Die Holobionten - Revolution

Das Mikrobiom und seine Bedeutung für unsere Gesundheit

Martin Grassberger

INTERVIEW

Universität die Fachgebiete Human- und Gesundheitsökologie, Evolutionäre Medizin, Forensische Medizin sowie Pathologie lehrt. Oder Vorträge hält. Oder an Publikationen schreibt.

Plädoyer für Biolandwirtschaft

Zudem ist Martin Grassberger ausgebildeter landwirtschaftlicher Facharbeiter. Er weiß, wovon er spricht, wenn er sich für regenerative Biolandwirtschaft und eine Abkehr von industriellen Methoden auf dem Acker einsetzt. Sein Garten läßt jedenfalls zum Verweilen und Sinnieren ein – und zum Beobachten vielfältig surrenden, brummenden, flatternden Lebens.

„Ohne gesunde Nahrung gibt es kein gesundes Leben. Lebensmittel sind Information für uns."

Essen selbst anzubauen ist für einen Naturwissenschafter wohl nicht alltäglich. Woher kommt das? Sieht man als Gerichtsmediziner, dass wir an falscher Ernährung sterben?

Grassberger: Es stimmt schon: Bei Leichenöffnungen sieht man die körperlichen Endpunkte einer lebenslang falschen Ernährung, und das ist eindrucksvoll. Zu sagen, das sei der Grund, warum ich mich damit beschäftige, wäre jedoch zu kurz gegriffen. Die Frage müsste eher andersherum lauten: Wie kann jemand, der sich sein Leben lang mit Natur und Landwirtschaft beschäftigt hat, Gerichtsmediziner werden? Die Antwort ist völlig unspektakulär: zufällig. Meine Liebe zur Natur hängt sicher damit zusammen, dass ich in ländlicher Umgebung aufgewachsen bin und fast jeden Sommer mit meinen Eltern im Südwesten von England bei Freunden auf einem Bauernhof verbracht habe. Die Gerüche, die Hunde, der Wald, die Wiesen, der Stall ... all dies hat mich geprägt.

Was aber war es, das Sie für die Gerichtsmedizin begeistern konnte?

Grassberger: Die Gerichtsmedizin ist eine Art Schnittmenge meiner beiden Studien Medizin und Biologie – oder auch von Leben und Tod. Deshalb bin ich wohl dort gelandet. Vor allem der postmortale Teil wird sehr biologisch. Da geht es um Vorgänge, bei denen ehemals lebende Strukturen in Einzelteile zerlegt werden. Und dann stehen chemische Elemente wieder zur Verfügung – wie Lagerstätte – und es wird neues Leben daraus gebaut.

Auf dem Weg vom Zerlegen zum Neubeginn gibt es spannende Stationen, gerade was Ernährung betrifft: Sauerteig, Hefe, fermentiertes Gemüse ... Offenbar machen wir uns diese Abbauprozesse gern zunutze.

Grassberger: Ohne mikrobiologische Prozesse läuft generell nicht viel. Ob das nun Genussmittel von Wein bis Bier, Käse, Kimchi, Sauergurken oder Sauerkraut sind oder unsere Geruchswahrnehmung, die auch von Mikroben beeinflusst werden dürfte. Und das Mikrobiom – jene Billionen von Bakterien und Pilzen, die unseren Körper besiedeln – ist ja überhaupt unsere zentrale Software-Einheit.

Ihr Buch „Das leise Sterben" wurde 2020 als Wissenschaftsbuch des Jahres ausgezeichnet. Sie schreiben darin, dass es einen unmittelbaren Zusammenhang zwischen dem Anstieg chronischer Krankheiten, der Zerstörung der Natur und der Sackgasse gibt, in die uns die industrielle Landwirtschaft geführt hat. Was macht die Ernährung mit uns?

Grassberger: Ohne gesunde Nahrung gibt es kein gesundes Leben. Lebensmittel sind Information. Für uns. Und zwar im naturwissenschaftlichen Sinn. Das einfachste Beispiel ist, dass ein Lebensmittel Insulin anzeigen kann, ein anderes aber nicht. Das ist eine Information, die der Körper bekommt und reagiert: Was tu ich jetzt, um mit dieser aufgenommenen Nahrung umzugehen? Es ist eine Information fürs Mikrobiom, wer sich dort vermehren kann und wer nicht. Ein anderes Beispiel sind sekundäre Pflanzeninhaltsstoffe, die alleine oder in Verbindung mit dem Mikrobiom auf die epigenetische Expression wirken. Und dann gibt's noch etwas ganz Neues: Es ist möglicherweise an, dass microRNAs, also ganz kurze Gen-Abschnitte, aus Pflanzen direkt auf den Menschen übergehen und dort das Ablesen von Genen unterbinden können. Und dass sie dadurch – zum Beispiel was Tumorentstehung oder -verhinderung betrifft – möglicherweise für die Wirkung mancher Lebensmittel verantwortlich sind. Da wird's dann richtig spannend ...

Bedeutet das, dass auch Pflanzenschutz- und Düngemittel unmittelbar auf oder in uns wirksam werden?

Grassberger: Das heißt, dass es nicht egal ist, was da ist. Es ist auch nicht so, dass sich das mechanistisch zerlegen lässt und wir sagen können, solange die Makro- und Mikronährstoffe in der richtigen Komposition hast, lebst du gesund. Es kommt eben darauf an. Die angesprochenen Spritzmittel wirken sich Studien zufolge jedenfalls negativ auf das Mikrobiom aus.

Es zeigt sich, dass eine Ernährung, die ähnlich der sogenannten mediterranen gestaltet ist, vor Krankheiten schützt. Bei manchen den Verlauf bessert oder sogar heilen kann. Und was ist das? Eine saisonale und regionale Pflanzenvielfalt mit hoher Nährstoffdichte. Wenn möglich aus einem lebendigen Erdboden und frei von Schadstoffen. Aber nebenbei bemerkt ist es mehr, was Menschen in manchen Zonen der Erde besonders alt werden lässt: moderate Bewegung, ausgeprägtes Sozialleben und ein gewisses Naturerlebnis.

Inwiefern spielt das Naturerlebnis eine Rolle?

Grassberger: Intakte Natur tut uns nicht nur als Lieferantin von Lebensmitteln gut. Was von Pflanzen als flüchtigen organischen Stoffen abgegeben wird, ist wahrscheinlich ebenso beteiligt wie das mikrobielle Leben. Wir wissen auch, dass es in Haushalten, wo viele Bakterien oder deren Bestandteile in der Luft sind, weniger Allergien gibt. Aber die Medizin sagte bisher: Bakterien sind Krankheitserreursacher. Natürlich kann es passieren, dass du in einem Stall eine furchtbare Krankheit bekommst. Aber die Chance ist sehr gering. Und das ist auch etwas, worauf ich in meinem neuen Buch hinweise. Es ist nicht gut oder schlecht, nicht gesund oder krank, nicht entweder-oder. Diese Dichotomie, die wir gerne hätten, gibt es nicht. Es müssen alles permanent in der Gesamtschau betrachtet werden. Es kommt eben immer darauf an ...

Können wir das? Können wir alles in der Gesamtschau sehen – und verdauen?

Grassberger: Da das Leben ziemlich komplex ist, wohl eher nicht. Wenn ich jemanden permanent Negativschlagzeilen aussetze, was alles Schlimmes passieren wird, dann resigniert er paradox oder steckt den Kopf in den Sand. Deswegen glaube ich auch, dass man positive Aspekte hervorkehren sollte. Wo liegen die Vorteile, die Natur zu erhalten? Wie gut tut es dir? Sich engagieren bedeutet, Dinge zum Thema zu machen. Und das in einem positiven Frame.

Ist das ein Lösungsansatz?

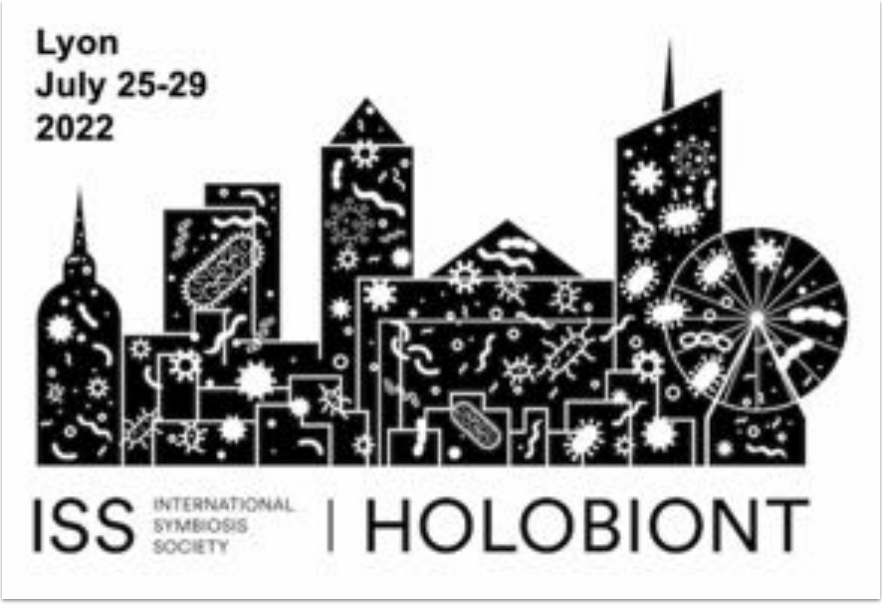
Grassberger: Ich bin überzeugt, dass ich etwas gernhaben muss, damit ich es erhalten will. Wenn es gelingt, in der Jugend die Beziehung zu einer intakten Natur herzustellen, will man sie später auch. Vielleicht ähnlich wie Naturvölker, die mit einer animistischen Weltsicht leben: Da leben Steine, es gibt „Berg der Bär" und insgesamt eine innige Beziehung zu Mutter Natur. ♥

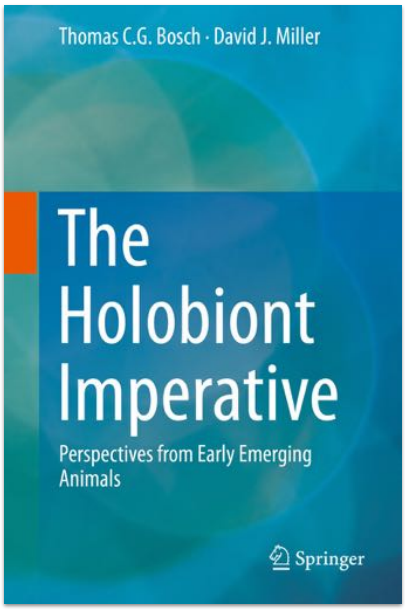
BUCH

„Das unsichtbare Netz des Lebens"

Basierend auf umfassenden ökologischen Betrachtungen und unter Berücksichtigung neuester wissenschaftlicher Erkenntnisse der Mikrobiom-Forschung zeigt Martin Grassberger in seinem neuen Buch Schlüsse über die fundamentalen Wechselwirkungen zwischen Mensch und Umwelt. Und er beschreibt, was gutes, gesundes Leben trotz beunruhigender Entwicklungen möglich machen könnte. Die enthaltenen Zugänge, Denkansätze und Antworten sind so vielfältig wie das berufliche Spektrum des Autors, der sich selbst als „Generalist" bezeichnet – mit allen Vor- und Nachteilen und nicht selten heftigen Gegenstimmen.

„Das unsichtbare Netz des Lebens", Martin Grassberger, Residenz Verlag, 240 S., 2021





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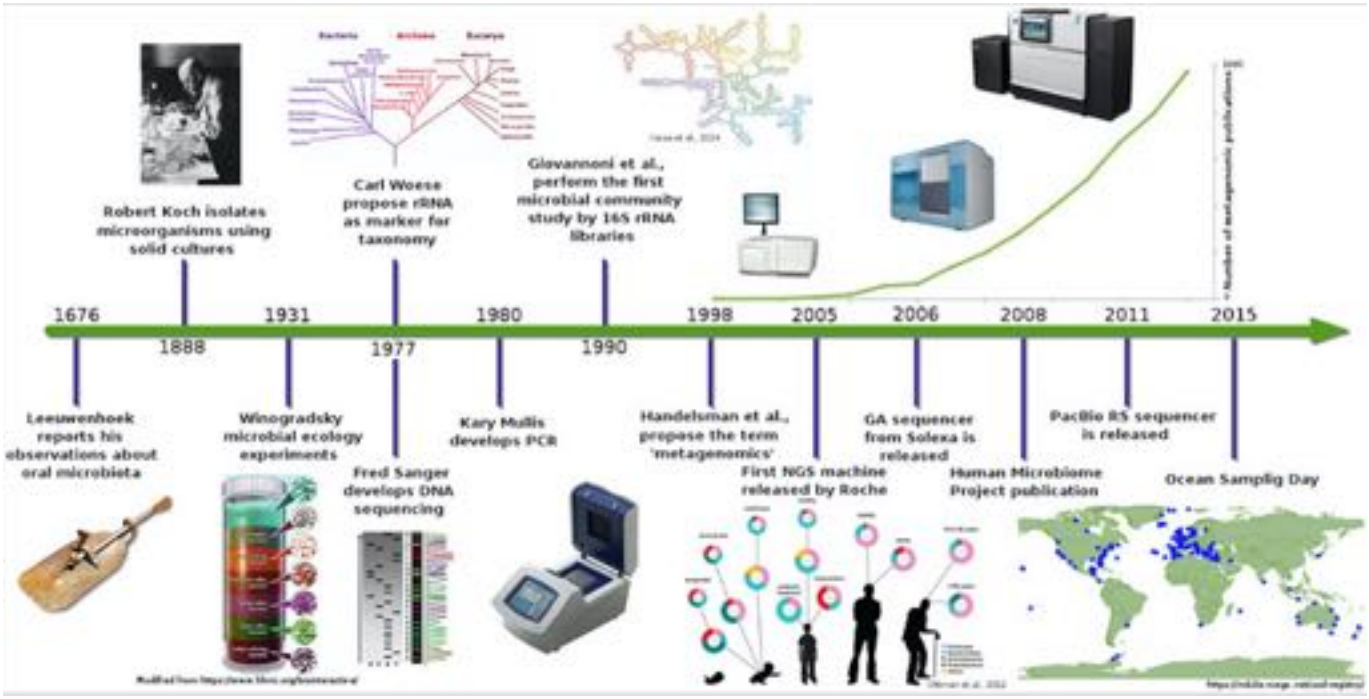
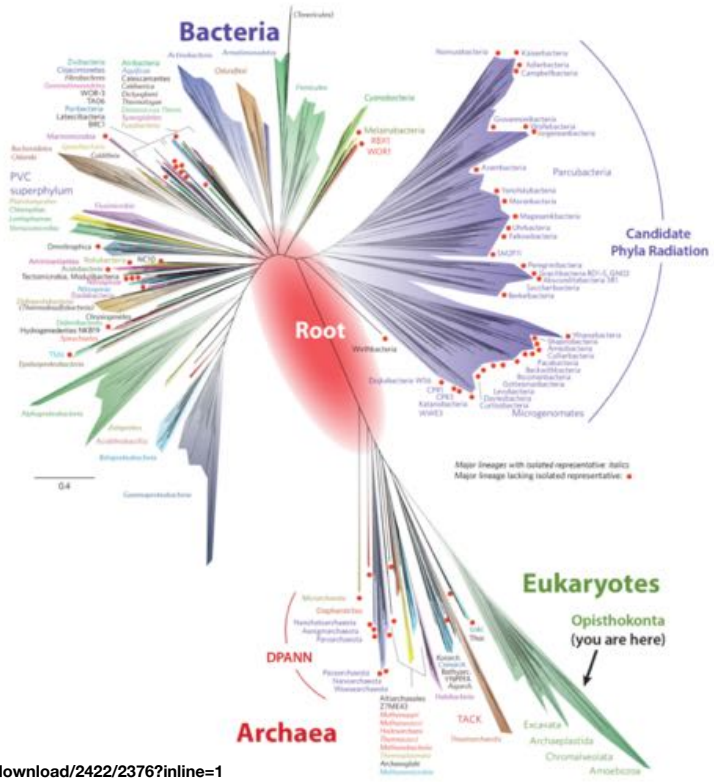
Bodengesundheit
Pflanzengesundheit
Klimaresilienz
Nachhaltige Ressourcennutzung
Biodiversität
Ernährungssicherheit
menschliche Gesundheit





