Minireview

Microbial nutrient niches in the gut

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Summary

The composition and function of the mammalian gut microbiota has been the subject of much research in recent years, but the principles underlying the assembly and structure of this complex community remain incompletely understood. Processes that shape the gut microbiota are thought to be mostly niche-driven, with environmental factors such as the composition of available nutrients largely determining whether or not an organism can establish. The concept that the nutrient landscape dictates which organisms can successfully colonize and persist in the gut was first proposed in Rolf Freter’s nutrient niche theory. In a situation where nutrients are perfectly mixed and there is balanced microbial growth, Freter postulated that an organism can only survive if it is able to utilize one or a few limiting nutrients more efficiently than its competitors. Recent experimental work indicates, however, that nutrients in the gut vary in space and time. We propose that in such a scenario, Freter’s nutrient niche theory must be expanded to account for the co-existence of microorganisms utilizing the same nutrients but in distinct sites or at different times, and that metabolic flexibility and mixed-substrate utilization are common strategies for survival in the face of ever-present nutrient fluctuations.

Introduction

The gut microbiota is the community of commensal, beneficial, and pathogenic microorganisms that inhabit the gastrointestinal tract of humans and other animals. Forces that shape the composition of the gut microbiota, as well as other microbial communities, can include stochastic processes such as dispersal, genetic diversification, and ecological drift. However, deterministic interactions between species, individuals, and the environment also create defined niches and thereby influence community composition. The ecological niche was described by Charles Elton in 1927 as the ecological component of a habitat related to an organism’s tolerances and requirements, with a focus on its nutrient-foraging capacities (Elton, 1927). Elton’s niche concept was later generalized by Hutchinson, who envisioned a niche as a multidimensional space of resources and environmental conditions that together define where an organism can survive and grow (Hutchinson, 1957). Importantly, the range of possible conditions under which a species can grow – referred to as its fundamental niche – can be much broader than its actual niche. In this realized niche, the overall potential of a species to exploit its fundamental niche is limited by factors such as environmental conditions, nutrient availability, and the presence of competitors, predators, or phages. Species with overlapping fundamental niches can co-exist by adjusting to each other and segregating their realized niches in a process called niche differentiation. If niche differentiation is not possible, the competing species most well-adapted to the niche would be expected to outcompete and completely exclude the inferior competitor.

The gut environment and potential niche space can be determined by the host in a variety of ways. The host immune system can act as an environmental filter to limit or expand available niches. However, niche space in the gut is thought to be largely determined by the abundance and types of nutrients derived from host diet as well as secreted into the gut by the host. This review will focus on key aspects of nutrient niches in the gut microbiota, considering the gut as a dynamic ecosystem in which spatial and temporal heterogeneity in the nutrient landscape shape the composition of the microbiota.
Survival of the fittest

Hundreds to thousands of co-existing species of microorganisms inhabit the mammalian gut (O’Hara and Shanahan, 2006). The mechanisms underlying the assembly and structure of the microbiota are, however, far from being fully understood. Due to its simplicity, the neutral theory of community assembly has been proposed as a reasonable starting point, or ‘null model’, to explain microbiota assembly. Neutral theory assumes that all species are equally-fit competitors and that the presence and abundance of a species in an ecosystem is shaped only by stochastic processes such as dispersal (i.e. movement of organisms across space) and ecological drift (i.e. random fluctuations in population size) (Caswell, 1976; Hubbell, 2001; Rosindell et al., 2011). Under these conditions, organisms in the community are randomly lost and are replaced at random by individuals from within the community or by immigration of individuals from outside the community. The observation that temporal fluctuation of taxa is not accompanied by major differences in function (as determined with metagenomics) (Thaiss et al., 2014) could be taken as evidence of stochastic fluctuations of equally-fit species. High levels of dispersal leads to accumulation of diversity into local microbial communities, thus increasing alpha diversity (Chase and Myers, 2011), as well as to the homogenization of communities, thus decreasing beta diversity (Cadotte, 2006). Increased alpha diversity and decreased beta diversity are observed in the gut microbiota of tribal populations in comparison to non-tribal populations, suggesting that better sanitation and other hygienic practices associated with industrialization might affect the dispersal of gut organisms and thereby influence the composition of the gut microbiota (De Filippo et al., 2010; Yatsunenko et al., 2012; Schnorr et al., 2014; Martinez et al., 2015). Neutral theory has been used with some success to explain the assembly of microbial communities in diverse environments, including host-associated microbiomes (Sloan et al., 2006; Woodcock et al., 2007; Costello et al., 2012; Jeraldo et al., 2015; Venkataraman et al., 2015; Burns et al., 2016; Sala et al., 2016). For example, the composition of the healthy lung microbiota can be explained by dispersal of bacteria from other body parts (Venkataraman et al., 2015). However, models based on neutral theory could only incompletely explain the composition of the gut microbiota for several domestic vertebrates, with deviations particularly apparent for the most abundant species (Jeraldo et al., 2012; Sala et al., 2016). In a screening of stool samples from hundreds of individuals residing in the United States, only one sample had a microbiota composition consistent with neutral theory, strongly suggesting that, despite potential dispersal limitations, deterministic processes are key in shaping the microbiota (Li and Ma, 2016). A clear illustration of the importance of deterministic processes such as niche adaptation is that although germ-free mice can be stably colonized with microbial communities collected from diverse habitats (soil, microbial mats, termite gut, fish gut, and human skin, tongue and gut), these communities are outcompeted and driven to extinction when challenged by an invading mouse gut microbiota (Seedorf et al., 2014). Also of note, for many of the tested allochthonous communities the gut environment selected for organisms having polysaccharide utilization genes. Specifically, the ability to degrade starch, a major component of the laboratory mouse diet, largely determined colonization success, highlighting the importance of the nutrient landscape as a driving force in microbiota assembly.

Though various factors such as host genotype, immune status, and health state can affect the composition of the gut microbiota, the primary driver appears to be the composition and intake levels of host diet (Tumbaugh et al., 2009; Wu et al., 2011; David et al., 2014b; Zarrinpar et al., 2014; Carmody et al., 2015). In 1983, Rolf Freter formulated the nutrient niche theory, which asserts that ecological niches in the gut are defined by available nutrients and that a species can only colonize if it is able to most efficiently use a particular limiting nutrient (Fig. 1A) (Freter et al., 1983a,b). The levels of one, or maximally a few, limiting nutrients would therefore be predicted to dictate the abundance of each species (Fig. 2A). Nutrient niche theory is supported by observations in gnotobiotic mouse models that the concentration of individual dietary components can explain the relative abundance of each member of a 10 species community (Faith et al., 2011) and that Bacteroides celulosolyliticus levels are controlled by levels of dietary arabinoxylan (Wu et al., 2015). The nutrient niche theory is also supported by numerous in vivo and in vitro diet supplementation studies showing that different prebiotics can target very specific organisms or groups of organisms in a complex gut community (Macfarlane et al., 2008; Ramirez-Farias et al., 2009; Martinez et al., 2010; Walker et al., 2011; Ivarsson et al., 2014; Chung et al., 2016; Duncan et al., 2016). In a natural, fully-developed gut microbiota, one might expect all available nutrient niches to be occupied. A new incoming species, whether it be a commensal or pathogen, should be unable to establish unless it can outcompete a resident species or a vacant niche arises due to a new component in the diet or elimination of a competitor, as may occur during antibiotic administration or inflammation. Supporting this notion, commensal Escherichia coli strain Nissle 1917 can outcompete Salmonella enterica serovar Typhimurium (S. Typhimurium) due to its superior iron uptake.
Fig. 1. Niche-space diagrams representing nutrient niche concepts related to the abiotic (A-C) and biotic (D, E) environment. The total niche space is shown as a large ellipse and the realized niche for each species is represented as a circle. Species are represented by letters a-k.

