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REVIEW

Salmonella versus the Microbiome

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SUMMARY A balanced gut microbiota contributes to health, but the mechanisms maintaining homeostasis remain elusive. Microbiota assembly during infancy is governed by competition between species and by environmental factors, termed habitat filters, that determine the range of successful traits within the microbial community. These habitat filters include the diet, host-derived resources, and microbiota-derived metabolites, such as short-chain fatty acids. Once the microbiota has matured, competition and habitat filtering prevent engraftment of new microbes, thereby providing protection against opportunistic infections. Competition with endogenous *Enterobacterales*, habitat filtering by short-chain fatty acids, and a host-derived habitat filter, epithelial hypoxia, also contribute to colonization resistance against *Salmonella* serovars. However, at a high challenge dose, these frank pathogens can overcome colonization resistance by

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using their virulence factors to trigger intestinal inflammation. In turn, inflammation increases the luminal availability of host-derived resources, such as oxygen, nitrate, tetrathionate, and lactate, thereby creating a state of abnormal habitat filtering that enables the pathogen to overcome growth inhibition by short-chain fatty acids. Thus, studying the process of ecosystem invasion by *Salmonella* serovars clarifies that colonization resistance can become weakened by disrupting host-mediated habitat filtering. This insight is relevant for understanding how inflammation triggers dysbiosis linked to noncommunicable diseases, conditions in which endogenous *Enterobacterales* expand in the fecal microbiota using some of the same growth-limiting resources required by *Salmonella* serovars for ecosystem invasion. In essence, ecosystem invasion by *Salmonella* serovars suggests that homeostasis and dysbiosis simply represent states where competition and habitat filtering are normal or abnormal, respectively.

KEYWORDS colonization resistance, microbiome, microbiota, *Salmonella*

INTRODUCTION

The idea that communicable diseases are due to infection with pathogens emerged with the inception of Louis Pasteur's germ theory in 1865 (1) and Robert Koch's invention of approaches to establish causality in 1882 (2). These game-changing discoveries became a guiding principle of a new discipline, bacteriology, which is the precursor of modern-day microbiology and immunology. Subsequent discoveries of diphtheria toxin in 1888 (3) and Shiga toxin in 1903 (4, 5) gave rise to the concept that pathogens cause disease because they elaborate virulence factors that manipulate host physiology. The century following these seminal discoveries has seen countless studies on how virulence factors enable pathogens to overcome host defenses in individuals with an intact immune system to cause disease. However, this historic focus on host pathogen interaction has left a third player in obscurity, our host-associated microbial communities, the microbiota.

Although research from the 1950s shows that a disruption of the microbiota enhances susceptibility to infection (6), the idea that virulence factors could play a role in overcoming growth inhibition by resident microbial communities was not explored until microbiota analysis became possible by advances in sequencing technologies during the first decade of the 21st century (7–9). Subsequent work shows that virulence factors can target the host to manipulate the environment inhabited by the microbiota (10–13). Through this chain of events, virulence factors can alter the microbiome, which is
T1/F1 defined ecologically as the microbiota and its host environment (14, 15) (Table 1 and Fig. 1). The fact that mucosal pathogens can use virulence factors to manipulate the microbiome renders them useful tools for microbiome research (16). As a result, studies on how virulence factors manipulate the host/microbiota interface are beginning to assemble into a framework for a "new bacteriology" which studies pathogen physiology and gene regulation in the natural context of the microbiome (17).

Here, we will review this new chapter in bacteriology using the paradigm that spearheaded many advances: studies on the pathogenesis of *Salmonella* serovars. We will start by briefly outlining the conceptual framework of microbiome research, followed by discussing how the microbiome protects against infection and how *Salmonella* serovars use their virulence factors to overcome this line of defense. *Salmonella enterica* subspecies *enterica* serovar Typhimurium (*S.* Typhimurium) is commonly studied as a representative of the species, because it is an important human pathogen (18, 19). *S.* Typhimurium was first described as the causative agent of a typhoid-like disease in mice (20), a mammalian species that is commonly used to model the disease process (21). The luminal *S.* Typhimurium population reaches high numbers in the murine large intestine (22), which also harbors the largest microbial community in the human body. Most of our discussion will therefore revolve around the interaction of *S.* Typhimurium with the microbiota of the large intestine.

TABLE 1 Microbiome vocabulary

Term	Definition
Colonization resistance	Mechanisms executed by microbiota-nourishing immunity that prevent engraftment of a specific microorganism through competition and habitat filtering
Communicable disease	Disease caused by an infectious agent that is transmitted from one animal or person to another, through direct contact, or indirectly through fomites or vectors
Dominant taxa	The most abundant taxa in a community, exerting a strong influence on other taxa
Dysbiosis	A state of abnormal competition or habitat filtering
Ecosystem engineering	The process by which a keystone species modifies a habitat, thereby strongly effecting other organisms
Facultative anaerobic bacteria	Bacteria that can grow in the presence of (and often can respire) oxygen at atmospheric levels but can grow fermentatively when oxygen is absent
Foundation species	A species that provides the foundation for a habitat by physically modifying the environment, thereby structuring communities of other organisms
Habitat filters	Factors that select for microbial traits licensing growth and survival in a host habitat patch
Habitat patch	The dynamic environment on a host surface where the microbiota assembles
Historical contingency	Dependence of the taxon composition on the order and timing of species arrival during microbiota assembly
Homeostasis	The outcome of normal competition and normal habitat filtering, which in turn generates microbiota resistance and microbiota resilience
Keystone species	A species that has a disproportionally large effect on its habitat relative to its abundance within the microbial community
Microbiome	The microbiota and its host environment
Microbiota	Host-associated microbial communities
Microbiota-nourishing immunity	A subdivision of the immune system, composed of the microbiota and host-derived habitat filters, which confers colonization resistance on body surfaces
Microbiota resilience	The ability of the microbiota to return to a healthy equilibrium state after perturbation
Microbiota resistance	Temporal stability in the taxon composition of mature host-associated microbial communities
Niche modification	A mechanism that uses microbiota-mediated habitat filtering to prevent engraftment of microorganisms that harbor inadequate trait combinations
Niche preemption	A mechanism that uses direct competition for critical resources with members of the microbiota to prevent engraftment of similar microorganisms
Noncommunicable disease	Medical condition that is not caused by an infectious agent but is due to an underlying defect in host physiology that is not transmissible
Nutrient niche	An ecological position defined by critical resources that support growth of a suitable occupant
Obligate anaerobic bacteria	Bacteria that cannot respire oxygen and cannot grow under atmospheric oxygen concentrations
Opportunistic infection	Infection with opportunistic pathogen
Opportunistic pathogens	Microbes associated with disease in immunocompromised members of a host species
Pathogens (or frank pathogens)	Microbes associated with communicable diseases in immunocompetent members of a host species
Priority effects	The ability of resident microbes to prevent engraftment of new microorganisms through niche preemption and/or niche modification
Sterilizing immunity	The part of our immune system that preserves tissue sterility by detecting and distinguishing microbial intruders from self and subsequently triggering innate and adaptive immune responses aimed at removing the intruder from tissue
Virulence factors	Molecules produced by pathogens to overcome host defenses and cause disease

THE GUT MICROBIOME

Competition and Habitat Filtering Govern Gut Microbiota Assembly

Principles of community assembly. The infant is thought to be sterile *in utero* (23), suggesting that birth marks the beginning of microbiota assembly. According to ecological theory of plant community assembly, this process is governed by two drivers: competition and habitat filtering. In plant communities, competition involves interactions among species whereas habitat filtering encompasses interactions between species and their abiotic environment (24). These assembly rules also apply to the human gut microbiota (25, 26), except here the host provides a biotic environment that responds dynamically to microbiota-derived signals, which adds additional layers of complexity.

The host could be viewed as an ecological foundation species (27), who filters the habitat of the gut microbiota using biotic factors, which include physical barriers (e.g., peristalsis), the emission of chemicals (e.g., gastric acid and bile acids), the excretion of antimicrobial proteins (e.g., defensins), the secretion of immunoglobulin A (IgA), and epithelial release of resources that shape microbial growth (e.g., mucin) (28, 29). In addition to host-derived habitat filters, the range of successful traits within the

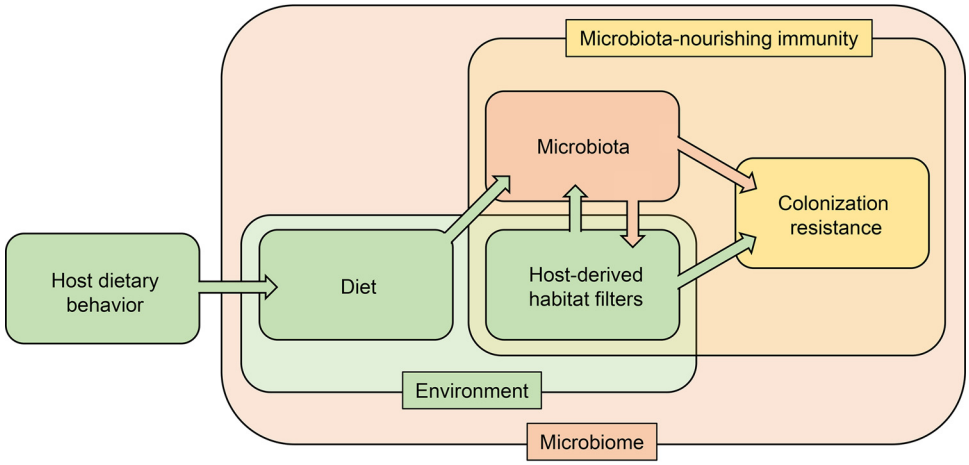


FIG 1 Composition of the term microbiome. The microbiome is defined as the microbiota and its environment. The latter is determined by host-derived habitat filters and the diet, which is controlled by host behavior. Host-derived habitat filters shape the size, species composition and biogeography of the microbiota and in turn the microbiota contributes to host nutrition and immune education. Microbiota-nourishing immunity is composed of the microbiota and host-derived habitat filters, which form a host-microbe chimera that functions in conferring colonization resistance.

microbiota in the gastrointestinal tract is influenced by microbiota-derived habitat filters (e.g., short-chain fatty acids) and by an important abiotic habitat filter: the diet (30). Since the choice of diet is governed by host behavior, diet could also be viewed as an aspect of host-mediated habitat filtering (Fig. 1).

Competition and habitat filtering select for different functional traits of coexisting species. Competition is common among pairs of similar species and can lead to competitive exclusion, thereby limiting the number of similar coexisting species (31). In contrast, habitat filtering limits the range of successful strategies among coexisting species (32), which can drive species with particular traits or phenotypes to dominate the microbial community.

Habitat filtering establishes dominant taxa in the colonic microbiota. One important host-derived habitat filter that shapes the abundance of species inhabiting the colon is epithelial hypoxia. The healthy colonic epithelium permanently resides in a state of physiological hypoxia (<1% oxygen) (33), which limits the amount of oxygen diffusing into the lumen of the colon, thereby maintaining anaerobiosis (34). As a result, obligate anaerobic bacteria dominate the microbial community in the colon (35), a phenotypic convergence in a key ecological trait. Elevating epithelial oxygenation disrupts this biotic habitat filter, thereby increasing oxygen availability in the intestinal lumen, which results in an expansion of facultative anaerobic bacteria in the colonic microbiota (36), a microbial signature of dysbiosis (37).