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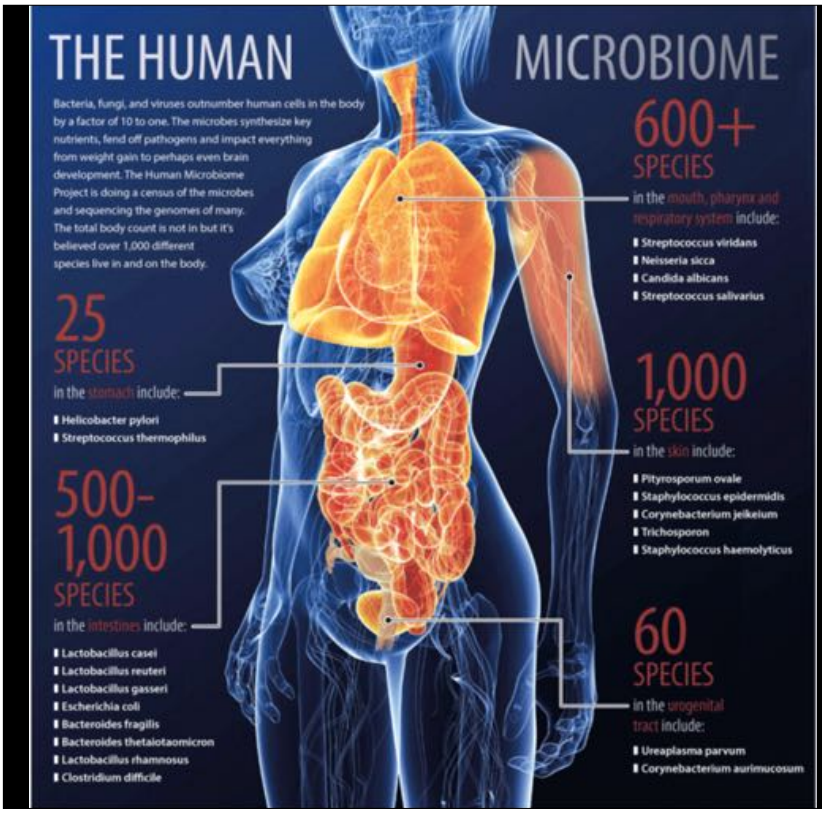
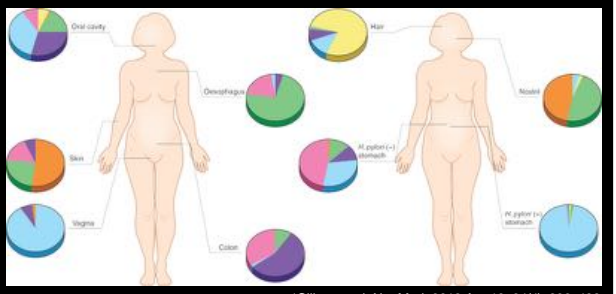




*Gilbert et al. Nat Med. 2018 Apr 10; 24(4): 392–400.

Das Mikrobiom

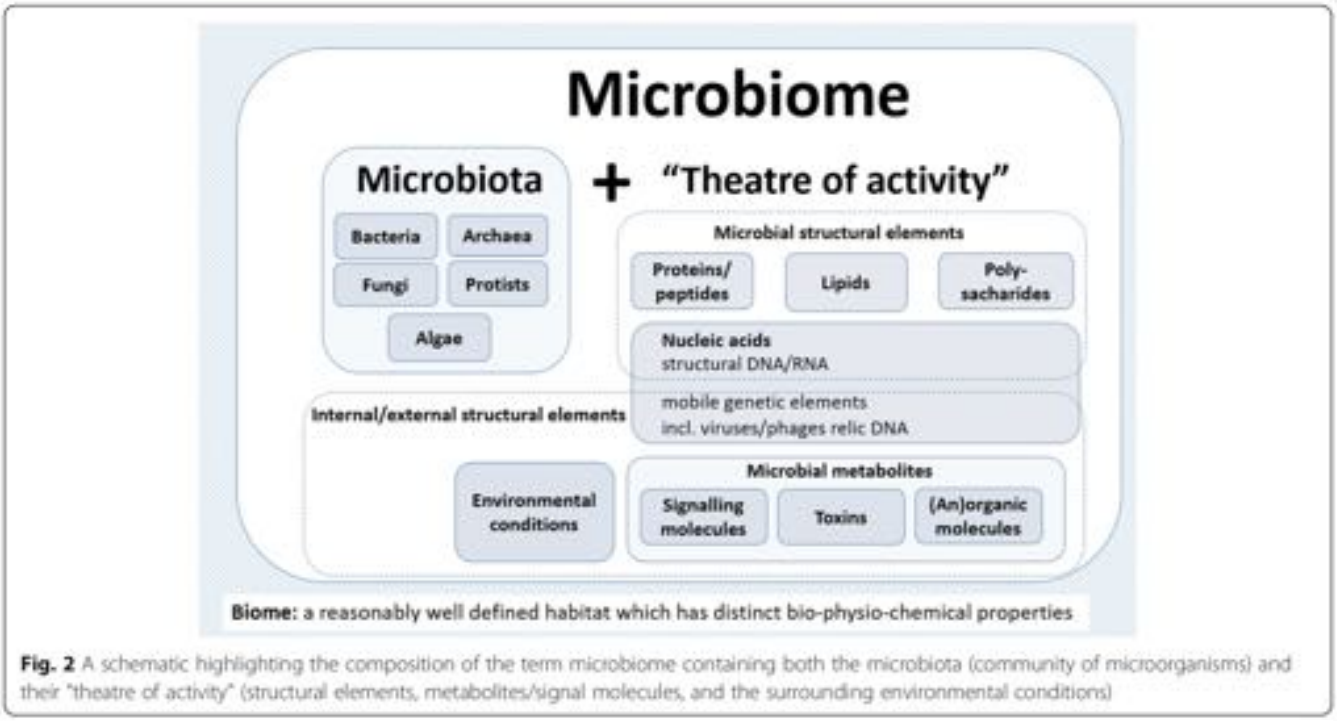
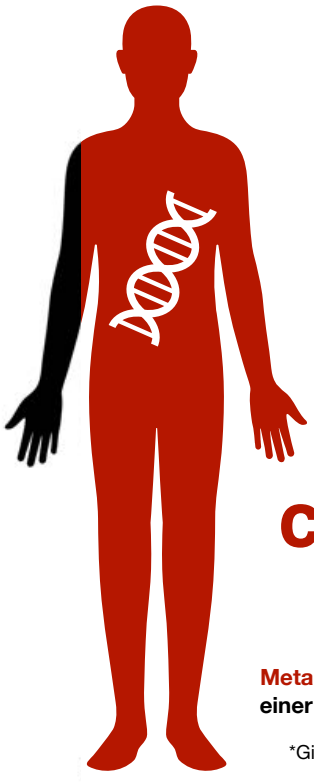


Fig. 2 A schematic highlighting the composition of the term microbiome containing both the microbiota (community of microorganisms) and their "theatre of activity" (structural elements, metabolites/signal molecules, and the surrounding environmental conditions)

Berg *et al. Microbiome* (2020) 8:103
https://doi.org/10.1186/s40168-020-00875-0

30 Billionen Zellen

ca. 20.000 Gene



39 Billionen Bakterien

ca. 2.000.000 Gene*

Metagenom = gesamtes genomisches Potenzial einer mikrobiellen Gemeinschaft

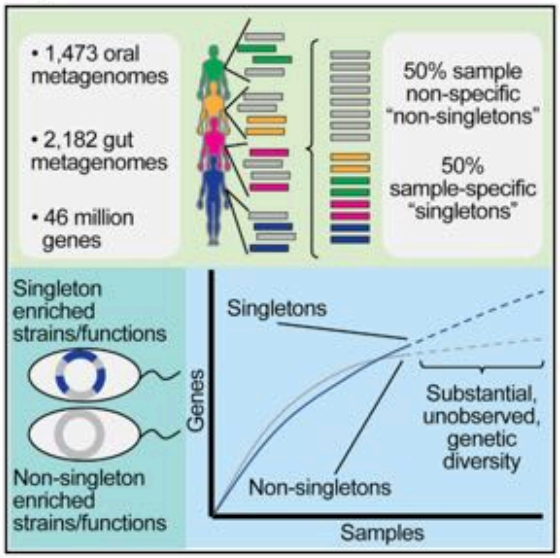
*Gilbert et al. Nat Med. 2018 Apr 10; 24(4): 392–400.

Resource

Cell Host & Microbe

The Landscape of Genetic Content in the Gut and Oral Human Microbiome

Graphical Abstract



Authors

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In Brief

Tierney et al. presents a meta-analysis of metagenomes covering 3,655 samples from two body sites. They identify 45,666,334 non-redundant genes in the human oral and gut microbiome, and half of every person's microbial gene content is completely unique. These rare genes, denotes singletons, predominantly arise from extremely rare microbial strains.

Tierney et al., 2019, Cell Host & Microbe 26, 283–295
August 14, 2019

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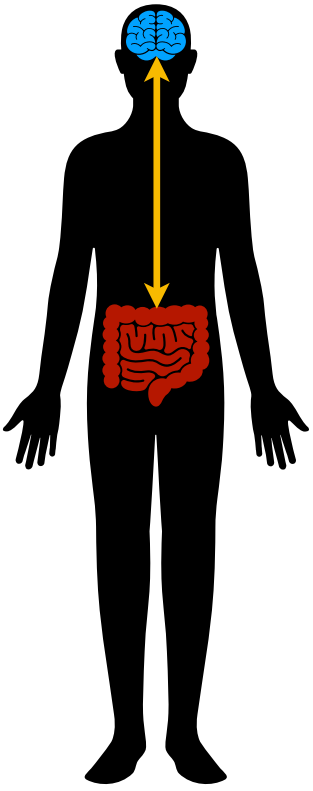
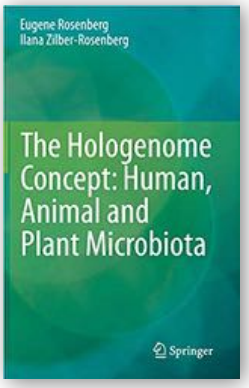
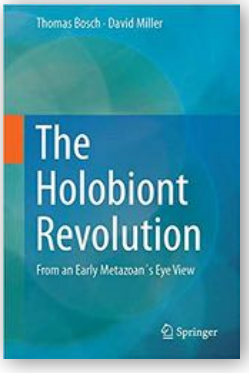
https://doi.org/10.1016/j.chom.2019.07.008

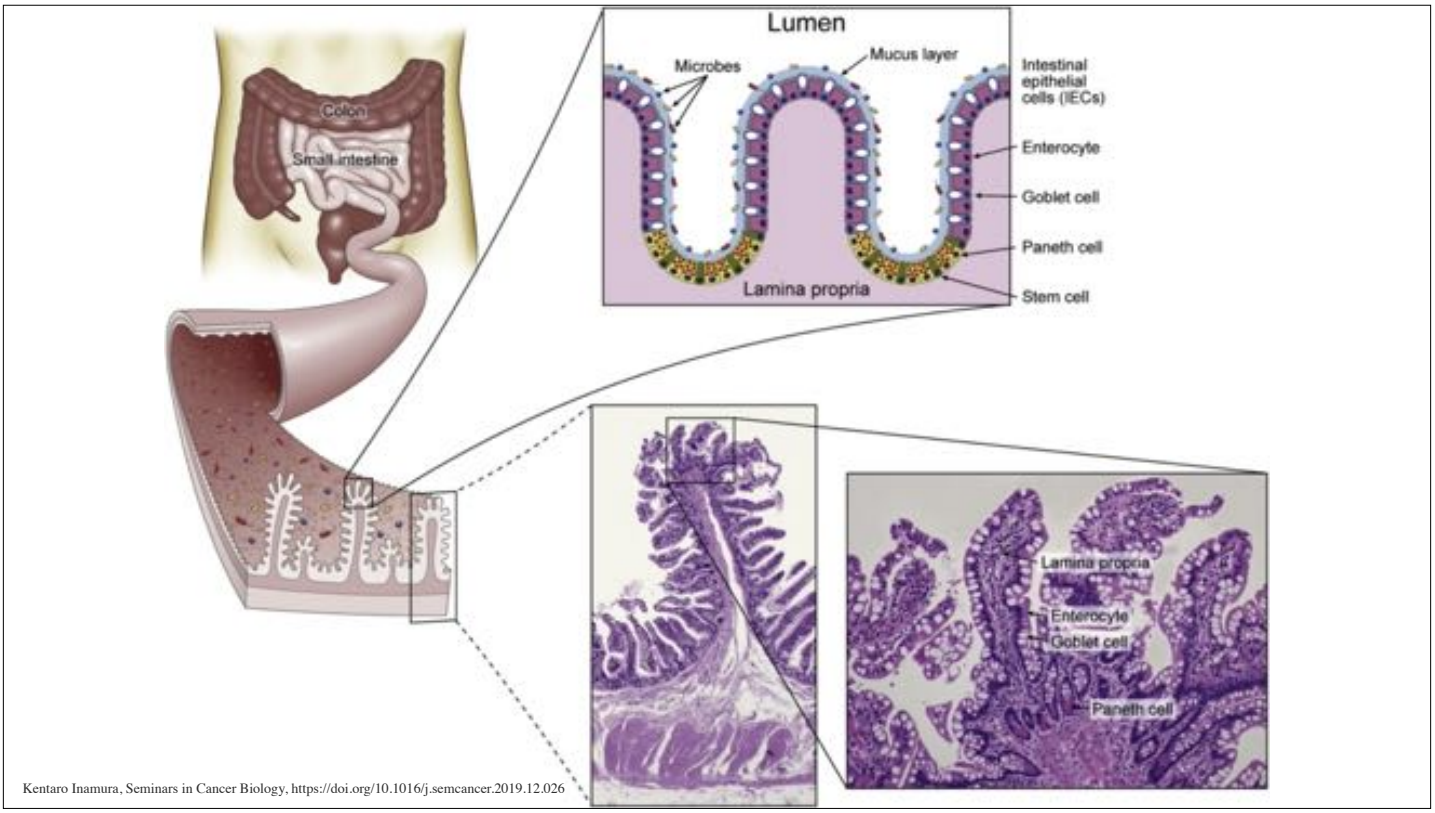
„Holobiont“
„Metaorganismus“
„Gesamtlebewesen“

