Does Modification of the Large Intestinal Microbiome Contribute to the Anti-Inflammatory Activity of Fermentable Fiber?

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Abstract

Fiber is an inadequately understood and insufficiently consumed nutrient. This review examines the possible causal relation between fiber-induced microbiome changes and the anti-inflammatory activity of fiber. To demonstrate the dominant role of fermentable plant fiber in shaping the intestinal microbiome, animal and human fiber-feeding studies are reviewed. Using culture-, PCR-, and sequencing-based microbial analyses, a higher prevalence of *Bifidobacterium* and *Lactobacillus* genera was observed from the feeding of different types of fermentable fiber. This finding was reported in studies performed on several host species including human. Health conditions and medications that are linked to intestinal microbial alterations likely also change the nutrient environment of the large intestine. The unique gene clusters of *Bifidobacterium* and *Lactobacillus* that enable the catabolism of plant glycans and the ability of *Bifidobacterium* and *Lactobacillus* to reduce the colonization of proteobacteria probably contribute to their prevalence in a fiber-rich intestinal environment. The fiber-induced microbiome changes could contribute to the anti-inflammatory activity of fiber. Although most studies did not measure fecal microbial density or total daily fecal microbial output (colon microbial load), limited evidence suggests that the increase in intestinal commensal microbial load plays an important role in the anti-inflammatory activity of fiber. Various probiotic supplements, including *Bifidobacterium* and *Lactobacillus*, showed anti-inflammatory activity only in the presence of fiber, which promoted microbial growth as indicated by increasing plasma short-chain fatty acids. Probiotics alone or pure fiber administered under sterile conditions showed no anti-inflammatory activity. The potential mechanisms that could mediate the anti-inflammatory effect of common microbial metabolites are reviewed, but more in vivo trials are needed. Future studies including simultaneous microbial composition and load measurements are also important. *Curr Dev Nutr* 2018;2:nzx004.

Introduction

The definition and classification of fibers have been reviewed previously (1). Although these plant-based materials have diverse structural features, none of them can be digested in the small intestine by mammalian digestive enzymes. In the anaerobic large intestinal lumen, some of them are known to be degraded by microbial enzymes to promote commensal bacterial growth (2, 3). This unique property of fiber to undergo fermentative degradation in the large intestine gave rise to nomenclature such as "fermentable fiber" and "prebiotics" (2, 4, 5). Fermentable fibers are mostly soluble in water and thus the term "soluble fiber" is also used. Chemically, fermentable fiber can be glucose-based (polydextrose and resistant starch), fructose-based (fructo-oligosaccharide and inulin), galactose-based (galacto-oligosaccharide and agaro-oligosaccharide), or hexose derivatives such as D-galacturonic acid polymer (pectin) or galactose- and mannose-based polymer (guar gum). Some pentose carbohydrates, such as arabinose and xylose-based arabinoxylan, are also fermentable fiber.

Fiber is essential for optimal health based on its unique ability to increase fecal volume and decrease fecal transit time (6, 7). Total fiber is included in the US Dietary Reference Intake tables (8).

Keywords: fiber, microbiome, *Bifidobacterium*, inflammation, intestinal commensal microbial load

Manuscript received May 7, 2017. Revision accepted November 21, 2017. Published online November 28, 2017. doi: https://doi.org/10.3945/cdn.117.001180
Supported by the University at Buffalo.
Author disclosure: no conflicts of interest.

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Abbreviations used: AHR, aryl hydrocarbon receptor; FXR, farnesoid X receptor; OTU, operational taxonomic unit; PXR, pregnane X receptor.

It is not certain, however, whether a special requirement for fermentable fiber is needed. One limitation in understanding fiber nutrition is the lack of a comprehensive database for fiber, especially soluble or fermentable fiber, in food items. Using purified fermentable fiber with different structural features, anti-inflammatory activity has been observed in human and animal model studies (9). Inflammation is the cause and consequence of many diseases (10–16), and therefore fiber can also have an impact on health outside the gastrointestinal system. Indeed, anti-inflammatory activity has been observed with fibers under different physiologic and pathologic conditions (9).

However, the mechanism leading to the anti-inflammatory activity of fiber is not clear. Is it possible that this activity of fiber relates to the promotion of certain microbes in the large intestine? If this is the case, we can then make several predictions. First, we expect similarities among various fermentable fibers in their ability to modify the intestinal microbiome. This would explain why fermentable fibers with different structural features can show similar anti-inflammatory activity (9). Second, the presence or absence of fermentable fiber should serve as an important modifier of the intestinal microbiome. This is consistent with the anti-inflammatory activity of fermentable fiber having been observed under many different physiologic and pathologic conditions (9). Third, microbiome changes by themselves, such as an increase in the target bacterial taxonomic units, should also exhibit anti-inflammatory activity independent of fiber supplementation. This would support the hypothesis that a unique microbiome mediates the anti-inflammatory effect of fermentable fiber. Lastly, specific microbial metabolites should also exhibit anti-inflammatory activity. This last suggestion would provide a possible mechanism for the hypothesized causal relation between a unique microbiome and the anti-inflammatory activity of fermentable fiber. The purpose of this review is to use the relevant literature to address the above 4 points.

Current status of knowledge

Intestinal microbiome and the method of analysis

The presence of an extensive, mostly anaerobic, microbial population in the large intestine of healthy humans and animals has long been recognized. This symbiotic relationship is important for host health as germ-free animals show poor intestinal development (17). The earliest method for the analysis of the intestinal microbiome depended on the ability to culture isolated microbes (18). The development of sequence-based analyses such as PCR and restriction fragment length polymorphism increased the capability to quantify microbes that are difficult to culture. Further development of 16S ribosomal RNA sequence-based operational taxonomic unit (OTU) analysis allowed a more complete understanding of the host-bacteria symbiotic relationship (19–22). The advancement in DNA sequencing technology and data analysis algorithms has led to the application of 16S-independent shotgun metagenomic sequencing for comprehensive OTU analysis (23).

OTU analysis has both strengths and limitations. Because of its sequence-driven comprehensive coverage at multiple taxonomic levels, it is better at predicting bacterial diversity than earlier techniques. However, because most intestinal bacterial species have not been cultured and sequenced, OTU analysis is still limited in resolving diversity below the genus level. Moreover, OTU analysis by itself gives information on the relative prevalence but not the absolute quantity of different genera. Although the older methods of analyses detect only a limited fraction of the intestinal microbiome, the data can be expressed as per gram physiologic sample and thus provide information on the absolute amount of a particular bacterial genus or species.

Shotgun metagenomic sequencing of 1135 fecal samples from a Dutch cohort revealed the presence of DNA from all 4 domains: bacteria, archaea, viruses, and nonhost eukaryotes (23). Among the sequences amplified from the fecal samples, 97.6% came from bacteria, consistent with the previous conclusion on bacterial dominance in the intestinal microbiome (24).

