Metabolic Teamwork between Gut Microbes and Hosts

In processing energy, furnishing key nutrients, and detoxifying xenobiotics, microbial diversity matters for hosts

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Symbiotic relationships between microbes and their animal and plant hosts shape our world. Interest in these host-microbial interactions is intensifying, and researchers from many disciplines within biology are striving to understand their functional and evolutionary significance.

Those of us studying animal feeding, digestion, and nutrition appreciate the key role microbes played in shaping the biodiversity of vertebrates. For instance, microbial fermentations unlock energy from cellulose, the most abundant organic compound on Earth. Thus, gut microbes enable animals to thrive as herbivores, a primordial step that led to a huge diversification of animal species. Modern molecular analytic techniques make it possible for us to learn more about these important symbioses.

Biodiversity in Host-Microbial Systems

Phylogenetic analyses indicate that fermentative digestion evolved repeatedly and independently in vertebrates. Further, herbivores have diverse gut structures, thereby providing many different environmental situations for gut microbes (Fig. 1). Consider three distinct examples.

In herbivores with foregut fermentation, the microbial fermentation chamber is proximal to the small intestine. This configuration developed independently in four clades of mammals, including ruminants such as cows and deer, colubid monkeys, sloths, macropod marsupials such as the kangaroo, and at least once in birds, including the hoatzin, Opisthocomus hoazin in South America. These groups all share a key feature: their resident microbial communities have first crack at ingested nutrients before any food reaches the host small intestine. Yet, as described below, there are some examples that illustrate important differences among foregut fermenters.

The nutritional milieu of foregut fermenters differs from that of hindgut fermenters, animals in which the fermentation chamber is distal to the stomach and small intestine (Fig. 1). Because the small intestine absorbs most soluble carbohydrates, proteins, and lipids, the residue that arrives at the hindgut contains lower levels of those nutrients but more of structural materials such as cell walls. Thus, microbes in hindguts receive the dregs compared with what microbes in foreguts receive, a fact with important implications for host-microbial processing.

Some vertebrate hosts process food much more slowly than others because of

Summary

- Microbial diversity in the gut tremendously increases metabolic pathways accessible to hosts for energy, essential nutrients, and detoxifying xenobiotics.
- Differences in gut structure yield diverse niches and microbiota.
- Diversity at the microbial species level sometimes lacks functional significance because of redundancies in the metagenome.
- Specificity within the microbiota matters in certain cases, such as glycan processing by acetogens versus methanogens and the detoxification of particular xenobiotics.

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differences in gut morphology or metabolic mode. The period that digesta remains in the gut is called digesta retention time and is typically measured with marked food particles. For instance, reptiles have digesta retention times 5–10 times longer than those of similar-sized mammals. Among mammals, sloths have particularly long retention times. Such differences have important implications for the kinds of microbial community that these hosts can sustain.

In general, reptiles operate at lower and more variable body temperatures than do mammals and birds, another host variable that may influence gut microbiota. Differences in nutrient milieu, retention time, and temperature can foster diverse microbial niches and mixtures that older culture-based methods vastly underestimate. Recent efforts to reevaluate microbial richness in the rumen, for example, by analyzing 16S rRNA gene sequences suggest that the typical rumen contains 300–400 bacterial “species,” on the basis of operational taxonomic units (OTUs)—a figure that is about 10 times higher than culture-based estimates.

Furthermore, similar analyses of gut microbial communities in the fermentative chambers of previously unexamined herbivores typically indicate high proportions of previously undescribed sequences, suggesting the presence of novel microbial species. Indeed, on average, 62% of OTUs within guts of mammalian hosts were not observed in any other species, according to a recent survey across 60 mammal species by Ruth Ley, Jeffrey Gordon, and their collaborators at Washington University in St. Louis, Mo.

