nature microbiology

Perspective

https://doi.org/10.1038/s41564-025-02139-9

How nutrient starvation impacts the gut microbiome

Received: 31 March 2023

Accepted: 3 September 2025

Published online: 30 September 2025

Check for updates

Sylvie Estrela[1,6] ✉, Jonathan Z. Long[2,3] & Kerwyn Casey Huang[1,4,5] ✉

Even when the gut is rich in nutrients, microorganisms can experience nutrient deprivation owing to factors such as fluctuations in host feeding patterns, microbial competition and selective nutrient uptake by the host. Nutrient starvation affects microbial survival, microbiome dynamics and intestinal stability, yet remains underexplored. This Perspective explains how nutrient deprivation shapes microbial physiology, ecology and evolution to drive complex interactions both among microbial species and between microorganisms and their host. We discuss host lifestyles that can result in microbial starvation, including diet shifts, fasting and hibernation. We also highlight critical gaps in our understanding of how starvation affects microbial community assembly, stress responses and cross-feeding from lysed cells, with implications for chronic infections and therapeutic strategies. We outline technological developments needed to unravel microbial survival strategies under nutrient deprivation. Understanding how starvation in all its forms shapes the gut ecosystem will be important to ultimately advance microbiome engineering and health interventions.

Bacterial life involves exposure to dynamic environmental conditions. Adapting to these fluctuations is crucial for growth and survival. A common, usually inevitable, transition is between nutrient-rich (feast) and nutrient-poor (starvation) conditions. These extremes impose distinct selective pressures: feasting selects for rapid growth, whereas starvation selects for survival[1]. In contrast to the wide range of studies asking how nutrient-rich conditions affect the growth of single microbial species, much less effort has focused on the effects of nutrient deprivation. Most studies of bacteria under starvation conditions have focused on a few model species such as *Escherichia coli*[2] and to some extent *Bacillus subtilis*[3] and *Bacteroides thetaiotaomicron*[4–9], or on pathogens like *Staphylococcus aureus*[10] and *Mycobacterium tuberculosis*[11]. Very few studies have investigated starvation in non-model commensals, and even less in the context of complex communities[9], which has left many important questions about the ecological relevance of starvation unanswered.

The animal gut is a highly dynamic environment, with diurnal fluctuations in both nutrients[12] and microbiome composition that can be modulated through time-restricted feeding[13]. Bacteria can undergo nutrient starvation during periods of fasting, whether short like the periods between meals or extremely long such as during hibernation. More generally, any species that is unable to access any of the nutrients that it requires is nutrient deprived. In this scenario, bacterial starvation can be viewed as a physiological or metabolic state that varies across species rather than being globally imposed by the environment. Bacteria can experience nutrient deprivation resulting from many causes, including diet shifts and competition with other microorganisms or the host that deplete a preferred nutrient. Thus, the gut environment can be nutrient rich for some species and nutrient poor for others depending on the distribution of available nutrients and individual requirements. These factors can be directly or indirectly affected by host behaviours, such as weight-loss plans and religious fasting. Although gut commensals may have some forms of environmental 'memory'[14,15] that enable them to retain physiological or metabolic adaptations from previous nutritional conditions, host behaviours such as diet changes are probably largely unanticipated by their microbial inhabitants. The

[1]Department of Bioengineering, Stanford University, Stanford, CA, USA. [2]Department of Pathology, Stanford University School of Medicine, Stanford, CA, USA. [3]Sarafan ChEM-H, Stanford University, Stanford, CA, USA. [4]Department of Microbiology and Immunology, Stanford University School of Medicine, Stanford, CA, USA. [5]Chan Zuckerberg Biohub, San Francisco, CA, USA. [6]Present address: Department of Nutrition, Texas A&M University, College Station, TX, USA. ✉e-mail: sestrela@tamu.edu; kchuang@stanford.edu

https://doi.org/10.1038/s41564-025-02139-9

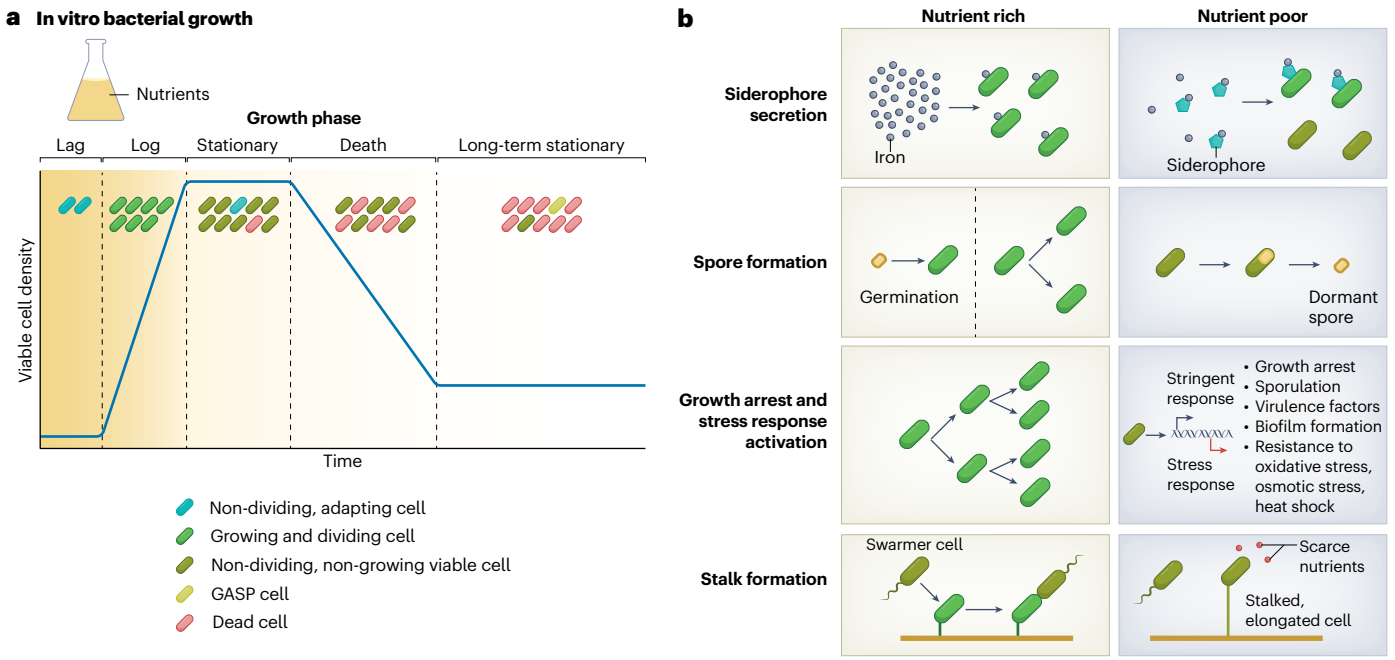

Fig. 1 | Bacterial strategies to cope with nutrient starvation. a, Bacterial growth typically follows distinct growth phases in batch culture in laboratory settings with distinct phenotypes. Lag phase features non-growing or slow-growing, adapting cells, whereas exponential (log) phase is driven by growing and dividing cells. Stationary phase is when cell division is balanced by cell death and the number of viable cells remains relatively constant. Death phase is when most cells lose viability and die. Finally, long-term stationary phase is when a small fraction of cells survive and can persist for extended periods by recycling nutrients and cellular debris from dead cells. In *E. coli*, GASP mutants start to emerge during this phase, a phase that remains largely unexplored in other species. **b**, Bacteria use physiological adaptations that enable their survival under nutrient limitation. Some produce siderophores to obtain iron in iron-limited conditions. Spore formation enables bacteria to persist in harsh environmental conditions, such as starvation, for extended periods of time; when favourable conditions return, spores germinate and cells reinitiate growth and division. Many bacteria activate the stringent response, which arrests growth and can lead to the activation of genes involved in sporulation, virulence and biofilm formation. Some bacteria activate the general stress response, which upregulates genes involved in resistance to oxidative stress, osmotic stress and heat shock. Stalk formation is a normal part of the *C. crescentus* life cycle, and under phosphate starvation, *C. crescentus* enters a non-replicative state characterized by an increase in cell length and the development of a significantly longer stalk that enables greater nutrient uptake.

ability to deal with nutrient limitation should therefore be an intrinsic, primary component of the fitness of any gut microorganism, and may be critical for its long-term survival and propagation to other hosts. Taken together, the potential implications of starvation conditions on gut health and chronic infections are vast but understudied, and the degree of importance and most relevant consequences remain undetermined.

