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Review Article

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Publication date:
2024-07

Permanent link:
https://doi.org/10.3929/ethz-b-000685087

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Originally published in:
Science 385(6706), https://doi.org/10.1126/science.adi3338

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Title: Host control of the microbiome: mechanisms, evolution and disease

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Published in: Science 385, 271 (2024)
https://doi.org/10.1126/science.adi3338

Print Summary:

Background

Many multicellular organisms, including humans, carry microbial communities on or associated with their epithelial surfaces. An organism's microbiota can be critical for healthy functioning, with the capacity to protect against infection, provide nutrients, promote immune development, and even influence cognition.

The many potential benefits of a microbiome - i.e. the microbiota plus associated host factors - can foster the view that humans harbour an intrinsically helpful ecosystem in their gut regulated primarily by diet. In reality, members of the microbiota face chronic competition for resources and physical positioning in a highly dynamic environment where large numbers of cells are expelled each day. Immigration of new strains, alongside rapid and short-sighted microbial evolution, poses the continual threat of symbionts that grow rapaciously but harm the host, including 'cheater' genotypes and pathogens. In response to this pressure, hosts have evolved a wide range of control mechanisms that continually monitor and manipulate their symbionts to limit harm and promote the benefits received. Examples like the human microbiome, therefore, can be conceptualised as an 'ecosystem on a leash', where symbionts interact in diverse ecological communities that are strongly shaped by host control.

Advances

In this review of a diverse literature, we show how host control mechanisms influence almost every aspect of microbiome biology. Our focus is the mammalian microbiome, but we also examine well-characterized examples from invertebrate and plant microbiomes. First, we explore the biology of host control, including immunity, barrier function, physiological homeostasis, transit and host behavior. The expected outcome of many host control mechanisms is to promote beneficial symbionts over harmful ones (partner choice), but control can also function by changing the behaviour and metabolism of symbionts to make them more beneficial (partner manipulation).

The rapid evolution of microbes can be an opportunity for host control if it can generate natural selection for beneficial traits within a microbiome. However, symbiont evolution can also be a problem if it enables symbionts to evade host control, and some microbes have found ways to harness control mechanisms against us with disastrous effects on health.

Outlook

There is a great interest in the benefits that microbiomes provide for their hosts. Here, we have argued that many of these benefits can be traced back to mechanisms of host control. For hundreds of millions of years, multicellular hosts have been under natural selection to increase the benefits from their symbionts, and the result is an amazing set of adaptations that are able to control diverse and highly evolvable microbial communities. The realisation that microbiomes are the product of a perpetual tension between host control and symbiont evolution helps to makes sense of much of microbiome biology and disease. Indeed, the power of host control mechanisms over complex microbiotas suggests that many of them will provide therapeutic targets to reshape the microbiome for better health.

Examples of host control. Examples of host control. The Hawaiian bobtail squid light organ selects for bioluminescent bacteria. Many animals avoid rotten foods to reduce pathogen colonization. Some legumes house nitrogen-fixing bacteria in root nodules and control them by cutting off nutrients to nodules that fix too little nitrogen. The panda is a recently evolved herbivore with a gut microbiota that lacks the enzymes to efficiently break down plant material and is an example of poor host control. [Photo of Euprymna scolopes, the Hawaiian bobtail squid, was provided by M. McFall-Ngai, Caltech; photo of a young capuchin monkey courtesy of Tambako the Jaguar (www.flickr.com/photos/tambako), CC BY-ND 2.0 DEED; photo of a giant panda courtesy of La Priz (www.flickr.com/photos/sujuhyte), CC BY-ND 2.0 DEED; photo of a young soybean plant courtesy of the United Soybean Board (www.flickr.com/photos/unitedsoybean), CC BY 2.0 DEED]

Abstract: Many species, including humans, host communities of symbiotic microbes. There is a vast literature on the ways these microbiomes affect hosts, but here we argue for an increased

focus on how hosts affect their microbiomes. Hosts exert control over their symbionts via diverse mechanisms, including immunity, barrier function, physiological homeostasis and transit. These mechanisms enable hosts to shape the ecology and evolution of microbiomes and generate natural selection for microbial traits that benefit the host. Our microbiomes result from a perpetual tension between host control and symbiont evolution, and we can leverage the host's evolved abilities to regulate the microbiota to prevent and treat disease. The study of host control will be central to our ability to both understand and manipulate microbiotas for better health.

Main Text

Many multicellular organisms, including humans, carry microbial communities on or associated with their epithelial surfaces. An organism's microbiota can be critical for healthy functioning, with the capacity to protect against infection, provide nutrients, promote immune development, and even influence cognition(*1*). The many potential benefits of a microbiome i.e., the microbiota plus associated host factors, can foster the view that humans harbour an intrinsically helpful ecosystem in their gut regulated primarily by diet. In reality, members of the microbiota face chronic competition for resources and physical positioning in a highly dynamic environment where large numbers of cells are expelled each day(*2*). Immigration of new strains, alongside rapid and short-sighted microbial evolution, poses the continual threat of symbionts that grow rapaciously but harm the host(*3*-*8*). In response to this pressure, hosts have evolved a wide range of mechanisms that continually monitor and manipulate their symbionts to limit harm and promote the benefits received(*3, 9*) (Box 1). Examples like the human microbiome, therefore, can be conceptualised as an 'ecosystem on a leash', where symbionts interact in diverse ecological communities that are strongly shaped by host control(*3*).

In this review, we show how the host's control mechanisms influence almost every aspect of microbiome biology. Our focus is the mammalian microbiome, but we also examine well-characterized examples from invertebrate and plant microbiomes. First, we explore the biology of host control, including immune responses and other aspects of host physiology (Fig. 1). These mechanisms affect the microbiota by changing symbiont composition, changing symbiont phenotypes, or both. The rapid evolution of microbiomes can be an opportunity for hosts if they can generate natural selection for beneficial traits but also poses a problem if it enables symbionts to evade host control. The power of host control mechanisms over complex microbiotas suggests that many host factors will provide therapeutic targets to reshape the microbiome for better health.