Besides differences among animal species, microbial biodiversity can vary among populations within species and even among individuals within populations. The genetic, developmental, and environmental (e.g., diet) determinants of all this microbial biodiversity in guts remain to be determined. Interpreting the functional significance of this microbial biodiversity will require a detailed understanding of processes in which microbes are involved. One of the better understood of those processes is fermentative digestion of cellulose.

**Cellulose Fermentations Involving Microbial Consortia**

When microbial communities living within the rumen of herbivores degrade cellulose and other
glycans, they yield short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, for the host to absorb to meet its energy needs (Fig. 2). The metabolic pathways that produce SCFAs involve sequential fermentations by several microbial taxa in consortia.

These pathways are part of a complex ecological food web whose microbial members exchange intermediates. When more than one microbial species within a community performs the same reactions, they create a functional redundancy. Thus, the overall degradative process goes on, even though some species may replace others with similar metabolic roles. Indeed, some fraction of microbial biodiversity may have relatively little functional significance.

A few decades ago, some ecologists fermented plant foods in vitro to estimate the digestive efficiency of wild ruminants, namely that fraction of the energy or nutrients in food available to its consumer. This approach to measuring digestive efficiencies is cheaper than is capturing wild animals and then collecting both their food and excreta to determine what they digested. Researchers validate in vitro fermentation estimates by comparing them with whole-animal studies (Fig. 3).

Surprisingly, whether the rumen inoculum was from a deer or a cow and regardless of the diet consumed, the results are about the same across several dozen of these studies. However, our recently developed view of how high gut microbial biodiversity creates functional redundancy helps to explain these results.

In other cases, differences in gut microbial communities lead to important functional differences. For example, microbes may be involved in removing hydrogen that builds up in these systems through one of several alternative pathways (Fig. 2). One such group includes methanogens that reduce hydrogen to methane, which vertebrate hosts cannot use as an energy source. Many methanogens are members of the archaea, with relatively long generation times. Another group for removing hydrogen consists of acetogenic bacteria with shorter generation times. They produce acetate, which hosts can absorb for use as an energy source.

**Biodiversity Matters for Foregut Fermenters**

Ruminants such as cows and macropod marsupials such as kangaroos are both foregut fermenters. However, kangaroos apparently contain no methanogenic microbes and produce relatively little methane, whereas 10–15% of the energy flow for ruminants is lost as methane gas.

Differences in gut morphology help to account for this difference. The ruminant foregut is like a continuous stirred-tank reactor that retains food particles until they are small enough...
to exit. In contrast, the macropod marsupial foregut is tubular, with outpouches that retard flow but nothing like the particle size-dependent mechanism in ruminants. Thus, digesta retention times are much shorter in marsupials than in similar-sized ruminants.

Differences between ruminants and kangaroos provoke other questions. For instance, are kangaroos more efficient than ruminants at extracting energy from food? Kangaroos are less efficient at digesting Lucerne hay, which is mainly cellulose, because shorter digesta retention times provide less contact between fermentative microbes and this food, according to Ian Hume of the University of Sydney in Australia. That loss puts kangaroos on an equal footing with sheep in overall digestive efficiency.

Such differences have economic implications. Livestock producers would like to reduce methane losses from ruminants while increasing their efficiency in converting plant materials into milk and meat products. There are also global implications. The 1.5 billion cattle on the planet generate more than 100 million tons of methane per year, which is about 20% of emissions contributing to global warming. Conservation researchers in Australia suggest that shifting from ruminant cattle and sheep to kangaroos for meat could be useful for decreasing the Australian contributions to greenhouse gases.

**Host-Microbial Nutrient Processing**

Microbes provide their vertebrate hosts with more than energy-rich fermentation products. They also synthesize nutrients, including essential amino acids, that are absorbed directly or during recycling when the host degrades and absorbs the microbes.

