Gut Microbiota Developments With Emphasis on Inflammatory Bowel Disease: Report From the Gut Microbiota for Health World Summit 2016

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In the past decades the view of the gut microbiota has transformed from fighting the bad bugs with antibiotics to protecting the good bugs that function as a defense barrier and contribute to overall health. The gut microbiota is now commonly recognized as a separate "organ" that, together with the human genome and the immune system, constitutes 1 of the 3 pillars that support human health. The complexity of interactions of the microbiota with not only the host genome and the immune system, but also with the endocrine system, brain, and nutrition, makes it a challenge to grasp the overall picture regarding the role of the microbiota in human health. However, in recent years the Gut Microbiota for Health organization (GMFH) has made considerable progress toward this goal. The GMFH as an organization aims to extract relevant available knowledge from the rapidly accumulating body of basic scientific data and extrapolate it to clinical settings. The GMFH organization represents a collaborative effort between the American Gastroenterological Association and the European Society of Neurogastroenterology & Motility, and is steered by a joint scientific committee composed of members from both societies. At the GMFH World Summit held on March 5 and 6, 2016, in Miami, leading microbiome experts from all over the world presented state-of-the-art gut microbiota science to an audience of scientists, clinicians, nutritionists, students, and representatives from food and pharmaceutical industry, as well as journalists. This meeting summary highlights the updates presented at this summit, including the pitfalls and future promises regarding the microbiome, with special emphasis on inflammatory bowel disease (IBD), an entity in which the involvement of the microbiota is now widely accepted.

Diet: What Has Changed in the Environment?

With an increased global spread of Western lifestyle, the incidence of Western diseases, in particular cancer and autoimmune diseases such as IBD, continues to increase. Modern lifestyle, in particular the increased consumption of fast foods, sugar, and decreased consumption of fiber, fruits, and vegetables, may contribute to this increase in diseases by disrupting the microbiome from an early age. Andrew Gewirtz showed that emulsifiers, commonly added to Western foods to improve shelf-life, change the location (ie, increase the mucosal-adherent bacteria) and composition of gut bacteria and thereby promote chronic inflammation. In addition, Bernd Schnabl presented data demonstrating that chronic alcohol abuse disrupts the intestinal barrier and can modify microbiota composition. He showed that such a disturbance of the gut microbiota composition can extend to effects beyond the intestine, and affect distant organs such as the liver, for example, by bacterial translocation of pathogens or their products through the blood stream. Gut microbes (and dietary habits) might therefore also be involved in the extra-intestinal comorbidity of IBD.

Important work presented by Kishore Vipperla, on behalf of Stephen J. O' Keefe's group, suggests a connection between diet and colon cancer. Their work showed that switching from a Western African American diet to a rural African diet for 2 weeks distinctly changes gut microbiota composition, and lowers risk parameters for colorectal cancer, demonstrated by increased saccharolytic fermentation and butyrate production, and decreased secondary bile acid synthesis. A dietary switch from African to Western diet showed the opposite effects. Vipperla's advice was to increase the fiber content in our diet to 50 g/d and reduce fat by half to establish a microbiota composition that is low risk for the development of colorectal carcinoma. This is especially relevant for IBD patients, because they carry an increased risk for inflammation-induced colon cancer.

These studies likely demonstrate only a fraction of the dietary effects on the microbiota and health. In IBD, there is still no consensus on the exact role of diet on disease state, but the link between diet and microbes is clear. Therefore, because microbes are involved in the etiology of IBD, there is reason to believe diet contributes to some degree as well. As highlighted at the GMFH Summit during the Panel Discussion, some gastroenterologists have observed substantial success with dietary intervention in IBD patients, such as the specific carbohydrate diet, but current data are too

Abbreviations used in this paper: FMT, fecal microbiota transplantation; GMFH, Gut Microbiota for Health; IBD, inflammatory bowel disease.

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limited to suggest general guidelines.[1] Compounding progress factors of dietary intervention trials are a poor compliance to dietary therapy, absence of appropriate controls, a lack of understanding as to patient-specific responses, as well as limited funding.

Life Events That Alter Gut Microbiota

Beside dietary habits, life events can alter the gut microbiota composition. One of these life-events is pregnancy, which was discussed by Omry Koren. He showed that in healthy pregnant women (n = 93) the gut microbiota composition differed distinctly between the first and third trimesters, with microbial diversity in the third trimester becoming aberrant, characterized by an increase in *Proteobacteria* and *Actinobacteria*. It was discussed that these gestational age–dependent microbiota alterations have also been demonstrated in IBD patients, with flares of colitis being remarkably less frequent in the third trimester.

