HHS Public Access

Author manuscript

Curr Opin Gastroenterol. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Curr Opin Gastroenterol. 2017 November ; 33(6): 417–421. doi:10.1097/MOG.0000000000000401.

How diet can impact gut microbiota to promote or endanger health

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Abstract

Purpose of review—Disturbances of the intestinal microbiota have been increasingly implicated in driving various diseases associated with a broad range of chronic inflammatory state. Such diseases have increased in incidence since the mid 20th century, and have roughly correlated with societal changes in food production during this period.

Purpose of review—Consider how changes in diet may have impacted gut microbiota and exploring whether targeted modulated of diet might be a means of optimizing microbiota composition to promote health.

Summary—Recent literature demonstrates that modulation of diet has potential to both beneficially and detrimentally impact microbiota composition and how it interacts with its host. Herein, we discuss recent studies by ourselves and others that demonstrate the potential for changes in diet to have profound impacts on the gut microbiota in ways that can have beneficial or detrimental effects on host health.

Keywords

Microbiota; Inflammatory bowel disease; low-grade inflammation; metabolic disease; fiber; emulsifiers; cancer

Introduction: Characteristics of a “bad” (i.e. disease-promoting) microbiota

The intestinal tract is inhabited by a large and diverse population of bacteria, collectively termed gut microbiota. The average human gut microbiota contains about 100 trillion bacteria, comprised of 500–1000 distinct species that collectively provide benefits to the host, especially in terms of mediating metabolism, pathogen exclusion, and promoting maturation of the immune system. However, a wide body of research has also associated

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Competing interest

None.

alterations in microbiota composition with a broad range of diseases states including, but by no means limited to, inflammatory bowel disease (IBD), colon cancer, and metabolic syndrome. Hence, the gut microbiota can be considered a "frenemy" (friend/enemy) in that it brings key benefits, has potential to cause problems and, in any case, can't practically be removed.

While there are multiple potential mechanisms by which microbiota can lead to such diseases, we speculate that one central mechanism is by promoting inflammation, wherein IBD can be viewed as a state of "classic" or robust inflammation while metabolic syndrome is now appreciated to be a state of "low-grade" inflammation, both of which might promote cancer. While the high degree of heterogeneity in microbiota composition amongst both healthy and diseased individuals precludes a simple reliable species-based stratification of health-promoting and disease-driving microbiotas, some general guidelines re features of such microbiomes has begun to emerge across multiple studies in mice and humans. Specifically, microbiotas associated with health are diverse temporally stable, have relatively high levels of Bacteroidetes and Bifidobacteria, which are thought to play important roles in metabolism, and relatively low levels of Firmicutes and Proteobacteria [1–5]. Microbiotas with such composition are functionally associated with expressing low levels of pro-inflammatory molecules such as LPS and flagellin and are located almost exclusively in the lumen and outer regions of the mucus layer [6–9]. Conversely, microbiotas from mice and humans with colitis and metabolic syndrome often have less species diversity, high levels of Proteobacteria, LPS, and flagellin, and penetrate the inner mucus later to encroach upon host epithelial cells [6–9].

The characteristics of disease-associated microbiotas are likely, at least to some extent, both a cause and consequence of inflammation. For example, Proteobacteria species are rapidly induced by inflammation and many Proteobacteria species express high levels of pro-inflammatory molecules such as flagellin and LPS [10,11]. In any case, a range of inflammatory phenotypes can be transferred upon microbiota transfer, indicating that the altered microbiota community is not purely a consequence of inflammation but rather plays a role in driving inflammation and associated phenotypes. Hence, the disease-associated microbiotas are considered dysbiotic and there is a strong interest in understanding what role diet might play in disturbing the microbiota and developing paradigms to modulate gut microbiota as a means to restore health and prevent disease.

