REVIEW

Chronic Inflammatory Diseases: Are We Ready for Microbiota-based Dietary Intervention?

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SUMMARY

Accumulating evidence supports the orchestrating role of the intestinal microbiota in chronic inflammatory disorders. As more dietary factors are identified as potential mediators of microbiota composition and function, will personal dietary intervention based on microbiota composition soon be part of disease management?

The last 15 years have witnessed the emergence of a new field of research that focuses on the roles played by the intestinal microbiota in health and disease. This research field has produced accumulating evidence indicating that dysregulation of host-microbiota interactions contributes to a range of chronic inflammatory diseases, including inflammatory bowel diseases, colorectal cancer, and metabolic syndrome. Although dysregulation of the microbiota can take complex forms, in some cases, specific bacterial species that can drive specific clinical outcomes have been identified. Among the numerous factors influencing the intestinal microbiota composition, diet is a central actor, wherein numerous dietary factors can beneficially or detrimentally impact the host/microbiota relationship. This review will highlight recent literature that has advanced understanding of microbiota-diet-disease interplay, with a central focus on the following question: Are we ready to use intestinal microbiota composition-based personalized dietary interventions to treat chronic inflammatory diseases? *(Cell Mol Gastroenterol Hepatol 2019;8:61–71; https://doi.org/10.1016/j.jcmgh.2019.02.008)*

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The intestinal microbiota is a vast and complex community of microorganisms that includes 10^{14} bacteria per intestine and about 100–500 different species per individual.[1,2] Among its numerous functions, the gut microbiota is essential to promote maturation of the intestinal immune system and help digestion by permitting extraction of calories and nutrients that would otherwise be eliminated in feces. Besides these beneficial roles, the gut microbiota can also turn detrimental to its host and, if not well-managed, can lead to the development of inflammatory diseases such as inflammatory bowel disease (IBD) and metabolic syndrome.[3–5] Importantly, the large post–mid-20th century increase in the incidence of IBD and metabolic

syndrome highlights the pivotal role of nongenetic factors in determining the extent to which individuals genetically prone to disease actually develop it. Nongenetic factors previously shown to influence the intestinal microbiota and development of colitis are listed in Table 1.

During the last 15 years, numerous studies have reported alterations in microbiota composition in both preclinical and clinical models of chronic inflammatory diseases. Although those alterations may, in part, be driven by the disease state, recent work has highlighted that an altered microbiota can also play a role in driving the disease, with the observation that disease can be transferred to germ-free mice by microbiota transplantation. For example, a pioneering study by Turnbaugh et al[6] revealed that colonization of germ-free mice with an "obese microbiota" caused the recipient mice to gain more weight than those who received a "lean microbiota." Mechanistic investigations have highlighted the importance of some specific microbiota members in driving detrimental outcomes, such as intestinal inflammation.[7,8]

Altogether, these findings suggest that microbiota could be seen as a next-generation medicine, with the hypothesis that therapeutic/dietary interventions can be based on individual microbiota composition.

Lessons Learned From Cancer Therapy

The concept of microbiota composition-based therapy is most advanced in the research area of cancer therapeutics, particularly in determining drug efficacy. Recent studies have highlighted how intestinal bacteria can impact efficacy of anticancer drugs,[9] with the findings that cancer patients can be stratified into responders and non-responders to immunotherapy on the basis of their intestinal microbiota composition. This suggests that microbiota should be considered when assessing therapeutic intervention.[10–13] For example, Gopalakrishnan et al[12] identified that fecal microbiota composition differs between patients with metastatic melanoma that responded or not to anti–programmed

Table 1. Nongenetic Factors Previously Shown to Influence Intestinal Microbiota in a Way That Triggers Intestinal Inflammation

