



Exposure of the Host-Associated Microbiome to Nutrient-Rich Conditions May Lead to Dysbiosis and Disease Development— an Evolutionary Perspective

 Tim Lachnit,^a Thomas C. G. Bosch,^a Peter Deines^a

^aZoological Institute, Christian-Albrechts University Kiel, Kiel, Germany

ABSTRACT Inflammatory diseases, such as inflammatory bowel diseases, are dramatically increasing worldwide, but an understanding of the underlying factors is lacking. We here present an ecoevolutionary perspective on the emergence of inflammatory diseases. We propose that adaptation has led to fine-tuned host-microbe interactions, which are maintained by secreted host metabolites nourishing the associated microbes. A constant elevation of nutrients in the gut environment leads to an increased activity and changed functionality of the microbiota, thus severely disturbing host-microbe interactions and leading to dysbiosis and disease development. In the past, starvation and pathogen infections, causing diarrhea, were common incidences that reset the gut bacterial community to its “human-specific-baseline.” However, these natural clearing mechanisms have been virtually eradicated in developed countries, allowing a constant uncontrolled growth of bacteria. This leads to an increase of bacterial products that stimulate the immune system and ultimately might initiate inflammatory reactions.

KEYWORDS dysbiosis, fasting, holobiont, host-microbe homeostasis, inflammatory disease, metaorganism, microbiome, overfeeding, starvation

The human body is associated with a huge diversity of different microbes colonizing skin, gut, teeth, and even epithelia of the lungs. Together with our microbes, we form a synergist relation, which is termed holobiont or metaorganism (1, 2). Disturbance of this host-microbe homeostasis can lead to dysbiosis (microbial imbalance on or inside the host) and/or disease development (3–5).

In the last several decades, inflammatory diseases, such as inflammatory bowel disease (IBD), are on the rise (6, 7). Different hypotheses have been put forward as potential explanations for this phenomenon, such as the hygiene hypothesis (8), the keystone-pathogen hypothesis (9), or genetic predisposition (10). Although there is evidence for different genetic predispositions that are associated with inflammatory diseases, they can explain only approximately 20% of the disease (11). Eighty percent is unexplained, and there is a lively debate on whether environmental factors could be a key trigger for the onset of disease and disease development (10).

It is well documented that inflammatory diseases are accompanied by changes in microbial density (12) or microbial community composition (13). However, comprehensive sequencing approaches have not yet led to the identification of a key pathogen, nor to the discovery of a specific pathobiome that is responsible for the disease (14). On the contrary, it is becoming more and more apparent that our associated microbiota is not as specific as we thought and that, even within the same individual, microbial community composition underlies strong temporal variability (13). So far, one common observation in the context of Western lifestyle and inflammatory disease is a reduction of microbial diversity (15). Although sequencing depth has dramatically increased by the development of new technologies, 16S rRNA amplicon sequencing only provides

Citation Lachnit T, Bosch TCG, Deines P. 2019. Exposure of the host-associated microbiome to nutrient-rich conditions may lead to dysbiosis and disease development—an evolutionary perspective. *mBio* 10:e00355-19. <https://doi.org/10.1128/mBio.00355-19>.

Editor Margaret J. McFall-Ngai, University of Hawaii at Manoa

Copyright © 2019 Lachnit et al. This is an open-access article distributed under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/).

Address correspondence to Tim Lachnit, tlachnit@zoologie.uni-kiel.de.

Published 14 May 2019

an overview of the associated bacterial members. Knowing that there is enormous variation within the genetic repertoire of bacteria featuring the same 16S rRNA sequence, researchers now search for insights into the interplay of bacteria within the gut by analyzing DNA (metagenomics), RNA (metatranscriptomics), proteins (metaproteomics), and metabolites (metabolomics) in order to elucidate their functional interactions within metaorganisms. Whether this approach will finally lead to the development of a more targeted approach to reconstitute natural host-microbe homeostasis in order to treat inflammatory disease is questionable as it is so far not clear if a disturbed microbiota is the cause or the consequence of inflammatory diseases (4).

Emerging infectious diseases are on the rise in not only the human population. Similar trends can be observed in the ocean over the last decade. Time series exist for only a few species such as corals and oysters, but both show the same overall pattern—an exponential rise in disease outbreaks (16, 17). Today, disease syndromes have been described for a variety of aquatic organisms of natural and cultured populations, including fish, seagrass, seaweeds, sponges, corals, and other invertebrates (18–21). As for inflammatory diseases in humans, in many cases the causative agents are unknown. It is evident, however, that a number of complex diseases in the aquatic environment are linked to a dysbiotic state of the microbiome (22–25). Anthropogenic impact, such as urbanization and global climate change, is one factor that can alter the microbiota of key habitat-forming species, such as corals and seaweeds, with potential ecological consequences (24, 25).

Here we introduce an alternative perspective and propose that host-secreted metabolites play a major role in maintaining symbiotic interactions by nourishing the associated microbes. Changes in the environment that interfere with this nutrient dependency of host-associated bacteria may severely disturb host-microbe interactions and thus lead to dysbiosis and disease development.