Alteration of diet alters microbiota composition

Appreciation of the importance of microbiota composition and ability to analyze it by sequencing are relatively recently occurrences. Combined with the lack of archived fecal specimens dating back to the 20th century has largely precluded efforts to directly define the extent to which the microbiotas has changed within societies. Nonetheless, with the observations that diet has changed and that diet impacts microbiota, such changes have likely occurred and diet has likely played a role. In humans, long-term dietary habits (e.g. vegans *vs.* omnivores) correlate with overall differences in microbiota composition [12] and, in carefully controlled feeding studies, switching from a vegan to an omnivorous diet result in rapid modest but significant changes in microbiota composition. Another approach to

investigating how societal changes may have impacted the microbiota is to compare microbiota composition between western and relatively undeveloped societies. Such studies indicate broad differences in composition especially in terms of reduced microbial diversity and reduced levels of bacteria thought to function in digestion of complex plant-derived carbohydrates [13]. Collectively, such studies support the role of diet as an important determinant of microbiota composition. The notion that diet impacts microbiota is also supported by a variety of studies in rodents. For example, switching mice from standard rodent chow to a compositionally-defined diet enriched in fat, results in a rapid change in microbiota composition, including a marked increase in levels of Proteobacteria [14]. Such changes in microbiota composition clearly precede increased adiposity, consistent with the notion that they play a role in driving low-grade inflammation that promotes adiposity in this model, instead of being a pure consequence of the disease. While mechanisms by which such changes in macronutrient content alter microbiota composition are not well defined, it has long been known that various macronutrients favor select bacteria that are most efficient at metabolizing them, which likely plays a central role hence dictating the overall microbiota community structure. Yet, host factors are also key contributors in mediating how diet impacts microbiota. For example, dietary lipid intake has a strong effect on bile acids which mediate lipid digestion and, in turn, bile acids impact, and are impacted, by gut microbiota composition [15,16]. Yet, the details that govern such impacts and the extent to which analogous paradigms apply to other nutrients are not known, and further studies are needed to mechanistically understand the interrelationships between diet content and microbiota composition.

Fiber: needed for health, but type, amount, and context matter

While increased consumption of fats and simple sugars are plausible factors to have contributed to changes in microbiota that may have contributed to increased incidence in chronic inflammatory diseases since the mid 20th century, the macronutrient whose levels have changed most during this period is dietary fiber. Dietary fiber can be broadly categorized as soluble, which is readily fermentable by bacteria in the GI tract of mice and humans or insoluble, e.g. cellulose, which is resistant to breakdown by mice and humans but can be fermented by ruminant animals with more extensive gastrointestinal tracts. Such fermentable fibers are thought to nourish a diverse microbial community, and consumption of a high-fiber diet in persons in rural agrarian societies is thought to underlie the high degree of microbiota diversity relative to residents of developed countries [13,17,18]. While the extent to which such diverse microbes directly impact their hosts are only beginning to be defined, one of their primary metabolic products, namely short chain fatty acids (SCFA), have long been appreciated to play a role in health. SCFA are thought to provide a major nutrient source for intestinal epithelial cells, and are also though to play a key role in promoting regulatory T-cells that serve to keep immune responses in-check, thus preventing inappropriate or excessive inflammation [19,20].

The importance of fermentable fiber can be readily appreciated by examining the consequences of its absence in mice diets. For example, Martens and colleagues observed that lack of fiber resulted in microbiota consuming the mucus layer, which made the intestine more prone to attack by invasive pathogens [21]. We observed that lack of

fermentable fibers results in greatly reduced epithelial cell proliferation that leads to a thin mucosa in which but bacteria readily encroach [22,23]. Such effects on host-microbiota interaction promoted low-grade inflammation that underlined a significant portion of metabolic syndrome induced by HFD, which is generally devoid of fermentable fiber, and were sufficient to promote a significant degree of adiposity even in the context of a low-fat diet [22,23]. Conversely, supplementing HFD with the fermentable fiber inulin but not the insoluble fiber cellulose resulted in a microbiota-dependent fortification of the mucosa that prevented microbiota encroachment and protected against HFD-induced metabolic syndrome [22,23]. Interestingly, such protective effects of fermentable fiber were not largely mediated by SCFA generation but rather were mediated by induction of IL-22, whose levels were depleted by lack of fiber and restored by inulin in a microbiota-dependent manner. Together, these results suggest that diets lacking fermentable fiber may result in malnourishment of the microbiota, which can lead to promotion of chronic inflammation.

