EDITORIAL

Friend or foe: how intestinal microbiome contribute to health and disease states

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In this issue, Allegra et al. provide an in-depth overview of how the microbiome influences hematologic malignancies. While largely overlooked in the past, the importance of the microbiome for human health is increasingly recognized. Whether convinced by disputes on causality or not, the modern medical doctor needs to remain informed on new insights in microbiome and disease. Several of these aspects will be dealt with here.

In the digestive tract, there is intensive contact between foreign antigens and the microbiome and here, our immune system is constantly exposed to a diversity of molecular microbial components and food. That immune system needs to remain tolerant against non-pathogenic antigens, and at the same time be capable of rapidly responding to potential pathogens to maintain tissue homeostasis. Failure in controlling balanced immune responses contributes to different pathogenic intestinal and systemic conditions.[1] The intestinal epithelium is covered by mucous layers of mucin, which serves as a physical barrier against the microbiome, and secretions of antimicrobial peptides protect intestinal crypts against bacterial overgrowth.[2,3] Secretion of polyspecific low affinity Immunoglobulin A (IgA) and lower quantities of higher affinity specific IgA regulate the composition of the intestinal microbiome.[4] Different pattern recognition receptors, on epithelium and immune cells, such as toll-like receptors, sense microbial components and direct immune responses against the microbiota.[5] Antigen presenting cells in the lamina propria help to promote mucosal tolerance by influencing T-cell differentiation, which is further supported by high numbers of regulatory T cells (Treg cells) in the gut, thereby maintaining tolerance against food and commensal antigens.[6] Also, innate lymphoid cells contribute to maintaining homeostasis at the gut lumen.[7] Early establishment of a healthy microbiome protects against pathogenic processes through prevention of intestinal colonization with pathogens, which has been called colonization resistance.[8,9] Due to recent advances in high-throughput sequencing and analytical tools, analysis of complex genomic bacterial datasets is now feasible, and has yielded an exponential increase of reported associations between disease states and microbiome composition. Whether many may seem indirectly meaningful, some other studies do contribute to completely new insights into how bacteria can drive human disease.

Under dysbiotic circumstances, bacterial products such as LPS and entire bacteria can translocate the epithelial lining, leading to continuous activation of CD4+ and CD8+ T cells and subsequently, autoimmunity.[10] Whereas distorted microbiome early after allogeneic hematopoietic cell transplantation can be identified and associated with development of acute graft versus host disease, the composition of the microbiome can also positively influence immune response, not only in hematopoietic cell transplantation (reviewed by Köhler and Zeiser)[11] but for instance, also in the outcome of cancer treatment. Efficacy of cancer immunotherapy with immune checkpoint antibodies can be diminished with administration of antibiotics, and superior efficacy is observed in the presence of specific gut microbes. This may offer future strategies to identify and correct defects in the microbiome to improve therapeutic efficiency.[12]

One of the reappearing questions concerns whether association between distinct microbiome profiles or bacterial species and diseases states reflect true causal relations, or whether it could merely be explained by changes secondary to inflamed tissues. Several well-designed studies may provide proof in favor of causality. For instance, Manfredo Vieiro et al. report in mice with genetic predisposition to lupus-like disease a translocation of gut pathobiont *Enterococcus gallinarum* to the liver and elsewhere to promote autoimmunity.

Antibiotic treatment reduced autoimmune phenomena and vaccination prevented translocation of this pathobiont. *E. gallinarum* DNA was recovered from liver tissue from patients with autoimmune diseases and *in vitro* assays with human cells proved autoimmune promoting effects, which supports the existence of similar bacterial-driven murine autoimmune processes in humans.[13] The potential of microbiota-mediated modulation of the immune system in humans was recently demonstrated in two patients with therapy refractory immune checkpoint inhibitor-associated colitis. They were successfully treated with fecal microbiota transplantation, with reconstitution of their gut microbiome and a relative increase in the proportion of Treg cells within the colonic mucosa.[14] Further studies are necessary to validate these findings.

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