Maintenance of host-microbe homeostasis. To gain a better understanding of host-microbe interactions, we must consider that all eukaryotic life has evolved in an aquatic environment under the constant exposure to bacteria. This adaptation has formed a synergistic relation between the eukaryotic host and its associated microbes. No surprise that all epithelial surfaces are colonized by bacteria, ranging from marine algae (26, 27), plankton (28), corals and other marine invertebrates (29), freshwater polyps (30, 31), and marine vertebrates (32) to humans (33). Host-microbe interactions take place at epithelial surfaces that are exposed to both the bacterial colonizers and the surrounding environmental conditions. Surfaces of aquatic organisms, for example, are permanently subjected to a colonizer pool and have to regulate bacterial colonization to inhibit invasion and overgrowth by bacteria. Planktonic bacteria, however, are at certain times growth limited (34, 35), and it is reasonable to assume that it is advantageous to attach to surfaces. Evidence for this comes from bacterial ectosymbionts from marine nematodes, where the evolution of longitudinal cell division enhances bacterial attachment to its host (36). Whereas this represents a very specific case, it is known that already the attachment of bacterial cells to nonliving amorphous surfaces and the formation of biofilms lead to an increase in bacterial growth (37). The biofilm serves as a trap for nutrients from the surrounding water, providing shelter for bacterial cells against bacterivores, and facilitates degradation of complex compounds due to collaboration of diverse bacteria (38). Living attached to a nutrient-rich epithelial surface, featuring a carbohydrate source such as mucins or polysaccharides, should therefore constitute a fitness advantage to the bacteria. This colonization process must, however, be controlled by the host to limit the amount of surface-colonizing organisms and to select for nonpathogenic or even for beneficial bacteria. Indeed, there are several studies that have shown antibacterial effects of marine seaweeds (39–41) and many others regarding the innate immune system of invertebrates and vertebrates that allow them to sense and shape bacterial colonization (42, 43).

Epithelial colonization: host secretion as nutrient resource. Under natural conditions, diverse bacterial communities cover epithelial surfaces of aquatic organisms. In

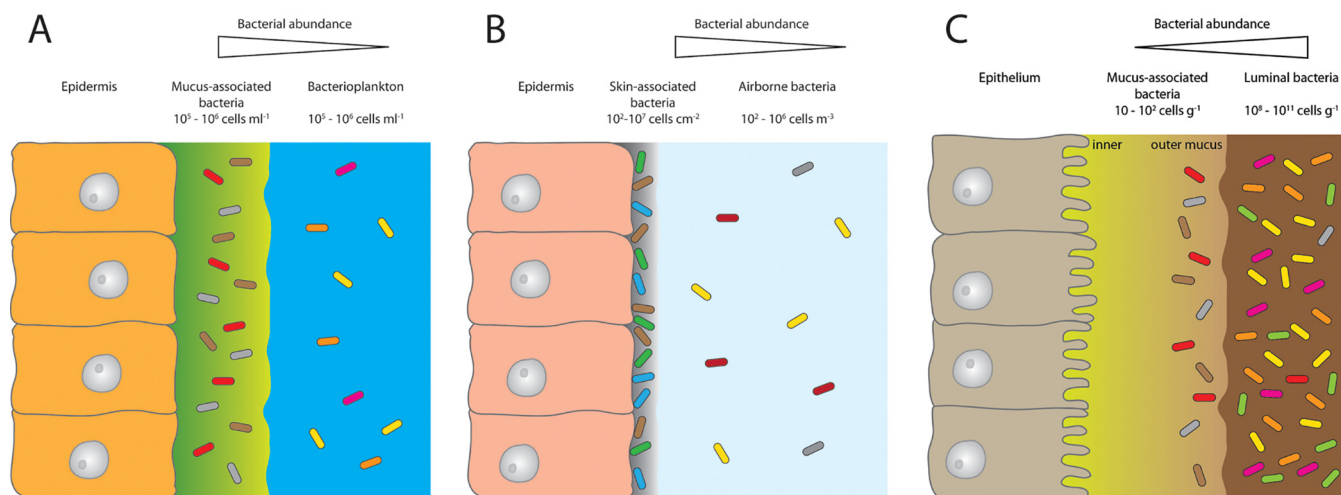


FIG 1 The relative abundance of bacteria associated with coral mucus (A), the human skin (B), and the mucosa of the gastrointestinal tract (C) in relation to the adjacent environments seawater, air, and the lumen of the gastrointestinal tract. Abundance data for the different environments were taken from references 19, 65, and 80 to 87.

environments that are low in dissolved organic matter (DOM) or particulate organic matter (POM), host-secreted metabolites can often present the only form of available nutrients (44). Examples include *Hydra*, which when kept in artificial *Hydra* medium (water plus salts) still features a complex host-associated bacterial community (30). Another example is corals, which have a mucus that is densely populated by a phylogenetically distinct bacterial community (e.g., references 2 and 45 to 47). Biomolecules released from the mucus may serve as potent chemoattractants for natural populations of coral reef bacteria (48). This finding supports the idea that the host is a major driver in providing access to resources for its surface-associated bacteria. In general, microbial abundances in coral mucus are roughly 1 order of magnitude higher than in the surrounding reef waters (49). Interestingly, when comparing the quantity of host surface-associated bacteria to that of the surrounding environment, we find the same pattern in aquatic and terrestrial organisms. For both, the abundance of surface-associated bacteria is always higher than in the surrounding environment (Fig. 1, corals [panel A] and human skin [panel B]). But there are also differences between the two systems. For terrestrial life, the rate of encountering bacteria is highly reduced as air bacterial counts make up only a fraction of reef water counts (Fig. 1, corals [panel A] versus human skin [panel B]). Further, the nutrient supply to, e.g., the skin environment from the air is almost zero. Skin-associated bacteria therefore have to live solely from secreted or surface-shed material. In the human gut, we find the exact opposite. Here bacterial abundances in the lumen exceed the mucus-associated bacteria by roughly a factor of 10^8 (Fig. 1C).