Of the 20 amino acids that are critical for vertebrates, 10 are considered essential because the vertebrates cannot synthesize them at all or in adequate amounts. Vertebrates can obtain essential amino acids, such as lysine, from their diet, but there is evidence that they also obtain them from their gut microbes (Fig. 4). For example, after urea containing the nitrogen-15 isotope is administered orally to cows, lysine containing that same isotope is found in proteins within tissues of those animals (Fig. 4, top). Because cows cannot produce the amino acid directly, they must have depended on microbes

![Diagram showing the digestibility of different foods consumed by white-tailed deer measured in whole-animal feeding trials with deer (in vivo, x-axis) or estimated using in vitro fermentation (y-axis). The digestibility of five different foods consumed by white-tailed deer is shown as different symbols. In many studies, as in this one, the inoculum source seems not to make a great difference. (Data from C. T. Robbins et al. J. Wildlife Management 39:67–79, 1975.)](image-url)
in the rumen to convert the labeled urea into lysine, which then is incorporated into microbial protein. When the microbes move from the rumen into the acidic part of the cow stomach and then to the intestine, cow enzymes digest the protein, enabling the animals to absorb the nitrogen-15 lysine. Nonruminant animals such as rats depend on the microbial community in the cecum and colon to incorporate isotope-labeled urea nitrogen into lysine. When rats reingest feces (coprophagy, or cecotrophy in rabbits), they digest and absorb labeled amino acid from those microbial proteins (Fig. 4, bottom). However, germ-free rats cannot incorporate isotope-labeled urea nitrogen into lysine. In theory, humans cannot incorporate lysine that might derive from isotope-labeled urea through proteins that the hindgut microbial community produces because they are hindgut fermenters and do not reingest feces. Amazingly, however, nitrogen-15 labeled lysine appears in human plasma proteins hours after labeled urea is administered. Thus, amino acids and perhaps other nitrogen-containing compounds may be cycling between humans and their microbiota, a process that could reduce dietary requirements for those nutrients. However, whether the fluxes of those amino acids or other essential nutrients between microbes and humans are great enough to contribute significantly to nutritional requirements is unresolved.

**Host-Microbial Processing of Toxins**

Gut microbes modify not only nutrients but xenobiotics such as toxins. For example, the fast-growing tropical legume *Leucaena leucocephala* is rich in nitrogen and hence is used as a feed supplement for cattle. However, its tissues contain mimosine, an amino acid that is toxic and that foregut microbes can transform into other toxic metabolites that intoxicate ruminants. In 1982, Australian ecologist Raymond Jones determined that *Leucaena* leaves are toxic for Australian goats but not Hawaiian goats. However, when Australian goats are inoculated with ruminal fluid from Hawaiian goats, the recolonized Australian goats become tolerant to mimosine. The bacterium that degrades and thus detoxifies mimosine metabolites was isolated from the rumen of the resistant goats and was subsequently named *Synergistes jonesii*. Once established, *S. jonesii* spreads readily among members of a herd. Hence, *S. jonesii* is being used to inoculate ruminants throughout the world, making it safe for them to eat *Leucaena* spp.
Biodiversity and Superorganisms

A striking picture emerges from studying host-microbial processing of energy, nutrients, and toxins. The gut microbial metagenome tremendously increases the diversity of metabolic pathways accessible to animal hosts, enabling them to metabolize many things that they otherwise could not.

Perhaps most importantly, gut microbes enable some animals to partake of cellulose, the single largest nutritional energy source on the planet. More generally, gut microbes enable animals to survive on diets with low levels of particular nutrients and high levels of particular toxins. In this sense, vertebrates become nutritional superorganisms, with microbial biodiversity providing the metagenome.

Diversity in gut structure and function, in diet, and in other features of animal hosts creates differences in nutrient milieu, digesta retention times, and temperatures that create diverse microbial niches and inhabitants. Sometimes that diversity lacks functional significance because of redundancies in the metagenome of gut microbiota. At other times, however, diversity matters, such as in processing glycans or specific xenobiotics. With new molecular tools for studying microbial communities, determining the details of gut microbial diversity will depend on scientists from different disciplines forming symbioses of their own.

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SUGGESTED READING


