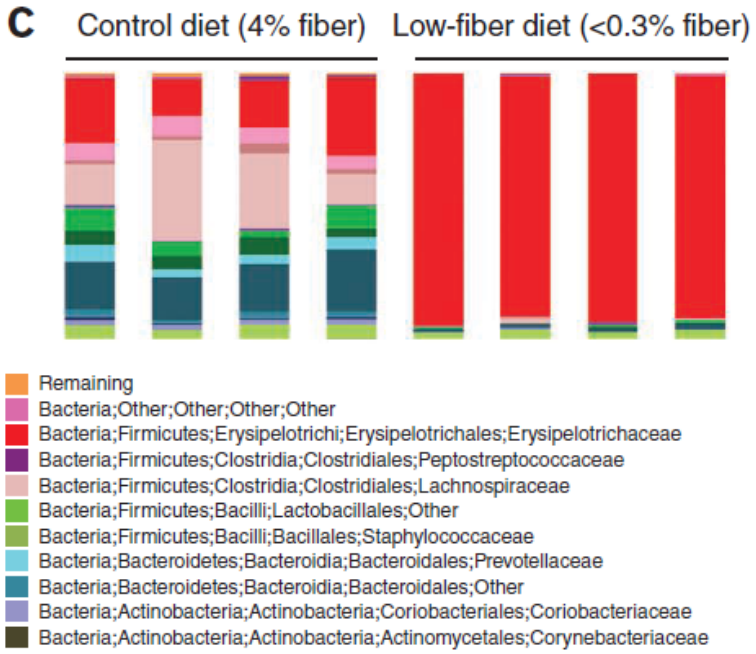
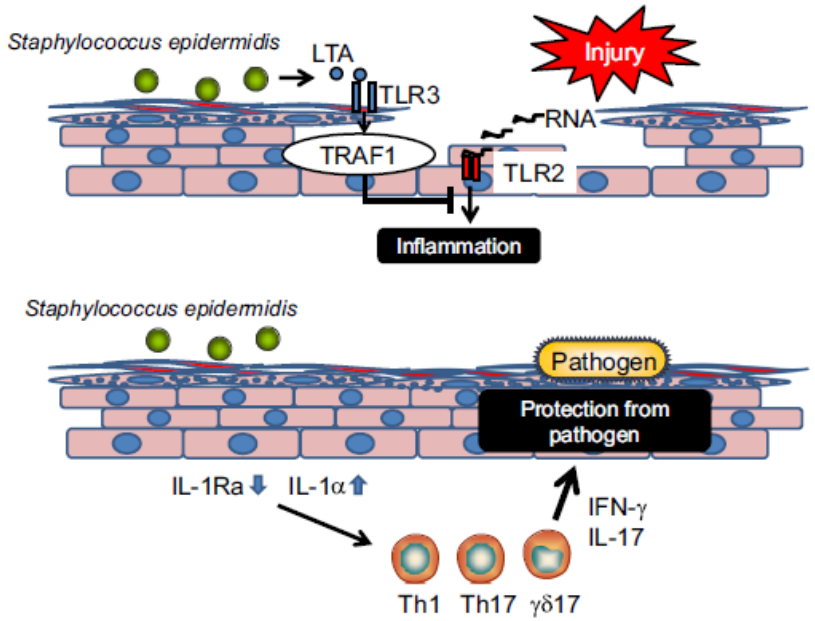




Microbiotas e Microbiomas

Estratégias de Estudo, Papel na Imunidade e Pre- e Probióticos como Imunoterápicos

Isabel de Miranda Santos
imsantos@fmrp.usp.br
Ramal 153267

VOLUME 87, No. 4 *THE QUARTERLY REVIEW OF BIOLOGY* DECEMBER 2012

We are all lichens.

A SYMBIOTIC VIEW OF LIFE: WE HAVE NEVER BEEN INDIVIDUALS

SCOTT F. GILBERT
Department of Biology, Swarthmore College
Swarthmore, Pennsylvania 19081 USA
Biotechnology Institute, University of Helsinki
00014 Helsinki, Finland
E-MAIL: SGILBER1@SWARTHMORE.EDU

JAN SAPP
Department of Biology, York University
Toronto, Ontario M3J 1P3 Canada
E-MAIL: JSAPP@YORKU.CA

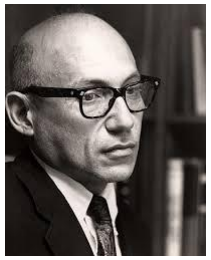
ALFRED I. TAUBER
Department of Philosophy, Boston University
Boston, Massachusetts 02215 USA
E-MAIL: AIT@BU.EDU

The five causes of disease

- Ischemia
- Neoplasia
- Infection
- Degeneration
- **Inflammation**

Aspectos Históricos e Alguns Fatos sobre Microbiotas

MicroFlora



A **microbiota** is "the ecological community of commensal, symbiotic and pathogenic microorganisms that literally share our body space" *Joshua Lederberg.*

- 50% da biomassa do planeta
- 1-3% da massa corporal (1,4 kg)
- Comensais X Simbióticos
- Ruminantes
- Terra Preta do Índio

Fig. 21 Terra-preta: Black-earth soils, anthropogenic in origin, supply some of the most significant evidences that the nature of Amazonia was gradually shaped by human interference. As archaeologist Michael Heckenberger argues, "Much of the landscape was not only anthropogenic in origin but intentionally constructed and managed." Today, we cannot assume that any part of Amazonia is pristine "without a detailed examination of the ground."

Fig. 21 *Terra-preta*: Black-earth soils, anthropogenic in

- Corpo humano é habitado por 100 trilhões de células microbianas
  - 10x mais que nº de células humanas***
  - Oferecem barreiras contra colonização por patógenos
  - Produzem substâncias utilizáveis pelo hospedeiro
  - Degradam produtos tóxicos

***Cell. Sender et al. 2016
Are We Really Vastly Outnumbered? Revisiting the Ratio of Bacterial to Host Cells in Humans.
1:1

- Caráter Anfibiôntico
  - Microrganismos podem se comportar como patógenos oportunistas em situações de:
    - desequilíbrio (ABXs, infecções, imunodeficiências, ...)
    - ao serem introduzidos em sítios estéreis ou não específicos
    - PAMPs *vs* **MAMPs**

- Pesquisas sobre microbiota e efeitos sobre sistema imune foram iniciados em 1999
  - papel em alergias

Allergy 2007: 62: 1223–1236

DOI: 10.1111/j.1398-9995.2007.01462.x

Review article

The role of the intestinal microbiota in the development of atopic disorders

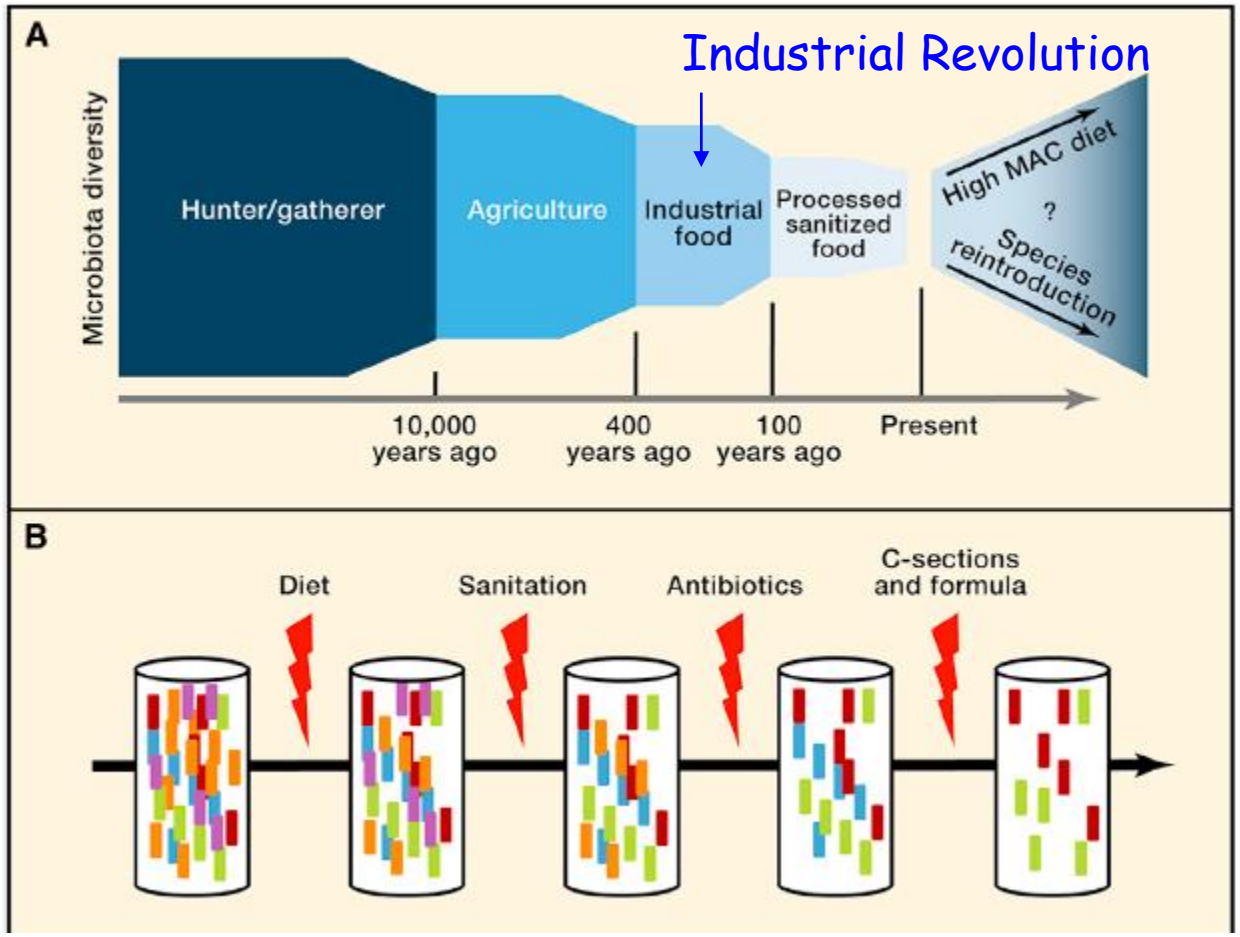
The prevalence of atopic diseases, including eczema, allergic rhinoconjunctivitis and asthma, has increased worldwide, predominantly in westernized countries. Recent epidemiological studies and experimental research suggest that microbial stimulation of the immune system influences the development of tolerance to innocuous allergens. The gastrointestinal microbiota composition may be of particular interest, as it provides an early and major source of immune stimulation and seems to be a prerequisite for the development of oral tolerance. In this review the observational studies of the association between the gut microbiota and atopic diseases are discussed. Although most studies indicated an association between the gut microbiota composition and atopic sensitization or symptoms, no specific harmful or protective microbes can be identified yet. Some important methodological issues that have to be considered are the microbiological methods used (traditional culture *vs* molecular techniques), the timing of examining the gut microbiota, the definition of atopic outcomes, confounding and reverse causation. In conclusion, the microbiota hypothesis in atopic diseases is promising and deserves further attention. To gain more insight into the role of the gut microbiota in the etiology of atopy, large-scale prospective birth cohort studies using molecular methods to study the gut microbiota are needed.

J. Penders[1], E. E. Stobberingh[2], P. A. van den Brandt[1], C. Thijs[3]

[1]Department of Epidemiology, Nutrition and Toxicology Research Institute Maastricht (NUTRIM), Maastricht University; [2]Department of Medical Microbiology, University Hospital of Maastricht; [3]Department of Epidemiology, Care and Public Health Research Institute (Caphri), Maastricht University, Maastricht, the Netherlands

Key words: atopic dermatitis; atopy; gut microbiota; oral tolerance; sensitization.

John Penders PhD
Department of Epidemiology
Nutrition and Toxicology Research Institute
Maastricht (NUTRIM),
Maastricht University,
P.O. Box 616, 6200 MD Maastricht,
The Netherlands.



Cell Metabolism 20, November 4, 2014

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

Erica D. Sonnenburg[1] and Justin L. Sonnenburg[1,*]
[1]Department of Microbiology and Immunology, Stanford University School of Medicine, 259 Campus Drive, Stanford, CA 94305, USA
*Correspondence: jsonnenburg@stanford.edu
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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.

↓ Atividade física; ≠ Dieta
↑ Medicamentos, saneamento, produtos de higiene

MACs are carbohydrates that are metabolically available to gut microbes.

- **Dietary** and resistant to degradation and absorption by the host;
- **Secreted by the host in the intestine** (e.g., mucus)
- **Produced by microbes** within the intestine.

Much of the cellulose *humans* consume is not metabolized by gut microbes and does not qualify as a MAC (exception: ruminal microbiota).

The amount of dietary MACs present in a single food source differs for each individual, since which carbohydrates are metabolized depends upon the membership of each person's microbiota: genes for the consumption of the algal polysaccharide porphyran in the microbiomes of Japanese individuals, rarely found in North American and European individuals

Microbioma: os genomas dos microorganismos de um ecossistema

antigenome	immunogenome	plastidome
bacteriome	immunome	plerome
basidiome	haptenome	proteinome
biome	karyome	proteome
cardiome	leptome	psychome
caulome	microbiome	regulome
chondriome	mnemome	rhabdome
cladome	mycetome	rhizome
coelome	neurome	stereome
epigenome	odontome	thallome
erythrome	osteome	tracheome
genome	pharmacogenome	transcriptome
geome	phenome	trichome
hadrome	phyllome	vacuome
histome	physiome	

"om" em sânscrito:
"o conhecimento pleno das Vedas"

Vedas: revelações obtidas por sábios após meditação intensa

Listed above we present a lexicome of terms, suffixed by *-ome*, extracted from the MEDLINE database, the *OED*, and the *Web of Science*. Our aim was to select terms using the *-ome* suffix in the sense of this article. For the most part this excludes the suffixes *-tome*, *-stome*, *-some*, *-drome*. Some terms are best known as the *-omics* derivative. Today, we should assume that further derivations are no longer from Greek or Sanskrit, that the *-ome* idea is borrowed from the multitude of terms already ensconced into English or the scientific lingua franca. Most of these terms are already in print; almost all should be self-revealing; a few are conjectural. Guess which of these *-omes* were made up only just now; even for these, there may well be an -omics.com to match.

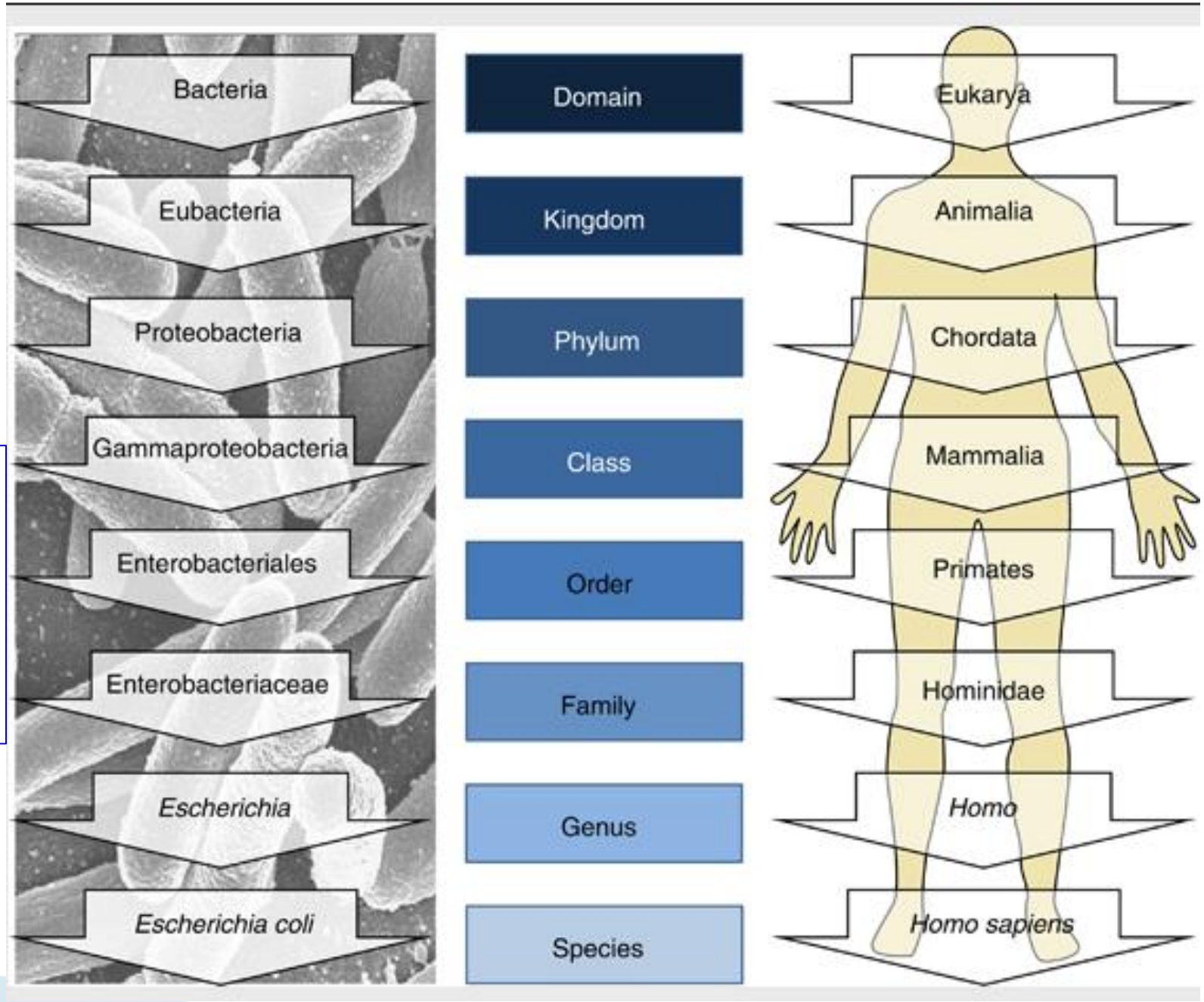
Estratégias para estudar o microbioma do corpo humano

Hierarchical organization of taxonomic levels used for classifying organisms.