While perhaps the simplest approach to remedy lack of dietary fiber is to encourage consumption of plant-based diets rich in fiber, it might also seem quite reasonable to consume fiber supplements and/or enrich foods with fermentable fiber. Indeed, Cani and colleagues have demonstrated that supplements of inulin result in a seemingly healthier microbiota composition and improved metabolic health although the discomfort (e.g. bloating, flatulence) associated with the effective doses makes the strategy somewhat impractical [24]. Moreover, our observations in mouse studies suggest that great caution is needed in considering approaches to supplement diets with purified fibers. Specifically, while enriching HFD with inulin prevented HDD-induced gut atrophy and greatly reduced metabolic syndrome [22,23], it did not restore gut microbiota composition per se but rather resulted in a new community structure altogether. Moreover, mice consuming inulin-enriched purified diets, of low or high fat content, developed extremely severe colitis upon exposure to the chemical DSS [23]. Moreover, prolonged maintenance of mice with dysbiosis, resulting from a range of discrete innate immune deficiencies, on inulin enriched purified diets developed a rare and deadly form of liver cancer, namely hepatocellular carcinoma (HCC). Neither severe DSS-induced colitis nor HCC was observed in mice fed inulin-enriched rodent chow, which is a relatively unrefined conglomerate of food scraps. Thus, while strategies to enrich foods with fermentable fiber may hold long-term potential to induce a more beneficial microbiota composition, at present, our relatively poor understanding of how various dietary components impact microbiota and host in a range of contexts may currently preclude safe engineering of foods as a means of promoting gut health.

Role of food additives in alterations of the host/microbiota relationship

Another change in human diets since the mid 20th century is consumption of a range of compounds added to processed foods. Some of these compounds are synthetic molecules, not found in nature, and thus would not have been seen by the microbiota or host before, while others exist in some foods consumed by humans but are added to processed foods in a non-natural context. In general, such food additives are permitted to be used as food additives by regulatory agencies on the grounds that they have been shown, in rodents, not to cause acute toxicity nor tumors, or because they have been deemed to have been in use for

some time and are generally recognized as safe (GRAS). However, the extent of a particular food additive to promote or trigger disease in hosts with a genetic predisposition to a particular disorder has not generally been considered. Nor has the regulatory process considered more subtle effects, such as altering gut microbiota in a way that promote chronic inflammation. For example, the food additive maltodextrin, which is widely used and has long had GRAS status, promotes virulence gene expression in *Escherichia coli* and promotes microbiota encroachment into the mucus layer in mice [25] [26], leading to speculation that this food additive might play a role in triggering IBD in person who are genetically predisposed to this disorder. Artificial sweeteners, which have been rigorously demonstrated not to cause acute toxicity or cancer at physiological doses, have been shown to have clear effects on the microbiota in both mouse and humans in a manner that promotes dysglycemia, which is one of the primary conditions many consuming these products are seeking to avoid [27]. Thus, the notion that a food additive is considered safe by regulatory agencies does not preclude detrimental effects on the microbiota or host.