Compounds	Model used	Effect on the intestinal microbiota	Effect on the host	Reference
Soluble fibers	C57/Bl6 WT treated with DSS C57/Bl6 IL10KO	Alteration of microbiota composition at the phylum level Impact on bacterial biomass and proinflammatory potential	Promotion of intestinal inflammation	55, 56
Aluminum	Colorectal distention in rats	Not studied	Orally administered low-dose aluminum induced visceral hypersensitivity	79
Maltodextrin	Biofilm formation assay In vitro adhesion to intestinal epithelial cells C57/Bl6 WT treated with DSS	Increased biofilm formation and adhesion ability of Crohn's disease–associated adherent and invasive *Escherichia coli* bacteria No alteration of mucosa-associated microbiota	Deregulation of intestinal antimicrobial defense Promotion of endoplasmic reticulum stress, mucus depletion	44, 80, 81
Dietary emulsifier (CMC and P80)	C57/Bl6 WT C57/Bl6 IL10KO C57/Bl6 TLR5KO	Alteration of microbiota composition Increase of microbiota proinflammatory potential Promotion of microbiota encroachment	Promotion of low-grade intestinal inflammation and metabolic disorders in WT and TLR5KO mice Promotion of colitis incidence and severity in IL10KO mice	20, 32, 82, 83
Thickener (carrageenan)	Pig	Microbiota composition alterations at the phylum level Decreased proportion of *A muciniphila*	Ulcerations in the large intestine	84–86
Artificial sweeteners	SAMP1/YitFc (SAMP) mice	Alteration of microbiota composition, promotion of proteobacteria	Exacerbation of ileal inflammation	87
Titanium dioxide nanoparticles	Adult zebrafish (*Danio rerio*) C57/Bl6 WT Wistar rats	Alteration of microbiota composition	Increase in levels of the inflammatory cytokines Colonic microinflammation	88–90

DSS, dextran sulfate sodium; WT, wild-type.

cell death protein 1 (PD-1) therapy. Patients who responded to this therapy had higher abundance of the *Faecalibacterium* genus in their fecal microbiota, whereas non-responders harbored a higher abundance of Bacteroidales order.[12] This finding importantly highlighted that an initial assessment of microbiota composition could be used as predictor of anti–PD-1 therapy success and could help to determine drug dose and frequency. Similarly, Routy et al[11] demonstrated a central role played by the gut microbiota in the therapeutic response induced by immune checkpoint inhibitors targeting the PD-1/PD-L1 axis, with the identification of responder and non-responder patients. Fecal metagenomics revealed that the relative abundance of *Akkermansia muciniphila* correlated with clinical responses to immune checkpoint inhibitors, and oral supplementation with *A muciniphila* after fecal microbiota transplantation (FMT) from non-responder feces was sufficient to restore the efficacy of PD-1 blockade in mice model.[11] Such studies highlight the future of microbiota-based precision medicine therapies,[9,14] with the concept that patients entering immunotherapy treatment for cancer may first have their microbiota composition analyzed to determine (1) what is the best therapeutic approach and (2) whether some patients could benefit from FMT before therapy to be converted from non-responders to responders. However, although these studies highlight the critical role of microbiota members in defining anti–PD-1 therapy responsiveness, no consensus was reached regarding the specific bacteria associated with therapeutic response, with quite different bacterial species/genus driving the associations reported in each independent study.[10–12] These findings suggest a potential unappreciated heterogeneity and the importance of performing thorough microbiota composition analysis by using uniformed sequencing platform and analysis workflow, as well as precise patient stratification based on cancer type, cancer stage, patient origin, etc.[9,15]

Lessons Learned From Research on Dietary Emulsifiers

We and others previously hypothesized that emulsifiers, which are added to most processed foods to aid texture and extend shelf life, might have played a role in the rapid post–mid-20th century increase in the incidence of chronic inflammatory diseases.[16–19] Investigation of this hypothesis led us to observe that emulsifiers induced a chronic intestinal inflammation that promotes development of chronic colitis in susceptible mice and metabolic syndrome in wild-type mice.[20] By treating mice with 2 commonly used emulsifiers, namely polysorbate 80 (P80) and carboxymethylcellulose (CMC), at doses seeking to model the broad consumption of the numerous emulsifiers that are incorporated into a large variety of processed foods, we observed changes in species composition of the gut microbiota and increased expression of proinflammatory molecules. Such alterations included increased lipopolysaccharide and flagellin, which can activate host proinflammatory gene expression. Moreover, CMC- and P80-induced alterations in microbiota resulted in enhanced capacity to infiltrate the dense mucus layer that lines the intestine. Mucosa-associated microbiota has been previously studied and is