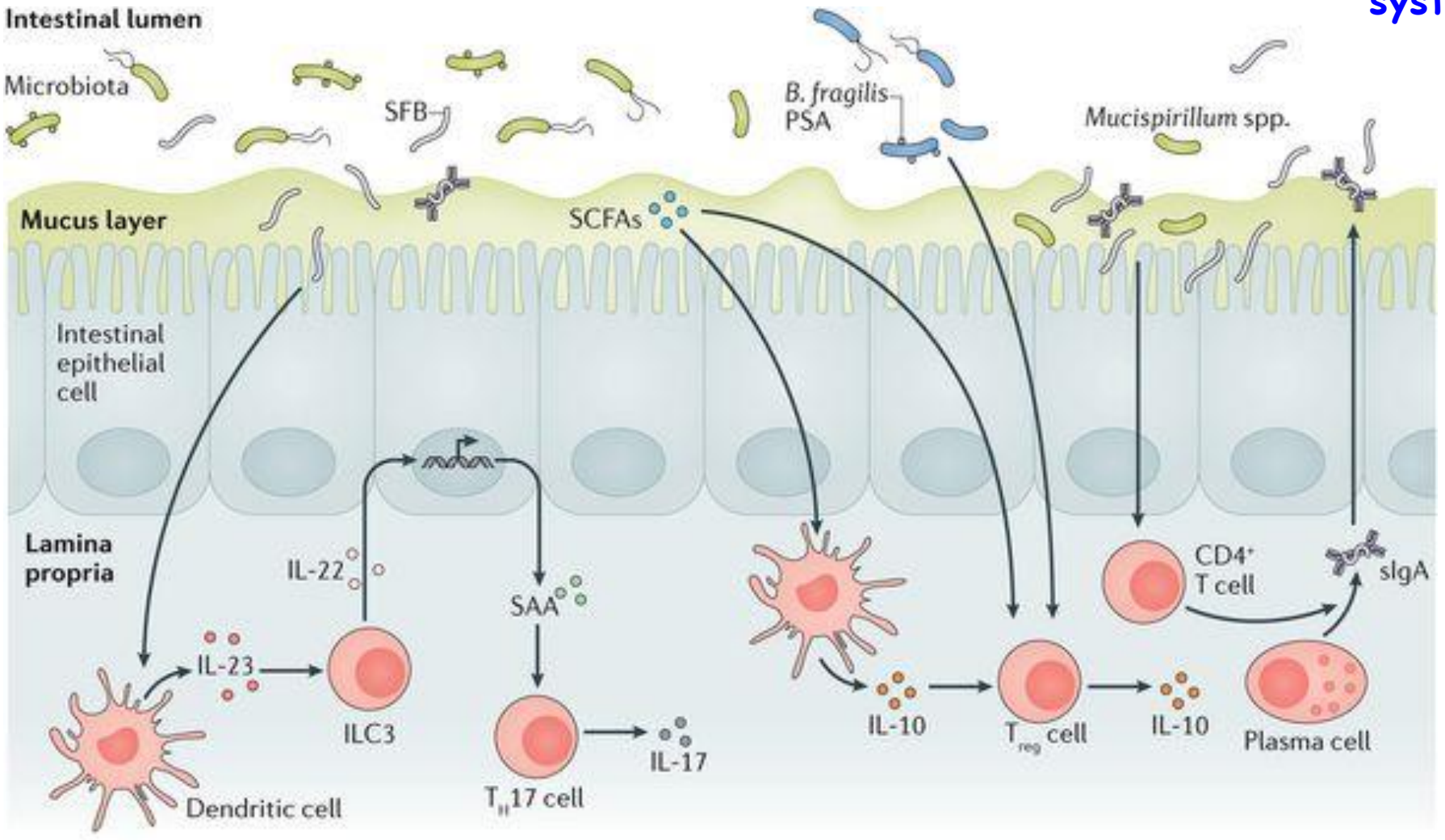
Analyzing the Human Microbiome: A "How To" guide for Physicians
AD Tyler, MI Smith, MS Silverberg

Am J Gastroenterology 109 (7): 983-993, 2014
pago

http://www.medscape.com/viewarticle/828715_2
grátis



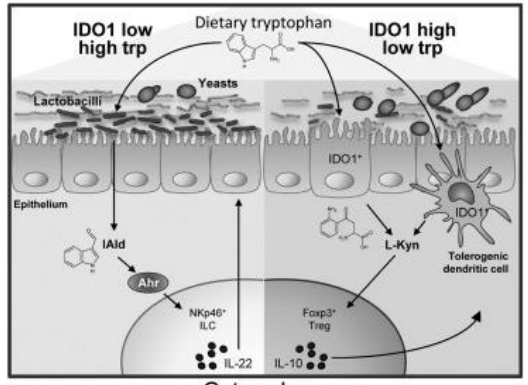
The microbiota shapes the immune system



Metabolite–innate immunity crosstalk originates before birth and involves the antibody-mediated transfer of microbial molecules to the offspring during pregnancy and in milk

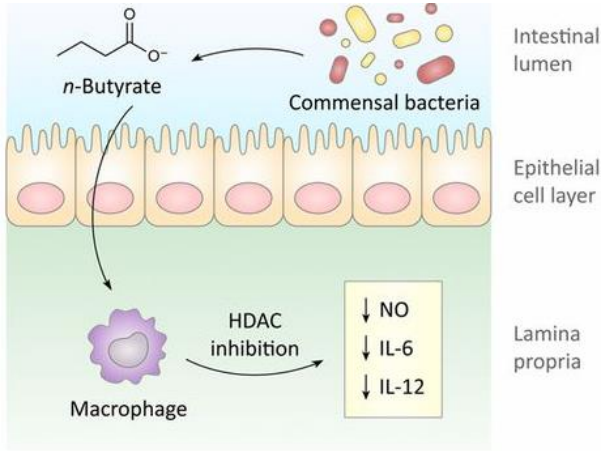
Communication between the microbiota and the innate immune system relies on metabolites

- Tryptophan metabolites in the case of ILCs



Gut ecology
Colonization resistance
Gut tolerance

- Short-chain fatty acids in the case of myeloid cells.



Department of Immunology, Weizmann Institute of Science, Rehovot 76100, Israel.

Correspondence to E.E.
eran.elinav@weizmann.ac.il

**These authors contributed equally to this work.*

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REVIEWS

Dysbiosis and the immune system

Maayan Levy, Aleksandra A. Kolodziejczyk*, Christoph A. Thaiss* and Eran Elinav*

Dysbiosis: a stable microbial community state that functionally contributes to the aetiology, diagnosis or treatment of a disease

Innate and adaptive immunity control the colonization niche of the (intestinal) **microbiota** through mechanisms including the production of antimicrobial peptides and IgA antibodies.

The (dysbiotic) **microbiota** may actively influence its colonization niche by **altering the functions of innate and adaptive** intestinal **immunity**.

Dysbiosis: associated with many immune-related human diseases
In many cases it remains to be established **whether dysbiosis is cause or consequence of disease**

Types of dysbiosis

- Blooms of pathobionts
  - e.g., Enterobacteriaceae in IBD (consequence or cause?)
- Loss of commensals
  - e.g., ↓ *Lactobacillus reuteri* in autism
- Loss of alpha diversity* within an anatomical site
  - e.g., abnormal diet, IBD, AIDS, type I diabetes

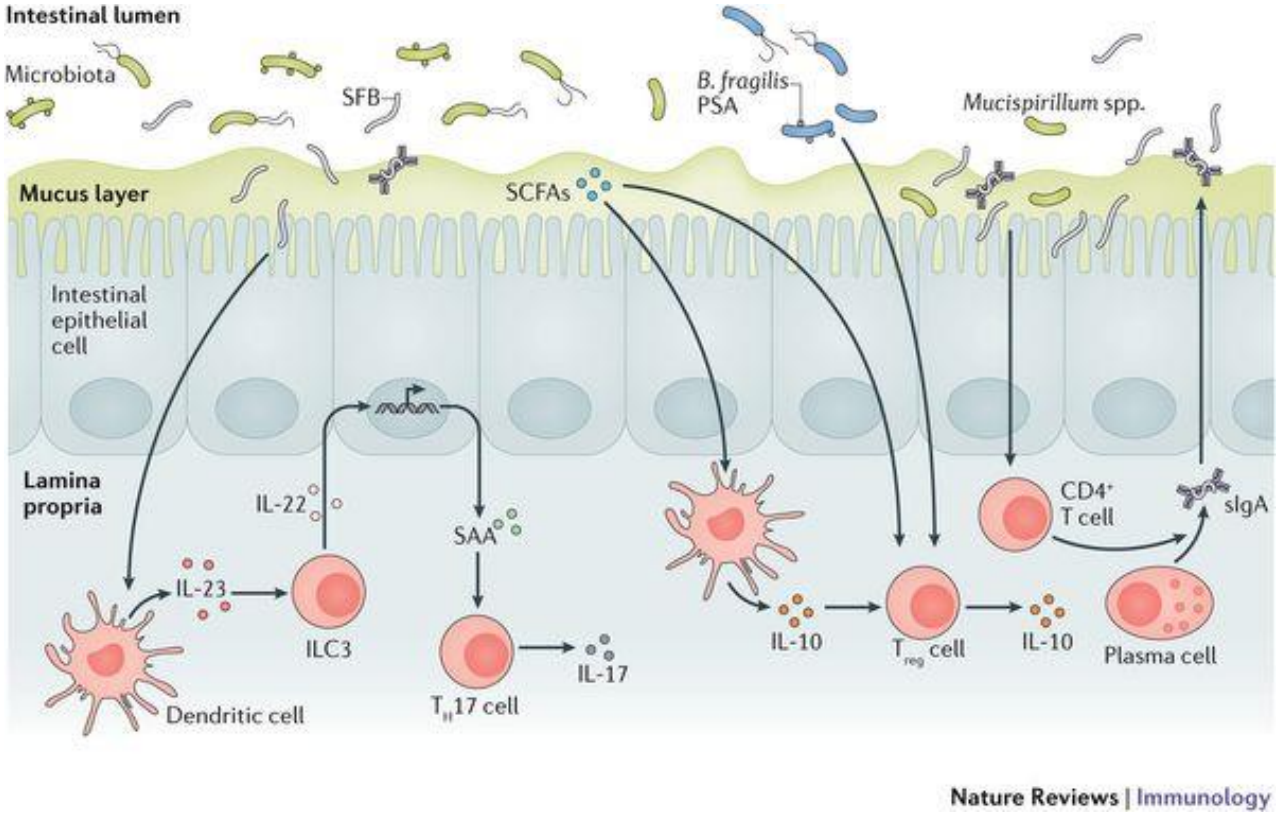
*Alpha diversity: species richness *within* a site;
Beta diversity: differences in species composition *between* sites

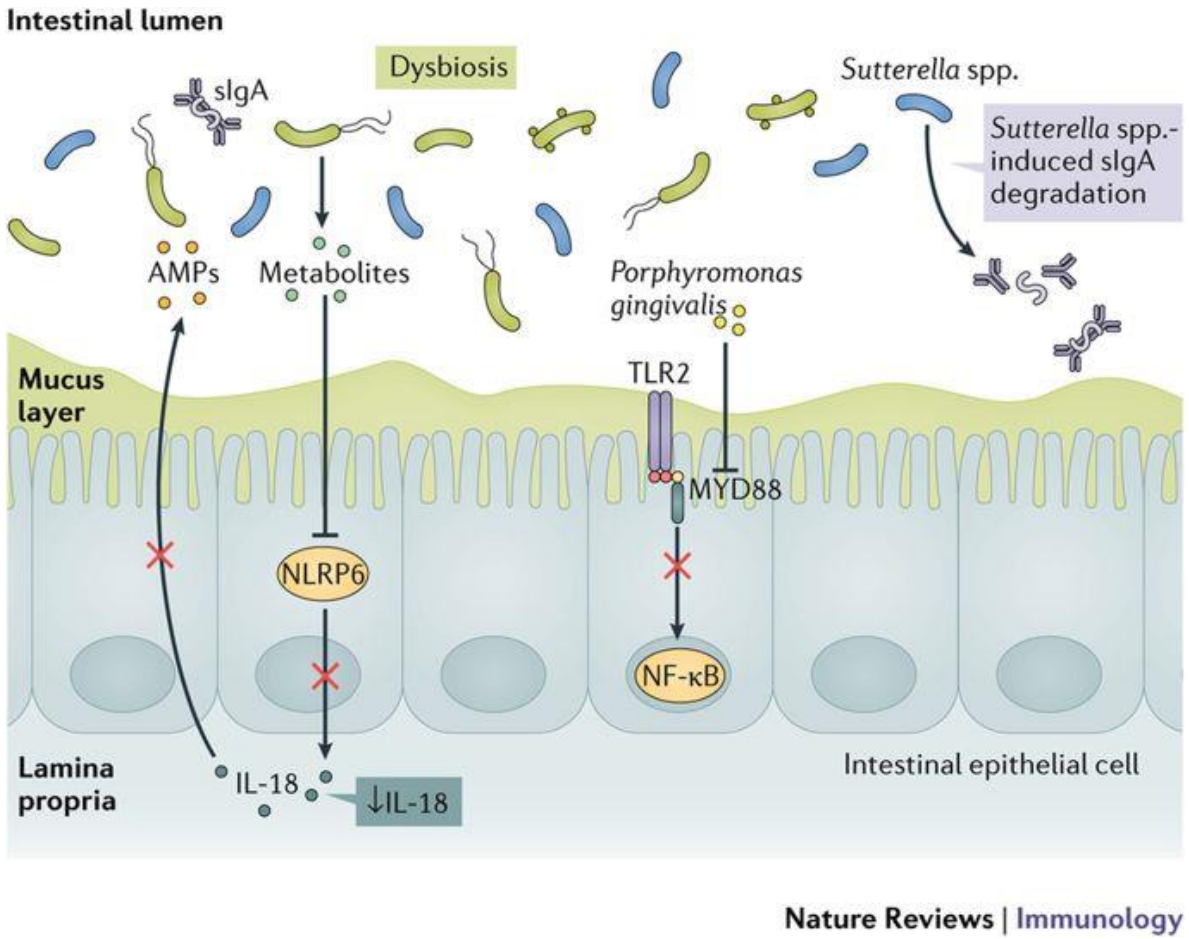
"desmatamento" da microbiota, em geral, é deletério para a saúde

Origins of dysbiosis

- Infection-inflammation
  - Inflammatogenic pathogens (*Salmonella enterica*); inflammation w/DSS; genetic deficiency of IL-10
  - Factors involved: release/sequestration of nutrients; intermicrobial competition and horizontal gene transfer, exploitation of antimicrobial peptides to control species; harnessing of aerobic and anaerobic cellular respiration (~"biological control")
- Diet and xenobiotics
  - e.g., ABXs, emulsifiers, artificial sweeteners Exemplos: da carboximetilcelulose e Polisorbato80; dieta tradicional *vs* industrializada
- Genetics
  - Twin studies; Polymorphisms in genes involved in metabolism (e.g., VitD receptor)
- Familial transmission
  - Form of birthing (C-section *vs* vaginal); household habits; pets; housing of experimental animals
- Other: disruption of circadian rhythm, physical injury…

