

Gut Bacteria have a novel sweet tooth: ribose sensing and scavenging from fiber

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ABSTRACT

Dietary fiber is known to influence symbiotic gut microbiota community structure and physiology; however, how and if dietary fiber can induce further exogenous nutrient uptake within gut microbes is ill-defined. Recent findings highlight how during periods of high-fiber consumption, a prevalent gut bacteria senses and scavenges the ubiquitous sugar ribose. This molecular adaptation exemplifies how particular gut microbes have developed a sophisticated system to scavenge nutrients in a diet-dependent manner.

ARTICLE HISTORY

Received 17 March 2020
Revised 04 May 2020
Accepted 11 May 2020

KEYWORDS

Fiber; microbiome; nutrition; ribose utilization; gut colonization

A Western diet is fiber light, ill-suited to promote gut microbiome diversity, and many adults in industrialized nations do not meet their recommended daily intake of around 30 g per day.¹ Diverse diets that contain increased levels of fiber, in contrast, afford a greater abundance of gut flora which may promote improved health.² Improving fiber consumption helps reverse some of the ill effects of the Western diet,³ but the specific role of gut microbes in mediating disease states through fiber consumption has remained enigmatic. In a recent issue of *Cell Host & Microbe*, Glowacki and colleagues tackle this issue and demonstrate how a high-fiber diet can foster competitive colonization of specific microbes through a novel nutrient utilization pathway.⁴

Microbiota depends heavily on microbiota-accessible-carbohydrates (MACs) for energy, which are primarily found in fiber rich foods. As early as the 1960s, a large intake of dietary fiber has been correlated with the lack of diabetes and heart disease;⁵ more recent studies reveal the ability of short-chain fatty acids (SCFAs), the end-products resulting from microbial fermentation of fiber-containing diets, to interface with host physiology and protect against inflammatory conditions like colitis.^{6,7} Further mechanistic understanding of how diet molds the collective community composition of the gut microbiome can inform future steps

toward therapeutically mitigating the maladaptive impact of the Western diet.⁸

Breakdown of dietary plant fiber into SCFAs by gut microbiota accounts for ~10% of absorbed calories and often involves the use of clustered sugar-cleaving multi-gene loci called polysaccharide-utilization loci (PULs).⁹ *Bacteroides*, a prominent genus in the human gut, is known to metabolize MACs from plant fibers via PULs and scaffold itself on intestinal walls to provide gut ecosystem stability.¹⁰ Their abundance, in part, is due to their ability to appropriate a multitude of traditional, non-digestible carbohydrates as energy sources;¹⁰ however, this capacity has never been observed in the nutrient assimilation of dietary nucleic acids like ribose. A large body of work has demonstrated that ribose plays various roles in metabolism and is used as a building block for both RNA and DNA, but scientists rarely think of ribose as a preferred bacterial energy source. In most environmental conditions, glucose is the favored carbon source for bacteria like *E. coli*: it facilitates faster growth than other sugars and is consumed first in a variety of sugar mixtures. Glowacki and coworkers show how a high-fiber diet can foster competitive colonization of *Bacteroides thetaiotaomicron* (*Bt*) in mice through ribose utilization.⁴ Furthermore, they demonstrate that exogenous ribose can affect gut microbial architecture.

To start investigating the relationship between fiber, ribose, and microbes, Glowacki *et al.* first characterized a PUL-dependent mechanism within *Bt* that catabolizes ribose and confers a colonization advantage to gut symbionts under high-fiber conditions. Genes coding for three enzymes – two ribokinases and one nucleoside hydrolase – on a particular *Bt* PUL suggested the potential ability of the PUL to obtain ribose from molecules like nucleosides. Upon further analysis, all individual genes in this PUL were upregulated around 100-fold in gnotobiotic mice fed both high and low fiber diets. *In vitro* growth of *Bt* in minimal media containing ribose as the only carbon source demonstrated an approximately 200-fold increase in *Bt* PUL gene expression compared to growth on glucose media. Absence of this PUL halted *Bt* growth on ribose, but growth on non-ribose media was unaffected. These results suggest *Bt* can efficiently use ribose as a carbon source. The *Bt* PUL was labeled as a ribose-utilization-system, or *rus*.

To determine the interplay between *Bt* *rus*, fiber and ribose content, mice were inoculated with equivalent proportions of *rus* and Δ *rus* and put on either a plant-derived fiber-rich (FR) diet or a fiber-free (FF) diet containing glucose,

lipids, protein, and cellulose. qPCR analysis of mouse fecal DNA after feeding for more than a month showed *Bt* outcompeted Δ *rus* in the FR diet while both strains had similar growth phenotypes in the FF diet (Figure 1). GC-MS analysis of both diets demonstrated only the FR diet had ribose present in both the free and covalently linked forms (RNA, nucleosides, etc.). Further feeding studies with water supplemented with either 1%-free ribose, RNA, and pyrimidine nucleosides indicated free ribose molecules promoted the growth of *Bt* at the expense of Δ *rus* in a manner similar to what was seen with the FR diet. Meanwhile, there was no difference in growth between Δ *rus* and *Bt* when grown in the presence of RNA and nucleosides. These results fit a model where *Bt* fitness is dependent on the *rus* locus activation and the presence of free ribose when the consumer is exposed to a high-fiber diet.