characterized by a distinct composition compared with luminal microbiota,[21–26] with important roles played by this community on maturation of the immune system (for example, the well-documented impact of segmented filamentous bacteria on Th17 cells[23,27]). However, the colonic inner mucus layer normally harbors a relatively low bacterial biomass,[28,29] which compositionally differs from luminal and mucosa-associated microbiota.[30] CMC and P80 alter this inner mucus environment by promoting microbiota encroachment in a way that triggers chronic colitis in mice genetically prone to this disorder.[20] In wild-type mice with normal immune systems, emulsifiers induced low-grade (ie, mild) intestinal inflammation and metabolic syndrome, characterized by increased adiposity and hyperglycemia. As a result of investigation into mechanisms underlying emulsifier-mediated promotion of inflammation, we identified that the effects of their consumption were eliminated in mice lacking a microbiota (germ-free), and that transplantation of microbiota from emulsifier-treated mice to wild-type germ-free recipient mice was sufficient to transfer some parameters of low-grade inflammation and metabolic syndrome, indicating a central role played by the microbiota in mediating the effects.

Importantly, we recently demonstrated that a complex microbiota community is required for emulsifier-mediated detrimental effects, with the observation that emulsifier consumption by gnotobiotic mice colonized with a highly restricted microbiota composed of only 8 bacteria, namely altered Schaedler flora (ASF),[31] was not sufficient to induce microbiota encroachment, intestinal inflammation, or altered metabolism.[32] These findings suggest that a complex microbiota containing some specific species is required to mediate detrimental effects of emulsifier exposure (Figure 1). In the coming years, microbiota composition analysis combined with the evaluation of inter-individual variations in response to emulsifier should identify specific species detrimentally impacted by such compounds. In other words, whereas some individuals may harbor a microbiota that will not be impacted by emulsifier exposure, other individuals may harbor some specific bacteria in their microbiota that make them susceptible to emulsifier-driven detrimental effects such as chronic intestinal inflammation and metabolic deregulations (Figure 1).