Multiple factors influence the composition of an individual's intestinal microbiome. For example, a maternal contribution to the initial microbiome has been observed. The first stool of newborn mice has been shown to have genetically similar microorganisms to those that were orally inoculated in their pregnant mothers (25). The exact route of maternal-fetal transmission is not clear. The birthing process can further modify the intestinal microbiome. Vaginally delivered newborns harbored bacteria found in their mother's vaginal environment, whereas skin microbiome contributed more to those born via cesarean delivery (26). However, the effect of delivery is not permanent (23). Living environment further modifies the intestinal microbiome. For example, pigs raised in an outdoor environment had a significantly higher abundance of Firmicutes, particularly *Lactobacillus*, than did those raised indoors (27). As expected, even subtle differences in host genetic background can influence the intestinal microbiome as shown in studies where different inbred strains of mice were raised on the same diet and in the same environment (28, 29). Nevertheless, these studies also reported a crucial effect of diet on the intestinal microbiome.

Intestinal microbiome changes upon fiber supplementation in animal studies

Results from animal studies on the effect of fermentable fiber feeding are summarized in **Table 1**. Observations from in vitro fiber fermentation were not included because of their limited relevance to the complex fermentation occurring in the human large intestinal lumen. Also excluded were studies using ruminants, aquatic, or avian species, studies with confounding factors including studies with disease models, studies without detailed dietary information, and studies with supplements that simultaneously introduced other nutrients.

Among the animal studies summarized in Table 1, cecal and fecal samples were primarily used to determine the intestinal microbiome, although some studies also analyzed intestinal contents. Analytical methods ranging from culture to OTU analysis were used. It is important to point out that only sequencing-based analyses have the ability to cover the entire microbiome and thus be useful for performing comprehensive diversity analyses. Other earlier methods can only quantify selective taxonomic groups where the analytic tools are available.

Three different types of microbiome-related observations could be found in the studies in Table 1: prevalence, diversity, and density. Prevalence describes the quantitative presence of a particular taxonomic group within a fixed amount of biological sample. Diversity can be used to describe the fiber feeding-induced microbial population pattern changes, if any. Density is defined as the total microbes within a fixed amount of cecal, colon, or fecal sample. A decrease in density does not necessarily reflect a reduction in total microbes at an anatomic site. For

TABLE 1 Summary of changes in the intestinal microbiome after increasing the intake of fermentable fiber in animal studies[1]

Host (age, sex, *n*/group)	Basal diet	Treatment	Duration (d)[2]	Effect of fiber on microbiome				
				Increase[3]	Decrease[3]	Diversity	Density	Ref[4]
Mouse								
BALB/c (3 wk, M, 8–11)	No-fiber diet	Supplement 3% FOS/d in tap water	14[CC]	*Bifidobacterium*[A] (gum arabic or XOS had no effects)	NA	NA	↑	(33)C
C57/BL/6J (9 wk, M, 8)	Purified 35% fat, 26% CHO diet	10% arabinoxylan mixed with 90% basal diet	28[C]	*Bacteroides/Prevotella*[B] *Bifidobacterium*[A] *Roseburia*[F]	NA	NA	↓ (↑total)	(30)G
ICR (4–6 wk, F, 10)	AIN-93M	10% rice bran into basal diet	28[F]	*Lactobacillus*[F] (from days 11–25)	NA	NA	NA	(44)C
BALB/c (adult, F, 10)	2% guar gum diet	10% guar gum into basal diet	14[F]		*E. coli*[P]	NA	↑	(51)S
C57/BL/6J (10 wk, M, 10)	Cereal-based 4% fiber diet	Supplement 0.3 g FOS/d in water (~10% of diet)	56[C]	Actinobacteria Proteobacteria Verrucomicrobia	Firmicutes	—	NA	(37)S
BALB/c (8 wk, F, 6)	AIN-93G	7.5% resistant maltodextrin into basal diet	14[C]	Coriobacteriaceae[A]	Clostridiales[F]	NA	NA	(174)T
C57/BL/6J (18 wk, obese M, 6)	AIN-93G-based 45% fat diet	10% FOS or 10% inulin in basal diet	28[F]	Coriobacteriaceae[A] *Lactobacillus*[F] Verrucomicrobiaceae[V]	Clostridiaceae[F] Ruminococcaceae[F]	↓	NA	(45)S
C57/BL/6N (5 wk, M, 8)	32% fat diet, plain water	Basal diet and 3% wt:wt AGOS in drinking water	28[F]	*Clostridium XVIII*[F] *Lactobacillus*[F] *Prevotella*[B]	*Clostridium XIVa*[F]	NA	NA	(46)T
C57/BL/6J (4 wk, M, 15)	Diet with 45% kcal from fat and supplemented with digestible corn starch	Basal diet with 20% resistant corn starch instead	70[C]	Lactobacillaceae[F] Ruminococcaceae[F]	*Clostridium*[F] Coriobacteriales[F] Lachnospiraceae[F] *Ruminococcus*[F]	NA	NA	(43)S
Rat								
Wistar (4 wk, M, 12)	AIN-93G	1% GOS in basal diet	14[F]	*Bacteroides*[B] *Bifidobacterium*[A] *Lactobacillus*[F]	NA	NA	↑	(38)P
Wistar (adult, M, 4–5)	Rapeseed oil and lard-based high-fat diet	9% pectin or 8% guar gum in basal diet	21[C]	Proteobacteria	Bacteroidetes (pectin group only) Firmicutes	↓	NA	(50)S
Wistar (4 wk, F, 5)	Purified diet with 5% cellulose	5% FOS replacing cellulose	28[C]	No significant difference in *Bacteroides*[B], *Bifidobacterium*[A], *Lactobacillus*[F]		NA	—	(52)P,G
Sprague Dawley (22 wk, F, 14)	High fat/sucrose diet	Basal diet plus 10% wt:wt FOS	40[F] (pregnancy & lactation)	*Bacteroides*[B] *Bifidobacterium*[A]	*Clostridium I*[F] *Clostridium IV*[F] *Clostridium XI*[F] *Roseburia*[F]	NA	NA	(40)P
Wistar (4 wk, M, 6)	20% soy protein diet without fiber	2% soy fiber added in the basal diet	14[C]	*Prevotella*[B]	*Clostridium*[F] *Roseburia*[F]	NA	NA	(175)G
Pig								
Yorkshire × Hampshire × Landrace (6 wk, MF, 4)	Corn-, soy-based diet	4% different types of inulin replacing corn starch in basal diet	35[CC]	*Bifidobacterium*[A] *Lactobacillus*[F]	NA	NA	NA	(34)T
Duroc × Landrace × Yorkshire (28 d, MF, 5)	Maize-, soy-based diet	10% wheat bran or pea fiber replacing 10% maize in basal diet	30[IC]	*Bifidobacterium*[A] (colon) *Lactobacillus*[F] (ileum)	*E. coli*[P]	NA	—	(35)P