Appreciation for the effects of starvation stretches back to the seminal work of Jacques Monod[16], who described the succession of bacterial growth phases in batch culture (Fig. 1a). Nonetheless, the advent of novel tools and expanded knowledge regarding the importance of microbiomes in host function provide motivation for revisiting this topic in many contexts. In this Perspective, we discuss current knowledge, mostly based on in vitro studies, about bacterial strategies for surviving nutrient starvation conditions relevant to gut bacteria, the relationship of bacterial starvation to host behaviours and avenues for future research (for a review on mechanisms of bacterial starvation response strategies in model organisms, see ref. 17). A primary purpose of this Perspective is to inspire more studies of gut bacterial and community behaviours in nutrient-poor conditions by focusing on fundamental unanswered questions and the challenges in addressing them. How does starvation affect microbial community assembly, diversity and stability? When does starvation result in bacterial cell death? And what are the consequences of starvation-induced cell death and lysis on the ecology and evolution of microbiomes? We compare the physiological, ecological and evolutionary consequences of short-term versus long-term nutrient deprivation, which could be likened to hunger and starvation, respectively. We also discuss when bacterial communities would be likely to experience nutrient starvation in a host. We consider how nutrient starvation affects the response of bacteria to other stresses and perturbations commonly found in the gut, including antibiotics, temperature, oxygen exposure and phages. Ultimately, such knowledge is fundamental for understanding the gut ecosystem and could provide new strategies for improving health and treating disease.

Physiological and evolutionary consequences of bacterial nutrient starvation

Bacteria have multiple strategies to cope with nutrient limitation (Fig. 1). A common initial response is to enhance acquisition and sequester scarce nutrients, for example, by producing siderophores to scavenge limited iron[18]. If scavenging fails and nutrients remain scarce, bacteria may enter a dormant state (stationary phase) or die[19]. However, death is not inevitable; some bacteria can survive starvation for years through the acquisition of genetic adaptations that give them a growth advantage in stationary phase (GASP) (Fig. 1a). These mutations are detrimental to the bacteria after return to nutrient-rich conditions[20]. With a few notable exceptions[21], most insights into genetic adaptation in the long-term stationary phase come from laboratory studies focused on model organisms, particularly *E. coli*[20,22,23]. Hence, it is difficult to know whether these effects represent general principles of how bacteria respond to starvation, particularly in the gut where many species have unique physiologies.

The degree and duration of nutrient limitation depends on the environment, which means that bacterial responses to nutrient starvation and their local ecology and lifestyle are deeply connected.

For instance, the way that enteric bacteria such as *E. coli* adapt to nutrient limitation may be due to their frequent transitions between nutrient-rich environments, such as the gut, and those that are nutrient-poor, like soil[24]. If *E. coli* is starved of carbon, nitrogen, phosphate, iron or any one of the amino acids, it enters growth arrest and activates stress responses to enhance survival. These responses include the stringent response, a specific signalling pathway triggered by nutrient limitation[25], and the general stress response, which is regulated by the sigma factor RpoS[26] (Fig. 1b). By contrast, the stringent response in *Caulobacter crescentus*, a species that mostly inhabits nutrient-poor, freshwater environments, requires starvation for multiple nutrients and a higher threshold for activation compared with most other species[27]. This requirement for more severe, multinutrient starvation is probably an adaptation to life in nutrient-poor habitats, which enables it to distinguish actual starvation from typical nutrient fluctuations and avoid unnecessary activation of costly stress responses. *C. crescentus* also exhibits responses distinct from enteric bacteria. Under phosphate starvation, it enters a non-replicative state characterized by an increase in cell length and elongation of its stalk appendage to scavenge nutrients[28] (Fig. 1b). In the prominent gut commensal *B. thetaiotaomicron*, the genes responsible for growth arrest during carbon starvation are also important for mouse gut colonization; this functional overlap is conserved across the *Bacteroides* genus but not in *E. coli*[4,29], which suggests that adaptation to feast and famine lifestyles may be specific to certain commensals.

To survive long periods without nutrients, some Gram-positive species can form spores, which are replicative units adapted for dispersal and survival under unfavourable conditions (Fig. 1b). In the gut, loss of the ability to sporulate in many Firmicutes species (for example, lactic acid bacteria) has been suggested to be an adaptation to the nutrient-rich gut environment[30]. However, other species (for example, the pathogen *Clostridioides difficile*[31]) have maintained the ability to sporulate. Understanding how dietary fluctuations and starvation for specific nutrients affect the evolutionary trajectory of sporulation loss and gain, and whether the presence of spore formers in the gut is primarily due to adaptation to other stresses such as antibiotics[32] and ethanol[33], remain open questions.

Starvation and the bacterial response to stressors and perturbations

In *E. coli*, rejuvenating cells emerging from starvation can exhibit a wide distribution of lag times depending on the growth conditions and the time scale over which starvation occurs[34,35]. Cells that take longer to start growing are in some cases protected from antibiotics (for example, persisters)[36,37], a result that suggests that starvation can have beneficial side effects. In addition, gradual versus acute starvation can lead to very different rejuvenation dynamics. During growth in minimal medium supplemented with amino acids, acute starvation via treatment with serine hydroxamate drives cells into a range of disrupted states that ultimately manifest in slow and heterogeneous lag times during rejuvenation[36]. By contrast, gradual starvation (through either nutrient depletion or gradual increases in serine hydroxamate concentration) induces a regulated response that enables cells to reach a relatively uniform stable state that ultimately results in rapid and homogeneous recovery[36]. These differences affect the fraction of persister cells present after starvation, which ultimately affects how bacteria survive antibiotic exposure. Sudden starvation also protects *E. coli* from heat stress[38], which could be relevant for bacteria in the gut during fever or exercise.

In addition to what could be considered side effects, the transcriptional program of bacteria may reflect co-adaptation to the multiple stressors inevitably present in any environment, particularly the gut. Bacteria exhibit similar physiological responses to both nutrient supply and osmotic stress, including the induction of genes under RpoS control, and in *E. coli*, entry into stationary phase confers cross-protection against osmotic stress[39]. It has been suggested that co-regulation of these stress responses is an evolutionary adaptation to frequent exposure to concurrent nutrient and osmotic fluctuations, such as the coupled feast–famine cycle and hydration changes[40] experienced by gut bacteria due to eating or dietary shifts and the nutrient–osmolyte concentration differences between the concentrated host and the comparatively dilute external environment. Co-regulation ensures that bacteria can efficiently cope with multiple stressors simultaneously to enhance their survival and competitiveness, as has been shown for oxygen and heat shock[41]. In *B. subtilis*, dormancy induced by resource limitation protects against phage infection because phages are unable to attach to endospores, which leads to reduced bacterial mortality[42]. Whether this benefit is a side effect or a co-adaptation remains to be determined.

Overall, the ability of starvation to protect bacteria against other stressors highlights the importance of the nutritional environment when studying stress responses. It raises the intriguing question of whether the molecular mechanisms of non-nutrient stress responses have been co-opted from nutrient stress responses. To address this possibility, further research on the commonalities and differences among stress responses is needed, especially in non-model organisms and in diverse communities and distinct environments that may fundamentally alter response behaviours.

Within-host conditions that induce bacterial nutrient starvation

Bacteria residing in or trying to invade new hosts are often exposed to environments in which nutrients are limited. Below, we discuss key host-mediated and microbiome-mediated mechanisms by which bacteria are starved of their preferred nutrients in a host.

Host immune responses to infection

During infection, many bacterial pathogens must acquire some nutrients from their hosts to proliferate. As a defence mechanism, animal hosts have evolved strategies to starve pathogens of their preferred nutrients (often metals such as iron) through specific depletion at infection sites (for instance, by producing proteins that bind free iron or sequester bacterial siderophores). This process is known as nutritional immunity[43] (Fig. 2a). In turn, pathogens have co-evolved strategies to circumvent such host-imposed starvation. Trace metals are acquired by hosts through their diet and then absorption in the gastrointestinal tract, which means that excess dietary metal can increase the risk of bacterial infections. Metal deficiencies can also increase infection risk owing to both weakened host immune systems and enhanced adaptation by pathogens to low-metal environments compared with commensals. As a result, hosts typically have mechanisms to tightly regulate metal levels[43]. Bacterial pathogens and hosts also compete for sugars[44], amino acids[45] and fatty acids[46]. To overcome host-imposed nutrient restrictions, many pathogens use nutritional virulence mechanisms, which involve the upregulation of virulence genes, such as those encoding toxins like extracellular proteases and lipases[47], that promote their survival by extracting nutrients from host tissues[47–49]. Understanding the mechanisms and evolutionary processes that underlie exploitation by pathogens and starvation by the host will provide new opportunities for nutrient-based therapeutic interventions against bacterial infections.