To understand the genetic mechanism of ribose utilization and the significance of these different ribose sources on gut microbial colonization, Glowacki *et al.* first conducted single and double gene deletions within the *rus* PUL and characterized their functionality. Of the 8 *rus* PUL genes,

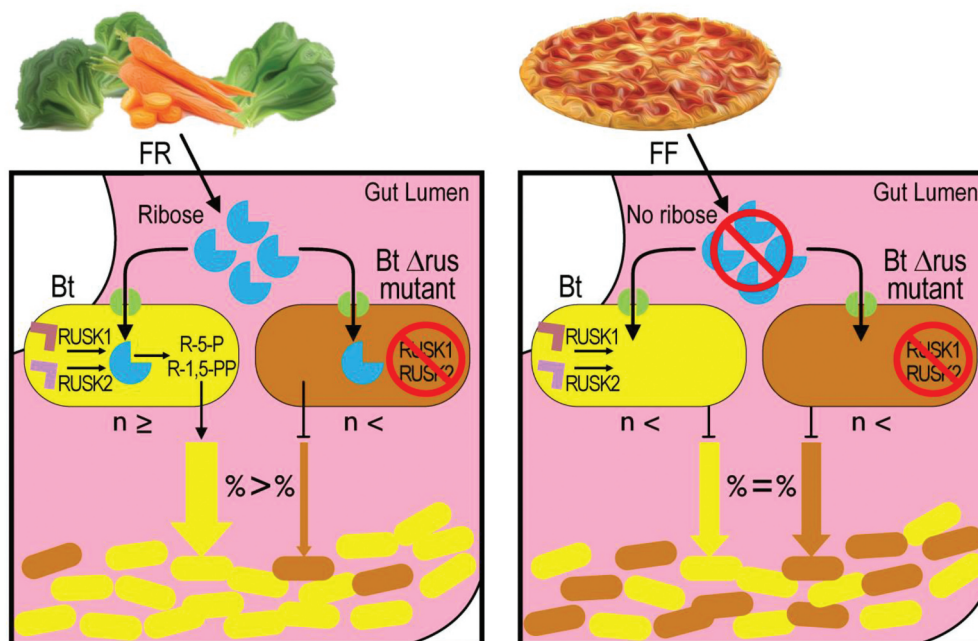


Figure 1. Diagram depicting dietary fiber-dependent ribose-microbe interaction. The *Bt* strain outcompeted Δ *rus* in a fiber-rich (FR) diet (left) while both strains grew at similar rates in the fiber-free (FF) diet (right). Specifically, the presence of *rusK1* and *rusK2* in *Bt* helps metabolize ribose, produce ribose-5-phosphate (R-5-P) and ribose-1,5-bisphosphate (R,1,5-PP), and confer a colonization advantage (left). The FF diet, on the other hand, had no ribose to metabolize and thus both strains remained at equilibrium (right).

single and double deletion mutants of two ribokinases (*rusK1*, *rusK2*), a transcriptional regulator (*rusR*), and a transporter (*rusT*) had either slowed or no growth on free ribose compared to *Bt*. The hindered growth of both Δ *rusR* and Δ *rusT* suggest their essential roles in ribose catabolism and transport, respectively. Interestingly, Δ *rusK1/rusK2* showed the same competitive defect exhibited by Δ *rus* in a FR diet (Figure 1). Identifying two ribokinases responsible for ribose-dependent colonization stability is noteworthy, given that dietary nucleic acids were previously thought to pass through the digestive tract. Deletion of the remaining four genes did not significantly impact growth. Assessing whether other potential sources of ribose affect *Bt* fitness, the aforementioned kinases, transcriptional regulator, and transport deletions did not grow on nucleosides while *Bt* did. This result, along with other findings in the paper, is consistent with *rus* involvement in ribose scavenging and ribose-dependent growth.

Glowacki and colleagues have shed new light onto diet-specific nutrient utilization and gut microbiota-dependent host physiology changes. Though fiber is not directly impacting *Bt* growth, fiber consumption can trigger nutrient utilization mechanisms that are unexpected and intriguing. High-fiber consumption appears to encourage the growth of specific bacteria through novel utilization of ribose. These insights can now be harnessed for microbial therapeutics. For example, *rusK1/rusK2* could be expressed in specific beneficial bacteria and these novel microbes used to populate the gut of patients. By increasing the fiber content of the patient's diet, enhanced levels of the beneficial microbes would be assured.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by the National Institutes of Health (US).

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