The evolutionary origin of two different microbial niches within the gut. From an evolutionary perspective (see reference 50), the development of a gut environment changed the existing host-microbe relationships by introducing another habitat and food source for the bacteria. The invagination during gastrulation delocalized the epithelial surface from the outside into the inner part of an organism and separated it from environmental conditions in the water. Consequently, this led to dramatic environmental changes for the associated microbiota due to a restricted exchange with the surrounding water. For example, oxygen and nutrient supply from the surrounding water became limited. Instead, associated microbes were less exposed to the diverse mixture of bacterial colonizers, grazers, and phages than were the plankton community. This in turn limited the microbial colonization of the gut environment, which became dependent on the feeding behavior of the eukaryotic host. In general, the uptake of food does not only allocate new bacteria into the gut, but it also offers an alternative

nutrient source for the gut microbiota and thus forms an additional habitat for bacteria. The development of a gut thus led to two different niches with distinct microbial populations: the gut mucus with its associated residential microbiota (which we here term “human-specific-baseline” microbiota) and the food that is being digested with its associated transient microbiota (luminal microbiome). While the growth of mucus-associated bacterial communities on the outside of organisms is restricted by host-secreted metabolites, mucus-associated bacteria in the gut are exposed to dynamic compositional changes of the digested/ingested food depending on: food consumption, food composition, frequency of feeding, digestive processing by the host, and also the enzymatic activity of the microbiota. Host-derived substances, such as bile acids, mucus, and urea, are important nutrient sources for the microbiota, with urea serving as a major nitrogen supply (51). These processes supply additional nutrients for mucus-associated bacteria and so continuously shape gut environmental conditions and affect microbial community composition (52–56).

Maintaining homeostasis: natural recurrent clearing mechanisms. In the evolutionary history of animals and humans, hunger was the default state. Finding food was always a costly endeavor. On evolutionary time scales, food availability was often limited and not only humans but also other organisms had to adapt to periods of food shortage (57, 58). There is increasing evidence that humans are well adapted to food shortages of up to 1 day. After that time, glycogen storage, which serves as an energy source, gets depleted and metabolism switches to gluconeogenesis (59). Already a longer nighttime fasting duration reduces the C-reactive protein (CRP) level when evening dinner contains less than 30% of the daily calorie needs (60). Fasting for even longer periods of time has been shown to have a huge impact on a variety of processes, such as changes in cellular pathways, prevention of disease development, and delay in aging not only in humans but also in animal models (59). Whereas fasting in lower eukaryotes leads to higher longevity and in rodents it protects against diabetes, cancer, heart disease, and neurodegeneration, in humans it helps to reduce obesity, hypertension, asthma, and rheumatoid arthritis (57). While such host metabolic changes induced by fasting are only partially understood, we here propose that an important factor that links fasting to our state of health is the effect of fasting on our gut microbiota. From many animals, including mice, alligators, pythons, and chickens, we know that fasting induces shifts in the gut microbiome (61). The same is true for hibernation, which has been shown to alter the diversity and composition of gut microbiota in ground squirrels (62). The authors could show that hibernation reduced populations of *Firmicutes* (which prefer polysaccharides) but increased populations of *Bacteroidetes* and *Verrucomicrobia*, capable of degrading mucin. This supports the idea that during a lack of nutrient availability, mucin glycans become the primary substrate for microbial metabolism during hibernation (63). In addition, fasting and hibernation not only lead to a changed microbiome composition but also suppress the immune system (64), thus increasing the tolerance of the host to its microbes.

In humans, food supply for the gut bacteria is also reduced during fasting, limiting uncontrolled growth of unspecific, non-mucus-adapted gut microbiota. Instead, the microbes that are favored are highly adapted to the gut environment in that they are able to degrade mucin or exist on host-derived secretions (65, 66). In the last century, food became permanently available and the amount of available food per capita increased by up to 10-fold in developed countries by the end of the century (67). These circumstances presented a new situation in which nutrients were continuously available not only for modern humans but also for their gut-associated bacteria.

While excessive food supply led to the loss of fasting events in the 20th century, sanitation conditions were improved at the same time in developed countries. The introduction of cleansing agents, purification of drinking water, and the invention of washing machines and refrigerators helped to reduce the risk of gastrointestinal pathogenic infections. This is in contrast to developing countries, where poor hygiene conditions and a higher risk for the population of contracting diarrheal diseases are

found (68). Recurrent gastrointestinal pathogenic infections are accompanied by periods of diarrhea and so regularly reduce the population of the unspecific luminal microbiota. During human evolution, this “cleaning” effect might have been important for maintaining health as it provides the mucosally adapted microbiota with the opportunity to proliferate. While events of diarrheal infections have been shown to be followed by a rapid, reproducible, and reversible change in microbial community structure (69), the effect of diarrheal flushing on total bacterial abundance is not known. Although mild and short-term forms of diarrhea might be beneficial for human health, pathogen-induced diarrhea can also have severe consequences, especially in children, leading to significant morbidity and mortality. Not only diarrhea but also artificial cleansing of the gut by bowel preparation for colonoscopy has an impact on the gut microbial community. Due to this procedure, microbial load in the gut is decreased by about 30-fold (70) and bacterial diversity is reduced in the short term but restored after approximately 14 days (70–72). Another crucial novelty of the last decades is the use of antibiotics, which have become a key weapon to fight malignant bacteria. Despite their benefits in combating disease, they massively challenge our microbiome, leading to the loss of beneficial microbes (73), and likely impair the restoration of a healthy microbiome.