Nutrient competition and colonization resistance

One of the major functions of the gut microbiome is to protect its host against colonization by pathogens, which can be accomplished through winning the competition for nutrients[50] (Fig. 2b). Bacterial communities cultured in vitro were able to recapitulate the variable sensitivity of mice to *Salmonella* colonization before and after antibiotic treatment[51]. This result suggests that starvation through microbial competition is a primary mechanism for combatting pathogens. In

https://doi.org/10.1038/s41564-025-02139-9

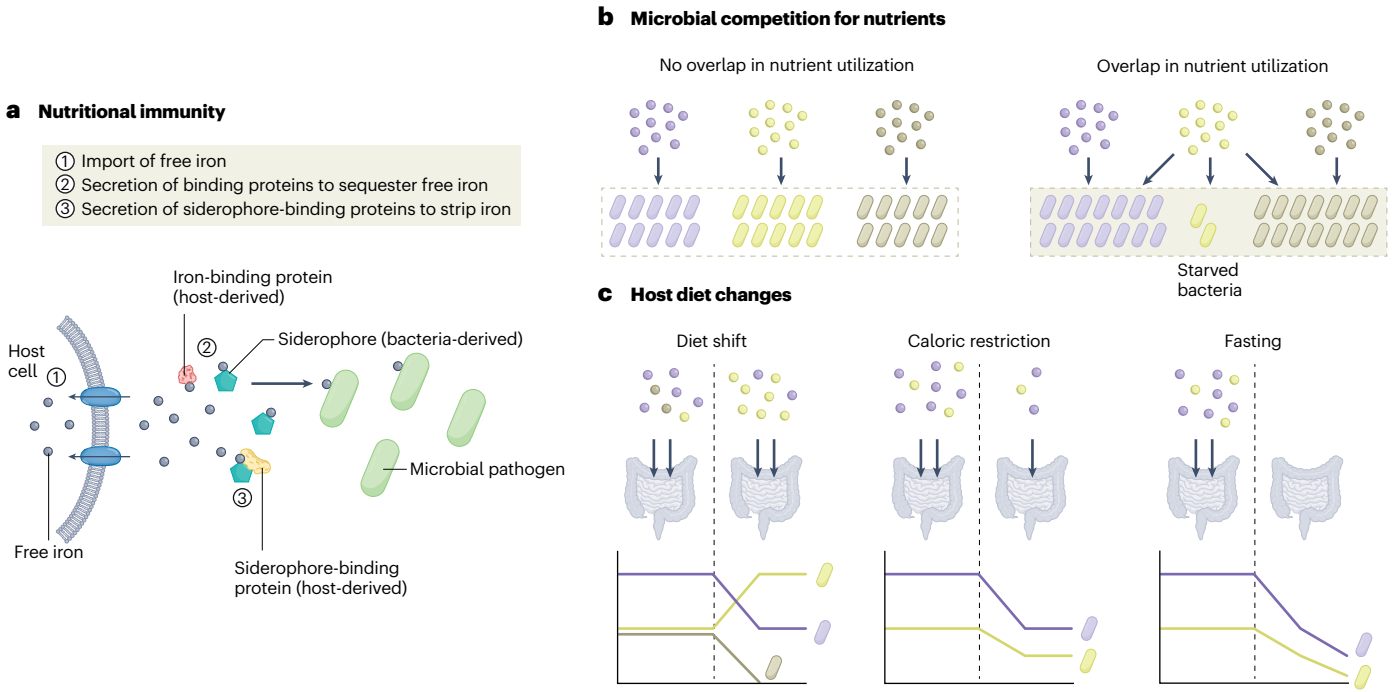

Fig. 2 | How bacteria experience nutrient starvation in a host. a, Nutrient starvation is often imposed by the host as an immune response to prevent infection by pathogens. For example, the host uses multiple mechanisms to restrict iron availability to invading pathogens, including import of free iron into host cells (1), secretion of proteins that bind and sequester extracellular iron (2) and secretion of proteins that bind and neutralize bacterial siderophores (3). **b**, Nutrient starvation can be imposed through competition with other bacteria. When nutrient preferences overlap, competition for nutrients increases and less competitive bacteria may become starved. This competition for shared nutrients between resident bacteria and invading pathogens is a potential mechanism of colonization resistance. **c**, Nutrient starvation can be imposed by the host during dietary shifts, caloric restriction or fasting. The schematics at the bottom indicate trajectories of species abundances from before to after the diet change. During a dietary shift, certain bacterial species become starved of their preferred nutrients and decrease in abundance, whereas other species increase in abundance owing to increased levels of the nutrients that they are better adapted to. Caloric restriction decreases total nutrient availability, which leads to a reduction in total bacterial abundance. Fasting imposes a drastic reduction in nutrient input (close to zero), which can lead to starvation and drive some bacterial species to extinction. In **b** and **c**, the circles represent nutrients; in **b**, arrows represent the nutrient preferences of the cells.

line with this phenomenon, a recent study showed that increasing microbiome diversity can enhance colonization resistance against pathogens[52], potentially because a more diverse microbiome is more likely to deplete the nutrients that pathogens need for growth. Future studies are required to establish how generalizable this finding is across communities, perhaps by elucidating the closest competitors of a pathogen (or other invading species)[53] and then determining whether successful invasion requires a privileged nutrient niche[53].

Host diet changes

A straightforward mechanism by which gut bacteria experience nutrient restriction is caloric restriction or fasting by the host, in which the overall levels of all nutrients decrease from a normal set point. Caloric restriction and fasting are distinguished by their degree and duration: caloric restriction typically involves long-term decreases in the amount of dietary nutrients (the types of nutrients may also change), whereas fasting is a switch between normal and (close to) zero dietary consumption (for instance, during a religious fast) (Fig. 2c). Hibernation, a natural fasting strategy used by many animals to cope with food scarcity owing to seasonal fluctuations, is typically preceded by a feasting period to help withstand the subsequent long-term fast. Regardless of the degree of nutrient restriction, reduced caloric intake affects both the host and the microbiome.

Nutrient starvation need not be as binary as fed versus fasting; it can also result from dietary shifts. For example, ketogenic diets involve reduced consumption of a single dietary component, effectively carbohydrate starvation, compensated by increased fat and protein intake. No-fat or low-fat diets can similarly be thought of as dietary lipid starvation. Although diet shifts do not necessarily involve a decrease in calories, they nonetheless involve a qualitative change in the types of nutrients available and a quantitative change in the levels of some of the nutrients that overlap between the diets. Thus, bacterial species that thrived in one diet may find themselves largely starved of their preferred nutrients after the shift, either due to direct changes in dietary makeup or to indirect effects on the microbiome, for example, the elimination of a cross-feeding partner[54].

Impact of feast–famine dynamics on the gut microbiome across animal hosts

Although dietary perturbations are generally highly complex, comparisons across studies are beginning to reveal conserved versus specific microbiome responses to feeding–fasting cycles (Fig. 3a) across both hosts and perturbation time scales.