eukaryoter Wirtsorganismus + symbiotischer Mikroben-Komplex

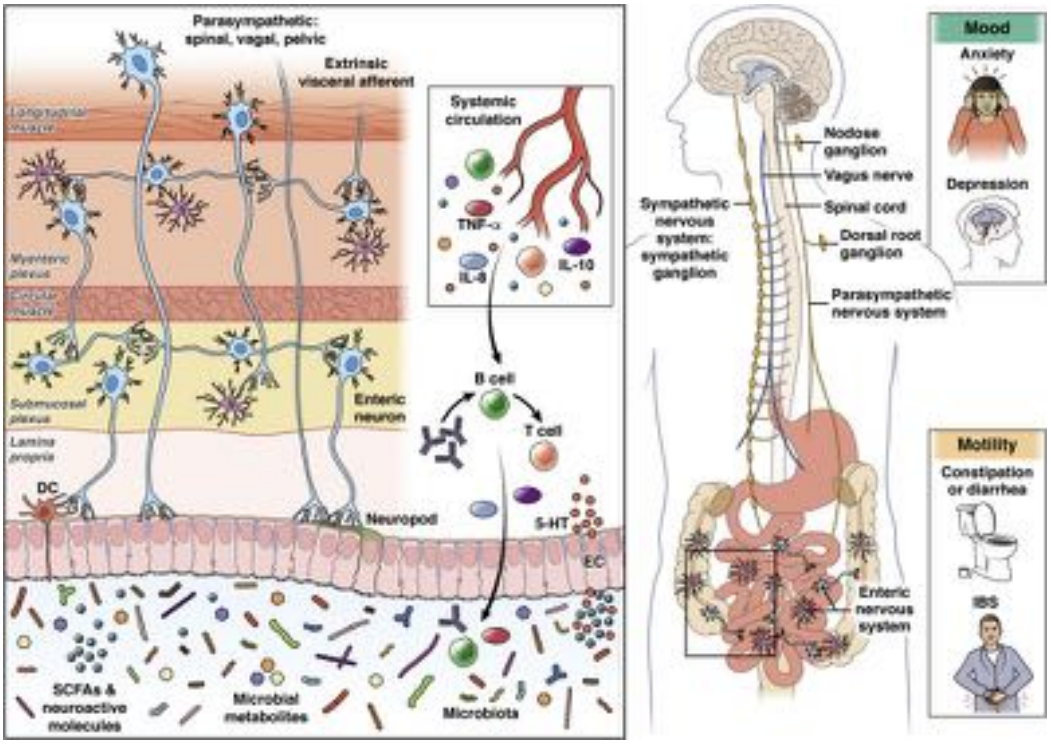




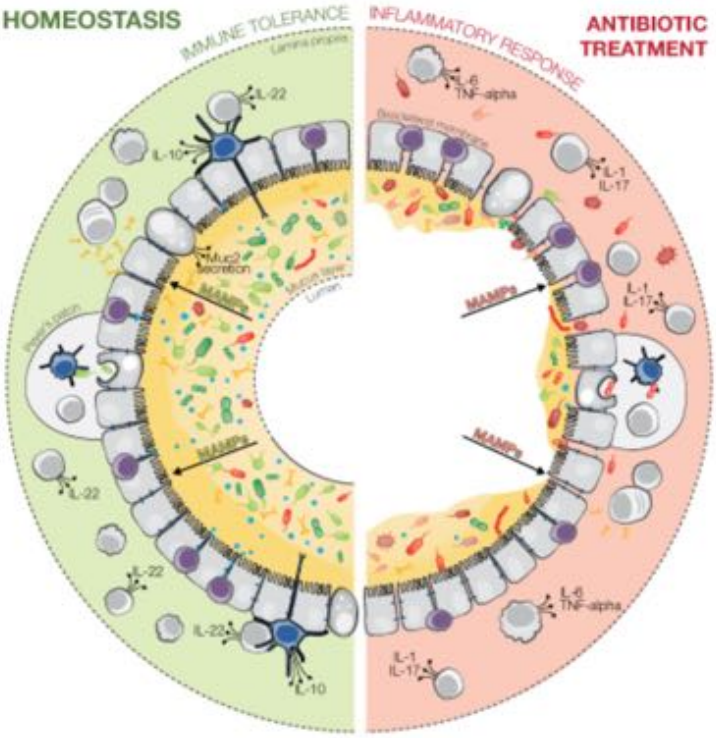




Kentaro Inamura, Seminars in Cancer Biology, https://doi.org/10.1016/j.semcancer.2019.12.026



Margolis KG et al. The Microbiota-Gut-Brain Axis: From Motility to Mood. Gastroenterology. 2021 Apr;160(5):1486-1501.



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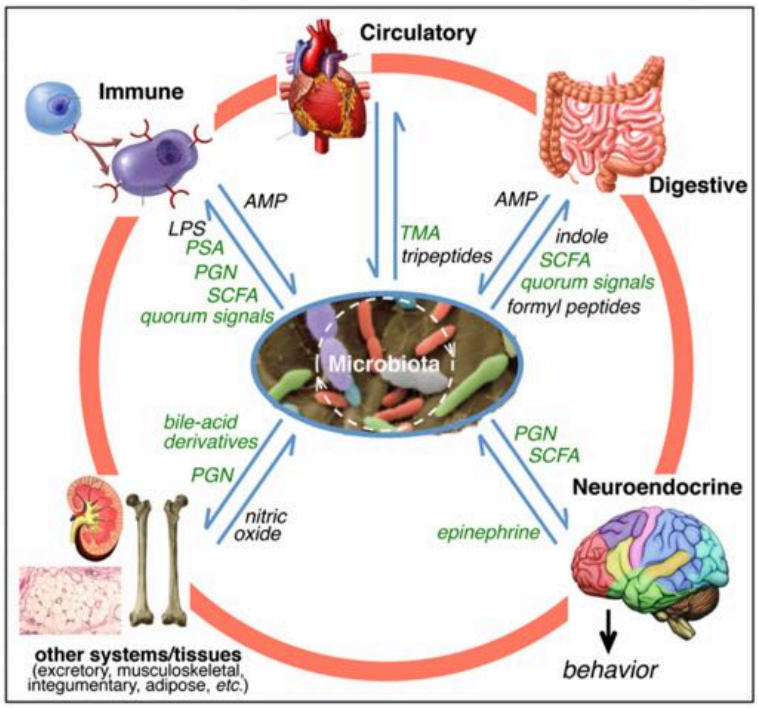
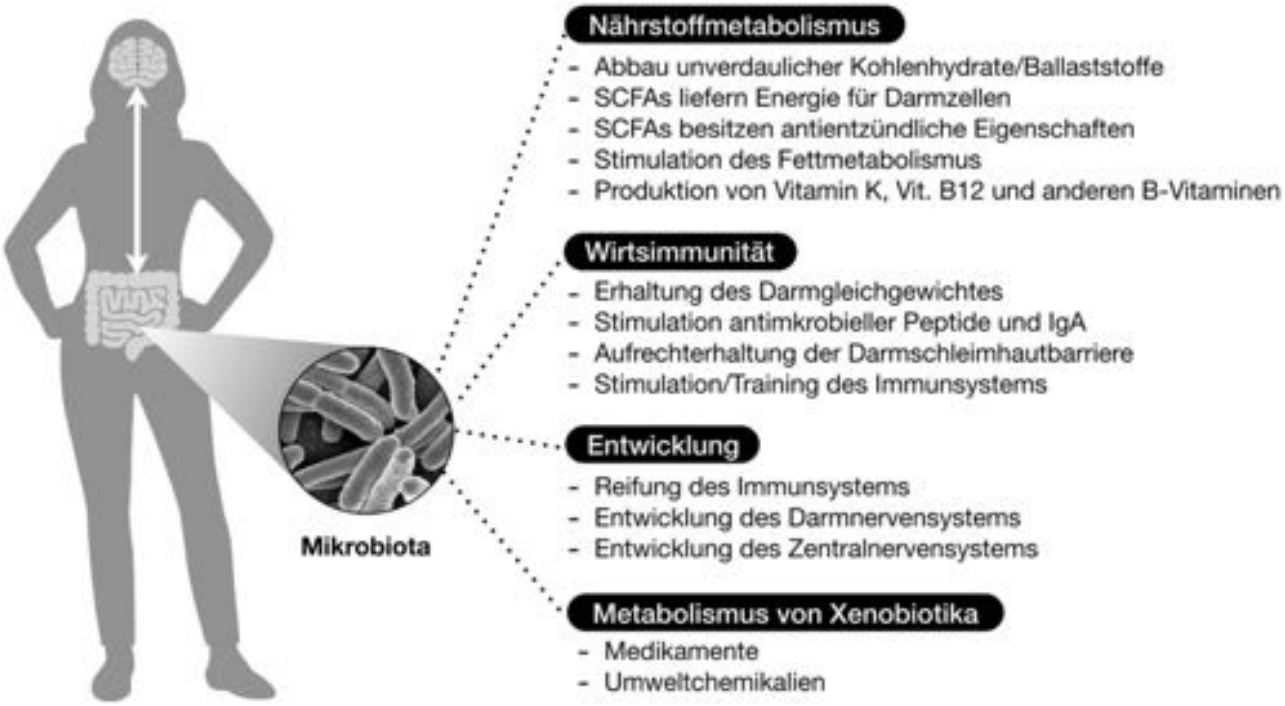


McFall-Ngai M et al. Animals in a bacterial world, a new imperative for the life sciences. Proc Natl Acad Sci U S A. 2013 Feb 26;110(9):3229-36.

Das Mikrobiom ist für viele essentielle Prozesse im Körper zuständig!



PNAS

Bacteria of the human gut microbiome catabolize red seaweed glycans with carbohydrate-active enzyme updates from extrinsic microbes

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Edited by Edward F. DeLong, Massachusetts Institute of Technology, Cambridge, MA, and approved October 7, 2012 (received for review June 28, 2012)

Humans host an intestinal population of microbes—collectively referred to as the gut microbiome—which encode the carbohydrate active enzymes, or CAZymes, that are absent from the human genome. These CAZymes help to extract energy from recalcitrant polysaccharides. The question then arises as to if and how the microbiome adapts to new carbohydrate sources when modern humans change eating habits. Recent metagenome analysis of microbiomes from healthy American, Japanese, and Spanish populations identified putative CAZymes obtained by horizontal gene transfer from marine bacteria, which suggested that human gut bacteria evolved to degrade algal carbohydrates—for example, consumed in form of sushi. We approached this hypothesis by studying such a polysaccharide utilization locus (PUL) obtained by horizontal gene transfer by the gut bacterium *Bacteroides plebeius*. Transcriptomic and growth experiments revealed that the PUL responds to the polysaccharide porphyran from red algae, enabling growth on this carbohydrate but not related substrates like agarose and carrageenan. The X-ray crystallographic and biochemical analysis of two proteins encoded by this PUL, *BACPLE_01689* and *BACPLE_01693*, showed that they are β-porphyranases belonging to glycoside hydrolase families 16 and 86, respectively. The product complex of the GH86 at 1.3 Å resolution highlights the molecular details of porphyran hydrolysis by this new porphyranase. Combined, these data establish experimental support for the argument that CAZymes and associated genes obtained from extrinsic microbes add new catabolic functions to the human gut microbiome.

Two phyla dominate the bacterial community of the adult distal gut in humans and in other mammals: the Firmicutes and the Bacteroidetes (1). Metagenomic studies and experiments with isolated strains revealed that members of the genus *Bacteroides* are broadly adapted to the degradation of host glycans and terrestrial plant material (2). This adaptation is exemplified by the enzyme systems devoted to starch, pectin, hemicelluloses, and other plant carbohydrates as well as host glycans (2, 3); the wide variety of genes encoding enzymes for the degradation of these carbohydrates dominate carbohydrate active enzyme, or CAZyme, arsenals in human gut metagenome datasets. Hence, the evolution of this carbohydrate catabolizing machinery is key for host and microbe possible CAZymes encoding genes that appear to have been acquired by HGT from marine microbes and which may target carbohydrates from red seaweeds (4).

The major matrix polysaccharides in the cell walls of red algae—which are the most common dietary red seaweed polysaccharides consumed by humans and present in many processed foods (11, 12)—are carrageenans (13), agars, and porphyran (14), and all contain sulfate esters that are absent in terrestrial plants. Furthermore, the sugar backbones can contain unique monosaccharides, such as the 3,6-anhydro-D-galactose present in the carrageenan of *Chondrus crispus* (Irish moss) and the 3,6-anhydro-L-galactose (LA) found in agars of *Gelidium* and *Gracilaria* spp. In both cases, the 3,6-anhydro-galactose is α-1,3 linked to D-galactose (G) and the resulting disaccharide is connected with β-1,4 linkages (*SI Appendix*, Fig. S1). Porphyran from *Porphyra* spp. belongs to the agar-family of polysaccharides, although the majority of the LA is replaced by L-galactose-6-sulfate (L6S), and C-6 methylations of G are frequent (14). The unique structural properties of these red algal galactans requires a distinct set of enzymes that are predominantly encoded in genomes of marine microbes and are far less frequent or absent in bacteria that break down terrestrial polysaccharides (4, 8). Thus, genetic and functional tracking of CAZymes with these rare specificities holds the potential to dissect carbohydrate resource partitioning by human gut microbes. For example, putative agarases, porphyranases, and alginate lyases have recently been identified in the intestinal microbiomes of Japanese (4), Spanish (15), and American (16) people, suggesting that their gut microbes may have adapted to novel algal carbohydrates in the modern diet. However, all of these previous studies focused on bioinformatic analysis and lacked functional characterizations of gut microbes and their enzymes, raising the question of whether these HGT events conferred active pathways to the human microbiome or simply introduced cryptic genes.

In this study, we used seaweed polysaccharides as substrates and established that a horizontally acquired integrative and conjugative element (ICE) expanded the catabolic repertoire of *B. plebeius* allowing it to use porphyran. Furthermore, through functional screening with additional algal substrates, two other gut *Bacteroides*, *B. uniformis* NP1 and *B. thetaiotaomicron* VPI-3731, were

