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INTRODUCTION

Introduction to the special focus issue on the impact of diet on gut microbiota composition and function and future opportunities for nutritional modulation of the gut microbiome to improve human health

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ABSTRACT
Over the past decade, application of culture-independent, next generation DNA sequencing has dramatically enhanced our understanding of the composition of the gut microbiome and its association with human states of health and disease. Host genetics, age, and environmental factors such as where and who you live with, use of pre-, pro- and antibiotics, exercise and diet influence the short- and long-term composition of the microbiome. Dietary intake is a key determinant of microbiome composition and diversity and studies to date have linked long-term dietary patterns as well as short-term dietary interventions to the composition and diversity of the gut microbiome. The goal of this special focus issue was to review the role of diet in regulating the composition and function of the gut microbiota across the lifespan, from pregnancy to old age. Overall dietary patterns, as well as perturbations such as undernutrition and obesity, as well as the effects of dietary fiber/prebiotics and fat composition are explored.

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Introduction

Over the past decade, application of culture-independent, next generation DNA sequencing has dramatically enhanced our understanding of the composition of the gut microbiome and its association with human states of health and disease.[1-3] Our understanding of human gut microbe metabolic function, microbe-microbe interactions and host-microbe interactions is less well developed, but is rapidly emerging due to the application of multiple omic technologies, including metagenomics, transcriptomics, metabolomics, proteomics and glycomics, applied to both the microbiota and the host.[4-6]

Host genetics, age, and environmental factors such as where and who you live with, use of pre-, pro- and antibiotics, exercise and diet influence the short- and long-term composition of the microbiome.[7-15] Dietary intake is a key determinant of microbiome composition and diversity and studies to date have linked long-term dietary patterns and well as short-term dietary interventions to the composition and diversity of the gut microbiome.[16-18] While studies in rodent models have shown that diet may be more impactful than genetics in shaping the gut microbiota,[19] Deblius and colleagues recently estimated the relative effect of the long-term dietary patterns as similar to genetics (medium to small effect), but noted that is difficult to rank.[7] Short term dietary interventions were assessed to have a small impact on the microbiome, whereas host species, age and lifestyle were the biologic covariates noted to have the largest impact.[7] However, it is likely that diet contributes in large part to the large differences observed between species,[20] across the lifespan[9] and with Western lifestyle.[21]

Therefore, the goal of this special focus issue was to review the role of diet in regulating the composition and function of the gut microbiota across the lifespan, from pregnancy to old age. Overall dietary patterns, as well as perturbations such undernutrition and obesity, as well as the effects of dietary fiber/prebiotics and fat composition are explored (Fig. 1).

Across the life-span

Intestinal microbiota development is a complex process that begins *in utero* and continues for the first 2–3 y of life.[22] Delineating this process in diverse populations of

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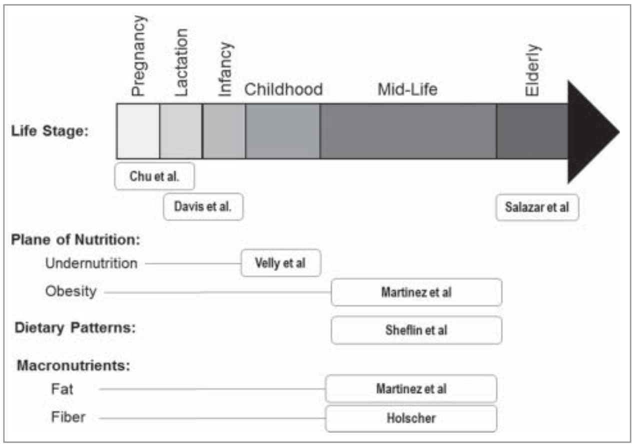

Figure 1. Schematic representation of articles in the special focus issue relative to life stage and nutrition.

infants and how it can be manipulated through diet is clinically important since current evidence suggest that the microbiota acquired in early life can program gastrointestinal, immune and neural development.[23-26] Furthermore, perturbations to this developmental trajectory, as evidenced by reduced microbial diversity or dysbiosis during early life has been linked to disorders in infancy and childhood.[26,27]

Pregnancy and lactation

In the first article, Chu and colleagues from the laboratory of Kjersti Aagaard reviewed how maternal nutrition during pregnancy and lactation affect the composition and function of the gut microbiota of the offspring.[28] They discuss the concept that gut microbes should be considered as a mediating factor in the relationship between early life nutrition and later life disease as a component of the Developmental Origins of Health and Disease (DOHaD) hypothesis. Recent work from her laboratory and others have shown that the intrauterine environment of healthy pregnancies is not sterile, supporting the potential for the microbiome to influence fetal developmental processes *in utero* as well as the maternal-fetal transmission of microbiota during pregnancy. Although additional preclinical and clinical research is needed in this area, the potential for nutrition to influence the maternal-fetal microbiota axis to influence neonatal development prenatally and during breastfeeding is compelling.

