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The Gut-Brain Axis in HTLV-1-associated Myelopathy: Linking Microbiome Dysbiosis and Neuroinflammation

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Abstract

Human T-lymphotropic virus type 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) has traditionally been considered a neuroimmunological disorder, but recent microbiome data suggest that gut dysbiosis may play a key role in its pathogenesis. In this commentary, we contextualize the first cross-sectional characterization of the gut microbiota across the HTLV-1 clinical spectrum, highlighting a consistent inversion of the Firmicutes-to-Bacteroidetes ratio and a marked depletion of the butyrate-producing genus *Faecalibacterium*, including *Faecalibacterium prausnitzii*, from asymptomatic carriers to advanced HAM. I propose a gut–brain axis model in which the loss of key butyrate producers, increased intestinal permeability, and enhanced microbial translocation amplify systemic immune activation and neuroinflammation, potentially creating a vicious cycle with HTLV-1-driven neurogenic bowel dysfunction and constipation. The paradoxical enrichment of Ruminococcus, along with functional shifts in microbial pathways such as pyrimidine metabolism, underscores the need for species- and strain-level resolution, integrated metabolomics, and mechanistic *in vivo* studies to move beyond associative signatures. Finally, we outline research priorities – longitudinal cohorts, multi-omics, and experimental models – to determine whether specific microbiota configurations predict progression to HAM and to inform microbiota-targeted interventions as adjunctive therapeutic strategies.

Keywords: HTLV-1, HAM/TSP, Gut–brain axis, Microbiome dysbiosis, Neuroinflammation

Commentary

The recent cross-sectional study by Fernandes *et al.* [1] provides the first comprehensive characterization of gut microbiome alterations across the clinical spectrum of HTLV-1 infection, from asymptomatic carriers to patients with established HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). This work represents a significant paradigm shift in understanding the pathogenesis of HTLV-1-associated diseases by implicating the gut microbiota as a potential modulator of disease progression. While the study establishes compelling associations between gut dysbiosis and HAM severity, several emerging questions and mechanistic insights warrant further discussion.

The gut-brain axis (GBA) framework has transformed our understanding of neurological diseases, particularly immune-mediated neuroinflammatory conditions [2,3]. Bidirectional communication between the gut microbiota and the central nervous system occurs through several pathways: production of microbial metabolites, especially short-chain fatty acids; modulation of intestinal barrier integrity; systemic immune activation; and neural signaling via the vagus nerve [4]. Although this framework has been extensively studied in multiple sclerosis and other autoimmune neurological conditions, its relevance to retroviral infections remains largely unexplored.

The study by Fernandes *et al.* [1]. shows that HTLV-1 infection is associated with a distinctive dysbiotic signature, characterized by an inverted Firmicutes-to-Bacteroidetes ratio at all stages of infection. This reversal is particularly notable because it occurs consistently, from asymptomatic carriers to advanced HAM patients, suggesting that this dysbiosis is a fundamental and robust alteration induced by the virus itself, rather than solely a consequence of disease severity. This observation raises important mechanistic questions: Does HTLV-1 directly or indirectly select for this altered microbial ecology? Is the dysbiosis a driver of immune activation or merely a consequence of altered intestinal physiology?

Among the most clinically relevant findings is the marked depletion of *Faecalibacterium*, particularly *Faecalibacterium prausnitzii*, in HAM patients compared with asymptomatic carriers. This genus is one of the most abundant and functionally important members of the healthy human microbiota, serving as a primary producer of butyrate, a short-chain fatty acid with potent anti-inflammatory properties [5]. The reduction of *Faecalibacterium* in HAM patients likely has significant implications for intestinal barrier function and systemic immune regulation.

Butyrate regulates intestinal permeability by strengthening tight junctions and promoting regulatory T cell (Treg) differentiation through histone deacetylase inhibition [6,7]. The depletion of butyrate-producing bacteria in HAM patients could lead to increased intestinal permeability ("leaky gut"), enhanced bacterial lipopolysaccharide (LPS) translocation, and consequently heightened systemic immune activation, a hallmark of HAM pathology. This hypothesis aligns with observations in other neuroinflammatory conditions, where reduced *Faecalibacterium* has been consistently associated with disease severity in Parkinson's disease [8], Alzheimer's disease [9], and multiple sclerosis [10]. However, the mechanistic link between microbiota-derived butyrate deficiency and HTLV-1-associated CNS inflammation remains to be experimentally validated.

The enrichment of *Ruminococcus*, particularly *Ruminococcus g2*, in HAM patients presents an intriguing paradox that warrants further investigation. Although *Ruminococcus* species are known producers of butyrate and other beneficial short-chain fatty acids, their dominance in HAM patients suggests a dysbiotic imbalance that disrupts microbial community stability and function. This contradiction highlights a key limitation of microbiota studies: characterizing single taxa in isolation cannot fully capture the complex ecological and functional dynamics of microbial communities [11,12].