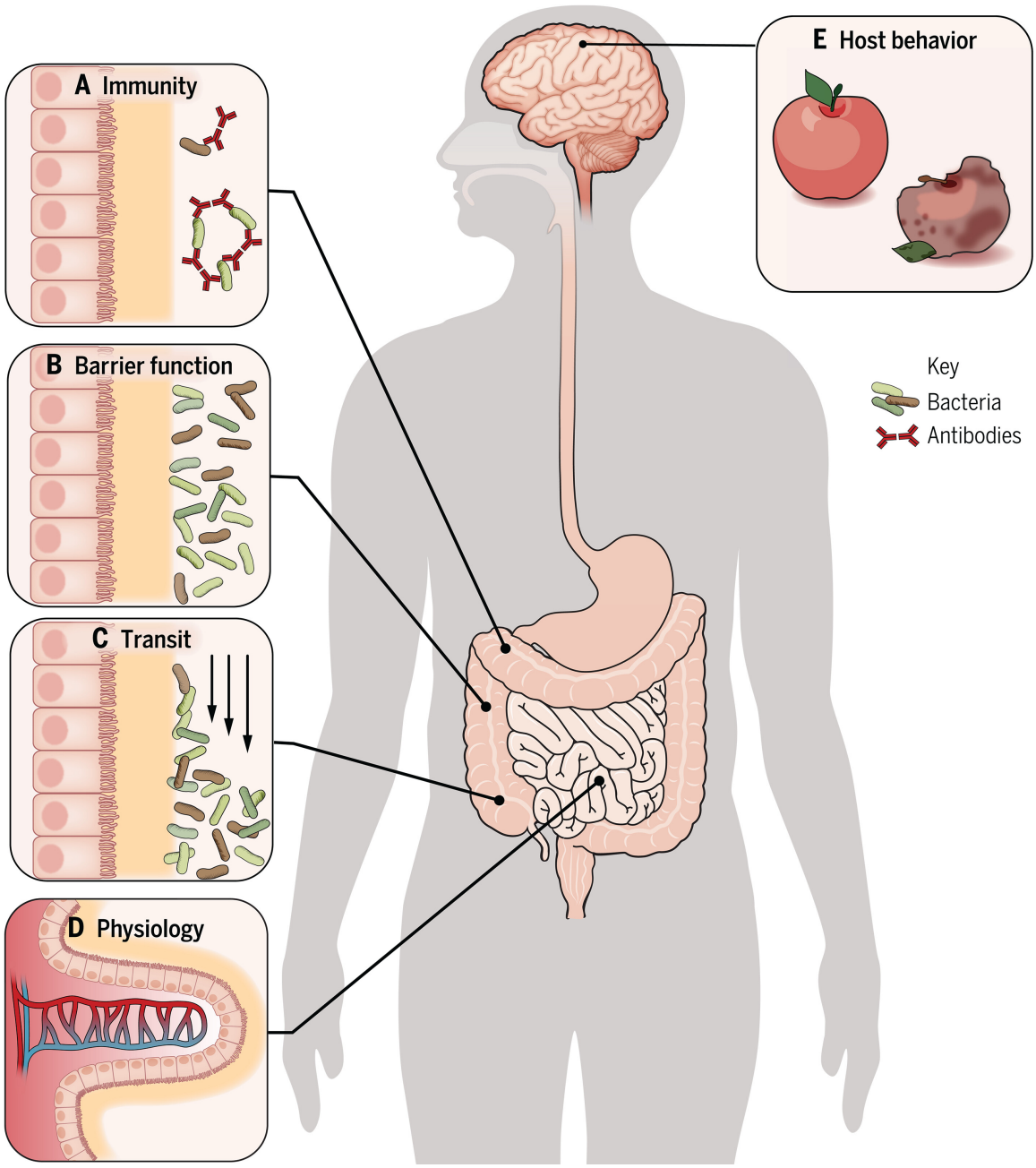

Fig 1. Mechanisms of host control over microbiomes. (A) Immunity: The immune system, which can rapidly learn associations between microbial phenotypes and genotypes, is the most sophisticated host control system known. In the mammalian gut, a key mechanism of action is through IgA, which can help to adhere bacteria to mucus but also to each other to generate bacterial aggregates that can be cleared by transit. (B) Barrier function: Hosts use barriers to keep symbionts at bay. The gut mucosa is an example of a key barrier, which limits microbial contact with host cells but allows metabolites to pass in both directions. (C) Transit: Hosts have the ability to move symbionts within their microbiomes using mechanisms such as peristalsis, which can rapidly purge symbionts that cause disease. (D) Physiology: Hosts control the physiology of their microbiomes in ways that strongly affect their symbionts, such as oxygen limitation by means of countercurrent blood flow, which promotes microbial fermentation. (E)

Host behavior: The ability of animals to avoid spoiled food can help to keep the microbiome free from pathogens. CREDIT: N. BURGESS/SCIENCE

Host control traits

The relationship between a host and its microbiota often appears to be one of cooperation, or mutualism, where both sides of the interaction stand to benefit (Box 1). In this context, host control mechanisms are an example of what is known as 'enforcement' in evolutionary biology(*10*). Enforcement mechanisms are traits that evolve, at least in part, to reduce selfish behaviour within a cooperative alliance. Examples that demonstrate the importance of enforcement abound and include the suppression of transposable elements in genomes, policing behaviours in social insect colonies, pollinators that reject plants without nectar, and reciprocal altruism in humans(*10*). Accordingly, one can define host control mechanisms as those that evolve, at least in part, to suppress harmful or selfish behaviours in the microbiome and promote the benefits for the host(*3*) (Fig. 1).

Diverse host traits may influence the composition of the microbiota and the benefits a host receives (Box 2) but, if these traits evolved for other reasons, they do not constitute host control in a meaningful sense. For example, it seems unlikely that gut peristalsis evolved because of the need for host control but rather to process food and ultimately expel waste(*11*). By contrast, the rapid change in gut transit rate that occurs upon infection does appear to be a host control mechanism that serves to help purge problem microbes(*12*). In some cases, it can be unclear if a trait evolved for host control purposes or for another reason, and this should be kept in mind when considering the examples we discuss. Our focus is on 'open' microbiomes where there is the potential for significant immigration and horizontal transfer of symbionts within each host generation(*9*). Some symbionts, like mitochondria, chloroplasts and intracellular symbionts of insects, are functionally integrated into host cells and transmitted vertically, which can reduce the requirement for host control(*4, 6, 9*).

Some host control mechanisms, such as adaptive immunity, can be highly specific to certain members of the microbiota, while others, such as oxygen deprivation, may affect hundreds of species(*13*). We take the mammalian gut microbiome as our key example but many of the mechanisms and principles are broadly applicable, including to other body sites, other vertebrates(*12, 14, 15*), invertebrates(*16, 17*), plants(*5, 18*) and even some single-celled hosts(*19*)(Fig. 2).

Innate and adaptive immunity

The vertebrate immune system is the most sophisticated host control mechanism known. It comprises innate immunity, which is evolutionarily ancient and detects conserved features of microbes and infection, and adaptive immunity, which is present only in jawed vertebrates and can generate new receptors within a host's lifetime to identify particular microbial strains. The study of immunity has historically focussed on infection and disease(*20*). However, it is becoming clear that immune mechanisms function more broadly to shape and control microbiomes, particularly at the critical epithelial surfaces that mark the divide between the microbiome and host proper(*21*).

Innate immunity has evolved alongside multicellularity in plants(*21*) and animals(*22*), with immune components tracing back to ancient prokaryote defenses against viral infection(*23*). The parallels between animal and plant immunity are striking: both employ a diverse set of Pattern

Recognition Receptors (PRRs) that bind many of the same common microbial signatures (*20, 21*), or recognise the influence of pathogen virulence on host cell function(*22*). Binding of host PRRs to common microbial signatures, known as Pathogen or Microbial Associated Molecular Patterns (PAMPs or MAMPs)(*20, 21*), drives a range of responses that can reshape microbiomes and help to maintain a normal host-microbiome relationship(*21, 24*).