Infancy

In the next article, Davis and coauthors from the laboratory of Sharon Donovan reviewed the development of the infant gut microbiome in the first year of life and how that process is influenced by breast- versus formula-feeding, prebiotic and probiotic addition to infant formula, and the addition of solid foods.[29] Despite the fact that the infant diet is much more homogenous than that of adult populations, geographical variation exists - even among infants in economically developed countries in Europe. The authors proposed that to more fully understand the ontogeny of the infant microbiota, a collaborative study that obtains stool samples "from a large cohort of infants located in various sites around the globe in which detailed records of dietary intake and other environmental factors are collected is needed to provide a more complete understanding of the development of the microbiota in infants who are breast- vs. formula-fed."[29]

Older age

The next paper in the supplement from the laboratory of Clara de los Reyes-Gavilán focuses on the other end of the age spectrum by reviewing how changes in physiologic function, dietary intake and nutritional status affect the microbiome in aged populations.[30] Aging is associated with a lower microbial diversity and alterations in the composition, which was associated with a change in diet that occurs upon entering a long-term residential facility.[31] These microbiota changes are clinically relevant as they were correlated with increased frailty and markers for inflammation and that the associations between the microbiota and health outcomes was strongest in long-stay subjects.[31] More recently, the same group showed that elderly subjects who were placed in residential facilities exhibited a change in their microbiota composition from one associated with health and youth to an elderly-associated microbiota.[32] Salazar and colleagues proposed that strategies directed at restoring the microbiota in the elderly must be addressed from a global perspective and nutritional strategies can use probiotics, prebiotics or specific nutrients to counterbalance alterations associated with aging.[30]

Effects of nutritional status

Our gut microbial consortia provide nutrients and energy to the host via the fermentation of non-digestible dietary components.[33] In the healthy state, détente is maintained between the microbiome and the metabolism and immune system of the host. However, dysbioses can lead to inflammation and infection and possible contributions to diabetes mellitus and obesity.[33] Indeed, alterations in the gut microbiota diversity and composition have been reported in states of under-,[34,35] and over-nutrition, obesity and its co-morbidities, including type 2 diabetes.[21,34,36] A number of potential mechanisms have been proposed to describe how the gut microbiota drives obesity and its metabolic complications, including interaction with metabolic processes and the immune system of the host.[36,37] The next 2 papers in the supplement describe the relationships between diet and the microbiome in undernourished[38] and obese[39] individuals, respectively.

Undernutrition

Velly and coauthors from the laboratory of Geoffrey Preidis provide an overview of the mechanisms of cross-talk between the gut microbiota, diet and the undernourished host.[38] Undernutrition contributes to approximately half of all deaths in children under 5 y of age. Malnutrition arises from a combination of inadequate dietary intake, which is exacerbated by enteric infections and inflammation. However, there is a growing appreciation for the concept that an abnormal gut microbial population associated with malnutrition can perpetuate the vicious cycle of pathophysiology, which can lead to persistent growth impairment in children.[38] Velly and colleagues highlight the differences in the composition and function of gut microbiota between undernourished and healthy children and review the factors specific to the host and the environment (including diet) that produce this altered microbiome and the consequences to the host physiology. Finally, they suggest opportunities for microbiome-targeted interventions to implement in the treatment of child undernutrition.[38]

Overnutrition

At the opposite end of the spectrum is obesity, which is estimated by the World Health Organization to affect 600 million individuals world-wide in both developed and developing countries.[40] Western style diets, which are typically high in fat and simple sugars influence microbiome structure and function.[21] In their review, Martinez and coauthors from the Eugene Chang's laboratory highlight the impact of obesity and Western diets on the gut microbiota and focus on the effect of high fat diets, including the level and type of fat consumed, and how rapidly diet-induced shifts in the microbiome occur. Lastly, they outline potential avenues for further research and propose strategies for microbiome-based interventions to prevent or treat diet-induced obesity.

Dietary patterns and specific macronutrients

As noted in the above, both short-term dietary interventions and long-term dietary patterns influence the composition and diversity of the gut microbiome.[16-20] Of the dietary components, non-digestible carbohydrates, or fiber, have received the most attention as it is the primary energy source for most gut microbes and influences bacterial fermentation, total bacterial numbers and species composition.[41,42] The final 2 papers in the supplement review the evidence linking dietary patterns with gut microbial composition and function[43] and how dietary fiber and prebiotics impact the microbiota.[44]

Dietary patterns

Sheflin and coauthors from the laboratory of Tiffany Weir review the current literature on diet effects on the microbiome and the generation of microbial metabolites of dietary constituents that may influence human health.[43] A particular focus of the review is on how animal- vs. plant-based diets impact the microbiome. They conclude that diet-induced differences in microbiome composition and microbial metabolites, such as volatile fatty acids, secondary bile acids, and products of protein degradation, have the potential to modulate the host environment for disease prevention or promotion.[43] Given that metabolic effects of plant and animal-based diets are likely driven by differences in macronutrient and phytochemical intake, these components are also discussed in the review.[43] The authors summarize areas where further research is required to realize the potential of exploiting diet-microbiota interactions for improved health, which includes a better understanding of the effects of non-nutrient dietary components, such as artificial sweeteners, and emerging novel food ingredients on the gut microbiota.[43]