The enrichment of *Ruminococcus* in HAM may reflect metabolic shifts driven by the inflammatory intestinal microenvironment in advanced disease. Chronic intestinal inflammation, constipation (which was significantly more prevalent in HAM patients in this study), and neurogenic bowel dysfunction characteristic of HAM could create ecological niches that favor *Ruminococcus* proliferation while suppressing *Faecalibacterium*. Alternatively, certain *Ruminococcus* strains may have strain-specific properties that promote pro-inflammatory responses, emphasizing the need for future strain-level characterization using shotgun metagenomic approaches.

An important clinical observation in the Fernandes *et al*. study is the significantly higher prevalence of constipation in HTLV-1-infected individuals, particularly among HAM patients (78.9% vs. 20.8% in healthy controls). This finding warrant attention because intestinal motility and transit time profoundly influence microbial composition [13]. The observed dysbiosis could therefore be both a cause and a consequence of neurogenic bowel dysfunction – a vicious cycle in which HTLV-1-driven neuroinflammation impairs intestinal innervation, leading to constipation and altered microbiota, which in turn perpetuate intestinal inflammation and systemic immune activation.

This bidirectional relationship suggests that microbiota-targeted interventions, such as fecal microbiota transplantation, targeted prebiotics, or probiotic supplementation, may restore microbial balance, potentially ameliorate gastrointestinal symptoms, and reduce systemic inflammation in HAM patients. However, these interventions require careful design and validation, especially given the complex host-microbe dynamics in the context of persistent retroviral infection.

The metagenomic functional analysis in the Fernandes study identified several differentially enriched KEGG modules and pathways in HAM patients, including alterations in pyrimidine metabolism, cysteine biosynthesis, and biofilm formation. While these findings are intriguing, they underscore a current limitation in microbiome research: the gap between computational functional predictions and experimentally validated metabolic capacity. Tools such as PICRUSt and MinPath generate valuable hypotheses, but direct measurement of microbial metabolites, such as short-chain fatty acids, secondary bile acids, and tryptophan metabolites, through untargeted metabolomics would strengthen mechanistic understanding.

The apparent enrichment of genes involved in pyrimidine metabolism in HAM patients is particularly noteworthy. Pyrimidines are essential nucleotide precursors required for rapid cell division and nucleic acid synthesis [14]. The increased abundance of genes in this pathway may reflect expanded populations of rapidly dividing bacteria responding to the inflammatory microenvironment or increased microbial metabolic demands to synthesize nucleotides for viral-driven host immune responses. This observation warrants integration with untargeted metabolomic analyses to determine whether circulating pyrimidine levels are altered in HAM patients and whether these alterations correlate with disease severity.

The Fernandes *et al.* study acknowledges several important demographic confounders, particularly the significant age difference between patient cohorts and healthy controls (mean age 54.9–58.3 years vs. 38.6 years) and the female predominance in the HTLV-1-infected groups. These factors are critical because aging is associated with microbiota dysbiosis, and sex hormones, especially estrogen, profoundly influence

both microbiota composition and immune responses [15]. Although recruiting age-matched, family-member healthy controls was a pragmatic strategy to minimize dietary and household confounding, future studies should include age- and sex-stratified analyses and consider longitudinal designs to distinguish these confounders from HTLV-1-specific effects. Furthermore, future clinical trials and longitudinal studies must rigorously control for potential confounding variables, such as dietary patterns and the use of medications (including laxatives and immunosuppressants), which were not fully accounted for in the initial cross-sectional analysis. Standardizing these factors will be critical to isolating the specific impact of HTLV-1 on the microbiome and ensuring the methodological soundness of future therapeutic interventions.

Several critical gaps require attention in future research. First, the lack of species-level confirmation in the qRT-PCR validation, particularly for *F. prausnitzii* and *R. bromii*, highlights the limitations of 16S rRNA sequencing for definitive species-level resolution. Although more resource-intensive, shotgun metagenomic sequencing would provide higher taxonomic resolution and enable direct assessment of genomic potential. Second, integration with metatranscriptomics and metabolomics would clarify which microbial genes are actively expressed and which metabolites are produced in the context of HTLV-1 infection. Third, mechanistic studies using germ-free or microbiota-depleted mouse models harboring HTLV-1 would help establish causality and identify specific microbial taxa or metabolites driving neuroinflammation. Fourth, longitudinal cohort studies following asymptomatic carriers and intermediate syndrome patients over time would provide critical insights into whether specific microbiota alterations precede or predict progression to HAM. Such studies would be invaluable for identifying early biomarkers of disease progression and potential intervention windows.

The study by Fernandes *et al.* [1]. marks a significant advance in HTLV-1 research by establishing a clear association between gut dysbiosis and disease progression. The robust genus-level findings, particularly the consistent inversion of the Firmicutes-to-Bacteroidetes ratio and the depletion of *Faecalibacterium* in advanced disease, provide a strong foundation for future mechanistic studies. However, the cross-sectional design limits causal inference. Future research using longitudinal cohort studies, high-resolution metagenomic analyses, functional metabolomics, and experimental models will be essential to translate these associations into actionable therapeutic strategies. As the field advances, a systems biology approach that integrates microbiota data with host genetics, immune profiling, and viral dynamics will likely yield the most comprehensive understanding of HTLV-1 pathogenesis and identify novel intervention points for this disease.

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