(*Continued*)

TABLE 1 (*Continued*)

Host (age, sex, *n*/group)	Basal diet	Treatment	Duration (d)[2]	Effect of fiber on microbiome				
				Increase[3]	Decrease[3]	Diversity	Density	Ref[4]
Duroc × Landrace × Yorkshire (28 d, MF, 5)	Maize-, soy-based diet	10–30% pea fiber replacing 10–30% maize in basal diet	132[C]	*Lactobacillus*[F]	NA	NA	—	(41)P
Shade Oak × Duroc × Hypor (12 wk, MF, 3)	Potato-, soy-based diet	33% resistant tapioca starch replacing potato starch in basal diet	84[F]	Erysipelotrichaceae[F] Lachnospiraceae[F] Prevotellaceae[B] Veillonellaceae[F]	Clostridiaceae[F]	↓	NA	(49)S
DanBred × Duroc (10 d, M, 8)	Cereal-based diet	2% inulin in basal diet	40[CC]	*Bifidobacterium*[A] (colon)	NA	NA	NA	(36)P
Landrace × Yorkshire (1 d, MF, 10)	Commercial milk replacer diet	Milk replacer supplemented with 0.8% GOS	26[F]	*Bifidobacterium*[A] *Lactobacillus*[F]	NA	NA	—	(39)P
Seghers hybrid × Piétrain (28 d, MF, 6)	Purified fiber-free diet	5% arabinoxylan replacing corn starch in basal diet	30[C]	*Lactobacillus*[F]	NA	NA	—	(42)P

[1]AGOS, agaro-oligosaccharide; CHO, carbohydrate; FOS, fructo-oligosaccharide; GOS, galacto-oligosaccharide; NA, information not available; XOS, xylo-oligosaccharide; —, no effect; ↑, increase; ↓, decrease.
[2]The superscript abbreviation shown after the duration description indicates the sample type used: C, cecal content; CC, cecal and colon content; F, feces; IC, ileum and colon content
[3]List of bacteria follows alphabetical order. The superscript abbreviation shown after each indicates the phylum it belongs to: A, Actinobacteria; B, Bacteroidetes; F, Firmicutes; P, Proteobacteria; V, Verrucomicrobiaceae.
[4]The letter shown after the reference number indicates the method used for microbial analysis: C, CFU determined by plating; G, 16S-rRNA-based denaturing gradient gel electrophoresis; P, quantitative PCR; S, 16S-rRNA-based sequencing and operational taxonomic unit analysis; T, terminal restriction fragment length polymorphism.

example, in the only study that measured total bacteria in the biological sample from each animal, an increase in the cecal total microbial load was reported despite a lower cecal microbial density after fiber feeding (30). Without the information on daily total fecal output in different groups, comparing fecal microbial density may not be useful.

Of the studies summarized in Table 1, only 6 studies used the sequencing-based analysis of prevalence and thus the results on prevalence are incomplete. Nevertheless, most studies found an increased presence in the phyla Actinobacteria (especially the genus *Bifidobacterium*), and/or Firmicutes such as *Lactobacillus* after fiber feeding. Some studies also observed a decrease in Clostridiaceae or *Clostridium*. Two studies reported a decrease in *Escherichia coli*, a member of Proteobacteria, although 2 others found an increase in Proteobacteria.

The review summarized in Table 1 further uncovered several important pieces of information. The studies included here were done using different basal diets and fermentable fiber supplementations given to male and female mice and rats of different strains as well as pigs of different breeds. The ages of the animals ranged from newly weaned to adult (Table 1, Host). The consistent outcome of increasing *Bifidobacterium* and *Lactobacillus* suggests that age, gender, and host genetic background do not alter the microbiome response to fermentable fibers. Although one study lasted for >100 d, a few studies found similar effects after 2 wk of fiber feeding (Table 1, Duration).

Because of the differences in substrate and oxygen availability along the gastrointestinal tract, it is expected that microbial composition varies among different parts of this tract (31, 32). Cecal samples and feces show different physical characteristics: the former freely dissociate from each other whereas the latter tend to aggregate (unpublished observation from the author's laboratory). However, based on the analyses done on cecal, colonic, and fecal samples in Table 1, it seems that the microbiome pattern change in feces represents the microbial response to fiber in the intestine reasonably well. Of the 21 studies in Table 1, an increase in Actinobacteria or *Bifidobacterium* in response to fermentable fiber was observed in 4 studies that examined the combined cecal and ileal and colonic contents (33–36); 2 studies that examined cecal content (30, 37); and 3 studies that examined feces (38–40). Also, of the 21 studies in Table 1, an increase in Lactobacillaceae or *Lactobacillus* in response to fermentable fiber was observed in 2 studies that examined the cecal and ileal and colonic contents (34, 35); 3 studies that examined cecal content (41–43); and 5 studies that examined feces (38, 39, 44–46). In a preliminary study using OTU-based Procrustes analysis of microbiomes (47), the 6 pairs of cecal-fecal samples from mice that were fed an AIN-93G diet or an AIN-93G diet supplemented with 5% inulin showed a modest cecal-fecal correlation ($P = 0.0445$) (unpublished observation from the author's laboratory). The consistency among these results supports the conclusion that fecal samples provide reasonably good representation at the genus level for the response of large intestinal microbiome to fermentable fiber.

Studies in animal models reveal some gaps in our knowledge of dietary regulation of the intestinal microbiome. A few recent OTU-based studies included the diversity analysis of the microbiome. Although supplementation with sugar beet pulp plus inulin was found to increase intestinal microbiome diversity if added to a diet with low fermentable fiber (48), the addition of purified fiber to a plant-based diet did not seem to have the same effect (37, 49). In fact, dietary supplementation with purified fiber tends to decrease microbiome diversity (45, 49, 50). It is not clear whether the changes in diversity as well as prevalence were due to preferential changes in the rate of growth or in the loss of certain

bacteria. Understanding the basis of the observed microbiome changes requires information on microbial density and total load. This information was lacking in the diversity studies discussed above.

Microbial density of cecal or fecal samples was measured in some other studies where microbial diversity was not analyzed (Table 1) (30, 33, 35, 38, 39, 41, 42, 51, 52). When fermentable fiber was added to a diet lacking well-fermented fiber, microbial density generally increased (33, 38, 51). In contrast, the addition of fermentable fiber to a plant-based or fiber-rich diet did not increase microbial density, probably because basal microbial density was already high (30, 33, 35, 38, 39, 41, 42, 51, 52). One study weighed the total cecum content and thus allowed the calculation of the total cecal microbial load. Although fiber addition to a high-fat diet led to a decrease in the microbial density of cecal samples in that study, the total microbial load in the cecum increased (30). In this case it seems that a preferential expansion of *Bifidobacterium*, *Prevotella*, and *Roseburia* led to the changes in the composition of the microbiome. Although fecal samples have been used most frequently for microbiome analysis, no studies have reported the total 24-h fecal bacterial load. Such measurements could provide information on the daily bacterial turnover in the large intestine.