Another major life event is birth, when maternal and environmental microbes colonize the newly born infant. Jose Clemente emphasized the importance of the first human–microbial contact for the development of a healthy microbial ecosystem. Infants born by cesarean section had a persistent alteration of their gut microbiota compared with vaginally delivered infants, who showed increased microbiota diversity. A recently published study by this group showed that partial restoration of the gut microbiota can be achieved in infants born by cesarean section via vaginal microbial transfer from the mother.[2] Notably, Jose Clemente also referred to a study by Sevelsted et al[3] demonstrating that IBD patients (among other chronic immune disorders) are more frequently born by cesarean section as compared with the general population. Although this study was recently contradicted by a meta-analysis that failed to demonstrate higher risk of IBD after cesarean section,[4] the children of IBD with IBD do carry a higher risk for IBD, probably owing to genetic and/or microbial factors. Therefore, hypothetically, children of IBD mothers might benefit at the time of birth from vaginal microbial transfer from healthy mothers.

Dr Victoria Ruiz then discussed the importance of the colonization of the gut microbiota from early life. Data were presented showing that early life antibiotics can cause robust and enduring alterations in the gut microbial composition. Broad spectrum antibiotics can induce dysbiosis and provide a niche for infection by pathogens. In contrast, narrow-spectrum antibiotics targeting specific pathogens may actually protect the commensal strains, resulting in minimal alterations in the overall microbiota composition.

Taken together, this session provided clear consensus regarding the impact of "early life" events on the microbiota and immune development, which could well be a critical window for disease prevention.

Gut Microbiota Dysbiosis in "IBD Subsets"

As was agreed on in the IBD workshop by Jonathan Braun and R. Balfour Sartor, there is no sole cause for IBD. Multiple factors are involved, including microbial, immunologic, genetic, and environmental factors, all of which interact. In each patient, these factors might contribute to disease to a different extent and be provoked by a specific trigger. The microbiota perturbations in IBD include reduced diversity and a depletion of beneficial bacteria and/or an increase of pathobionts, a so-called "dysbiosis."[5,6] Since not all IBD patients carry similar microbiotic signatures,[7] identification of defined IBD subsets will be imperative for the development of novel therapies, but progress has been limited so far in this respect. Jonathan Braun proposed in the workshop that identification of subsets of IBD based on the fecal metabolites of the bacteria, called "metabotypes," might be superior to defining the bacterial composition. Novel therapies could then target the functional end, that is, the metabolites of the microbiota rather than individual bacterial strains. Although patient classification into subsets is required for a refined targeted approach, multiple factors complicate the identification of the subtypes. These factors include genetic background (which may correlate with microbiota composition), lifestyle (including dietary habits), comorbidities, and drugs such as antibiotics. Furthermore, IBD-specific factors, such as the IBD type (Crohn's disease vs ulcerative colitis), age of onset, disease location, and behavior need to be taken into account. Microbiota, genetics, and disease-specific characteristics are all believed to be interrelated; therefore, the hope is that the number will be limited to tens of designated subsets, rather than thousands, which will constitute an important advance for designing rational novel avenues for microbiome-targeted treatment for IBD.

Gut Microbiota Interventions

Various state-of-the-art approaches for microbiota modulation were also discussed. Eamonn Quigley presented an "old" but still viable and safe approach, in which the target is one (or a few) bacteria stimulated by (prebiotics) or added to (probiotics) the diet. *Faecalibacterium prausnitzii* is one of the potential probiotic candidates for IBD, although its anaerobic nature has delayed its therapeutic development. Fortunately, prebiotics also have the capacity to stimulate beneficial bacteria and their functions such as butyrate production, which has anticarcinogenic and anti-inflammatory properties. Prebiotics that can stimulate probiotic bacteria (such as *F prausnitzii*) as well as their functional components include inulin, resistant starch, riboflavin, and diverse dietary fibers. However, to date, limited data for the use of prebiotics and probiotics in IBD exists[8] and further research was recommended.

A second method of microbiome modulation is the transplantation of fecal material from donor to patients (fecal microbiota transplantation [FMT]). FMT is highly effective for the treatment of recurrent *Clostridium difficile* toxin-induced colitis as discussed by Dale Gerding.[9] As highlighted by R. Balfour Sartor, the usefulness of FMT for IBD is currently under debate. In patients with ulcerative colitis, 1 randomized controlled trial compared FMT via enema with placebo and showed superiority for FMT.[10]