In general, the lack of natural cleaning mechanisms appears to result in a loss of the competitive advantage of the mucus-adapted bacteria while simultaneously favoring the non-mucus-adapted gut microbial bacteria that live on ingested food items of their host. During microbial breakdown of food residues, small molecules that can cross the epithelial border and get dispersed in the serum are produced. These molecules can either be harmful (e.g., uremic toxins) or beneficial (e.g., antioxidants) to the host (74). Depending on the food composition, the ratio of harmful to beneficial compounds can shift; so an increased protein fermentation, for example, increases the amounts of potential toxic compounds, such as ammonia, phenols, amines, indoles, and thiols (75). Interestingly, dietary shifts in the food quality in a Western-style diet (WSD), which is easily digestible by humans and microbes, being rich in sugars, fats, and proteins but having small amounts of fiber, can have adverse health effects, while diets rich in fiber are beneficial (76). There is initial evidence from a mouse model that the WSD alters the microbiome composition and so causes an increased penetrability of the mucus layer (77). By adding fibers to the diet, the authors were able to preserve the barrier function of the mucus (77). In contrast, a high dietary phosphate content of WSD can exacerbate intestinal inflammation in experimental colitis (78), pointing to an imbalance in the C/N/P ratio. The significance of C/N/P ratios in marine environments for the growth of organisms is well established (79), and it is reasonable to assume that it also plays a central role in the nutrient and microbiota homeostasis in the human gut.

Excess feeding may disrupt the homeostasis and lead to an altered microbiome, resulting in disease development: the overfeeding hypothesis. We here propose that overfeeding of the host-associated bacterial community, particularly with easily digestible, energy-dense, low-fiber-content foods, likely causes dysbiosis and the development of disease. Overfeeding uncouples natural host-microbe associations, leading to an increased activity and changed functionality of the associated microbiota. In previous times, starvation and also pathogen infections which lead to diarrhea were common incidences that may have helped to reset the gut microbial community to its “human-specific baseline.” However, these natural clearing mechanisms have been almost totally eradicated in developed countries, allowing an uncontrolled growth of bacteria which are not specifically adapted to the human host mucosal environment. This may lead to a changed composition and increase of bacterial by-products in the gut. Moreover, overfeeding by consuming a WSD may also impair the natural nutrient balance in the gut (C/N/P ratio), leading to an enhanced microbial degradation of the mucus barrier. Taken together, the reduction of the mucus barrier function and the increased release of bacterial by-products into the gut elevate nonself recognition of the host and stimulate the immune system. Additional nonself recognition and stimulation of the immune system anywhere in the body likely initiate an immune response,

which might contribute to the development of complex disease, such as atopic dermatitis, asthma, or diabetes.

ACKNOWLEDGMENTS

Work related to this topic was supported in part by grants from the Deutsche Forschungsgemeinschaft (DFG) and the Collaborative Research Center (CRC) 1182 (“Origin and Function of Metaorganisms”) and grants from the DFG Cluster of Excellence program “Inflammation at Interfaces.” T.L. acknowledges funding from the Volkswagen Foundation (funding program “Experiment!—In search of bold research ideas”). P.D. acknowledges funding from the European Union’s Framework Program for Research and Innovation Horizon 2020 (2014–2020) under the Marie Skłodowska-Curie grant agreement 655914 and from the Deutscher Akademischer Austausch Dienst (DAAD).

T.C.G.B. gratefully appreciates support from the Canadian Institute for Advanced Research (CIFAR) and thanks the Wissenschaftskolleg (Institute of Advanced Studies) in Berlin for a sabbatical leave. We thank two anonymous reviewers for their careful reading of our manuscript and their valuable and constructive comments and suggestions, which considerably improved the manuscript.