A second important habitat filter for the colonic microbiota is the diet. Milk oligosaccharides in breast milk represent an important maternal habitat filter, as these dietary carbohydrates do not nurture the infant, are poorly absorbed in the small intestine, and reach the colon (38). Milk oligosaccharides drive a predominance of *Bifidobacteriaceae* (phylum *Actinobacteria*) because these obligate anaerobes are among a select few bacteria that contain gene clusters for the consumption of these carbohydrates (39, 40). Weaning removes human milk oligosaccharides from the diet while introducing dietary fiber, an important habitat filter involved in shaping the colonic microbiota. Dietary fiber is composed of complex carbohydrates that are not degraded and absorbed by host enzymes in the upper gastrointestinal tract, thus making them available as carbon sources for the colonic microbiota (41, 42). Phenotypic traits conferring the ability to utilize dietary fiber are most abundant in members of the classes *Clostridia* (phylum *Firmicutes*) and *Bacteroidia* (phylum *Bacteroidetes*) (43). As a result, weaning is associated with a succession characterized by a

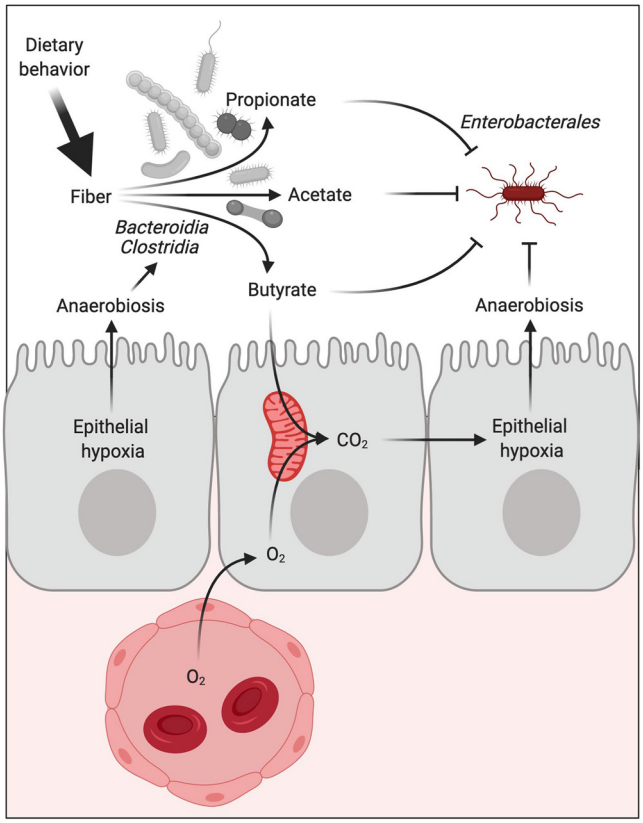


FIG 2 Habitat filtering in the adult colon. Epithelial hypoxia and dietary fiber filter the habitat in the large intestine to license growth of obligate anaerobic fiber eaters, which drives a dominance of the classes *Clostridia* and *Bacteroidia* in the fecal microbiota. Facultative anaerobic bacteria, such as members of the *Enterobacterales*, remain minority species because epithelial hypoxia limits critical resources they require for overcoming growth inhibition by short-chain fatty acids (acetate, butyrate, and propionate). (Created with BioRender.com.)

disappearance of *Bifidobacteriaceae* and an expansion of *Clostridia* and *Bacteroidia* in the gut microbiota (44).

These observations illustrate that the dominance of certain bacterial taxa in the colonic microbiota is the result of habitat filtering by the host, which involves the host's dietary behavior and host control over the flow of resources from the epithelial lining into the microbial habitat. In other words, dietary fiber and epithelial hypoxia "filter" the colonic environment in healthy adults so that obligate anaerobic bacteria with a diverse array of glycolytic enzymes predominate, which explains why *Clostridia* and *Bacteroidia* are the most abundant taxa in this habitat patch (35) (Fig. 2).

Competition and Habitat Filtering Maintain Microbiota Resistance and Resilience

Microbiota resistance. As the microbiota matures, ecological niches carved out through competition and habitat filtering become successively occupied by microorganisms that are acquired stochastically over time from maternal or environmental sources (45). Fecal microbiota transplantation in adult mice increases species diversity compared to the microbiota of both the donor and the recipient, which suggests that the microbiota assembly process does not reach full saturation (46), a property common to most ecosystems (47, 48). Nonetheless, established members of the microbial community can prevent engraftment of new arrivals either through competition, a process known as niche preemption, or through habitat filtering, an activity referred to as niche modification (45, 49). Niche preemption can involve competition between closely related species for critical resources, such as oxygen (50, 51). An example of niche modification is the production of short-chain fatty acids by

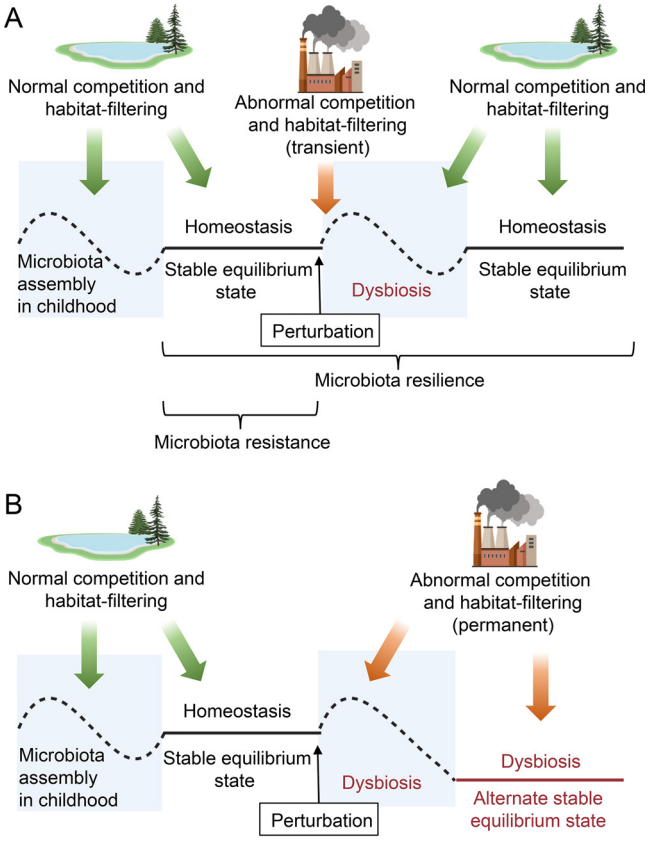


FIG 3 Normal competition and habitat filtering promote homeostasis, microbiota resistance and microbiota resilience. (A) After birth, the microbiota exhibits fluctuations as it assembles to fill nutrient niches created by competition and habitat filtering. Once microbiota assembly is complete, a state of normal competition and habitat filtering maintains homeostasis, characterized by a stable equilibrium state in which the microbiota composition remains invariable over time, a phenomenon termed microbiota resistance. A brief perturbation, such as a disruption of the microbiota with antibiotics, leads to a transient state of abnormal competition and habitat filtering, which causes dysbiotic fluctuation in the microbiota composition. However, once normal competition and habitat filtering resume, the microbiota reassembles to reach an equilibrium state that is functionally similar to that of the community prior to the perturbation. The ability of the microbiota to return to homeostasis after a perturbation is termed microbiota resilience. (B) A lasting perturbation, which can be caused for example by chronic intestinal inflammation, triggers a permanent state of abnormal competition and habitat filtering. As new nutrient niches created by abnormal competition and habitat filtering are filled, the microbiota composition shifts permanently to reach an alternate equilibrium state. Through this process, abnormal competition and habitat filtering maintain a perpetual state of dysbiosis. (Created with BioRender.com.)

Clostridia and *Bacteroidia* species (52, 53), which limits the range of successful metabolic strategies among bacterial species inhabiting the large intestine. Niche preemption and niche modification generate priority effects that enable founding members of a mature microbial community to prevent engraftment of additional microbes, thereby generating a stable equilibrium state with invariable species composition (54, 55). The resulting temporal stability of the taxon composition observed for mature gut-associated microbial communities is termed microbiota resistance (45, 56, 57) (Fig. 3A).

Since historical events that govern the initial exposure to microbes differ between individuals, the outcome of community assembly is different for each person, a phenomenon known as historical contingency (49). Combining historical contingency with microbiota resistance is predicted to generate considerable taxonomic diversity between gut-associated microbial communities from different individuals. Consistent with this idea, the taxon composition exhibits little overlap on the species level when the fecal microbiota composition is compared between healthy volunteers (58).

Microbiota resilience. The principles of microbial community assembly predict that competition and habitat filtering will select for comparable microbial traits in healthy individuals that consume a similar diet, which will result in assembly of microbial communities that are functionally similar even though they differ in their species composition. Consistent with this idea, antibiotics disrupt the fecal microbiota by permanently removing some microorganisms, but after completing therapy, habitat filtering ensures that vacated niches are occupied again by microbes harboring traits similar to those of their predecessors, thus returning the microbiota to a healthy equilibrium state despite the fact that recovery from antibiotic treatment changes the species composition (54). For example, oral administration of streptomycin diminishes microbial functions, such as short-chain fatty acid production, but concentrations of these metabolites return to normal levels after cessation of treatment (59), suggesting that reassembly of the microbiota returns metabolic traits to their ancestral state. Through this mechanism, competition and habitat filtering ensures that the microbiota returns to a healthy state after perturbation, a property called microbiota resilience (56, 60) (Fig. 3A).

Homeostasis versus dysbiosis. The taxonomic diversity in the microbiota composition between individuals (58) makes it all but impossible to determine what constitutes a balanced microbial community based on cataloguing microbial species names (61). Dysbiosis is commonly described as an imbalance in microbial communities characterized by a decrease in microbial diversity, the presence of potentially harmful microbes or the absence of beneficial ones (62), but this definition becomes untenable when homeostasis cannot be explained by the presence or absence of specific microbial species (63). Problems with a taxonomic definition for homeostasis and dysbiosis provide a compelling rationale for developing functional definitions for these terms (27). The processes that govern microbial community assembly suggest that homeostasis represents the outcome of normal competition and habitat filtering, which in turn generates microbiota resistance and microbiota resilience. Normal habitat filtering could be defined as an activity characteristic of or appropriate to a healthy or normally functioning host. Conversely, dysregulation of processes involved in microbial community assembly will trigger dysbiosis, which can be defined as a state resulting from abnormal competition or habitat filtering (Fig. 3B).