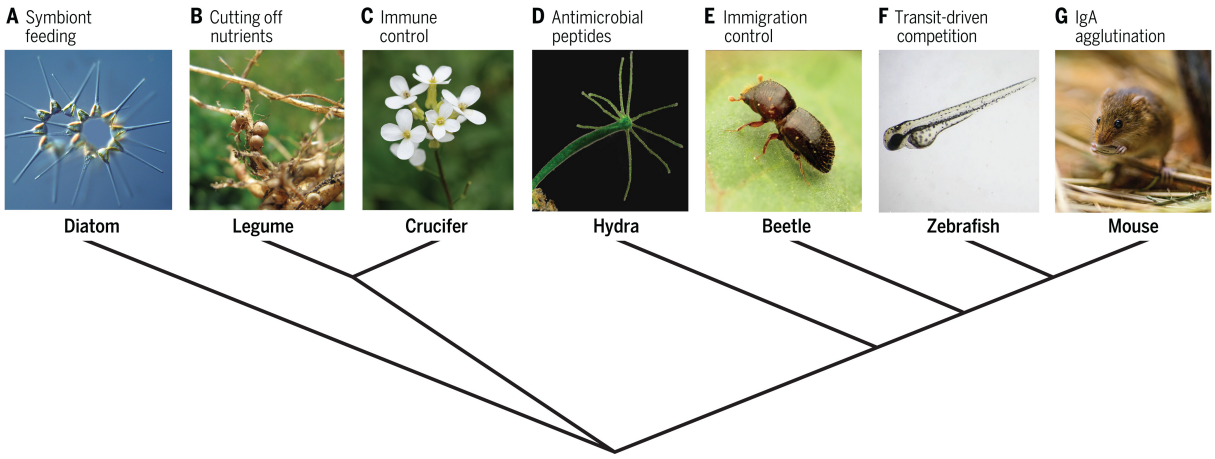

Fig. 2. Host control mechanisms are seen across diverse species. Evidence for host control from experimental studies is shown across a range of animal, plant, and single-celled species. (A) The diatom Asterionellopsis glacialis releases uncommon metabolites that enhance the attachment and growth of beneficial symbionts while suppressing opportunistic pathogens (19). (B) The legume Glycine max cuts off nutrient provision to root nodules in which symbionts are not fixing nitrogen (5). (C) The crucifer A. thaliana encodes pattern-triggered immune responses that are essential for maintaining a normal microbiota (18). (D) Various hydra species secrete antimicrobial peptides that maintain a distinct microbiota (16). (E) The ambrosia beetle Xylosandrus germanus favors ethanol-rich conditions within trees that promote its fungal garden symbiont over other microbes (17). (F) Gut transit in the zebra fish Danio rerio removes less-competitive strains from the host microbiota (14). Peristalsis may have originally evolved for digestive functions rather than host control, but changes in rate transit are consistent with host control (12) (Box 1). (G) Dimeric IgA agglutinates and enchains microbes for clearance from the mouse gut (15). [Image credits: diatom A. glacialis by Dr. A. Guillén, “Proyecto Agua” (https://www.flickr.com/photos/microagua), CC BY-NC-SA 2.0; soybean root nodules credited to Harry Rose (https://www.flickr.com/photos/macleaygrassman), CC BY 2.0 DEED; A. thaliana by Marie-Lan Nguyen (https://commons.wikimedia.org/wiki/File:Arabidopsis_thaliana_JdP_2013-04-28.jpg), CC BY 2.5; Hydra viridissima by Frank Fox (www.mikro-foto.de), CC BY-SA 3.0 DE DEED; ambrosia beetle X. germanus by Katja Schulz (https://www.flickr.com/photos/treegrow), CC BY 2.0; D. rerio. provided by Ho-Wen Chen, supported by the Li-Yih Lin Lab, Department of Life Science, National Taiwan Normal University (https://www.flickr.com/photos/chenhowen), CC BY-NC-ND 2.0; wild mouse by Tambako the Jaguar (www.flickr.com/photos/tambako), CC BY-ND 2.0 DEED]

In animals, a key class of host receptors is the toll-like receptors (TLRs), which detect a range of bacterial and viral PAMPs. Understanding how TLRs can distinguish between harmless and

harmful microbes with the same epitopes remains a key challenge in the field. One form of discrimination appears to be based upon position: TLRs can be placed in locations where microbes are typically not found, such as on the host-facing side of the epithelium(*25*), so that only invading pathogens will activate them. This spatial information helps the immune system respond preferentially to those species that pose greater threats (Box 1). TLR signalling plays a crucial role in establishing the relationship between host and microbiome, with genetic deficiency in key TLR signaling components resulting in aberrant adaptive immunity targeting the microbiome(*24*) and invasive disease driven by common microbiome constituents(*26*). In addition to monitoring components of microbial cells, immunity also monitors the metabolic output of microbiotas, something again seen in both plants(*27*) and animals(*28, 29*). Innate immune activation has important functions in a healthy microbiome and is linked to antimicrobial peptide expression(*30*), where knocking out the key antimicrobial RegIIIγ, a secreted antibacterial lectin, leads to the microbiota encroaching on the epithelium in mice(*31*).

The importance of antimicrobial peptides is also seen in invertebrates. Knocking out production in the marine invertebrate hydra shifts the mucosal microbiome composition away from the natural state(*16*), and there is evidence that fly species evolve specific antimicrobial peptides to match the bacterial threats in their environment(*32*). Phagocytes that ingest and kill microbes also appear to be an important facet of innate immunity in locations including the mammalian respiratory tract and in sponges, where vast numbers of phagocytes roam through the microbiome and appear to control its composition(*33*). While the healthy gut lumen of mammals is largely free of phagocytes, they can be released *en masse* into regions of the inflamed gut where they trap bacteria in secreted DNA nets, eliminate them via phagocytosis and help to reinforce the gut epithelial barrier(*34, 35*). Infection can also drive programmed cell death of host cells and the physical expulsion of infected host cells into the gut lumen(*36*). Plants lack mobile immune cells and phagocytes, but mechanisms including programmed cell death and antimicrobial products again serve to limit and stop invasive infections(*21*).

The evolution of vertebrates saw the elaboration of the animal immune system to include adaptive immunity as well as innate immune mechanisms. Critically, adaptive immunity enables the system to learn and change the chemical ligands that activate its receptors depending on the associated threat. The system achieves this by continuously sampling ligands from vertebrate body surfaces into mucosa-associated lymphoid tissues via M-cells and dendritic cells(*37*). While a role for Treg cells and IL-10 signalling has been established(*37*), what ultimately determines which antigens generate what type of response when sampled into the mucosa remains hard to predict. What is clear is that particulate antigens (i.e., whole bacteria, viruses) and bacterial toxins are highly effective in activating mucosal antibody responses. In contrast, some soluble antigens induce immune tolerance when ingested by young children, which is thought to help the mature immune system ignore many harmless ligands(*38*). Akin to innate immunity, antibody responses are likely biased towards species that breach the epithelial barrier because the key sites for immune surveillance and regulation are within host tissues i.e. within draining lymphoid tissues(*37*) (Box 1).

In healthy mammalian mucosa, a large population of plasma cells continuously produce immunoglobulin A (IgA). This dimeric antibody isotype is actively secreted onto epithelial surfaces by the Poly Ig Receptor. Upon secretion, IgA lacks any of the classic effector functions of other immunoglobulins, such as complement fixation(*39*). Instead, many IgA functions can be explained by its ability to crosslink antigens. In particular, bacterial aggregation via high-affinity binding increases the rate of bacterial clearance in the flow of the fecal stream (*15, 39, 40*). Some

evidence suggests that IgA can act as a carrot as well as a stick, for example by helping bacteria to colonise the mucus layer of the gut epithelium(*41*), or protecting them from bile acids and bacteriophages(*39, 42*). IgA is also made in the mammary glands and transferred to neonates along with IgM in milk where it is thought to perform similar functions as in adults. Innate immune components, such as uromodulin in the mammalian urinary tract(*43*) or C-type-lectins secreted into the gut of the Chinese mitten crab (*Eriocheir sinensis*)(*44*), also seem to function predominantly by aggregating bacteria, suggesting this may be a general protective mechanism in the mucosa.

A number of studies have investigated the importance of immunity for microbiome stability and composition. In plants, for example, mutations affecting immune signalling and antimicrobial responses disrupt a beneficial symbiosis between the endophytic fungus *Colletotrichum tofieldiae* and the roots of *Arabidopsis thaliana*(*45*), and knocking out genes associated with pattern-triggered immunity can cause harmful compositional changes in leaf microbiomes(*18*)(Fig. 2). In flies, the dysregulation of innate immunity via RNA interference alters symbiont communities in the intestine, leading to the dominance of one gut microbe and increased host mortality(*46*). In mice, the data can be complicated by host genotype, cage-effects and microbiome drift between hygienically isolated lines, which has generated controversy in the literature. For instance, many studies in mice that ablate a particular immune component find no detectable effect on microbiome composition(*31, 47, 48*). Nevertheless, some studies that have used littermates or bone marrow chimeras to minimize potential confounders do show clear impacts of the immune system on microbiome composition(*49, 50*). In sum, across studies and diverse host species, immunity is important for shaping and regulating microbiomes(*16, 18, 31, 44-46*).