Fasting as a survival strategy and dietary plan

Hibernation leads to an extreme change in host diet that affects host metabolism, especially lipid metabolites[55], and both the quantity and quality of nutrients available to the gut microbiome (Fig. 3b). In animals such as the 13-lined ground squirrel, hibernation affects the diversity and composition of both the luminal[56] and mucosal[57] microbiome. Hibernating squirrels exhibit reduced microbiome diversity, decreased abundance of the Firmicutes phylum and increased abundance of the Bacteroidetes and Verrucomicrobia phyla compared with active squirrels[57]. In hamsters, fasting results in an increased relative abundance of the Verrucomicrobia member *Akkermansia*[58], similar to hibernating squirrels. In free-ranging brown bears, hibernation leads to several

https://doi.org/10.1038/s41564-025-02139-9

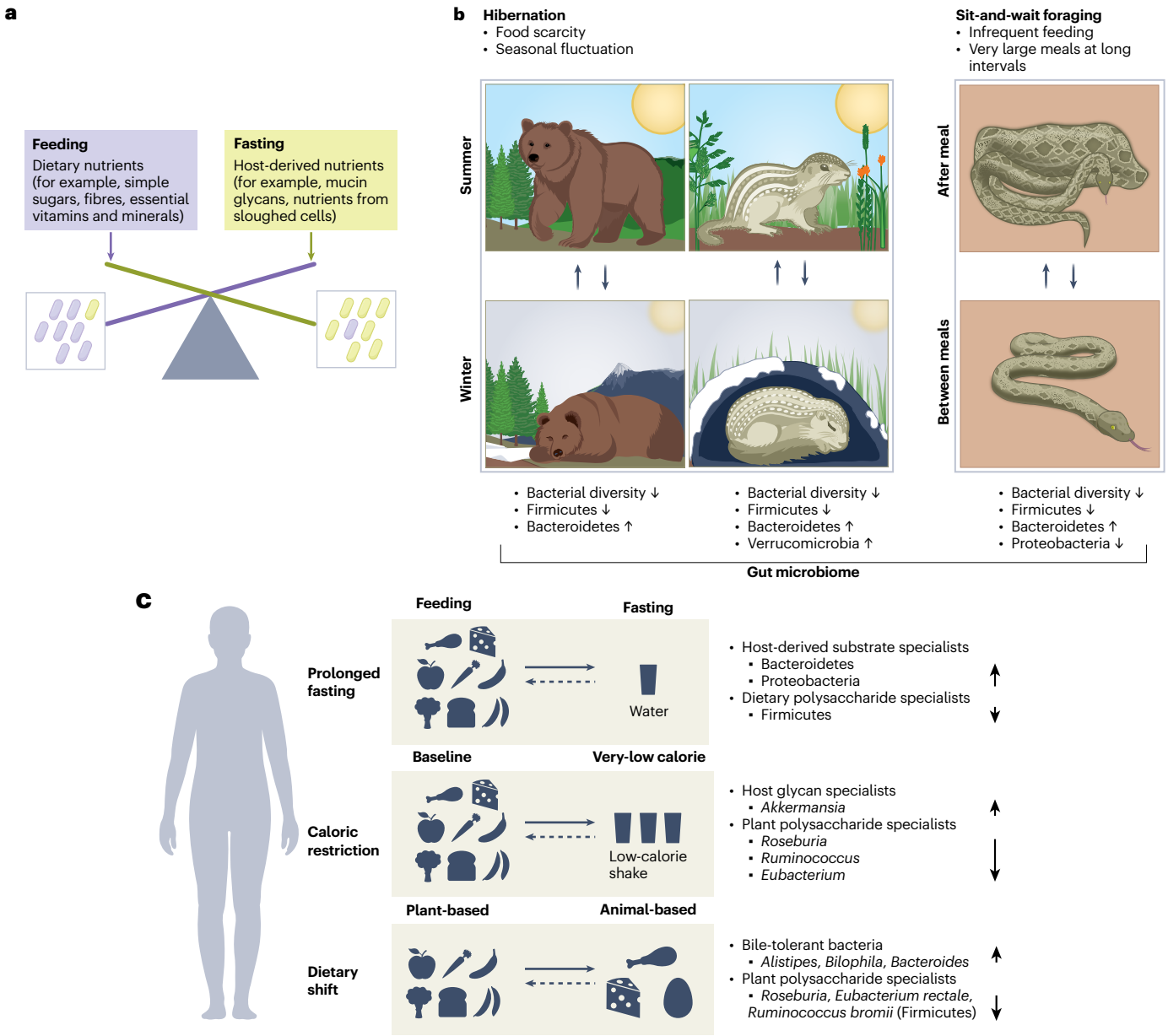

Fig. 3 | Effect of dietary perturbations on host-associated microbiomes. **a**, Feeding (feasting) increases the contribution of dietary nutrients, such as simple sugars and fibres, whereas fasting increases the contribution of non-dietary host-derived nutrients, including mucin glycans and nutrients from sloughed intestinal cells, in shaping the composition of the gut microbiome. **b**, Feast–famine cycles are common across diverse animal hosts owing to their lifestyles. Examples include hibernation in free-ranging brown bears and in 13-lined ground squirrels, and sit-and-wait foraging in the Burmese python. Such cycles have broad consequences for their microbiome, generally leading to decreases in bacterial diversity and changes in abundance of specific taxa. **c**, In humans, diverse practices like prolonged fasting, caloric restriction and dietary shifts have some common effects on the gut microbiome. For example, a shift from a plant-based to an animal-based diet leads to an increase in the abundance of bile-tolerant bacteria and a decrease in bacteria that specialize in degrading plant polysaccharides.

outcomes similar to squirrels, including less diverse microbiomes and reduced levels of Firmicutes and higher levels of Bacteroidetes compared with the active phase[59] (Fig. 3b). Hibernating brown bears also have less variable microbiomes across the population than in the summer, which perhaps reflects the role of nutrient fluctuations in microbiome variability[60], and reduced levels of Actinobacteria. Sit-and-wait foragers (for example, Burmese pythons; Fig. 3b) can fast for more than 1 month, in contrast to animals that feed very regularly (for example, mice). Such long-term fasting is associated with an increase in Bacteroidetes, a decrease in Firmicutes and a reduction in diversity and richness[61], a similar signature to hibernating squirrels and bears despite the global differences in microbiome composition across host species.

Intermittent fasting is an increasingly common form of temporary starvation in humans[62] that stimulates bacterial adaptation and may have effects on host health by affecting chronic infections, host metabolic regulation and longevity[63,64]. For instance, a 10-day fast intervention led to an increase in the relative abundance of Bacteroidetes and Proteobacteria, a decrease in Firmicutes and was associated with changes in health biomarkers such as serum glucose levels and fecal branched-chain amino acid levels[64] (Fig. 3c, top). Although intermittent fasting generally increases the diversity of the gut microbiome in humans, its effects on specific microbial taxa vary across studies[65]. In mice, intermittent fasting increases the relative abundance of *Akkermansia*, and the presence of the microbiome improves metabolic

homeostasis of the host[66]. The relative abundance of *Akkermansia* has also been shown to increase in humans following a very low calorie diet, at the expense of bacteria specializing in the breakdown of plant polysaccharides[67] (Fig. 3c, middle). Although the abundance of the human gut commensal *Akkermansia muciniphila* has been associated with positive metabolic outcomes in some contexts[68], the long-term health implications of its increased abundance during nutrient restriction, particularly alongside a loss of fibre-degrading bacteria, remain unclear.

Collectively, these results suggest that fasting favours taxa such as Bacteroidetes or Verrucomicrobia that specialize in the metabolism of host-derived *N*-linked glycans in shed epithelial cells or *O*-linked glycans attached to mucin glycoproteins, respectively, compared with taxa specializing in dietary glycans, like Firmicutes[69] (Fig. 3a). Experiments analysing the response of species in these phyla in vitro may reveal whether higher fitness during starvation is intrinsic to particular taxa. However, these responses are not universal. A comparative study across five vertebrate hosts and two gut regions found that changes to microbial diversity and composition during fasting were largely idiosyncratic, varying across host taxa and among hosts across gut regions[70]. Thus, the diet–microbiome–host triad may be more complex than previously thought. Questions arise as to the factors explaining such variability in response to long-term fasting. In hibernating mammals, temperature is a major confounding factor[58]. More generally, response variability could be due to differences in host lifestyles, resident microbiome composition and host physiological responses to fasting and other dietary perturbations. More work is needed to distinguish between shifts in microbial composition and metabolism that are directly due to dietary changes versus indirectly due to host physiological responses.

Dietary shifts

The composition of the gut microbiome can rapidly respond to dietary shifts, with qualitative changes within 24-48 h in some cases, as alterations to the set of available nutrients promote the growth of different sets of species[71]. For species that persist after a dietary shift, alterations in their abundance may be due to changes in growth rate as well as the competitive landscape. Species that decrease to very low abundance or become extinct after shifts are presumably starved of one or more essential nutrients, either due to the absence of such nutrients in the diet or their faster consumption by competitors (Fig. 2b,c). Consistent with this idea, among the Hadza hunter–gatherer population, the seasonal availability of various foods drives the disappearance and reappearance of certain taxa in their microbiomes[72].

