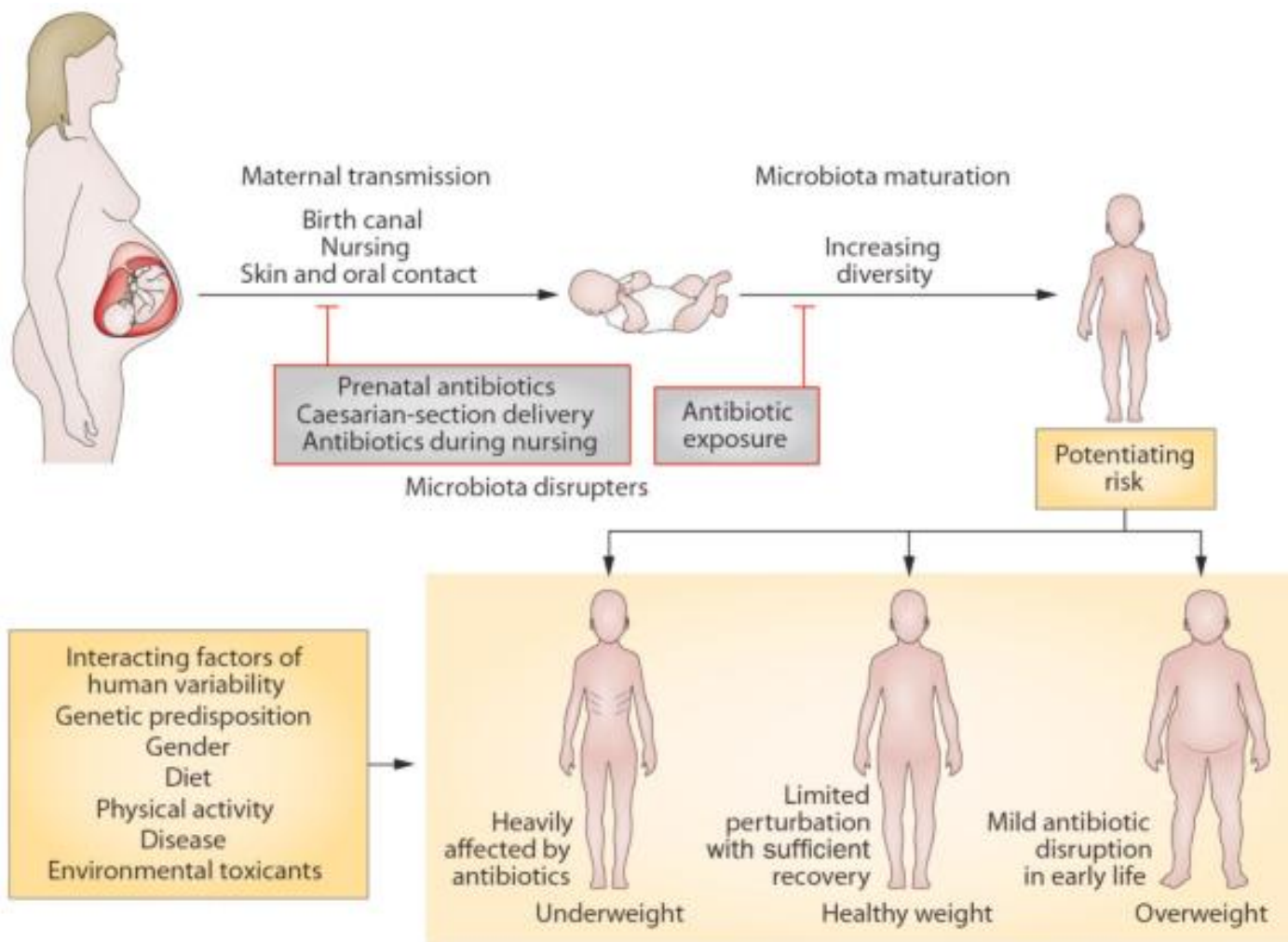
Laura M. Cox and **Martin J. Blaser**

Department of Medicine, New York University School of Medicine, VA Medical Center - Room 6026W, 423 East 23rd Street, New York, NY 10010, USA