REFERENCES

- Bosch TCG, McFall-Ngai MJ. 2011. Metaorganisms as the new frontier. *Zoology* 114:185–190. <https://doi.org/10.1016/j.zool.2011.04.001>.
- Rosenberg E, Koren O, Reshef L, Efrony R, Zilber-Rosenberg I. 2007. The role of microorganisms in coral health, disease and evolution. *Nat Rev Microbiol* 5:355–362. <https://doi.org/10.1038/nrmicro1635>.
- Van Rensburg JJ, Lin H, Gao X, Toh E, Fortney KR, Ellinger S, Zwickl B, Janowicz DM, Katz BP, Nelson DE, Dong Q, Spinola SM. 2015. The human skin microbiome associates with the outcome of and is influenced by bacterial infection. *mBio* 6:e01315-15. <https://doi.org/10.1128/mBio.01315-15>.
- Carding S, Verbeke K, Vipond DT, Corfe BM, Owen LJ. 2015. Dysbiosis of the gut microbiota in disease. *Microb Ecol Health Dis* 26:26191. <https://doi.org/10.3402/mehd.v26.26191>.
- Raymann K, Moran NA. 2018. The role of the gut microbiome in health and disease of adult honey bee workers. *Curr Opin Insect Sci* 26:97–104. <https://doi.org/10.1016/j.cois.2018.02.012>.
- Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. 2012. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 142:46–54.e42. <https://doi.org/10.1053/j.gastro.2011.10.001>.
- Ng WK, Wong SH, Ng SC. 2016. Changing epidemiological trends of inflammatory bowel disease in Asia. *Intest Res* 14:111–119. <https://doi.org/10.5217/ir.2016.14.2.111>.
- Rook G. 2012. Hygiene hypothesis and autoimmune diseases. *Clin Rev Allergy Immunol* 42:5–15. <https://doi.org/10.1007/s12016-011-8285-8>.
- Hajishengallis G, Darveau RP, Curtis MA. 2012. The keystone-pathogen hypothesis. *Nat Rev Microbiol* 10:717–725. <https://doi.org/10.1038/nrmicro2873>.
- Damas OM, Gomez L, Quintero MA, Rampersaud E, Slifer S, Beecham GW, Kerman DH, Deshpande AR, Sussman DA, Abreu MT, McCauley JL. 2017. Genetic characterization and influence on inflammatory bowel disease expression in a diverse Hispanic South Florida cohort. *Clin Transl Gastroenterol* 8:e87. <https://doi.org/10.1038/ctg.2017.13>.
- Blumberg RS. 2016. Environment and genes: what is the interaction? *Dig Dis* 34:20–26. <https://doi.org/10.1159/000442920>.
- Contijoch EJ, Britton GJ, Yang C, Mogno I, Li Z, Ng R, Llewellyn SR, Hira S, Johnson C, Rabinowitz KM, Barkan R, Dotan I, Hirten RP, Fu S-C, Luo Y, Yang N, Luong T, Labrias PR, Lira S, Peter I, Grinspan A, Clemente JC, Kosoy R, Kim-Schulze S, Qin X, Castillo A, Hurley A, Atreja A, Rogers J, Fasihuddin F, Saliq M, Nolan A, Reyes-Mercedes P, Rodriguez C, Aly S, Santa-Cruz K, Peters L, Suárez-Fariñas M, Huang R, Hao K, Zhu J, Zhang B, Losic B, Irizar H, Song W-M, Di Narzo A, Wang W, Cohen BL, DiMaio C, Greenwald D, Itzkowitz S, Lucas A, Marion J, Maser E, Ungaro R, Naymagon S, Novak J, Shah B, Ullman T, Rubin P, George J, Legnani P, Telesco SE, Friedman JR, Brodmerkel C, Plevy S, Cho JH, Colombel J-F, Schadt EE, Armann C, Dubinsky M, Kasarskis A, Sands B, Faith JJ. 2019. Gut microbiota density influences host physiology and is shaped by host and microbial factors. *Elife* 8:e40553. <https://doi.org/10.7554/eLife.40553>.
- Halfvarson J, Brislawn CJ, Lamendella R, Vázquez-Baeza Y, Walters WA, Bramer LM, D’Amato M, Bonfiglio F, McDonald D, Gonzalez A, McClure EE, Dunkleberger MF, Knight R, Jansson JK. 2017. Dynamics of the human gut microbiome in inflammatory bowel disease. *Nat Microbiol* 2:17004. <https://doi.org/10.1038/nmicrobiol.2017.4>.
- DeGruttola AK, Low D, Mizoguchi A, Mizoguchi E. 2016. Current understanding of dysbiosis in disease in human and animal models. *Inflamm Bowel Dis* 22:1137–1150. <https://doi.org/10.1097/MIB.0000000000000750>.
- Hedin CR, McCarthy NE, Louis P, Farquharson FM, McCartney S, Taylor K, Prescott NJ, Murrells T, Stagg AJ, Whelan K, Lindsay JO. 2014. Altered intestinal microbiota and blood T cell phenotype are shared by patients with Crohn’s disease and their unaffected siblings. *Gut* 63:1578–1586. <https://doi.org/10.1136/gutjnl-2013-306226>.
- Lafferty KD, Porter JW, Ford SE. 2004. Are diseases increasing in the ocean? *Annu Rev Ecol Syst* 35:31–54. <https://doi.org/10.1146/annurev.ecolsys.35.021103.105704>.
- Ward JR, Lafferty KD. 2004. The elusive baseline of marine disease: are diseases in ocean ecosystems increasing? *PLoS Biol* 2:E120. <https://doi.org/10.1371/journal.pbio.0020120>.
- Harvell CD, Kim K, Burkholder JM, Colwell RR, Epstein PR, Grimes DJ, Hofmann EE, Lipp EK, Osterhaus AD, Overstreet RM, Porter JW, Smith GW, Vasta GR. 1999. Emerging marine diseases—climate links and anthropogenic factors. *Science* 285:1505–1510. <https://doi.org/10.1126/science.285.5433.1505>.
- Bourne DG, Garren M, Work TM, Rosenberg E, Smith GW, Harvell CD. 2009. Microbial disease and the coral holobiont. *Trends Microbiol* 17:554–562. <https://doi.org/10.1016/j.tim.2009.09.004>.
- Gachon CMM, Sime-Ngando T, Strittmatter M, Chambouvet A, Kim GH. 2010. Algal diseases: spotlight on a black box. *Trends Plant Sci* 15:633–640. <https://doi.org/10.1016/j.tplants.2010.08.005>.
- Webster NS. 2007. Sponge disease: a global threat? *Environ Microbiol* 9:1363–1375. <https://doi.org/10.1111/j.1462-2920.2007.01303.x>.
- Egan S, Gardiner M. 2016. Microbial dysbiosis: rethinking disease in marine ecosystems. *Front Microbiol* 7:991. <https://doi.org/10.3389/fmicb.2016.00991>.
- Marzinelli EM, Campbell AH, Zozaya Valdes E, Vergés A, Nielsen S, Wernberg T, de Bettignies T, Bennett S, Caporaso JG, Thomas T, Steinberg PD. 2015. Continental-scale variation in seaweed host-associated bacterial communities is a function of host condition, not geography. *Environ Microbiol* 17:4078–4088. <https://doi.org/10.1111/1462-2920.12972>.
- Marzinelli EM, Qiu Z, Dafforn KA, Johnston EL, Steinberg PD, Mayer-Pinto M. 2018. Coastal urbanisation affects microbial communities on a dom-