Barrier function

Barriers that limit where microbes can colonise and grow are central to the control of microbiomes. Some barriers, like mammalian skin, block the passage of microbes and almost everything else. Others, including the mucosal epithelia in animals and the root epithelium in plants act as selective barriers, restricting microbial transit but allowing chemical exchange. Immunity helps to maintain all these barriers. For example, preliminary data suggest that the gut epithelium of the bean bug is reinforced by over 200 antimicrobial peptides(*51*). Barrier permeability can also change on demand: tight junctions form a seal between mammalian epithelial cells but can permeabilize to allow massive water and salt efflux that occurs during diarrhea(*12*). However, failure of this barrier can be fatal, allowing bacteria to colonise the bloodstream and vital organs.

Equally important to barrier function is mucus, which is both ancient and widespread in animals(*52, 53*). Mucus contains long, glycosylated proteins known as mucins, which self-assemble as a dynamic mesh and hydrated gel, whose pore size and rheological properties are selectivity modified by factors like pH, mucin concentration, and glycosylation(*54, 55*). Mucus covers several key epithelial surfaces inside the human body, including the gastrointestinal tract(*54, 55*). Other animals, including amphibians(*56*) and many marine invertebrates(*16, 53*) also have an external covering of mucus or mucus-like gel that houses a microbiota and enables gas exchange. Insects produce peritrophic gel, which contains mucins, to coat food particles in the gut (*57*), and plants have convergently evolved to release mucilage from their roots, which is a mucus-like gel again comprised primarily of glycoproteins(*58*). These gels not only act as

selective barriers and lubricants, but also as a food source and attachment site for microbes that hosts can leverage to shape the composition of the microbiota (*55, 59-64*).

Physiology and homeostasis

Key to a host's influence over its microbiota is the potential to define the niches that symbionts can inhabit (Box 1). These niches can vary in time and space and select for different microbiotas in different parts of a host(*64*). The ways that a host can shape niches are also diverse and include nutrient provision in the form of mucins, as just discussed, as well as other products. The human vaginal microbiome, for example, is unusual among mammals in being dominated by *Lactobacillus* species that maintain a low protective pH, possibly through host provision of glycogen(*65*). Similarly, the generation of bile acids in the mammalian intestine can strongly influence microbial metabolism in ways that discourage infection(*66*).

Oxygen control is critical in some microbiomes where it promotes the fermentation of complex carbohydrates and other substrates by symbionts (*28*). Anaerobic gut conditions are found in diverse animal groups, including insects as well as vertebrates(*67, 68*). It is often assumed that gut anoxia is driven by facultatively anaerobic microbes consuming oxygen. However, there is evidence that it is often hosts, rather than microbes, that remove the majority of oxygen from the gastrointestinal tract(*13*). Most notably, germ-free mice and germ-free cockroaches have similarly low partial pressures of oxygen throughout the gut when compared to animals with a microbiota(*67, 68*), and oxygen tension is also very low in the gut of germ-free honeybees(*69*). There is also evidence of active mechanisms that reduce oxygen levels along the gastrointestinal tract(*70*). The mammalian small intestine employs counter current mechanisms in the villi to help scavenge oxygen out of the blood before it reaches the lumen(*70*), ensuring that luminal content reaching the large intestine is already low in oxygen. In the healthy large intestine, rapid oxygen consumption by hypoxia-adapted epithelial cells brings down oxygen levels further. This process creates conditions that promote microbial fermentation(*13, 71*) and limit harmful facultatively anaerobic bacteria and other negative health outcomes(*28, 71*). A similar mechanism of oxygen control appears to operate via the epithelial cells of the cockroach gut(*67*).

The evolution of gross gut morphology also plays a significant role in physiological control and is particularly important for host species that depend upon microbial fermentation for energy (Fig. 3). While humans probably only derive a small percentage of their total energy from microbial fermentation, some herbivores, such as horses and termites, rely on their symbionts for the majority of their energy requirements(*72, 73*). Consistent with this, most ruminants, including cattle, have a four-chambered stomach that cultures anaerobes and absorbs copious microbial fermentation products before passing the same microbes to the hindgut to be digested as a protein source(*72*). A striking exception is the panda, whose recent evolution of herbivory has left it with a gut like its carnivorous ancestors. As a result, pandas appear to lack the ability to promote effective microbial fermentation of plant matter(*74*) (Fig. 3). The result is extremely inefficient digestion(*75*).

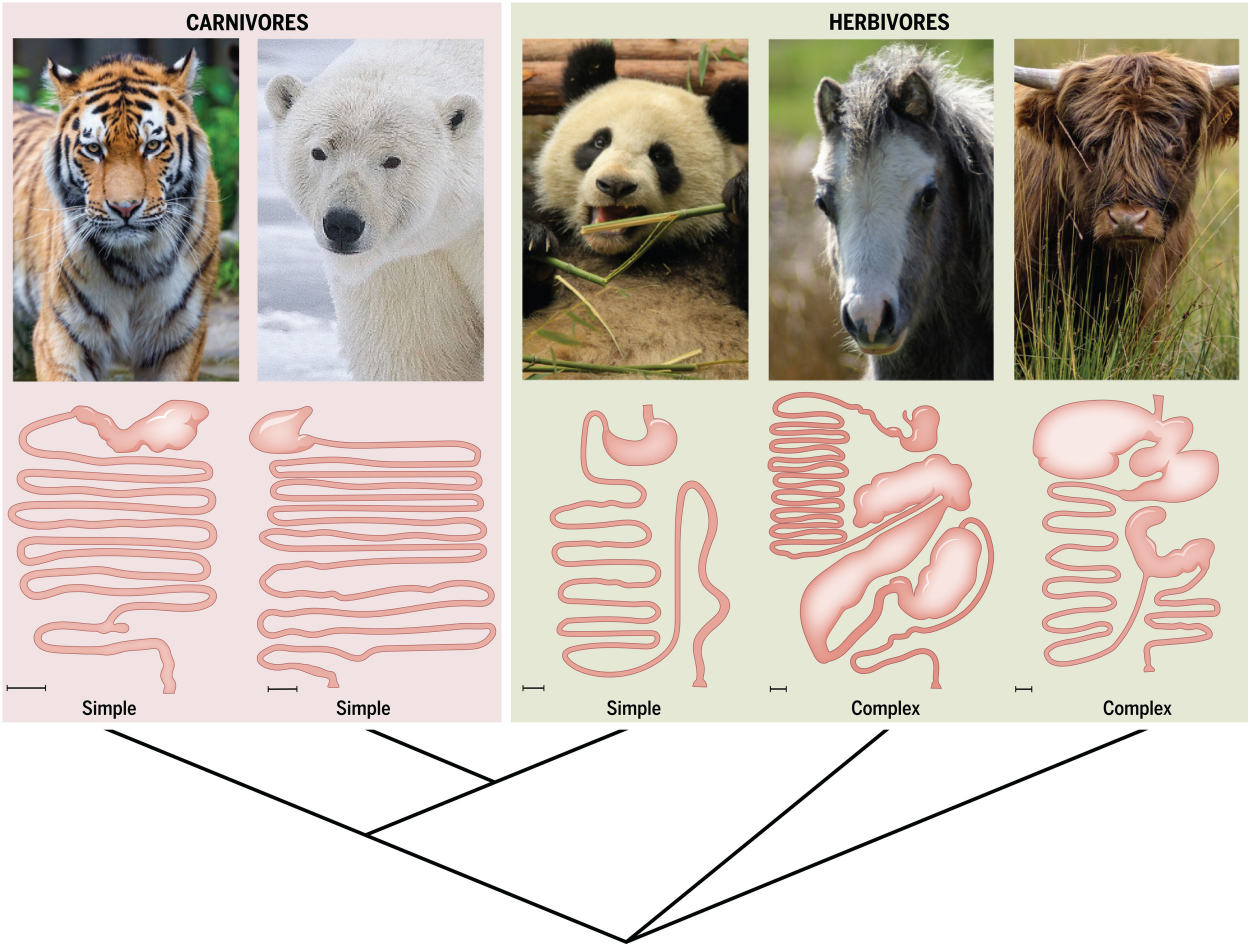

Fig. 3. Pandas as an example of poor host control. Diverse mammalian herbivores have evolved a complex and anaerobic gut, which enables the fermentation of plant materials (i.e., horse and cow) (149). By contrast, carnivores such as the polar bear have a much simpler gut morphology that is less able to promote microbial fermentation (150, 151). As a recently evolved strict herbivore, the panda also appears to lack the gut morphology and physiology to promote effective microbial fermentation of cellulose and has extremely inefficient digestion. Scale bars, 10 cm. [Photo of a young tiger credited to Tambako the Jaguar (www.flickr.com/photos/tambako), CC BY-ND 2.0 DEED; photo of a polar bear credited to Alan D. Wilson, CC BY-SA 3.0 DEED; photo of a giant panda credited to La Priz (www.flickr.com/photos/sujuhyte), CC BY-ND 2.0 DEED; photo of a wild horse credited to David Daniels (www.flickr.com/photos/spursfan_ace), CC BY-SA 2.0 DEED; photo of a highland cow credited to Gilles San Martin (https://www.flickr.com/photos/sanmartin/), CC BY-SA 2.0 DEED]