COLONIZATION RESISTANCE

A Host-Microbe Chimera Confers Colonization Resistance

Functions of the gut microbiota. Defining homeostasis functionally focuses attention on the role the gut microbiota plays in health. One function of a balanced colonic microbiota is to aid in the digestion of nutrients that cannot be broken down by host enzymes in the small intestine, such as fiber (64). Habitat filters that maintain anaerobiosis ensure that catabolism of fiber has to proceed though pathways that generate fermentation products, such as short-chain fatty acids (65). In turn, microbiota-derived fermentation products are absorbed by the host for nutrition, which provides us with an estimated 6 to 10% of our energy budget (66, 67). The microbiota has thus been likened to an organ containing our "second genome," which encodes digestive enzymes to harvest otherwise inaccessible nutrients (68, 69) (Fig. 4).

A second function of a balanced gut microbiota is to educate and prime our host defenses (70–76). Altered production of microbiota-derived metabolites during dysbiosis has been linked to a broad spectrum of noncommunicable diseases associated with chronic immune activation, such as colorectal cancer (77), atherosclerosis (78) and allergic airways disease (79). Comparison of germfree and conventional mice reveals that the microbiota profoundly influences functionality and development of both the mucosal and systemic immune systems (80, 81). It has thus been proposed that the microbiota should be viewed as an organ aiding in immune education (82) (Fig. 4).

The organ analogy has obvious limitations, as organs are passed down across generations, whereas heritability estimates for the human microbiota are low (83, 84).

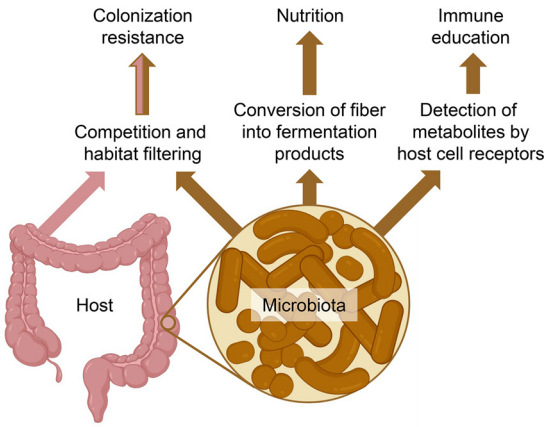


FIG 4 Functions of the gut microbiota. Nutrients (e.g., fiber) that evade absorption and degradation by host enzymes in the small intestine enter the colon, where they are converted into fermentation products by the gut microbiota. This metabolic activity of the gut microbiota has been likened to the function of an organ that contributes to host nutrition and immune education. Host-derived habitat filters and the microbiota form a host microbe chimera that performs a third function, termed colonization resistance, which prevents harmful microbes from entering the body. (Created with BioRender.com.)

Furthermore, the fact that germfree mice are viable suggests that the digestive function of the microbiota and its role in immune education are not essential for life. However, one could argue that the latter assertion is flawed, because germfree mice require dietary supplementation with microbial products (e.g., vitamin K) (85) and are exquisitely sensitive to infection. In the absence of a microbiota, environmental exposure would inevitably result in death from opportunistic infections. These considerations underscore that in addition to aiding nutrition and immune education, the microbiota executes a third function that contributes to health, which is to limit the ability of harmful microbes to gain a foothold and expand on body surfaces, a property known as colonization resistance (Fig. 4). Colonization resistance is a canonical nonspecific immune function that is essential for life. This vantage point suggests that our resident microbes should be considered effector cells of our immune system, an idea that requires an expansion of theory to incorporate microbial ecology into the classical framework of immunology (28).

Sterilizing immunity versus microbiota-nourishing immunity. One subdivision of our immune system ensures sterility of host tissues (sterilizing immunity) by detecting invading microorganisms and distinguishing them from self. In turn, self/nonself discrimination induces innate and adaptive immune responses that are aimed at removing the microbial intruders from tissue to restore sterility (86). However, whereas the goal of sterilizing immunity is to remove microbes from host tissues, the goal of our interaction with microbes inhabiting body surfaces is not to detect and remove them but rather to maintain and balance microbial communities for health (87). It has thus been proposed that host-derived habitat filters that shape microbial communities form a functional unit with the microbiota, termed microbiota-nourishing immunity, which constitutes an immune system subdivision that is separate from sterilizing immunity (28, 88) (Fig. 1).

Several fundamental differences between microbiota-nourishing immunity and sterilizing immunity justify such a subdivision. First, at the very core of sterilizing immunity lies the ability to discriminate between self and nonself, which needs to be applied to members of the microbiota. For instance, microbiota entering tissue during traumatic injury necessitates its elimination to restore sterility. However, whereas self/nonself discrimination by sterilizing immunity is essential for hunting down individual microbes in host tissue, this process is not critical for balancing the microbiota on body surfaces using host-derived habitat filters. Although microbiota-derived

metabolites can be detected by host cell receptors to regulate host-derived habitat filters (89–91), this process neither distinguishes individual microbes from self, nor does it trigger responses aimed at sterilizing body surfaces (92, 93).

Second, microbiota-nourishing immunity is a host-microbe chimera, in which the microbial contribution to colonization resistance is mediated through ecological priority effects executed by microbial effector cells (94). In contrast, all components involved in sterilizing immunity are host derived, which makes the idea that microbial cells could be considered effector cells of our immune system appear strange to card-carrying immunologists (28).

Third, although there is overlap between antimicrobial mechanisms employed by effector cells of sterilizing immunity and by host-derived habitat filters of microbiota-nourishing immunity (e.g., defensins), only the latter employs mechanisms that literally nourish the microbiota (e.g., milk oligosaccharides) (28). Thus, habitat filters of microbiota-nourishing immunity balance the microbiota using a carrot-and-stick approach that is never utilized by sterilizing immunity.

The emerging picture suggests that microbiota-nourishing immunity constitutes our first line of defense against mucosal pathogens, but our functional understanding of this immune system subdivision lags behind that of sterilizing immunity. Although the concept of microbiota-nourishing immunity is new (28, 88), there is a large body of work on colonization resistance reaching all the way back to the 1950s (6). Taking a fresh look at this literature through the novel lens of microbiota-nourishing immunity provides an opportunity to infuse the conceptual framework of a data-driven discipline, microbiome research, with a wealth of information on bacterial physiology and pathogenesis. Here, we will perform this task for *S.* Typhimurium, one the best-studied bacterial model organisms that has long been a workhorse of research in bacterial genetics and metabolism (95). *S.* Typhimurium is ideally suited for studying the interplay between the pathogen, the host, and its microbiota due to the availability of excellent animal models (21, 96).

Niche Modification by Microbiota-Derived Short-Chain Fatty Acids

Historical overview. A clinical appreciation for the protective functions of the gastrointestinal microbiota began in the 1940s and 1950s with the rapid introduction of antibiotics for the treatment of bacterial infections (97). Alongside the profound success of antibiotic therapies came the observation that patients often became susceptible to secondary bacterial infections after antibiotic treatment of a primary infection, implicating an unperturbed microbiota as a key player in the generation of colonization resistance (98–100). In an effort to study this phenomenon, Marjorie Bohnhoff at the University of Chicago pioneered the use of a mouse model for the study of microbiota-mediated colonization resistance (6). This model, which is still widely used today, involves oral pretreatment of mice with the antibiotic streptomycin. The treatment was found to significantly alter the abundance and composition of the large intestinal microbiota, measured by the contemporary standards of aerobic plate counts and Gram stain (101, 102). An acute susceptibility to intragastric *S.* Enteritidis infection coincides with this streptomycin-dependent alteration of the large intestinal microbiota, with the infectious dose being lowered to $<$10 CFU, whereas untreated mice resist colonization by *S.* Enteritidis challenges of as high as 10^6 CFU (6). This 10,000-fold increase in the challenge dose required for lethal *S.* Enteritidis infection in mice with an intact microbiota compared to mice with streptomycin-ablated microbiota illustrates that colonization resistance provides strong protection against low-dose pathogen challenge. Early work also contributed a prescient description of microbiota resilience, by demonstrating that a drastic reduction in the overall bacterial abundance and morphological diversity triggered by streptomycin treatment rebounded to pretreatment levels within 1 week (101, 102).

Initial studies on streptomycin-pretreated mice suggest that an intact microbiota has bacteriostatic or weakly bactericidal activity against *S.* Typhimurium, which is attributable to the metabolic functions of the microbiota (52). The most abundant by-

products of the fermentative metabolism of the colonic microbiota are the short-chain fatty acids acetate, propionate, and butyrate. Fecal concentrations of acetate are commonly measured in the 50 mM range, while propionate and butyrate levels vary widely from 5 to 30 mM. The observation that short-chain fatty acids are required to inhibit the growth of *S.* Enteritidis *in vivo*, in fecal homogenates *ex vivo*, and in rich media *in vitro* reveals their crucial role in mediating colonization resistance (53). However, the inhibitory mechanism of action of short-chain fatty acids requires an acidic environmental pH since only their protonated forms exhibit significant inhibitory effects on the growth of members of the *Enterobacterales* (*ord. nov.* [103]) the order *Salmonella* serovars belong to, by freely diffusing across cellular membranes (104). Initial characterization of the large intestinal environment of mice revealed that short-chain fatty acids are present at high concentrations alongside a mildly acidic pH (53, 101). Disturbance of the microbiota by streptomycin treatment lowers short-chain fatty acid concentrations and increases the luminal pH of the large intestine, thereby generating conditions that are favorable to growth of *Salmonella* serovars *in vivo* and *in vitro* (53, 101).

However, the inhibitory activity of short-chain fatty acids alone is not sufficient to explain how a low abundance of *Enterobacterales* is maintained in the microbiota because this would require short-chain fatty acids to be preset constantly at precisely the right concentration to check population growth, whereas any further increases in the concentration would drive this taxon to extinction (105). Rolf Freter thus proposed that the abundance of *Enterobacterales* in the fecal microbiota is determined by the availability of growth-limiting resources (106). During homeostasis, a low abundance of these growth-limiting resources maintains *Enterobacterales* as minority species in the microbiota (106). A first inkling of the possible nature of these growth-limiting resources comes from the early observation that depletion of short-chain fatty acids increases the redox potential in the cecum to conditions that approximate an aerobic broth culture (101), which predates the finding that streptomycin increases oxygen availability in the colon by more than 50 years (89). A more detailed discussion of growth-limiting resources that govern the abundance of *Enterobacterales* in the fecal microbiota is provided below in the section on host-derived habitat filters.

Mechanism of growth inhibition by short-chain fatty acids. More recent work on colonization resistance against *Salmonella* serovars and other *Enterobacterales* confirms the importance of short-chain fatty acids and provides mechanistic insights into their mode of growth inhibition (107–109). As weak acids, the degree of dissociation for acetate, propionate, and butyrate decreases as the environmental pH approaches their respective pK_a values (the negative base 10 logarithm of the acid dissociation constant) of 4.76, 4.87, and 4.82. In order to maintain a proton motive force and cellular homeostasis, *Enterobacterales* maintain their intracellular pH in the range of 7.2 to 7.8 (110–113). This cytosolic pH range is essential for driving ATP production by oxidative phosphorylation, which relies on protons translocating through ATP synthase and down their concentration gradient. When protonated short-chain fatty acids (HAc) diffuse into a bacterial cell, intracellular proton release ($H^+ + Ac^-$) disrupts pH homeostasis in the cytosol (101, 110, 114, 115). If enough protonated short-chain fatty acids are present in the environment, then this process will proceed until the intracellular pH matches the environmental pH, thereby disturbing cellular pH homeostasis (108). Therefore, the inhibitory capacity of short-chain fatty acids is determined both by their concentration and the luminal pH, which is described by the Henderson-Hasselbalch equation ($pH = pK_a + \log_{10}\{[Ac^-]/[HAc]\}$). Through this mechanism, short-chain fatty acids act as a habitat filter that maintains a low abundance of *Enterobacterales* during homeostasis.

