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Microbial perturbations and modulation in conditions associated with malnutrition and malabsorption

Daisy M.A.E. Jonkers, PhD, Assistant Professor, Head of Laboratory of Gastroenterology-Hepatology *

Division Gastroenterology-Hepatology, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center+, Maastricht, The Netherlands

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A B S T R A C T

The intestinal microbiota is a complex ecosystem, which can be considered an accessory organ. It involves complex microbe–microbe and host–microbe interactions with indispensable functions for the human host with regard to the intestinal epithelium and barrier function, the innate and adaptive immune system, and its large metabolic capacity. Saccharolytic fermentation results in the production of short chain fatty acids, which exert an array of beneficial effects, while proteolytic fermentation leads to an increase in potentially harmful metabolites. In addition, numerous other microbial metabolites are being produced with various intestinal as well as extra-intestinal effects. Their generation depends on the composition of the microbiota as well as the availability of substrates, which both vary along the GI tract.

Diet impacts the intestinal microbiota composition and activity in early infancy as well as in adults. Microbial perturbations have been demonstrated in subjects with under-nutrition and/or malabsorption. The bidirectional interactions between the microbiome, nutrient availability and GI function, can contribute to a vicious circle, further impairing health outcome in conditions associated with malnutrition and/or malabsorption. Integrated multivariate approaches are needed to further unravel the complex interaction between microbiome, diet and host factors, as well as possible modulation thereof by prebiotics or probiotics.

* Div. Gastroenterology-Hepatology, Maastricht University Medical Center+, PO Box 5800, 6200AZ Maastricht, The Netherlands. Tel.: +31 43 3884266; fax: +31 43 3875006.
E-mail address: d.jonkers@maastrichtuniversity.nl.

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The present overview will briefly outline the composition and function of the intestinal microbiota, its association with nutrient intake and availability, and will address the role of the intestinal microbiota in malnutrition and malabsorption.

Introduction

Alterations in the intestinal microbiota have been associated with a wide range of diseases, including gastrointestinal and liver diseases, but also metabolic diseases such as obesity and diabetes [1]. Their increasing incidence in line with western lifestyle, characterized by altered dietary intake, increased hygiene and availability of antibiotics [1,2], which can impact the gut microbiota, further supports the importance of this complex ecosystem. Studies aiming to unravel the contribution of the intestinal microbiota to health and disease are emerging and facilitated by high throughput sequencing and -omics approaches.

Also conditions associated with malnutrition and malabsorption, are associated with microbial perturbations, and are often inter-related. Insufficient nutrient intake and/or reduced nutrient absorption will impact the intestinal microbial composition and activity, and thereby its effects on host physiology.

The gut microbiome and host impact

The gut microbiome mainly consists of bacteria, but also comprises archea, fungi and viruses. The densely populated bacterial community exists of 10^{14} microorganism, and is shaped by host genetics and environmental factors. Acquisition starts at birth and subsequently develops with successive waves into an adult-like composition after weaning, affected *e.g.* by mode of delivery, infant feeding, medication use and the introduction of solid foods [3]. The number of bacterial genes (collectively defined as the microbiome) outnumbers the human genome by 150-fold [4]. Thereby, the gut ecosystem acts as a highly active (accessory) organ, involving complex microbe–microbe and host–microbe interactions with indispensable functions for the human host with regard to the immune system, the intestinal epithelium and barrier function, as well as its large metabolic capacity.

Although more than 1000 bacterial species have been identified and large inter-individual differences exist [4], the gut microbiota consists of a limited number of phyla, dominated by Bacteroidetes (comprising *e.g.* Bacteroides and Prevotella species) and Firmicutes (comprising *e.g.* Clostridium and Lactobacillus species), followed by members of Proteobacteria and Actinobacteria [2]. In 2011, Arumugam et al. described three robust clusters (*i.e.* 'enterotypes') driven by Bacteroides, Prevotella and Ruminococcus, respectively, which were not affected by geographic origin, age, gender or BMI [5], but were associated with long-term dietary preferences [6].

Bacterial numbers and diversity vary along the gastrointestinal (GI) tract, with 0-10^3 bacteria per ml in the acidic stomach, and further increasing from about 10^5 per ml in the upper small intestine towards 10^{12} per ml in the colon [7]. This is affected by luminal factors, such as the intestinal pH, oxygen tension, and nutrient availability, but also by spatial variation in mucosal factors [8,9]. The small intestine with its large digestive and absorptive capacity can be characterised by high levels of oxygen, (digestive) enzymes, antimicrobial peptides (*e.g.* α-defensins, lysozyme and C-type lectins produced by Paneth cells) and increased intestinal motility. The colon on the other hand, consists of a merely anaerobic environment, a reduced intestinal motility, high levels of (undigested) nutrients and increased numbers of mucus secreting Goblet cells with a thick mucus bilayer firmly attached to the epithelium [8]. Towards the (distal) large intestine, this results in a high bacterial density and diversity, dominated by anaerobes. In addition, regional differences exist in gut-associated lymphoid tissue structures, distribution of leucocyte population and lymph drainage [9]. The differences along the GI