A. Freter’s concept of nutrient niches considering well-mixed nutrients and equilibrium conditions: each species occupies a preferred nutrient niche.

B. Exploitation of the same nutrient niche by different species under non-equilibrium conditions (i.e. unbalanced growth): at different times g and h have the same nutrient niche as d and b respectively.

C. Extension of Freter’s theory assuming spatial structuring (i.e. Restaurant hypothesis): the same nutrient niche can be used by different species (e.g. a and i, e and j) at distinct sites.

D. Niche switching and niche partitioning due to metabolic flexibility of species. Changes in the nutrient landscape force e and c to switch their niches, and a and c partition the previous niche of a.

E. The effect of obligate and facultative dependencies, as well as keystone species. Nutrient fluctuations lead to disappearance of a keystone species k. Species e is completely dependent on the activity of k and goes extinct, while a is able to switch its niche and persist in the absence of k. R = species richness.
capacities (Deriu et al., 2013). Furthermore, it has been recently shown that an introduced strain of *Bifidobacterium longum* can colonize and persist in the human gut unless functionally-similar organisms, which are presumably better competitors for certain carbohydrates, are already present (Maldonado-Gómez et al., 2016). In some cases, more than one strain is needed to saturate potential nutrient niches available to incoming strains and thereby block colonization (Lawley et al., 2012; Stecher et al., 2013; Brugiroux et al., 2016). For instance, two commensal *E. coli* strains, HS and Nissle 1917, are required to prevent colonization of streptomycin-treated mice by the pathogen *E. coli* EDL933 (Maltby et al., 2013). HS and Nissle 1917 utilize different subsets of sugars that can be used by EDL933. Though HS has the genetic potential to use ten different

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mucosal-derived sugars, it actually only utilizes six of these in vivo (Maltby et al., 2013). Thus, the realized niche of HS differs from its fundamental niche. This example highlights that care must be taken in interpreting a species’ nutrient niche based on genome analysis alone, as this provides information about the fundamental, but not the realized, niche of an organism. Complementing genome analysis with transcriptomics proved to be crucial to understand how two strains of lactobacilli, Lactobacillus reuteri strain 100–23 and Lactobacillus johnsonii strain 100–33, both of which are able to use glucose and maltose, the two main fermentable carbohydrates in the mouse stomach, could cohabit in forestomach biofilms (Tannock et al., 2012). Despite having overlapping fundamental niches, both strains can coexist by restricting their realized niches and partitioning these resources, with 100–23 utilizing maltose and 100–33 utilizing glucose (Figs 1D and 2D). In a recent study of gene expression of pairs of co-occurring human gut microbes, it was observed that for 41% of all pairs of species, the presence of one of the organisms was associated with an altered transcriptional profile in the other (Plichta et al., 2016). Transcriptional changes were most pronounced in genes involved in nutrient uptake and anaerobic respiration, suggesting that nutrient niche partitioning is a prevalent phenomenon in the human gut microbiota (Plichta et al., 2016).

The dynamic gut

The restriction of an organism’s realized niche in a complex community lends support to Freter’s theory that the level of one or few nutrients controls the population size of any individual species. However, if a single limiting nutrient determines the success of a species it is surprising that day-to-day variations in diet do not destabilize the gut microbiota (David et al., 2014a). If nutrient niche theory is correct, successful species must have evolved to be versatile enough to switch their realized nutrient niche regularly. Alternatively, if a species was simultaneously utilizing multiple substrates (Kovarova-Kovar and Egli, 1998), the loss of an individual substrate might have a minor effect on its abundance. Salmonella, for example, utilizes diverse nutrients in vivo (Steeb et al., 2013). While there may be substrates that are indeed irreplaceable, such as hydrogen for Salmonella, many organic carbon substrates are perhaps interchangeable and used in parallel, which would account for the stability of populations (Fig. 2B). For example, in a gnotobiotic mouse model, B. cellulosityticus fitness was determined by 550 loci in its genome when mice were fed a high-fat, high-sugar diet, but only 34 loci were critical fitness determinants when mice were fed a low-fat, high-plant polysaccharide diet (Wu et al., 2015). This suggests that in a complex nutrient environment, such as a high-plant polysaccharide diet, there is more possibility for mixed-substrate utilization or niche switching. Taken together, these results indicate that while the population levels of some species may be controlled by a single substrate, others are likely involved in mixed-substrate utilization or are versatile enough to switch nutrient sources depending on availability (Figs 1D and 2B).

Nutrient niche theory is based on the premise of balanced microbial growth, such as occurs in a steady-state chemostat system. In most cases, however, dietary intake is not continuous and can vary widely in frequency, thereby creating temporal changes in the nutrient landscape. The gut microbiota of fasting or hibernating animals exhibits large fluctuations (Crawford et al., 2009; Sonoyama et al., 2009; Costello et al., 2010; Sommer et al., 2016). In Burmese pythons, fasting is associated with a loss in diversity and an increase in the abundance of Bacteroides and Akkermansia, most likely due to their ability to switch their metabolism from dietary glycans towards degradation of host-derived compounds such as mucin (Costello et al., 2010). Similarly, an increase in Akkermansia was also observed in fasted hamsters (Sonoyama et al., 2009). In brown bears, hibernation leads to an increase in Bacteroidetes, though not of Verrucomicrobia (Akkermansia), and a decrease in Firmicutes and Actinobacteria, who presumably rely on the presence of dietary fibres (Sommer et al., 2016). In fasting animals, nutrient-poor conditions may force many members of the gut microbiota to survive at low abundance or become dormant until the next meal. The slow intestinal transit induced by fasting or hibernation allows the persistence of dormant organisms inside the host, which can resume growth whenever nutrients conditions are again favourable. While fasting is a rather extreme case for most animals, even daily variation in dietary intake can affect the gut microbiota. For example, the intake of fibre-rich foods in humans correlates positively with next-day abundances of Bifidobacteria, Roseburia spp., and Eubacterium rectale (David et al., 2014a). Additionally, examination of gut microbiota in conventionally-raised mice showed differential diel variation in microbial structure and function, with the majority of oscillating operational taxonomic units (OTUs) belonging to the family Lachnospiraceae (Leone et al., 2015). Temporal variations in the nutrient landscape, whether they be stochastic due to daily variation in diet or rhythmic such as meal frequency, create the conditions for non-balanced microbial growth. What are the implications of non-balanced growth in the gut? According to the r/K selection theory introduced by the ecologists Robert MacArthur and E.O. Wilson, under non-equilibrium conditions competitive exclusion may
not be reached and organisms able to grow more quickly but less efficiently on a preferred nutrient (i.e. r-strategists) and organisms that grow more slowly but with higher affinity for a preferred nutrient (i.e. K-strategists) can co-exist with a balance in abundances that depends on the frequency of the nutrient fluctuations (Pianka, 1970). This would support a higher diversity and also allow organisms utilizing the same limiting nutrient to co-exist (Fig. 1B). It may be that feeding frequency and gut transit time are key factors in determining the outcome of r/K selection. Indeed, longer gut transit times and increased stool consistency (which is positively correlated with transit time) are associated with higher microbial richness (Roager et al., 2016; Vandeputte et al., 2016), suggesting that K-strategists are supported by longer periods of low nutrient conditions.