An important question that still needs to be addressed is the time-dependent effect of fiber. There was only one study where fecal samples were cultured to quantify *Lactobacillus* along a 28-d fiber supplementation time course (44). The results suggest the presence of adaptive changes: an increase in *Lactobacillus* that peaks at 2–3 wk of fiber supplementation followed by gradual decrease to the control level by 28 d. No information is available on the presence or absence of adaptive changes among other members of the microbiome, or on microbial diversity, density, or load.

Intestinal microbiome changes due to increased fiber intake in human studies

Overall, human studies lack dietary control prior to or even during trials. However, if the anti-inflammatory effect of fiber is related to its ability to change the intestinal microbiome, we would expect to see similar effects of fiber in the human intestinal microbiome as is observed in animal studies. **Table 2** summarizes human studies that have provided fiber intake information. As with the animal studies in Table 1, human studies with potential confounding factors were excluded, including human subjects with diseases, studies without dietary information, and studies with fiber supplements that also introduced (53) non-fiber nutrients.

The 3 measures of microbiome-related observations (prevalence, diversity, and density) follow the same definitions as were used in Table 1. Included in Table 2 are results of a range of studies from cross-sectional to the most stringent randomized, double-blind, placebo-controlled crossover study design. The subjects in Table 2 had a wide range of ages and were given different fermentable fibers for durations ranging from 14 d to 6 mo. With the exception of one study where samples were collected during colonoscopy, all other studies utilized fecal samples (Table 2). Overall, the effects of fermentable fiber on the intestinal microbiome are remarkably similar between the animal studies summarized in Table 1 and the human studies summarized in Table 2.

Most studies in Table 2 found an increase in the genera of *Bifidobacterium* and *Lactobacillus* upon fiber supplementation while the relative presence of the phyla of Bacteroidetes and Proteobacteria decreased in some studies. This pattern of changes was also observed in the single study analyzing colonoscopy samples (54). In the 2 studies that included observations on microbiome diversity, diversity was either unchanged or increased by fiber supplementation (53, 55). Fiber supplements also either increased or had no effect on microbial density (54, 56–65). No human studies determined the total microbial load and thus it is not possible to conclude whether the microbiome alterations were the result of preferential growth among some genera.

Some adult fiber supplement studies assessed the intestinal microbiome at >1 time point. Consistent effects among several time points ≤16 wk were reported (57, 59, 62, 64). In a multigenerational study using germ-free mice colonized with human intestinal microbiomes via oral gavage of feces, dietary fiber consistently increased the presence of Clostridiales and decreased the presence of Bacteroidales based on an OTU analysis (66).

Two studies examined the dose-dependent effect of fiber. A stepwise increase in the dose of galacto-oligosaccharide from 0 to 10 g/d led to a gradual increase in *Bifidobacterium* and a gradual decrease in *Bacteroides* in some individuals (62). Similar to many other biological processes, the effect of fiber on the microbiome was saturatable. Doubling the soluble corn fiber supplement from 10 to 20g/d for 1 mo did not lead to much additional change in the microbiome (55).

In the only study that collected colonic content during colonscopy (54), proximal and distal colonic samples had similar microbiome changes upon fiber supplementation. This is not surprising based on the similarity between cecal and fecal microbiomes in response to fiber supplementation in animal studies (Table 1).

Changes in the nutrient environment can explain other microbiome changes

A variety of factors such as nonfiber dietary component, development, and aging, as well as disease and medication, have also been reported to change the intestinal microbiome. Could those factors cause changes in the colonic nutrient environment? If so, could the nutrient environmental changes explain the observed microbiome changes? **Table 3** is a summary of some additional microbiome observations and the possible role of the nutrient environment in each case.

The first factor examined in Table 3 is dietary pattern. The first 3 mouse-feeding studies (67–69) included macromolecules that cannot be digested and absorbed in small intestine. These macromolecules would have appeared in the large intestine as microbial nutrients and thus affected microbiome composition. The increase in both the prevalence of *Bifidobacterium* and the microbiome diversity upon fruit or nut ingestion is similar to the outcome of fiber feeding shown in Tables 1 and 2. This is consistent with the fact that fruits and nuts are 2 known sources of plant fiber. Based on the consistent outcome among fiber, fruit, and nut studies, we would have expected to see a decrease in the prevalence of *Bifidobacterium* and microbiome diversity upon switching to a low-fiber diet. This was indeed observed in several high-fat (low-fiber) diet studies (67, 70, 71).

Relevant observations were also made in several infant development and elderly studies (Table 3). Although no detailed dietary information was available, the outcome can also be at least partly explained by nutrient availability to the microbes in the large intestine. The composition of breast milk is expected to vary among women. In addition, different preparations of infant formula have different compositions. As a result, fecal *Bifidobacterium* content was not consistently

TABLE 2 Summary of changes in the intestinal microbiome after increasing the intake of fermentable fiber in human subjects of various age groups[1]

