Vita

Genetics meets the gut mycobiome

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A new multi-cohort genome-wide study published in *Vita*[1] has revealed that host genetics shapes the gut mycobiome, alongside its impact on bacteria, further expanding the scope of microbiome research. While the study offers exciting links to immune and brain function, these new findings also underscore ongoing challenges in interpretation and reproducibility.

Over the past decade, microbiome research has largely centered on bacteria, progressively establishing links between host genetics, immune regulation, and microbial composition[2,3]. However, the fungal component of the gut microbiome — the mycobiome — has been relatively overlooked, despite increasing recognition of its roles in immune modulation and disease[4]. A new study by Shuai *et al.* addressed this gap by performing a genome-wide association analysis (GWAS) of gut fungi and bacteria in more than 7,000 individuals from multiple Chinese cohorts[1]. By integrating host genotypes with fungal (ITS2-based) and bacterial (16S-based) profiles, the authors identified not only host–bacterial associations but also host–fungal associations, providing one of the first systematic views of the genetic architecture underlying the human mycobiome.

One of the key contributions of this study is the demonstration that host genetics not only shapes bacterial communities, but also substantially influences gut fungal composition. Through the GWAS, the authors identified host-fungal associations comparable in number to those observed for bacteria, with several signals surpassing stringent study-wide significance thresholds (Fig. 1). These findings challenge the prevailing bacteria-centric paradigm in microbiome GWAS[4], suggesting that fungi are not passive or stochastic components but are rather structured by host genotype. Notably, the genetic architectures of fungi and bacteria differ substantially, e.g., in the genomic distribution of associated variants, implying that these microbial kingdoms may be regulated through distinct host biological pathways.

Functional annotation further revealed divergent biological signatures. The host genes associated with fungal traits were more strongly enriched in immune-related pathways, particularly those involved in T cell activation, whereas bacterial associations were enriched in central nervous system and G-protein-coupled receptor signaling pathways. This divergence was also reflected at the cellular level: fungal-associated loci preferentially colocalized with eQTLs in Th1 cells, whereas bacterial signals were predominantly linked to innate immune cells such as neutrophils. These findings suggest that the different microbial kingdoms may occupy distinct functional niches within the host immune system, with fungi potentially playing a more prominent role in adaptive immune regulation[5]. This perspective may help explain the involvement of fungi in chronic inflammation, autoimmune conditions, and allergic diseases, and it offers new entry points for targeted immunomodulation.

Beyond immune regulation, the most striking (and potentially controversial) aspect of this study is the extension of host–microbiome genetic associations to the gut–brain axis. The authors report that genes mapped from microbiome-associated loci were significantly enriched for expression in brain tissues, particularly in the frontal cortex and thalamus. Intriguingly, the abundance of the fungal genus *Eremothecium* was positively associated with thalamus and frontal cortex volumes. Follow-up *in vitro* experiments then suggested that this genus may influence neuroimmune responses through its metabolic capacity. *Eremothecium* exhibits strong riboflavin (vitamin B2) biosynthetic potential, and its metabolites have been shown to suppress inflammatory responses in microglial cells. Although still exploratory, this chain of evidence from genetic association to metabolic function and cellular effects provides a biologically plausible model for fungal involvement in gut–brain communication, expanding beyond current frameworks that have largely focused on bacterial metabolites. On the other hand, it is not yet clear whether fungal-derived metabolites reach the central nervous system in physiologically relevant concentrations, or whether they influence neurological outcomes *in vivo*. As such, the proposed gut–brain connection should be viewed as a hypothesis that warrants further investigation.

From a broader perspective, this study aligns with and advances several emerging trends in microbiome research. First, the field is shifting from descriptive analyses of microbial composition toward understanding how host factors selectively shape microbial niches, particularly through mechanisms such as glycosylation, mucosal barriers, and immune regulation[6]. Second, the concept of the multi-kingdom microbiome is gaining prominence, with increasing recognition of interactions between bacteria, fungi, and viruses and of their collective impact on host physiology[6,7]. By leveraging genetic correlation and colocalization analyses, this study provides initial evidence for cross-kingdom coupling. Third, research on the gut–brain axis is moving beyond correlative observations toward mechanistic insights, particularly those involving metabolite-mediated neuroimmune modulation, where fungal-derived metabolites may represent an underappreciated component[8].