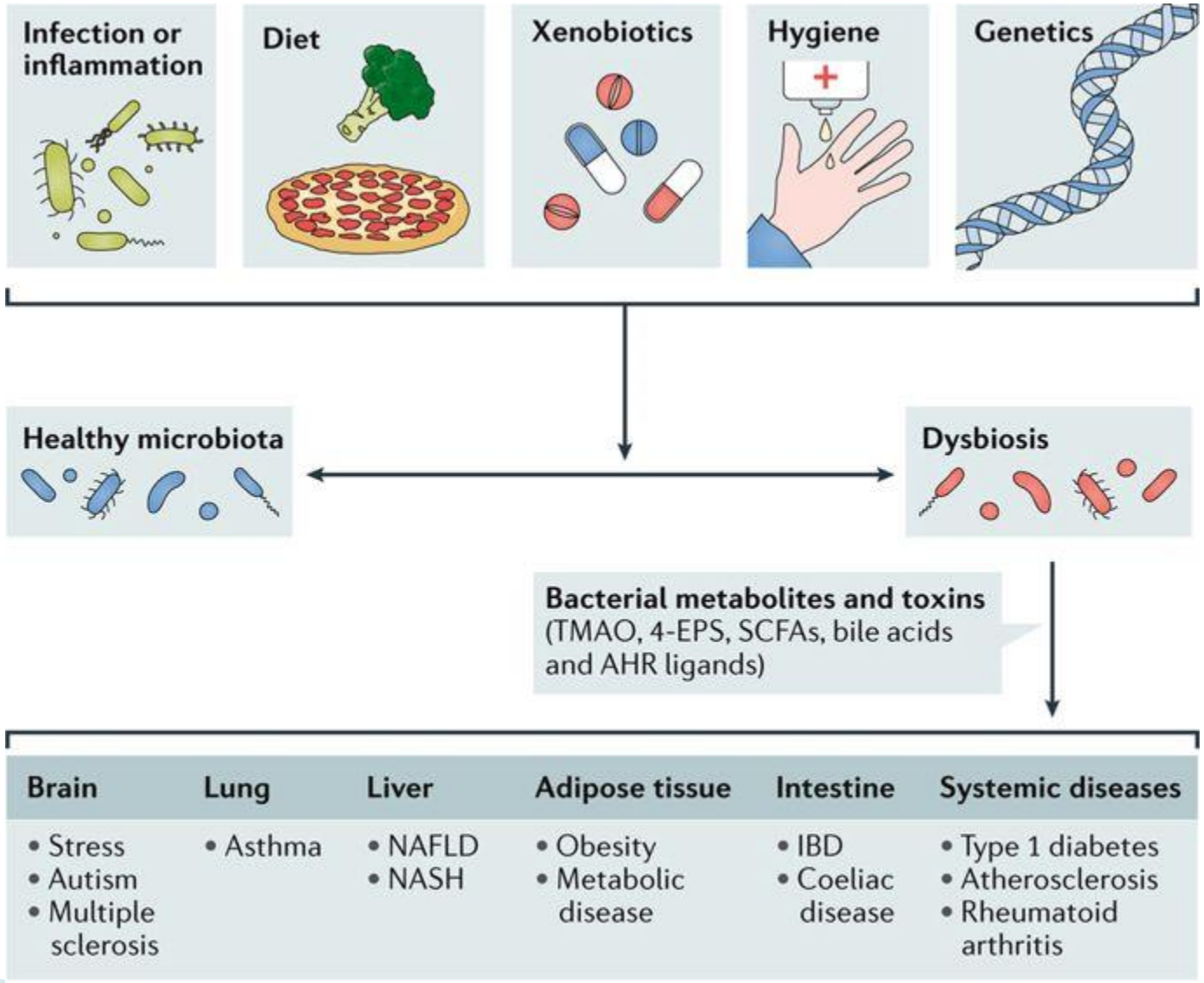
The impact of dysbiosis on the host immune system





AMPs, antimicrobial peptides; IL, interleukin; MYD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor-κB; NLRP6, NOD-, LRR- and pyrin domain-containing 6.

The intestinal microbiota and disease



4-EPS, 4-ethylphenylsulfate; AHR, aryl hydrocarbon receptor; IBD, inflammatory bowel disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SCFAs, short-chain fatty acids; TMAO, trimethylamine-*N*-oxide

Microbiota Intestinal

Dieta
Desenvolvimento da Imunidade
Alergias
Doença Inflamatória Intestinal
Resposta a Vacinas
~~Desnutrição~~
~~Disfunção Ovariana~~
~~Desenvolvimento do Sistema Nervoso Central~~

Bacteria in our gut depend on our diet, just as our health depends on their metabolism.

PNAS PNAS PNAS

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[b,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., B-4000 Liège, 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)

Gut microbial composition depends on different dietary habits just as health depends on microbial metabolism, but the association of microbiota with different diets in human populations has not yet been shown. In this work, we compared the fecal microbiota of European children (EU) and that of children from a rural African village of Burkina Faso (BF), where the diet, high in fiber content, is similar to that of early human settlements at the time of the birth of agriculture. By using high-throughput 16S rDNA sequencing and biochemical analyses, we found significant differences in gut microbiota between the two groups. BF children showed a significant enrichment in Bacteroidetes and depletion in Firmicutes ($P < 0.001$), with a unique abundance of bacteria from the genus *Prevotella* and *Xylanibacter*, known to contain a set of bacterial genes for cellulose and xylan hydrolysis, completely lacking in the EU children. In addition, we found significantly more short-chain fatty acids ($P < 0.001$) in BF than in EU children. Also, *Enterobacteriaceae* (*Shigella* and *Escherichia*) were significantly underrepresented in BF than in EU children ($P < 0.05$). We hypothesize that gut microbiota coevolved with the polysaccharide-rich

created selective pressure that favored pathogens specialized in colonizing human hosts and probably produced the first wave of emerging human diseases (5). It has been hypothesized that bacteria specialized in human-associated niches, including our gut commensal flora, underwent intense transformation during the social and demographic changes that took place with the first Neolithic settlements (6).

Western developed countries successfully controlled infectious diseases during the second half of the last century, by improving sanitation and using antibiotics and vaccines. At the same time, a rise in new diseases such as allergic, autoimmune disorders, and inflammatory bowel disease (IBD) both in adults and in children has been observed (5), and it is hypothesized that improvements in hygiene together with decreased microbial exposure in childhood are considered responsible for this increase (7). The GI microflora plays a crucial role in the pathogenesis of IBD (8), and recent studies demonstrate that obesity is associated with imbalance in the normal gut microbiota (9, 10).

The aim of this study was to compare the gut microbiota of

Fig. 1. Life in a rural village of Burkina Faso. (*A*) Village of Boulpon. (*B*) Traditional Mossi dwelling. (*C*) Map of Burkina Faso (modified from the United States CIA's World Factbook, 34). (*D*) Millet and sorghum (basic components of Mossi diet) grain and flour in typical bowls. (*E*) Millet and sorghum is ground into flour on a grinding stone to produce a thick porridge called Tô.

Sequencing of 16S rRNA Gene Amplicons.

For each sample, 16S rRNA genes 16S rRNA genes are amplified using a primer set specific for V5 and V6 hypervariable 16S RNA region. The forward primer contained the sequence of the Titanium A adaptor and a barcode sequence. Pyrosequencing is carried out using primer A on a 454 Life Sciences Genome Sequencer FLX instrument (Roche) following Titanium chemistry. Data are submitted to the Sequence Read Archive (SRA)

As of September 2010, 65% of the SRA was human genomic sequence, with another 16% relating to human metagenome sequence reads. Much of this data was deposited through the 1000 Genomes Project. In June 2011, the data contained within the SRA passed 100 Terabases of DNA in volume.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
1	Customer ID	15	67	73	33	13	65	4	48	11	75	50	21	74	24	52	28	717	78
2	DNAVision ID	DNA12085	DNA12085	DNA12085	DNA12085	DNA12085	DNA12085	DNA12085	DNA12085	DNA12085	DNA12085	DNA12085	DNA12085	DNA12085	DNA12085	DNA12085	DNA12085	DNA12085	DNA12085
3	Total Number of reads	490	1496	1732	2218	2393	4885	2595	1505	1348	3281	8446	25865	18699	19463	6867	6620	13789	5307
4	Assigned reads	348	1039	1089	1552	1725	3640	1810	930	911	2015	5963	17827	9337	13498	2973	4552	5737	3666
5	Assignation	71.02 %	69.45 %	62.88 %	69.97 %	72.09 %	74.51 %	69.75 %	61.79 %	67.58 %	61.41 %	70.60 %	68.92 %	49.93 %	69.35 %	43.29 %	68.76 %	41.61 %	69.08 %
6	Acetobacteraceae	1.15 %	1.64 %	0.18 %	0.58 %	3.71 %	4.48 %	0.28 %	7.10 %	0.11 %	0.35 %	0.44 %	0.71 %	0.46 %	0.23 %	0.00 %	1.01 %	0.00 %	0.76 %
7	Acholeplasmataceae	2.30 %	0.10 %	0.09 %	0.13 %	0.93 %	0.25 %	0.61 %	0.32 %	0.99 %	0.15 %	2.05 %	0.26 %	0.16 %	1.96 %	0.00 %	0.04 %	0.00 %	0.08 %
8	Acidimicrobidae_incertae_s	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.11 %	0.05 %	0.05 %	0.07 %	0.16 %	0.02 %	0.00 %	0.18 %	0.00 %	0.08 %
9	Actinomycetaceae	0.57 %	0.19 %	0.09 %	2.38 %	1.91 %	1.92 %	0.88 %	1.61 %	1.76 %	0.10 %	1.54 %	1.57 %	0.22 %	1.47 %	0.00 %	0.11 %	0.00 %	0.30 %
10	Actinosynnemataceae	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.01 %	0.00 %	0.02 %	0.00 %	0.00 %	0.00 %	0.03 %
11	Aerococcaceae	1.15 %	3.56 %	4.32 %	3.67 %	4.06 %	3.35 %	3.59 %	3.98 %	2.63 %	2.98 %	3.61 %	3.09 %	4.41 %	3.35 %	0.00 %	10.41 %	0.00 %	3.14 %
12	Aeromonadaceae	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.02 %	0.00 %	0.00 %
13	Alcaligenaceae	0.00 %	0.38 %	1.84 %	0.39 %	0.75 %	0.25 %	0.11 %	0.00 %	1.43 %	0.55 %	0.15 %	0.75 %	0.54 %	7.14 %	0.03 %	0.57 %	0.02 %	0.93 %
14	Alteromonadaceae	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.05 %	0.00 %	0.00 %	0.02 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %
15	Anaeroplasmataceae	0.00 %	0.00 %	0.00 %	0.00 %	0.23 %	0.00 %	0.00 %	0.11 %	0.00 %	0.05 %	0.13 %	0.04 %	0.01 %	0.07 %	0.00 %	0.00 %	0.00 %	0.03 %
16	Aurantimonadaceae	0.00 %	0.10 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.05 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %
17	Bacillaceae	0.29 %	3.08 %	0.09 %	0.19 %	0.06 %	1.51 %	0.28 %	0.00 %	0.11 %	4.32 %	0.23 %	0.20 %	0.55 %	0.16 %	0.00 %	0.97 %	0.00 %	1.61 %
18	Bacillales_incertae_sedis	0.00 %	0.10 %	0.00 %	0.00 %	0.00 %	0.05 %	0.00 %	0.00 %	0.00 %	0.15 %	0.03 %	0.01 %	0.12 %	0.01 %	0.00 %	0.13 %	0.00 %	0.05 %
19	Bacteriovoracaceae	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.05 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.01 %	0.05 %	0.01 %	0.00 %	0.00 %	0.00 %	0.03 %
20	Bacteroidaceae	0.00 %	0.77 %	0.00 %	0.00 %	0.00 %	0.05 %	0.00 %	0.00 %	0.00 %	1.09 %	0.18 %	0.03 %	0.05 %	0.05 %	0.37 %	0.04 %	0.17 %	0.16 %
21	Bdellovibrionaceae	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.04 %	0.00 %	0.00 %
22	Beutenbergiaceae	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.03 %	0.06 %	0.00 %	0.00 %	0.00 %	0.02 %	0.00 %	0.01 %	0.00 %	0.00 %	0.07 %	0.00 %	0.08 %
23	Bifidobacteriaceae	0.00 %	1.06 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.07 %	0.00 %	0.00 %
24	Bogoriellaceae	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.02 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %
25	Brevibacteriaceae	0.00 %	0.10 %	0.00 %	0.00 %	0.23 %	0.08 %	0.06 %	0.11 %	0.00 %	0.00 %	0.15 %	0.15 %	0.20 %	0.10 %	0.00 %	0.31 %	0.00 %	0.11 %
26	Brucellaceae	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.02 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %
27	Burkholderiaceae	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.08 %
28	Burkholderiales_incertae_s	0.00 %	0.67 %	0.00 %	0.00 %	0.00 %	0.14 %	0.06 %	0.00 %	0.00 %	0.00 %	0.00 %	0.13 %	0.19 %	0.07 %	0.00 %	0.04 %	0.00 %	0.22 %
29	Caldilineaceae	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.03 %	0.00 %	0.00 %	0.02 %	0.00 %	0.05 %
30	Campylobacteraceae	0.00 %	0.10 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %
31	Cardiobacteriaceae	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.08 %

Sheet1 Plan1

Family

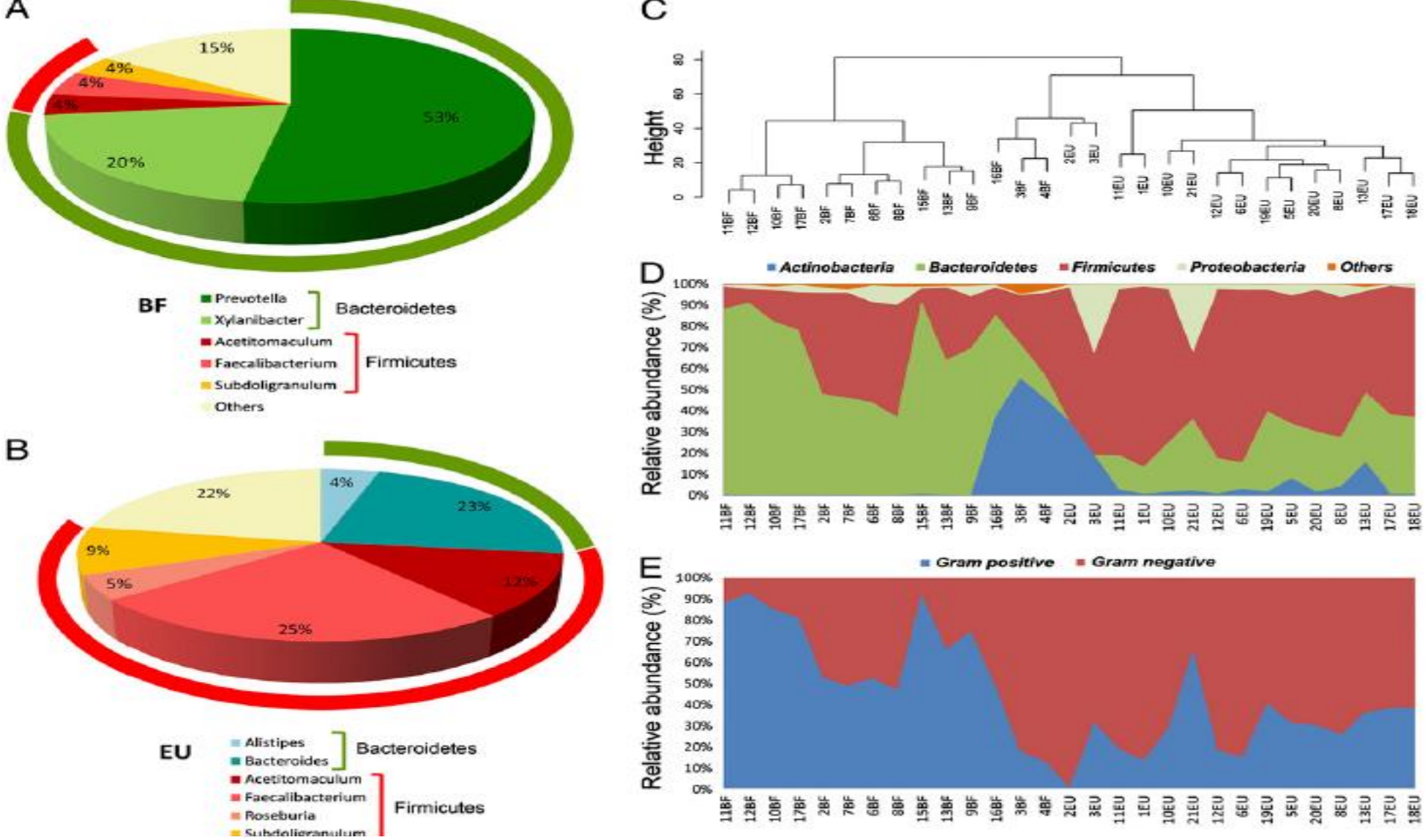


Fig. 2. 16S rRNA gene surveys reveal a clear separation of two children populations investigated. (*A* and *B*) Pie charts of median values of bacterial genera present in fecal samples of BF and EU children (>3%) found by RDP classifier v. 2.1. Rings represent corresponding phylum (Bacteroidetes in green and Firmicutes in red) for each of the most frequently represented genera. (*C*) Dendrogram obtained with complete linkage hierarchical clustering of the samples from BF and EU populations based on their genera. The subcluster located in the middle of the tree contains samples taken from the three youngest (1–2 y old) children of the BF group (16BF, 3BF, and 4BF) and two 1-y-old children of the EU group (2EU and 3EU). (*D*) Relative abundances (percentage of sequences) of the four most abundant bacterial phyla in each individual among the BF and EU children. Blue area in middle shows abundance of Actinobacteria, mainly represented by *Bifidobacterium* genus, in the five youngest EU and BF children. (*E*) Relative abundance (percentage of sequences) of Gram-negative and Gram-positive bacteria in each individual. Different distributions of Gram-negative and Gram-positive in the BF and EU populations reflect differences in the two most represented phyla, Bacteroidetes and Firmicutes.