Dietary fiber and prebiotics

The human host does not contain digestive enzymes that are capable of breaking the molecular linkages contained in most complex carbohydrates and plant polysaccharides. Thus, these polysaccharides pass through the upper gastrointestinal tract and are metabolized by microbes in the colon. This metabolism generates water and gases, including carbon dioxide and methane, and metabolites, including the volatile fatty acids. In her review, Hannah Holscher summarizes the current evidence linking dietary fiber and prebiotic consumption to human gastrointestinal microbiota composition and function, including the effects of physiochemical properties of the complex carbohydrates, adequate intake and treatment dosages, and the phenotypic composition of the human microbiota.[44] In addition to human trials, animal, *in vitro*, and computational research are all needed to advance our understanding of the physiologic effects of dietary fibers and prebiotics in both healthy and disease states and to delineate mechanisms of action.

Future opportunities for nutritional modulation of the gut microbiome to improve human health

The gut microbiome, also referred to as our second genome, integrates external signals to exert nutritional, metabolic, and immunomodulatory functions that are relevant to health and well-being of the host.[45-47] There are immense opportunities to use personalized nutritional interventions to prevent and/or treat acute and chronic diseases including gastrointestinal[48] and fatty liver diseases,[49] obesity,[36,50] cardiovascular disease[51] and even neuropsychiatric disorders.[52,53] In addition to modulating microbial composition and/or richness, diet composition can impact the microbial metabolome,[47] which could increase or decrease the risk of disease. As reviewed by Sheflin et al.[43] in this supplement, the microbiota is a potentially important link between dietary choline and atherosclerosis via the catabolism of choline to form the gas TMA (trimethylamine) that is metabolized by the liver to form TMA oxide (TMAO). Foods rich in choline, include eggs, liver, and peanuts. Another example could be to increase the intake of fermentable fiber or prebiotics in patients with Irritable Bowel Disease (IBD) to promote the production of short chain fatty acids, which in turn stimulate intestinal hormone secretion, and modify immune function to reduce inflammation.[47,48,54]

Despite some promising clinical data, many limitations and challenges currently limit our ability to integrate patient-specific microbial data into the clinical realm.[45-47] These range from our ability to implement low cost, high throughput sequencing methods to enable rapid characterization of the microbiome. In addition, due to limitations in the depth of sequencing and the completeness of databases for bioinformatics, species-level identification of microbes associated with disease states is incomplete. Emerging sequencing technologies may enable identification of genera and species involved in clinically relevant disease states.[55] In addition to characterizing a patient's microbiome composition and function to assist in personalized diagnostic assessment, disease prevention, and treatment,[45] it will likely be important to more fully characterize the microbiome metabolites in feces and serum[47] and potentially host genetic risk of disease to assess disease susceptibility.

As noted by Hannah Holscher in her review,[44] multidisciplinary research approaches are needed to holistically advance our understanding of mechanisms underlying host-microbe interactions on host physiology. In addition, physicians and registered dietitian nutritionists (RDN) have the opportunity to plan a key role in translating evidence on the role that diet plays in shaping the microbiome to clinical recommendations that help patients make healthy choices.[48,49] However, to incorporate findings from the gut microbiome into clinical practice, RDNs must understand the data that are being generated by specific patient cohorts through microbiome analysis. As summarized by Harvie and colleagues,[56] "the RDN's role in collaborations investigating the microbiome will be to design dietary interventions, provide the dietary education to patients, ensure food composition data are available for the nutrient of interest, and measure dietary intake and adherence to the interventions."

Lastly, there are vast opportunities to develop more effective pre-, pro- and synbiotics that are targeted toward specific disease states. Fecal microbiota transplantation has been shown to be a highly effective method in the treatment of refractory *Clostridium difficile* infection and there is expanding interest in using FMT in the prevention and management of gastrointestinal and non-gastrointestinal diseases.[57] However, the potential of modifying dietary intake of the donor or the recipient to optimize engraftment of the FMG has been largely unexplored.

A recent round table identified areas where knowledge of the gut microbiome could fuel innovation in physiologic and therapeutic outcomes.[58] They identified 4 domains of innovation that could derive from ongoing efforts in deciphering the interactions between human cells and intestinal microbiome as a central component of human health, namely:[1] development of stratification and monitoring tools;[2] identification of new target and drug discovery, as a part of our supra-genome;[3] exploitation of microbiota as a therapeutic target that can be modulated;[4] and finally as a source of live biotherapeutics and adjuvants.[58] The Experts in nutrition and clinical dietetics could actively contribute to several of these areas, particularly 3 and 4, and I encourage greater cross-disciplinary collaboration to achieve the full potential of diet to modify the intestinal microbiome to improve human health.

Disclosure of potential conflicts of interest

The author reports no conflicts of interest.

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