Lessons Learned From Patient Cohort Studies

FMT has recently gained interest as a possible novel treatment option for chronic inflammatory diseases including IBD. Indeed, even though treatments of such disorders by FMT are quite exploratory at present, the interest in its potential is attested to by the increasing number of publications describing FMT as therapy for IBD.[33] However, the clinical outcomes in the various studies are excessively heterogenous, with studies reporting no improvement, deterioration, improvement, improvement but no remission, and/or clinical remission.[34–38] These studies once again demonstrated heterogeneity in therapeutic outcomes and suggest that personalized intervention based on microbiota composition of the donor and/or the recipient microbiota
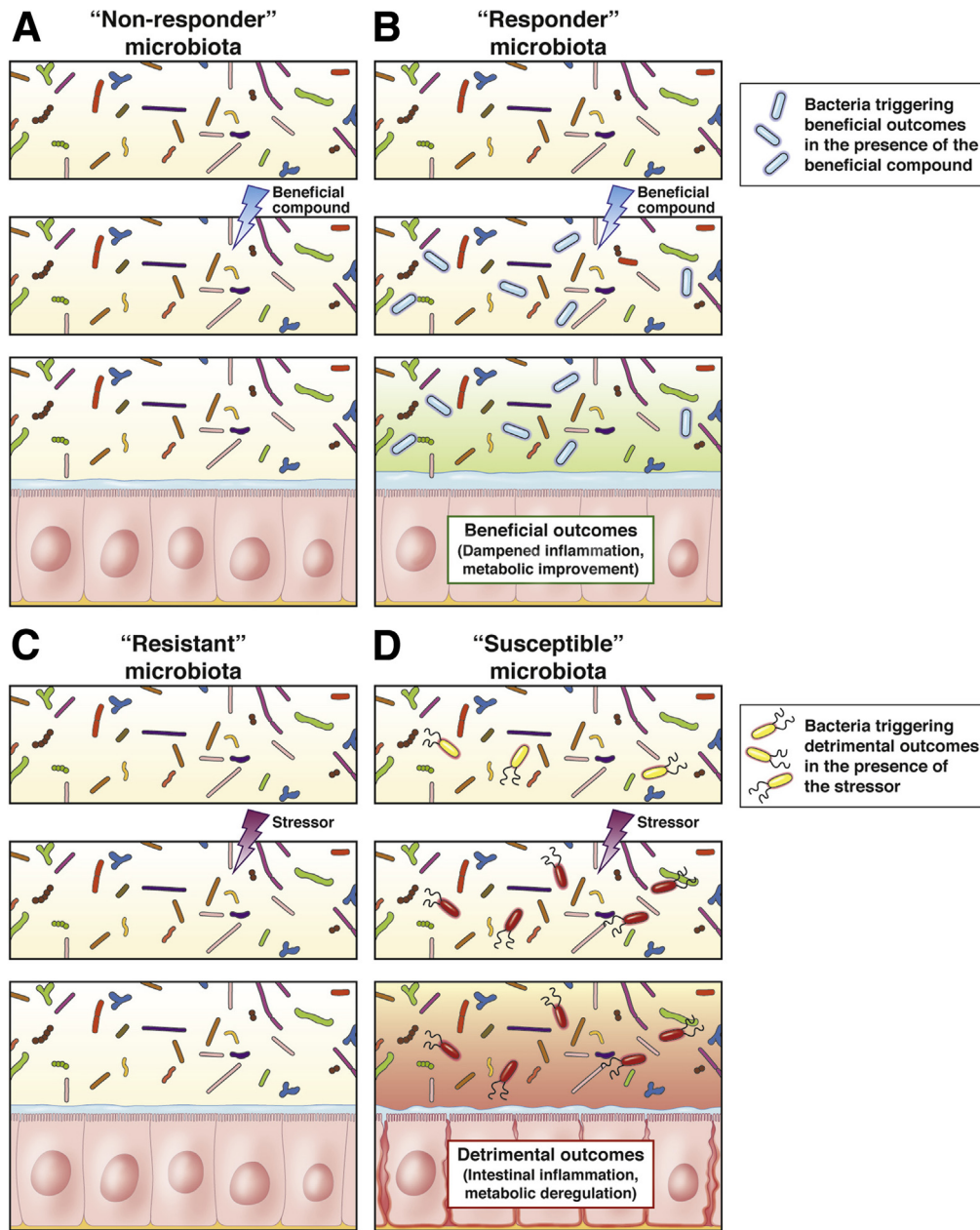
Figure 1. Overview of the resistant and susceptible concept. (*A* and *B*) In the presence of a beneficial compound, some microbiota might not respond (*A*), whereas some others might be responsive (*B*) by harboring specific bacterial species able to trigger beneficial outcomes. (*C* and *D*) In the presence of a detrimental compound, some microbiota might be resistant (*C*), whereas some others might be susceptible (*D*) by harboring specific bacterial species able to trigger detrimental outcomes.

may be needed, even if coming with quite some challenges. Currently, the notion that FMT can successfully treat diseases characterized by gut inflammation is best supported by the successful use of FMT in treatment of recurrent *Clostridium difficile* infection, which results in severe colitis. This approach allows a donor microbiota to recolonize the gastrointestinal tract of a patient with a complex microbial community, thus conferring "colonization resistance" to *C difficile* infection and preventing pathogenesis.[39] Although specific approaches to FMT treatment of recurrent *C difficile* vary across institutions, it generally uses clinical stratification of both donors and recipients to transplant microbiota that will reach high success rates of engraftment.[40]

Analogously, a proper diagnosis strategy and clinical classification of IBD patients, and perhaps fecal donors, would seem warranted for successful FMT-based IBD therapy.