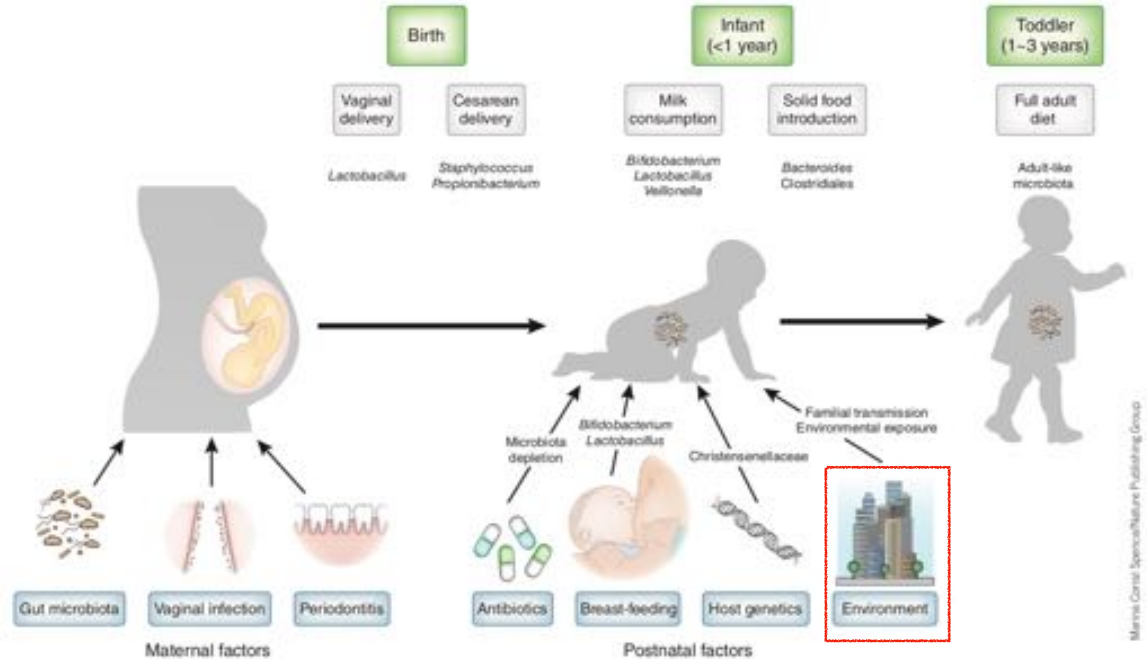
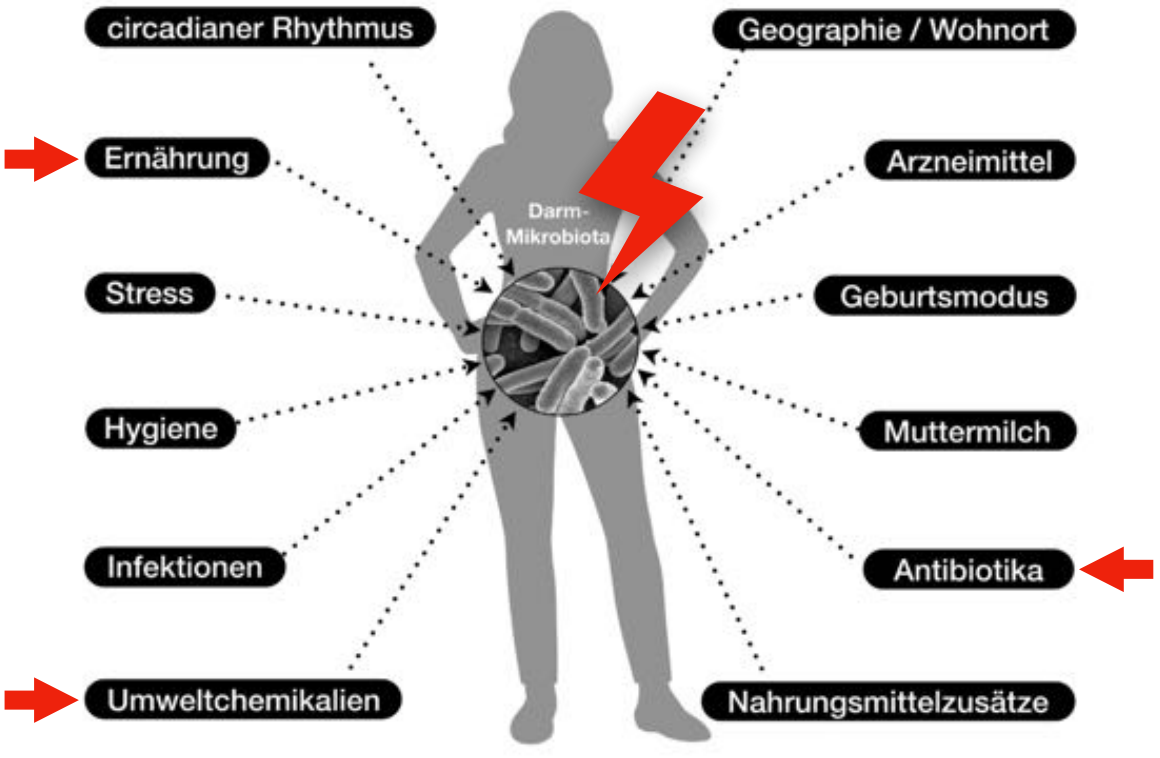
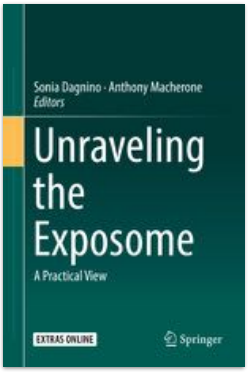
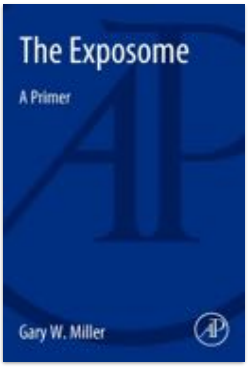
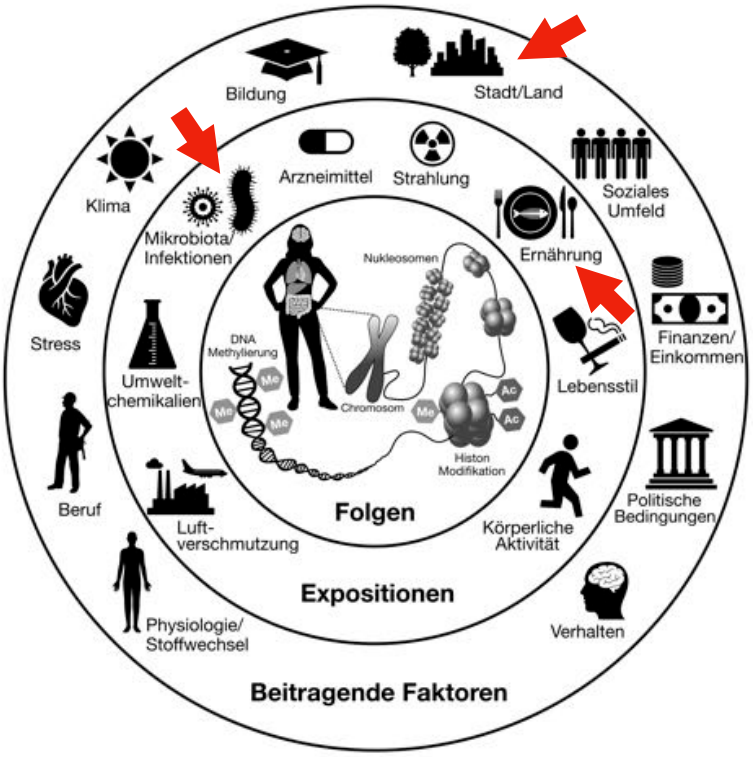


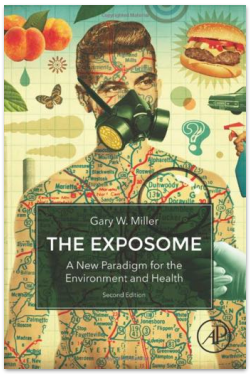
Figure 1 Factors shaping the neonatal microbiome. Maternal vaginal infections or periodontitis can result in bacteria invading the uterine environment. Gut and oral microbiota could be transported through the bloodstream from the mother to the fetus. Delivery mode shapes the initial bacterial inoculum of the newborn. Postnatal factors such as antibiotic use, diet (such as breast-feeding versus formula, and introduction of solid food), genetics of the infant and environmental exposure further configure the microbiome during early life. As diet diversifies with age, the microbiome gradually shifts toward an adult-like configuration, which is usually reached by age 3. Bacteria associated with the different processes are indicated.

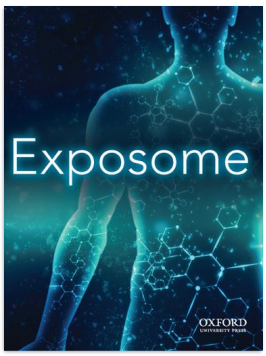












Chronische niederschwellige („stille“) Entzündung

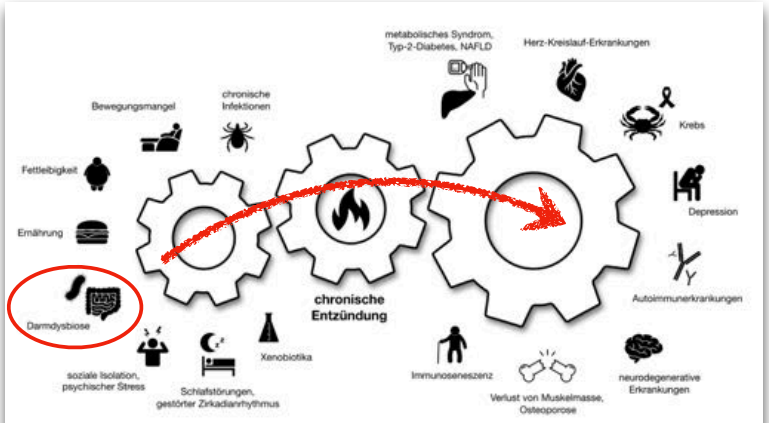
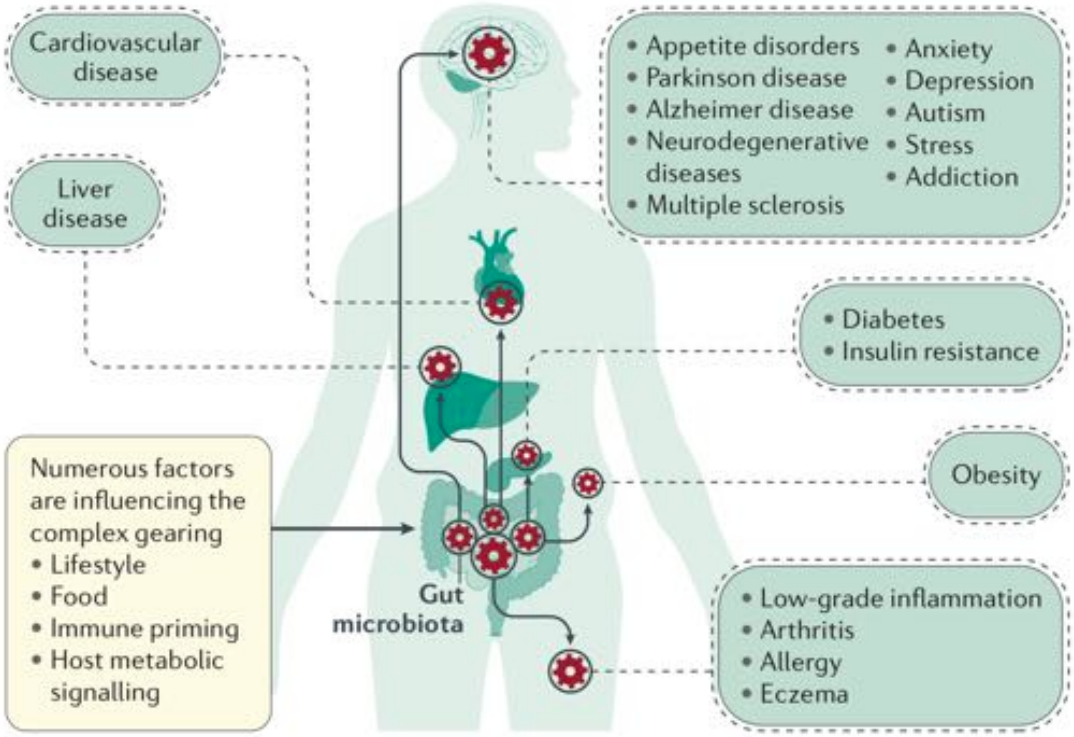


Abbildung 8: Derzeit bekannte Ursachen und Folgen einer niedriggradigen systemischen chronischen Entzündung. Die häufigsten Auslöser von SCI (links, gegen den Uhrzeigersinn) chronische Infektionen, Bewegungsmangel, (viszerale) Fettleibigkeit, Ernährung, Darmdysbiose, soziale Isolation, psychischer Stress, Schlafstörungen und gestörter zirkadianer Rhythmus und Exposition gegenüber Xenobiotika wie Luftschadstoffen, gefährlichen Abfallprodukten, Industriechemikalien und Tabakrauchen. Rechts die Folgen (im Uhrzeigersinn): metabolisches Syndrom, Typ-2-Diabetes, nichtalkoholische Fettleber (NAFLD), Herz-Kreislauf-Erkrankungen, Krebs, Depression und Angststörungen, Autoimmunerkrankungen, neurodegenerative Erkrankungen, Verlust von Muskelmasse (Sarkopenie), Osteoporose und Verschlechterung des Immunsystems mit fortschreitendem Alter (Immunoseneszenz); nach Furman et al. 2019.[94]

Tabelle: Auswahl von Krankheiten mit Verbindung zum Mikrobiom und einer chronischen Entzündungsreaktion

Erkrankung, Krankheitsbild oder Krankheitskategorie	Verbindung zum Mikrobiom nachgewiesen oder vermutet	Durch eine chronische schwelende Entzündungsreaktion (mit)verursacht oder damit einhergehend
Chronisch-entzündliche Darmerkrankungen (IBD); Morbus Crohn, Colitis ulcerosa	√	√
Reizdarmsyndrom (IBS)	√	√
Zöliakie	√	√
Systemischer Lupus erythematodes (SLE)	√	√
Diabetes Typ 1	√	√
Rheumatoide Arthritis (RA)	√	√
Allergien	√	√
Atopische Dermatitis (Neurodermitis)	√	√
Psoriasis	√	√
Asthma	√	√
Multiple Sklerose (MS)	√	√
Fettleibigkeit (Adipositas)	√	√
metabolisches Syndrom (Insulinresistenz, erhöhte Blutfette, Bluthochdruck)	√	√
Diabetes Typ 2	√	√
Hypertonie	√	√
Atherosklerose/Herz-Kreislauf-Erkrankungen	√	√
Verschiedene Krebsformen wie z.B. Darmkrebs	√	√
Nichtalkoholische Fettlebererkrankungen (NAFLD)	√	√
Autismus-Spektrum-Störung (ASD)	√	√
Alzheimer-Demenz	√	√
Parkinson-Krankheit	√	√
Multiple Sklerose (MS)	√	√
Clostridioides difficile-Infektion (CDI)	√	Akute Entzündung
Chronisches Nierenerkrankungen	√	√
Neuropsychiatrische Erkrankungen wie Depressionen und Angststörungen	√	√



the bmj

STATE OF THE ART REVIEW

The role of the gut microbiome in systemic inflammatory disease

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Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason

ABSTRACT

The role of the gut microbiome in models of inflammatory and autoimmune disease is now well characterized. Renewed interest in the human microbiome and its metabolites, as well as notable advances in host mucosal immunology, has opened multiple avenues of research to potentially modulate inflammatory responses. The complexity and interdependence of these diet-microbe-metabolite-host interactions are rapidly being unraveled. Importantly, most of the progress in the field comes from new knowledge about the functional properties of these microorganisms in physiology and their effect in mucosal immunity and distal inflammation. This review summarizes the preclinical and clinical evidence on how dietary, probiotic, prebiotic, and microbiome based therapeutics affect our understanding of wellness and disease, particularly in autoimmunity.