Transit

Many animal hosts are also able to influence the position of symbionts. Mucus production creates a perpetual flow away from epithelial surfaces, which can be increased under immune activation to clear problematic microbes(*63*). The action of cilia moves microbes and particles along epithelial surfaces in situations as diverse as the surface of coral, the mammalian lung and the intestines of lung fish(*53*). While cilia are efficient at propelling a single layer of mucus

under laminar flow, they are not sufficient for bulk transport of large volumes of fluid, as occurs in the gut of most vertebrates. Instead, smooth muscle enables the powerful and regulated contractions of peristalsis. Intestinal contractions are extremely complex and vary from near-stationary mixing contractions to strong peristaltic waves that push material along the gut and, ultimately, out of the body (*76*). The majority of the fluid in the human intestine results from secretions (6-7 litres secreted compared with 2-3 litres from food and drink)(*77*), which means the relative rates of secretion and resorption are also critical for transit.

The full potential of gut transit is clearest in the animal diarrhea response, where a combination of altered water resorption and increased gut motility can expel most gut microbes(*78*). This response serves to help clear pathogens(*12*), but also decimates the microbiota and its metabolic output(*2*). Even under normal conditions, gut transit can reduce microbial density, which is evident in the small intestine where transit is rapid and symbiont density is low(*64*). Densities are much higher in the large intestine where there are a range of mechanisms to limit symbiont loss, including turbulent mixing(*2*), and regular antiperistalsis contractions(*76*) that can send microbes in the opposite direction to normal. Loss is further limited by blind end structures such as the appendix and cecum, and the colon physiology of some species acts to separate and retain microbe-rich particles from food waste(*79*). Despite such measures, peristalsis can create an adverse environment for symbionts, which must attach, swim or divide to compensate for its effects(*2, 14*). The high turnover that results from peristalsis means that composition can shift rapidly, but this dynamic environment also creates opportunities for hosts to shape their microbiome.

Host behaviour

Behavioural choice enables hosts to favour the immigration of beneficial symbionts over harmful ones. For example, an aversion to ingestion of spoiled foods may reduce the probability of ingesting pathogens(*80*). Some species, including mammals, can also rapidly learn new associations between tastes and subsequent illness to avoid a dangerous food thereafter(*81*), with recent work suggesting a role for the immune system in such learning(*82*). As well as avoiding harmful symbionts, hosts display behaviours associated with ingesting beneficial symbionts. A preference for sour flavours, for example, may help primates, rats, and wild pigs to ingest lactic acid bacteria(*83*). In addition, many small mammals, including rodents and lagomorphs, produce and eat microbiota-rich droppings, which helps them to both meet their nutritional requirements and stabilise their microbiotas(*84*). Behaviour also enables the vertical transmission of specialised symbionts between relatives in species, including the bee wolf(*85*), termites(*86*), and the koala where the mother feeds her joey both milk and a specialised form of faecal matter known as pap (*87*). Social insects display many additional behaviors that help to regulate their collective microbiotas, including the use of tree resin to limit pathogens by wood ants(*88*), and the patrolling of the fungus garden in leafcutters to remove parasitic fungi(*89*).

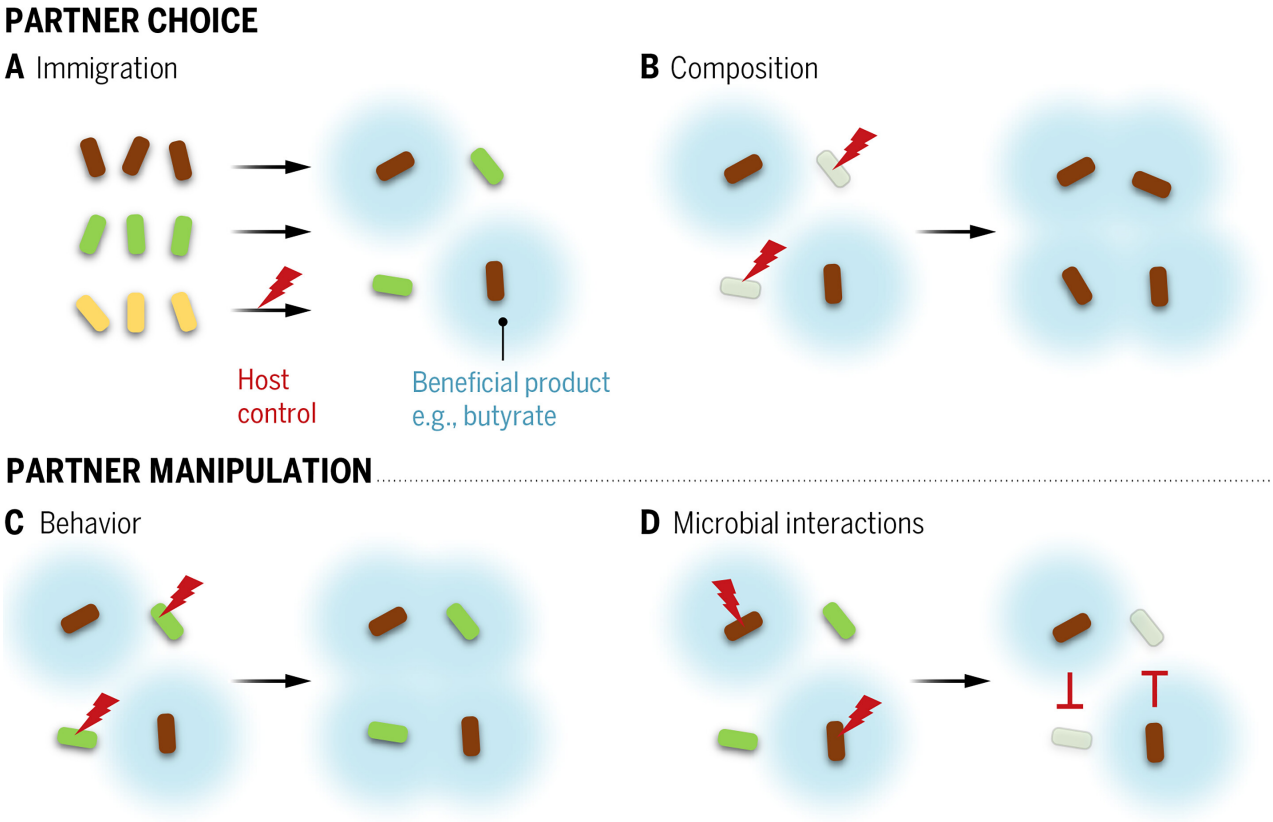

Fig. 4. How does host control influence microbiomes? Four ways that host control (red lightning bolts) can increase the benefits received from symbionts. In each case, the brown bacterial strain is the favored strain that produces a beneficial product, shown by a blue halo around the bacteria, for example, short-chain fatty acids such as butyrate. (A) Immigration control: The host limits colonization by some strains (yellow) that do not make the beneficial product. (B) Compositional control: The host selects against the established strain (green) that does not make the product. (C) Behavioral control: The host changes the metabolism of the green strain by, for example, providing a precursor so that it now makes the beneficial product (blue halo). (D) Control of microbial interactions: The host promotes competition between symbionts (red inhibition symbols), and the beneficial strain (brown) eliminates the green strain. The top two cases are examples of partner choice because they act by promoting the abundances of beneficial symbionts over nonbeneficial symbionts. The bottom cases are examples of partner manipulation that act by changing the behavior of symbionts, where these changes in behavior may also lead to subsequent changes in abundances (10).