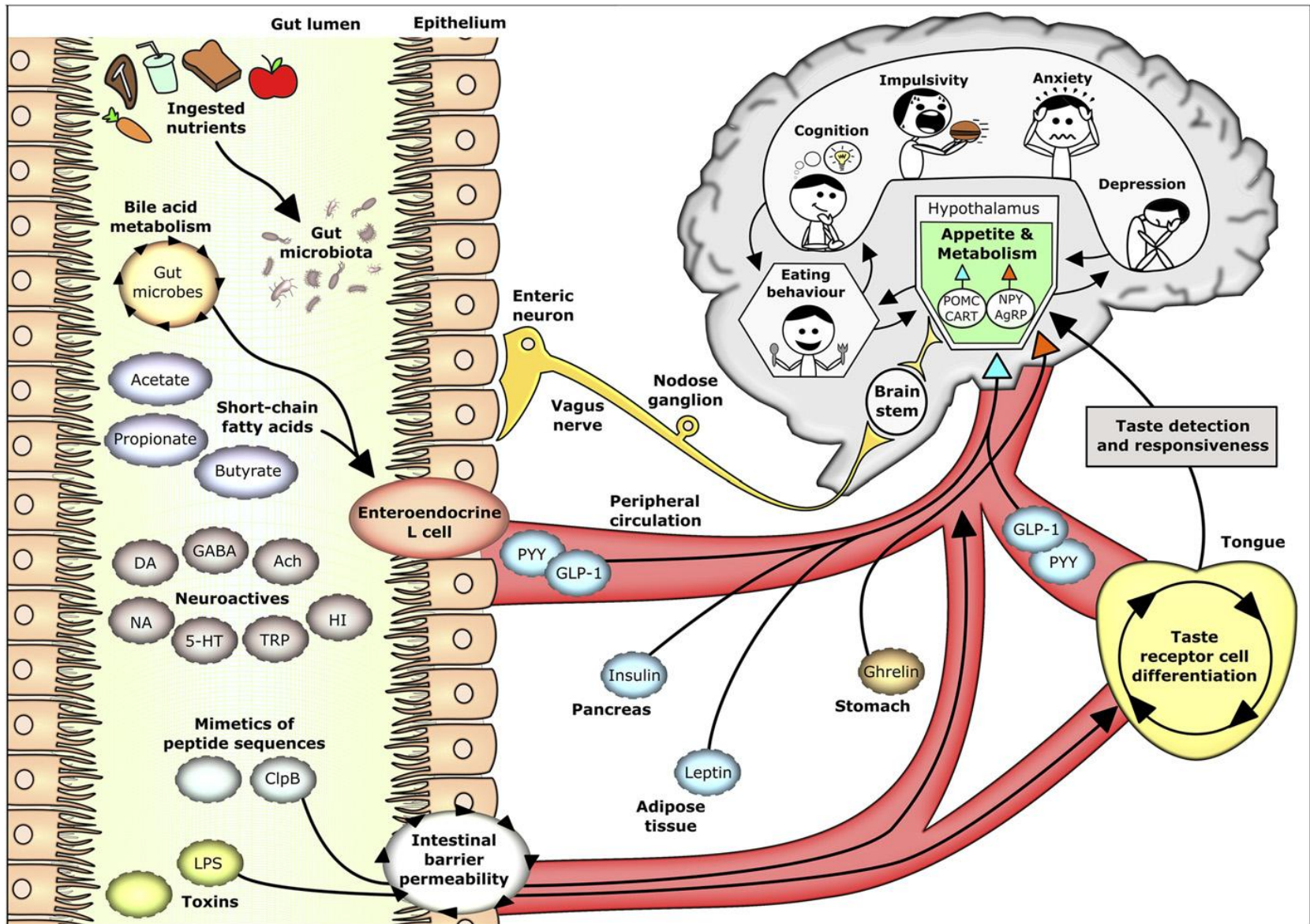
Abstract

The intestinal microbiota can influence host metabolism. When given early in life, agents that disrupt microbiota composition and consequently its metabolic activity, can influence body mass of the host by either promoting weight gain or stunting growth, which is consistent with effects of the microbiota on development. In this Perspective, we posit that microbiota disruptions in early-life can have long-lasting effects on body weight in adulthood. Furthermore, we examine the dichotomy between antibiotic-induced repressed or promoted growth and review the experimental and epidemiological evidence that supports these phenotypes. Considering the characteristics of the gut microbiota in early life as a distinct dimension of human growth and development, as well as comprehending its susceptibility to perturbation, will allow for increased understanding of human physiology and could lead to development of interventions to stem current epidemic diseases, such as obesity and types 1 and 2 diabetes mellitus.