Compartmentalized gut

Stool is often used as a proxy for the intestinal microbiota due to relative ease of sampling. However, the mammalian intestinal tract has multiple compartments with different physicochemical and nutrient conditions and, as a consequence, different microbial communities (Fig. 3). In the small intestine, rapid intestinal transit as well as higher levels of oxygen (He et al., 1999) select for fast-growing facultative anaerobes that can compete with the host and other microorganisms for simple sugars. In the human ileum these include Proteobacteria (mainly E. coli) and Streptococcus spp. (Zoetendal et al., 2012; Donaldson et al., 2016) as well as Bacteroidetes and members of Clostridium clusters IX (Veillonella spp.) and XIVa, which may grow on fermentation products such as acetate and lactate that are secreted by abundant facultative anaerobes (Zoetendal et al., 2012). The murine small intestine is enriched in Lactobacillaceae, Bacteroidales and Desulfovibrionaceae (Gu et al., 2013; Donaldson et al., 2016). Simple, easily-metabolizable nutrients are largely depleted in the small intestine by host absorption or microbial utilization and the vast majority of species that populate the large intestine are strict anaerobes that ferment complex polysaccharides and other refractory dietary compounds as well as secreted host compounds such as mucin. Lower levels of bile acids and secreted antimicrobial compounds as well as a less acidic pH in the large intestine also likely contribute to a higher cell density and diversity compared with the small intestine (Booijink et al., 2010; Zoetendal et al., 2012). Because of the higher density of cells in the large intestine, stool samples are generally considered to be representative of the colonic microbiota (Gu et al., 2013; Yasuda et al., 2015). The majority of organisms found in stool samples from healthy humans are facultative or obligate anaerobes belonging to Firmicutes and Bacteroidetes phyla (Donaldson et al., 2016). Similarly, the murine colonic microbiota includes members of the Firmicutes and Bacteroidetes such as Ruminococcaceae, Lachnospiraceae, Bacteroidaceae, Prevotellaceae and Rikenellaceae families (Nava et al., 2011; Gu et al., 2013). The capacity to degrade dietary fibres is a common trait shared by these taxa (Flint et al., 2012). However, the fermentation potential of different fibre types can be species- and strain-dependent. For example, amendment of human stool with amylase-treated wheat bran results in an increase in members of the Lachnospiraceae such as Eubacterium xylanophilum and Butyrivibrio spp. (Duncan et al., 2016). Dietary supplementation with resistant starch (RS) boosts the relative abundance of Ruminococcus bromii and Eubacterium rectale (for RS types 2 and 3) as well as Bifidobacterium adolescentis and Parabacteroides distasonis (for RS type 4) (Martinez et al., 2010; Walker et al., 2011). Inulin also increases the relative abundance of B. adolescentis as well as Faecalibacterium prausnitzii in humans (Ramirez-Farias et al., 2009), while in rats the main utilizers of administered 13C-labeled inulin are Bacteroides uniformis, Blautia glucerasea, Clostridium indo-lis and Bifidobacterium animalis (Tannock et al., 2014). These results highlight that dietary fibres can distinctive-ly modulate the composition of the colonic microbiota.

Different communities are observed not only along the length of the intestinal tract but also along its cross-sectional axis (Fig. 3). The epithelial tissue delimiting the lumen secretes a layer of mucus that is a nutrient source for some gut bacteria and supports an immature biofilm characterized by low cell density, with an estimated 10^5–10^6 cells in the mucus compared to 10^{11}–10^{12} in the lumen (De Weirdt and Van de Wiele, 2015). Studies of human biopsies have reported that the colonic mucus layer is slightly enriched in some taxa such as Lachnospiraceae, Ruminococcaceae, Bacteroidaceae and Coriobacteriaceae (Ouwerkerk et al., 2013; De Weirdt and Van de Wiele, 2015; Lavelle et al., 2015). Bacteroides spp. and lactic acid bacteria including L. crispatus spp., Weissella spp. and Lactococcus spp. were also found to be abundant in the mucosa-associated microbiota (Hong et al., 2011). Roseburia intestinalis and E. rectale, butyrate producers belonging to Clostridium cluster XIVa, also preferentially colonize mucs in an in vitro gut model (Van den Abbeele et al., 2013). In mice, the mucosal interfold regions are highly enriched in Firmicutes, mainly Lachnospiraceae and Ruminococcaceae (Nava et al., 2011; Li et al., 2015). Furthermore, the epithelium of the colon forms invaginations, called colonic crypts, where partial oxygen pressure as well as specific types and concentrations of host glycans can be found. These characteristics make the crypts a reservoir for mucus-degrading bacteria like...
Bacteroides fragilis (Macfarlane and Gibson, 1991; Lee et al., 2013). It should be noted, however, that differences between lumen and mucosal communities tend to be relatively small, which is likely due to extensive mucus shedding and mixing in the lumen.

The ability to metabolize the glycans and peptide backbone of mucin glycoproteins is likely to be a key factor in determining which microorganisms physically associate with the mucus layer. Non-mucolytic bacteria, however, are also found in the mucus layer (Li et al., 2015), and may use this niche either merely as a physical habitat or by scavenging partially-degraded mucins cleaved by mucolytic organisms. Both commensal and pathogenic organisms that do not possess machinery for degradation of mucins can benefit from host-derived nutrients by taking advantage of glycan subunits liberated by specialist degraders (Li et al., 2015). The glycans that decorate mucin are highly sulfated and desulfation of mucins may also support the growth of sulfate-reducing bacteria (SRB) such as Desulfovibrio spp. (Willis et al., 1996; De Weirdt and Van de Wiele, 2015) (Fig. 3). Sialylation of mucin glycans is also observed along the large intestine, and liberation of sialic acid by B. thetaiotaomicron, which secretes a sialidase but lacks the capacity to metabolize sialic acid, supports the growth of pathogens such as Clostridium difficile and S. Typhimurium (Ng et al., 2013). Similarly, E. coli was found to replicate preferentially in the mucus during re-growth after antibiotic treatment, possibly due to the utilization of sialic acid and other mucosal monosaccharides.

**Fig. 3.** Spatial heterogeneity of the gut microbiota in the gastrointestinal tract. Gradients of pH and oxygen along the longitudinal axis limit the bacterial load in the proximal regions of the small intestine, whereas the large intestine carries high bacterial loads. Simple nutrients abound in the small intestine and sustain the growth of taxa able to effectively scavenge these compounds. In contrast, the large intestine is populated by taxa that can break down recalcitrant compounds. There is also spatial heterogeneity along the cross-sectional axis of the intestine, with the mucus layer and the lumen harboring distinct microbial communities that reflect differences on nutrient availability. Fine-scale spatial structuring is observed in both the mucus and lumen, with a heterogeneous distribution of nutrients sustaining different bacterial communities at particular sites.
(Wadolkowski et al., 1988; Chang et al., 2004). Some mucin degraders, however, have developed strategies to overcome competition with non-mucolytic species for cleaved products. Ruminococcus gnavus, for example, produces an intramolecular trans-sialidase that acts on mucin and other glycoproteins, releasing 2,7-anhydro-Neu5Ac instead of sialic acid (Tailford et al., 2015), which it can utilize but many other species cannot.