Microbiota e produção de ácidos graxos de cadeia curta (SCFAs), moléculas imunorreguladoras

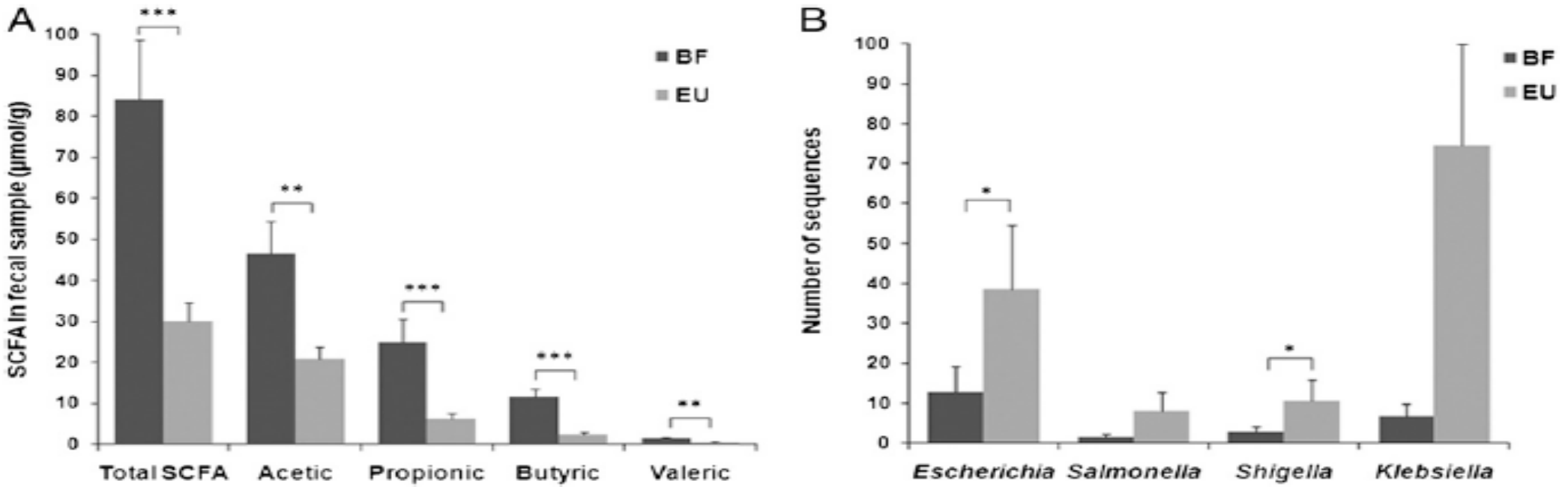


Fig. 3. SCFA-producing bacteria could help to prevent establishment of some potentially pathogenic intestinal bacteria. (*A*) Quantification of SCFAs in fecal samples from BF and EU populations by SPME-GC-MS. (*B*) Number of sequences relative to principal *Enterobacteriaceae* genera, in BF and EU children microbiota. Mean values (±SEM) are plotted. Asterisks indicate significant differences (one-tailed Student *t* test of all data points: $*P < 0.05$; $**P \leq 0.01$; $***P \leq 0.001$).

LETTER

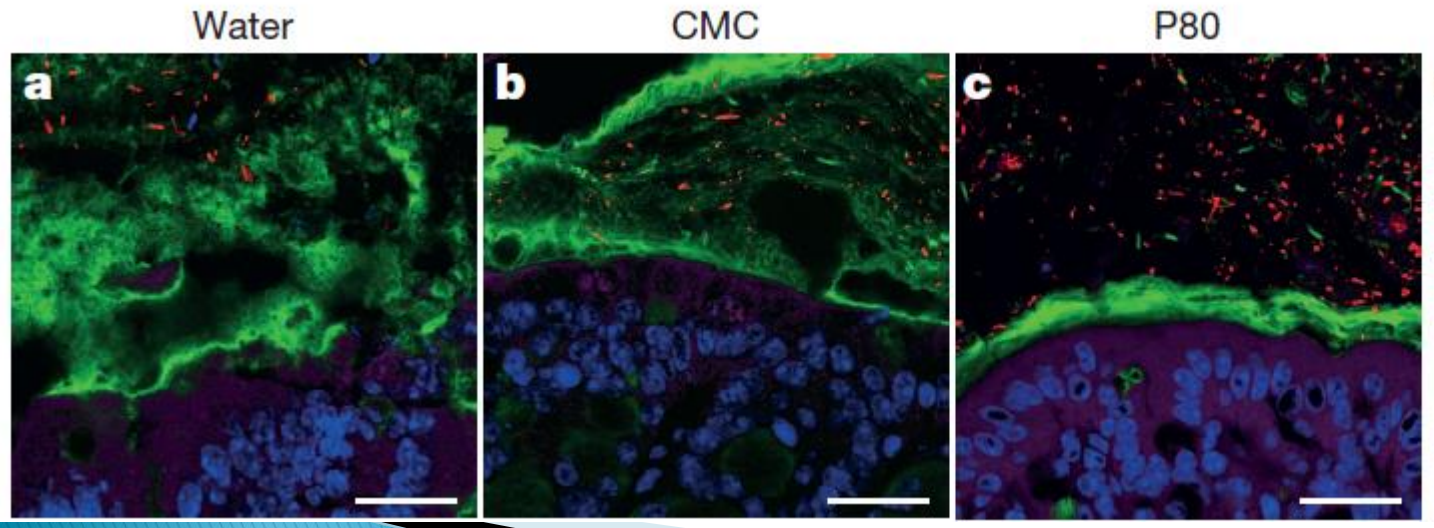
doi:10.1038/nature14232

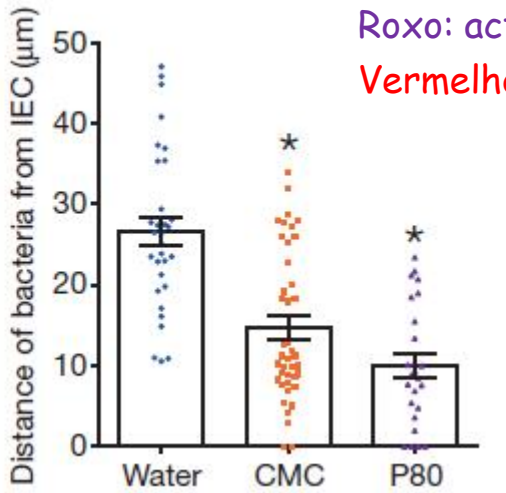
Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome

Benoit Chassaing[1], Omry Koren[2], Julia K. Goodrich[3], Angela C. Poole[3], Shanthi Srinivasan[4], Ruth E. Ley[3] & Andrew T. Gewirtz[1]

Two common emulsifiers, carboxymethylcellulose and polysorbate-80, induced low grade inflammation and obesity/metabolic syndrome in wild-type hosts and promoted robust colitis in mice predisposed to this disorder.

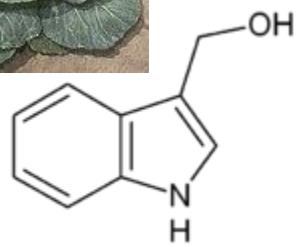
Emulsifier-induced metabolic syndrome was associated with microbiota encroachment, altered species composition and increased pro-inflammatory potential.

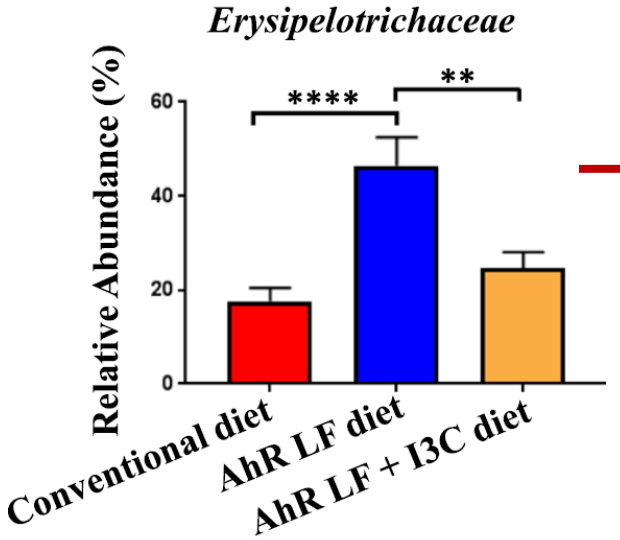




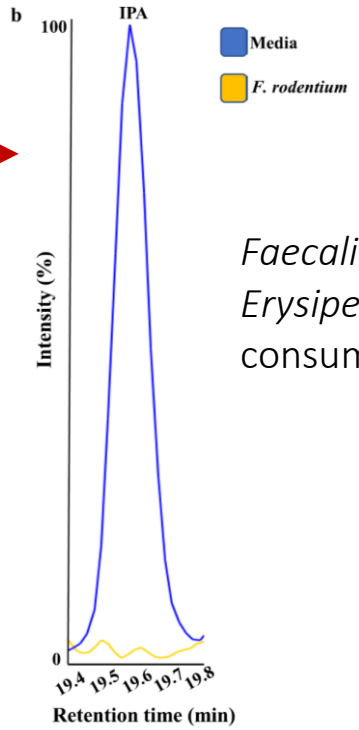
Verde: muco
Roxo: actina
Vermelho: bactérias

Indole-3-carbinol (C_9H_9NO; I3C), is produced by the breakdown of glucobrassicin, a glucosinolate

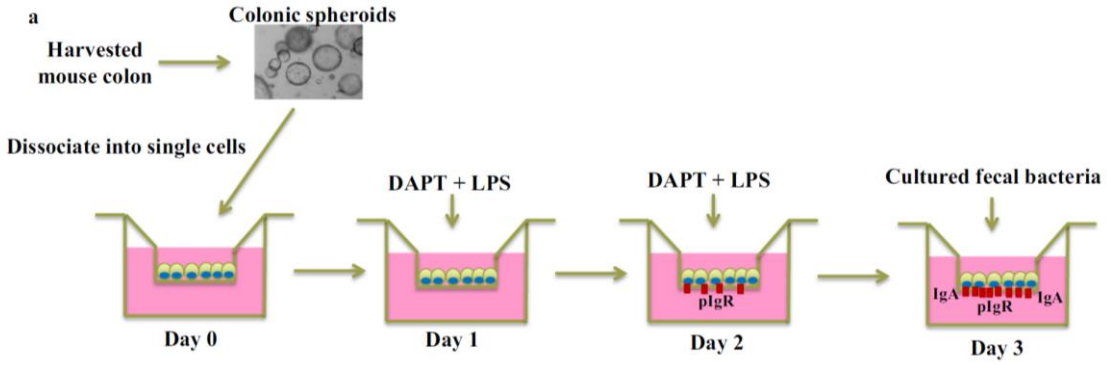




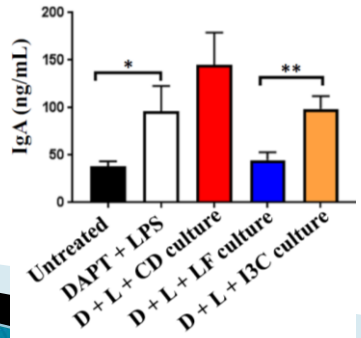
IPA: indole-3-propionic acid



Faecalibaculum rodentium, an *Erysipelotrichaceae* species, consumes the AhR ligand IPA



Fecal microbiota from mice on an AhR ligand-free diet directly reduce secretory IgA levels



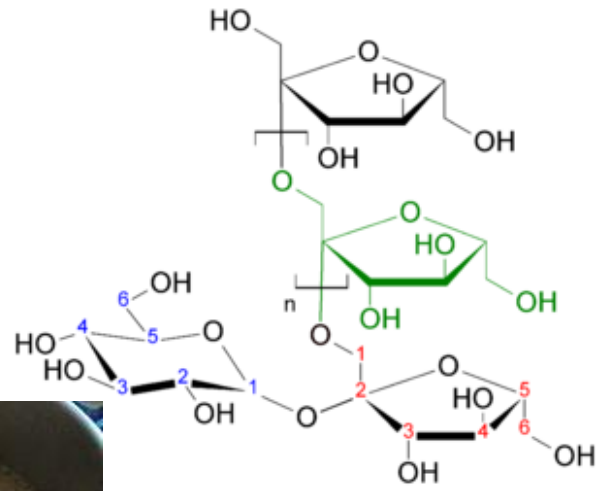
SCIENTIFIC REPORTS
nature research

OPEN

Depletion of dietary aryl hydrocarbon receptor ligands alters microbiota composition and function

Received: 5 January 2019
Accepted: 24 September 2019
Published online: 11 October 2019

Kyle M. Brawner[1], Venkata A. Yeramilli[1], Lennard W. Duck[2], William Van Der Pol[3],



Inulin fibre promotes microbiota-derived bile acids and type 2 inflammation

https://doi.org/10.1038/s41586-022-05380-y

Received: 10 January 2021

Accepted: 22 September 2022

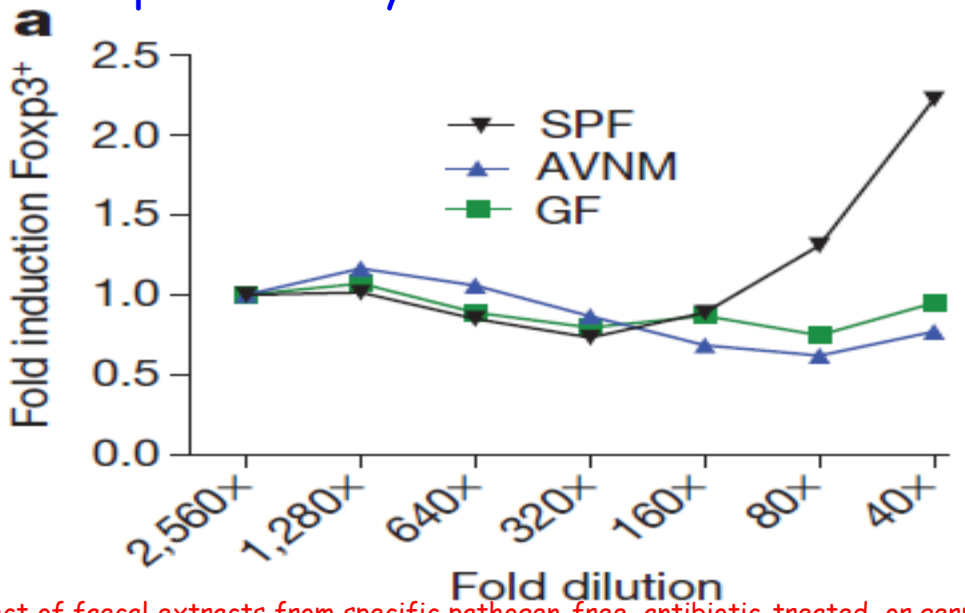
Published online: 2 November 2022

Check for updates

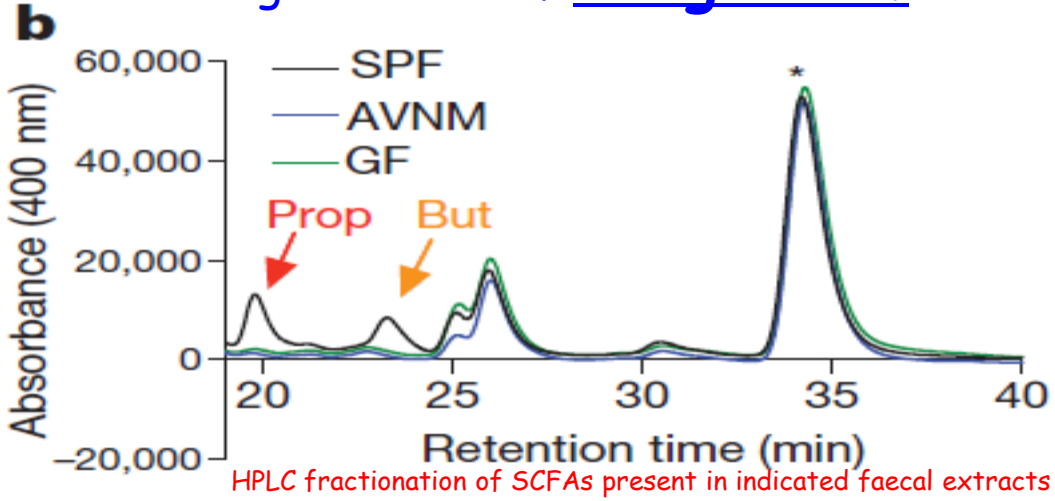
Mohammad Arifuzzaman[1,2,3], Tae Hyung Won[4], Ting-Ting Li[1,2,3], Hiroshi Yano[1,2,3], Sreehaas Digumarthi[1,2,3], Andrea F. Heras[5], Wen Zhang[1,2,3], Christopher N. Parkhurst[1,2,3], Sanchita Kashyap[1,2,3], Wen-Bing Jin[1,2,3], Gregory Garbès Putzel[1,2,3], Amy M. Tsou[1,2,3,6], Coco Chu[1,2,3], Qianru Wei[1,2,3], Alex Grier[1,2,3], JRI IBD Live Cell Bank Consortium*, Stefan Worgall[5], Chun-Jun Guo[1,2,3]✉, Frank C. Schroeder[4]✉ & David Artis[1,2,3]✉

Dietary fibres can exert beneficial anti-inflammatory effects through microbially fermented short-chain fatty acid metabolites[1,2], although the immunoregulatory roles of most fibre diets and their microbiota-derived metabolites remain poorly defined.