- inant marine holobiont. *NPJ Biofilms Microbiomes* 4:1. <https://doi.org/10.1038/s41522-017-0044-z>.
25. Ziegler M, Roik A, Porter A, Zubier K, Mudarris MS, Ormond R, Voolstra CR. 2016. Coral microbial community dynamics in response to anthropogenic impacts near a major city in the central Red Sea. *Mar Pollut Bull* 105:629–640. <https://doi.org/10.1016/j.marpolbul.2015.12.045>.
 26. Lachnit T, Meske D, Wahl M, Harder T, Schmitz R. 2011. Epibacterial community patterns on marine macroalgae are host-specific but temporally variable. *Environ Microbiol* 13:655–665. <https://doi.org/10.1111/j.1462-2920.2010.02371.x>.
 27. Egan S, Harder T, Burke C, Steinberg P, Kjelleberg S, Thomas T. 2013. The seaweed holobiont: understanding seaweed-bacteria interactions. *FEMS Microbiol Rev* 37:462–476. <https://doi.org/10.1111/1574-6976.12011>.
 28. Grossart H-P, Dziallas C, Leunert F, Tang KW. 2010. Bacteria dispersal by hitchhiking on zooplankton. *Proc Natl Acad Sci U S A* 107:11959–11964. <https://doi.org/10.1073/pnas.1000668107>.
 29. Bourne DG, Morrow KM, Webster NS. 2016. Insights into the coral microbiome: underpinning the health and resilience of reef ecosystems. *Annu Rev Microbiol* 70:317–340. <https://doi.org/10.1146/annurev-micro-102215-095440>.
 30. Fraune S, Bosch T. 2007. Long-term maintenance of species-specific bacterial microbiota in the basal metazoan Hydra. *Proc Natl Acad Sci U S A* 104:13146–13151. <https://doi.org/10.1073/pnas.0703375104>.
 31. Franzenburg S, Fraune S, Altrock PM, Künzel S, Baines JF, Traulsen A, Bosch T. 2013. Bacterial colonization of Hydra hatchlings follows a robust temporal pattern. *ISME J* 7:781–790. <https://doi.org/10.1038/ismej.2012.156>.
 32. Apprill A. 2017. Marine animal microbiomes: toward understanding host-microbiome interactions in a changing ocean. *Front Mar Sci* 4:222. <https://doi.org/10.3389/fmars.2017.00222>.
 33. Human Microbiome Project Consortium. 2012. Structure, function and diversity of the healthy human microbiome. *Nature* 486:207–214. <https://doi.org/10.1038/nature11234>.
 34. Rivkin RB, Anderson MR. 1997. Inorganic nutrient limitation of oceanic bacterioplankton. *Limnol Oceanogr* 42:730–740. <https://doi.org/10.4319/lo.1997.42.4.0730>.
 35. Pinhassi J, Gómez-Consarnau L, Alonso-Sáez L, Sala MM, Vidal M, Pedrós-Alió C, Gasol JM. 2006. Seasonal changes in bacterioplankton nutrient limitation and their effects on bacterial community composition in the NW Mediterranean Sea. *Aquat Microb Ecol* 44:241–252. <https://doi.org/10.3354/ame044241>.
 36. Leisch N, Verheul J, Heindl NR, Gruber-Vodicka HR, Pende N, Den Blaauwen T, Bulgheresi S. 2012. Growth in width and FtsZ ring longitudinal positioning in a gammaproteobacterial symbiont. *Curr Biol* 22:R831–R832. <https://doi.org/10.1016/j.cub.2012.08.033>.
 37. Zobell CE. 1943. The effect of solid surfaces upon bacterial activity. *J Bacteriol* 46:39–56.
 38. Flemming HC, Wingender J, Szewzyk U, Steinberg P, Rice SA, Kjelleberg S. 2016. Biofilms: an emergent form of bacterial life. *Nat Rev Microbiol* 14:563–575. <https://doi.org/10.1038/nrmicro.2016.94>.
 39. Lachnit T, Wahl M, Harder T. 2010. Isolated thallus-associated compounds from the macroalga *Fucus vesiculosus* mediate bacterial surface colonization in the field similar to that on the natural alga. *Biofouling* 26:247–255. <https://doi.org/10.1080/08927010903474189>.
 40. Maximilian R, De Nys R, Holmström C, Gram L, Givskov M, Crass K, Kjelleberg SA, Steinberg PD. 1998. Chemical mediation of bacterial surface colonisation by secondary metabolites from the red alga *Delisea pulchra*. *Aquat Microb Ecol* 15:233–246. <https://doi.org/10.3354/ame015233>.
 41. Lachnit T, Fischer M, Künzel S, Baines JF, Harder T. 2013. Compounds associated with algal surfaces mediate epiphytic colonization of the marine macroalga *Fucus vesiculosus*. *FEMS Microbiol Ecol* 84:411–420. <https://doi.org/10.1111/1574-6941.12071>.
 42. Deines P, Lachnit T, Bosch T. 2017. Competing forces maintain the Hydra metaorganism. *Immunol Rev* 279:123–136. <https://doi.org/10.1111/imr.12564>.
 43. Thaiss CA, Zmora N, Levy M, Elinav E. 2016. The microbiome and innate immunity. *Nature* 535:65–74. <https://doi.org/10.1038/nature18847>.
 44. Mühlenbruch M, Grossart HP, Eigemann F, Voss M. 2018. Mini-review: phytoplankton-derived polysaccharides in the marine environment and their interactions with heterotrophic bacteria. *Environ Microbiol* 20:2671–2685. <https://doi.org/10.1111/1462-2920.14302>.