In humanized mice (ex-germ-free mice colonized with a human stool sample), a shift from a fibre-rich diet to a fibre-poor diet results in many apparent extinctions, particularly of bacteria known to be adapted to fibre degradation[73]. However, such extinctions are sometimes reversible when a fibre-rich diet is restored[74], a result that confirms the importance of particular nutrients for directly maintaining these species at undetectable levels. During long-term maintenance on a fibre-poor diet, successive generations of mice exhibit progressively more extinct species[74], many of which do not recover when the fibre-rich diet is restored. It remains unclear whether these extinctions are physiologically similar to when starvation of planktonic bacteria induces cell death, as opposed to competitive interactions in the microbiome, including killing by other members as the microbiome composition changes. Quantifying the transcriptional signature of species as they go extinct during a diet shift could provide insights into their responses and whether starvation is the primary driver. Moreover, it is unclear how long the diet shift must persist to irreversibly change the microbiome, although the time scale over which dietary shifts exert deleterious starvation effects will probably be distinct across species and environments. Experiments to test the effect of these factors are difficult to carry out in humans but may be addressable in controlled in vitro environments or in gnotobiotic mice.

Many studies have focused on broad compositional shifts in the gut microbiome in response to dietary changes, which can involve bacteria that increase host inflammation (for example, Proteobacteria[75]), or produce beneficial compounds such as short-chain fatty acids (SCFAs) (for example, bifidobacteria and lactobacilli[76]). Diet-induced compositional changes can alter the ability of the host to digest fibre[77], proteins[78] and plant compounds such as isoflavones[79], which further modifies the nutrient landscape. Over time, the host and microbiome adapt to the new nutrient environment, with changes in the metabolic output and interactions in the microbiome that lead to further compositional changes. Shifts to a high-fat, low-fibre diet that mimics the diets of Western populations typically result in decreased microbial diversity and associated reductions in beneficial bacteria, potentially with negative consequences for host health[80]. By contrast, plant-based, vegan or vegetarian diets enhance diversity and the abundance of fibre-degrading microorganisms[80]. From a mechanistic standpoint, it is thought that fibre degradation has positive impacts on host health through SCFA production, which reduces inflammation and promotes intestinal barrier integrity[81]. However, this outcome relies on the host having a reservoir of fibre-degrading species, otherwise undigested fibre can have negative consequences on the immune system. In patients with irritable bowel disease, the inability to ferment undigested fibres often leads to pro-inflammatory responses and compromised gut barrier integrity[82]. Thus, the combined effects of diet and microbiome starvation on host health may depend on the context and hence be challenging to predict.

Some gut microorganisms have sufficient metabolic flexibility that they can regulate their preferred nutrients depending on what is provided in the host diet. Although this flexibility may be constrained in the context of a diverse community with many competitors, it can also provide a competitive advantage. For instance, a study using gnotobiotic mice colonized with a defined community of human gut bacteria showed that *Bacteroides cellulosilyticus* was able to reshape its transcriptional activity and resource use in response to dietary changes[83]. Its broader repertoire of polysaccharide utilization loci and greater metabolic flexibility compared with other species gave it a competitive edge in diverse nutrient environments. Bacteria can also acquire de novo mutations on relatively short time scales[84] that are adaptive during a dietary shift[85]. In a community, particularly one as dense as the gut microbiome, there may also be enhanced opportunities for horizontal transfer of genes important for survival in a new environment. It is an open question as to whether mutants are maladapted once a nutrient-rich environment is restored, akin to the trade-off in GASP mutants between stationary-phase survival and rapid growth[2,20]. Mapping the common and unique adaptations that result from fasting, caloric restriction, hibernation and dietary shifts, particularly in the highly controlled context of manipulating the nutrient environment of a single species or a community in vitro, could provide a rigorous framework for defining a spectrum of starvation.

In humans, dietary shifts from a high-sugar and low-fat diet to a low-sugar and high-fat diet starves bacteria well adapted to sugars and poorly adapted to fats (Fig. 3c, bottom). The duration of the shift and adaptation of gut commensals to starvation can have long-term impacts on gut microbiome composition[14,77]. The wide diversity of human diets may exert a similarly wide range of effects on the gut microbiome; currently, the dearth of information about microbial responses to starvation makes it challenging to predict host outcomes.

Another key aspect of dietary shifts involves variations in micronutrient and vitamin intake. For example, taurine is a semi-essential amino acid that can be synthesized by mammalian hosts from cysteine but is primarily obtained through diet. In humans, taurine intake can vary widely, from zero for plant-based (for example, vegan) diets to around 10 g per day, as taurine is abundant in shellfish, meats and energy drinks. In the human gut, *Bilophila wadsworthia* is a key taurine-utilizing bacterium[86] that thrives on animal-based diets[14]

(Fig. 3c, bottom). However, it is unclear how the gut microbiome collectively responds to taurine restriction or starvation in individuals on vegetarian or vegan diets compared with the taurine feast of animal-based diets. Given the importance of taurine for human health[87], a better understanding of diet-induced variations in taurine levels and their potential effects on host metabolism, including the endogenous synthesis of taurine, is needed to determine the full scope of nutrients for which the microbiome faces shortages.

Conclusions and future perspectives

Nutrient availability is an integral part of how microbiomes assemble; therefore, understanding how microorganisms respond when nutrients become scarce should be a major focus of future research. As most bacteria on Earth are probably in a state of starvation, an improved understanding of the microbial responses to starvation will be critical to fully grasp microbiome dynamics and stability and could provide opportunities for the rational design of nutrition-based interventions. Although we know very little about microbial starvation responses in the gut, recent studies have started to derive relatively simple assembly rules for communities in nutrient-replete conditions[53,88]. Hopefully, similar mechanistic insights will be realized for the complex realities of nutrient-deprived environments. Targeted studies in vitro and in animal models should reveal the extent to which community behaviours can be predicted based on the starvation responses of each constituent microorganism. Moreover, the development of devices that can sample the gut microbiome in situ (Box 1) could enable the development of novel microbiome engineering approaches. For instance, targeted nutrient delivery to particular gut regions to promote beneficial species while starving undesirable bacteria or control of local inflammation through nutrients could be impactful strategies to promote gut health.

Despite the potential future importance of these research areas, many challenges remain. The gut is a complex ecosystem, and changing a single nutrient factor can have unpredictable consequences through direct, indirect and higher-order interactions. As a result, microbiome variability across individuals and strain-dependent metabolic capabilities may require personalized interventions. Although animal models provide some control over host variables, such as microbiome and diet, important physiological differences with respect to human behaviour, including feeding patterns and host metabolism, may be integral to fully understanding starvation conditions. Because starvation affects microbial abundance, measurement strategies that quantify both absolute and relative abundances as well as viability may be critical (Box 1).

Dietary changes lead to significant shifts not only in the gut microbiome but also in host physiology. The primary goal of the host is to maintain homeostasis and to ensure that its energy needs are met. To achieve this goal, animals have developed mechanisms to respond to nutrient perturbations, such as shifting to ketosis during carbohydrate restriction[89]. In this physiological state, lipid stores are mobilized and fat becomes the primary fuel source for adipocytes and myocytes. These highly evolved strategies to deal with nutrient-based stressors distinguish the host from the more malleable gut microbiome, which can adapt to dietary fluctuations through the introduction of new species and by exploiting the metabolic flexibility of its members. Host–microbe symbioses may be particularly beneficial during nutrient deprivation. This is the case for microbiome-mediated nitrogen recycling that benefits hibernating 13-lined ground squirrels during the winter fast[90]. Another example is when the endosymbiont *Buchnera aphidicola* increases the expression of genes for essential amino acid synthesis to aid its aphid host during suboptimal nutrition[91,92]. Thus, dietary interventions designed to enhance host resilience to nutrient stress need to consider the interplay between host homeostasis and promotion of a beneficial gut microbiome.

Recent studies have highlighted the role of diet in shaping health outcomes, such as the use of ketogenic diets to manage epilepsy[93] and microbiome-directed complementary food formulations to counteract malnutrition in children[94,95]. However, unlike drugs and pharmaceuticals for which we typically have detailed knowledge of specific molecule–target interactions, our understanding of how nutrients affect the host and microbiome at a molecular level is limited. This knowledge gap highlights the need for future research to determine these interactions, with the aim of combining precision pharmacology with precision nutrition to optimize health outcomes.