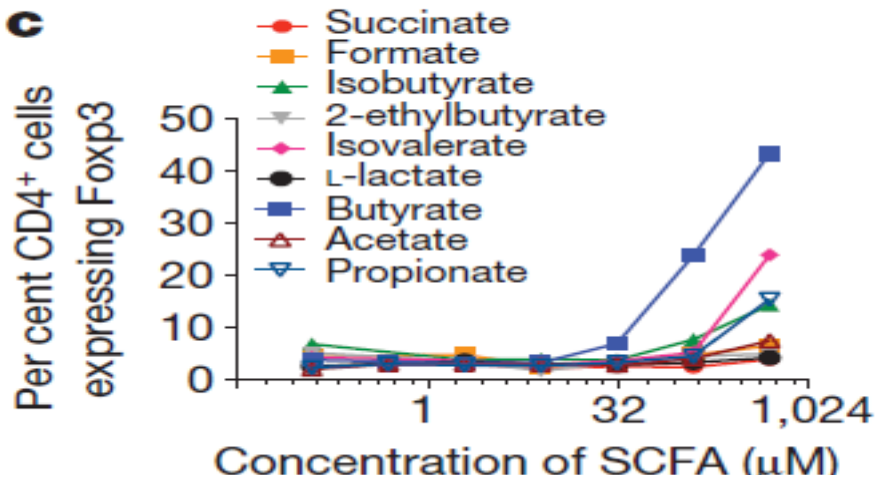
SCFAs produced by commensal bacteria stimulate in vitro generation of **Treg cells.**

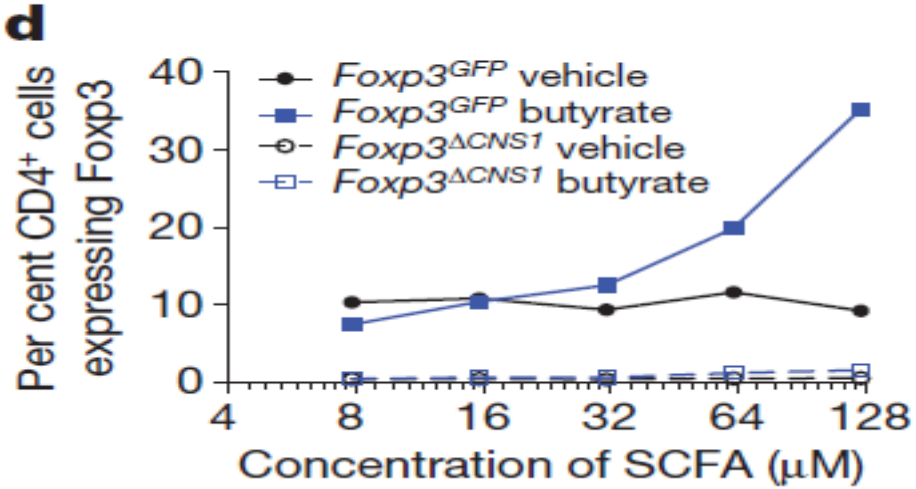


Effect of faecal extracts from specific pathogen-free, antibiotic-treated, or germ-free mice on in vitro induction of Foxp3 expression in naive T cells



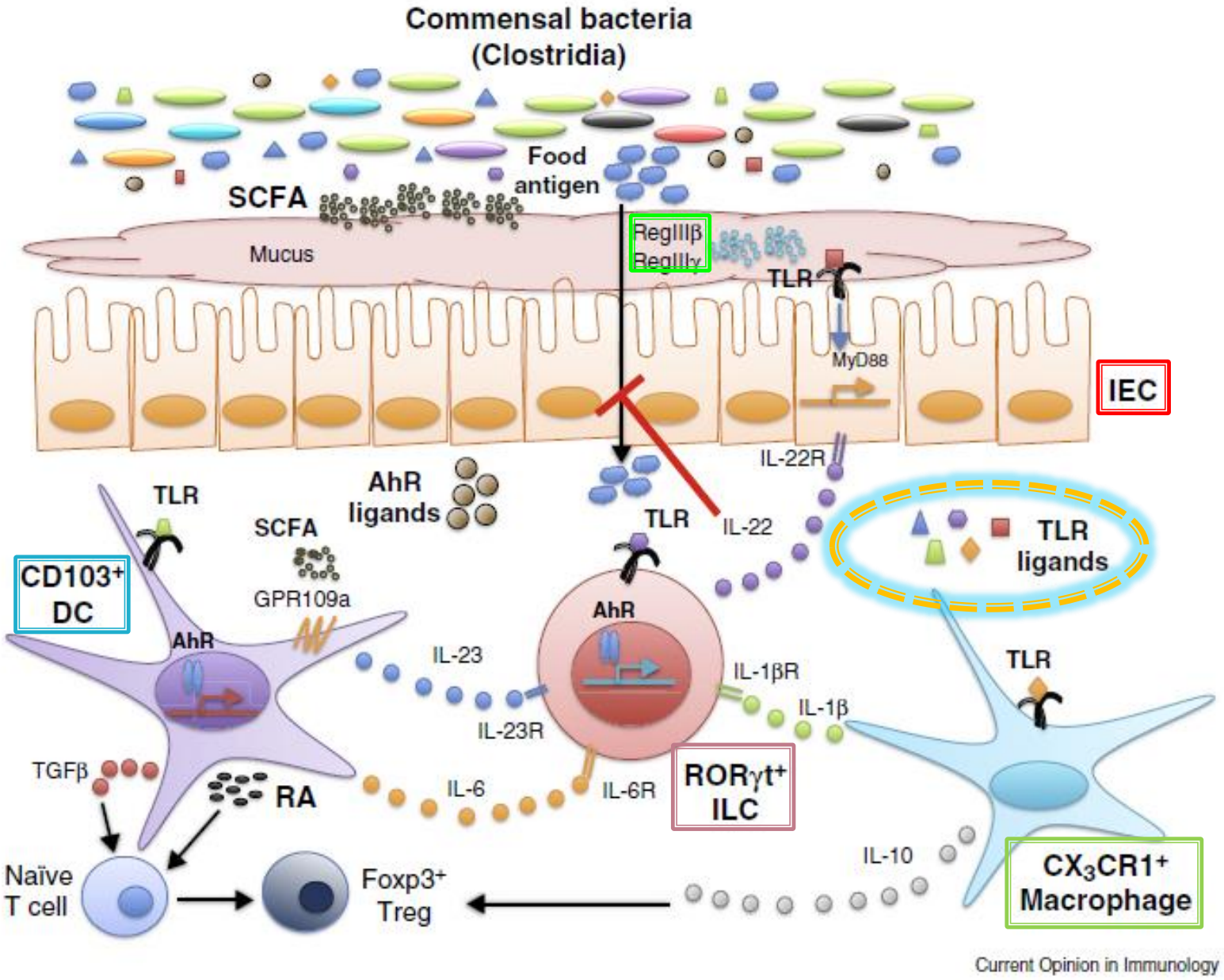
HPLC fractionation of SCFAs present in indicated faecal extracts





Effect of indicated purified SCFAs on in vitro induction of Foxp3 expression in naive T cells

Pathways through which commensal bacteria regulate allergic responses to food.



Commensal bacteria and their TLR ligands, AhR ligands and SCFAs influence intestinal homeostasis.

- TLR ligands act on IEC, CD103+ DC, CX3CR1+ macrophages, and RORgt+ ILC to promote cytokine secretion.
- TGF-b and RA produced by activated DC and IL-10 from macrophages induce conversion of naïve T cells to Foxp3+ Treg and expand this population.
- SCFAs produced by bacterial fermentation of dietary fiber act on DC via GPCRs to further promote RA production and reinforce the tolerogenic environment + Tregs.
- AhR ligands from diet or bacterial metabolism act on DC and ILC.
- IL-22 produced by ILC in response to cytokine stimulation (IL-23, IL6, or IL-1b) by DC or macrophages or by AhR stimulation act on epithelium to promote barrier integrity by inducing expression of AMPs RegIIIb and RegIIIg, increasing epithelial proliferation, and promoting mucus secretion.

This network maintains homeostasis and prevents responses to food.

Taylor Feehley and Cathryn R Nagler, 2014

frontiers in Immunology

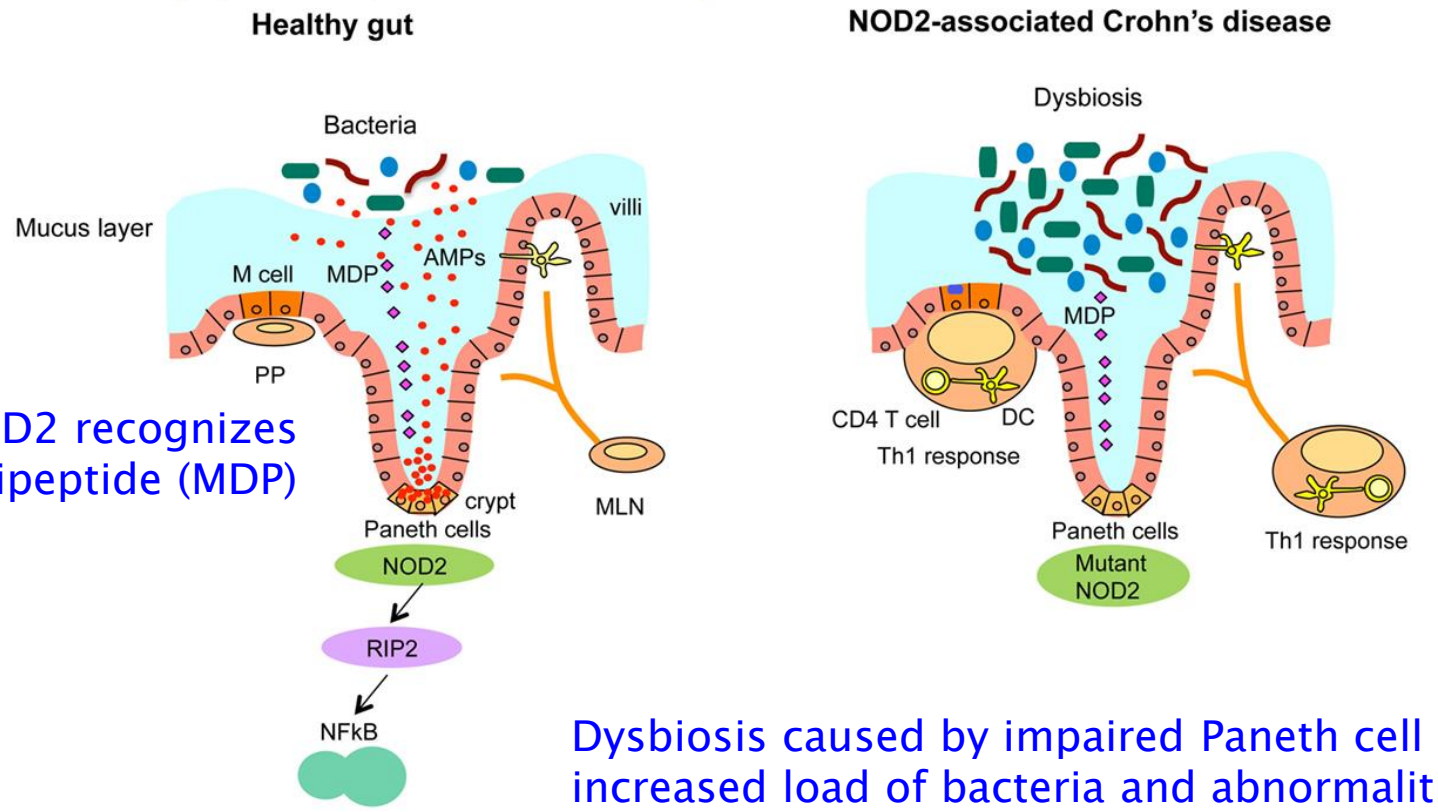
REVIEW
published: 20 September 2016
doi: 10.3389/fimmu.2016.00367

Check for updates

Nod2: A Critical Regulator of Ileal Microbiota and Crohn's Disease

*Tabasum Sidiq, Sayuri Yoshihama, Isaac Downs and Koichi S. Kobayashi**

Genome-wide association studies (GWAS) revealed 163 susceptibility loci for inflammatory bowel disease, 30 of them being specific to CD. Among them, *NOD2* was the first gene identified as a risk factor for ileal CD, discovered by the genetic mapping study of the CD susceptibility locus

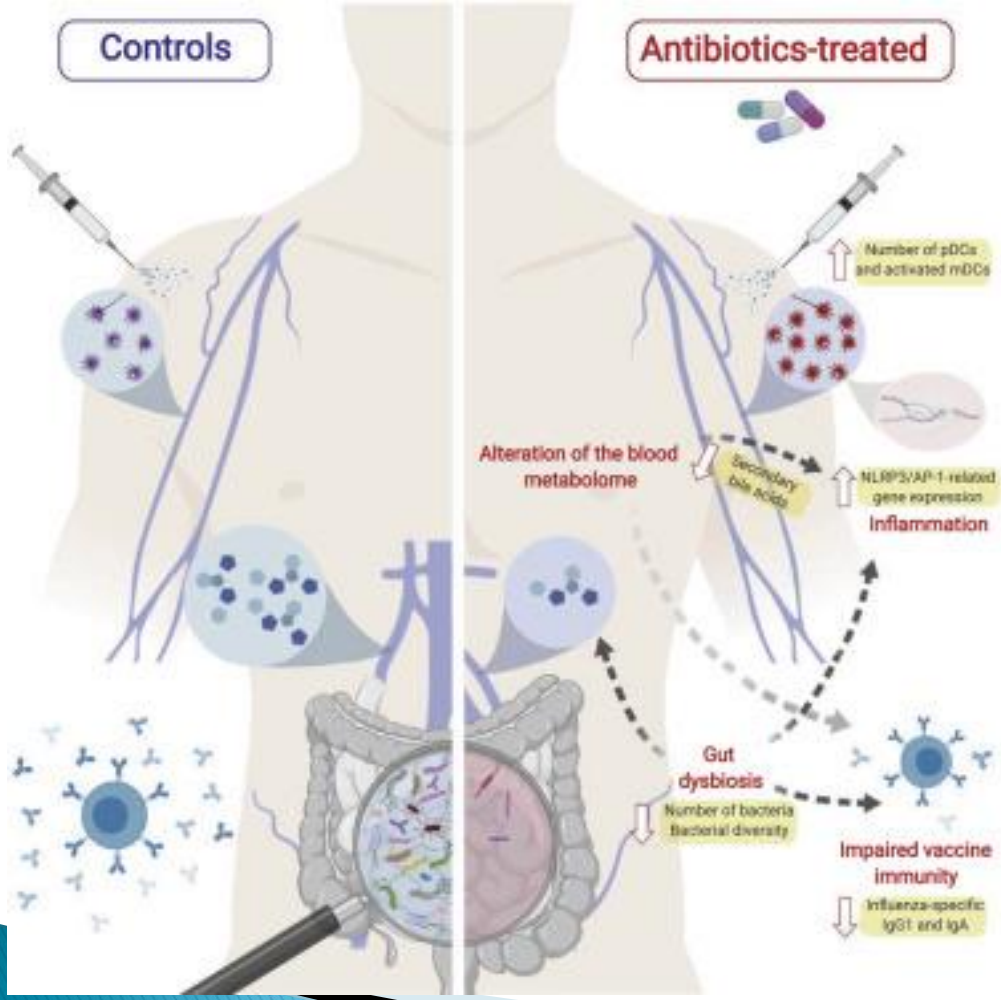


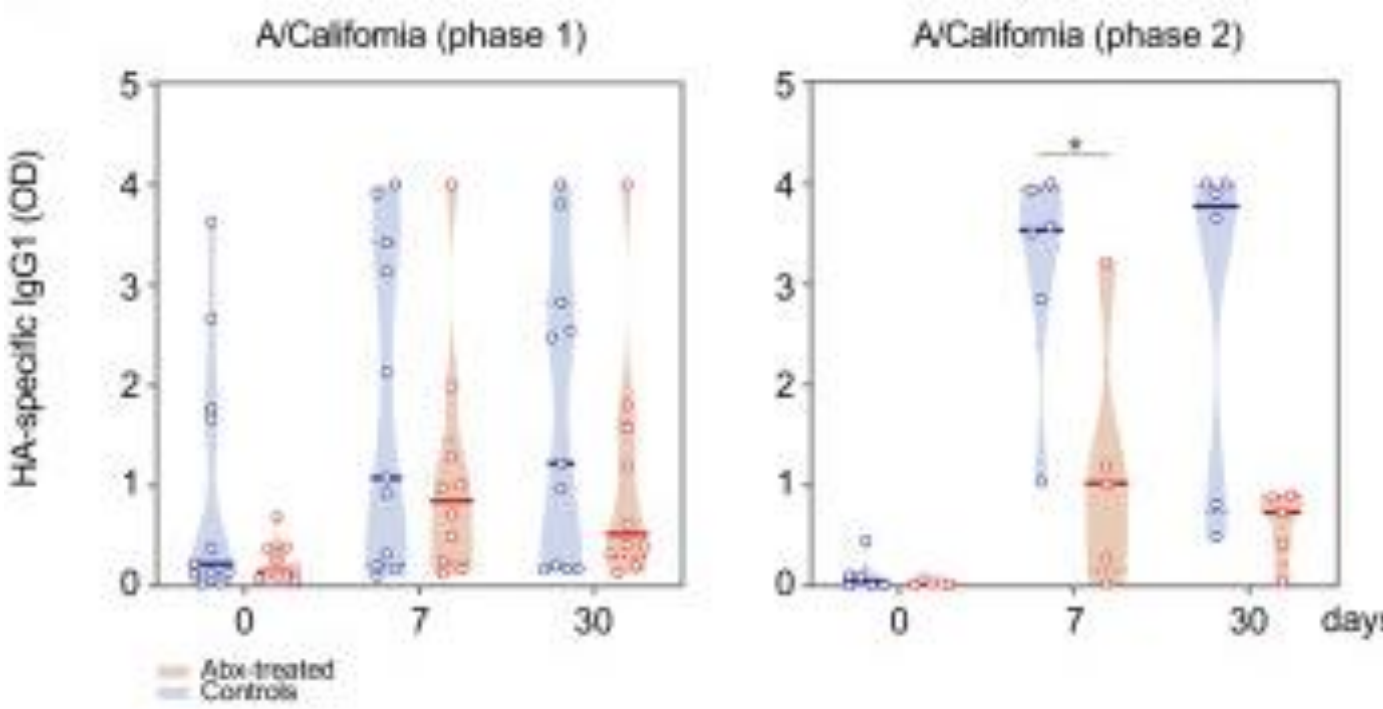
Normal NOD2 recognizes muramyl dipeptide (MDP)

Dysbiosis caused by impaired Paneth cell function is characterized by increased load of bacteria and abnormalities of Peyer's patches (PP) and mesenteric lymph nodes (MLN) that stimulate the mucosal immune system to induce Th1 immune response, leading to chronic inflammation.