Type	Cohort[2] (*n*)	Treatment[3]	Duration[4]	Effect of fiber on microbiome				Ref[6]
				Increase[5]	Decrease[5]	Diversity	Density	
Observational study								
Cross-sectional on fibers from different sources	58 ± 13 y old (82)	Self-administered FFQ followed by USDA nutrient database	Before nongastrointestinal or oncologic surgery[F]	Clostridia[F] (fruit, vegetable) *Bifidobacterium*[A] (bean)	Porphyromonadaceae[B] (bean)	NA	NA	(176)S
Clinical Trial								
Controlled 64% carbohydrate diet supplement	21–48 y old (8)	15 g FOS/d replacing sucrose in biscuits	45 d, FOS on days 16–30[F]	*Bifidobacterium*[A]	*Bacteroides*[B] Clostridia[F] *Fusobacterium*[FU]	NA	—	(56)C
Controlled 58–64% carbohydrate diet supplement	20–34 y old (11)	4 g FOS/d as supplement in tablet and drink	42 d total, FOS on days 7–32[F]	*Bifidobacterium*[A]	NA	NA	↑	(57)C
Supplement	Fiber: 35–72 y old (14); Control: 31–81 y old (15)	Fiber group given a mixture of 2.5 g inulin and 2.5 g FOS supplement 3 times/d	14 d fiber then 1 d colonoscopy preparation diet[CO]	*Bifidobacterium*[A] *Eubacterium*[F] *Lactobacillus*[F]	NA	NA	—	(54)C
Randomized double-blind placebo-controlled	18–45 y old pregnant women: fiber (17); no (16)	3 g GOS/FOS 9:1 mix or placebo (6 g maltodextrin), 3 times/d in drink	From 24 to 37 wk of pregnancy[F]	*Bifidobacterium*[A]	NA	NA	—	(58)F,P
Randomized double-blind placebo-controlled crossover	64–79 y old (41)	5.5 g GOS/d or placebo (maltodextrin) in water	70 d each with 28-d washout in between[F]	*Bifidobacterium*[A] *Clostridium*[F] *Eubacterium*[F] *Lactobacillus*[F] *Enterococcus*[F]	*Bacteroides*[B] *Desulfovibrio*[P] *E. coli*[P]	NA	—	(59)F
Randomized double-blind placebo-controlled supplement	Healthy formula-fed infant: fiber (22); no fiber (24)	Infant formula with or without 6 g GOS/FOS 9:1 mix/L	6 mo (from birth to 6 mo old)[F]	*Bifidobacterium*[A]	NA	NA	NA	(177)F
Randomized double-blind placebo-controlled crossover	20–42 y old (31)	10 g very-long-chain inulin/d or placebo (maltodextrin) in water	14 d low-pre- and -probiotic diet and then 21 d each with 21-d washout in between[F]	*Bifidobacterium*[A] *Lactobacillus*[F]	*Bacteroides-Prevotella*[B]	NA	—	(60)F
Supplement	21 y old (17)	10 g inulin 2 times/d	28 d[F]	*Bifidobacterium*[A]	NA	NA	NA	(178) G,P
Blind supplement	19–50 y old (18)	0, 2.5, 5, 10 g GOS/d in chocolate chew (sugar and corn syrup in the control chew)	21 d each in rising dose, then 14-d washout[F]	*Bifidobacterium*[A]	*Bacteroides*[B]	NA	↑	(61,62) G,P,S
Randomized double-blind placebo-controlled crossover	Men aged 28 ± 4 y (20)	0 or 21 g/d polydextrose or soluble corn fiber in 3 snack bars	21 d each with no washout[F]	Clostridiaceae[F] *Dialister*[F] *Faecalibacterium*[F] *Lactobacillus*[F]	*Bifidobacterium*[A] *Dorea*[F] *Eubacterium*[F] *Ruminococcus*[F]	NA	NA	(179)S

(*Continued*)

TABLE 2 (*Continued*)

Type	Cohort[2] (*n*)	Treatment[3]	Duration[4]	Effect of fiber on microbiome				Ref[6]
				Increase[5]	Decrease[5]	Diversity	Density	
Randomized double-blind placebo-controlled	Healthy formula-fed infant: Fiber (53) No fiber (55)	Infant formula with or without 8 g FOS and inulin 1:1 mix/L	3 mo (from birth to 3 mo old)[F]	NA	*Bacteroides*[B] Enterobacteriaceae[P]	NA	—	(63)P
Randomized double-blind placebo-controlled crossover	18–65 y old with mean BMI >30 (45)	5.5 g GOS/d or placebo (maltodextrin) in water	84 d each with 28-d washout in between[F]	*Bifidobacterium*[A]	*Bacteroides*[B] *Desulfovibrio*[P]	NA	—	(64)F
Controlled 53% carbohydrate diet randomized double-blind crossover	12–15 y old (24)	0 or 12 g soluble corn fiber supplement/d in 2 meals	21 d each separated by 7-d washout[F]	Clostridiales[F] *Parabacteriodes*[B] Ruminococcaceae[F]	*Coprococcus*[F] *Enterococcus*[F]	—	NA	(53)S
Randomized dose-response double-blind crossover	Females aged 11–14 y (28)	0, 10 or 20 g soluble corn fiber supplement/d, ½ in muffin, ½ in drink (maltodextrin placebo)	28 d each separated by 28-d washout[F]	*Bifidobacterium*[A] *Dialister*[F] Lachnospiraceae[F] *Parabacteriodes*[B]	*Anaerostipes*[F] *Dorea*[F] Ruminococcaceae[F]	↑	NA	(55)S
Randomized dose-response double-blind placebo-controlled	19–56 y old (10/group, total 100)	0, 5, 10, 20 g HMOs/d or placebo (glucose) as breakfast drink	14 d[F]	*Bifidobacterium*[A] (10 and 20 g/d groups)	NA	NA	NA	(180)S
Supplement	University undergraduate students	48 g raw potato starch/d (50% resistant starch) in 2 meal drinks	7 d after 3-d acclimation[F]	*Bifidobacterium*[A]	NA	NA	NA	(181)S
Randomized dose-response double-blind	18–50 y old (8/group, total 24)	8, 14, 21 g soluble corn fiber/d in 2 beverages	14 d[F]	*Bifidobacterium*[A] (8 g/d group)	NA	NA	—	(65)F
Randomized double-blind placebo-controlled	45–70 y old, BMI 28–40 (44)	15 g GOS/d or placebo (maltodextrin) in 3 meal drinks	84 d[F]	*Bacteroides*[B] *Bifidobacterium*[A] *Prevotella*[B]	NA	NA	NA	(182)CH

[1]BMI is given in kg/m^2. FOS, fructo-oligosaccharide; GOS, galacto-oligosaccharide; HMO, human milk oligosaccharides, 2′-*O*-fucosyllactose, lacto-*N*-neotetraose, or mix of the 2; NA, information not available; —, no effect; ↑, increase; ↓, decrease.
[2]Cohorts included both genders unless indicated otherwise.
[3]In observational study, this column shows fiber intake measurement.
[4]In observational study, this column shows the study population. The superscript abbreviation shown after the study duration description indicates the sample type used: CO, colon content collected during colonoscopy; F, feces.
[5]List of bacteria follows alphabetical order. The superscript abbreviation shown after each indicates the phylum it belongs to: A, Actinobacteria; B, Bacteroidetes; F, Firmicutes; FU, Fusobacteria; P, Proteobacteria.
[6]The letters shown after the reference number indicate the method used for microbial analysis. C: CFU determined by plating; CH, human intestinal tract chip; F, 16S rRNA-based FISH (fluorescence in-situ hybridization) analysis; G, 16S-rRNA-based denaturing gradient gel electrophoresis; P, quantitative PCR; S, 16S-rRNA-based sequencing and operational taxonomic unit analysis.

higher in breastfed infants in these studies (72–74). In contrast, infant twins (identical or fraternal) living in the same household with similar dietary exposure have similar microbiomes (75). Elders in nursing homes have reduced exposure to environmental microbes because of their restricted mobility. This limitation would also reduce their exposure to a wide variety of food and thus encourage the development of similar and lower-diversity intestinal microbiomes within the same facility (76).