The evolutionary consequences of prolonged nutrient deprivation present another intriguing area of study. Investigating these evolutionary processes could reveal new avenues for manipulating the microbiome in ways that favour beneficial species and suppress harmful ones.

BOX 1

Tools for studying nutrient starvation in microbiomes

Interrogation of bacterial responses to nutrient starvation will benefit from high-throughput and precise measurements of single-cell growth and viability, as well as strategies to study starvation in complex bacterial communities. Characterization of microbial metabolic activity as a proxy for nutrient availability in natural environments is challenging, although methodologies such as nanoSIMS can quantify the incorporation of labelled substrates in single microbial cells in complex communities[96]. Live/dead cell staining can be used to quantify membrane integrity as a proxy for cell viability[97], and methods based on fluorescence in situ hybridization can be used for differentiating species and determining their spatial distribution in a community[98]. Live imaging and flow cytometry of obligate anaerobes, as many gut commensals are, is challenging; hence, their growth and viability remain underexplored. It will be fascinating to explore the effects of nutrient starvation on anaerobic species with recently developed tools—such as droplet microfluidics for high-throughput cultivation[99], single-cell RNA sequencing for transcriptional programming[100] and fluorescent proteins that function in anaerobic environments[101]—to analyse subcellular organization.

A particularly important aspect of starvation is the potential for cell death and its ensuing effects on the population. Lysed cells form a mixture of dead bacterial biomass and debris known as 'necromass', which can in principle be used by other microorganisms for growth. Bacterial necromass recycling has been studied in marine[102] and soil[103] environments using ^{13}C-labelling, which has revealed substantial variability across species but potentially as much as ~25% assimilation[103]. Given the variable and stressful conditions in the gut, including shifts in nutrient availability, variation in pH and oxygen levels and the presence of exogenous stressors like antibiotics and host-derived immune factors, it would not be surprising to observe a high fraction of dead cells and biomass turnover. Moreover, interbacterial competition, such as toxin production or type VI secretion system-dependent killing known to occur in the gut environment[104], can contribute to necromass, whereas starved cells may be sensitized to killing[105,106]. However, gut necromass dynamics remain largely unexplored, which is partly due to the difficulty of sampling in the human gut. The development of noninvasive devices that sample multiple regions of the human gut and are sufficiently inexpensive for longitudinal sampling[107,108], combined with high-throughput cultivation plus functional and metabolic profiling of model bacterial communities[51,88,109,110], could help uncover the diversity of bacterial survival strategies across gut environments and their potential implications for health and disease.

Looking ahead, the potential to engineer the gut microbiome through targeted nutrient manipulation is both exciting and vast. The future of microbiome research lies not only in understanding how these communities assemble and function under optimal conditions but also in deciphering how they survive, adapt and even thrive when nutrients are scarce. Through a refined understanding of microbial survival mechanisms and community dynamics under starvation conditions, we can begin to explore therapeutic strategies that leverage these insights.

References

1. Kjelleberg, S. *Starvation in Bacteria* (Springer, 1993).
2. Finkel, S. E. Long-term survival during stationary phase: evolution and the GASP phenotype. *Nat. Rev. Microbiol.* **4**, 113–120 (2006).
3. Bernhardt, J., Weibezahn, J., Scharf, C. & Hecker, M. *Bacillus subtilis* during feast and famine: visualization of the overall regulation of protein synthesis during glucose starvation by proteome analysis. *Genome Res.* **13**, 224–237 (2003).
4. Schofield, W. B., Zimmermann-Kogadeeva, M., Zimmermann, M., Barry, N. A. & Goodman, A. L. The stringent response determines the ability of a commensal bacterium to survive starvation and to persist in the gut. *Cell Host Microbe* **24**, 120–132 (2018).
5. Townsend, G. E. et al. A master regulator of *Bacteroides thetaiotaomicron* gut colonization controls carbohydrate utilization and an alternative protein synthesis factor. *mBio* https://doi.org/10.1128/mbio.03221-19 (2020).
6. Ontai-Brenning, A., Hamchand, R., Crawford, J. M. & Goodman, A. L. Gut microbes modulate (p)ppGpp during a time-restricted feeding regimen. *mBio* **14**, e0190723 (2023).
7. Groisman, E. A., Han, W. & Krypotou, E. Advancing the fitness of gut commensal bacteria. *Science* **382**, 766–768 (2023).
8. Han, W. et al. Gut colonization by *Bacteroides* requires translation by an EF-G paralog lacking GTPase activity. *EMBO J.* **42**, e112372 (2023).
9. Liu, B. et al. Starvation responses impact interaction dynamics of human gut bacteria *Bacteroides thetaiotaomicron* and *Roseburia intestinalis*. *ISME J.* **17**, 1940–1952 (2023).
10. Watson, S. P., Clements, M. O. & Foster, S. J. Characterization of the starvation-survival response of *Staphylococcus aureus*. *J. Bacteriol.* **180**, 1750–1758 (1998).
11. Berney, M. & Cook, G. M. Unique flexibility in energy metabolism allows mycobacteria to combat starvation and hypoxia. *PLoS ONE* **5**, e8614 (2010).
12. Zeng, X. et al. Gut bacterial nutrient preferences quantified in vivo. *Cell* **185**, 3441–3456 (2022).
13. Zarrinpar, A., Chaix, A., Yooseph, S. & Panda, S. Diet and feeding pattern affect the diurnal dynamics of the gut microbiome. *Cell Metab.* **20**, 1006–1017 (2014).
14. David, L. A. et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* **505**, 559–563 (2014).
15. Koropatkin, N. M., Cameron, E. A. & Martens, E. C. How glycan metabolism shapes the human gut microbiota. *Nat. Rev. Microbiol.* **10**, 323–335 (2012).
16. Monod, J. The growth of bacterial cultures. *Annu. Rev. Microbiol.* https://doi.org/10.1146/annurev.mi.03.100149.002103 (1949).
17. Dworkin, J. & Harwood, C. S. Metabolic reprogramming and longevity in quiescence. *Annu. Rev. Microbiol.* **76**, 91–111 (2022).
18. Kramer, J., Özkaya, Ö & Kümmerli, R. Bacterial siderophores in community and host interactions. *Nat. Rev. Microbiol.* **18**, 152–163 (2020).
19. Lennon, J. T. & Jones, S. E. Microbial seed banks: the ecological and evolutionary implications of dormancy. *Nat. Rev. Microbiol.* **9**, 119–130 (2011).
20. Avrani, S., Katz, S. & Hershberg, R. Adaptations accumulated under prolonged resource exhaustion are highly transient. *mSphere* https://doi.org/10.1128/msphere.00388-20 (2020).
21. Shoemaker, W. R. et al. Microbial population dynamics and evolutionary outcomes under extreme energy limitation. *Proc. Natl Acad. Sci. USA* **118**, e2101691118 (2021).
22. Katz, S. et al. Dynamics of adaptation during three years of evolution under long-term stationary phase. *Mol. Biol. Evol.***38**, 2778–2790 (2021).
23. Ratib, N. R., Seidl, F., Ehrenreich, I. M. & Finkel, S. E. Evolution in long-term stationary-phase batch culture: emergence of divergent *Escherichia coli* lineages over 1,200 days. *mBio* https://doi.org/10.1128/mbio.03337-20 (2021).
24. Boutte, C. C. & Crosson, S. Bacterial lifestyle shapes stringent response activation. *Trends Microbiol.* **21**, 174–180 (2013).
25. Irving, S. E., Choudhury, N. R. & Corrigan, R. M. The stringent response and physiological roles of (pp)pGpp in bacteria. *Nat. Rev. Microbiol.* **19**, 256–271 (2021).
26. Battesti, A., Majdalani, N. & Gottesman, S. The RpoS-mediated general stress response in *Escherichia coli*. *Annu. Rev. Microbiol.* **65**, 189–213 (2011).
27. Boutte, C. C. & Crosson, S. The complex logic of stringent response regulation in *Caulobacter crescentus*: starvation signalling in an oligotrophic environment. *Mol. Microbiol.* **80**, 695–714 (2011).
28. Hallgren, J., et al. Phosphate starvation decouples cell differentiation from DNA replication control in the dimorphic bacterium *Caulobacter crescentus*. *PLoS Genet.* **19**, e1010882 (2023).
29. Krypotou, E. et al. Bacteria require phase separation for fitness in the mammalian gut. *Science* **379**, 1149–1156 (2023).
30. Browne, H. P., et al. Host adaptation in gut Firmicutes is associated with sporulation loss and altered transmission cycle. *Genome Biol.* **22**, 204 (2021).
31. Egan, M., Dempsey, E., Ryan, C. A., Ross, R. P. & Stanton, C. The sporobiota of the human gut. *Gut Microbes* **13**, 1863134 (2021).
32. Lawley, T. D. et al. Antibiotic treatment of *Clostridium difficile* carrier mice triggers a supershedder state, spore-mediated transmission, and severe disease in immunocompromised hosts. *Infect. Immun.* **77**, 3661–3669 (2009).
33. Browne, H. P. et al. Culturing of 'unculturable' human microbiota reveals novel taxa and extensive sporulation. *Nature* **533**, 543–546 (2016).
34. Cesar, S., Willis, L. & Huang, K. C. Bacterial respiration during stationary phase induces intracellular damage that leads to delayed regrowth. *iScience* **25**, 103765 (2022).
35. Şimşek, E. & Kim, M. Power-law tail in lag time distribution underlies bacterial persistence. *Proc. Natl Acad. Sci. USA* **116**, 17635–17640 (2019).
36. Kaplan, Y. et al. Observation of universal ageing dynamics in antibiotic persistence. *Nature* **600**, 290–294 (2021).
37. Moreno-Gámez, S. et al. Wide lag time distributions break a trade-off between reproduction and survival in bacteria. *Proc. Natl Acad. Sci. USA* **117**, 18729–18736 (2020).
38. Schink, S. J. et al. MetA is a "thermal fuse" that inhibits growth and protects *Escherichia coli* at elevated temperatures. *Cell Rep.* **40**, 111290 (2022).
39. Brauer, A. M., Shi, H., Levin, P. A. & Huang, K. C. Physiological and regulatory convergence between osmotic and nutrient stress responses in microbes. *Curr. Opin. Cell Biol.* **81**, 102170 (2023).
40. Zimmerman, C. A. et al. A gut-to-brain signal of fluid osmolarity controls thirst satiation. *Nature* **568**, 98–102 (2019).
41. Tagkopoulos, I., Liu, Y.-C. & Tavazoie, S. Predictive behavior within microbial genetic networks. *Science* **320**, 1313–1317 (2008).
42. Schwartz, D. A., Shoemaker, W. R., Măgălie, A., Weitz, J. S. & Lennon, J. T. Bacteria–phage coevolution with a seed bank. *ISME J.* **17**, 1315–1325 (2023).