Antibiotics-Driven Gut Microbiome Perturbation Alters Immunity to Vaccines in Humans

Cell, 2019. Hagan et al.



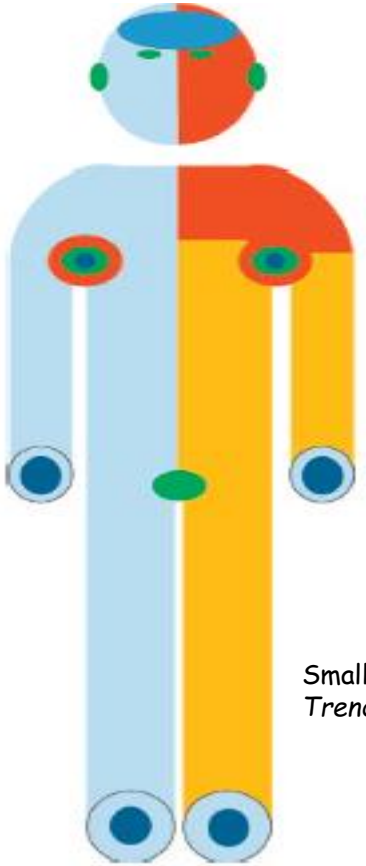


Microbiota da Pele

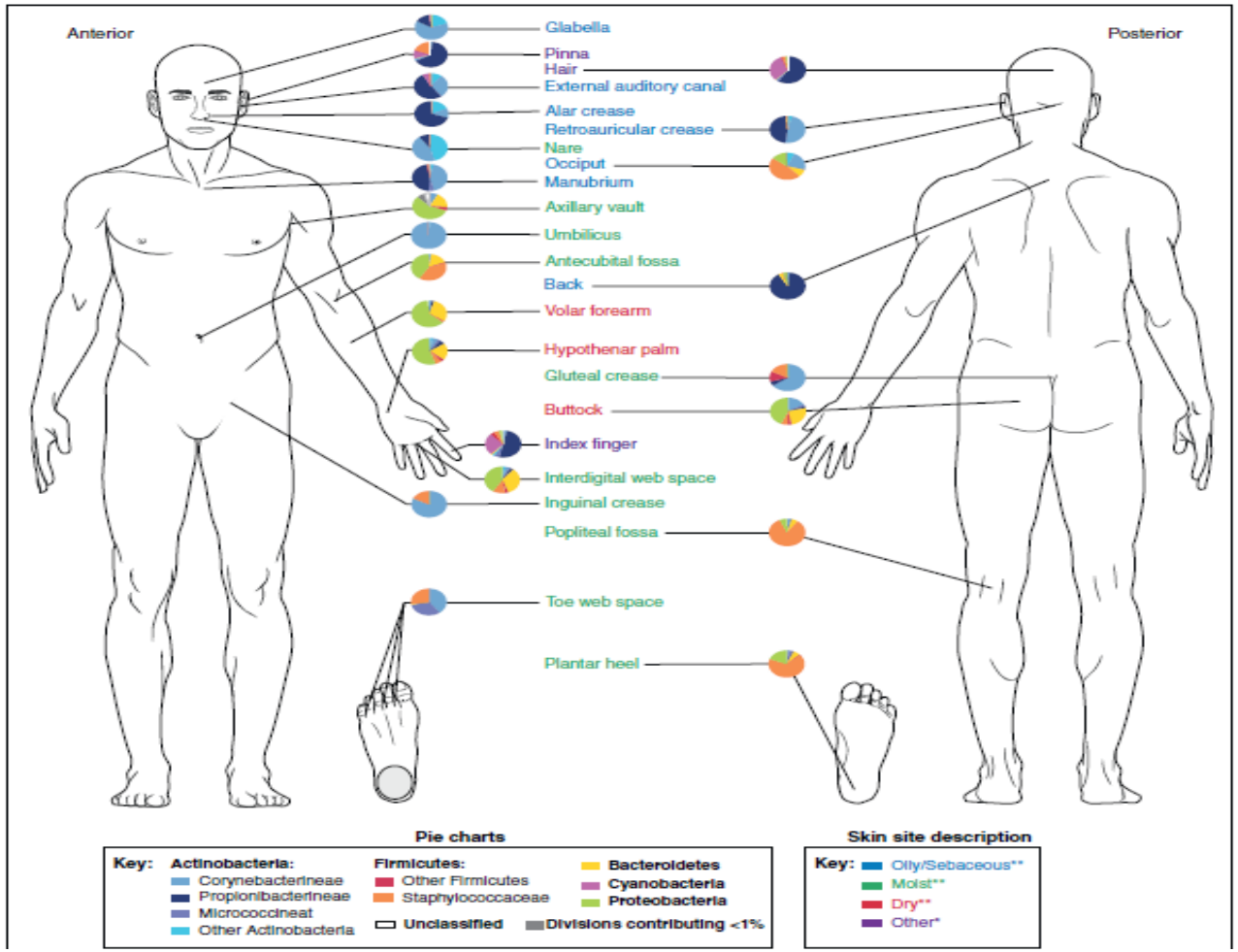
- Acne
- ~~Cicatrização~~
- ~~Psoríase~~
- ~~Atração de vetores hematófagos de doenças~~

Topographical diversity of human skin microbiome is determined by distribution of skin glands…

Key:
- Apocrine glands — Lipids, steroids, and proteins - **CHEMICAL COMMUNICATION**
- Eccrine glands, high density
- Eccrine glands, low density
  — Water; salts, proteins, amino acids, urea, ammonia, lactic acid - **Thermoregulation**
- Sebaceous glands, high density
- Sebaceous glands, low density
  — Sebum lipids - **Lubrification**



Smallegange RC, et al. Sweaty skin: an invitation to bite? *Trends Parasitol.* 2011



Kong H., Skin microbiome: genomics-based insights into the diversity and role of skin microbes. *Trends in Molecular Medicine*, 2011

Vitamin B_{12} modulates the transcriptome of the skin microbiota in acne pathogenesis

Dezhi Kang,[1] Baochen Shi,[1] Marie C. Erfe,[2] Noah Craft,[2] Huiying Li[1,3]*

Various diseases have been linked to the human microbiota, but the underlying molecular mechanisms of the microbiota in disease pathogenesis are often poorly understood. Using acne as a disease model, we aimed to understand the molecular response of the skin microbiota to host metabolite signaling in disease pathogenesis. Metatranscriptomic analysis revealed that the transcriptional profiles of the skin microbiota separated acne patients from healthy individuals. The vitamin B_{12} biosynthesis pathway in the skin bacterium *Propionibacterium acnes* was significantly down-regulated in acne patients. We hypothesized that host vitamin B_{12} modulates the activities of the skin microbiota and contributes to acne pathogenesis. To test this hypothesis, we analyzed the skin microbiota in healthy subjects supplemented with vitamin B_{12}. We found that the supplementation repressed the expression of vitamin B_{12} biosynthesis genes in *P. acnes* and altered the transcriptome of the skin microbiota. One of the 10 subjects studied developed acne 1 week after vitamin B_{12} supplementation. To further understand the molecular mechanism, we revealed that vitamin B_{12} supplementation in *P. acnes* cultures promoted the production of porphyrins, which have been shown to induce inflammation in acne. Our findings suggest a new bacterial pathogenesis pathway in acne and provide one molecular explanation for the long-standing clinical observation that vitamin B_{12} supplementation leads to acne development in a subset of individuals. Our study discovered that vitamin B_{12}, an essential nutrient in humans, modulates the transcriptional activities of skin bacteria, and provided evidence that metabolite-mediated interactions between the host and the skin microbiota play essential roles in disease development.

Science Translational Medicine.org 24 June 2015 Vol 7 Issue 293 293ra103

The metatranscriptional activities of the skin microbiota in acne patients are distinct from those in healthy individuals

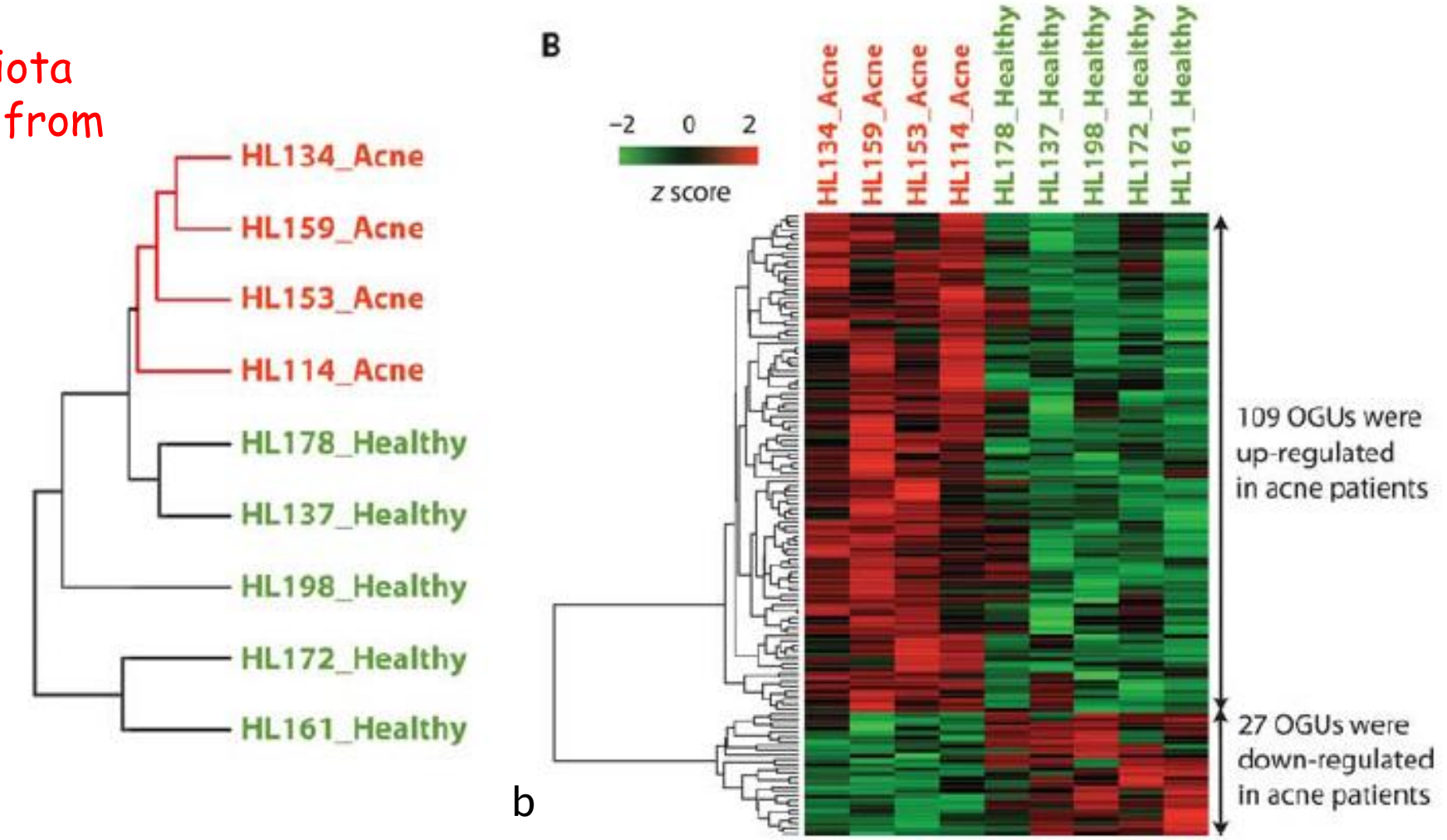
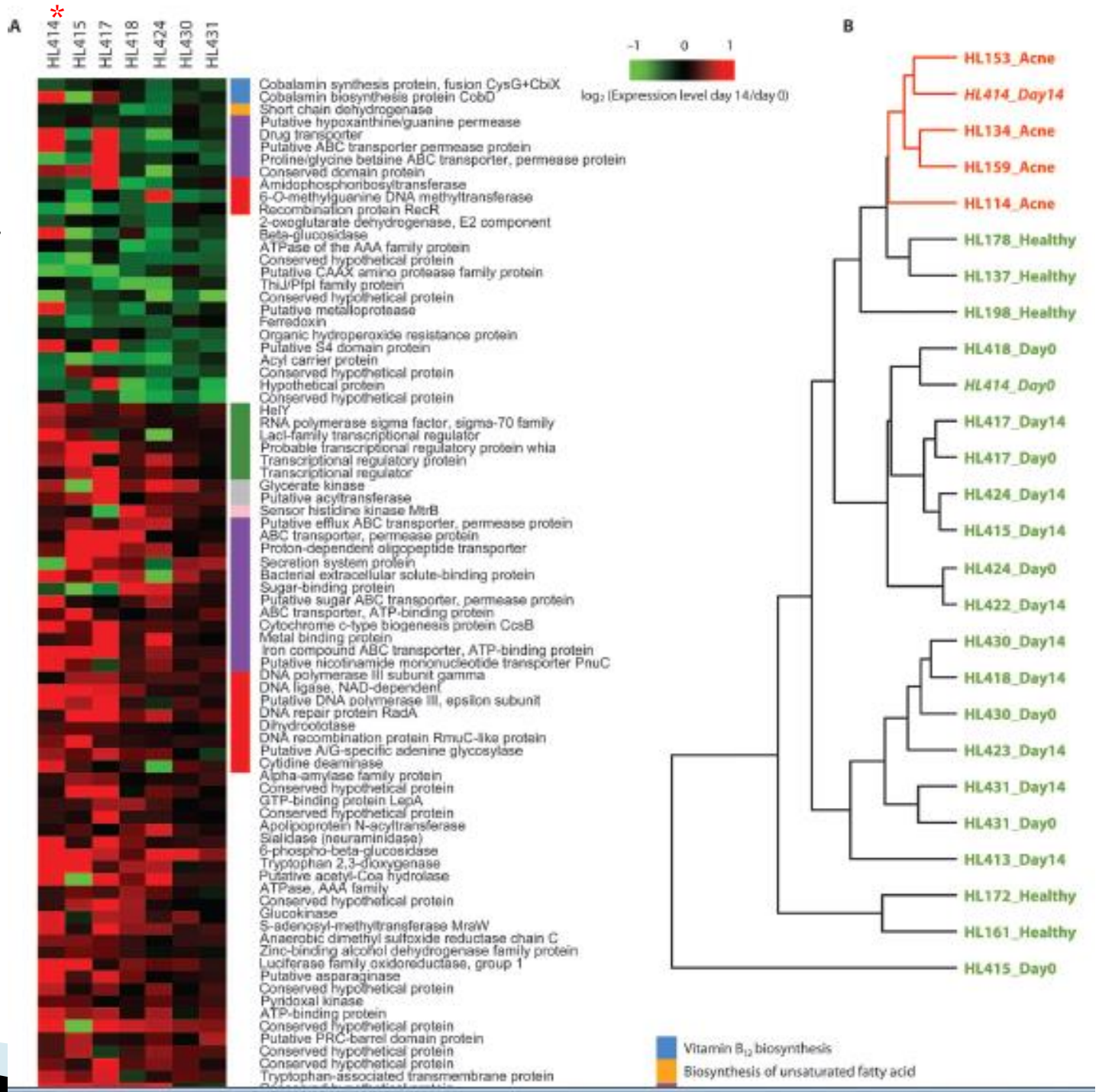


Fig. 1. The gene expression profiles of *P. acnes* in the skin microbiota were distinct between acne patients and healthy individuals. (**A**) On the basis of the gene expression of *P. acnes* in the skin microbiota, acne patients (labeled in red, "Acne") formed a separate cluster from healthy individuals (labeled in green, "Healthy") in an unsupervised hierarchical clustering analysis. (**B**) One hundred thirty-six differentially expressed *P. acnes* OGUs were identified between acne patients and healthy individuals. Among them, 109 OGUs were up-regulated and 27 OGUs were down-regulated in acne patients. The OGU names are listed in table S2.