One general class of such compounds that are incorporated into many processed foods is emulsifiers. Emulsifiers are detergent-like molecules that stabilize mixtures, especially of immiscible liquids. Most processed foods contain one or more emulsifier that allow such foods to maintain desired textures and avoid separation into distinct parts (e.g. oil and water layers). Two synthetic emulsifiers, namely carboxymethycellulose (CMC) and polysorbate 80 (P80), promote bacterial overgrowth in the murine small intestine and facilitate translocation of bacteria across model gut epithelia [28,29], suggesting the possibility that these agents might have contributed to the increased incidence of IBD and/or promote low-grade inflammation and metabolic syndrome. In support of this hypothesis, we recently observed that both CMC and P80 promoted microbiota encroachment and increased levels of pro-inflammatory flagellin and LPS, which correlated with a change in microbiota composition, low-grade inflammation, and a metabolic syndrome phenotype [7]. This phenotype was dependent upon the presence of the microbiota (i.e. no emulsifier-induced phenotype was observed in germ-free mice) while transplant of microbiotas from emulsifier-treated mice to germ-free mice transferred the aggressive microbiota and some features of metabolic syndrome [7]. CMC and P80 treatment also increased incidence of chronic colitis in mice genetically predisposed to this disorder [7]. These results support the notion that substances that are non-toxic by classical readouts may alter the gut microbiota and promote inflammation that may take a number of different forms in a range of hosts. While the mechanism remains under investigation, we hypothesize that emulsifiers may act directly on the microbiota to change its composition and gene expression in a manner that promotes inflammation. In support of this possibility, we recently observed that, in an *ex vivo* model of human microbiota, CMC and P80, respectively, altered microbiota gene expression and composition in a manner that increased expression its ability to encroach upon the mucosa when transplanted into mice [30]. Molecular mechanisms of such emulsifier effects on bacteria are under investigation, and the potential these compounds to directly the microbiota does not exclude the possibility that they also have direct effects on the intestinal mucosa, which is a possibility that remains under investigation. Also underway are studies to determine the extent to which these results in a rodent model translate to humans. Regardless, we submit that CMC and P80 are but 2 examples of a wide range of food

additives that have not been adequately studied for safety especially in terms of their ability to promote low-grade inflammation and its associated diseases.

Conclusion: Perspective

As outlined herein, diet is a major influencer on microbiota composition and, as such, holds great power to promote health and disease in ways that are only beginning to be appreciated. While it might seem exceedingly logical to harness that power to improve health, at present, lack of understanding of the mechanisms that underlie diet's impact on microbiota make engineering of food to promote gut health a risky endeavor. Rather, we submit more basic studies of how diet influences microbiota and its consequences on host health are needed. Such studies will likely involve rodents but also require validation in humans, whose microbiotas seem inherently more resistant to perturbation by diet than is the case for mice. Importantly, whether achieved by modulation of one's food choices or better engineering of processed foods, approaches to optimize microbiota for health promotion may not be "one size fits all" but rather may require "personal nutrition" wherein foods may be designed for specific individuals to optimize their particular microbiota. Indeed, a recent pioneering study indicates microbiotas composition greatly facilitates design of personalized diets to reduce post-prandial dysglycemia [31]. Nonetheless, at present, a preponderance of studies supports the more generalized recommendation that consumption of foods naturally rich in fermentable fiber promote gut health and suggest that some ubiquitous food additives might be driving societal increases in microbiota-mediated chronic inflammatory diseases.

Acknowledgments

Funding

This work was supported by NIH grant DK099071 and DK083890. BC is a recipient of the Career Development Award from the Crohn's and Colitis Foundation of America (CCFA).

Abbreviations

IBD	Inflammatory bowel disease
CDD	compositionally-defined diet
HFD	high-fat diet
SCFA	short-chain fatty acid

References

1. Lloyd-Price J, Abu-Ali G, Huttenhower C, et al. The healthy human microbiome. Genome Med. 2016; 8:51. [PubMed: 27122046]
2. Kostic AD, Gevers D, Siljander H, Vatanen T, Hyotylainen T, Hamalainen AM, Peet A, Tillmann V, Poho P, Mattila I, et al. The dynamics of the human infant gut microbiome in development and in progression toward type 1 diabetes. Cell Host Microbe. 2015; 17:260–273. [PubMed: 25662751]
3. Human Microbiome Project C. Structure, function and diversity of the healthy human microbiome. Nature. 2012; 486:207–214. [PubMed: 22699609]