Similarly, another approach to beneficially manipulate the intestinal microbiota in the IBD population is through dietary modulation, which may also highly benefit from considering inter-individual variations in microbiota composition. Association study between dietary intake and incidence of IBD has pointed to food components as impacting IBD development. Indeed, certain food components such as polyunsaturated fatty acids, omega-6 fatty acids, and meat seem to predispose for IBD, whereas fibers and fruits or vegetables were associated with a decreased

risk of Crohn's disease (CD) and ulcerative colitis, respectively.[41] Results from dietary therapy, such as exclusive enteral nutrition (which is using exclusive liquid feeding with either elemental or polymeric formulas) for IBD, remain inconclusive.[42,43] Because IBDs are multifactorial diseases and IBD population is highly heterogeneous, performing dietary intervention in the IBD population to investigate the role of a food component or a food additive without considering this inter-individual variation might not provide conclusive results. An example highlighting this concept is a study demonstrating that the ubiquitous dietary component maltodextrin enhanced CD-associated adherent invasive *Escherichia coli* (AIEC) biofilm formation.[44] Hence, on the basis of the observation that only 30%–40% of the CD population harbor AIEC bacteria,[4,45,46] we can hypothesize that if a research clinical trial using maltodextrin-free diet were to be performed at the IBD population level, results will show different results for AIEC+ and AIEC– subjects (Figure 2A). On the other hand, if such maltodextrin-free diet clinical trial were to focus on the CD population carrying AIEC bacteria, we can expect much clearer beneficial clinical outcomes (Figure 2B).

Other important investigations focusing on the obese population have highlighted the importance of the intestinal microbiota in clinical trials, particularly in regard to dietary intervention. In an elegant study by Clément and Cani groups, the authors found that baseline of *A muciniphila* abundance within the intestinal microbiota associated with better clinical outcomes after a 6-week dietary intervention in the obese population.[47] By stratifying the population on the basis of *A muciniphila* level, they indeed found that patients harboring a higher level of this specific bacteria had greatest benefits from the dietary intervention.[47] Hence, one can speculate that such observation may apply to other bacteria, and that the success of dietary intervention aiming to improve metabolic health may highly benefit from individualization based on microbiota composition.[47,48]

In a similar vein of research, a recent study demonstrated that colonization of the gastrointestinal tract by probiotic is dependent on and can be predicted by microbiota composition,[49] suggesting that some microbiota might be more predisposed to benefit from probiotic treatment. Importantly, although patients can be stratified by their ability to be colonized, functional outcomes were not addressed in this study, and numerous reports actually suggest that a daily probiotic does not necessarily need to colonize to exert its beneficial effect.[50,51] Interestingly, probiotic treatment was also recently found to have a detrimental impact on microbiota recolonization after antibiotic use, highlighting that stable colonization of the gastrointestinal tract by such species may also be detrimental.[52]

Lessons Learned From Preclinical Research on Purified Soluble Fiber

In a recent study, we unexpectedly observed that in mice, enriching purified diets with soluble fiber inulin led to icteric hepatocellular carcinoma (HCC), with up to 40%

penetrance rate in male mice and 20% in female mice.[53] In this model, we identified a central role played by the intestinal microbiota, with the observation that HCC susceptibility was transferred to normally unaffected mice by co-housing. Mechanistically, soluble fiber–induced HCC was prevented by inhibition of microbial fermentation. This study also revealed that an analysis of the microbiota composition could predict the likelihood of an animal to develop soluble fiber–induced HCC.[53] Moreover, HCC penetrance was impacted by the animal provider, highlighting further that a specific microbiota is required for the development of soluble fiber–driven HCC and suggesting that in this case, the intestinal microbiota could be more determinant than host genetics for precision medicine.[54]

Similarly, we identified that although soluble fiber supplementation was beneficial in a model of diet-induced obesity in wild-type mice,[55] it was associated with exacerbation of colitis in genetically susceptible mice (IL10KO).[56] Altogether, these findings suggest that precision dietary supplementation based on personal gut microbiota might be a promising future direction to manage intestinal and extraintestinal disorders. For example, *Prevotella* genus is known to be an effective producer of short-chain fatty acid through dietary fiber degradation,[57,58] and one can imagine dietary recommendation for daily fiber intake based on *Prevotella* relative abundance in the gastrointestinal tract to avoid detrimental impacts on the liver.