Vitamin B12 supplementation in the host altered the transcriptome of P. acnes in the skin microbiota

HL414, but not others in healthy cohort, developed acne after vitamin B12 supplementation,



Induction of a chemoattractive proinflammatory cytokine response after stimulation of keratinocytes with *Propionibacterium acnes* and coproporphyrin III.

Schaller *et al*. Br. J. Dermatol. 153, 66–71 (2005)

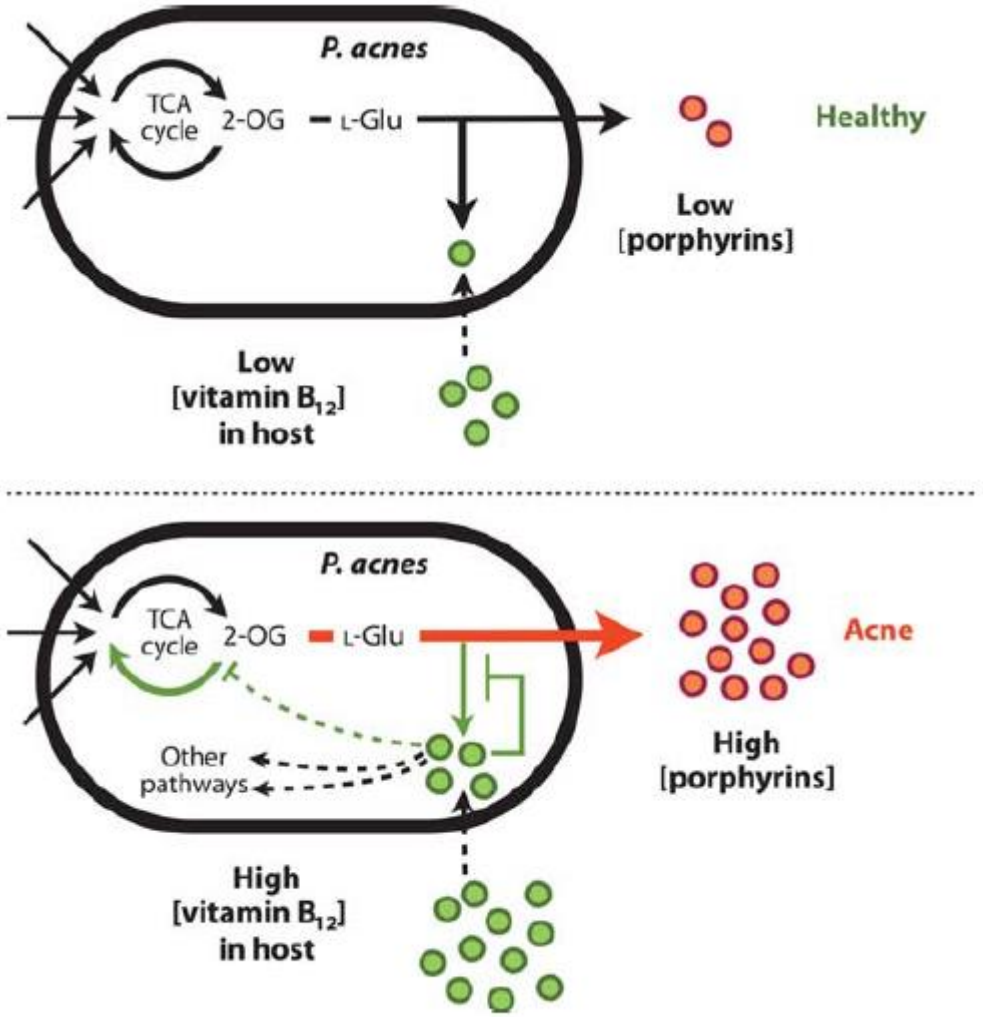


Fig. 7. A model of vitamin B_{12} modulating the transcriptional and metabolic activities of the skin bacterium *P. acnes* in acne pathogenesis. In

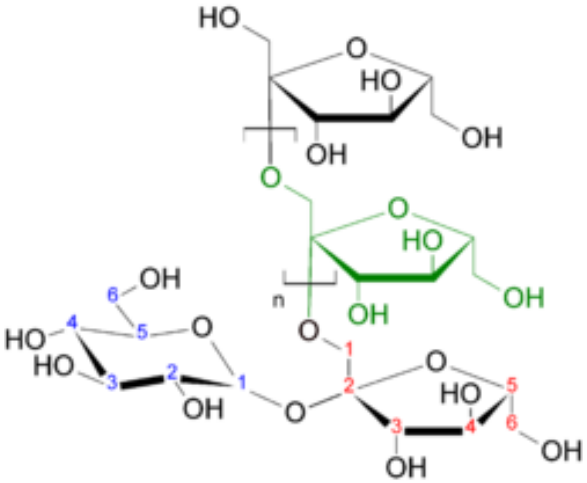
Terapias baseadas em manipulação da microbiota

- **Probiotics:**
  - live bacteria which are intended to colonize the large intestine, although as of 2018, there is no evidence that adding dietary bacteria to healthy people has any added effect

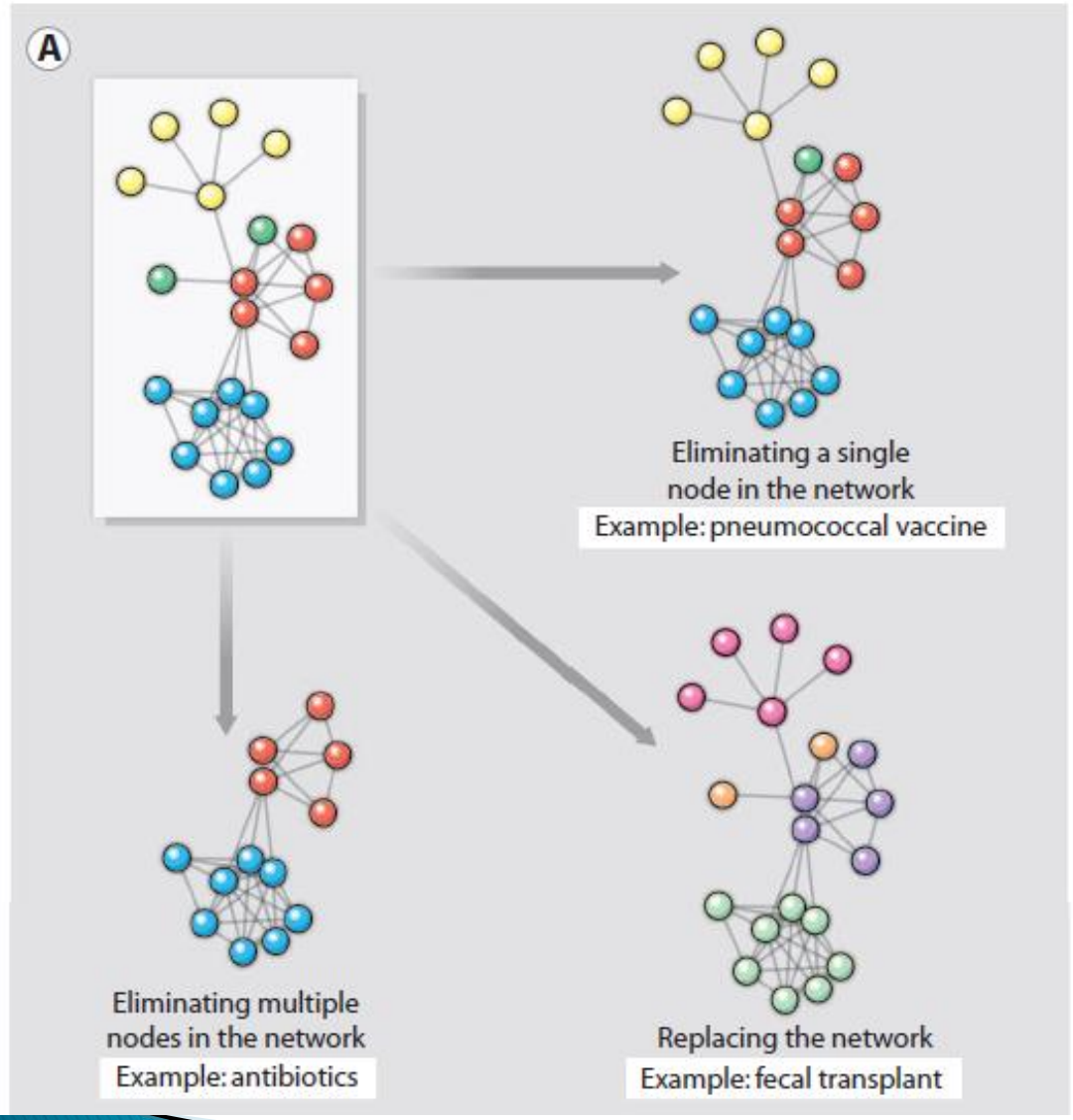
- **Prebiotics**
  - a food or dietary supplement product that may induce the growth or activity of beneficial microorganisms
  - A prebiotic may be a fiber, but a fiber is not necessarily always a prebiotic

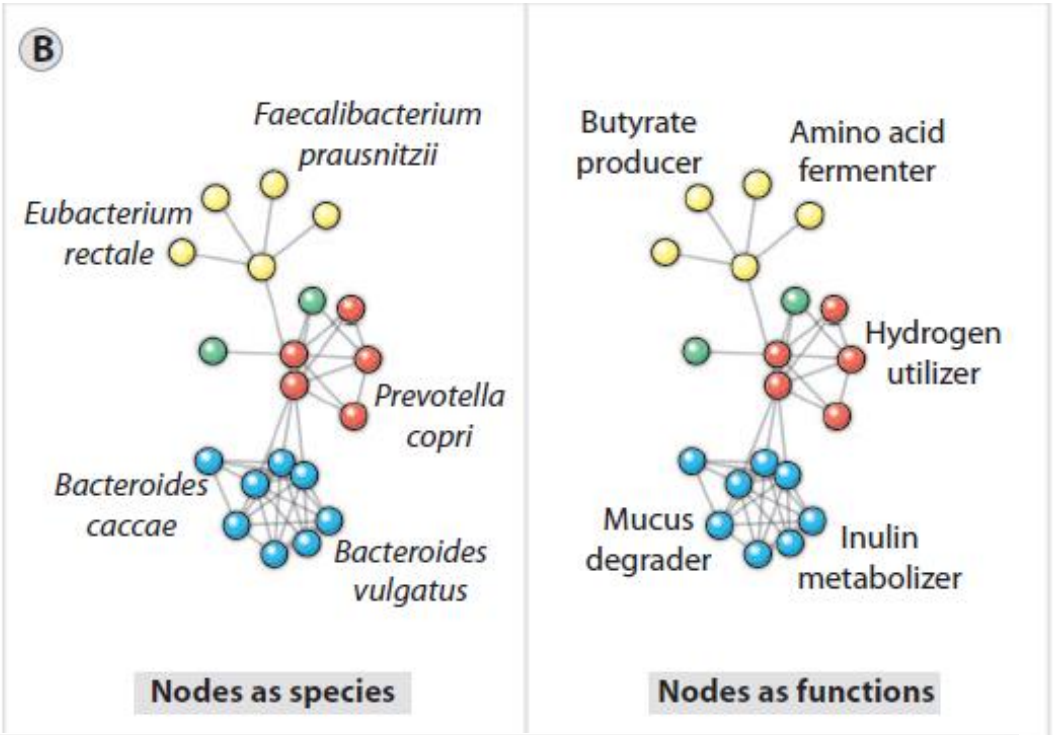
- **Synbiotics**
  - **food ingredients or dietary supplements combining probiotics and prebiotics in a form of synergism, hence synbiotics**
  - "*mixtures of probiotics and prebiotics that beneficially affect the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract, by selectively stimulating the growth and/or by activating the metabolism of one or a limited number of health-promoting bacteria, thus improving host welfare*"
  - **research on this concept is preliminary, with no high-quality evidence from clinical research that such benefits exist**

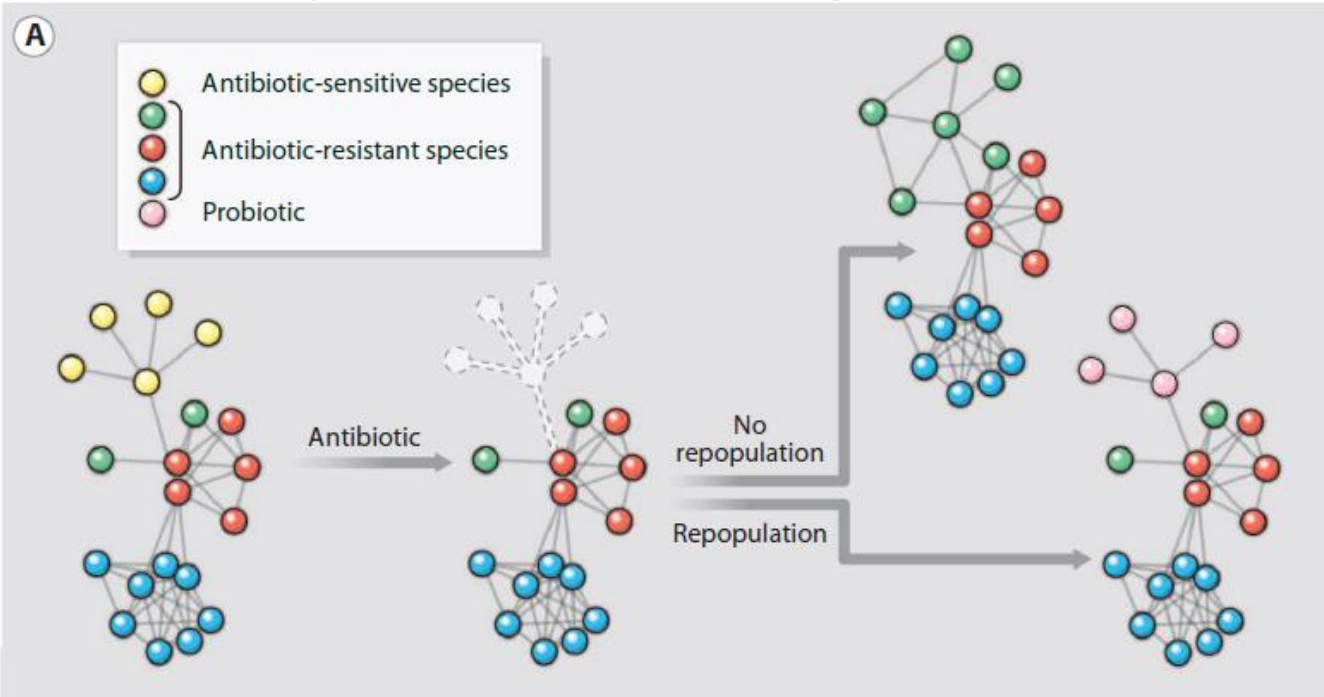
- **Examples**
  - **Bifidobacteria and Fructooligosaccharides (FOS)**
  - **Lactobacillus rhamnosus GG and inulins**



Microbial communities as networks.







TRANSPLANT INFECTIOUS DISEASE
AN OFFICIAL JOURNAL OF THE TRANSPLANTATION SOCIETY

Transplant Infectious Disease, ISSN 1398-2273

Case report

Fecal microbiota transplantation for fulminant *Clostridium difficile* infection in an allogeneic stem cell transplant patient

K. Neemann, D.D. Eichele, P.W. Smith, R. Bociek, M. Akhtari, A. Freifeld. Fecal microbiota transplantation for fulminant *Clostridium difficile* infection in an allogeneic stem cell transplant patient.
Transpl Infect Dis 2012: **14**: E161–165. All rights reserved

Abstract: We present a case of severe *Clostridium difficile* infection (CDI) in a non-neutropenic allogeneic hematopoietic stem cell transplant recipient who was treated successfully with fecal microbiota therapy after standard pharmacologic therapy had failed. Following naso-jejunal instillation of donor stool, the patient's

K. Neemann[1], D.D. Eichele[2], P.W. Smith[1], R. Bociek[3], M. Akhtari[3], A. Freifeld[1]

[1]Infectious Diseases Division, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA, [2]Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA, [3]Section of Hematology/Oncology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA

The data to date indicate that probiotics may have a role in treatment, but their efficacy is less than ideal.