 45. Rohwer F, Breitbart M, Jara J, Azam F, Knowlton N. 2001. Diversity of bacteria associated with the Caribbean coral *Montastraea franksi*. *Coral Reefs* 20:85–91. <https://doi.org/10.1007/s003380100138>.
 46. Rohwer F, Seguritan V, Azam F, Knowlton N. 2002. Diversity and distribution of coral-associated bacteria. *Mar Ecol Prog Ser* 243:1–10. <https://doi.org/10.3354/meps243001>.
 47. Sweet MJ, Croquer A, Bythell JC. 2011. Development of bacterial biofilms on artificial corals in comparison to surface-associated microbes of hard corals. *PLoS One* 6:e21195. <https://doi.org/10.1371/journal.pone.0021195>.
 48. Tout J, Jeffries TC, Petrou K, Tyson GW, Webster NS, Garren M, Stocker R, Ralph PJ, Seymour JR. 2015. Chemotaxis by natural populations of coral reef bacteria. *ISME J* 9:1764–1777. <https://doi.org/10.1038/ismej.2014.261>.
 49. Silveira CB, Rohwer FL. 2016. Piggyback-the-winner in host-associated microbial communities. *NPJ Biofilms Microbiomes* 2:16010. <https://doi.org/10.1038/npjbiofilms.2016.10>.
 50. Schröder K, Bosch T. 2016. The origin of mucosal immunity: lessons from the holobiont Hydra. *mBio* 7:e01184-16. <https://doi.org/10.1128/mBio.01184-16>.
 51. Shen TCD, Chehoud C, Ni J, Hsu E, Chen YY, Bailey A, Laughlin A, Bittinger K, Bushman FD, Wu G. 2016. Dietary regulation of the gut microbiota engineered by a minimal defined bacterial consortium. *PLoS One* 11:e0155620. <https://doi.org/10.1371/journal.pone.0155620>.
 52. Li H, Limenitakis JP, Fuhrer T, Geuking MB, Lawson MA, Wyss M, Brugiroux S, Keller I, Macpherson JA, Rupp S, Stolp B, Stein JV, Stecher B, Sauer U, McCoy KD, Macpherson AJ. 2015. The outer mucus layer hosts a distinct intestinal microbial niche. *Nat Commun* 6:8292. <https://doi.org/10.1038/ncomms9292>.
 53. Conlon MA, Bird AR. 2014. The impact of diet and lifestyle on gut microbiota and human health. *Nutrients* 7:17–44. <https://doi.org/10.3390/nu7010017>.
 54. Flint HJ, Duncan SH, Louis P. 2017. The impact of nutrition on intestinal bacterial communities. *Curr Opin Microbiol* 38:59–65. <https://doi.org/10.1016/j.mib.2017.04.005>.
 55. Muegge BD, Kuczynski J, Knights D, Clemente JC, González A, Fontana L, Henrissat B, Knight R, Gordon JL. 2011. Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans. *Science* 332:970–974. <https://doi.org/10.1126/science.1198719>.
 56. Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. 2016. Diet-induced extinctions in the gut microbiota compound over generations. *Nature* 529:212–215. <https://doi.org/10.1038/nature16504>.
 57. Prentice AM. 2005. Starvation in humans: evolutionary background and contemporary implications. *Mech Ageing Dev* 126:976–981. <https://doi.org/10.1016/j.mad.2005.03.018>.
 58. Fontana L, Partridge L. 2015. Promoting health and longevity through diet: from model organisms to humans. *Cell* 161:106–118. <https://doi.org/10.1016/j.cell.2015.02.020>.
 59. Longo VD, Mattson MP. 2014. Fasting: molecular mechanisms and clinical applications. *Cell Metab* 19:181–192. <https://doi.org/10.1016/j.cmet.2013.12.008>.
 60. Marinac CR, Sears DD, Natarajan L, Gallo LC, Breen CI, Patterson RE. 2015. Frequency and circadian timing of eating may influence biomarkers of inflammation and insulin resistance associated with breast cancer risk. *PLoS One* 10:e0136240. <https://doi.org/10.1371/journal.pone.0136240>.
 61. Hanning I, Diaz-Sanchez S. 2015. The functionality of the gastrointestinal microbiome in non-human animals. *Microbiome* 3:51. <https://doi.org/10.1186/s40168-015-0113-6>.
 62. Carey HV, Walters WA, Knight R. 2013. Seasonal restructuring of the ground squirrel gut microbiota over the annual hibernation cycle. *Am J Physiol Integr Comp Physiol* 304:R33–R42. <https://doi.org/10.1152/ajpregu.00387.2012>.
 63. Carey HV, Assadi-Porter FM. 2017. The hibernator microbiome: host-bacterial interactions in an extreme nutritional symbiosis. *Annu Rev Nutr* 37:477–500. <https://doi.org/10.1146/annurev-nutr-071816-064740>.
 64. Secor SM, Carey HV. 2016. Integrative physiology of fasting. *Compr Physiol* 6:773–825. <https://doi.org/10.1002/cphy.c150013>.
 65. Donaldson GP, Lee SM, Mazmanian SK. 2016. Gut biogeography of the bacterial microbiota. *Nat Rev Microbiol* 14:20–32. <https://doi.org/10.1038/nrmicro3552>.
 66. Sonnenburg JL, Xu J, Leip DD, Chen CH, Westover BP, Weatherford J, Buhler JD, Gordon JL. 2005. Glycan foraging in vivo by an intestine-adapted bacterial symbiont. *Science* 307:1955–1959. <https://doi.org/10.1126/science.11109051>.