Lessons Learned From General Population-based Studies

Because of recent advances in nucleic acid sequencing methods that have dramatically increased the cost-effectiveness of microbiota composition analyses techniques, important progress has recently been made by investigating microbiota composition at the population level together with detailed characterization of clinical outcomes. Among these recent studies, one assessed factor can contribute to postprandial blood glucose level elevation after a meal, a defining parameter of prediabetes and a major risk factor for type 2 diabetes. Although inter-individual variations in postprandial blood glucose level had been previously described, they were yet not well-understood. In this research, Zeevi et al[59] monitored glucose levels of 800 participants in response to almost 50,000 meals, and they importantly found high inter-individual variability of blood glucose levels after an identical meal, suggesting that dietary recommendations at the population level may have limited utility. In addition, the authors used machine-learning algorithm that integrated multiple parameters, including gut microbiota composition, and they demonstrated that such algorithm can accurately predict postprandial glycemic response to a specific meal. Such findings elegantly demonstrate the microbiota power in determining clinical outcomes and further support the concept of integrating microbiota inter-individual variations for clinical research.[60] A tool based on multiple factors, including microbiota composition, that is able to precisely predict glycemic response could be highly beneficial for the type 1 diabetic
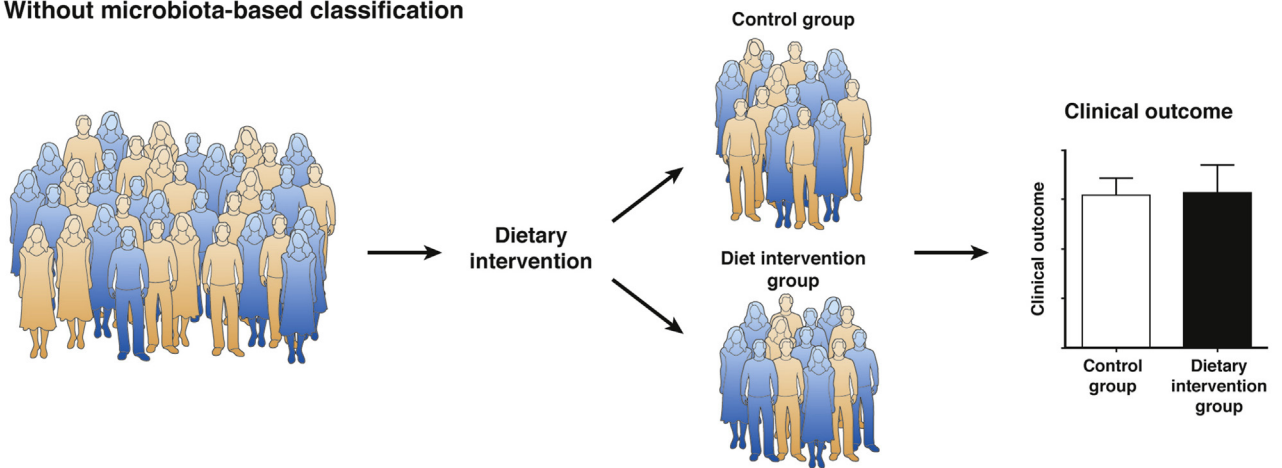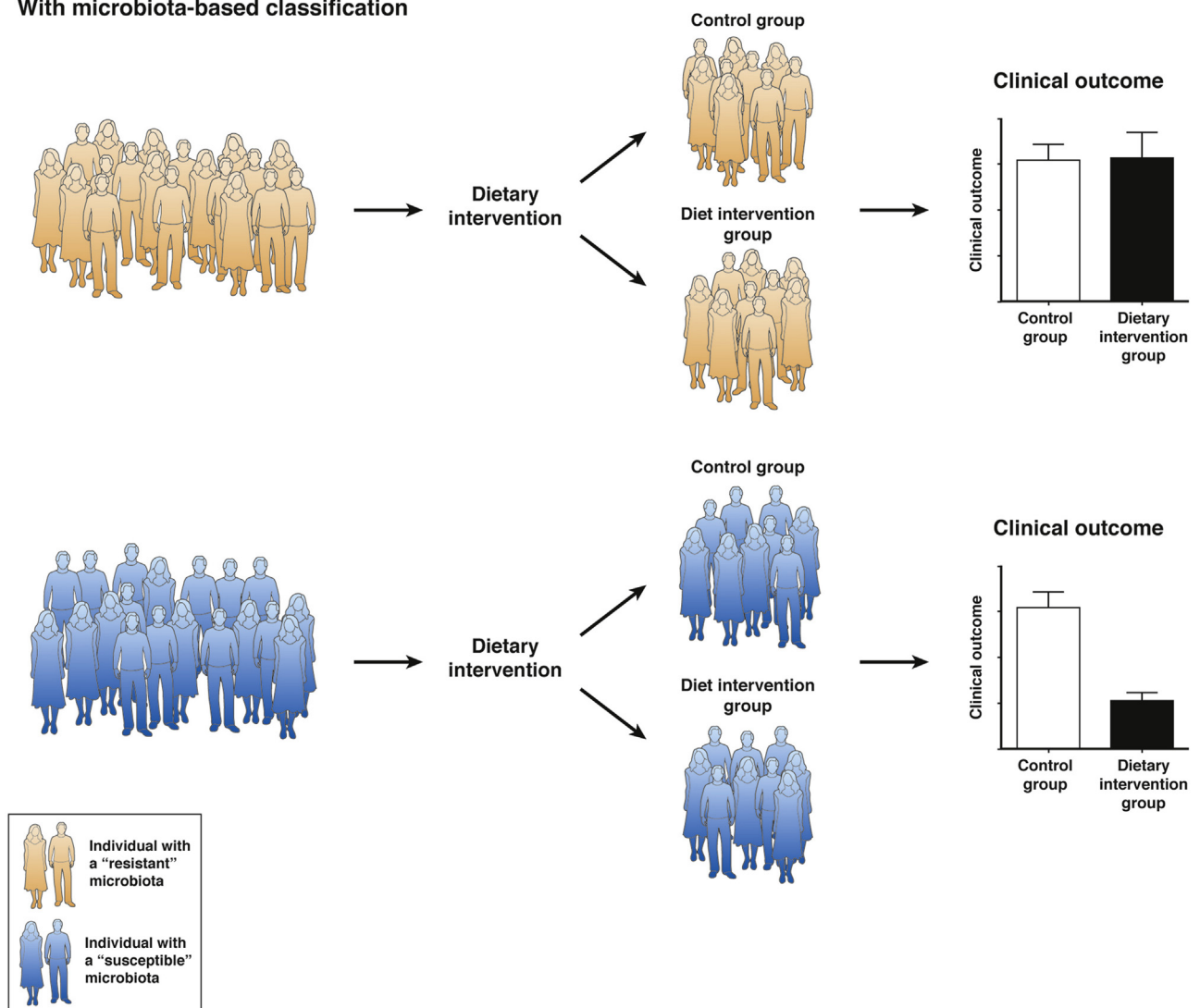
Figure 2. Importance of microbiota-based classification in research clinical trial. (*A*) Without a classification based on the resistant and susceptible status of the individuals, a dietary intervention aiming to supplement a beneficial compound or withdraw a detrimental one will lead to the absence of significant clinical outcome between the treated and the control groups. (*B*) By classifying the participants on the basis of their microbiota status (resistant or susceptible), significant clinical outcomes can be observed in the susceptible population, whereas no effect is observed in the population harboring a resistant microbiota.

population by providing personalized dietary recommendations as well as optimized dosing of insulin to precisely control blood glucose levels.[60]