In contrast, "Fecal Microbiota Transplantation (FMT)" is proving to be an effective alternative intervention. Case reports and small case series to date suggest that recurrent CDI can be cured with a single treatment.

The material is readily available and very inexpensive.

The rationale behind FMT is simple: antibiotics and other factors disrupt the normal balance of colonic flora and reduce "colonization resistance," allowing pathogenic *C. difficile* strains to grow, leading to the typical clinical presentations of diarrhea and pseudomembranous colitis; by reintroducing normal flora via donor feces, the imbalance can be corrected, the cycle interrupted, and normal bowel function re-established."

Ancient Roots

Stool transplantation is far from new and not limited to human conditions.

Fourth century Chinese medical literature mentions its use for treating food poisoning and severe diarrhea.

The influential 16th century Chinese physician, herbalist, and acupuncturist, Li Shizhen, used "yellow soup," "golden syrup," and other remedies containing fresh, dried, or fermented stool to treat abdominal diseases.

Today's veterinarians practice "transfaunation," a treatment for ruminating animals, known to the Italian anatomist, Fabricius Aquapendente (1533-1619). In transfaunation, stomach microorganisms are transferred from healthy donor animals to a sick animals, often leading to cures.

LETTERS
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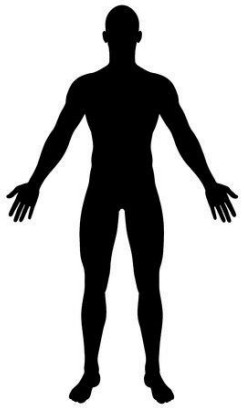
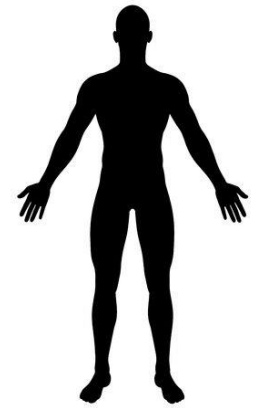
Gut bacteria responding to dietary change encode sialidases that exhibit preference for red meat-associated carbohydrates

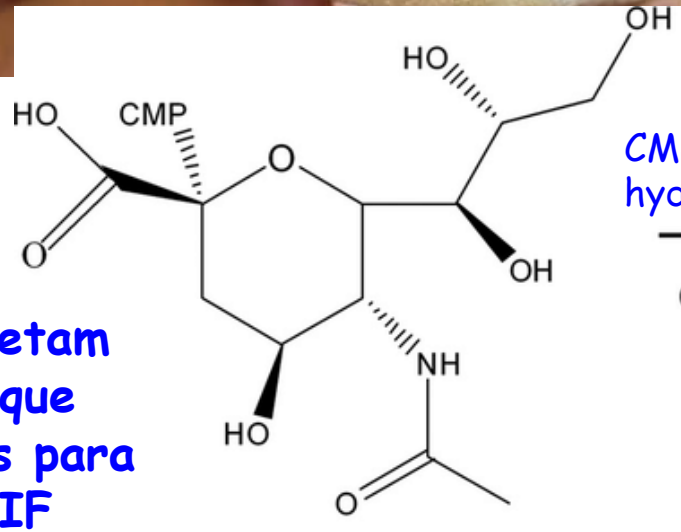
Livia S. Zaramela[1,10], Cameron Martino[1,2,10], Frederico Alisson-Silva[3,4,9,10], Steven D. Rees[5], Sandra L. Diaz[3,4], Léa Chuzel[6], Mehul B. Ganatra[6], Christopher H. Taron[6], Patrick Secrest[3,4], Cristal Zuñiga[1], Jianbo Huang[5], Dionicio Siegel[5], Geoffrey Chang[5], Ajit Varki[3,4] and Karsten Zengler[1,7,8*]

Dietary habits have been associated with alterations of the human gut resident microorganisms contributing to obesity, diabetes and cancer[1]. In Western diets, red meat is a frequently eaten food[2], but long-term consumption has been associated with increased risk of disease[3,4]. Red meat is enriched in *N*-glycolylneuraminic acid (Neu5Gc) that cannot be synthesized by humans[5]. However, consumption

(Neu5Ac) to Neu5Gc[19–21]. It is currently unknown how bound-Neu5Gc is metabolized in the gut. Once free, sialic acids can be taken up through membrane-associated transporters and used as carbon, nitrogen or energy sources, or used to sialilate bacterial cell surface glycans[16]. In addition, changes in the intestinal concentration of sialic acids, for example induced by inflammation, can alter the expression of bacterial genes involved in sialic acid catabolism

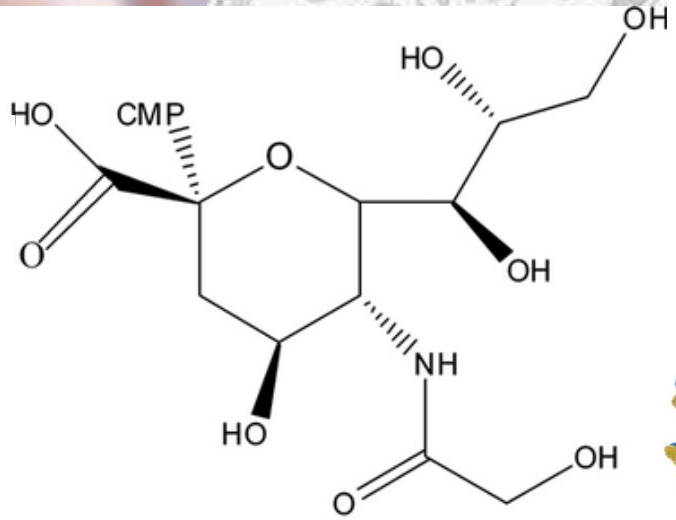






CMP-Neu5Ac hydroxylase

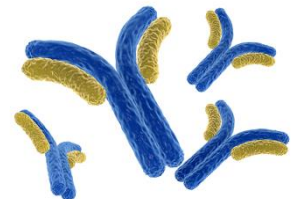
CMAH



Padrões de ácidos siálicos afetam suceptibilidade a patógenos, que aderem a padrões específicos para invadir o hospedeiro, e.g., VIF

N-acetylneuraminic acid (Neu5Ac)

N-glycolylneuraminic acid (Neu5Gc)



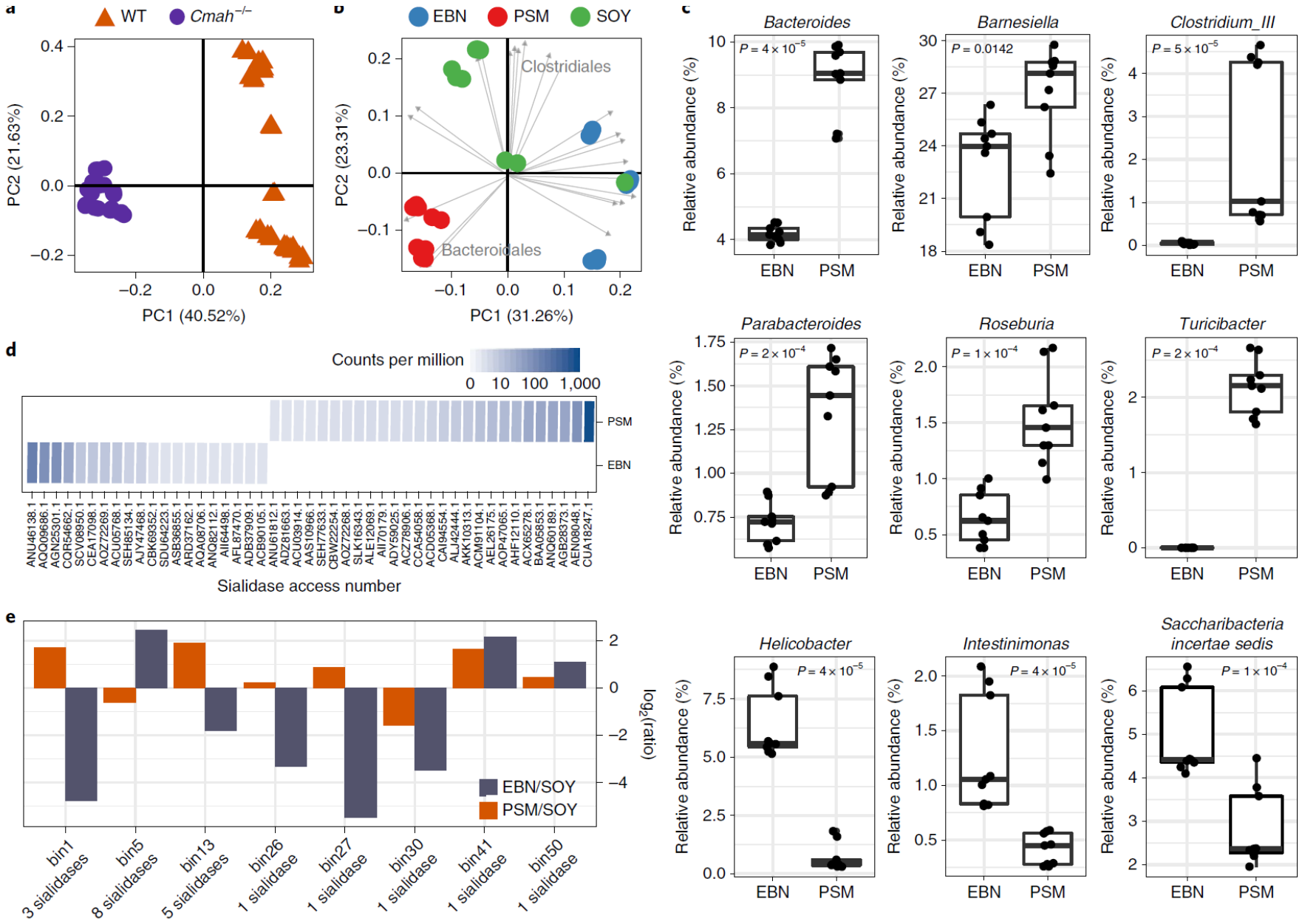
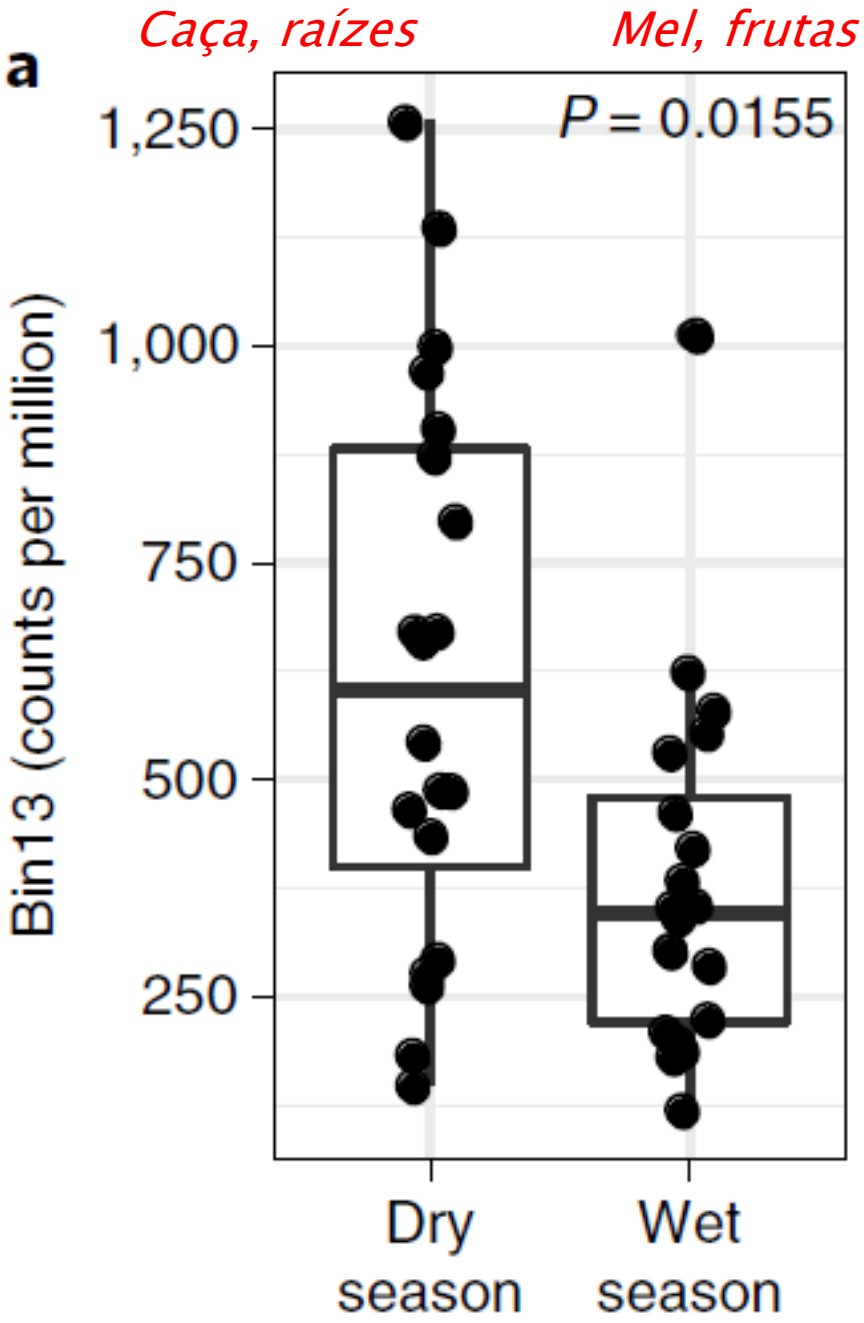


Fig. 1 | Composition of gut microbial community of mice fed on soy, PSM or EBN diet. a, Beta-diversity analysis of WT versus *Cmah*$^{-/-}$ mouse. Pairwise

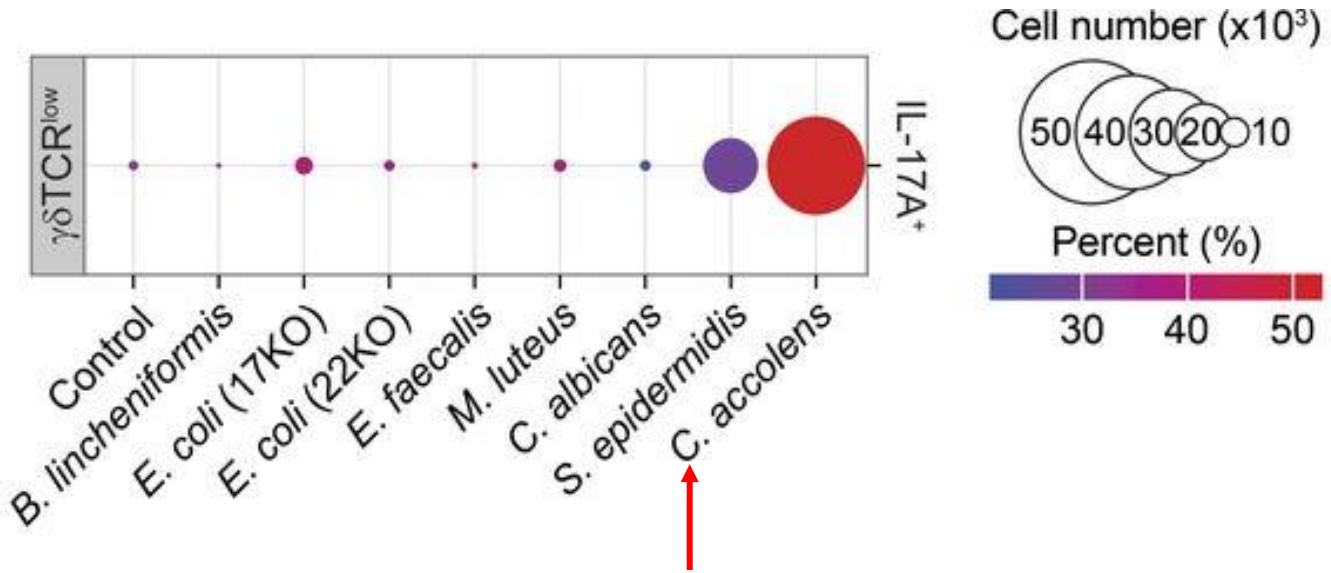
Caça, raízes *Mel, frutas*



- Sialidases with preference for Neu5Gc are enriched in the gut microbiota of mice and humans on consumption of a Neu5Gc-rich diet.
- Cleavage of Neu5Gc from foods entering the gut can prevent incorporation of this non-human sugar into the colon tissue.
- Hypothesis: gut microbiome with an under representation of bacteria with Neu5Gc-preferring sialidases could result in increased xenosialitis and be a potential contributing factor to inflammation-mediated promotion of diseases.
- Results lay the foundation to define a strategy for translation of pre- or probiotics to prevent incorporation or to eliminate Neu5Gc from tissues of red meat eaters, thereby reducing the risk of xenosialitis and other diseases associated with red meat consumption.

Relative abundance of bin13 in samples from Hadza hunter-gatherers population

Action of skin microbiota on immunity of host skin



Nos of IL-17-producing γδ lymphocytes in skin vary according to species of microbial commensals.

Contextual control of skin immunity by ***Corynebacterium***.

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