Interestingly, genetically-dictated changes in the host mucus carbohydrate landscape can impact the gut microbiota. The FUT2 gene encodes an α1,2-fucosyltransferase responsible for the fucosylation of secreted mucin glycans and lack of a functional copy of this gene alters the composition of the gut microbiota (Rausch et al., 2011; Kashyap et al., 2013). The gut microbiota of mice lacking fucosylated host glycans have reduced alpha diversity and decreased levels of members of the order Clostridiales (Kashyap et al., 2013). In humans, an unclassified species belonging to the family Lachnospiraceae was also identified as indicator species in individuals lacking a functional FUT2 gene (Rausch et al., 2011). Remarkably, germ-free mice do not maintain ileal fucosylation after weaning, but colonization with the microbiota from conventionally-housed mice restores it (Umesaki et al., 1981). This suggests a feedback loop between members of the microbiota and the host, whereby some commensal species can induce host secretion of specific nutrients and benefit from these nutrients. This is also possibly a mechanism for host selection of certain species that may have been refined over long-term co-evolution (Schluter and Foster, 2012). Not all bacteria are capable of inducing fucosylation. Mono-colonization of mice with segmented filamentous bacteria (SFB) or Bacteroides thetaiotaomicron induces fucosylation, while Lactobacillus murinus does not (Umesaki et al., 1995; Bry et al., 1996; Goto et al., 2014). Both SFB and B. thetaiotaomicron can live in the mucus layer, in close proximity with the host epithelium. Interestingly, while B. thetaiotaomicron is able to induce fucosylation, a mutant unable to use L-fucose as a carbon source is much less effective in inducing fucosylation (Bry et al., 1996), suggesting that the host may be able to sense and respond to fucose levels in the lumen.

**Fine-scale spatial structuring**

Freter postulated that in addition to competition for nutrients, competition for adhesion sites may also play an important role in survival in the intestines (Freter et al., 1983a,b). This idea was based on the observation that E. coli could persist if they were the first colonizers of germ-free mice and then a complex conventional microbiota was introduced, but E. coli could not establish in mice that had already been colonized by a conventional microbiota. While Freter’s interpretation of this phenomenon was that there was competition for free adhesion sites on the intestinal wall (Freter et al., 1983b), this could also be interpreted as a priority effect in which there is an advantage in colonizing first and establishing a large population size before the introduction of other functionally-similar species (Fukami, 2015). For example, colonization of antibiotic-treated hamsters with non-toxicigenic Clostridium difficile protects against a subsequent challenge with epidemic C. difficile, most likely due to the occupation of the vacant nutrient niche by the non-epidemic strain (Nagaro et al., 2013). More recently, however, Leatham and co-authors reported that the mouse intestine selects for non-motile E. coli that have improved growth on mucosal sugars, but that the non-motile population does not completely outcompete motile E. coli in vivo (Leatham et al., 2005; Leatham-Jensen et al., 2012). The remaining motile population had mutations in the gene coding for EnvZ, a kinase which together with OmpR forms a two-component signal-transduction system that regulates outer membrane protein profiles (Leatham-Jensen et al., 2012; Adediran et al., 2014). Remarkably, the envZ mutant prevents expansion of non-motile E. coli in di-associated mice, suggesting that the mutation confers higher affinity for certain adhesion sites and that E. coli can reside in the mucus layer in mixed biofilms scavenging simple sugars released locally by other organisms (Leatham-Jensen et al., 2012; Adediran et al., 2014). These studies led to the development of the ‘Restaurant hypothesis’, which states that organisms with the same nutritional preferences can coexist if they are part of spatially-distinct biofilms where they obtain nutrients locally (Figs 1C, 2C and 3) (Leatham-Jensen et al., 2012; Adediran et al., 2014; Conway and Cohen, 2015).

The Restaurant hypothesis suggests that fine-scale spatial structuring would be important to overall ecosystem diversity (Fig. 1C). Analyses of human biopsies have found distinct mucosal-associated microbiota not only along the length of the large intestine (Zhang et al., 2014), but also in biopsies collected only one centimetre apart (Hong et al., 2011), supporting the idea of heterogeneity in mucus-associated communities on a small spatial scale. Fine-scale spatial structuring also likely exists in luminal communities, as a high level of spatial heterogeneity and discrete patches have been observed in selected bacteria in feces (Swidsinski et al., 2008) (Fig. 3). Patchiness in feces may be due to aggregates of interacting microorganisms, micro-environments originating from detached mucus, or heterogeneity of nutrient availability due to dietary fibres. The insoluble and liquid fractions of human feces have distinct microbiota and there is a specialized community associated with food...
particles (Walker et al., 2008). In homogenized diets, such as powder diets used for laboratory mice, there is a reduction of diversity in the microbiota compared to the same diet in pellet form (Clavel et al., 2014). Thus, dietary fibre seems to promote microbial diversity both by providing nutrient niches as well as creating spatial structure, indicating that the Restaurant hypothesis may also be applicable to luminal communities.

No microbe is an island: interactions and dependencies in nutrient niches

Functional redundancy, or the co-existence of functionally-similar organisms, is often considered to be an important feature of the gut ecosystem that contributes to robustness and resilience (Moya and Ferrer, 2016). However, some key metabolic activities may be restricted to one or few species, called ‘keystone’ species or taxa. A keystone species has a large impact on the rest of the community (Figs 1E and 2E), and has sometimes also been defined as having a disproportionately low abundance relative to its impact on the ecosystem (Paine, 1966; Paine, 1969; Mills et al., 1993), though the low abundance criterion is not always applied. For example, degradation of dietary compounds such as starch by amylases of R. bromii leads to increased starch utilization by a number of other gut species (Ze et al., 2012). Because many community members depend on this primary starch degrader to provide them with soluble growth substrates, R. bromii is thought to be a keystone species. Co-culture of Akkermansia muciniphila, a mucus degrader, enhances growth of Bacteroides vulgatus in mucin as the sole carbon source, thus functioning as a keystone species in the utilization of mucosal compounds (Png et al., 2010). Hydrogenotrophic organisms, which are largely dependent on the activity of fermenters for hydrogen and other compounds such as sulfate and sulfite cleaved from dietary- and host-derived compounds, may also be keystones due to their ability to modulate hydrogen levels and thereby affect the activity of fermentative organisms and the energy extraction efficiency of the entire community (Carbonero et al., 2012; Rey et al., 2013).

Members of the Bacteroides are able to use a wide range of polysaccharides and a number of closely-related species can co-exist in the gut by cross-feeding, resulting in complete polysaccharide utilization. For instance, Bacteroides ovatus releases glycoside hydrolases to break down inulin, but can utilize inulin without extracellular degradation (Rakoff-Nahoum et al., 2016). Extracellular inulin breakdown by B. ovatus, however, allows B. vulgatus to use cleaved inulin products which would have been unavailable to it (Rakoff-Nahoum et al., 2014; Rakoff-Nahoum et al., 2016). B. vulgatus, in turn, increases B. ovatus fitness, presumably through detoxification of inhibitory substances or production of growth-promoting factors. These secreted glycoside hydrolases can be viewed as public goods, yielding polysaccharide breakdown products that allow the growth of other organisms otherwise unable to grow on it. Production of public goods results in a complex polysaccharide utilization network that contributes to the creation of organized ecological units within the gut microbiota (Rakoff-Nahoum et al., 2014; Rakoff-Nahoum et al., 2016). The presence of insoluble substrates in the gut may serve as a scaffold to spatially organize public goods-based interactions not only between the Bacteroidales, but also Firmicutes and other less abundant members of this ecosystem (Walker et al., 2008). Theoretical considerations suggest that dependencies and cooperation would be intrinsically unstable (Oliveira et al., 2014). This instability may be partially ameliorated by dependencies that can be fulfilled by many different organisms, such as the relationship between fermenters and hydrogenotrophs. Additionally, cooperation may be non-obligate and the metabolic versatility of cooperators may allow them to switch their realized niche in the absence of their partner, thereby facilitating conditional cooperation (Figs 1E and 2E).

