A multiple sclerosis patient-oriented multiomics analysis tells us where to go next: Commentary for: "Alterations of host-gut microbiome interactions in multiple sclerosis"

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The gut microbiota has profound influences on human health through close interactions with its host. The emergence of next-generation sequencing and gnotobiotic technologies has allowed us to understand the overall picture of gut microbiota and explore the functional significance of alterations in the gut. Studies have identified the specific microbial taxa associated with various human diseases. In research focusing on central nervous system (CNS) diseases, there is a growing interest in the so-called "gut-brain axis", which assumes the impact of intestinal environment on brain health and CNS disorders.

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the CNS with an onset in young adulthood. Studies indicate that the number of patients with MS, now estimated to be 2.8 million, has been increasing for decades all over the world. The pooled incidence rate since 2013 across 75 reporting countries is 2.1 per 10,000 persons/year.[1] As genetic risk factors for MS are considered to be unchanged during this period of time, there should be non-genetic risk factors that would account for the increase of MS. Among various risk factors for MS, the importance of gut microbiota has been highlighted in recent studies.[2–6] Following the discovery of dysbiosis and increased or decreased taxa associated with MS, including a reduction of butyrate-producing bacteria,[1,2] the functional significance of altered microbiome was further investigated. In a study fecal microbiota from MS patients or healthy subjects were transferred into germ-free mice and the recipient mice were immunized with myelin antigen for inducing a conventional mouse model of MS, experimental autoimmune encephalomyelitis (EAE).[4] Clinical signs of EAE reflecting the CNS inflammation induced by Th17 cells were more serious in the mice transferred with MS patient-derived fecal samples, compared with those transferred with fecal samples of healthy subjects. In another study, fecal microbiota samples were transferred into TCR transgenic mice, which spontaneously develop signs of MS.[5] The results of this study were essentially similar to those of,[4] indicating that microbiota of MS patients had disease-enhancing effects compared with that of healthy subjects.

Dietary contents have changed dramatically over the last decades. The change is characterized by a reduction in dietary fiber and an increase of high-fat consumption. Published data in healthy subjects and gnotobiotic mice have revealed that dietary changes may strongly affect the structure of gut microbiota. Accordingly, it can be argued that a reduction of SCFA production in the gut of patients with Japanese patients with MS may result from "westernization" of lifestyle.[7] Previous epidemiological studies regarding the diet of MS patients also supports this hypothesis.

While comprehensive microbiome data has been gradually accumulating in the last five years, a limited number of studies have evaluated the interactions between microbial components and various sources of clinical and laboratory data based on a multi-layered analysis. In this issue of EBioMedicine, Cantoni et al. performed an elegant series of multiomics analysis, based on the data of gut microbiome, peripheral immune cells, serum metabolites, and dietary contents, which were obtained from 24 MS patients and 25 healthy subjects.[8] They revealed a significant correlation between the increase of total intake of meat, the increased abundance of peripheral T helper 17 (Th17) cells, and the corresponding gut microbial components and serum metabolites in patients with MS. The

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obtained results support a previously proposed axis,[7] starting from a reduced intake of dietary fiber to a reduction in SCFA production in the gut, which causes a reduced frequency of peripheral regulatory T cells and an enhancement in CNS inflammation.[6,9] The study conclusively showed close interactions between commensal micro-organisms and MS, which is in concert with previous and recent studies demonstrating the significant role of diet in MS.[9]

While oral intake of long-chain fatty acids (LCFA) leads to an induction of Th17 cells and worsening of EAE,[8] short-chain fatty acids, such as butyrate and propionate, seems to be preventive for development of EAE.[9] Consistently, a recent clinical study revealed that oral proprionic acid treatment in MS induces regulatory T cells and stabilize the clinical course of MS.[10] Given that diet and dietary components play a role in the immune system, increased efforts should be directed towards exploring similarity in the gut microbiome among family members sharing a diet.[8]

Although the results are persuasive due to the power of advanced multi-omics analysis, this study[8] had several limitations, such as the patient cohort was relatively small and did not touch on the differences by disease subtypes of MS (relapsing remitting-MS, or progressive MS). Additional information regarding disease activity and clinical severity of MS patients would help to obtain deeper insights into the pathogenesis. Another limitation of the study was whether the result is the cause or the consequence of MS. Verification experiments using a rodent model will enhance the scientific significance of this study.

Even with little scientific evidence, any information about the management of MS, like desirable diet for MS, would attract attention of patients, which has been often rejected or scorned. The new findings in the paper[8] clearly support the role of diet in the pathogenesis of MS, and have strong impact on biological research, clinical practice, and daily life. Although results of the past 16S rRNA analysis had some problems in reproducibility across countries or laboratories, the multi-omics data[8] has provided affirmation that the dysbiosis and altered gut microbiome in MS is a real phenomenon. In summary, this work opens a way to diet and microbiome data-assisted management of MS, useful for prevention of disease progression.

Declaration of interests

There is no conflict of interest to disclose.

Contributors

T.Y. and D. T. wrote this manuscript.

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