Medical conditions or the use of medications to treat these conditions could indirectly change the intestinal microbiome due to alterations in the diet as well as intestinal environment as described in the last part of Table 3. Inflammation can lead to tissue damage and the ex-

TABLE 3 Summary of observations on the intestinal microbiome changes that can at least be partially explained by the intestinal nutrient environment[1]

Host	Method	Observations on the intestinal microbiome (ref)	Intestinal nutrient environment as a factor (ref)
Dietary pattern			
M	S	Feeding salmon cartilage proteoglycan led to alteration in the intestinal microbiome (68)	Proteoglycan can be used by intestinal commensal as a substrate (183) and thus its ingestion can affect the microbiome
M	S	Fruit or nut supplementation led to microbiome changes such as increases in *Bifidobacterium* and diversity (67, 69)	Fruits and nuts are good dietary sources of fermentable fibers and other prebiotic compounds (67, 184)
H,M,P	S	High-fat diet led to changes such as the depletion of *Bacteroides* and *Bifidobacterium* and a decrease in diversity (67, 70, 71)	High-fat diet led to lower intake of fermentable fiber and thus a lower fiber presence in the intestine (185). It can also increase the unabsorbed fat in the colon (186)
Development and aging			
H	A, P	Fraternal twins shared developmental changes (75)	Twins likely given the same breast milk, formula, and solid food
H	P, S	Breastfed and formula-fed infants did not have consistent differences in intestinal microbiome from study to study (72–74)	The composition of breast milk and infant formula can be different from study to study so the impact on the intestinal microbiome varied
H	S	Infant gut microbiome developed features of the adult microbiome upon switching to table food (187)	Infant microbiome had functional genes for the metabolism of polysaccharide in table food prior to the diet switching (187). Table food introduction likely leads to the preferential expansion of those species that have already colonized in the infant gut
H	S	Different birth delivery modes led to transient but not long-term difference in microbiome (23, 26, 188)	The effect of delivery mode was overridden by later-life dietary factors which then contribute to the interindividual variations (23)
H	S	Elderly in long-term care facility has less microbiome diversity and the composition correlates with residence location (76)	Residents in each long-term care facility have limited but quite uniform food choices and the food choices could be different between facilities (189)
Disease and medication			
H	C, G, P, S, T	Patients with IBD have altered intestinal microbiome such as a decrease in Bacteroidetes and Firmicutes and higher γ-Proteobacteria (190–194)	IBD could lead to different dietary patterns (195) and lower fruit and fiber intake (196, 197). Although dietary protein is usually well digested and absorbed in the small intestine, host mucin and cellular protein at the site of tissue inflammation/damage could serve as unique substrates for microbes (78, 81)
H	M, S	Patients using PPIs showed decreased diversity and higher presence of oral bacteria (23, 198)	PPI users have different dietary pattern (199). Higher gastric luminal pH in PPI users could spare orally ingested microbes and thus a have better chance for orally ingested microbes to reach the colon (85,87)

[1] Hosts included both sexes. A, microarray; C, bacterial culturing; G, 16S-rRNA-based denaturing gradient gel electrophoresis; H, human; IBD, inflammatory bowel disease; M (method), megagenomic sequencing analysis; M (host), mouse; P (method), qPCR; P (host), primate; PPI, proton pump inhibitor; ref, reference; S, 16S rRNA sequencing and operational taxonomic unit analysis; T, terminal restriction fragment length polymorphism.

cessive presence of mucin and endogenous cellular components in the lumen (77). These cellular components are chemically different from plant-based fiber and serve as a carbon source for certain intestinal microorganisms (78–82). In patients using proton pump inhibitors, increased stomach pH can reduce protein digestion in the stomach and small intestine (83, 84). The appearance of this undigested dietary protein in the colon then changes the large intestinal nutrient environment (85) and thus can affect the microbiome. Excessive protein intake in normal individuals was also found to affect the intestinal microbiome (86). Increased stomach pH also allows a better survival of oral bacteria passing through on their way to the lower gastrointestinal tract (87).

In vitro studies on the potential mechanisms leading to changes in bacterial population following fiber feeding

Do changes in the microbiome always involve the acquisition of new bacterial strains from the environment? In studying infection by toxin-producing *Clostridium difficile*, it was concluded that the pathologic strains were initially present in the healthy intestine as minority members of the community and expanded when the intestinal environment became favorable (88, 89). The finding suggests that microbiome changes in response to fiber could also be the results of preferential population expansion. This is consistent with the observation that fermentable fiber supplementation leads to similar intestinal microbial

responses in humans and animals, although these host organisms reside in different environments (Tables 1 and 2).

Two possible factors contribute to the preferential expansion and thus higher prevalence of *Bifidobacteria* and *Lactobacillus* upon fiber feeding. One factor may be that their genomes evolved to utilize fermentable fibers (90, 91). *Bifidobacterium* possesses unique gene clusters that enable the catabolism of glycans and glyco-conjugates (92). The ability of *Lactobacillus* to use plant materials and its niche adaptability have recently been reviewed (93). In contrast, Proteobacteria such as *E. coli* ferment simple sugars and amino acids preferentially (94). Some members of *Fusobacterium* are predominantly nonsaccharolytic (82). *Desulfovibrio* specializes in the reduction of sulfur found in protein and animal mucopolysaccharides (95, 96). Thus dietary supplementation with complex fermentable fiber does not give *E. coli*, *Fusobacterium*, or *Desulfovibrio* a growth advantage. In fact, a decrease in *E. coli*, *Fusobacterium*, and *Desulfovibrio* were observed in the fecal samples of some human subjects after increased fiber intake (Table 2).

The second factor contributing to the preferential expansion of *Bifidobacteria* and *Lactobacillus* is an interaction among bacterial species. The increased prevalence of *Bifidobacteria* and *Lactobacillus* upon fiber feeding may further reduce the colonization by Proteobacteria. There may be direct competition in colonization as shown in a germ-free mouse study using an artificial bacterial community to restrict *Vibrio cholera* colonization (97). In the literature, bacterial metabolites such as SCFAs have often been considered as growth regulators of the intestinal microbiome (98). Some probiotic culture supernatants were found to have bactericidal activity against intestinal *E. coli* (99), although these supernatants failed to reduce the adhesion of *E. coli* to intestinal epithelial cells and enhanced the biofilm formation of *E. coli*.

Evidence that fiber-induced microbiome changes exhibit anti-inflammatory activity

The anti-inflammatory activity of structurally different fermentable fibers has been reviewed (9). If the microbiome change upon fiber feeding contributes to the anti-inflammatory activity, we would expect similar microbiome changes to show anti-inflammatory activity in the absence of fermentable fiber. Indeed, in cell studies, anti-inflammatory activity of probiotic *Bifidobacterium* and *Lactobacillus* was observed in both macrophage (100–102) and intestinal cells (103, 104). However, the relation between so-called "beneficial bacteria" and anti-inflammatory activity is not unique. Even *E. coli* M17 and *Saccharomyces boulardii* were found to have anti-inflammatory activity in cultured macrophage and dendritic cells, respectively (105, 106).