Short-chain fatty acid producers. Acetate is produced by a broad range of bacterial species and cannot be attributed to a specific taxon within the gut microbiota. In contrast, *Bacteroidaceae* (class *Bacteroidia*) are the main producers of propionate (107), whereas the bulk of butyrate production in the colon is attributed to *Ruminococcaceae*

(class *Clostridia*) and *Lachnospiraceae* (class *Clostridia*) (116, 117). Variation in the abundance of *Bacteroidaceae* between different inbred mouse lines reveals that propionate production by members of this family contributes to colonization resistance against *S.* Typhimurium (107). Colonization resistance in mice harboring a gut microbiota with low *Bacteroidaceae* abundance can be strengthened by administering *Bacteroides thetaiotaomicron*, but not a *B. thetaiotaomicron* mutant deficient for propionate production (107). Similarly, a streptomycin-mediated depletion of *Ruminococcaceae* and *Lachnospiraceae* weakens colonization resistance against *S.* Typhimurium, which can be restored by administering butyrate or butyrate-producing *Clostridia* isolates (89, 118).

Beyond short-chain fatty acids. Recent work suggests that suppression of *S.* Typhimurium growth by microbiota-mediated habitat filtering is not limited to the production of short-chain fatty acids, but also includes a depletion of critical resources, such as amino acids. A microbiota-mediated depletion of amino acids filters the environment to exclude bacteria that lack amino acid biosynthesis pathways (119), a selective pressure that helps maintain prototrophy in *S.* Typhimurium. This selective pressure no longer acts on *Salmonella* serovars that are exclusively associated with extraintestinal disease, such as the human-adapted *S.* Typhi or *S.* Paratyphi A (120), which might explain why these pathogens are auxotrophic for tryptophan or cysteine and arginine, respectively (121, 122). Depletion of the gut microbiota with antibiotics increases the concentrations of amino acids in the colonic lumen (123). In turn, *S.* Typhimurium can take advantage of the increased availability of amino acids after antibiotic treatment by utilizing aspartate as an exogenous electron acceptor for fumarate respiration (124).

Host-Derived Habitat Filters Uphold Colonization Resistance

Microbial signatures of dysbiosis. *Salmonella* serovars belong to the order *Enterobacterales* (*ord. nov.* [103], phylum *Proteobacteria)*, a taxon comprising less than 0.1% of the human fecal microbiota in healthy volunteers (35). However, disruption of the microbiota during antibiotic therapy weakens colonization resistance, which gives rise to a dysbiotic expansion of endogenous *Enterobacterales* in the fecal microbiota (125). Hence, the main experimental approach for studying colonization resistance against *Enterobacterales* has been to disrupt the microbiota using antibiotics, causing the majority of studies to become fixated on microbial factors contributing to this nonspecific immune function. As a result, conventional wisdom, summarized in a number of recent review articles (126–130) stipulates that colonization resistance is mediated solely by the gut microbiota through a "battle of the bugs," a process that does not involve the host.

However, the advent of microbiome research is beginning to shift this paradigm by revealing that in addition to the microbiota, the host makes important contributions to colonization resistance against *Enterobacterales* (Fig. 4) (34, 131). During homeostasis, anaerobiosis in the large intestine maintains a dominance of obligate anaerobic bacteria (Fig. 5A). However, profiling of the human fecal microbiota reveals that an expansion of facultative anaerobic *Enterobacterales* is one of the most consistent and robust ecological patterns associated with dysbiosis (37), which is commonly observed in the absence of antibiotic therapy. For example, this microbial signature of dysbiosis is associated with chronic alcohol consumption (132), radiotherapy (133), malnutrition (134), and inflammaging (chronic, sterile, low-grade inflammation associated with aging) (135) and is observed in individuals with inflammatory bowel disease (IBD) (136), colorectal cancer (77), necrotizing enterocolitis (137), HIV enteropathy (138), graft-versus-host disease (139), and infectious diarrhea (140). There is now mounting evidence that in many of these diseases, a dysbiotic expansion of *Enterobacterales* in the fecal microbiota is driven by an underlying dysregulation of host-mediated habitat filtering.

Host phagocytes transform the gut environment during inflammation. Studies on *Salmonella* pathogenesis spearheaded this research by showing that, paradoxically, severe acute intestinal inflammation drives a pathogen expansion in the gut microbiota (7, 8), in part because phagocytes migrating into the intestinal lumen release

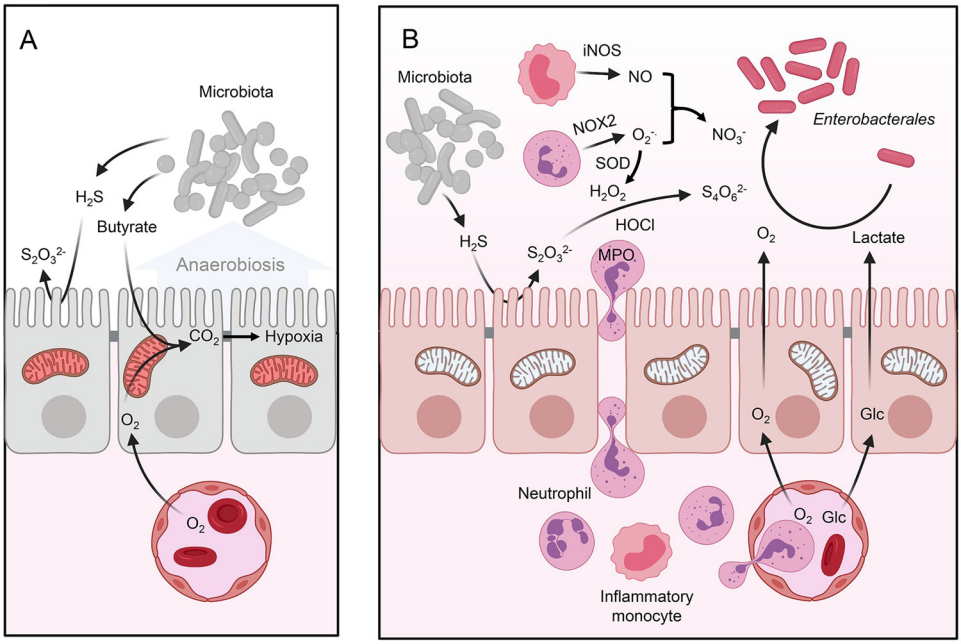


FIG 5 Intestinal inflammation creates a state of abnormal habitat filtering. (A) During homeostasis, microbiota-derived butyrate maintains high oxygen (O_2) consumption in the colonic epithelium through mitochondrial oxidative phosphorylation (246–248). The resulting epithelial hypoxia limits diffusion of oxygen into the gut lumen to preserve anaerobiosis, which maintains a dominance of obligate anaerobic bacteria in the gut microbiota (89). Sulfate-reducing bacteria generate hydrogen sulfide (H_2S) (249), which is detoxified by epithelial sulfide oxidases to thiosulfate ($S_2O_3^{2-}$) (250, 251). (B) During intestinal inflammation, neutrophils and inflammatory monocytes migrate into the intestinal lumen. Inflammatory monocytes are the dominant source of inducible nitric oxide synthase (iNOS), which generates nitric oxide (NO) (252). Nitric oxide can react with superoxide (O_2^-) produced by phagocyte NADPH oxidase (NOX2) to form peroxynitrite (253), which decomposes to nitrate (NO_3^-) in the gut lumen (254). Superoxide is converted by superoxide dismutase (SOD) to hydrogen peroxide (H_2O_2), which is converted to hypochloric acid (HOCl) by neutrophil myeloperoxidase (MPO). These reactive oxygen species oxidize thiosulfate to tetrathionate ($S_4O_6^{2-}$) (10). Intestinal inflammation reduces mitochondrial bioenergetics in the colonic epithelium, thereby reducing epithelial oxygen consumption (154). The resulting loss of epithelial hypoxia increases diffusion of oxygen into the intestinal lumen to disrupt anaerobiosis. Catabolism of glucose (Glc) by host cells through aerobic glycolysis increases the luminal concentration of host-derived lactate (59). Through these mechanisms, intestinal inflammation elevates the availability of oxygen, lactate, nitrate and tetrathionate in the colonic lumen to create a state of abnormal habitat filtering that drives an expansion of facultative anaerobic *Enterobacterales*, which is a microbial signature of dysbiosis in the fecal microbiota (36, 37). (Created with BioRender.com.)

antimicrobial compounds, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) (10, 141). Although direct exposure to these antimicrobial compounds can kill the pathogen (142, 143), phagocyte-derived ROS and RNS diffuse into the gut lumen, where they react to form nontoxic by-products, such as tetrathionate and nitrate, which serve as electron acceptors for anaerobic respiration, thereby promoting *S.* Typhimurium growth (10, 141, 144, 145) (Fig. 5B). Subsequent work shows that intestinal inflammation also weakens colonization resistance against other members of the *Enterobacterales* through similar mechanisms. For instance, intestinal inflammation triggered by virulence factors of the enteric pathogen *Yersinia enterocolitica* causes the pathogen to expand in the gut microbiota through tetrathionate respiration (12). Similarly, nitrate respiration drives a dysbiotic expansion of commensal *E. coli* (order *Enterobacterales*) in mouse models of *Toxoplasma gondii*-induced colitis (146), chemically induced colitis (147, 148), or genetically induced colitis (147, 148). Host-derived nitrate also weakens colonization resistance against *Klebsiella oxytoca* in a mouse model of cancer cachexia (149). In conclusion, migration of phagocytes into the intestinal lumen during intestinal inflammation lowers colonization resistance against *Enterobacterales* by inducing a state of abnormal habitat filtering, which creates increased luminal concentrations of electron acceptors that drive an expansion of facultative anaerobic bacteria through anaerobic respiration (131).