Impact of Dysbiosis on Pregnancy and Childhood



Microbiota-Gut-Brain Axis: Modulator of Host Metabolism and Appetite^{1,2}



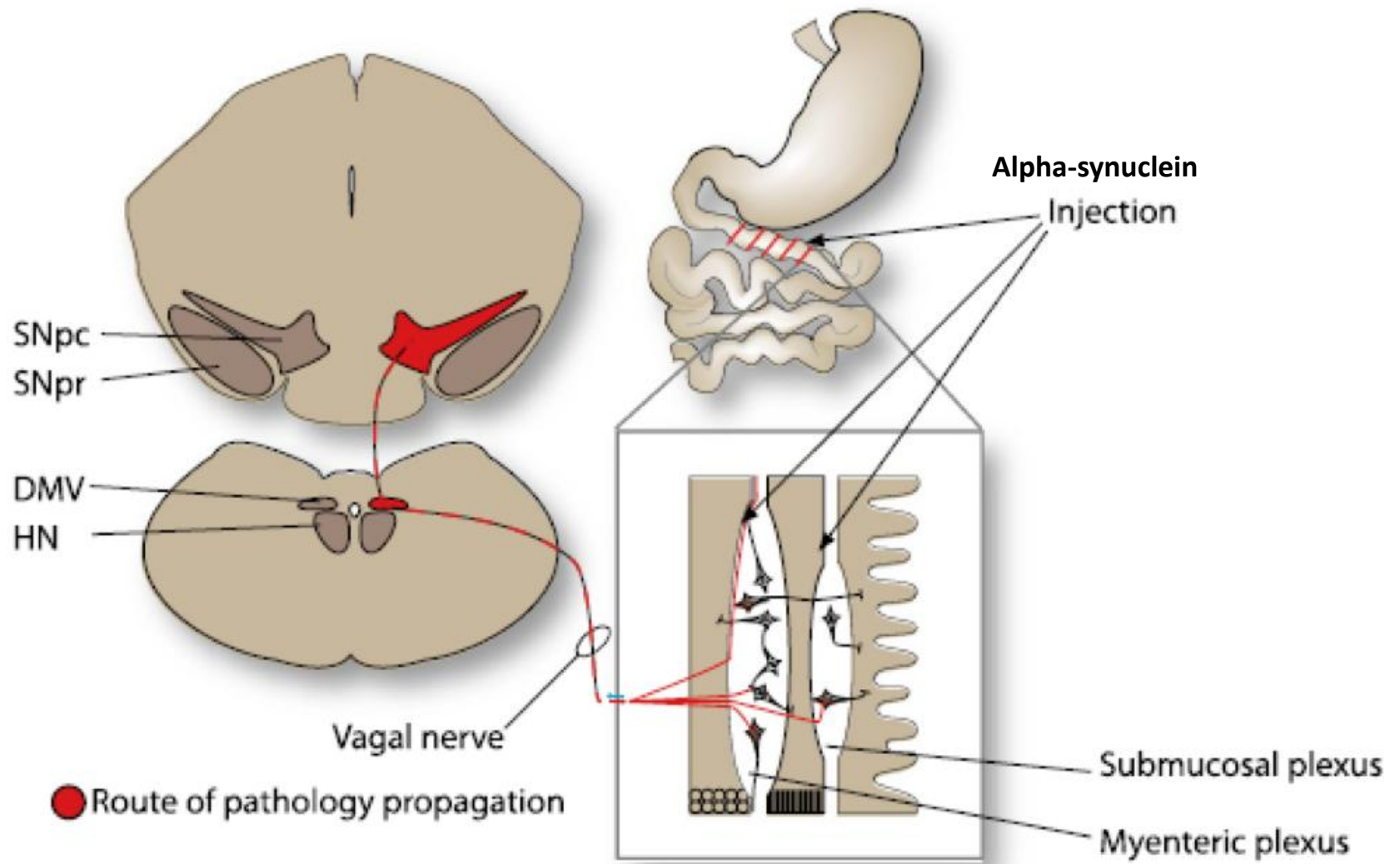
Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats

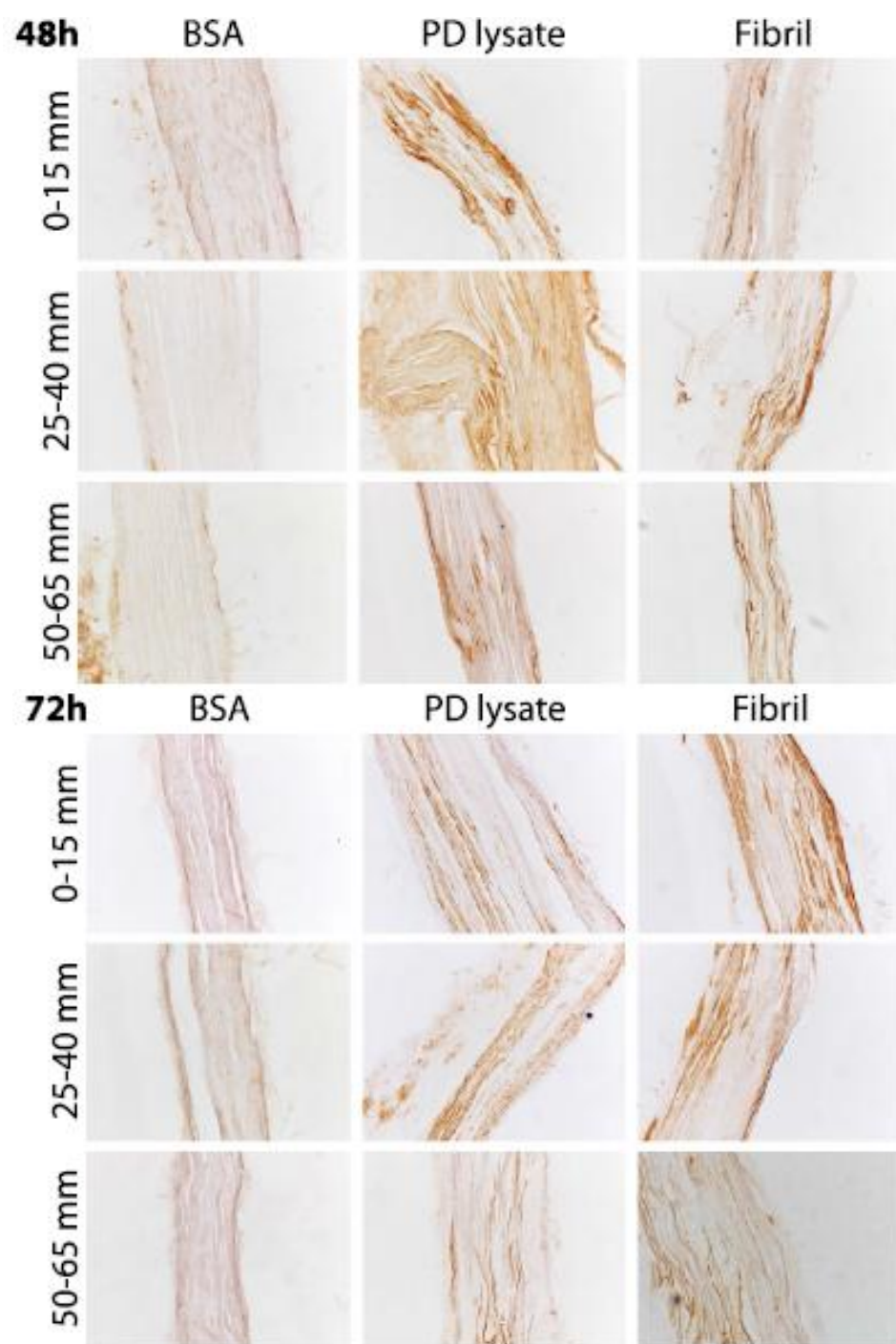
Staffan Holmqvist · Oldriska Chutna · Luc Bousset · Patrick Aldrin-Kirk · Wen Li · Tomas Björklund · Zhan-You Wang · Laurent Roybon · Ronald Melki · Jia-Yi Li

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Abstract The cellular hallmarks of Parkinson's disease (PD) are the loss of nigral dopaminergic neurons and the formation of α -synuclein-enriched Lewy bodies and Lewy neurites in the remaining neurons. Based on the topographic distribution of Lewy bodies established after autopsy of brains from PD patients, Braak and coworkers hypothesized that Lewy pathology primes in the enteric nervous system and spreads to the brain, suggesting an active retrograde transport of α -synuclein (the key protein

component in Lewy bodies), via the vagal nerve. This hypothesis, however, has not been tested experimentally thus far. Here, we use a human PD brain lysate containing different forms of α -synuclein (monomeric, oligomeric and fibrillar), and recombinant α -synuclein in an *in vivo* animal model to test this hypothesis. We demonstrate that α -synuclein present in the human PD brain lysate and distinct recombinant α -synuclein forms are transported via the vagal nerve and reach the dorsal motor nucleus of the vagus in the brainstem in a time-dependent manner after