4. Faith JJ, Guruge JL, Charbonneau M, Subramanian S, Seedorf H, Goodman AL, Clemente JC, Knight R, Heath AC, Leibel RL, et al. The long-term stability of the human gut microbiota. Science. 2013; 341:1237439. [PubMed: 23828941]

5. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010; 464:59–65. [PubMed: 20203603]

6. Chassaing B, Koren O, Carvalho FA, Ley RE, Gewirtz AT. AIEC pathobiont instigates chronic colitis in susceptible hosts by altering microbiota composition. Gut. 2013

**7. Chassaing B, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE, Gewirtz AT. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. Nature. 2015; 519:92–96. (Demonstrates ability of select food additives to impact microbiota and promote inflammaztory diseases). [PubMed: 25731162]

8. Chassaing B, Ley RE, Gewirtz AT. Intestinal epithelial cell toll-like receptor 5 regulates the intestinal microbiota to prevent low-grade inflammation and metabolic syndrome in mice. Gastroenterology. 2014; 147:1363–1377. e1317. [PubMed: 25172014]

*9. Chassaing B, Raja SM, Lewis JD, Srinivasan S, Gewirtz AT. Colonic Microbiota Encroachment Correlates With Dysglycemia in Humans. Cell Mol Gastroenterol Hepatol. 2017; 4:205–221. (Indicates aggressive microbiota is a featute of metabolic disease in humans). [PubMed: 28649593]

10. Carvalho FA, Koren O, Goodrich JK, Johansson ME, Nalbantoglu I, Aitken JD, Su Y, Chassaing B, Walters WA, Gonzalez A, et al. Transient inability to manage proteobacteria promotes chronic gut inflammation in TLR5-deficient mice. Cell Host Microbe. 2012; 12:139–152. [PubMed: 22863420]

11. Butto LF, Haller D. Dysbiosis in intestinal inflammation: Cause or consequence. Int J Med Microbiol. 2016; 306:302–309. [PubMed: 27012594]

12. Wu GD, Compher C, Chen EZ, Smith SA, Shah RD, Bittinger K, Chehoud C, Albenberg LG, Nessel L, Gilroy E, et al. Comparative metabolomics in vegans and omnivores reveal constraints on diet-dependent gut microbiota metabolite production. Gut. 2014

13. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature. 2012; 489:220–230. [PubMed: 22972295]

14. Hildebrandt MA, Hoffmann C, Sherrill-Mix SA, Keilbaugh SA, Hamady M, Chen YY, Knight R, Ahima RS, Bushman F, Wu GD. High-fat diet determines the composition of the murine gut microbiome independently of obesity. Gastroenterology. 2009; 137:1716–1724. e1711–1712. [PubMed: 19706296]

15. Ridlon JM, Kang DJ, Hylemon PB, Bajaj JS. Bile acids and the gut microbiome. Curr Opin Gastroenterol. 2014; 30:332–338. [PubMed: 24625896]

16. Devkota S, Wang Y, Musch MW, Leone V, Fehlner-Peach H, Nadimpalli A, Antonopoulos DA, Jabri B, Chang EB. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in Il10−/− mice. Nature. 2012; 487:104–108. [PubMed: 22722865]

*17. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G, Lionetti P. 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. 2010; 107:14691–14696. (Suggests strong sicietal impacts of loss of fiber in dfiets). [PubMed: 20679230]

18. Albenberg LG, Wu GD. Diet and the intestinal microbiome: associations, functions, and implications for health and disease. Gastroenterology. 2014; 146:1564–1572. [PubMed: 24503132]

19. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly YM, Glickman JN, Garrett WS. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013; 341:569–573. [PubMed: 23828891]