Epithelial metabolism shapes the gut microbiota. Research on *Salmonella* pathogenesis was also at the forefront of discovering that the metabolism of the colonic epithelium functions as a control switch, mediating a shift between homeostatic and dysbiotic microbial communities (34). Virulence factors of *S.* Typhimurium trigger a shift in epithelial energy metabolism from mitochondrial oxidative phosphorylation to aerobic glycolysis, thereby reducing epithelial oxygen consumption in the colonic epithelium (118). The resulting loss of epithelial hypoxia increases the amount of oxygen diffusing into the intestinal lumen, thereby disrupting anaerobiosis and driving a pathogen expansion through aerobic respiration (50, 59, 118) (Fig. 5B). Loss of epithelial hypoxia in the colon is also induced by virulence factors of *Citrobacter rodentium*, a murine pathogen that expands in the colonic microbiota by exploiting the resulting increase in luminal oxygen bioavailability to fuel its growth (9, 11, 150, 151). Reduced mitochondrial bioenergetics in the colonic epithelium not only are linked to aerobic growth of enteric pathogens but also contribute to a weakening of colonization resistance against commensal *Enterobacterales* in mouse models of noncommunicable diseases, such as ulcerative colitis (152, 153) or colorectal cancer (154). Collectively, these data suggest that physiological hypoxia of the colonic surface limits growth of *Enterobacterales* during homeostasis (34, 36). However, conditions that reduce mitochondrial bioenergetics in the colonic epithelium increase the luminal availability of host-derived oxygen, thereby creating a state of abnormal habitat filtering that lowers colonization resistance against *Enterobacterales* (155).

Notably, a loss of epithelial hypoxia weakens colonization resistance against *S.* Typhimurium even in the presence of normal concentrations of microbiota-derived short-chain fatty acids (89). These results appear to be at odds with *in vitro* findings that the presence of short-chain fatty acids inhibits growth of *Enterobacterales* in murine fecal homogenates and that oxygen alone is not sufficient to overcome this growth inhibition (108). A factor lacking in the *in vitro* experiments is a shift in epithelial energy metabolism, which is required to lower colonization resistance against an avirulent *S.* Typhimurium strain (i.e., a strain lacking both type III secretion systems [T3SSs]) in mice harboring normal levels of microbiota-derived short-chain fatty acids (89). These observations suggest that when cells derive energy through aerobic glycolysis (the conversion of glucose into lactate even in the presence of oxygen [156]), the epithelium releases factors in addition to oxygen that weaken colonization resistance against *S.* Typhimurium.

Metabolite profiling reveals that lactate is the most abundant metabolite in the gut lumen during *S.* Typhimurium-induced colitis, while only small amounts of this compound are detected in mock-infected mice (59). A similar increase in the luminal lactate concentration is also observed after antibiotic treatment, but this increase is blunted when mice are treated with a PPAR-γ (peroxisome proliferator-activated receptor gamma) agonist that polarizes host cell metabolism toward oxidative phosphorylation, which is consistent with the idea that an increase in the luminal lactate concentration is mostly derived from a conversion of glucose into lactate by host cells (59). During its expansion in the gut microbiota, *S.* Typhimurium converts lactate into pyruvate using a NAD-independent lactate dehydrogenase (encoded by *lldD*), which transfers electrons from lactate to oxygen using cytochrome *bd* oxidase (encoded by *cydA*), thus linking lactate utilization in the gut to the presence of host-derived oxygen (59). Notably, *S.* Enteritidis can overcome growth inhibition by short-chain fatty acids *in vitro* when lactate is added to murine fecal homogenates (53), pointing to catabolism of host-derived lactate as a possible mechanism to overcome niche modification by microbiota-derived short-chain fatty acids. Finally, the terminal steps in acetate production through the phosphotransacetylase-acetate kinase (Pta-AckA) pathway are required for *S.* Typhimurium to overcome colonization resistance in chickens (157). Thus, it is tempting to speculate that epithelial release of lactate and oxygen cooperatively enables *S.* Typhimurium to ramp up intracellular acetate production to limit

diffusion of microbiota-derived acetic acid into the cytosol, thereby preventing disruption of pH homeostasis. However, additional work is needed to test this hypothesis.

Considering all of these studies suggests that an increased abundance of *Enterobacterales* is a microbial signature of dysbiosis that often involves abnormal habitat filtering by the host. During homeostasis, epithelial hypoxia limits the availability of respiratory electron acceptors (i.e., oxygen and nitrate), thereby filtering the habitat to ensure *Enterobacterales* remain minority species within the colonic microbiota. However, intestinal inflammation and/or a loss of epithelial hypoxia weaken colonization resistance by inducing a state of abnormal habitat filtering. In turn, abnormal habitat filtering leads to an elevated release of host-derived critical resources that enable commensal and pathogenic *Enterobacterales* to overcome niche modification by microbiota-derived short-chain fatty acids. The abundance of these limiting resources determines the abundance of *Enterobacterales* in the gut microbiota. In other words, limited availability of critical resources, such as respiratory electron acceptors and lactate, keeps a tight rein on *Enterobacterales*, which is responsible for the low abundance of this taxon during homeostasis. However, conditions that enlarge the availability of limiting resources drive dysbiosis characterized by an *Enterobacterales* expansion.

Niche Preemption by Endogenous *Enterobacterales*

Competition with closely related species. In addition to habitat filtering by the microbiota and the host, colonization resistance against *Salmonella* serovars also involves competition with closely related bacterial species that are resident in the gut microbiota. Commensal species within the *Enterobacterales* that are closely related genetically to *Salmonella* serovars (103) are a normal constituent in the fecal microbiota of humans (35) and other mammals (158). There are currently no approaches to specifically deplete *Enterobacterales* from the gut microbiota to ascertain their contribution to colonization resistance. However, not all laboratory mice harbor endogenous *Enterobacterales* (51), which is due to variability in animal husbandry practices between vendors. Many vendors of laboratory mice engraft germfree animals with altered Schaedler flora (159) to establish a baseline microbiota in their foundation breeding colonies, prior to transferring animals into barrier production, where microbiota assembly proceeds while animals are screened to prevent specific pathogens from entering the colony (specific-pathogen-free mice) (160). The screening procedures for specific pathogens differ between vendors, resulting in mice from some suppliers to remain *Enterobacterales*-free, while specific-pathogen-free procedures from others do not exclude commensal or opportunistic *Enterobacterales* from engrafting during microbiota assembly. Notably, comparison of genetically similar mice from different vendors reveals that the presence of endogenous *Enterobacterales*, which are minority species in the gut microbiota, results in a 100-fold increase in colonization resistance against *S.* Typhimurium, illustrating that competition with closely related species plays an important role in protecting against infection (51). Commensal *Enterobacterales*, such as *E. coli*, also enhance colonization resistance against *Salmonella* serovars in gnotobiotic mice (161), gnotobiotic piglets (162), or day-of-hatch chicks (50) or in a mouse model of high-fat diet (163).

Keystone species limit the availability of critical resources. Recent work is beginning to elucidate the mechanisms through which endogenous *Enterobacterales* contribute to colonization resistance against *Salmonella* serovars. Germ-free mice engrafted with defined microbial communities fail to confer colonization resistance against *S.* Typhimurium when pathways involved in microbial respiration are underrepresented compared to microbiota of conventional mice (164). However, colonization resistance can be strengthened by supplementing the defined microbial community with facultative anaerobic species, including *E. coli*, *Streptococcus danieliae*, and *Staphylococcus xylosus*, a correlation that points to the presence of respiratory pathways in the microbial community as a factor important for protection against *S.* Typhimurium infection (164). Interestingly, a commensal avian *E. coli* isolate competes more successfully with *S.* Enteritidis for oxygen when the commensal establishes gut colonization in neonatal

chicks prior to pathogen challenge, compared to when both species are introduced simultaneously (50). This finding suggests that endogenous *Enterobacterales* have a competitive advantage over similar species that attempt to enter the ecosystem since priority effects provide them with access to growth-limiting resources. Although the precise mechanisms by which niche preemption enables endogenous *Enterobacterales* to gain priority access to oxygen remain obscure, an intact aerobic metabolism (i.e., a functional cytochrome *bd* oxidase) is required for endogenous *E. coli* to confer colonization resistance against *Salmonella* serovars in mice (51). Thus, one of the mechanisms contributing to colonization resistance against *Salmonella* serovars is competition with endogenous *Enterobacterales* for host-derived respiratory electron acceptors.

In addition to respiratory electron acceptors, *Enterobacterales* compete for nutritional resources. For example, the concentrations of many monosaccharides become elevated in colon contents during antibiotic treatment (123), which supports growth of *S.* Typhimurium in the gut (165, 166). Some monosaccharides become oxidized (167) because an antibiotic-mediated depletion of short-chain fatty acids induces nitric oxide production by recruiting inflammatory monocytes to the colonic mucosa (168) and by increasing inducible nitric oxide synthase (iNOS) production in the colonic epithelium (89). Oxidation of monosaccharides by RNS in the gut lumen generates acidic sugars, such as glucarate and galactarate, which drive a postantibiotic expansion of *S.* Typhimurium (167). There is evidence to suggest that pathogen engraftment in the microbiota can be blocked through nutrient competition with endogenous *Enterobacterales*. *Klebsiella michiganensis* is a commensal member of the *Enterobacterales* that confers colonization resistance against *E. coli* in a mouse model (169). However, *K. michiganensis*-mediated colonization resistance against *E. coli* is lost when mice receive galactitol, a poorly absorbed sugar alcohol that reaches the colon, where it promotes growth of *E. coli* over *K. michiganensis*, because the latter cannot utilize this carbon source (169). These data suggest that antibiotic treatment generates an environment in which growth of *Enterobacterales* is fueled by monosaccharide catabolism. Niche preemption mediated by endogenous *Enterobacterales* likely involves competition for these critical resources with pathogens that attempt to enter the ecosystem.

In essence, although members of the *Enterobacterales* are minority species within the gut microbiota that are often present at levels below the limit of detection by conventional microbiota profiling (51), they play a key role in conferring protection against facultative anaerobic pathogens, such as *Salmonella* serovars. Thus, endogenous *Enterobacterales* have a disproportionally large effect on colonization resistance relative to their abundance within the microbial community, which renders them keystone species. Studies on the underlying mechanism reveal that endogenous *Enterobacterales* contribute to colonization resistance through niche preemption, a process that involves competition with *Salmonella* serovars for critical resources, such as respiratory electron acceptors and monosaccharides.

NICHE OPPORTUNITIES CREATED BY VIRULENCE FACTORS

Ecosystem Engineering by Virulence Factors Licenses Pathogen Engraftment

Pathogens overcome colonization resistance—opportunists do not. A mature gut microbiota is resistant to change (45, 56, 57) because the microbiome prevents engraftment of newly arriving commensal or opportunistic microbes through competition and habitat filtering (49). The phenomenon of microbiota resistance is testament to the fact that once the microbiota reaches a stable equilibrium state, priority effects pose an all-but-impenetrable barrier to engraftment of new commensal or opportunistic bacterial species belonging to the *Enterobacterales*. For example, priority effects prevent replacement of resident endogenous *Enterobacterales* present in the human fecal microbiota (35), with recently emerged opportunistic pathogens, such as carbapenem-resistant *Enterobacteriaceae* (CRE), thereby limiting community spread of CRE. Due to priority effects, the only way for opportunistic CRE to engraft in the gut microbiota is during microbiota assembly or after microbiota disruption (e.g., after antibiotic

therapy). Disruption of the microbiota with antibiotics can clear a niche (54) and provide an advantage for opportunistic CRE over antibiotic-sensitive competitors. As a result, an antibiotic-mediated disruption of the gut microbiota predisposes patients in the intensive care unit to developing carriage and nosocomial infection with CRE, which commonly includes strains of *Klebsiella pneumoniae* and *E. coli* (170–174). Due to weakened colonization resistance in individuals on broad-spectrum antibiotics, nosocomial CRE infections are readily transmitted between patients by hospital workers. In turn, a weakening of colonization resistance drives an expansion of CRE in the gut microbiota, which is a source of opportunistic bloodstream infections in immunocompromised patients (175, 176). Due to the lack of treatment options, 40% of CRE infections lead to death (177, 178), which makes these opportunistic pathogens one of the most urgent threats to public health worldwide (179).