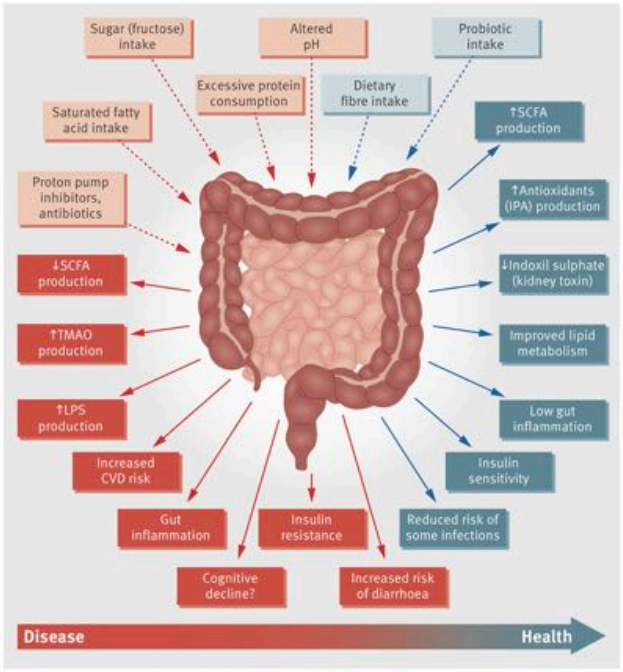

Fig 1 | Schematic representation of the role of the gut microbiota in health and disease giving some examples of inputs and outputs. CVD=cardiovascular disease; IPA=indolepropionic acid; LPS=lipopolysaccharide; SCFA=short chain fatty acids; TMAO=trimethylamine N-oxide

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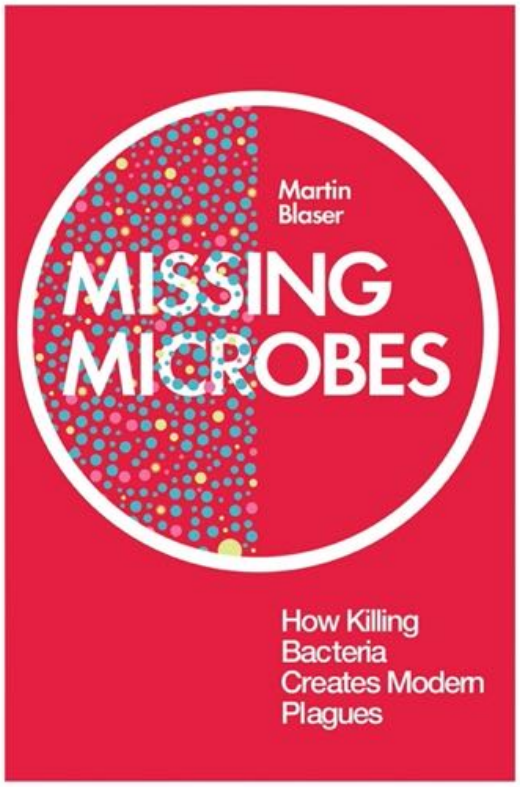
Disappearance of the Human Microbiota: How We May Be Losing Our Oldest Allies

Nov. 8, 2019 SHARE THIS

"The microbiota is not accidental," says Dr. Martin Blaser, Director of the Center for Advanced Biotechnology and Medicine at Rutgers University and author of *Missing Microbes*. "The microbiota has co-evolved with us over very long periods of time, and it performs beneficial functions for us, just as we perform beneficial functions for it...We are all working together as an ecological unit." Since our species–and all of life–has existed on earth, we have been in the company of microbes: microbes reside in our intestines, on our skin, and in the environments we live in. These bugs have at times been opportunistic pathogens, preying on the vulnerabilities of individuals and populations, but they have more frequently been some of our oldest evolutionary friends.

The trouble is, the microbiota as we've known it is disappearing.



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RESEARCH ARTICLE

May/June 2022 Volume 13 Issue 3

Association of Diet and Antimicrobial Resistance in Healthy U.S. Adults

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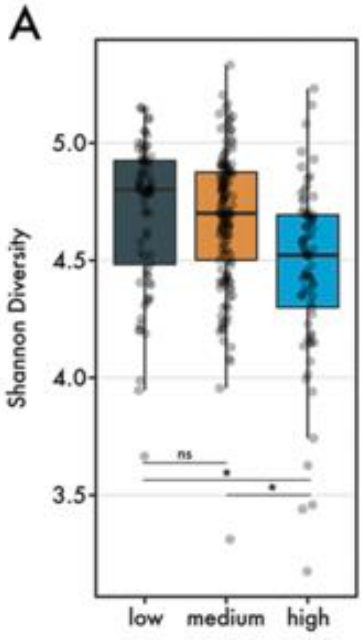
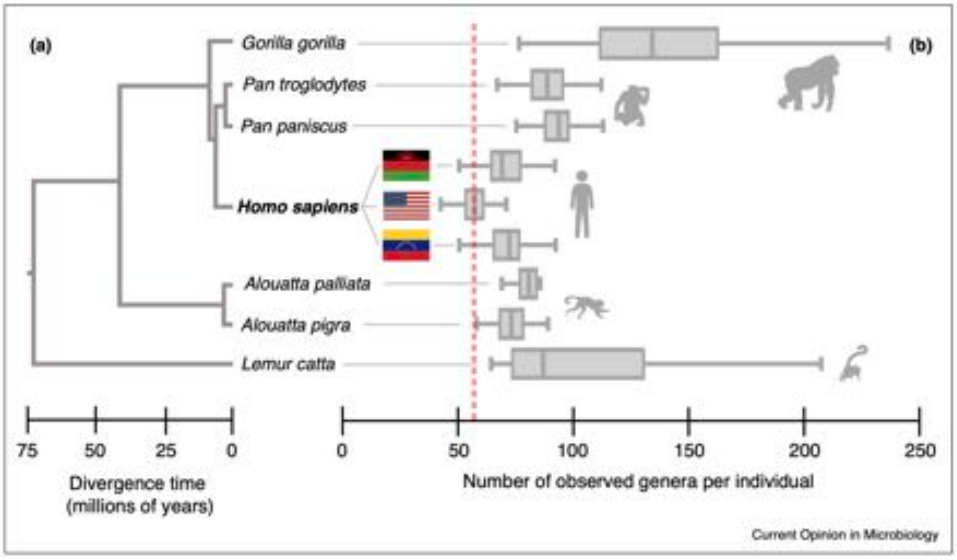
ABSTRACT Antimicrobial resistance (AMR) represents a significant source of morbidity and mortality worldwide, with expectations that AMR-associated consequences will continue to worsen throughout the coming decades. Since resistance to antibiotics is encoded in the microbiome, interventions aimed at altering the taxonomic composition of the gut might allow us to prophylactically engineer microbiomes that harbor fewer antibiotic resistant genes (ARGs). Diet is one method of intervention, and yet little is known about the association between diet and antimicrobial resistance. To address this knowledge gap, we examined diet using the food frequency questionnaire (FFQ; habitual diet) and 24-h dietary recalls (Automated Self-Administered 24-h [ASA24®] tool) coupled with an analysis of the microbiome using shotgun metagenome sequencing in 290 healthy adult participants of the United States Department of Agriculture (USDA) Nutritional Phenotyping Study. We found that aminoglycosides were the most abundant and prevalent mechanism of AMR in these healthy adults and that aminoglycoside-O-phosphotransferases (*aph3-dprime*) correlated negatively with total calories and soluble fiber intake. Individuals in the lowest quartile of ARGs (low-ARG) consumed significantly more fiber in their diets than medium- and high-ARG individuals, which was concomitant with increased abundances of obligate anaerobes, especially from the family *Clostridiaceae*, in their gut microbiota. Finally, we applied machine learning to examine 387 dietary, physiological, and lifestyle features for associations with antimicrobial resistance, finding that increased phylogenetic diversity of diet was associated with low-ARG individuals. These data suggest diet may be a potential method for reducing the burden of AMR.





Humans in industrialized societies harbor the fewest gut bacterial genera of any primate.
(a) Time calibrated phylogeny of primate species for which comparable 16S rDNA gut-microbiome datasets are available [9•,17,49,50]. **(b)** Box and whisker plots show the mean number of bacterial and archaeal genera detected within individual gut microbiomes of each primate species. Datasets were merged and analyzed in QIIME [51] following the methods of [9•]. Humans from the United States, Malawi, and Venezuela were sampled from urban centers, rural communities, and traditional Amazonian villages, respectively [17]. Dashed red line highlights the mean bacterial richness within individuals from the United States.

nature COMMUNICATIONS

ARTICLE

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Gut microbiome of the Hadza hunter-gatherers

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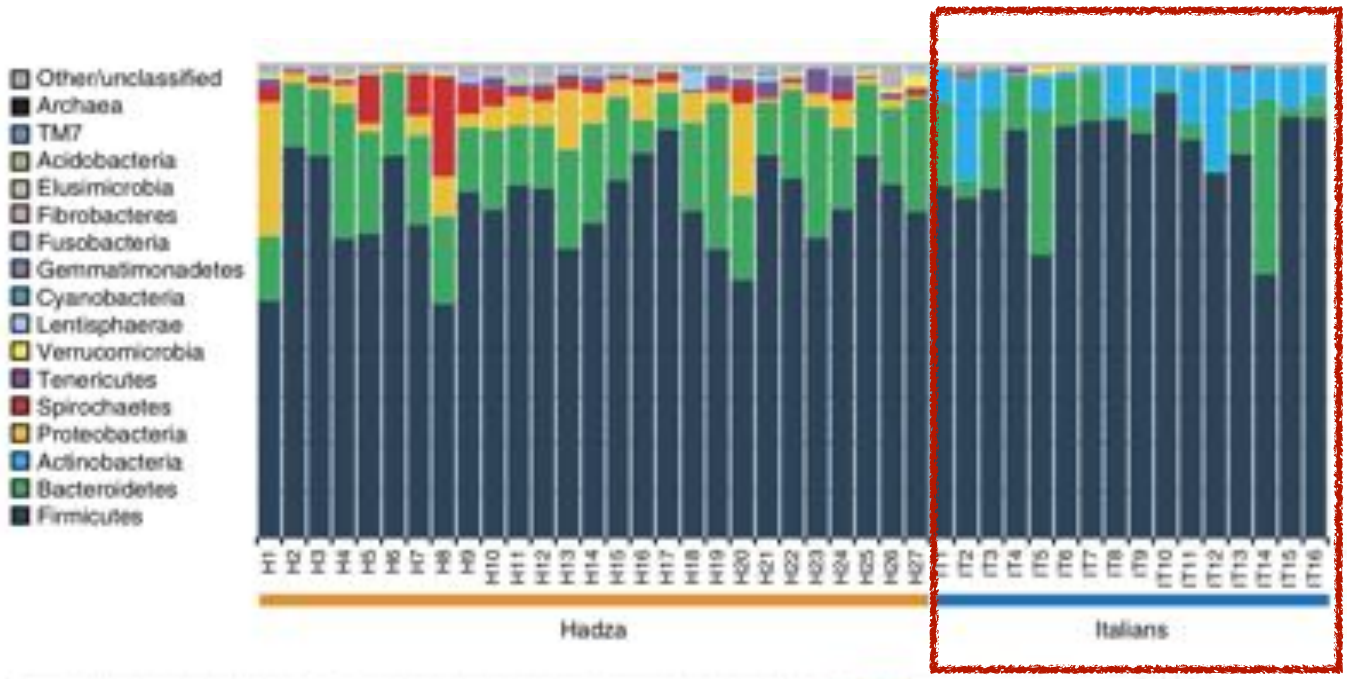
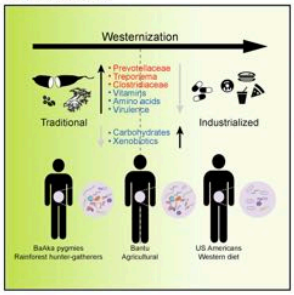


Article

Cell Reports

Gut Microbiome of Coexisting BaAka Pygmies and Bantu Reflects Gradients of Traditional Subsistence Patterns

Graphical Abstract



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Andres Gomez, Klara J. Petrzelkova, Michael B. Burns, ..., Bryan A. White, Steven R. Leigh, Ran Blekhman

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In Brief

Gomez et al. show that coexisting BaAka hunter-gatherers and Bantu agriculturalists have distinct gut microbiomes, which reflect gradients of traditional subsistence strategies. A comparison with US Americans suggests that agriculture and industrialization have triggered loss of traditional microbes and increased carbohydrate and xenobiotic metabolism in humans.

Highlights

- BaAka hunter-gatherers and Bantu agriculturalists have distinct gut microbiomes
- Microbiome profiles follow a gradient that reflects the degree of traditional lifestyle
- Comparisons with US Americans show western-like microbiome patterns in the Bantu
- Westernization drives sugar/xenobiotic processing and loss of traditional microbes

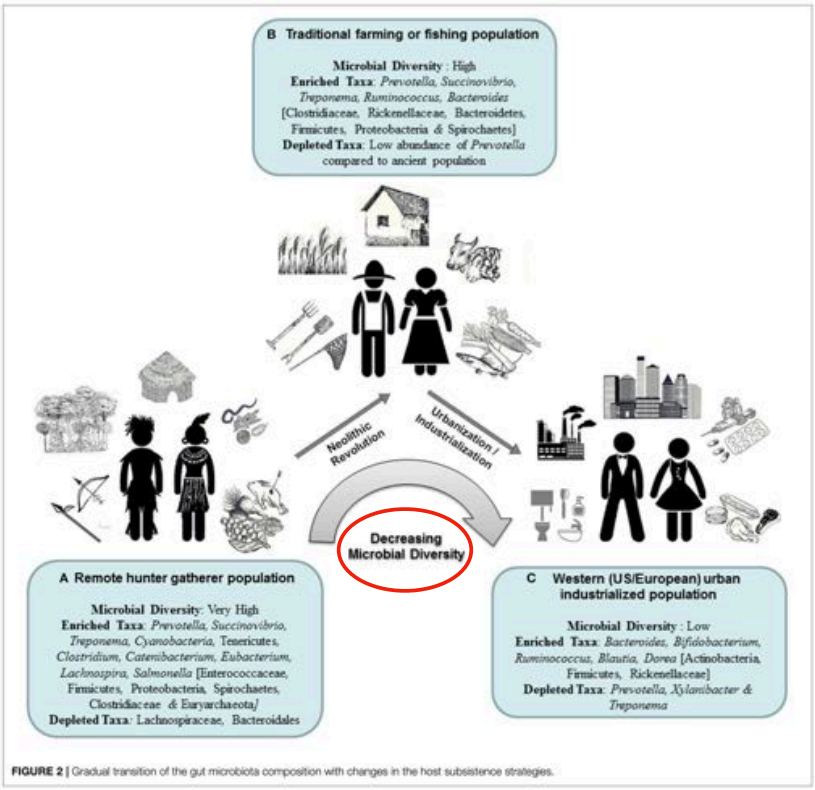

FIGURE 2 | Gradual transition of the gut microbiota composition with changes in the host subsistence strategies.

Gupta VK, Paul S, Dutta C. Geography, Ethnicity or Subsistence-Specific Variations in Human Microbiome Composition and Diversity. Front Microbiol. 2017

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Contemporary Review

CONTEMPORARY REVIEW

The Impact of Environmental Chemicals on the Gut Microbiome

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ARTICLE

Extensive impact of non-antibiotic drugs on human gut bacteria

Lisa Maier[1*], Mihaela Pruteanu[1*], Michael Kuhn[2*], Georg Zeller[3], Anja Telzerow[4], Exene Erin Anderson[5], Ana Rita Brochado[1], Keith Conrad Fernandez[1], Hitomi Dose[1], Hirotada Mori[5], Kiran Raosaheb Patil[6], Peer Bork[2,4,7,8] & Athanasios Typas[1,2]

A few commonly used non-antibiotic drugs have recently been associated with changes in gut microbiome composition, but the extent of this phenomenon is unknown. Here, we screened more than 1,000 marketed drugs against 40 representative gut bacterial strains, and found that 24% of the drugs with human targets, including members of all therapeutic classes, inhibited the growth of at least one strain in vitro. Particular classes, such as the chemically diverse antipsychotics, were overrepresented in this group. The effects of human-targeted drugs on gut bacteria are reflected on their antibiotic-like side effects in humans and are concordant with existing human cohort studies. Susceptibility to antibiotics and human-targeted drugs correlates across bacterial species, suggesting common resistance mechanisms, which we verified for some drugs. The potential risk of non-antibiotics promoting antibiotic resistance warrants further exploration. Our results provide a resource for future research on drug–microbiome interactions, opening new paths for side-effect control and drug repurposing, and broadening our view of antibiotic resistance.

Pharmaceutical agents have both beneficial and undesirable effects. Studies on the mechanisms of action and off-target spectra of various drugs aim to improve their efficacy and reduce their side effects. Although many drugs have gastrointestinal side effects and the gut microbiome itself is pivotal for human health[1], the role of the gut microbiota in these processes is rarely considered. Recently, consumption of drugs designed to target human cells and not microbes, such as antidiabetics (metformin[2]), proton pump inhibitors (PPIs)[3,4], nonsteroidal anti-inflammatory drugs[5] and atypical antipsychotics (AAPs)[6], has been associated with changes in microbiome composition. A larger cohort study suggested that medication can alter gut microbiome composition more generally[7]. As it is unclear whether such effects are direct and go beyond the few drug classes studied, we systematically profiled interactions between drugs and individual gut bacteria. We aimed to generate a comprehensive resource of drug actions on the microbiome, which could facilitate more in-depth clinical and mechanistic studies, ultimately improving therapy and drug design.