20. Park J, Kim M, Kang SG, Jannasch AH, Cooper B, Patterson J, Kim CH. Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway. Mucosal Immunol. 2015; 8:80–93. [PubMed: 24917457]

21. Desai MS, Seekatz AM, Koropatkin NM, Kamada N, Hickey CA, Wolter M, Pudlo NA, Kitamoto S, Terrapon N, Muller A, et al. A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic

Mucus Barrier and Enhances Pathogen Susceptibility. Cell. 2016; 167:1339–1353. e1321. [PubMed: 27863247]

*22. Chassaing B, Miles-Brown J, Pellizzon M, Ulman E, Ricci M, Zhang L, Patterson AD, Vijay-Kumar M, Gewirtz AT. Lack of soluble fiber drives diet-induced adiposity in mice. Am J Physiol Gastrointest Liver Physiol. 2015; 309:G528–541. (Indicates essential role of fiber for gut health). [PubMed: 26185332]

23. Miles JP, Zou Z, Vijay-Kumar M, Pelizzon M, Ulman E, Ricci M, Gewirtz AT, Chassaing B. Supplementation of low- and high-fat diets with fermentable fiber exacerbates severity of DSS-induced acute colitis. Inflamm Bowel Dis. 2017

24. Salazar N, Dewulf EM, Neyrinck AM, Bindels LB, Cani PD, Mahillon J, de Vos WM, Thissen JP, Gueimonde M, de Los Reyes-Gavilan CG, et al. Inulin-type fructans modulate intestinal Bifidobacterium species populations and decrease fecal short-chain fatty acids in obese women. Clin Nutr. 2015; 34:501–507. [PubMed: 24969566]

25. Nickerson KP, McDonald C. Crohn's disease-associated adherent-invasive Escherichia coli adhesion is enhanced by exposure to the ubiquitous dietary polysaccharide maltodextrin. PLoS One. 2012; 7:e52132. [PubMed: 23251695]

26. Nickerson KP, Chanin R, McDonald C. Deregulation of intestinal anti-microbial defense by the dietary additive, maltodextrin. Gut Microbes. 2015; 6:78–83. [PubMed: 25738413]

27. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, Israeli D, Zmora N, Gilad S, Weinberger A, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature. 2014; 514:181–186. [PubMed: 25231862]

28. Swidsinski A, Ung V, Sydora BC, Loening-Baucke V, Doerffel Y, Verstraelen H, Fedorak RN. Bacterial overgrowth and inflammation of small intestine after carboxymethylcellulose ingestion in genetically susceptible mice. Inflamm Bowel Dis. 2009; 15:359–364. [PubMed: 18844217]

29. Roberts CL, Keita AV, Duncan SH, O'Kennedy N, Soderholm JD, Rhodes JM, Campbell BJ. Translocation of Crohn's disease Escherichia coli across M-cells: contrasting effects of soluble plant fibres and emulsifiers. Gut. 2010; 59:1331–1339. [PubMed: 20813719]

30. Chassaing B, Van de Wiele T, De Bodt J, Marzorati M, Gewirtz AT. Dietary emulsifiers directly alter human microbiota composition and gene expression ex vivo potentiating intestinal inflammation. Gut. 2017

**31. Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, Ben-Yacov O, Lador D, Avnit-Sagi T, Lotan-Pompan M, et al. Personalized Nutrition by Prediction of Glycemic Responses. Cell. 2015; 163:1079–1094. (Demonstrates that microbiota composition is a key determinant of how diet impacts glycemic control). [PubMed: 26590418]

Key points

1) Change in diet alters nutrients available to microbiota favoring growth of some species resulting in a change of microbiota composition.

2) Fiber content, type and amount, are one pivotal determinant in impacting microbiota composition and how it impacts intestine.

3) Food additives, including emulsifiers can result in an “aggressive” microbiota that encroaches upon its host and promotes inflammation.