The bacterial families and genera that were enriched upon fermentable fiber supplementation (Tables 1 and 2) overlap with those found in commercial probiotics (107). To delineate the mechanisms behind the anti-inflammatory activity of fermentable fiber, the effects of probiotics are reviewed below. Relevant publications are divided into 2 sets based on the nature of the control diet. The first set includes those using a fermentable fiber-containing diet such as a normal human diet or commercial plant-based rodent chow. The second set includes those using purified standard rodent diets (AIN-76 or AIN-93) which contain only poorly fermented cellulose. Some studies even compared the anti-inflammatory effects of prebiotics (fermentable fiber), probiotics (purified bacteria), and synbiotics (prebiotics plus probiotics).

Anti-inflammatory activity was consistently found in probiotic studies done in the presence of fermentable fiber. A chow-fed neonatal mouse study examined the effects of pre-, pro-, and synbiotic oral supplementation on pathogen-mediated intestinal inflammation (108). Both prebiotic inulin and *Lactobacillus acidophilus* had anti-inflammatory activity and synbiotic treatment led to a further reduction of inflammation. Probiotic *Bifidobacterium bifidum* PRL2010 (109), *Lactobacillus reuteri* (110), or *Lactobacillus casei* BL23 (111) reduced chemical-induced colitis or lesions in chow-fed mice. Chow-fed rats also showed reduced inflammation following chemical-induced colitis when probiotic *E. coli* Nissle 1917 was given (112). Nissle 1917 similarly showed anti-inflammatory effects in chow-fed mice subjected to lipopolysaccharide-induced sepsis (112). Another probiotic strain, *Lactobacillus fermentum*, also reduced lipopolysaccharide-induced inflammatory responses in chow-fed mice (113). In a trial of ulcerative colitis patients, synbiotic therapy (*Bifidobacterium longum* plus inulin) led to reduced inflammation (114). The anti-inflammatory effect of *Lactobacillus* can also be observed in chow-fed IL10-knockout mice that were prone to colitis (100, 115) and chow-fed rats with gastric lesions (116, 117). A diet containing high amounts of poorly fermented cellulose (30%) also showed a microbial growth-dependent anti-inflammatory effect in mouse models (118).

In contrast, in studies involving purified diets with only 5% cellulose, no anti-inflammatory effects of probiotics were observed. Synbiotic supplementation of AIN-76 diet with probiotic *Bifidobacterium lactis* and prebiotic-resistant starch resulted in protection against chemical-induced colon carcinogenesis in rats (119). This effect was not observed when the AIN-76 diet was supplemented with *B. lactis* alone (119). Resistant starch alone resulted in limited protection (119). A similar rat model was used to demonstrate the antitumorigenic activity of prebiotic inulin and a probiotic mix (*Lactobacillus rhamnosus* and *B. lactis*) in a modified AIN-76 diet (120). While inulin by itself offered some protection, probiotics by themselves had no effect (120). In rats given an AIN76-based high-fat and low-cellulose diet, inulin and synbiotic supplementations both showed anti-inflammatory activity but probiotic supplementation alone (*L. rhamnosus* and *B. lactis* in combination) had no effect (121). In a mouse study using AIN-93 diet, substituting standard casein or whey protein with ADM soy protein isolate resulted in anti-inflammatory activity (122). Because the soy protein isolate contains a significant amount of dietary fiber, fiber may have contributed to the anti-inflammatory effect observed in this study. Adding probiotic *L. rhamnosus* GG to the soy diet did not lead to further reduction of chemical-induced colon inflammation. *L. rhamnosus* GG, by itself, also did not have anti-inflammatory effect in an AIN-93-based diet (122). In vitro under sterile conditions, pure fiber showed little protection against the fungal toxin-induced inflammatory responses of cultured intestinal cells (123).

The contrasting outcomes of in vivo probiotic supplementation studies in the presence and absence of fermentable fiber as summarized above provide some insights into the anti-inflammatory activity of fermentable fiber. First, the ability of fermentable fiber to promote the growth of bacteria is important as probiotic supplementation of a purified diet with 5% poorly fermented cellulose had no effect. When indicators of bacterial growth such as total intestinal content of SCFAs or deconjugation of primary bile salts were measured, these indicators only increased in the presence of fermentable fiber (119, 124).

Probiotics by themselves had no effect on SCFAs or bile salts (119, 124). Second, different probiotics all have similar protective effects. This observation suggests that the anti-inflammatory and antitumorigenic effects observed were not unique to a particular species or even genus of bacteria. In fact, even commercially cultivated Gram-negative *E. coli* showed protective effects (112).

The importance of total bacterial load in the colon

Recent sequencing-based intestinal microbiome analyses have made significant discoveries pertaining to microbial composition and diversity (125–128). These 2 areas have thus become a focus of health impact. However, unique composition and diversity may not be the only important factors in a healthy microbiome. Equally healthy populations were found to have different microbial composition and diversity (125, 126). As reviewed above, anti-inflammatory effects can be observed by the supplementation of different probiotics as long as a favorable growth condition, i.e., abundance of fermentable fiber, is available. In vitro analysis has directly linked glycan substrate degradation by *Bacteroides* to polysaccharide capsule biosynthesis (129). Thus, it is possible that simply having a higher total commensal microbial load in the colon is important for health. Unfortunately, very little information is available on this, perhaps because of practical difficulties in quantifying total microbial load, especially in human studies.

Several pieces of indirect evidence support the importance of total commensal microbial load in health promotion. Intestinal microbial losses seen after acute secretory diarrhea were similar to those seen in *V. cholera* infection (130). Antibiotic treatments that lead to the disruption of the intestinal microbiome (131, 132) are a major cause of recurrent *C. difficile* infection (133). Microbiome transplantation using feces from healthy individuals can cure *C. difficile* infection with no specific requirement for a particular microbial composition or diversity (134–136).

Some limited evidence also supports the hypothesis that the anti-inflammatory activity of fiber may come from its ability to increase the intestinal commensal microbial load. One rodent study in Table 1 found an increased total microbial load (total bacterial DNA in daily feces) after dietary supplementation with the fermentable fiber, arabinoxylan (30). Three other rodent studies in Table 1 (33, 38, 51) and 2 human studies in Table 2 (57, 61) found an increased fecal bacterial density (bacteria DNA/g feces) after feeding the fermentable fibers, fructo-oligosaccharide, galacto-oligosaccharide, or guar gum. The above 4 types of fermentable fibers were all found to have the anti-inflammatory activity (42, 50, 108, 120, 121, 137, 138).

To further test the physiologic importance of total commensal microbial load in the large intestine, future studies on fiber and microbiome need to include the measurement of 24-h fecal microbial output and mean fecal microbial DNA density.