A key difference between infection with opportunistic pathogens, such as CRE, and frank pathogens, such as *Salmonella* serovars, is that only the latter can overcome host defenses in individuals with an intact immune system. In other words, whereas CRE infection requires that colonization resistance is weakened by antibiotics, *Salmonella* serovars can engraft in individuals even when their microbiota-nourishing immunity is intact. In immunocompetent individuals, both CRE and *Salmonella* serovars initially enter an ecosystem that does not support their growth because the host and the microbiota limit critical resources through competition and habitat filtering. As a result, CRE numbers decline, resulting in an extinction of the opportunistic pathogen. Colonization resistance can also lead to an extinction of *Salmonella* serovars, particularly when the challenge dose is low (51) (Fig. 6). However, if the challenge dose is high enough to ensure the pathogen can deploy its virulence factors prior to becoming extinct, the initial decline in *S.* Typhimurium numbers is halted and followed by a marked expansion, resulting in pathogen engraftment in the gut ecosystem (118). *S.* Typhimurium virulence factors are long known to trigger disease in an immunocompetent host (180–182), a characteristic that distinguishes frank pathogens from opportunists, but the importance of virulence factors in overcoming colonization resistance has come to light only recently (7, 8). Importantly, virulence factors of *S.* Typhimurium weaken colonization resistance not by targeting the microbiota but by manipulating the physiology of host cells, thereby inducing a state of abnormal habitat filtering that opens new niche opportunities (183).

Virulence factors carve out a new nutrient niche for the pathogen. The main virulence factors of *S.* Typhimurium are two T3SSs that enable the pathogen to invade the epithelial lining (T3SS-1) (180) and survive in host tissue (T3SS-2) (181). Each T3SS injects several dozen proteins, called effectors, into the cytosol of epithelial cells (for T3SS-1) or macrophages (for T3SS-2) (184) to induce bacterial entry (185) or ensure the spread of bacteria in tissue (186), respectively. For a detailed discussion type III secreted effector proteins and their activity on host cell physiology, the reader is referred to a recent review article devoted to this subject (187).

The presence of bacteria in tissue induces sterilizing immunity by activating pathogen recognition receptors (188–193), thereby triggering innate immune responses that orchestrate severe acute intestinal inflammation (182, 194, 195). Detection of fecal leukocytes in salmonellosis patients illustrates that *Salmonella*-induced intestinal inflammation is accompanied by migration of phagocytes into the intestinal lumen (196), where these host cells contribute to the production of tetrathionate and nitrate as discussed above (10, 141) (Fig. 6). In addition, migration of neutrophils into the intestinal lumen leads to a depletion of *Clostridia* (197, 198), the main butyrate producers in the gut microbiota (116, 117), thereby reducing butyrate concentrations in colon contents (118). Since butyrate is an agonist of PPAR-γ, a nuclear receptor that activates mitochondrial bioenergetics in the colonic epithelium, depletion of this short-chain fatty acid shifts the epithelial energy metabolism toward aerobic glycolysis, thereby increasing epithelial oxygenation and diffusion of oxygen into the intestinal lumen (89, 118).

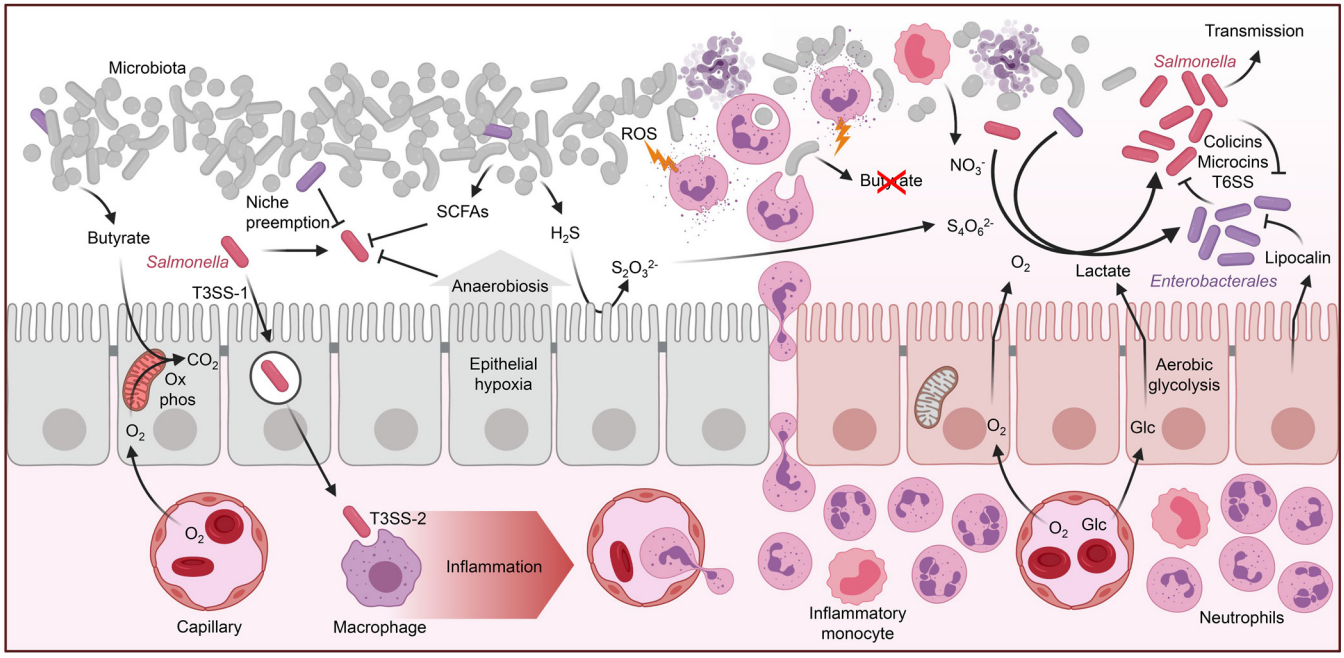


FIG 6 *S.* Typhimurium uses its virulence factors for ecosystem engineering. During homeostasis, conversion of microbiota-derived butyrate to carbon dioxide (CO_2) through mitochondrial oxidative phosphorylation (Ox phos) results in high epithelial oxygen (O_2) consumption, which maintains epithelial hypoxia. Epithelial cells detoxify microbiota-derived hydrogen sulfide (H_2S) by conversion into thiosulfate ($S_2O_3^{2-}$). Upon entry, *S.* Typhimurium uses its virulence factors to invade the intestinal epithelium (T3SS-1) and survive in macrophages in host tissue (T3SS-2). However, prior to the development of host responses, anaerobiosis and niche preemption by endogenous *Enterobacterales* limit access of the luminal *S.* Typhimurium population to resources critical for overcoming growth inhibition by short-chain fatty acids (SCFAs). As a result, the luminal *S.* Typhimurium population decreases, which can lead to a pathogen extinction if the challenge dose is low. In the meantime, the virulence factor-mediated tissue invasion is detected by the innate immune system, which results in orchestration of an inflammatory response characterized by cellular infiltrates that are dominated by neutrophils. The inflammatory response eventually clears the subpopulation of the pathogen that resides in tissue, but it also induces migration of phagocytes into the intestinal lumen. Luminal phagocytes release reactive oxygen species (ROS) and reactive nitrogen species that generate host-derived electron acceptors, including tetrathionate ($S_4O_6^{2-}$) and nitrate (NO_3^-). Luminal neutrophils also deplete butyrate-producing *Clostridia* from the gut microbiota, which reduces mitochondrial bioenergetics in the intestinal epithelium. The consequent shift in epithelial energy metabolism to aerobic glycolysis, the conversion of glucose (Glc) into lactate, is associated with elevated epithelial release of oxygen and lactate. In turn, these changes in the luminal environment create a state of abnormal habitat filtering, thereby providing *S.* Typhimurium with critical resources (nitrate, tetrathionate, oxygen, and lactate) to expand in the gut microbiota, which is required for pathogen transmission by the fecal oral route. The new nutrient niche created by virulence factor-induced inflammation also supports growth of endogenous *Enterobacterales*, provided they can overcome growth inhibition by lipocalin-2 (Lipocalin), an antimicrobial protein released by epithelial cells during intestinal inflammation. Through this chain of events, virulence factor-mediated ecosystem engineering creates a new nutrient niche in which *S.* Typhimurium and endogenous *Enterobacterales* battle for supremacy using their antimicrobial weaponry, including colicins, microcins and type VI secretion systems (T6SS). (Created with BioRender.com.)

Salmonella-induced colitis also makes host-derived lactate the most abundant metabolite in the gut lumen (59).

Collectively, these virulence factor-induced changes in the gut environment trigger a state of abnormal habitat filtering, which is characterized by markedly elevated luminal concentrations of critical resources to support pathogen growth, including tetrathionate (10), nitrate (144, 145), oxygen (118), and lactate (59) (Fig. 6). These observations establish the concept that *S.* Typhimurium uses its virulence factors for ecosystem engineering, a process culminating in the generation of a new nutrient niche that supports pathogen engraftment into the gut ecosystem (94, 183). The consequent expansion of *S.* Typhimurium in the gut microbiota is required for pathogen transmission by the fecal-oral route (118, 199), which represents the principal driving force of natural selection for this strategy of ecosystem invasion.

New niche opportunities create competition. A drawback of ecosystem engineering is that the new nutrient niche generated by *S.* Typhimurium virulence factors can also be occupied by endogenous *Enterobacterales*. Since *S.* Typhimurium and endogenous *Enterobacterales* encounter the newly engineered nutrient niche simultaneously, presumably neither one gains an advantage through priority effects, which levels the playing field. During the fierce competition that ensues for niche occupancy,

contestants deploy antimicrobial weaponry to gain the upper hand in battling for critical resources. *S.* Typhimurium-induced intestinal inflammation increases concentrations of bile acids in the colon (200), a signal to induce expression of a type VI secretion system (T6SS), which is used by the pathogen to kill commensal competitors, such as *K. oxytoca* (201) (Fig. 6). One of the resources *S.* Typhimurium and endogenous *Enterobacterales* compete for is iron because the availability of this trace element is reduced in the inflamed gut. Reduced iron availability during inflammation requires bacteria to release small molecular weight ferric iron chelators, termed siderophores, to acquire this essential metal (202). The siderophore produced by most *Enterobacterales*, enterobactin, is neutralized by the host protein lipocalin-2 (203, 204), which is released into the gut lumen during intestinal inflammation (205, 206). *Salmonella* serovars adapt to this environment by producing a glycosylated derivative of enterobactin, termed salmochelin (207), which is not neutralized by lipocalin-2 (208), thus providing the pathogen with a growth advantage over competitors that rely solely on enterobactin for iron acquisition (209). However, the probiotic *E. coli* strain Nissle 1917 releases salmochelin derivatives conjugated to antimicrobial peptides, termed microcins M and H47 (210), which are internalized by salmochelin uptake systems of *Salmonella* serovars, thereby providing the commensal with a competitive advantage over the pathogen (211). The need to synthesize outer membrane siderophore receptors in the inflamed gut also provides an opportunity to battle related *Enterobacterales* by releasing colicins, which are bacteriocins with limited host range that commonly use siderophore receptors to enter their target cell (212). However, the T6SS is only induced when inflammation increases the concentration of bile acids (201), and neither microcins nor colicins provide a competitive advantage in the absence of intestinal inflammation because iron limitation generated by this host response induces expression of receptors for microcins and colicins in *Enterobacterales* (211, 212). Thus, *Enterobacterales* restrict the use of their antimicrobial weaponry to a state of abnormal habitat filtering.