How does host control influence microbiomes?

Hosts therefore have evolved a diverse and sophisticated set of mechanisms that allow them to control and shape their microbiomes. From an evolutionary perspective, the goal of host control is to increase the fitness benefits that a host receives from its microbiota (Fig. 4, Box 1). But how do host control mechanisms achieve this goal? Host control can increase the benefits to a host by either altering which symbionts are present ('partner choice' in evolutionary biology) or by changing the phenotype of the symbionts that are there ('partner manipulation'), or both(*10*) (Fig. 4). Here we discuss four key effects that host control can have on symbionts (Fig. 4), which can

be broadly divided into partner choice (symbiont immigration and composition) or partner manipulation (symbiont behaviour and interactions).

Symbiont immigration

An important goal for hosts is to influence which species arrive and establish in their microbiomes out of the set of transmissible microbes present in other hosts and the wider environment(*9, 90*)(Fig. 4A). This form of partner choice includes regulating the process of microbiome assembly during host development(*91*). A barrier to assembly can occur when some symbionts depend on one another for nutrients, because some species may be unable to colonise without others being present(*91*). One solution for a host is to ensure that the desired sets of symbionts arrive together via transmission from a relative(*86, 87*), although theory predicts that there can also be an evolutionary incentive to avoid perfect vertical transmission in order to obtain beneficial combinations of symbionts that suit the current environment (*92*). Another way to shape microbiome assembly is to provide specific nutrients for symbionts: human milk contains diverse oligosaccharides and urea that cannot be metabolised by the baby but can by certain colonising bacteria(*93, 94*). In addition, milk contains immunoglobulins that shape which microbes colonize the infant mucosa(*95*), possibly by providing specific strains with an attachment site(*41*).

The acidic stomach found in diverse vertebrates limits the global rate of immigration into the gut and some species, including vultures and humans, have an extremely low gut pH, which may be linked to high pathogen exposure(*96*). Hosts also use physiological control to select for high quality symbionts from among immigrating strains and species. The anoxic gut of many animals, for example, helps to screen for microbes capable of fermentation. In the bobtail squid light organ screening occurs via the generation of challenging growth conditions, which include reactive oxygen and nitrogen species(*97, 98*), and fungus-growing ambrosia beetles favour ethanol-rich conditions within host trees to select for their fungal garden symbiont over other microbes(*17*). Another way to control immigration is to treat resident symbionts differently to newcomers. The mosquito, *Aedes aegypti*, releases antimicrobial peptides from its gut epithelium. However, it also releases C-type lectins that coat resident symbionts protecting them from the antimicrobials (*99*).

Composition of established symbionts

In addition to immigration control, a host can benefit from influencing the abundances of established microbes (Fig. 4B). Resources can be restricted to problem symbionts or provided for beneficial ones. In the mammalian microbiome, lipocalin 2 is released during inflammation where it binds to the iron-scavenging siderophores of some bacteria to limit their iron uptake(*100*). Leguminous plants house nitrogen-fixing bacteria in specialised root nodules but cut off resources to nodules that supply too little nitrate(*5*)(Fig. 2). In addition, the large quantities of carbohydrates and mucilage released from plant roots can feed the rhizosphere microbiome (*58*). In some cases, this mucilage surrounds aerial roots and appears to select for fungal partners that suppress the growth of environmental, but not nitrogen-fixing, bacteria(*101*). Mucus production has comparable potential to influence animal microbiomes by preferentially feeding microbes that can break down the complex carbohydrates in mucin(*55*), such as members of the *Bacteroidaceae* and *Akkermansia muciniphila*(*62*). Analogously, honeybees

secrete organic acids to support the colonization of core symbionts such as *Snodgrassella alvi*, which cannot metabolize sugars(*102*). Theoretical work suggests that such host feeding can be a particularly powerful mode of host control, because fed strains have the potential to bloom and exclude other microbes from epithelial surfaces(*60*).

Hosts can also shift microbiota composition by modulating adhesion with host tissues and between microbes(*59*). For example, the main impact of adaptive immunity on the gut microbiota is mediated by adhesion. IgA contributes to bacterial expulsion by promoting bacteria-bacteria agglutination, which forms aggregates that are then removed by peristalsis(*15, 39*), but, as discussed, IgA may also assist colonisation by promoting bacterial-mucin interactions in the outer mucosa(*39, 41*). Bacteria also attach to mucin when feeding on it using glycan-binding proteins(*62*). An interesting possibility is that, when combined with the negative effects of peristalsis on unattached microbes, this adhesion will enrich for symbionts with the biochemistry for mucin metabolism. Our understanding of the fine scale spatial structure within the mammalian microbiomes remains limited(*64*). However, the stratified mucus layer of the distal intestine, which includes the glycocalyx and inner and outer mucus layers, has the potential to generate multiple niches where microbes can attach and grow(*64*). Broadly consistent with this, the composition of the microbiota at the mucosa and in the gut lumen can differ in mammals(*103*), and there is evidence that some bacterial species rely on mucus foraging(*61, 62*) or IgA attachment(*41*) to be able to compete in the gut. However, potential pathogens such as *E. coli* can also survive in the mucosa, where its capacity for mobility, oxygen tolerance and use, and ability to forage on host lipids enable survival(*103*), which may reflect some of the limits to host control. Nonetheless, if hosts can select for a community dominated by mucus-associated symbionts, as opposed to those that do not interact with mucin, the risks of pathogenicity may be reduced because mucus adherence appears to make bacteria less likely to breach the epithelium(*104*). Moreover, while adhesion to dense mucus may increase microbial density close to the epithelium, theoretical work predicts that hosts can retain the ability to shed these sticky symbionts from the mucosa by increasing the rate of mucus production(*59*).

Symbiont metabolism and behaviour

In addition to regulating microbiota composition, a host can directly influence the behaviour of resident symbionts to increase the benefits it receives (Fig. 4C). In practice, mechanisms that influence microbial behaviour may also change abundances and composition (Fig. 4B, above). For example, after a bacterial infection, mice increase production of the bile acid taurine, which both increases the frequency of microbial species capable of taurine metabolism (partner choice) and promotes taurine metabolism in those that can perform it (partner manipulation) (Fig. 4). The result is an increased production of sulfide, which inhibits respiration and limits the potential for future infections by pathogens that rely on respiration(*66*). However, in some cases, hosts are able to influence the metabolism of individual symbionts with a limited impact on overall microbiome composition. For example, leguminous plants synthesize leghemoglobins(*105*), which are analogues of animal haemoglobins that bind and buffer free oxygen in the nanomolar range. This buffering enables nitrogen fixation by the plants' symbiotic bacteria that depend on oxygen-sensitive nitrogenase enzymes, while still maintaining sufficient oxygen flux to support bacterial respiration, which is needed to meet the energy requirements of nitrogen fixation.