A high-throughput drug screen on gut bacteria

To systematically map interactions between drugs and human gut bacteria, we monitored the growth of 40 representative isolates upon treatment with 1,197 compounds in modified Gifu anaerobic medium (mGAM) broth, which partially recapitulates the species relative abundances in human gut microbiomes[8], under anaerobic conditions at 37°C (Extended Data Fig. 1a). We used the Prestwick Chemical Library, which consists mostly of off-patent Federal Drug Administration (FDA)-approved compounds with high chemical and pharmacological diversity. Most compounds are administered to humans (1,079), and they cover all main therapeutic classes (Supplementary Table 1). Three quarters (835) of the compounds are human-targeted drugs (that is, have molecular targets in human cells), whereas the rest are anti-infectives: 156 with antibacterial activity (144 antibiotics, 12 antiseptics) and 88 effective against fungi, viruses or parasites (Fig. 1a).

All compounds were screened at 20 μM, which is within the range of what is commonly used in high-throughput drug screens[9].

For our screen to be representative of the gut microbiome of healthy individuals, we selected a set of ubiquitous gut bacterial species (Supplementary Table 2). Prevalence and abundance in the human gut, and phylogenetic diversity, were our main selection criteria (Extended Data Fig. 1b), although we were occasionally constrained by strain availability or irreproducible growth in mGAM. In total, we included 40 human gut isolates from 38 bacterial species and 21 genera (*Escherichia coli* and *Bacteroides fragilis* were represented by two strains each), accounting together for 78% of the median assignable relative abundance of the human gut microbiome at genus level (60% at species level; Extended Data Fig. 1c). Most strains were commensals, covering 31 of 60 sequenced species detected at a relative abundance of 1% or more and prevalence of at least 50% in fecal samples from asymptomatic humans from three continents (Extended Data Fig. 1d). In addition, the set included four pathobionts (*Clostridium difficile*, *Clostridium perfringens*, *Fusobacterium nucleatum* and an enterotoxigenic strain of *B. fragilis*), a probiotic (*Lactobacillus paracasei*) and two commensal *Clostridia* species (*C. ramosum* and *C. saccharolyticum*). All 38 species are found in the gut of healthy individuals and are part of a larger strain resource panel for the healthy human gut microbiome[8].

We screened all compounds in multiwell plates, measuring optical density over time to monitor growth, and quantifying the area under the growth curve (AUC) up to the time point at which controls with unperturbed growth transitioned to stationary phase (see Methods; Extended Data Fig. 2). We obtained at least three biological replicates per strain, and these replicates correlated highly (Extended Data Fig. 2c). We then tested for significant deviations from the normalized AUC distribution of samples with unperturbed growth, combining *P* values across replicates and correcting for multiple hypothesis testing on the complete matrix of compounds and strains (see Methods; Extended Data Fig. 2). Drugs that significantly reduced the growth of

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*These authors contributed equally to this work.

ARTICLE

https://doi.org/10.1038/s41467-019-14177-z OPEN

Impact of commonly used drugs on the composition and metabolic function of the gut microbiota

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The human gut microbiota has now been associated with drug responses and efficacy, while chemical compounds present in these drugs can also impact the gut bacteria. However, drug–microbe interactions are still understudied in the clinical context, where polypharmacy and comorbidities co-occur. Here, we report relations between commonly used drugs and the gut microbiome. We performed metagenomics sequencing of faecal samples from a population cohort and two gastrointestinal disease cohorts. Differences between users and non-users were analysed per cohort, followed by a meta-analysis. While 19 of 41 drugs are found to be associated with microbial features, when controlling for the use of multiple medications, proton-pump inhibitors, metformin, antibiotics and laxatives show the strongest associations with the microbiome. We here provide evidence for extensive changes in taxonomy, metabolic potential and resistome in relation to commonly used drugs. This paves the way for future studies and has implications for current microbiome studies by demonstrating the need to correct for multiple drug use.

Zuviel Hygiene oder zu wenig „Dreck“ ?

- „Hygienehypothese“
- „Old Friends Hypothesis“
- „Biodiversitäts Hypothese“

„Nature deficit disorder“

Current perspectives

Disconnection of man and the soil: Reason for the asthma and atopy epidemic?

Leena von Hertzen, PhD, and Tari Haahtela, MD, PhD *Helsinki, Finland*

Intense search has been going on to find factors responsible for the asthma and atopy epidemic in Western societies. Attention has increasingly been devoted to environmental saprophytes, which, in addition to gut commensals, might be the major players in the development and fine tuning of immunologic homeostasis. This review outlines current evidence for the role of environmental saprophytes in the development of atopic disease and considers the consequences of urbanization in reducing contacts with soil microorganisms. The major microbial components that have been shown to possess immunomodulatory capacity and their respective Toll-like receptors are also discussed, as are the possible mechanisms underlying the ability of saprophytes to confer protection against atopic disease. (J Allergy Clin Immunol 2006;117: 334-44.)

Key words: *Allergy, asthma, atopy, hygiene hypothesis, saprophytes, urbanization*

Abbreviations used
TLR: Toll-like receptor
Treg cell: Regulatory T cell

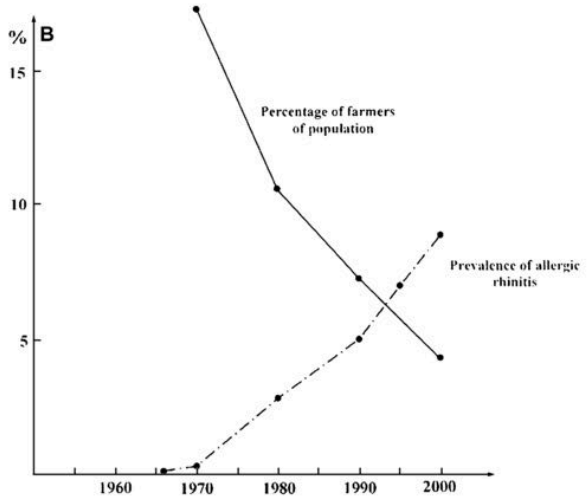
The current asthma and atopy epidemic in Western societies has raised a common concern and questions of factors involved. Although in some countries prevalence rates in atopic diseases appear to have leveled off,[1-4] trends are still on the increase in many other countries.[5,6]

Numerous studies have consistently shown that high asthma and atopy rates are associated with urbanization and Western lifestyle.[7,8] Accumulating data suggest that something that is necessary for the normal maturation of the immune system might be lacking in our affluence.[9] Conversely, farm environment and a more traditional lifestyle in nonaffluent countries appear to confer protection against atopic disease.[8,10,11] Although the ultimate factors responsible for the asthma and atopy epidemic have remained unidentified, a common denominator for both living on a farm and in a nonaffluent environment is the heavy exposure to microorganisms in soil and vegetation.

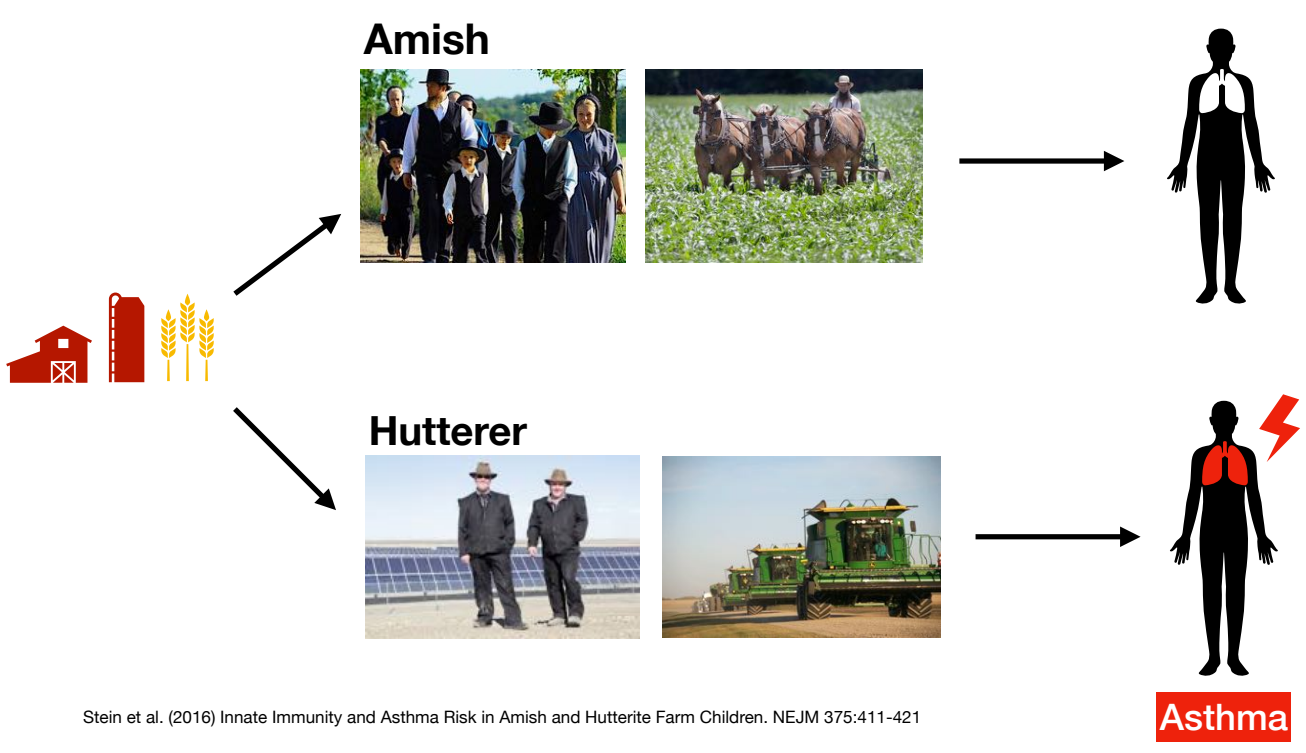
Most of the microorganisms we encounter do not cause any overt infection but are still recognized by the innate immune system. Microbes in this respect need not be alive because even nonviable microbial components interact with the innate immune system. Persistent and moderate environmental exposure to microbial components might play a decisive role in the normal maturation of the immune system in childhood.[12] It has been proposed that certain microorganisms that have been present throughout the mammalian evolutionary history are recognized by the innate immune system as "no danger" signals and thus do not trigger inflammatory responses but instead have the ability to induce tolerance through rapid regulatory T (Treg) cell responses.[13] These organisms include saprophytic mycobacteria, lactobacilli, and some intestinal parasites that are able to elicit Treg cell responses *in vivo*[14-17] and *in vitro*.[18] The list of such microbes will certainly grow in the next few years.

The focus of the research in the context of the hygiene hypothesis has largely shifted from overt infections and the T_H1/T_H2 paradigm to noninfectious organisms, Treg cells, and Toll-like receptors (TLRs), as new data have been accumulated and the paradigm was found to be unable to unambiguously explain some important epidemiologic findings.[19,20] Indeed, diseases of immune dysregulation, including atopic diseases, are now considered to develop, more or less, as a result of failure in Treg cell function.[13] Immune defense mechanisms that evolved during the long history of humankind in a hostile environment appear now to be less appropriate when living in a clean environment.[21]

HYPOTHESIS



von Hertzen L, Haahtela T. Disconnection of man and the soil: reason for the asthma and atopy epidemic? J Allergy Clin Immunol. 2006 Feb;117(2):334-44.



Stein et al. (2016) Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children. NEJM 375:411-421

Research

Original Investigation

Early Exposure to Dogs and Farm Animals and the Risk of Childhood Asthma

Tove Fall, PhD; Cecilia Lundholm, MSc; Anne K Örtqvist, PhD; Katja Fall, PhD; Fang Fang, PhD; Åke Hedhammar, PhD; Olle Kämpe, PhD; Erik Ingelsson, PhD; Catarina Almqvist, PhD

Supplemental content at jamapediatrics.com

IMPORTANCE The association between early exposure to animals and childhood asthma is not clear, and previous studies have yielded contradictory results.

OBJECTIVE To determine whether exposure to dogs and farm animals confers a risk of asthma.

DESIGN, SETTING AND PARTICIPANTS In a nationwide cohort study, the association between early exposure to dogs and farm animals and the risk of asthma was evaluated and included all children born in Sweden from January 1, 2001, to December 31, 2010 (N = 1 011 051), using registry data on dog and farm registration, asthma medication, diagnosis, and confounders for parents and their children. The association was assessed as the odds ratio (OR) for a current diagnosis of asthma at age 6 years for school-aged children and as the hazard ratio (HR) for incident asthma at ages 1 to 5 years for preschool-aged children. Data were analyzed from January 1, 2007, to September 30, 2012.

EXPOSURES Living with a dog or farm animal.

MAIN OUTCOMES AND MEASURES Childhood asthma diagnosis and medication used.

RESULTS Of the 1 011 051 children born during the study period, 376 638 preschool-aged (53 460 [14.2%] exposed to dogs and 1729 [0.5%] exposed to farm animals) and 276 298 school-aged children (22 629 [8.2%] exposed to dogs and 958 [0.3%] exposed to farm animals) were included in the analyses. Of these, 18 799 children (5.0%) in the preschool-aged children's cohort experienced an asthmatic event before baseline, and 28 511 cases of asthma and 906 071 years at risk were recorded during follow-up (incidence rate, 31 cases per 1000 years at risk). In the school-aged children's cohort, 11 585 children (4.2%) experienced an asthmatic event during the seventh year of life. Dog exposure during the first year of life was associated with a decreased risk of asthma in school-aged children (OR, 0.87; 95% CI, 0.81-0.93) and in preschool-aged children 3 years or older (HR, 0.90; 95% CI, 0.83-0.99) but not in children younger than 3 years (HR, 1.03; 95% CI, 1.00-1.07). Results were comparable when analyzing only first-born children. Farm animal exposure was associated with a reduced risk of asthma in both school-aged children and preschool-aged children (OR, 0.48; 95% CI, 0.31-0.76, and HR, 0.69; 95% CI, 0.56-0.84), respectively.

CONCLUSIONS AND RELEVANCE In this study, the data support the hypothesis that exposure to dogs and farm animals during the first year of life reduces the risk of asthma in children at age 6 years. This information might be helpful in decision making for families and physicians on the appropriateness and timing of early animal exposure.