Outlook: characterizing realized nutrient niches

Assembly of the gut microbiota is largely deterministic and driven by the nutrient landscape created by diet and host secretions. The realized metabolic niche of members of the microbiota is shaped both by nutrient availability as well as the presence of other competing or cooperating species and resulting niche partitioning (Figs 1 and 2). Freter’s classic nutrient niche theory, which states that the abundance of each species is determined by a single limiting nutrient, is a conceptually useful model of assembly that has been supported by experimental work in gnotobiotic animal experiments. However, the validity of this model has been challenged by observations of mixed-substrate utilization and metabolic flexibility as well as heterogeneity in nutrient levels in time and space. These processes weaken competitive exclusion and allow for increased diversity, which is likely critical for ecosystem robustness.

A deeper understanding of the in situ metabolic niche of individual members of the microbiota is needed in order to better comprehend the relative importance of the above-mentioned processes. As metabolic strategies that define the realized niche are highly dependent on ecological context, this is best explored by direct analysis of the complex microbe. To dissect these niches, specialized tools that allow for study of the activity of complex microbial communities should be applied.
These include metatranscriptomics (Franzosa et al., 2014; Franzosa et al., 2015; Plichta et al., 2016), metaproteomics and metabolomics (Ferrer et al., 2013; Therriot et al., 2014; Franzosa et al., 2015), stable isotope probing (Tannock et al., 2014; Young et al., 2015), as well as single-cell tools such as FISH and single-cell stable isotope probing (Berry et al., 2013; Stecher et al., 2013; Berry et al., 2015) which can uniquely be used to study fine-scale spatial heterogeneity in composition and activity. An improved understanding of nutrient niches and assembly of the gut microbiota will open the way to customized design of communities and novel therapeutic strategies to effectively modulate the microbiota to improve health.

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References

Adeyiran, J., Leatham-Jensen, M.P., Mokrzycki, M.E., Frimodt-Moller, J., Krogfelt, K.A., Kazmierczak, K., et al. (2014) An Escherichia coli Nissle 1917 missense mutant colonizes the streptomycin-treated mouse intestine better than the wild type but is not a better probiotic. Infect Immun 82: 670–682.

Berry, D., Stecher, B., Schintlmüller, A., Reichert, J., Brugiroux, S., Wild, B., et al. (2013) Host-compound foraging by intestinal microbiota revealed by single-cell stable isotope probing. Proc Natl Acad Sci U S A 110: 4720–4725.

Berry, D., Mader, E., Lee, T.K., Woebken, D., Wang, Y., Zhu, D., et al. (2015) Tracking heavy water (D2O) incorporation for identifying and sorting active microbial cells. Proc Natl Acad Sci U S A 112: E194–E203.

Booijink, C.C., El-Aidy, S., Rajilic-Stojanovic, M., Hellig, H.G., Troost, F.J., Smidt, H., et al. (2010) High temporal and inter-individual variation detected in the human ileal microbiota. Environ Microbiol 12: 3213–3227.

Brugiroux, S., Beutler, M., Pfann, C., Garzetti, D., Ruscheweyh, H.J., Ring, D., et al. (2016) Genome-guided design of a defined mouse microbiota that confers colonization resistance against Salmonella enterica serovar Typhimurium. Nat Microbiol 2: 16215.

Bry, L., Falk, P.G., Midtvedt, T., and Gordon, J.I. (1996) A model of host-microbial interactions in an open mammalian ecosystem. Science 273: 1380–1383.

Burns, A.R., Stephens, W.Z., Stagaman, K., Wong, S., Rawls, J.F., Guillemin, K., and Bohannan, B.J. (2016) Contribution of neutral processes to the assembly of gut microbial communities in the zebrafish over host development. ISME J 10: 655–664.

Cadotte, M.W. (2006) Dispersal and species diversity: a meta-analysis. Am Nat 167: 913–924.

Carbonero, F., Benefiel, A.C., Alizadeh-Ghamsari, A.H., and Gaskins, H.R. (2012) Microbial pathways in colonic sulfur metabolism and links with health and disease. Front Physiol 3: 448.

Carmody, R.N., Gerber, G.K., Luevano, J.M., Jr., Gatti, D.M., Somes, L., Svenson, K.L., and Turnbaugh, P.J. (2015) Diet dominates host genotype in shaping the murine gut microbiota. Cell Host Microbe 17: 72–84.

Caswell, H. (1976) Community structure: a neutral model analysis. Ecol Monogr 46: 327–354.

Chang, D.E., Smalley, D.J., Tucker, D.L., Leatham, M.P., Norris, W.E., Stevenson, S.J., et al. (2004) Carbon nutrition of Escherichia coli in the mouse intestine. Proc Natl Acad Sci U S A 101: 7427–7432.

Chase, J.M., and Myers, J.A. (2011) Disentangling the importance of ecological niches from stochastic processes across scales. Philos Trans R Soc B Biol Sci 366: 2351–2363.

Chung, W.S., Walker, A.W., Louis, P., Parkhill, J., Vermeiren, J., Bosscher, D., et al. (2016) Modulation of the human gut microbiota by dietary fibres occurs at the species level. BMC Biol 14: 3.

Clavel, T., Desmarchelier, C., Haller, D., Gerard, P., Rohn, S., Lepage, P., and Daniel, H. (2014) Intestinal microbiota in metabolic diseases: from bacterial community structure and functions to species of pathophysiological relevance. Gut Microbes 5: 544–551.

Conway, T., and Cohen, P. (2015) Applying the restaurant hypothesis to intestinal microbiota. Microbe Mag 10: 324–328.

Costello, E.K., Gordon, J.I., Secor, S.M., and Knight, R. (2010) Postprandial remodeling of the gut microbiota in Burmese pythons. ISME J 4: 1375–1385.

Costello, E.K., Stagaman, K., Dethlefsen, L., Bohannan, B.J., and Relman, D.A. (2012) The application of ecological theory toward an understanding of the human microbiome. Science 336: 1255–1262.

Crawford, P.A., Crowley, J.R., Sambandam, N., Muegge, B.D., Costello, E.K., Hamady, M., et al. (2009) Regulation of myocardial ketone body metabolism by the gut microbiota during nutrient deprivation. Proc Natl Acad Sci U S A 106: 11276–11281.

David, L.A., Materna, A.C., Friedman, J., Campos-Baptista, M.I., Blackburn, M.C., Perrotta, A., et al. (2014a) Host lifestyle affects human microbiota on daily timescales. Genome Biol 15: R89.

David, L.A., Maurice, C.F., Carmody, R.N., Gootenberg, D.B., Button, J.E., Wolfe, B.E., et al. (2014b) Diet rapidly and reproducibly alters the human gut microbiome. Nature 505: 559–563.

De Filippo, C., Cavalleri, D., Di Paola, M., Ramazzotti, M., Poulet, J.B., Massart, S., et al. (2010) Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci U S A 107: 14691–14696.