43. Murdoch, C. C. & Skaar, E. P. Nutritional immunity: the battle for nutrient metals at the host–pathogen interface. *Nat. Rev. Microbiol.* **20**, 657–670 (2022).
44. Liang, Q. et al. Sialic acid plays a pivotal role in licensing *Citrobacter rodentium*'s transition from the intestinal lumen to a mucosal adherent niche. *Proc. Natl Acad. Sci. USA* **120**, e2301115120 (2023).
45. Pal, R. R. et al. Pathogenic *E. coli* extracts nutrients from infected host cells utilizing injectisome components. *Cell* **177**, 683–696 (2019).
46. van der Meer-Janssen, Y. P., van Galen, J., Batenburg, J. J. & Helms, J. B. Lipids in host–pathogen interactions: pathogens exploit the complexity of the host cell lipidome. *Prog. Lipid Res.* **49**, 1–26 (2010).
47. Kuhn, H. W., et al. BB0562 is a nutritional virulence determinant with lipase activity important for *Borrelia burgdorferi* infection and survival in fatty acid deficient environments. *PLoS Pathog.* **17**, e1009869 (2021).
48. Abu Kwaik, Y. & Bumann, D. Microbial quest for food in vivo: 'nutritional virulence' as an emerging paradigm. *Cell. Microbiol.* **15**, 882–890 (2013).
49. Kaiser, J. C. & Heinrichs, D. E. Branching out: alterations in bacterial physiology and virulence due to branched-chain amino acid deprivation. *mBio* https://doi.org/10.1128/mbio.01188-18 (2018).
50. Caballero-Flores, G., Pickard, J. M. & Núñez, G. Microbiota-mediated colonization resistance: mechanisms and regulation. *Nat. Rev. Microbiol.* **21**, 347–360 (2023).
51. Aranda-Díaz, A. et al. Establishment and characterization of stable, diverse, fecal-derived in vitro microbial communities that model the intestinal microbiota. *Cell Host Microbe* **30**, 260–272 (2022).
52. Spragge, F. et al. Microbiome diversity protects against pathogens by nutrient blocking. *Science* **382**, eadj3502 (2023).
53. Ho, P.-Y., Nguyen, T. H., Sanchez, J. M., DeFelice, B. C. & Huang, K. C. Resource competition predicts assembly of gut bacterial communities in vitro. *Nat. Microbiol.* **9**, 1036–1048 (2024).
54. Hammarlund, S. P., Chacón, J. M. & Harcombe, W. R. A shared limiting resource leads to competitive exclusion in a cross-feeding system. *Environ. Microbiol.* **21**, 759–771 (2019).
55. Olsen, L., Thum, E. & Rohner, N. Lipid metabolism in adaptation to extreme nutritional challenges. *Dev. Cell* **56**, 1417–1429 (2021).
56. Carey, H. V., Walters, W. A. & Knight, R. Seasonal restructuring of the ground squirrel gut microbiota over the annual hibernation cycle. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **304**, R33–R42 (2013).
57. Dill-McFarland, K. A. et al. Hibernation alters the diversity and composition of mucosa-associated bacteria while enhancing antimicrobial defence in the gut of 13-lined ground squirrels. *Mol. Ecol.* **23**, 4658–4669 (2014).
58. Sonoyama, K. et al. Response of gut microbiota to fasting and hibernation in Syrian hamsters. *Appl. Environ. Microbiol.* **75**, 6451–6456 (2009).
59. Sommer, F. et al. The gut microbiota modulates energy metabolism in the hibernating brown bear *Ursus arctos*. *Cell Rep.* **14**, 1655–1661 (2016).
60. Ho, P.-Y., Good, B. H. & Huang, K. C. Competition for fluctuating resources reproduces statistics of species abundance over time across wide-ranging microbiotas. *eLife* **11**, e75168 (2022).
61. Costello, E. K., Gordon, J. I., Secor, S. M. & Knight, R. Postprandial remodeling of the gut microbiota in Burmese pythons. *ISME J.* **4**, 1375–1385 (2010).
62. Di Francesco, A., Di Germanio, C., Bernier, M. & De Cabo, R. A time to fast. *Science* **362**, 770–775 (2018).
63. Maifeld, A. et al. Fasting alters the gut microbiome reducing blood pressure and body weight in metabolic syndrome patients. *Nat. Commun.* **12**, 1970 (2021).
64. Mesnage, R., Grundler, F., Schwiertz, A., Le Maho, Y. & de Toledo, F. W. Changes in human gut microbiota composition are linked to the energy metabolic switch during 10 d of Buchinger fasting. *J. Nutr. Sci.* **8**, e36 (2019).
65. Paukkonen, I., Törrönen, E.-N., Lok, J., Schwab, U. & El-Nezami, H. The impact of intermittent fasting on gut microbiota: a systematic review of human studies. *Front. Nutr.* **11**, 1342787 (2024).
66. Li, G. et al. Intermittent fasting promotes white adipose browning and decreases obesity by shaping the gut microbiota. *Cell Metab.* **26**, 672–685 (2017).
67. von Schwartzenberg, R. J. et al. Caloric restriction disrupts the microbiota and colonization resistance. *Nature* **595**, 272–277 (2021).
68. Depommier, C. et al. Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study. *Nat. Med.* **25**, 1096–1103 (2019).
69. Sonnenburg, J. L. et al. Glycan foraging in vivo by an intestine-adapted bacterial symbiont. *Science* **307**, 1955–1959 (2005).
70. Kohl, K. D., Amaya, J., Passement, C. A., Dearing, M. D. & McCue, M. D. Unique and shared responses of the gut microbiota to prolonged fasting: a comparative study across five classes of vertebrate hosts. *FEMS Microbiol. Ecol.* **90**, 883–894 (2014).
71. Leeming, E. R., Johnson, A. J., Spector, T. D. & Le Roy, C. I. Effect of diet on the gut microbiota: rethinking intervention duration. *Nutrients* **11**, 2862 (2019).
72. Smits, S. A. et al. Seasonal cycling in the gut microbiome of the Hadza hunter–gatherers of Tanzania. *Science* **357**, 802–806 (2017).
73. Desai, M. S. et al. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell* **167**, 1339–1353 (2016).
74. Sonnenburg, E. D. et al. Diet-induced extinctions in the gut microbiota compound over generations. *Nature* **529**, 212–215 (2016).
75. Shin, N.-R., Whon, T. W. & Bae, J.-W. Proteobacteria: microbial signature of dysbiosis in gut microbiota. *Trends Biotechnol.* **33**, 496–503 (2015).
76. Fusco, W. et al. Short-chain fatty-acid-producing bacteria: key components of the human gut microbiota. *Nutrients* **15**, 2211 (2023).
77. Sonnenburg, E. D. & Sonnenburg, J. L. Starving our microbial self: the deleterious consequences of a diet deficient in microbiota-accessible carbohydrates. *Cell Metab.* **20**, 779–786 (2014).
78. Windey, K., De Preter, V. & Verbeke, K. Relevance of protein fermentation to gut health. *Mol. Nutr. Food Res.* **56**, 184–196 (2012).
79. Atkinson, C., Frankenfeld, C. L. & Lampe, J. W. Gut bacterial metabolism of the soy isoflavone daidzein: exploring the relevance to human health. *Exp. Biol. Med.* **230**, 155–170 (2005).
80. Beam, A., Clinger, E. & Hao, L. Effect of diet and dietary components on the composition of the gut microbiota. *Nutrients* **13**, 2795 (2021).
81. Martin-Gallausiaux, C., Marinelli, L., Blottière, H. M., Larraufie, P. & Lapaque, N. SCFA: mechanisms and functional importance in the gut. *Proc. Nutr. Soc.* **80**, 37–49 (2021).
82. Armstrong, H. K. et al. Unfermented β-fructan fibers fuel inflammation in select inflammatory bowel disease patients. *Gastroenterology* **164**, 228–240 (2023).