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environmental microbiology

Environmental Microbiology (2016) **18**(5), 1326–1337 doi:10.1111/1462-2920.12895

Exposure to soil, house dust and decaying plants increases gut microbial diversity and decreases serum immunoglobulin E levels in BALB/c mice

„Exposition gegenüber Boden, Hausstaub und verrottendem Pflanzenmaterial erhöht die mikrobielle Vielfalt im Darm und verbessert die angeborene Immunität“

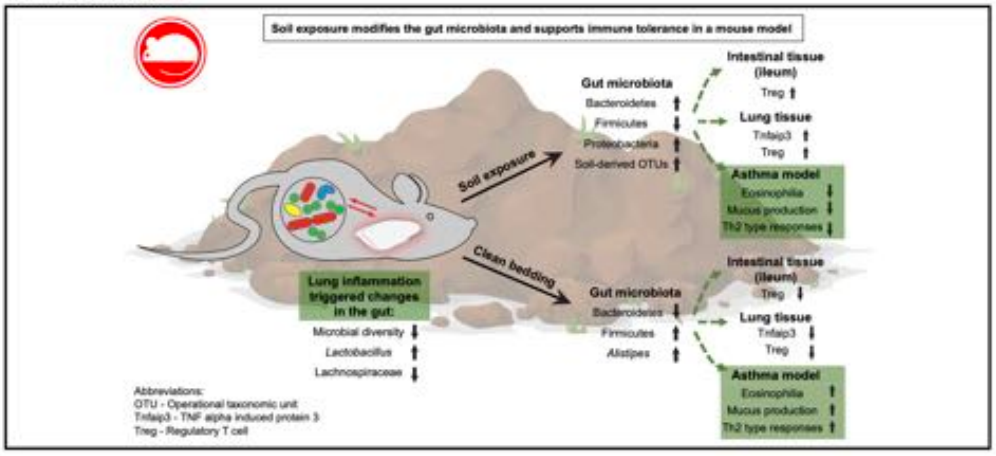
Environmental and occupational disease

Soil exposure modifies the gut microbiota and supports immune tolerance in a mouse model

Noora Ottman, PhD,[a,b*] Lasse Ruokolainen, PhD,[a*] Alina Suomalainen, MSc,[c] Hanna Sinkko, PhD,[d] Piia Karisola, PhD,[c] Jenni Lehtimäki, PhD,[a] Maili Lehto, PhD,[e] Ilkka Hanski, PhD,[a†] Harri Alenius, PhD,[b,c] and Nanna Fyhrquist, PhD[b,c]

Helsinki, Finland, and Stockholm, Sweden

GRAPHICAL ABSTRACT



Naturally-diverse airborne environmental microbial exposures modulate the gut microbiome and may provide anxiolytic benefits in mice

Craig Liddicoat [a,e,1], Harrison Sydnor [a], Christian Cando-Dumancela [d], Romy Dresken [a], Jiajun Liu [b,c,2], Nicholas J.C. Gellie [a,3], Jacob G. Mills [a,4], Jennifer M. Young [a,d], Laura S. Weyrich [e,f,5], Mark R. Hutchinson [b,c,6], Philip Weinstein [a,7], Martin F. Breed [a,d,*,8]

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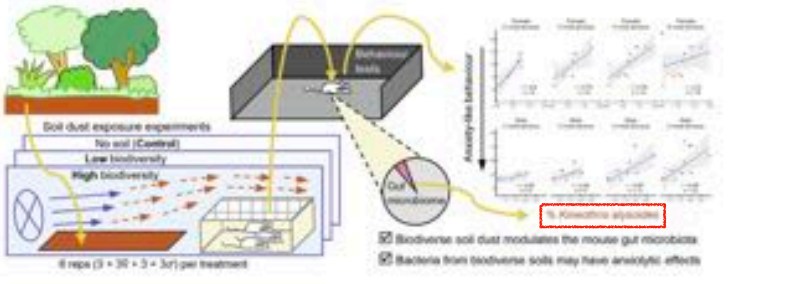
HIGHLIGHTS

- The effect of biodiverse aerobiomes on gut microbiota was previously untested.
- We demonstrate that exposure to biodiverse soil dust modulates mouse gut microbiota.
- Biodiverse soil exposure may help supplement butyrate-producing bacteria in the gut.
- These bacteria appear to moderate anxiety-like behaviour in the most anxious mice.
- We suggest a new hypothesis linking biodiverse soils, gut health and mental health.

GRAPHICAL ABSTRACT



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Behavioural Processes

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

Ingestion of *Mycobacterium vaccae* decreases anxiety-related behavior and improves learning in mice

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ABSTRACT

Coevolution of microbes and their hosts has resulted in the formation of symbiotic relationships that enable animals to adapt to their environments and protect themselves against pathogens. Recent studies show that contact with tolerogenic microbes is important for the proper functioning of immunoregulatory circuits affecting behavior, emotionality and health. Few studies have examined the potential influence of ambient bacteria, such as *Mycobacterium vaccae* on the gut–brain–microbiota axis. In this preliminary research, we show that mice fed live *M. vaccae* prior to and during a maze learning task demonstrated a reduction in anxiety-related behaviors and maze completion time, when tested at three maze difficulty levels over 12 trials for four weeks. Treated mice given *M. vaccae* in their reward completed the maze twice as fast as controls, and with reduced anxiety-related behaviors. In a consecutive set of 12 maze trials without *M. vaccae* exposure, treated mice continued to run the maze faster for the first three trials, and with fewer errors overall, suggesting a treatment persistence of about one week. Following a three-week hiatus, a final maze run revealed no differences between the experimentals and controls. Additionally, *M. vaccae*-treated mice showed more exploratory head-dip behavior in a zero maze, and *M. vaccae* treatment did not appear to affect overall activity levels as measured by activity wheel usage. Collectively, our results suggest a beneficial effect of naturally delivered, live *M. vaccae* on anxiety-related behaviors and maze performance, supporting a positive role for ambient microbes in the immunomodulation of animal behavior.

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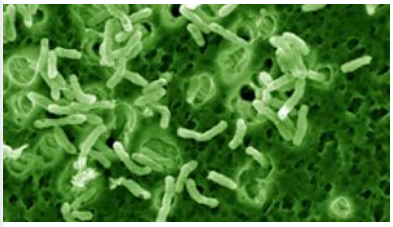

https://www.colorado.edu/today/2017/01/05/study-linking-beneficial-bacteria-mental-health-makes-top-10-list-brain-research

http://www.bacteriainphotos.com/mycobacterium%20vaccae.html

PERSPECTIVE

Regulation of the immune system by biodiversity from the natural environment: An ecosystem service essential to health

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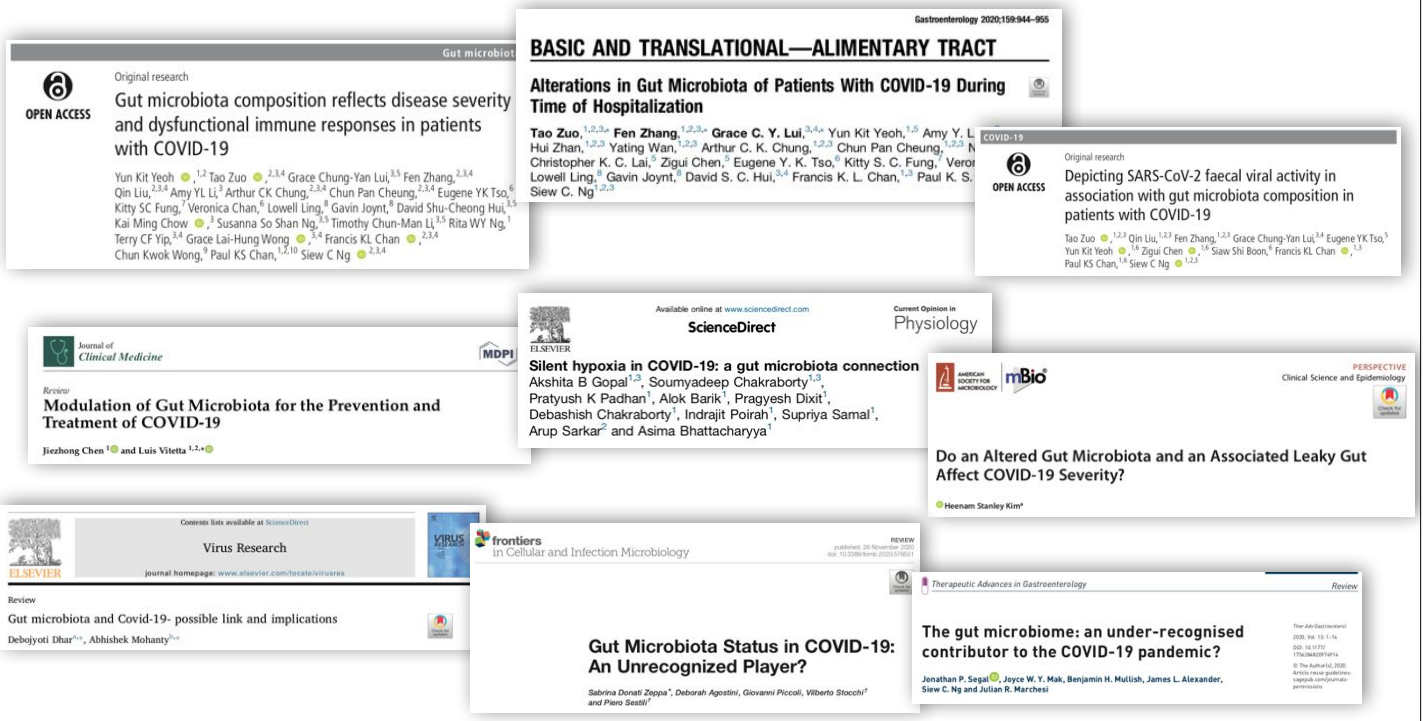
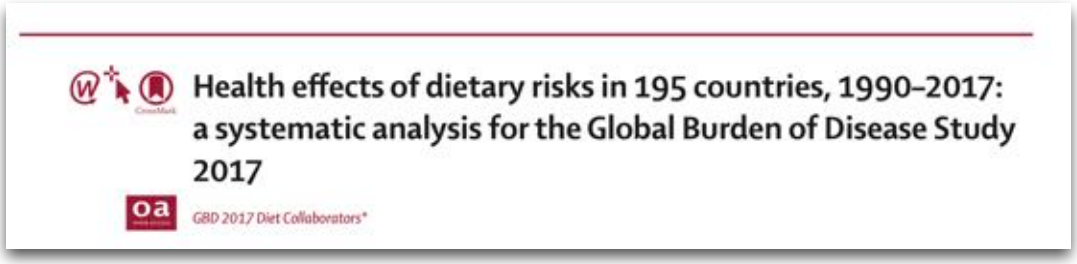
Edited by Ruslan Medzhitov, Yale University School of Medicine, New Haven, CT, and approved October 1, 2013 (received for review July 23, 2013)

Epidemiological studies suggest that living close to the natural environment is associated with long-term health benefits including reduced death rates, reduced cardiovascular disease, and reduced psychiatric problems. This is often attributed to psychological mechanisms, boosted by exercise, social interactions, and sunlight. Compared with urban environments, exposure to green spaces does indeed trigger rapid psychological, physiological, and endocrinological effects. However, there is little evidence that these rapid transient effects cause long-term health benefits or even that they are a specific property of natural environments. Meanwhile, the illnesses that are increasing in high-income countries are associated with failing immunoregulation and poorly regulated inflammatory responses, manifested as chronically raised C-reactive protein and proinflammatory cytokines. This failure of immunoregulation is partly attributable to a lack of exposure to organisms ("Old Friends") from mankind's evolutionary past that needed to be tolerated and therefore evolved roles in driving immunoregulatory mechanisms. Some Old Friends (such as helminths and infections picked up at birth that established carrier states) are almost eliminated from the urban environment. This increases our dependence on Old Friends derived from our mothers, other people, animals, and the environment. It is suggested that the requirement for microbial input from the environment to drive immunoregulation is a major component of the beneficial effect of green space, and a neglected ecosystem service that is essential for our well-being. This insight will allow green spaces to be designed to optimize health benefits and will provide impetus from health systems for the preservation of ecosystem biodiversity.





„Unsere Ergebnisse zeigen, dass eine suboptimale Ernährung weltweit für mehr Todesfälle verantwortlich ist als jedes andere Risiko, einschließlich des Tabakrauchens…“

Lancet 2019; 393: 1958–72
Published Online
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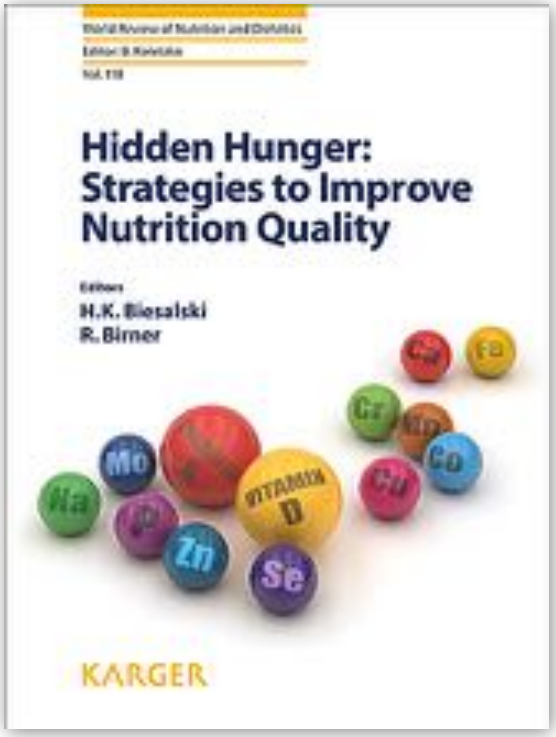
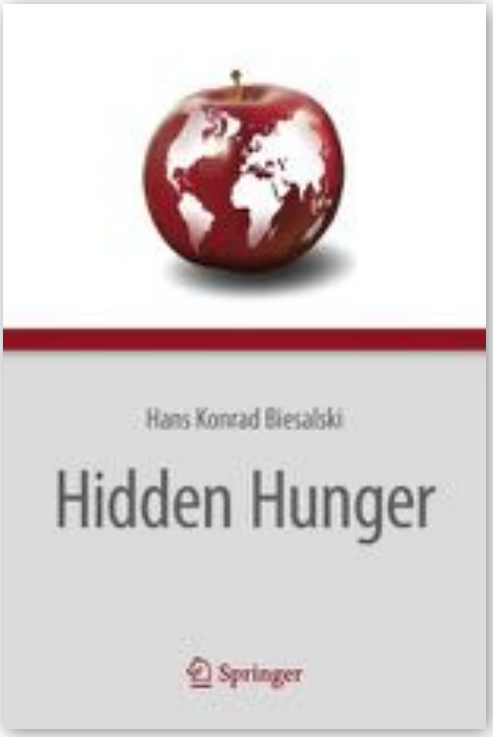
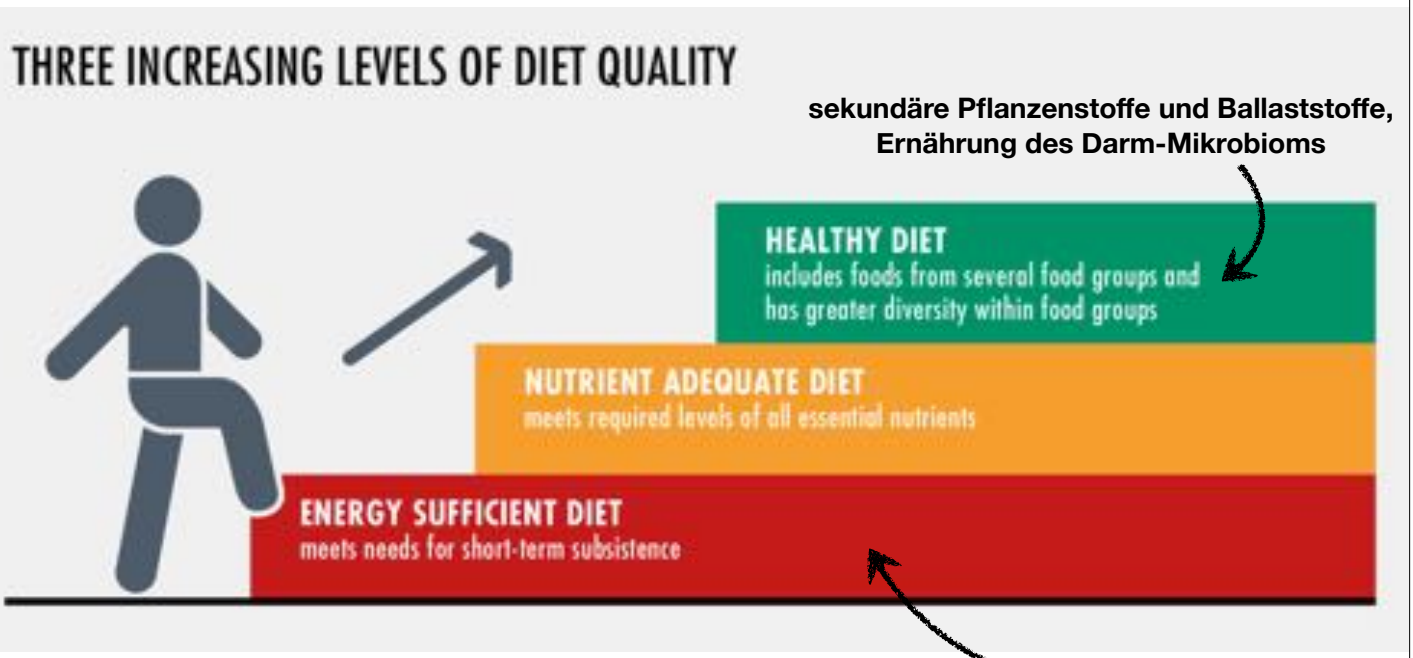
http://dx.doi.org/10.1016/
S0140-6736(19)30041-8