De Weir, R., and Van de Wiele, T. (2015) Micromanagement in the gut: microenvironmental factors govern colon mucosal biofilm structure and functionality. NPJ Biofilms Microbiomes 1: 15026.

Deriu, E., Liu, J.Z., Pezeshki, M., Edwards, R.A., Ochoa, R.J., Contreras, H., et al. (2013) Probiotic bacteria reduce
**Salmonella** Typhimurium intestinal colonization by competing for iron. *Cell Host Microbe* **14**: 26–37.

Donaldson, G.P., Lee, S.M., and Mazmanian, S.K. (2016) Gut biogeography of the bacterial microbiota. *Nat Rev Microbiol* **14**: 20–32.

Duncan, S.H., Russell, W.R., Quartieri, A., Rossi, M., Parkhill, J., Walker, A.W., and Flint, H.J. (2016) Wheat bran promotes enrichment within the human colonic microbiota of butyrate-producing bacteria that release ferulic acid. *Environ Microbiol* **18**: 2214–2225.

Elton, C.S. (1927) *Animal Ecology*. London: Sidwich & Jackson.

Faith, J.J., McNulty, N.P., Rey, F.E., and Gordon, J.I. (2011) Historical contingency in community biogeography of the bacterial microbiota. *Nat Rev Microbiol* **11**: 109–123.

Ferrer, M., Ruiz, A., Lanza, F., Haange, S.B., Oberbach, A., Till, H., et al. (2013) Microbiota from the distal guts of lean and obese adolescents exhibit partial functional redundancy besides clear differences in community structure. *Environ Microbiol* **15**: 211–226.

Flint, H.J., Scott, K.P., Duncan, S.H., Louis, P., and Forano, E. (2012) Microbial degradation of complex carbohydrates in the gut. *Gut Microbes* **3**: 289–306.

Franzosa, E.A., Morgan, X.C., Segata, N., Waldron, L., Reyes, J., Earl, A.M., et al. (2014) Relating the metatranscriptome and metagenome of the human gut. *Proc Natl Acad Sci U S A* **111**: E2329–E2338.

Franzosa, E.A., Hsu, T., Sirola-Madi, A., Shafquat, A., Abu-Al, G., Morgan, X.C., and Huttenhower, C. (2015) Sequencing and beyond: integrating molecular ‘omics’ for microbial community profiling. *Nat Rev Microbiol* **13**: 360–372.

Freter, R., Bricker, H., Botney, M., Cosen, D., and Aranik, A. (1983a) Mechanisms that control bacterial populations in continuous-flow culture models of mouse large intestinal flora. *Infect Immun* **39**: 676–685.

Freter, R., Bricker, H., Fekete, J., Vickersman, M.M., and Carey, K.E. (1983b) Survival and implantation of *Escherichia coli* in the intestinal tract. *Infect Immun* **39**: 686–703.

Fukami, T. (2015) Historical contingency in community assembly: integrating niches, species pools, and priority effects. *Annu Rev Ecol Evol Syst* **46**: 1–23.

Goto, Y., Obata, T., Kunisawa, J., Sato, S., Ivanov, I.I., Lamicichane, A., et al. (2014) Innate lymphoid cells regulate intestinal epithelial cell glycosylation. *Science* **345**: 1254009.

Gu, S., Chen, D., Zhang, J.N., Lv, X., Wang, K., Duan, L.P., et al. (2013) Bacterial community mapping of the mouse gastrointestinal tract. *PLoS One* **8**: e74957.

He, G., Shankar, R.A., Chzhan, M., Samouilov, A., Kuppusamy, P., and Zweier, J.L. (1999) Noninvasive measurement of anatomic structure and intraluminal oxygenation in the gastrointestinal tract of living mice with spatial and spectral EPR imaging. *Proc Natl Acad Sci U S A* **96**: 4586–4591.

Hong, P.Y., Croix, J.A., Greenberg, E., Gaskins, H.R., and Mackie, R.I. (2011) Pyrosequencing-based analysis of the mucosal microbiota in healthy individuals reveals ubiquitous bacterial groups and micro-heterogeneity. *PLoS One* **6**: e25042.

Hubbell, S.P. (2001) *The Unified Neutral Theory of Biodiversity and Biogeography*. Princeton, NJ: Princeton University Press.

Hutchinson, G.E. (1957) Concluding remarks. *Cold Spring Harb Symp Quant Biol* **41**: 415–427.

Ivarsson, E., Roos, S., Liu, H.Y., and Lindberg, J.E. (2014) Fermentable non-starch polysaccharides increases the abundance of *Bacteroides-Prevotella-Porphyromonas* in ileal microbial community of growing pigs. *Animal* **8**: 1777–1787.

Jeraldo, P., Sipos, M., Chia, N., Bruc, J.M., Dhillon, A.S., Konkel, M.E., et al. (2012) Quantification of the relative roles of niche and neutral processes in structuring gastrointestinal microbiomes. *Proc Natl Acad Sci U S A* **109**: 9692–9698.

Kashyap, P.C., Marcobal, A., Ursell, L.K., Smits, S.A., Sonnenburg, E.D., Costello, E.K., et al. (2013) Genetically dictated change in host mucus carbohydrate landscape exerts a diet-dependent effect on the gut microbiota. *Proc Natl Acad Sci U S A* **110**: 17059–17064.

Kovarova-Kovar, K., and Egli, T. (1998) Growth kinetics of suspended microbial cells: from single-substrate-controlled growth to mixed-substrate kinetics. *Microbiol Mol Biol Rev* **62**: 646–666.

Lavelle, A., Lennon, G., O’Sullivan, O., Docherty, N., Balfe, A., Maguire, A., et al. (2015) Spatial variation of the colonic microbiota in patients with ulcerative colitis and control volunteers. *Gut* **64**: 1553–1561.

Lawdy, T.D., Clare, S., Walker, A.W., Stares, M.D., Connor, T.R., Raisen, C., et al. (2012) Targeted restoration of the intestinal microbiota with a simple, defined bacteriotherapy resolves relapsing *Clostridium difficile* disease in mice. *PLoS Pathog* **8**: e1002995.

Leatham-Jensen, M.P., Frimodt-Moller, J., Adediran, J., Mokszycki, M.E., Banner, M.E., Caughron, J.E., et al. (2012) The streptomycin-treated mouse intestine selects *Escherichia coli envZ* missense mutants that interact with dense and diverse intestinal microbiota. *Infect Immun* **80**: 1716–1727.

Leatham, M.P., Stevenson, S.J., Gauger, E.J., Krogfelt, K.A., Lins, J.J., Haddock, T.L., et al. (2005) Mouse intestinal selects nonmotile *flhDC* mutants of *Escherichia coli* MG1655 with increased colonizing ability and better utilization of carbon sources. *Infect Immun* **73**: 8039–8049.

Lee, S.M., Donaldson, G.P., Mikulski, Z., Boyajian, S., Ley, K., and Mazmanian, S.K. (2013) Bacterial colonization factors control specificity and stability of the gut microbiota. *Nature* **501**: 426–429.

Leone, V., Gibbons, S.M., Martinez, K., Hutchison, A.L., Huang, E.Y., Cham, C.M., et al. (2015) Effects of diurnal variation of gut microbes and high-fat feeding on host circadian clock function and metabolism. *Cell Host Microbe* **17**: 681–689.

Li, H., Limenitakis, J.P., Fuhrer, T., Geuking, M.B., Lawson, M.A., Wyss, M., et al. (2015) The outer mucus layer hosts a distinct intestinal microbial niche. *Nat Commun* **6**: 8292.