Migration of alpha-synuclein from the upper intestine to the brain

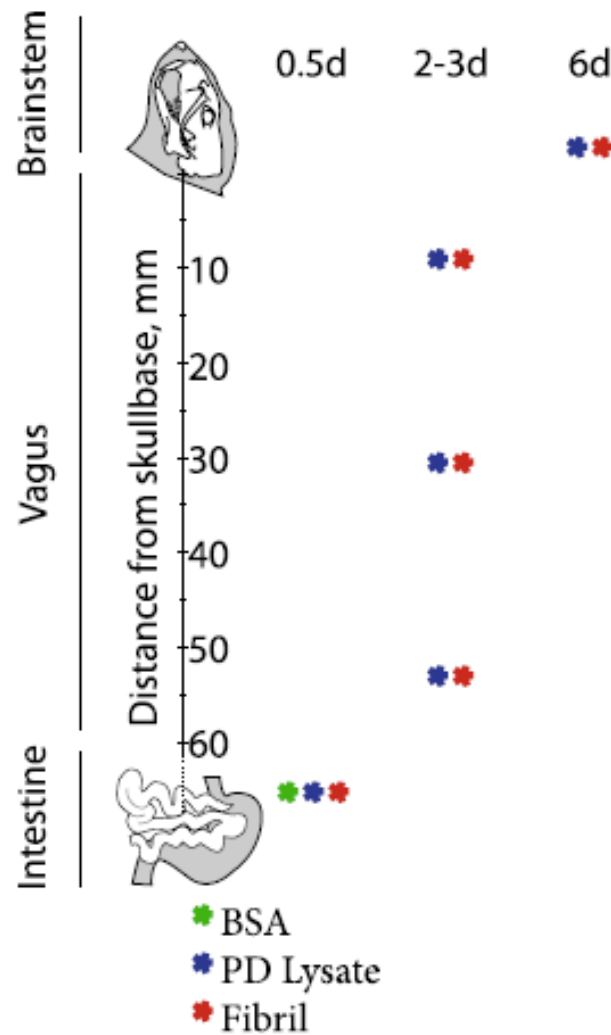


Fig. 7 An overview of uptake and transport of BSA and α -synuclein in the PD brain lysate or synthetic recombinant α -synuclein fibrils, in the intestines, along the vagal nerve and in the medulla oblongata, at different time points