All things considered, colonization resistance of mature microbial communities constitutes a formidable barrier that blocks an engraftment of commensal or opportunistic *Enterobacterales*. As a result, windows of opportunity for engrafting these species are limited to microbiota assembly in childhood or to episodes of weakened colonization resistance, which can be induced, for example, by antibiotics (Fig. 3A). In contrast, pathogenic *Enterobacterales*, such as *Salmonella* serovars, can overcome colonization resistance in immunocompetent individuals by using their virulence factors for ecosystem engineering (Fig. 6). The pathogen remodels the gut ecosystem by using its virulence factors to trigger intestinal inflammation. The consequent changes in the metabolite landscape create a state of abnormal habitat filtering that provides niche opportunities, which is a crucial determinant of the pathogen's success in ecosystem invasion. Importantly, this strategy for ecosystem invasion is limited to pathogens, because ecosystem engineering by virulence factors generates collateral damage, thereby producing signs of disease, the defining characteristic of pathogens. However, a drawback of this strategy for ecosystem invasion is that virulence factors engineer a nutrient niche that also accommodates related *Enterobacterales* species. As a result, the nutrient niche engineered by virulence factors of the pathogen provides a playground in which *S.* Typhimurium and endogenous *Enterobacterales* use their antimicrobial weaponry to fight for supremacy (94).

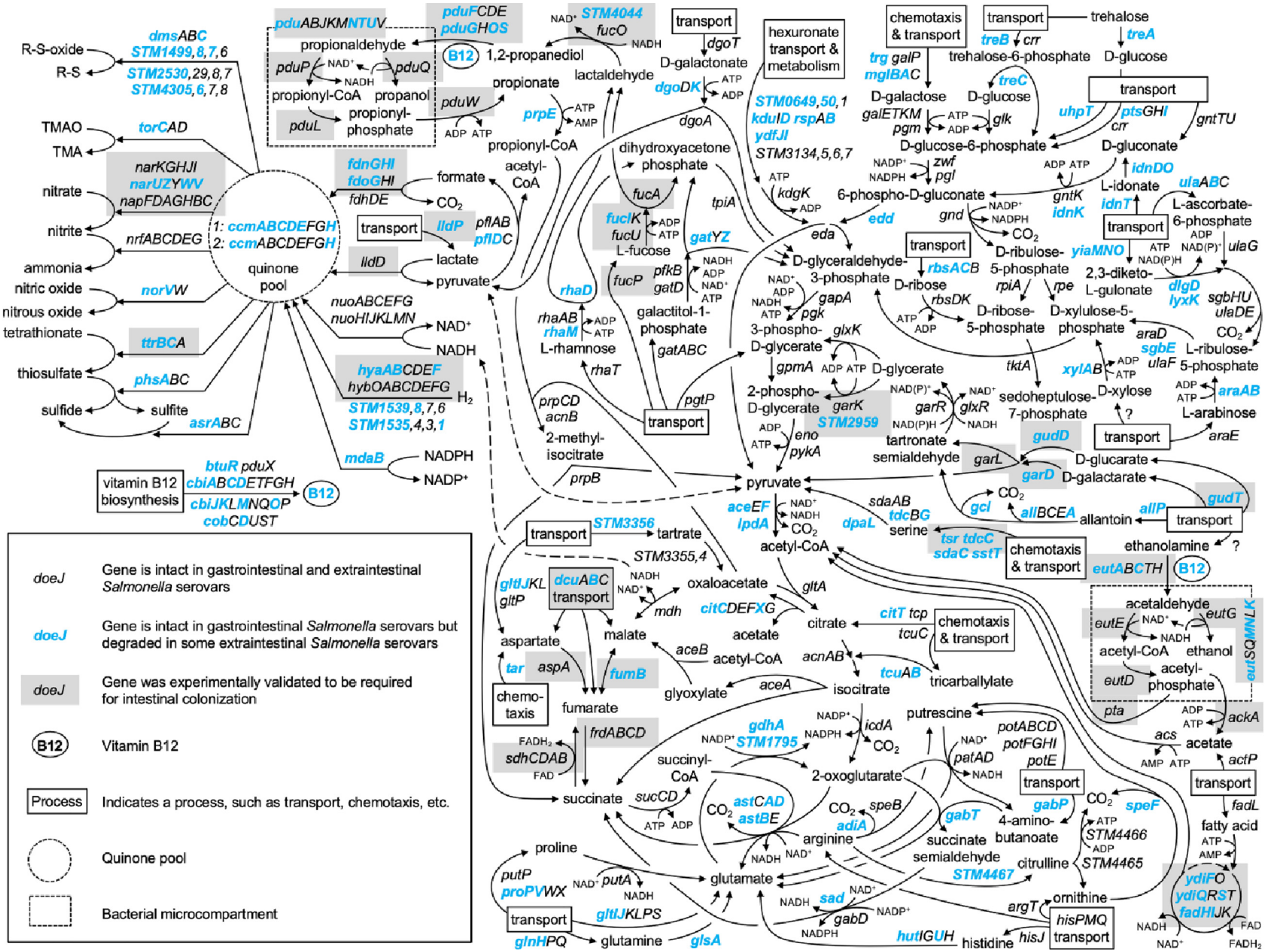
Reconstructing *Salmonella*'s Nutrient Niche from the Ruins

Genome-guided assembly of a metabolic network for gut colonization. Information on how intestinal inflammation alters the luminal habitat is key to understanding why this condition gives rise to imbalances in the gut microbiota that are linked to various noncommunicable diseases, such as IBD (152), colorectal cancer (77), or cardiovascular disease (78). Intestinal inflammation induced by *Salmonella* serovars can be used to model this state of abnormal habitat filtering, but our knowledge of the consequent changes in the luminal environment is still incomplete. The metabolic pathways the pathogen uses to fuel its growth in the inflamed gut can provide a window into the

nutrient niche *S.* Typhimurium occupies, which in turn offers clues about how inflammation alters the habitat of the gut microbiota (96). Notably, an experiment of nature makes it possible to identify these metabolic pathways through whole-genome comparison of *Salmonella* serovars (213–215).

Whereas the vast majority of *Salmonella* serovars are associated with gastroenteritis in humans, an infection that remains localized to the intestine and mesenteric lymph nodes, a few specialists have evolved to cause exclusively extraintestinal disease (e.g., *S.* Typhi) (216, 217). These specialists transmit from an extraintestinal reservoir (e.g., the gallbladder in case of *S.* Typhi) and no longer cause gastroenteritis in their respective hosts, thereby removing the driving force of natural selection for maintaining metabolic pathways required for growth in the inflamed gut (120). Consequently, genes that provide an adaptation to the nutrient niche gastrointestinal *Salmonella* serovars (e.g., *S.* Typhimurium) occupy in the inflamed intestine are dispensable in extraintestinal *Salmonella* serovars and are beginning to randomly degrade by point mutation. This ongoing experiment of nature explains the large numbers of degraded genes (pseudogenes) detected in the genomes of extraintestinal *Salmonella* serovars compared to gastrointestinal pathogens (218–222), a prominent genetic fingerprint that resembles an unsaturated mutagenesis of the pathways required for pathogen growth in the lumen of the inflamed gut (213, 223, 224). However, the emergence of extraintestinal *Salmonella* serovars is a relatively recent event linked to the Neolithic transition toward an agricultural and pastoralist economy (225, 226), suggesting that there was limited time for genome decay to leave its mark on their genomes. Since the process of genome degradation is quite incomplete, analysis of a single *Salmonella* serovar does not unveil a decaying metabolic network. Instead, whole-genome comparison of multiple extraintestinal and gastrointestinal *Salmonella* serovars is required to bring a network of genes to light that is degrading in genomes of extraintestinal pathogens but intact in genomes of gastrointestinal pathogens (Fig. 7) (213–215).

The metabolic network identified by such an *in silico* analysis contains more than 400 genes (213), only a fraction of which has yet been tested experimentally for their contribution to growth in an inflamed intestine (Fig. 7). The emerging experimental validation of these *in silico* predictions shows that genes for the import of host-derived lactate (*lldP*) and its cytochrome *bd* oxidase-dependent conversion into pyruvate (*lldD*), are required for luminal growth of *S.* Typhimurium during colitis (59). Pyruvate generated through this reaction can be converted by pyruvate formate lyase (encoded by *pflDC*) into acetyl coenzyme A (acetyl-CoA) and formate, two metabolites important for growth in the gut. The conversion of acetyl-CoA into acetate (*ackA pta*) is required for intestinal colonization of *S.* Enteritidis (157). Formate is degraded to carbon dioxide (CO_2) and hydrogen (H_2) by a nitrate respiration-dependent formate dehydrogenase (encoded by *fdnGHI*), which is required for growth of *E. coli* in the inflamed intestine (153). Hydrogen generated through this reaction supports growth of *S.* Typhimurium in the gut by serving as an electron donor (*hybOABCDEFG*) (227) for fumarate respiration (*frdABCD*), which is powered by exogenous aspartate or malate (*dcuABC*, *aspA*, and *fumB*) (124). Chemotaxis toward nitrate (encoded by *tsr*) (228), nitrate respiration (mediated by a periplasmic nitrate reductase encoded by *napFDAGHBC*) (145) and tetrathionate respiration (mediated by a tetrathionate reductase encoded by *ttrABC*) (10) are required for growth of *S.* Typhimurium in the niche it occupies in the inflamed intestine, in part because anaerobic respiration powers bacterial microcompartments that function in the catabolism of microbiota-derived fermentation products, including 1,2-propanediol (*pduABCDEGHJKLMNOPQSTUVWX*) (229) and ethanolamine (*eutSPQTDMNEJGHABCLKR*) (230). Nitrate respiration is also required for *S.* Typhimurium to catabolize microbiota-derived fermentation products, including succinate (231) (*sdhCDAB*) and butyrate (*ydiFO ydiQRST fadHIJK*) (232, 233). Finally, catabolism of some monosaccharides plays a role during *S.* Typhimurium gut colonization, as shown for fucose (*fucAO fucPIKUR*), glucarate (*gudDT*), and galactarate (*garDL STM2959*) (165, 167). Thus, the computer-generated concept that gene decay in extraintestinal *Salmonella*



doeJ — Gene is intact in gastrointestinal and extraintestinal *Salmonella* serovars

doeJ — Gene is intact in gastrointestinal *Salmonella* serovars but degraded in some extraintestinal *Salmonella* serovars

doeJ — Gene was experimentally validated to be required for intestinal colonization

B12 — Vitamin B12

Process — Indicates a process, such as transport, chemotaxis, etc.