Discussion and Perspective

The recent and rapid evolution of the microbiome field of research has demonstrated the importance of the microbiome in determining health and disease outcomes. Furthermore, it suggests that microbiome analysis should be added to clinical trials, especially as relates to dietary research, because this information may be essential for correctly appreciating clinical outcomes (Figure 2). Indeed, although a dietary intervention aiming to withdraw and/or supplement specific macro/micronutrients to treat/prevent a chronic inflammatory disease may fail at the population level, the identification of subpopulation harboring specific bacteria that can mediate the beneficial effect may reveal positive outcome of such dietary interventions (Figure 2). Hence, the importance that the intestinal microbiota may have on the outcome of clinical intervention in chronic inflammatory diseases, either drug-based or dietary-based, should now be appreciated and routine feces collection considered. Furthermore, it is estimated that one-third of clinical trials are terminated as a result of hepatotoxicity in subset of patients. Microbiota composition should be investigated in such scenarios because it may allow for those drugs to be used by the population carrying resistant microbiota, whereas they should be avoided by the population harboring a susceptible microbiota that will lead to hepatotoxicity.[48,61] Other factors known to have an impact on microbiota composition, such as gender, genetic factors, and circadian rhythm, will also need to be considered in future studies investigating microbiota-based therapeutic interventions.[62–73] Regarding the latter, for example, microbiota shows host-synchronized circadian variations in its composition,[74] and recent studies highlighted deregulation and disconnection of such microbiota rhythm in chronic inflammatory disease.[75] Hence, microbiota-based therapy will also need to consider multiple important variables including circadian rhythm, for example by targeting a deleterious bacterium at the time of the day when it is the most abundant or by aiming to reconnect microbiota and host rhythms.

Importantly, microbiota composition–based individual classification can be investigated before dietary intervention as well as retrospectively. Indeed, although the ultimate goal of such approach is to classify patients on the basis of their microbiota composition before dietary intervention, further research is needed to better define what are a "resistant" and a "susceptible" microbiota. As an example highlighting this concept, although we have started to identify some specific bacteria triggering emulsifier detrimental effects, fully defining resistant and susceptible microbiota will likely need to be done retrospectively after dietary intervention, with individuals being classified on the basis of their therapeutic response. We envision that such data can be used to identify, within the general population, individuals harboring a microbiota more likely to be beneficially impacted by emulsifier withdraw. Moreover, with the impact of the intestinal microbiota on drug metabolism,[76,77] microbiota composition analysis should now be considered in patient pharmacogenomics analysis.

Conclusion

We submit that deeper understanding of the human microbiota will lead to the identification and comprehension of resistant and susceptible microbiota, allowing health care providers to provide precise, tailored dietary and therapeutic recommendations for their patients. Clearly, additional research is warranted to uncover the determinants and mechanisms by which gut microbiome composition would render a human subject as resistant or susceptible to a particular intervention. To date, most studies have relied on analyzing microbiota composition via 16S rRNA gene sequencing, but accurately predicting responses may require analysis of metagenomes (all the genomic content of a microbiota) and/or metatranscriptomes (all the genes actively expressed by a microbiota) to successfully identify responders and non-responders. Moreover, in addition to the species level, identification of microbiota members at the strain level may need to be investigated.[78] In addition, it appears important to determine which microbiota subpopulation is to be used to properly stratify patient populations: fecal microbiota, luminal microbiota, mucosa-associated microbiota, or inner mucus–associated microbiota, especially because these microbiota subtypes are not communicating with the host or responding to dietary intervention in the same way. Our recently developed technique of laser capture microdissection to specifically collect and identify inner mucus–associated bacteria could help in this endeavor.[30] Moreover, even such extensive analysis may not yield optimal predictive power, and hence we envision that developing functional assays to test how individual microbiotas respond to a particular treatment will be needed. Such need for further studies notwithstanding, routine sampling of stool in dietary-based or drug-based clinical intervention should already be considered to broadly assess microbiota composition in clinical trials, including retrospective analysis. Such approaches may soon begin to unlock the potential of the microbiota in serving as a predictor of clinical outcome in dietary intervention.

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