Accepted Article

Role of colonic microbiota in colorectal carcinogenesis: A systematic review

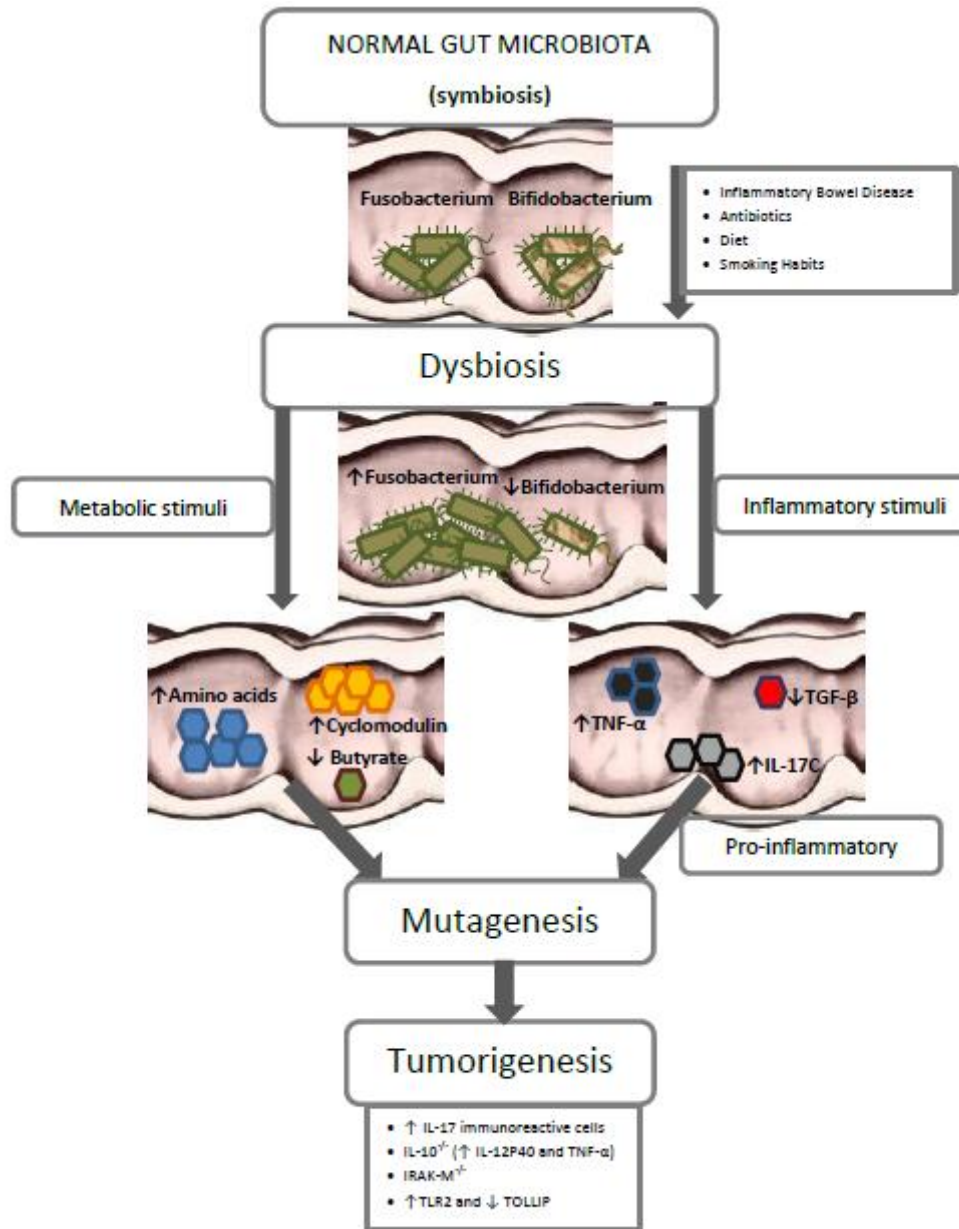
Marta Borges Canha

DOI: [10.17235/reed.2015.3830/2015](https://doi.org/10.17235/reed.2015.3830/2015)

Link: [PDF](#)

Please cite this article as: Borges Canha M. Role of colonic microbiota in colorectal carcinogenesis: A systematic review. Rev Esp Enferm Dig 2015. doi: 10.17235/reed.2015.3830/2015.





The role of the microbiota in inflammation, carcinogenesis, and cancer therapy

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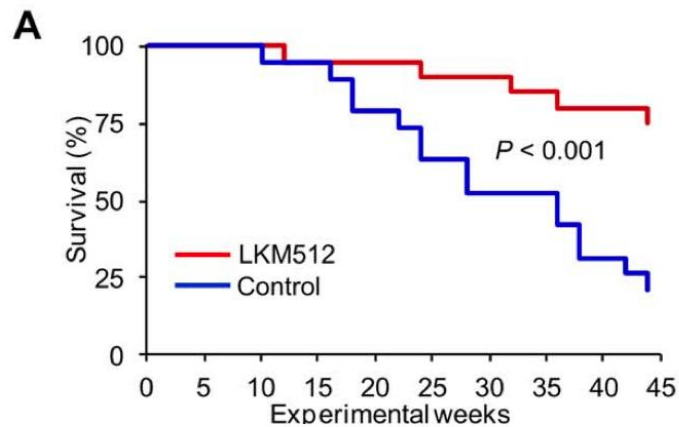
⁴ Université Paris-Sud, Kremlin Bicêtre, France

Commensal microorganisms colonize barrier surfaces of all multicellular organisms, including those of humans. For more than 500 million years, commensal microorganisms and their hosts have coevolved and adapted to each other. As a result, the commensal microbiota affects many immune and nonimmune functions of their hosts, and de facto the two together comprise one metaorganism. The commensal microbiota communicates with the host via biologically active molecules. Recently, it has been reported that microbial imbalance may play a critical role in the development of multiple diseases, such as cancer, autoimmune conditions, and increased susceptibility to infection. In this review, we focus on the role of the commensal microbiota in the development, progression, and immune evasion of cancer, as well as some modulatory effects on the treatment of cancer. In particular, we discuss the mechanisms of microbiota-mediated regulation of innate and adaptive immune responses to tumors, and the consequences on cancer progression and whether tumors subsequently become resistant or susceptible to different anticancer therapeutic regimens.