Oxygen control is also important for many animal species. Respiration allows microbes to maximize the energy (ATP) extracted from nutrients by electron transfer to oxygen or alternative

acceptors like NO_3^-. However, as a result, respiration can greatly reduce the energy available to the host, because symbionts can then fully oxidize energy-rich compounds to CO_2 and H_2O. By restricting oxygen supply, therefore, hosts can force microbes to use weaker electron acceptors like pyruvate and generate fermentation products, such as butyrate and other short chain fatty acids. These products retain metabolic potential and can be further metabolized by host tissues that have free access to oxygen(*28*). In the human colon, intestinal epithelial cells consume these products, which also consumes oxygen and generates a positive feedback loop to further promote microbial fermentation. This loop is continually monitored by gut epithelial cells, because a reduction in fermentation products like butyrate can destabilize hypoxia-inducible factor (HIF), a transcription factor coordinating barrier protection (*13, 29*).

Symbiont behaviour is also controlled by barriers that limit microbial encroachment into host tissue. Mucus production in mice both protects epithelial surfaces and contributes to the rheological properties of fecal materials, which helps separate the microbiota from the host(*106*). Hosts can further reinforce barriers by influencing symbiont movement and adhesion. Swimming bacteria pose a threat because they can resist peristaltic or cilia-mediated transit(*107*) and breach epithelial barriers(*4, 108*). In response, diverse anti-flagella mechanisms have evolved in both animals and plants(*4, 109*). Mammals can secrete a protein called Ly6/PLAUR domain containing 8 (Lypd8) from the gut epithelium, which binds to bacterial flagella and inhibits swimming(*110*). Another host strategy is to produce decoy molecules that provide an alternative binding site and thereby limit attachment to the epithelium(*111*). Some antimicrobial peptides also modify symbiont behaviour: the mammalian antimicrobial peptide Y supresses the hyphal, and invasive, form of the fungus *Candida albicans* in the mouse gut. In the presence of the peptide, the fungus stays in its yeast form and does not attach and invade host tissue(*112*).

Symbiont interactions

The symbionts within microbiomes can strongly influence one another's growth and survival (*3, 9*). Hosts can benefit from shaping these interactions, a form of ecological engineering (Fig. 4D). Ecological interactions among microbes can be negative or positive and are important for microbiome composition in that competitive exclusion can eliminate species while cross feeding can create new niches. Ecological interactions also influence microbiome productivity(*91, 113*) and resistance to pathogen invasion(*114*), as well as how microbiotas respond to perturbations such as antibiotic treatment (ecological stability). For example, strong cooperative interactions between symbionts can be destabilising when they cause mutual dependence, such that a population decline in one species drives the decline of another. Strongly competitive interactions can also destabilise a microbiota, as well as drive extinctions, when they drive down symbiont growth rates (*113*). Limiting the strength of interactions between symbionts, therefore, has the potential to benefit a host by both promoting stability and coexistence.

One host strategy to regulate symbiont interactions is to house beneficial symbionts in a dedicated organ or tissue, which can limit competition with less beneficial, but faster growing microbes. Such structures occur widely for housing endosymbiotic bacteria in insects and marine invertebrates(*85, 97, 98*), and nitrogen-fixing bacteria in plants(*5*). In mammals, the introduction of spatial structure via crypts(*115*) or blind-ended structures like the caecum may also help to limit competition among symbionts(*113*). Feeding symbionts from epithelial surfaces(*113*), such as by the provision of mucins, may also reduce competition and generate new niches(*62, 116*). Another intriguing possibility is that hosts can manipulate the cell-cell signalling of bacteria in

the microbiota to promote cooperative phenotypes, with the discoveries that mammalian cells make a mimic of the widely-used quorum sensing autoinducer AI-2(*117*) and the cnidarian *Hydra* modifies the quorum sensing signal of one of its key symbionts, which promotes colonisation(*118*).

In some cases, hosts appear to promote interactions between species. Mucus provides a location for phages to attach in wait for bacteria, which is thought to improve barrier function by promoting parasitic interactions between bacteria and phages(*119*). Host generated peristalsis can also promote interaction strength because increasing flow rate and mixing contractions will tend to homogenize populations of different strains and species, thereby increasing the likelihood that different symbionts will meet and interact(*2, 64*). This mixing can have benefits when species are interacting metabolically to provide nutrients for a host, as occurs in our large intestine where acetate producers feed the butyrate producers that feed us, as well as in ruminants(*120*)(Fig. 3). Moreover, when such metabolic interactions are based upon exploitation with one species benefiting at the other's expense, this generates a negative-feedback loop that can be stabilising for the microbiome(*113*). However, gut transit also has the potential to limit diversity and stability: a two species community in zebra fish was found to be destabilised by peristaltic movements because it promoted the competitive exclusion of one symbiont by the other(*14*).

Promoting competition may have benefits on evolutionary timescales if it selects for vigorously growing bacteria that provide benefits for the host, such as the ability to outgrow and intoxicate incoming pathogens(*66, 114*). However, symbiont evolution can be a double-edged sword if it enables evolutionary escape from host control, as we discuss next.

Symbiont evolution and counter adaptation

The generation time of symbionts is typically extremely short relative to their host's. In ecological terms, this enables rapid shifts in the species composition of microbiotas driven by differences in symbiont death and growth rates. Short generation times also mean that symbionts can evolve rapidly i.e., there is ample time for genetic changes within the populations of single species(*9, 40, 121, 122*). The potential for evolutionary adaptation is most clear when microbes are first introduced into a host and experience natural selection driven by a novel environment(*123*). Evolutionary pressures experienced by symbionts may also change over the course of a host's lifetime, as is likely to occur during the development of the anoxic gut in humans(*124*). For symbionts that are established in a host, natural selection may only rarely be a force for change. Often, natural selection will oppose change, pruning variations that stray from the host's favoured phenotypes (i.e., purifying selection)(*9*). Nonetheless, one also sees ongoing signatures of natural selection in mature hosts. For example, studies of established mouse and human microbiomes have found evidence of positive selection on bacterial genes associated with carbohydrate utilization(*121, 125*) and IgA affinity(*121*). Host control mechanisms also have the potential to influence evolutionary processes on even longer time scales by promoting the specialisation of symbionts and co-diversification with the host(*126*).

Symbiont evolution can be a boon for the host if harnessed effectively. New species that colonise the human microbiota may experience natural selection to be non-motile(*4*), interact with mucus(*121*), and produce butyrate(*13*). This means that strains that were once pathogenic may evolve to become neutral(*127*), and strains that were once neutral may evolve to provide significant benefits(*4*). Consistent with such pressures - and the diverse mechanisms that hosts

use to counter swimming bacteria - a recent phylogenetic analysis suggested that bacteria that are symbionts of animals have a higher evolutionary rate of flagella loss than free-living species(*4*).

Despite the potential benefits for a host, symbiont evolution also raises the potential for escape from host control. As a result, evolutionary theory predicts that control mechanisms will only be maintained if they can limit counter-evolution in symbionts(*4*). Consistent with this prediction, control mechanisms often target microbial phenotypes (i.e., trait-based discrimination), rather than a particular strain or species (i.e., genotype-based discrimination)(*3*). Trait-based discrimination is important for a host because, if a given symbiont evolves and changes its phenotype, they will be treated differently. Such trait-based control is seen in the great majority of examples we have discussed. In the bobtail squid, for example, loss of light production by the symbiont *Vibrio fischeri* makes it non-competitive in the squid's light organ(*97, 98*). The notable exception to trait-based discrimination is adaptive immunity(*39*) which recognises microbial genotypes by their unique chemical signatures. However, because of the ability to learn new associations, adaptive immunity is also able to modify responses should a formerly beneficial symbiont evolve to become harmful.

To further limit counter-evolution, host control can target microbial traits that are constrained against counter-evolution. For example, control mechanisms that feed symbionts may be hard to exploit if they require a microbe to acquire multiple metabolic loci, such as those required for mucin metabolism(*62*). Punitive host control mechanisms also appear to target microbial traits that are constrained against evolutionary escape. Recognition of flagellin by toll-like receptor 5 (TLR5) promotes inflammation and the production of anti-flagellin IgA that limits swimming(*128, 129*). Avoidance of this response, therefore, may carry significant benefit to some bacterial species. However, TLR5 binds to a highly conserved region of bacterial flagellin where amino-acid changes typically lead to swimming defects, which limits the scope for counter adaptation(*4, 130*).