67. Barnard ND. 2010. Trends in food availability, 1909–2007. *Am J Clin Nutr* 91:1530S–1536S. <https://doi.org/10.3945/ajcn.2010.28701G>.
68. Fletcher SM, McLaws M-L, Ellis JT. 2013. Prevalence of gastrointestinal pathogens in developed and developing countries: systematic review and meta-analysis. *J Public Health Res* 2:42–53. <https://doi.org/10.4081/jphr.2013.e9>.
69. David LA, Weil A, Ryan ET, Calderwood SB, Harris JB, Chowdhury F, Begum Y, Qadri F, LaRocque RC, Turnbaugh PJ. 2015. Gut microbial succession follows acute secretory diarrhea in humans. *mBio* 6:e00381-15. <https://doi.org/10.1128/mBio.00381-15>.
70. Jalanka J, Salonen A, Salojärvi J, Ritari J, Immonen O, Marciani L, Gowland P, Hoad C, Garsed K, Lam C, Palva A, Spiller RC, de Vos WM. 2015. Effects of bowel cleansing on the intestinal microbiota. *Gut* 64:1562–1568. <https://doi.org/10.1136/gutjnl-2014-307240>.
71. Drago L, Toscano M, De Grandi R, Casini V, Pace F. 2016. Persisting changes of intestinal microbiota after bowel lavage and colonoscopy. *Eur J Gastroenterol Hepatol* 28:532–537. <https://doi.org/10.1097/MEG.0000000000000581>.
72. Shobar RM, Velineni S, Keshavarzian A, Swanson G, DeMeo MT, Melson JE, Losurdo J, Engen PA, Sun Y, Koenig L, Mutlu EA. 2016. The effects of bowel preparation on microbiota-related metrics differ in health and in inflammatory bowel disease and for the mucosal and luminal microbiota compartments. *Clin Transl Gastroenterol* 7:e143. <https://doi.org/10.1038/ctg.2015.54>.
73. Blaser MJ. 2016. Antibiotic use and its consequences for the normal microbiome. *Science* 352:544–545. <https://doi.org/10.1126/science.aad9358>.
74. Schultz PG, Peters EC, Liu J, Wikoff WR, Anfora AT, Siuzdak G, Lesley SA. 2009. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proc Natl Acad Sci U S A* 106:3698–3703. <https://doi.org/10.1073/pnas.0812874106>.
75. Ramezani A, Massy ZA, Meijers B, Evenepoel P, Vanholder R, Raj DS. 2016. Role of the gut microbiome in uremia: a potential therapeutic target. *Am J Kidney Dis* 67:483–498. <https://doi.org/10.1053/j.ajkd.2015.09.027>.
76. Sawicki CM, Livingston KA, Obin M, Roberts SB, Chung M, McKeown NM. 2017. Dietary fiber and the human gut microbiota: application of evidence mapping methodology. *Nutrients* 9:125. <https://doi.org/10.3390/nu9020125>.
77. Schroeder BO, Birchenough GMH, Ståhlman M, Arike L, Johansson MEV, Hansson GC, Bäckhed F. 2018. Bifidobacteria or fiber protects against diet-induced microbiota-mediated colonic mucus deterioration. *Cell Host Microbe* 23:27–40.e7. <https://doi.org/10.1016/j.chom.2017.11.004>.
78. Sugihara K, Masuda M, Nakao M, Abuduli M, Imi Y, Oda N, Okahisa T, Yamamoto H, Takeda E, Taketani Y. 2017. Dietary phosphate exacerbates intestinal inflammation in experimental colitis. *J Clin Biochem Nutr* 61:91. <https://doi.org/10.3164/jcbs.16-117>.
79. Moreno AR, Martiny AC. 2018. Ecological stoichiometry of ocean plankton. *Annu Rev Mar Sci* 10:43–69. <https://doi.org/10.1146/annurev-marine-121916-063126>.
80. Glasl B, Herndl GJ, Frade PR. 2016. The microbiome of coral surface mucus has a key role in mediating holobiont health and survival upon disturbance. *ISME J* 10:2280–2292. <https://doi.org/10.1038/ismej.2016.9>.
81. Koren O, Rosenberg E. 2006. Bacteria associated with mucus and tissues of the coral *Oculina patagonica* in summer and winter. *Appl Environ Microbiol* 72:5254–5259. <https://doi.org/10.1128/AEM.00554-06>.
82. Weinbauer MG, Kerros ME, Motegi C, Wilhartz IC, Rassoulzadegan F, Torretón JP, Mari X. 2010. Bacterial community composition and potential controlling mechanisms along a trophic gradient in a barrier reef system. *Aquat Microb Ecol* 60:15–28. <https://doi.org/10.3354/ame01411>.
83. Tropini C, Earle KA, Huang KC, Sonnenburg JL. 2017. The gut microbiome: connecting spatial organization to function. *Cell Host Microbe* 21:433–442. <https://doi.org/10.1016/j.chom.2017.03.010>.
84. Sender R, Fuchs S, Milo R. 2016. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol* 14:e1002533. <https://doi.org/10.1371/journal.pbio.1002533>.
85. Chassaing B, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE, Gewirtz AT. 2015. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature* 519:92–96. <https://doi.org/10.1038/nature14232>.
86. Prussin AJ, Garcia EB, Marr LC. 2015. Total concentrations of virus and bacteria in indoor and outdoor air. *Environ Sci Technol Lett* 2:84–88. <https://doi.org/10.1021/acs.estlett.5b00050>.
87. Leyden JJ, McGinley KJ, Nordstrom KM, Webster GF. 1987. Skin microflora. *J Invest Dermatol* 88:65–72.