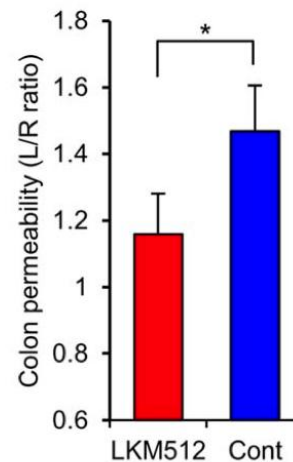
Keywords: Cancer · Cancer Therapy · Cancerogenesis · Inflammation · Microbiota

Longevity in Mice Is Promoted by Probiotic-Induced Suppression of Colonic Senescence Dependent on Upregulation of Gut Bacterial Polyamine Production

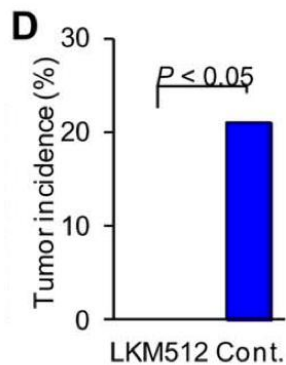
Mitsuharu Matsumoto^{1,2*}, Shin Kurihara^{3,4}, Ryoko Kibe², Hisashi Ashida⁴, Yoshimi Benno²



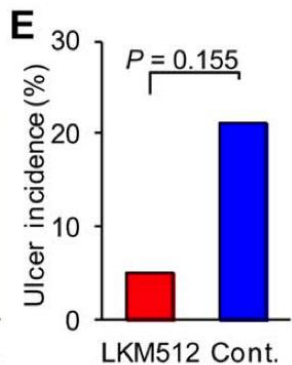
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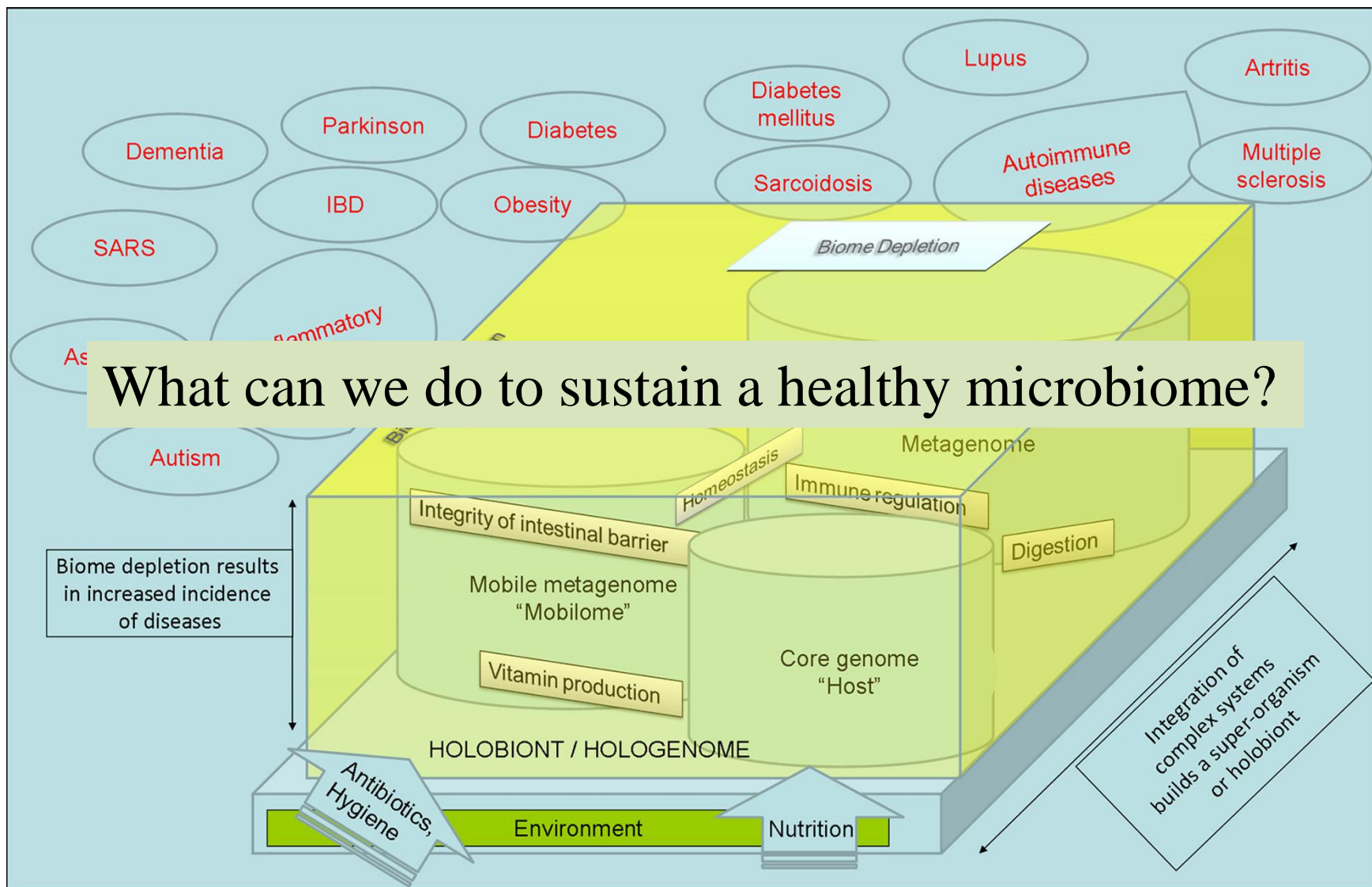
E