Despite such host adaptations, some symbionts evolve ways to circumvent, or even exploit, host control mechanisms. These counterstrategies are important because they provide compelling evidence for the role of host control on symbiont evolution. Counterstrategies are also expected to be widespread, but their identification typically requires detailed knowledge of both host and microbe biology. As a result, many potential examples come from well-studied pathogens. For example, *Shigella flexneri* suppresses the inflammasome response that would otherwise expel infected epithelial cells into the gut lumen(*131*), and *Clostridum difficile* (now *Clostridioides difficile*) both suppresses gut motility(*132*) and resists host iron sequestration by having ferrosome organelles that store iron(*133*). There is also evidence of evolutionary responses to host control in non-pathogenic symbionts. One such example is the recent discovery that some gut bacteria carry a form of flagellin that still binds to TLR5 but silences its signalling(*134*). Diverse symbionts also appear to have evolved resistance to host antimicrobial peptides (AMPs). Rather than being an issue for the host, this resistance bolsters the ability of the microbiome to outcompete incoming pathogens that remain susceptible to the AMPs(*30*). Thus, symbiont counter adaptations to control may not always be problematic. However, what prevents harmful species from adopting the same counter adaptations is not always clear.

Rather than just evading host control, some microbes harness the very systems that are supposed to control them. The plant pathogen *Agrobacterium tumefaciens* exploits a key host immune protein to shuttle its own DNA into the plant nucleus and control host physiology for its own benefit(*135*). Another fascinating example is the subversion of the host inflammatory response

by the gut pathogen *Salmonella enterica*(*28*). This bacterium enters host cells in the gut epithelium and releases immunogenic molecules that set off a massive inflammatory response. While this response knocks down *S. enterica* alongside the resident gut microbiota, the pathogen can quickly recover and outgrow the resident species owing to its ability to respire using electron acceptors that are generated as by-products of the immune response. In this way, *S. enterica* manages to hijack the most complex of host control mechanisms to proliferate and disperse.

Conclusion

It is challenging to manipulate microbiomes for better health. Antibiotics can help with some disorders but are a crude manipulation that decimates the microbiome and contributes to the evolution of drug resistance. As a result, there is a great interest in potential alternatives, including phage therapy, fecal microbiota transplants and the delivery of specific microbial consortia(*114, 136, 137*). However, like antibiotics, these strategies all focus on the microbes themselves. An alternative is to focus on the host control mechanisms that we have discussed here. These mechanisms have been shaped by natural selection to cope with the diversity and variability inherent in microbiomes, and even to limit the evolution of resistance.

Applications include a role for diagnosis - where markers of host physiology and control can be more similar among conditions and individuals than microbiota composition(*28*) (Box 2) - but also preventing and treating disease. Central among such strategies is vaccination, with recent work demonstrating the potential for vaccines to target specific bacteria in the gut microbiome (*138, 139*). Another strategy is to bolster host control over symbiont metabolism by, for example, restoring the anaerobic environment in the gut (*13, 28*) or regulating key nutrients like iron(*100*), nitrate(*140*) or mucin-derived glycans(*116, 141*). More generally, any strategies that promote a healthy mucus layer and the integrity of the host epithelial barrier have clear potential health benefits. Such treatments may become particularly important as we age and microbiomes become more variable and disease prone (*64, 142*), a likely symptom of the decline in mechanisms of host control.

There is a great interest in the many ways that microbiotas affect hosts, including humans. Here, we have argued that many of these effects can be traced back to mechanisms of host control. For hundreds of millions of years, multicellular hosts have been under natural selection to increase the benefits from their symbionts, and the result is an amazing set of adaptations that are able to regulate and control diverse microbial communities. Understanding these mechanisms will be central for both understanding microbiomes and manipulating them for better health.

Box 1. The evolution of cooperation and the problem of cheating

Many host-associated microbiomes appear to provide benefits for both the host in return for nutrients and a relatively stable environment(*1, 3*). One might assume that these mutual benefits alone are sufficient to explain cooperation between hosts and their microbiotas(*4*), but the evolutionary literature cautions strongly against this assumption(*5-8*). Consider, for example, a symbiont that invests in making a product that feeds the host. Even though the host benefits, genotypes that do not make the product and instead use the resources for growth are expected to thrive (sometimes known as 'cheaters' in evolutionary biology)(*5*) . The rapid generation time of symbionts can greatly exacerbate the problem by allowing short-sighted symbiont evolution to occur within a host generation(*4, 8, 60*).

Host control mechanisms can reverse this evolutionary trajectory by generating natural selection for cooperation within the host(*4, 9, 127*). However, this outcome requires hosts to find ways to promote beneficial genotypes over cheaters and pathogens(*7*). One way is to isolate clonal populations of beneficial symbionts in special organs or tissues where behaviour can be monitored and regulated e.g. nitrogen-fixing bacteria in root nodules and light-producing bacteria in the bobtail squid light organ(*5, 97, 98*). Another way is to identify harmful genotypes by location: immune systems often respond very differently to microbes that breach the epithelium than those that do not(*25*). However, in some cases, such spatial information is lacking. The lumen of the large intestine, for example, appears to function primarily by creating nutrient niches. Here, the anaerobic environment and provision of complex carbohydrates favours microbes that ferment the carbohydrates into products that the host can use(*13, 28, 60*) (Fig 1 and 3), such that microbes lacking this ability may be at a competitive disadvantage. When combined with other mechanisms, such as the ability of the adaptive immune system to target specific genotypes with IgA(*138, 139*), this environmental control appears sufficient to regulate the lumen microbiota. However, how host control operates effectively upon such diverse microbiotas is not always clear and is an interesting question for future work.

Box 2. Genome-wide association studies, host genetics, and host control

Several studies have asked whether host genetics can explain the variability in microbiota composition among individuals, which can identify interesting aspects of microbiome biology e.g. via genome-wide association studies (GWAS). It might appear that such studies, which sometimes do not find effects(*146*), are a way to assess the importance of host control mechanisms. However, there are problems with this conclusion because genetic association relies on traits having significant standing genetic variation with functional consequences. For the most important host control traits, such as the anaerobic gut, this variation may not be present because of strong purifying selection to maintain trait function.

A second issue is that microbiota composition is a complex and variable phenotype to associate with host genetics (as compared to something like disease risk)(*147*). Even if there is variation in host genotype that influences composition, e.g. screening for microbes capable of fermentation, it may be impossible to detect the effects of host genetics because different microbes can provide the same function for different hosts. Consistent with this, microbial genotypes change over time in the human microbiome due to replacement events within bacterial species(*121, 148*), but the functional effects on the host may not. In a similar vein, changing diet can shift the abundances of taxa within the gut microbiota, but such shifts do not imply an absence of host control, which is only expected to constrain changes that have negative consequences for the host. However,

variability introduced by diet can again confound any links between host genetics and microbiome variation.

A final issue is that, even when effects of host genetics are detected, they may not represent host control. The key association found in one large twin study was a negative link between host lactase expression and the abundance of lactose-consuming *Bifidobacterium(149)*, which is better explained by host diet preferences for milk rather than host control. While association studies do not directly assess the importance of host control, they can be a route to understand some control mechanisms as some do display genetic variability. For example, there is a common allele of TLR5 (which detects bacterial flagellin) in humans that appears to render it non-functional, which is associated with an increased risk of bacterial infections(*150*), but decreased risk of autoimmune disease(*151*).

Acknowledgments: We thank A. Baumler and C. Greyson-Gaito for helpful discussions and comments on the manuscript.

Funding: K.R.F. is supported by the following sources:

Wellcome Trust Investigator award 209397/Z/17/Z

European Research Council Grant 787932

Author contributions: All authors contributed to the planning and writing of the manuscript.

Competing interests: The authors declare no competing interests.

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