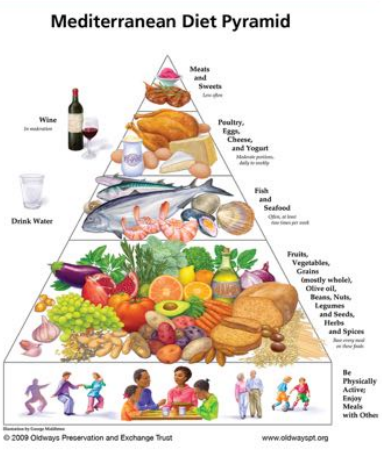




sekundäre Pflanzenstoffe und Ballaststoffe, Ernährung des Darm-Mikrobioms

ausreichend „Kalorien“

Alte Ernährungstraditionen



Vielseitig und Abwechslungsreich, pflanzenbasiert, frisch, chemiefrei und saisonal

Open access Original research

BMJ Nutrition, Prevention & Health

Plant-based diets, pescatarian diets and COVID-19 severity: a population-based case–control study in six countries

Hyunju Kim,[1,2] Casey M Rebholz,[1,2] Sheila Hegde,[3] Christine LaFiura,[4] Madhunika Raghavan,[4] John F Lloyd,[5] Susan Cheng,[5] Sara B Seidelmann[6,7]

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For numbered affiliations see

ABSTRACT

Background Several studies have hypothesised that dietary habits may play an important role in COVID-19 infection, severity of symptoms, and duration of illness. However, no previous studies have investigated the association between dietary patterns and COVID-19.

Methods Healthcare workers (HCWs) from six countries (France, Germany, Italy, Spain, UK, USA) with substantial exposure to COVID-19 patients completed a web-based survey from 17 July to 25 September 2020. Participants provided information on demographic characteristics, dietary information, and COVID-19 outcomes. We used multivariable logistic regression models to evaluate the association between self-reported diets and COVID-19 infection, severity, and duration.

What this paper adds

- In 2884 front-line healthcare workers from six countries (France, Germany, Italy, Spain, UK, USA), individuals who reported following plant-based diets and plant-based diets or pescatarian diets that were higher in vegetables, legumes and nuts, and lower in poultry and red and processed meats, had 73% and 59% lower odds of moderate-to-severe COVID-19, respectively.
- Plant-based diets or pescatarian diets are healthy dietary patterns, which may be considered for protection against severe COVID-19.

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Hindawi
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Review Article

Phytochemicals That Influence Gut Microbiota as Prophylactics and for the Treatment of Obesity and Inflammatory Diseases

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Gut microbiota (GM) plays several crucial roles in host physiology and influences several relevant functions. In more than one respect, it can be said that you "feed your microbiota and are fed by it." GM diversity is affected by diet and influences metabolic and immune functions of the host's physiology. Consequently, an imbalance of GM, or dysbiosis, may be the cause or at least may lead to the progression of various pathologies such as infectious diseases, gastrointestinal cancers, inflammatory bowel disease, and even obesity and diabetes. Therefore, GM is an appropriate target for nutritional interventions to improve health. For this reason, phytochemicals that can influence GM have recently been studied as adjuvants for the treatment of obesity and inflammatory diseases. Phytochemicals include prebiotics and probiotics, as well as several chemical compounds such as polyphenols and derivatives, carotenoids, and thiosulfates. The largest group of these comprises polyphenols, which can be subclassified into four main groups: flavonoids (including eight subgroups), phenolic acids (such as curcumin), stilbenoids (such as resveratrol), and lignans. Consequently, in this review, we will present, organize, and discuss the most recent evidence indicating a relationship between the effects of different phytochemicals on GM that affect obesity and/or inflammation, focusing on the effect of approximately 40 different phytochemical compounds that have been chemically identified and that constitute some natural reservoir, such as potential prophylactics, as candidates for the treatment of obesity and inflammatory diseases.

frontiers in Nutrition

REVIEW
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Polyphenol-Mediated Gut Microbiota Modulation: Toward Prebiotics and Further

María Carolina Rodríguez-Daza[1,2†], Elena C. Pulido-Mateos[1,2†], Joseph Lupien-Meilleur[1,2†], Denis Guyonnet[3], Yves Desjardins[1,4] and Denis Roy[1,2]*

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The genome of gut microbes encodes a collection of enzymes whose metabolic functions contribute to the bioavailability and bioactivity of unabsorbed (poly)phenols. Datasets from high throughput sequencing, metabolome measurements, and other omics have expanded the understanding of the different modes of actions by which (poly)phenols modulate the microbiome conferring health benefits to the host. Progress have been made to identify direct prebiotic effects of (poly)phenols; albeit up to date, these compounds are not recognized as prebiotics *sensu stricto*. Interestingly, certain probiotics strains have an enzymatic repertoire, such as tannase, α-L-rhamnosidase, and phenolic acid reductase, involved in the transformation of different (poly)phenols into bioactive phenolic metabolites. *In vivo* studies have demonstrated that these (poly)phenol-transforming bacteria thrive when provided with phenolic substrates. However, other taxonomically distinct gut symbionts of which a phenolic-metabolizing activity has not been demonstrated are still significantly promoted by (poly)phenols. This is the case of *Akkermansia muciniphila*, a so-called antiobesity bacterium, which responds positively to (poly)phenols and may be partially responsible for the health benefits formerly attributed to these molecules. We surmise that (poly)phenols broad antimicrobial action free ecological niches occupied by competing bacteria, thereby allowing the bloom of beneficial gut bacteria. This review explores the capacity of (poly)phenols to promote beneficial gut bacteria through their direct and collaborative bacterial utilization and their inhibitory action on potential pathogenic species. We propose the term dupli*biotic*, to describe an unabsorbed substrate modulating the gut microbiota by both antimicrobial and prebiotic modes of action. (Poly)phenol dupli*biotic* effect could participate in blunting metabolic disturbance and gut dysbiosis, positioning these compounds as dietary strategies with therapeutic potential.

Keywords: polyphenols, prebiotics, antimicrobial action, polyphenol-associated enzymes, *Akkermansia muciniphila*, dupli*biotic*, *Lactiplantibacillus plantarum*, trophic interactions

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Invited Review Article

Shaping the gut microbiota by bioactive phytochemicals: An emerging approach for the prevention and treatment of human diseases

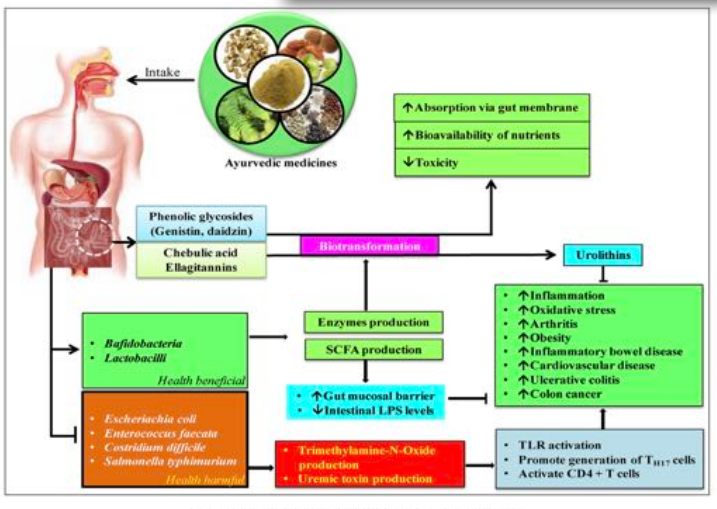

Fig. 1. Role of plant products in regulating GM and human health.

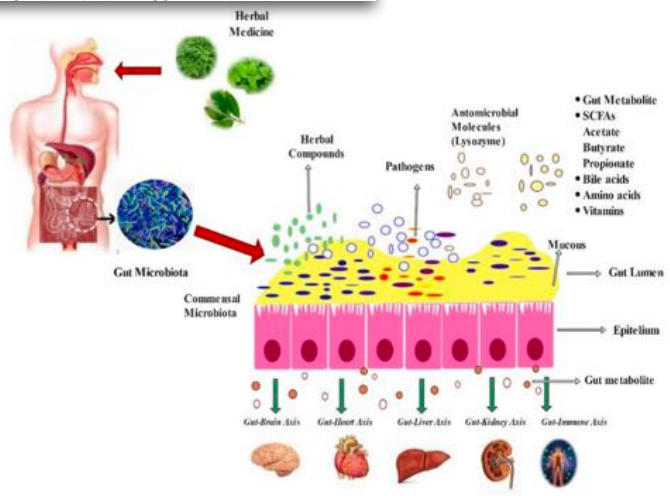

Fig. 3. Role of plant products and dietary intakes in the enhancement of GM and related functions in the body.

PERSPECTIVE
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Relating Urban Biodiversity to Human Health With the 'Holobiont' Concept

Jacob G. Mills[1], Justin D. Brookes[1], Nicholas J. C. Gellie[1], Craig Liddicoat[1], Andrew J. Lowe[1], Harrison R. Sydnor[1], Torsten Thomas[2], Philip Weinstein[1], Laura S. Weyrich[3] and Martin F. Breed[1]*

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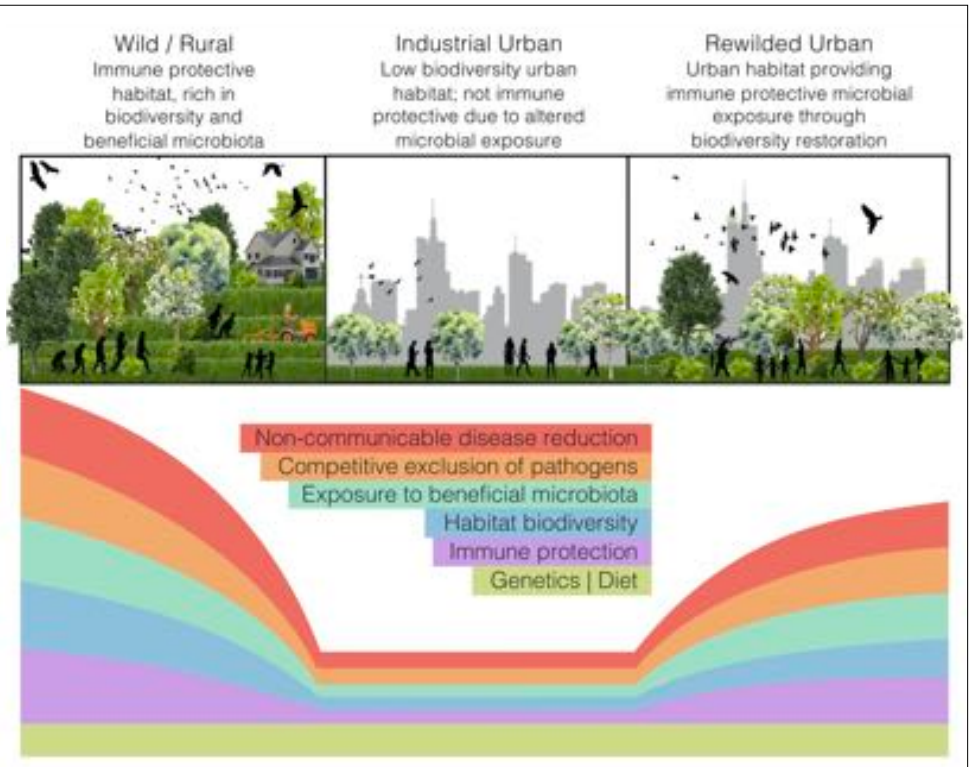
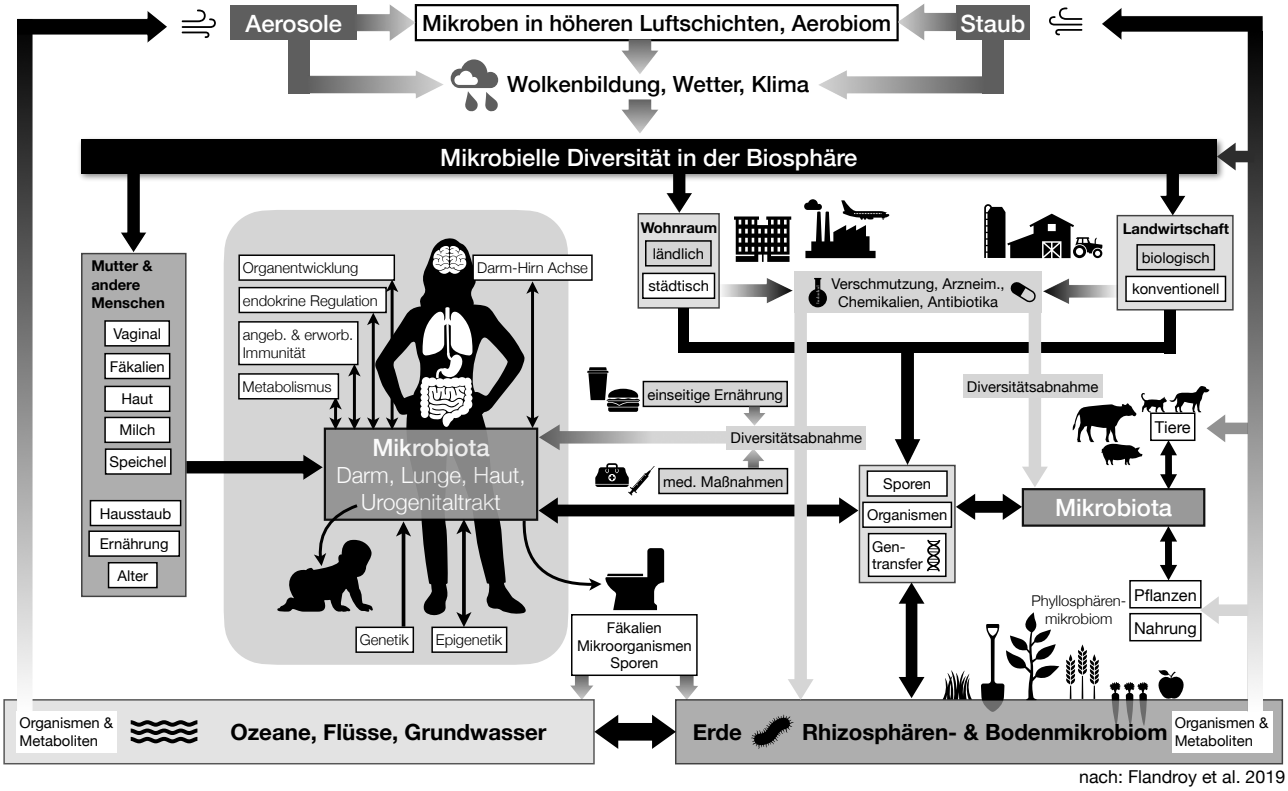


Mills et al. (2019) Relating Urban Biodiversity to Human Health With the 'Holobiont' Concept. Front. Microbiol. 10:550.



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