Quinone pool

Bacterial microcompartment

FIG 7 Reconstruction of a metabolic network required for growth in an engineered nutrient niche. Whole-genome comparison of 5 genomes representing extraintestinal *Salmonella* serovars and 10 genomes representing gastrointestinal *Salmonella* serovars reveals metabolic pathwaysgastrointestinal pathogens use to fuel their growth in the inflamed gut (213). The graphic shows pathways that are degrading in

(Continued on next page)

serovars defines a large metabolic network required for growth of gastrointestinal *Salmonella* serovars in the gut lumen (213–215) has been validated by numerous experimental studies (59, 124, 145, 153, 157, 167, 229, 231, 233). However, the majority of genes in this web still remain to be analyzed.

Predicting the metabolic landscape in *Salmonella*'s nutrient niche. Glancing at the hypothetical metabolic pathways identified by comparative genome analysis (213) provides a preview of the resources that might be available in the nutrient niche engineered by *S.* Typhimurium virulence factors. The metabolic network suggests that *S.* Typhimurium has access to numerous monosaccharides (including glucose, gluconate, galactose, galactonate, trehalose, rhamnose, ribose, xylose, arabinose, idonate, 2,3-diketo-gulonate, hexunonate, and galactitol) and amino acids (including serine, histidine, arginine, glutamate, aspartate, and proline) (Fig. 7), indicating its nutrient niche differs from the habitat of the noninflamed gut, where the microbiota depletes these critical resources (119, 165). It is also apparent from this model that the inflammatory host response might generate several respiratory electron acceptors in addition to nitrate (144), tetrathionate (10), and oxygen (118), which includes sulfite, thiosulfate, nitric oxide, nitrite, *S*-oxides (R_2-SO), and *N*-oxides (R_3-N^+-O^-), such as trimethylamine *N*-oxide (TMAO) (Fig. 7). Whereas nitric oxide is directly derived from inflammatory monocytes (141), *S*-oxides and *N*-oxides can be generated in the gut lumen when ROS and RNS diffuse away from host cells and react with organic sulfides and tertiary amines present in the intestinal lumen (234, 235). Furthermore, ROS and RNS released by luminal phagocytes react to form nitrate and tetrathionate, which are converted to nitrite and thiosulfate through nitrate respiration and tetrathionate respiration, respectively (10, 141, 147). Finally, sulfite is the product of thiosulfate respiration (236). Thus, the projected generation of an array of different respiratory electron acceptors in the gut lumen (Fig. 7) is expected to require recruitment of phagocytes into the intestinal lumen, which is a by-product of intestinal inflammation triggered by *S.* Typhimurium virulence factors (131).

In a nutshell, *in silico* analysis predicts that T3SS-1- and T3SS-2-mediated intestinal inflammation engineers a nutrient niche that is characterized by an increased availability of diverse repertoires of monosaccharides, amino acids, and respiratory electron acceptors (213). These sweeping changes in the luminal metabolite landscape are projected to create a state of abnormal habitat filtering to support pathogen engraftment and drive its expansion in the gut microbiota, which is required for transmission (118, 199). The latter provides the ultimate driving force of natural selection that maintains the metabolic network depicted in Fig. 7 in gastrointestinal *Salmonella* serovars (213).

CONCLUDING REMARKS

What *Salmonella* Serovars Teach Us about Dysbiosis

To summarize the findings discussed above, the host and its microbiota cooperate to execute a nonspecific host defense mechanism, termed colonization resistance, which prevents ecosystem invasion by opportunistic pathogens. Microbiota-derived short-chain fatty acids filter the environment to exclude bacteria lacking mechanisms to maintain pH homeostasis with the available resources. The resources used for maintenance of pH homeostasis in *Clostridia* and *Bacteroidia* remain to be described, but the dominance of these obligate anaerobic bacteria in the gut microbiota is testament to their ability to avert disruption of pH homeostasis by short-chain fatty acids. Facultative anaerobic *Enterobacterales*, on the other hand, require respiratory electron acceptors (such as oxygen and nitrate) and additional unidentified host-derived resources to overcome growth inhibition by short-chain fatty acids. Hence, the availability of

FIG 7 Legend (Continued)
genomes of extraintestinal *Salmonella* serovars (genes in blue font) but are intact in genomes of gastrointestinal *Salmonella* serovars. The metabolic network predicted by this *in silico* analysis provides a window into the nutrient niche that is engineered by *S.* Typhimurium virulence factors in the gut. (Adapted from reference 213.)

these critical resources determines the abundance of *Enterobacterales* within the gut microbiota. During homeostasis, epithelial hypoxia severely limits the availability of respiratory electron acceptors, thereby relegating *Enterobacterales* to an existence as minority species within the gut microbiota (Fig. 2). Despite their low abundance, these minority species have a disproportionally large effect on colonization resistance against *Salmonella* serovars by limiting the pathogen's access to critical resources through priority effects, which identifies endogenous *Enterobacterales* as keystone species within the gut microbiota.

During homeostasis, engraftment of opportunistic pathogens, such as CRE, is efficiently blocked through niche modification by microbiota-derived short-chain fatty acids, habitat filtering by epithelial hypoxia, and niche preemption by endogenous *Enterobacterales*. However, frank pathogens, such as gastrointestinal *Salmonella* serovars, can use their virulence factors to overcome these defenses in an immunocompetent individual by disturbing host-mediated habitat filtering. Ecosystem invasion forces gastrointestinal *Salmonella* serovars to overcome growth inhibition by microbiota-derived short-chain fatty acids, an ecological problem demanding an increased availability of critical resources, such as respiratory electron acceptors, that are kept in short supply by host-mediated habitat filtering and are poorly accessible to the pathogen due to competition with endogenous *Enterobacterales*. Success in gut ecosystem invasion requires the pathogen to endure until its virulence factors generate inflammatory host responses that boost the luminal availability of these critical resources, an outcome that becomes more likely when the challenge dose is high. Framing the outcome of infection as an ecological problem highlights the importance of virulence factors in remodeling the gut ecosystem by triggering inflammation, a host response that ultimately creates a state of abnormal habitat filtering, thereby providing new niche opportunities for the pathogen. These considerations identify gastrointestinal *Salmonella* serovars as ecosystem engineers, a pathogenic strategy inevitably linked to disease (i.e., gastroenteritis).

S. Typhimurium virulence factors engineer a nutrient niche that also accommodates related *Enterobacterales* species (Fig. 6). Thus, the state of abnormal habitat filtering created by *S.* Typhimurium virulence factors might share features with noncommunicable diseases associated with an expansion of *Enterobacterales* in the fecal microbiota (37, 237). Notably, *S.* Typhimurium virulence factors induce this state of abnormal habitat filtering by targeting only the host (7, 10, 118, 144). Extrapolating this insight to noncommunicable diseases suggests that a dysbiotic *Enterobacterales* expansion in the fecal microbiota is secondary to an underlying defect in host-mediated habitat filtering (34, 36, 131). Recent studies using mouse models of IBD and colorectal cancer provide compelling experimental support for this concept (147, 148, 150, 152–154, 238). Thus, lessons learned from studying *S.* Typhimurium ecosystem invasion paved the way for developing a mechanistic understanding of factors driving a microbial signature of dysbiosis in the fecal microbiota, which is observed in a spectrum of noncommunicable diseases.

Where Do We Go from Here?

New strategies to rebalance the microbiota. The finding that dysbiosis is linked to many human diseases has generated hopes that microbiome research will identify novel treatment strategies. Whereas targeting the microbes themselves with fecal microbiota transplants (239), probiotics (240), antibiotics (241), or precision editing of the microbiota (148, 238) shows promise in treating some conditions, great challenges remain to adapt these therapies to the broad spectrum of diseases associated with dysbiosis. By trailblazing the concept that an expansion of *Enterobacterales* in the fecal microbiota is a signature of dysbiosis that is triggered by an underlying defect in host-mediated habitat filtering (34, 36, 131), research on *S.* Typhimurium pathogenesis has created great prospects for identifying alternative treatment targets for remediating dysbiosis. Provided that dysbiosis results from abnormal habitat filtering by the host, it stands to reason that the microbiota can be rebalanced by normalizing host-mediated habitat filtering. A proof of concept for this therapeutic strategy comes from studies

on IBD. Environmental risk factors for IBD include a history of antibiotic usage and a Western-style high-fat diet (242–244). These environmental risk factors cooperate to reduce mitochondrial bioenergetics in the colonic epithelium, thereby increasing epithelial oxygenation in the murine colon (152). In turn, oxygen emanating from the epithelial surface drives an expansion of endogenous *Enterobacterales* in the fecal microbiota, which exacerbates pre-IBD (152). Treatment with an agonist of PPAR-γ, a nuclear receptor in the colonic epithelium that activates mitochondrial bioenergetics, restores epithelial hypoxia, thereby blunting an *Enterobacterales* expansion in mice with pre-IBD (152) and in ulcerative colitis patients (245). Thus, host-derived habitat filters represent promising treatment targets for rebalancing the microbiota in a broad range of noncommunicable diseases linked to gut dysbiosis.

Expanding the microbiome toolbox. Studies on *S.* Typhimurium ecosystem invasion have provided first insights into how normal habitat filtering can be disrupted, but our understanding of host-derived habitat filters in the colon is still incomplete. Furthermore, identifying host-derived habitat filters that govern microbiota assembly at body surfaces other than the colon represents an immense task that remains to be achieved before we can hope to understand dysbiosis at these habitats. Following the example of *Salmonella* serovars, virulence factors of pathogens colonizing other surfaces, such as the respiratory tract or the reproductive tract, provide countless opportunities for identifying host-derived habitat filters at these sites. In turn, this information is expected to reveal what conditions contribute to normal habitat filtering at these body surfaces and how virulence factors induce a state of abnormal habitat filtering that enables pathogens to invade the respective ecosystem. Researchers in bacterial pathogenesis are well positioned to produce such mechanistic insights into how normal habitat filtering maintains homeostasis at various body surfaces. Input from the bacterial pathogenesis field will be needed to identify habitat filters because this information cannot be gleaned simply from cataloging bacterial species names. In turn, identification of habitat filters will aid in the interpretation of microbiota profiling data by linking microbial signatures of dysbiosis to the disruption of habitat filtering by virulence factors. As more information becomes available, it might become possible to read microbiota profiling data in ways similar to a blood test result. In the not so distant future, a microbial signature of dysbiosis at a given body surface might indicate an underlying defect in a specific host-derived habitat filter, which in turn might suggest a treatment aimed at normalizing that function. These prospects make the study of ecosystem invasion by mucosal pathogens one of the most exciting emerging areas in microbiome research.

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