Li, L., and Ma, Z.S. (2016) Testing the neutral theory of biodiversity with human microbiome datasets. *Sci Rep* **6**: 31448.

Macfarlane, G.T., and Gibson, G.R. (1991) Formation of glycoprotein-degrading enzymes by *Bacteroides fragilis*. *FEMS Microbiol Lett* **61**: 289–293.

Macfarlane, G.T., Steed, H., and Macfarlane, S. (2008) Bacterial metabolism and health-related effects of galacto-
olfosaccharides and other prebiotics. *J Appl Microbiol* **104**: 305–344.

Maldonado-Gomez, M.X., Martinez, I., Bottacini, F., O’Callaghan, A., Ventura, M., van Sinderen, D., et al. (2016) Stable engraftment of *Bifidobacterium longum* AH1206 in the human gut depends on individualized features of the resident microbiome. *Cell Host Microbe* **20**: 515–526.

Maltby, R., Leatham-Jensen, M.P., Gibson, T., Cohen, P.S., and Conway, T. (2013) Nutritional basis for colonization resistance by human commensal *Escherichia coli* strains HS and Nissle 1917 against *E. coli* O157:H7 in the mouse intestine. *PLoS One* **8**: e53957.

Martinez, I., Stegen, J.C., Maldonado-Gomez, M.X., Eren, A.M., Siba, P.M., Greenhill, A.R., and Walter, J. (2015) The gut microbiota of rural papua new guineans: composition, diversity patterns, and ecological processes. *Cell Rep* **11**: 527–538.

Martinez, I., Kim, J., Duffy, P.R., Schlegel, V.L., and Walter, J. (2010) Resistant starches types 2 and 4 have differential effects on the composition of the fecal microbiota in human subjects. *PLoS One* **5**: e15046.

Mills, L.S., Soule, M.E., and Doak, D.F. (1993) The keystone-species concept in ecology and conservation. *BioScience* **43**: 219–224.

Moya, A., and Ferrer, M. (2016) Functional redundancy-induced stability of gut microbiota subjected to disturbance. *Trends Microbiol* **24**: 402–413.

Nagaro, K.J., Phillips, S.T., Cheknis, A.K., Sambol, S.P., Zukowski, W.E., Johnson, S., and Gerding, D.N. (2013) Nontoxigenic *Clostridium difficile* protects hamsters against challenge with historic and epidemic strains of toxigenic BI/NAP1/027 *C. difficile*. *Antimicrob Agents Chemother* **57**: 5266–5270.

Nava, G.M., Friedrichsen, H.J., and Stappenbeck, T.S. (2011) Spatial organization of intestinal microbiota in the mouse ascending colon. *ISME J* **5**: 627–638.

Ng, K.M., Ferreyra, J.A., Higginbottom, S.K., Lynch, J.B., Kashyap, P.C., Gopinath, S., et al. (2013) Microbiota-liberated host sugars facilitate post-antibiotic expansion of enteric pathogens. *Nature* **502**: 96–99.

O’Hara, A.M., and Shanahan, F. (2006) The gut flora as a forgotten organ. *EMBO Rep* **7**: 688–693.

Oliveira, N.M., Niehus, R., and Foster, K.R. (2014) Evolutionary limits to cooperation in microbial communities. *Proc Natl Acad Sci U S A* **111**: 17941–17946.

Ouwерkerk, J.P., de Vos, W.M., and Belzer, C. (2013) Glycobiome: bacteria and mucus at the epithelial interface. *Best Pract Res Clin Gastroenterol* **27**: 25–38.

Paine, R.T. (1966) Food web complexity and species diversity. *Am Nat* **100**: 65–75.

Paine, R.T. (1969) A note on trophic complexity and community stability. *Am Nat* **103**: 91–93.

Plank, E.R. (1970) On r- and K-Selection. *Am Nat* **104**: 592–597.

Plichta, D.R., Juncker, A.S., Bertalan, M., Rettedal, E., Gautier, L., Varela, E., et al. (2016) Transcriptional interactions suggest niche segregation among microorganisms in the human gut. *Nat Microbiol* **1**: 16152.

Png, C.W., Linden, S.K., Gilshenan, K.S., Zoetendal, E.G., McSweeney, C.S., Sly, L.I., et al. (2010) Mucoytic bacteria with increased prevalence in IBD mucosa augment in vitro utilization of mucin by other bacteria. *Am J Gastroenterol* **105**: 2420–2428.

Rakoff-Nahoum, S., Coyne, M.J., and Comstock, L.E. (2014) An ecological network of polysaccharide utilization among human intestinal symbionts. *Curr Biol* **24**: 40–49.

Rakoff-Nahoum, S., Foster, K.R., and Comstock, L.E. (2016) The evolution of cooperation within the gut microbiota. *Nature* **533**: 255–259.

Ramírez-Farias, C., Szlezak, K., Fuller, Z., Duncan, A., Holtrop, G., and Louis, P. (2009) Effect of inulin on the human gut microbiota: stimulation of *Bifidobacterium adolescentis* and *Faecalibacterium prausnitzii*. *Br J Nutr* **101**: 541–550.

Rausch, P., Rehman, A., Kunzel, S., Hasler, R., Ott, S.J., Schreiber, S., et al. (2011) Colonic mucosa-associated microbiota is influenced by an interaction of Crohn disease and FUT2 (Secretor) genotype. *Proc Natl Acad Sci U S A* **108**: 19030–19035.

Rey, F.E., Gonzalez, M.D., Cheng, J., Wu, M., Ahern, P.P., and Gordon, J.I. (2013) Metabolic niche of a prominent sulfate-reducing human gut bacterium. *Proc Natl Acad Sci U S A* **110**: 13582–13587.

Roager, H.M., Hansen, L.B., Bahl, M.I., Frandsen, H.L., Carvalho, V., Gobel, R.J., et al. (2016) Colonic transit time is related to bacterial metabolism and mucosal turnover in the gut. *Nat Microbiol* **1**: 16093.

Rosindell, J., Hubbell, S.P., and Etienne, R.S. (2011) The unified neutral theory of biodiversity and biogeography at age ten. *Trends Ecol Evol* **26**: 340–348.

Sala, C., Vitali, S., Giampieri, E., de Val, I.F., Remondini, D., Garagnani, P., et al. (2016) Stochastic neutral modelling of the Gut Microbiota’s relative species abundance from next generation sequencing data. *BMC Bioinformatics* **17(Suppl 2):** 16.

Schluter, J., and Foster, K.R. (2012) The evolution of mutualism in gut microbiota via host epithelial selection. *PLoS Biol* **10**: e1001424.

Schnorr, S.L., Candela, M., Rampelli, S., Centanni, M., Consolandi, C., Basaglia, G., et al. (2014) Gut microbiome of the Hadza hunter-gatherers. *Nat Commun* **5**: 3654.

Seedorf, H., Griffin, N.W., Ridaaura, V.K., Reyes, A., Cheng, J., Rey, F.E., et al. (2014) Bacteria from diverse habitats colonize and compete in the mouse gut. *Cell* **159**: 253–266.

Sloan, W.T., Lunn, M., Woodcock, S., Head, I.M., Nee, S., and Curtis, T.P. (2006) Quantifying the roles of immigration and chance in shaping prokaryote community structure. *Environ Microbiol* **8**: 732–740.