The possible role of bacterial metabolites in the anti-inflammatory activity of fermentable fiber

If active microbial growth is needed for the anti-inflammatory effect of fermentable fiber as summarized above, could certain microbial metabolites contribute to this anti-inflammatory activity? Since the anti-inflammatory effects of fiber were also observed in nongastrointestinal tissues (9, 139), microbial metabolites that circulate throughout the body could be important. Intestinal microbes have unique as well as shared metabolic pathways with their hosts. A wide range of chemicals have been both predicted computationally and isolated from intestinal microbiomes (140, 141). These bacterial metabolites can be detected in the host blood and urine (142, 143). The possible anti-inflammatory activities of many of these bacterial metabolites have been studied using cultured cells or animal models (144, 145).

Fermentable fiber can contribute directly to the production of these metabolites by serving as substrates or indirectly by altering the microbiome and thus affecting the degradation of nonfiber. In this review, the focus is on bacterial metabolites that are known to be affected by fiber and have established molecular targets for their physiologic activity. The list of such metabolites may expand in the future since the physiologic significance of bacterial metabolites for the host is still being actively examined.

SCFAs are the best-studied bacterial metabolites. They can be made from fermentable fiber by many commensal microbial species and probiotics. In fact, the plasma concentration of SCFAs is a general indicator of overall intestinal microbial fermentation (51, 119, 146, 147). When the concentrations of plasma SCFAs were measured, studies that showed an anti-inflammatory effect of probiotics had higher concentrations of plasma SCFAs independent of the microbial genus and fermentable fiber source (50, 119, 120). At the molecular level, SCFAs activate several G-protein-coupled cell membrane receptors and inhibit several histone deacetylases (148–152). The immune modulatory role of SCFAs in the intestine has been directly demonstrated in mouse models and appears to be mediated through the molecular targets mentioned above (153, 154). SCFAs also reduce the severity of transplantation-induced graft-versus-host disease (154). Additionally, they reduce the level of proinflammatory cytokines and the severity of colitis in a regulatory T cell–dependent manner (153).

Other organic acids produced during fiber fermentation have also been subjects of interest. For example, fecal and plasma lactate concentrations rose when rats were given fermentable fiber (155–158). Organic acids can also serve as ligands of some G-protein-coupled cell membrane receptors (159). However, the increase in organic acids often coincides with the increase in SCFAs after fiber feeding. In addition, host enzymes using nonfiber nutrients can produce organic acids. Hypothesis-driven studies are needed before the physiologic importance of these bacteria-produced organic acids can be concluded.

The metabolites of bile salts may also contribute to the anti-inflammatory activity of fiber. The wide spectrum of biological activities of bile acids has recently been reviewed (160, 161). Primary bile salts are made in the liver and secreted into the small intestine. After serving their function in the absorption of dietary fat, taurine- and glycine-conjugated bile salts mostly return to the liver through transporter-mediated enterohepatic cycling in the terminal ileum (162). In the colon, leftover bile salts can be deconjugated by bacterial bile salt hydrolase found mainly in Gram-positive intestinal bacteria including the probiotics *Lactobacillus* and *Bifidobacterium* (161, 163, 164). In a mouse study, dietary inulin or inulin plus *Bifidobacterium*, but not *Bifidobacterium* by itself, can promote bile salt deconjugation (124).

The deconjugation reaction, by removing the growth-promoting bile salts and generating the growth-inhibiting free bile acids, can directly limit the growth of *C. difficile*, (165, 166). *C. difficile* expansion is a leading cause of diarrhea during antibiotic treatment. Bile salt deconjugation also allows the conversion of hepatic primary bile acids

to secondary bile acids by bacterial enzymes (162). Secondary bile acids have higher affinity for bile acid receptors including nuclear farnesoid X receptor (FXR)α and the cell membrane G-protein-coupled receptor TGR5 (160, 161). Bile acids additionally have affinity for the nuclear pregnane X receptor (PXR), which also binds to a wide spectrum of other endogenous and exogenous chemicals (167). The PXR gene has FXR binding sites. Feeding mice with bile acid led to an FXR-dependent induction of PXR expression (168). Several lines of evidences support an anti-inflammatory activity of bile acids in the liver and intestine. Bile acids showed anti-inflammatory activity in cell studies (160, 161). Patients with inflammatory bowel diseases showed altered bile acid profiles (160, 161). Finally, mice with a FXRα or TGR5 gene knockout suffered from increased inflammation in the liver and intestine (160). However, in vivo rescue experiments using bile acids have not been done.

Colonic bacteria can degrade dietary or endogenous tryptophan to unique indoles, including skatole (169). These metabolites can bind to the nuclear aryl hydrocarbon receptor (AHR). AHR activation or gene knockout can promote or suppress inflammatory responses and have been linked to beneficial or harmful biological effects, respectively (169, 170). Two recent studies examined the effect of dietary fiber on tryptophan catabolism in the intestine. Fiber-rich soybean husk supplementation to dogs led to a change in the intestinal microbiome with an increase in fecal SCFAs and a decrease in fecal indole and skatole (157). SCFAs and indole are likely produced by different intestinal microbes that use different carbon sources (171). Patients with end-stage renal disease and restricted fruit and vegetable intake exhibited the expansion of indole-forming microbes and reduction of SCFA-producing microbes (171). Because AHR has a wide spectrum of ligands, the contribution of bacteria-produced tryptophan metabolites likely depends on other environmental and dietary conditions. The physiologic importance of tryptophan metabolites is thus far from conclusive.

Conclusions

Fiber is a required nutrient with a US Dietary Reference Intake of ~30 g/d for adults. In developed countries, ingestion of fiber is generally low relative to recommended amounts (172). A US National Health and Nutrition Examination Survey found that only 10.3% of adults have sufficient fiber intake and the average intake is <50% of the daily requirement (173). The anti-inflammatory activity of fiber has been studied extensively (9). In this review, the ability of various fermentable fibers to increase *Bifidobacteria* and *Lactobacillus* and likely the total microbial load in the intestine is hypothesized as the mechanism leading to the anti-inflammatory activity of fermentable fiber. Diets containing only poorly fermentable fiber lead to a reduced fecal microbial content and cannot support the growth of probiotics such as *Bifidobacteria* and *Lactobacillus*. These low–fermentable fiber diets also fail to show an anti-inflammatory effect. The emerging nutritional importance of fermentable fiber supports the need to promote fiber ingestion and a specific recommendation for a daily fermentable fiber requirement.

Acknowledgments

The author thanks Wei Zheng and Kairui Wang at the University at Buffalo for the technical assistance that led to the unpublished observations. The author also thanks Christine E Campbell and Charlotte Lindqvist at the University at Buffalo for critical comments and editing of the manuscript, and Yijun Sun at the University at Buffalo for discussions during the development of the manuscript. The sole author had responsibility for all parts of the manuscript.

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