C



CONCLUSION





f2-M contains aerobic and anaerobic bacterial life strains cultured with addition with 20 highly organic extracts from berries and plants.

" WE CANNOT SOLVE
OUR PROBLEMS WITH
THE SAME THINKING WE
USED WHEN WE
CREATED THEM. "

ALBERT EINSTEIN

 LIFE
QUOTES
TheBestLifeQuotes.com



F₂-M

Recent Case studies - Herpes

Patient suffers from frequent herpes attack which usually takes around 3 weeks to dry and recover



30 May 2015



3 June 2015

F₂-M

Recent Case studies - Eczema

Patient suffers from frequent incidents of eczema especially during times of stress



31 May 2015



2 June 2015

F₂-M

Recent Case studies – Mouth Ulcer

Patients comment: “All cleared up...no more bad pain! In fact, it was already less painful upon 1st application of the liquid.”



1 June 2015



4 June 2015

Patient had a very painful and swollen abscess in the neck and even after taking anti-biotics and with antibiotic cream, the abscess did not subside. On the 2nd of April, f2-M was applied over 2 days with following results



2 April 2016



4 April 2016

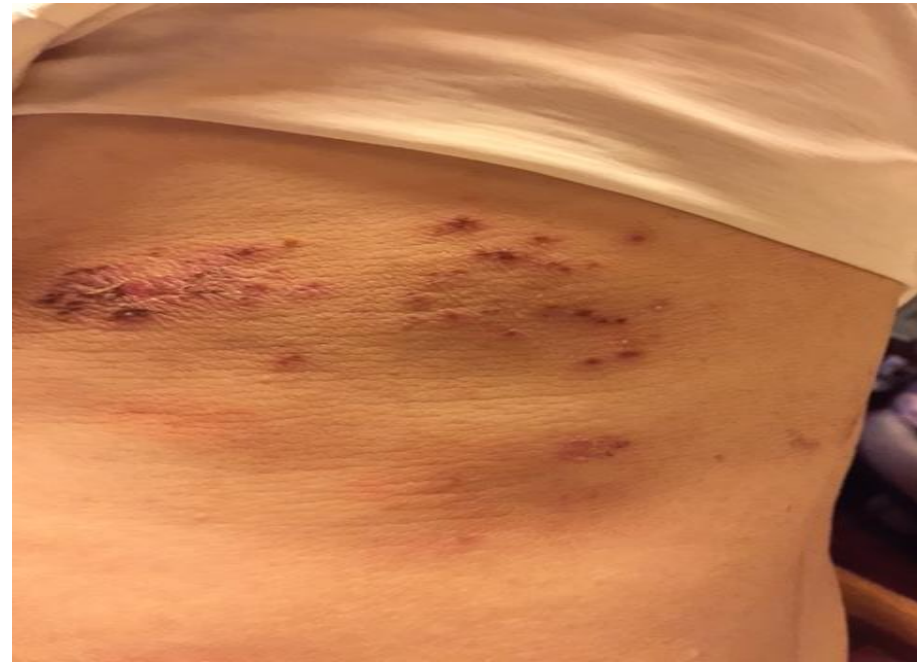
F₂-M

Recent Case studies – Herpes Zoster

Patient suffering from an acute Zoster (shingles) attack. Application of F2M was intended to ease the pain so that the patient can travel to KL for a cellular and anti-infection (Gepon) treatment.



Day 1



Day 6