Sommer, F., Stahlman, M., Ilkayeva, O., Arneumo, J.M., Kindberg, J., Josephsson, J., et al. (2016) The gut microbiota modulates energy metabolism in the hibernating brown bear *Ursus arctos*. *Cell Rep* **14**: 1655–1661.

Sonoyama, K., Fujiwara, R., Takemura, N., Ogawara, T., Watanabe, J., Ito, H., and Morita, T. (2009) Response of gut microbiota to fasting and hibernation in Syrian hamsters. *Appl Environ Microbiol* **75**: 6451–6456.

Stecher, B., Berry, D., and Loy, A. (2013) Colonization resistance and microbial ecophysiology: using gnotobiotic mouse models and single-cell technology to explore the intestinal jungle. *FEMS Microbiol Rev* **37**: 793–829.
Steeb, B., Claudi, B., Burton, N.A., Tienz, P., Schmidt, A., Farhan, H., et al. (2013) Parallel exploitation of diverse host nutrients enhances Salmonella virulence. *PLoS Pathog* 9: e1003301.

Swidsinski, A., Loening-Baucke, V., Verstraelen, H., Osowska, S., and Doerffel, Y. (2008) Biosis of fecal microbiota in healthy subjects and patients with chronic idiopathic diarrhea. *Gastroenterology* 135: 568–579.

Tailford, L.E., Crost, E.H., Kavanaugh, D., and Juge, N. (2015) Mucin glycan foraging in the human gut microbiome. *Front Genet* 6: 81.

Tannock, G.W., Wilson, C.M., Loach, D., Cook, G.M., Eason, J., O’Toole, P.W., et al. (2012) Resource partitioning in relation to cohabitation of *Lactobacillus* species in the mouse forestomach. *ISME J* 6: 927–938.

Tannock, G.W., Lawley, B., Munro, K., Sims, I.M., Lee, J., Butts, C.A., and Roy, N. (2014) RNA-stable-isotope probing shows utilization of carbon from inulin by specific bacterial populations in the rat large bowel. *Appl Environ Microbiol* 80: 2240–2247.

Thaiss, C.A., Zeevi, D., Levy, M., Zilberman-Schapia, G., Suez, J., Tengeler, A.C., et al. (2014) Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell* 159: 514–529.

Theriot, C.M., Koenigsknacht, M.J., Carlson, P.E., Jr., Hatton, G.E., Nelson, A.M., Li, B., et al. (2014) Antibiotic-induced shifts in the mouse gut microbiome and metabolome increase susceptibility to *Clostridium difficile* infection. *Nat Commun* 5: 3114.

Turnbaugh, P.J., Ridaura, V.K., Faith, J.J., Rey, F.E., Knight, R., and Gordon, J.I. (2009) The effect of diet on the human gut microbiome: a metagenetic analysis in humanized gnotobiotic mice. *Sci Transl Med* 1: 6ra14.

Umesaki, Y., Tohyama, K., and Mutai, M. (1981) Appearance of fucolipid after conventionalization of germ-free mice. *J Biochem* 90: 559–561.

Umesaki, Y., Okada, Y., Matsumoto, S., Imaoka, A., and Setoyama, H. (1995) Segmented filamentous bacteria are indigenous intestinal bacteria that activate intraepithelial lymphocytes and induce MHC class II molecules and fucosyl asialo GM1 glycolipids on the small intestinal epithelial cells in the ex-germ-free mouse. *Microbiol Immunol* 39: 555–562.

Van den Abbeele, P., Belzer, C., Goossens, M., Kleebergez, M., De Vos, W.M., Thas, O., et al. (2013) Butyrate-producing *Clostridium* cluster XIa species specifically colonize mucins in an in vitro gut model. *ISME J* 7: 949–961.

Vanpeppelt, D., Falony, G., Vieira-Silva, S., Tito, R.Y., Joossens, M., and Raes, J. (2016) Stool consistency is strongly associated with gut microbiota richness and composition, enterotypes and bacterial growth rates. *Gut* 65: 57–62.

Venkataraman, A., Bassis, C.M., Beck, J.M., Young, V.B., Curtis, J.L., Huffnagle, G.B., and Schmidt, T.M. (2015) Application of a neutral community model to assess structuring of the human lung microbiome. *MBio* 6: 1.

Wadolkowski, E.A., Laux, D.C., and Cohen, P.S. (1988) Colonization of the streptomycin-treated mouse large intestine by a human fecal *Escherichia coli* strain: role of growth in mucus. *Infect Immun* 56: 1030–1035.

Walker, A.W., Duncan, S.H., Harmsen, H.J., Holtrop, G., Wellin, G.W., and Flint, H.J. (2008) The species composition of the human intestinal microbiota differs between particle-associated and liquid phase communities. *Environ Microbiol* 10: 3275–3283.

Walker, A.W., Ince, J., Duncan, S.H., Webster, L.M., Holtrop, G., Ze, X., et al. (2011) Dominant and diet-responsive groups of bacteria within the human colonic microbiota. *ISME J* 5: 220–230.

Willis, C.L., Cummings, J.H., Neale, G., and Gibson, G.R. (1996) In vitro effects of mucin fermentation on the growth of human colonic sulphate-reducing bacteria. *Anaerobe* 2: 117–122.

Woodcock, S., van der Gast, C.J., Bell, T., Lunn, M., Curtis, T.P., Head, I.M., and Sloan, W.T. (2007) Neutral assembly of bacterial communities. *FEBS Microbiol Ecol* 62: 171–180.

Wu, G.D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y.Y., Keilbaugh, S.A., et al. (2011) Linking long-term dietary patterns with gut microbial enterotypes. *Science* 334: 105–108.

Wu, M., McNulty, N.P., Rodionov, D.A., Khoroshkin, M.S., Griffin, N.W., Cheng, J., et al. (2015) Genetic determinants of in vivo fitness and diet responsiveness in multiple human gut *Bacteroides*. *Science* 350: aac5992.

Yasuda, K., Oh, K., Ren, B., Tickle, T.L., Franzosa, E.A., Wachtman, L.M., et al. (2015) Biogeography of the intestinal mucosal and luminal microbiome in the rhesus macaque. *Cell Host Microbe* 17: 385–391.

Yatsunenko, T., Rey, F.E., Manary, M.J., Trehan, I., Dominguez-Bello, M.G., Contreras, M., et al. (2012) Human gut microbiome viewed across age and geography. *Nature* 486: 222–227.

Young, W., Egert, M., Bassett, S.A., and Bibiloni, R. (2015) Detection of silicic acid-utilising bacteria in a caecal community batch culture using RNA-based stable isotope probing. *Nutrients* 7: 2109–2124.

Zarrinpar, A., Chaix, A., Yooshef, S., and Panda, S. (2014) Diet and feeding pattern affect the diurnal dynamics of the gut microbiome. *Cell Metab* 20: 1006–1017.

Ze, X., Duncan, S.H., Louis, P., and Flint, H.J. (2012) *Ruminococcus bromii* is a keystone species for the degradation of resistant starch in the human colon. *ISME J* 6: 1535–1543.

Zhang, Z., Geng, J., Tang, X., Fan, H., Xu, J., Wen, X., et al. (2014) Spatial heterogeneity and co-occurrence patterns of human mucosal-associated intestinal microbiota. *ISME J* 8: 881–893.

Zoetendal, E.G., Raes, J., van den Bogert, B., Armugam, M., Booijink, C.C., Troost, F.J., et al. (2012) The human small intestinal microbiota is driven by rapid uptake and conversion of simple carbohydrates. *ISME J* 6: 1415–1426.