83. McNulty, N. P., et al. Effects of diet on resource utilization by a model human gut microbiota containing *Bacteroides cellulosilyticus* WH2, a symbiont with an extensive glycobiome. *PLoS Biol.* **11**, e1001637 (2013).
84. Dapa, T. et al. Within-host evolution of the gut microbiome. *Curr. Opin. Microbiol.* **71**, 102258 (2023).
85. Dapa, T., Ramiro, R. S., Pedro, M. F., Gordo, I. & Xavier, K. B. Diet leaves a genetic signature in a keystone member of the gut microbiota. *Cell Host Microbe* **30**, 183–199 (2022).
86. Devkota, S. et al. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in *Il10*$^{-/-}$ mice. *Nature* **487**, 104–108 (2012).
87. Singh, P. et al. Taurine deficiency as a driver of aging. *Science* **380**, eabn9257 (2023).
88. Aranda-Díaz, A., et al. Assembly of stool-derived bacterial communities follows "early-bird" resource utilization dynamics. *Cell Syst.* **16**, 101240 (2025).
89. Kolb, H., et al. Ketone bodies: from enemy to friend and guardian angel. *BMC Med.* **19**, 313 (2021).
90. Regan, M. D. et al. Nitrogen recycling via gut symbionts increases in ground squirrels over the hibernation season. *Science* **375**, 460–463 (2022).
91. Start, C. C., Anderson, C. M. H., Gatehouse, A. M. R. & Edwards, M. G. Dynamic response of essential amino acid biosynthesis in *Buchnera aphidicola* to supplement sub-optimal host nutrition. *J. Insect Physiol.* **158**, 104683 (2024).
92. Akman Gündüz, E. & Douglas, A. Symbiotic bacteria enable insect to use a nutritionally inadequate diet. *Proc. R. Soc. B Biol. Sci.* **276**, 987–991 (2009).
93. Lum, G. R., et al. Ketogenic diet therapy for pediatric epilepsy is associated with alterations in the human gut microbiome that confer seizure resistance in mice. *Cell Rep.* **42**, 113521 (2023).
94. Gehrig, J. L. et al. Effects of microbiota-directed foods in gnotobiotic animals and undernourished children. *Science* **365**, eaau4732 (2019).
95. Chen, R. Y. et al. A microbiota-directed food intervention for undernourished children. *N. Engl. J. Med.* **384**, 1517–1528 (2021).
96. Musat, N., Foster, R., Vagner, T., Adam, B. & Kuypers, M. M. Detecting metabolic activities in single cells, with emphasis on nanoSIMS. *FEMS Microbiol. Rev.* **36**, 486–511 (2012).
97. Stevenson, T. J., Duddleston, K. N. & Buck, C. L. Effects of season and host physiological state on the diversity, density, and activity of the arctic ground squirrel cecal microbiota. *Appl. Environ. Microbiol.* **80**, 5611–5622 (2014).
98. Shi, H. et al. Highly multiplexed spatial mapping of microbial communities. *Nature* **588**, 676–681 (2020).
99. Villa, M. M. et al. Interindividual variation in dietary carbohydrate metabolism by gut bacteria revealed with droplet microfluidic culture. *mSystems* https://doi.org/10.1128/msystems.00864-19 (2020).
100. Wang, B. et al. Single-cell massively-parallel multiplexed microbial sequencing (M3-seq) identifies rare bacterial populations and profiles phage infection. *Nat. Microbiol.* **8**, 1846–1862 (2023).
101. Chia, H. E., Marsh, E. N. G. & Biteen, J. S. Extending fluorescence microscopy into anaerobic environments. *Curr. Opin. Chem. Biol.* **51**, 98–104 (2019).
102. Müller, A. L. et al. Bacterial interactions during sequential degradation of cyanobacterial necromass in a sulfidic arctic marine sediment. *Environ. Microbiol.* **20**, 2927–2940 (2018).
103. Geesink, P., et al. Bacterial necromass is rapidly metabolized by heterotrophic bacteria and supports multiple trophic levels of the groundwater microbiome. *Microbiol. Spectr.* **10**, e0043722 (2022).
104. Coyne, M. J. & Comstock, L. E. Type VI secretion systems and the gut microbiota. *Microbiol. Spectr.* https://doi.org/10.1128/microbiolspec.psib-0009-2018 (2019).
105. Troselj, V., Treuner-Lange, A., Søgaard-Andersen, L. & Wall, D. Physiological heterogeneity triggers sibling conflict mediated by the type VI secretion system in an aggregative multicellular bacterium. *mBio* https://doi.org/10.1128/mbio.01645-17 (2018).
106. Mashruwala, A. A., Qin, B. & Bassler, B. L. Quorum-sensing- and type VI secretion-mediated spatiotemporal cell death drives genetic diversity in *Vibrio cholerae*. *Cell* **185**, 3966–3979 (2022).
107. Folz, J. et al. Human metabolome variation along the upper intestinal tract. *Nat. Metab.* **5**, 777–788 (2023).
108. Shalon, D. et al. Profiling the human intestinal environment under physiological conditions. *Nature* **617**, 581–591 (2023).
109. Baker, J. L. et al. *Klebsiella* and *Providencia* emerge as lone survivors following long-term starvation of oral microbiota. *Proc. Natl Acad. Sci. USA* **116**, 8499–8504 (2019).
110. Cheng, A. G. et al. Design, construction, and in vivo augmentation of a complex gut microbiome. *Cell* **185**, 3617–3636 (2022).

Acknowledgements

We thank members of the Huang Laboratory for helpful discussions. This work was funded by NSF Award EF-2125383 (to K.C.H.) and NIH Award RM1 GM135102 (to K.C.H.). K.C.H. is a Chan Zuckerberg Biohub Investigator.

Author contributions

Conceptualization: S.E. and K.C.H. Writing original draft: all authors. Writing, review and editing: all authors. Funding acquisition: K.C.H.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence should be addressed to Sylvie Estrela or Kerwyn Casey Huang.

Peer review information *Nature Microbiology* thanks Hannah Carey and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.