Editorial

The multiple sclerosis microbiome?

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Provenance: This is a Guest Editorial Commissioned by Section Editor Mingzhu Gao, MD (Department of Laboratory Medicine, Wuxi Second Hospital, Nanjing Medical University, Wuxi, China).

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Humans comprise of trillions of microbes; >90% reside in our guts. The cost of sequencing microbial genes has greatly diminished, facilitating interrogation of the gut microbiota. Gut-brain communications likely involve the immune system (1,2); of particular relevance in multiple sclerosis (MS). MS is an inflammatory and neurodegenerative immune-mediated disease, often impacting young adults, with many unmet needs. The exact cause(s) are unknown, current drugs are modestly effective, not without risk, and are not indicated for all. Further, there are few good measures or biomarkers of disease activity.

Jangi and colleagues (3) sequenced stool samples (16S rRNA) from 60 relapsing-remitting MS cases attending a Boston hospital clinic and 43 controls from a genetics-related study. While global measures of gut diversity (alpha, beta) were similar between groups, taxa-level (Genera) findings differed. The MS cases exhibited higher abundances of *Methanobrevibacter* (*Archaea*) and *Akkermansia* and lower *Butyricimonas* ($P<0.05$, false discovery rate threshold was 0.1). However, the cases had longstanding MS (average disease duration =12.8 years), were older than controls (by >7 years) and included more men (32% *vs.* 14%, respectively). Despite these differences, some findings may be informative while others may be a consequence of physiological changes related to MS. For instance, the methane producing *Methanobrevibacter* are associated with constipation and irritable bowel syndrome (4), and may indicate underlying bowel dysfunction which is common in MS (5). Future studies could assess gut transit times to help tease out the direction of this relationship. Over half the cases were also exposed to an MS immunomodulatory drug (>6 months), and compared to the non-exposed had higher *Prevotella* and *Sutterella* and decreased *Sarcina* ($P<0.05$, false discovery rate threshold was 0.1). A potential disruption in the microbiota-host immune balance was also observed. Immune-related gene expression in peripheral blood was assessed in a subset of 18 cases and 18 controls with particularly high or low *Methanobrevibacter*. Differences were observed between the relative abundances of these *Archaea* (and two other genera—*Akkermansia* and *Butyricimonas*), with the direction and strength of association (correlation) differing between cases and controls and by MS immunomodulatory drug exposure.

Jangi *et al*. also found higher levels of methane in the breath of 41 different MS cases relative to 32 controls, concurring with the earlier *Methanobrevibacter* findings. While of interest, it does not tease out consequence from causality.

In conclusion, these findings, combined with others (3,6-11), suggest subtle, rather than large differences in the MS gut microbiota composition. Similar modest differences, are reported in other autoimmune disease and are suggestive of ongoing inflammation (12,13). Further, gut microbiota composition has also been associated with relapse risk in paediatric MS (11). Larger, longitudinal studies are needed to better understand potential confounders, from comorbidity to concomitant medications. Whether observed changes pre-date MS or are a consequence of MS, its treatment or related comorbidities remains unknown. While the potential for harnessing the gut microbiota to

improve outcomes in MS, or use as a biomarker of disease activity have yet to be realized, important first steps have been made to characterize the MS microbiome. Further work is needed to clarify the causality of such findings.

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Footnote

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