Despite these advances, several limitations warrant careful

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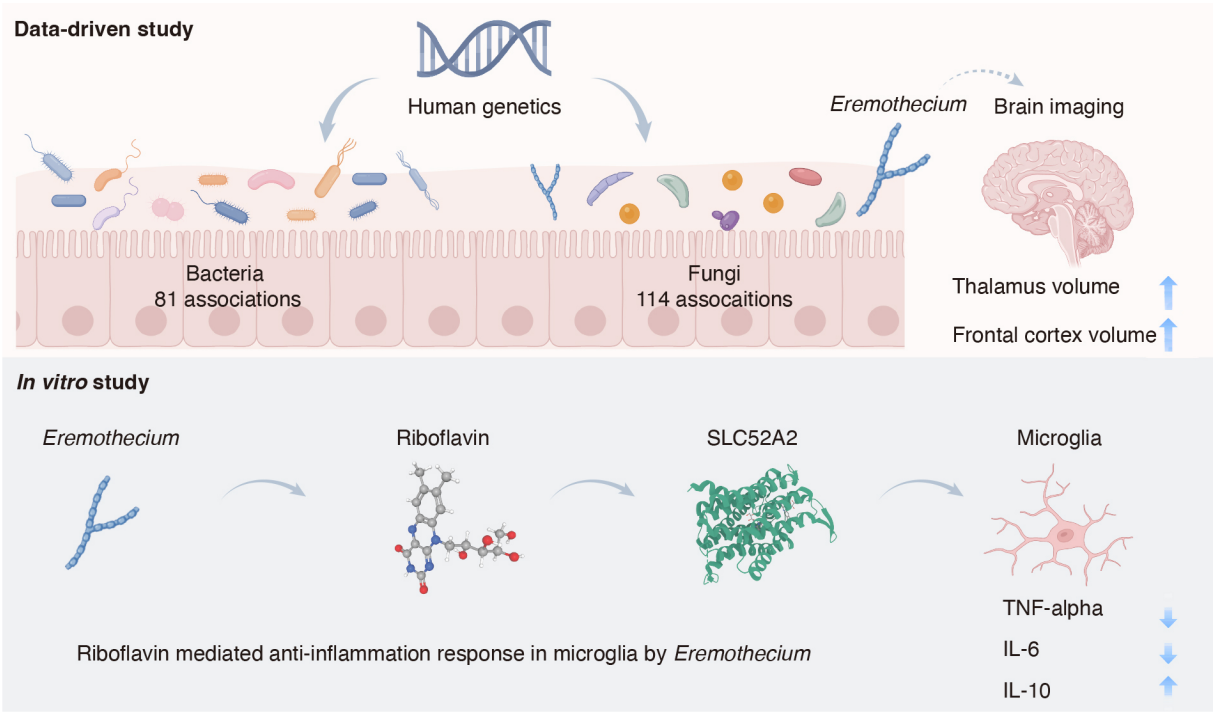

Fig. 1 Host genetic regulation of multi-kingdom microbiome interactions and its potential link to neuroimmune function. A GWAS across multiple cohorts (top) identified host genetic variants associated with both gut bacteria (81 associations) and fungi (114 associations). Fungal associations include taxa such as *Eremothecium*, which were further linked to brain structural features, including increased volumes of the thalamus and frontal cortex. Through *in vitro* experiments (bottom), *Eremothecium* was shown to produce riboflavin (vitamin B2), which modulates microglial inflammatory responses via the riboflavin transporter SLC52A2, leading to decreased TNF-α and IL-6 and increased IL-10 expressions. These findings suggest a potential pathway connecting host genetics, the gut mycobiome, microbial metabolism, and neuroimmune regulation, although causal relationships remain to be established.

consideration. Amplicon-based sequencing (ITS2 and 16S) inherently limits taxonomic resolution, particularly for fungi, thereby constraining functional interpretation. In addition, the limited replication of genetic associations in external datasets highlights ongoing challenges in the reproducibility of microbiome GWAS across populations[9]. Although the authors applied Mendelian randomization, the relatively weak genetic instruments for microbial traits necessitate cautious interpretation of causal inference.

Looking forward, this study provides a valuable foundation for future work. Improving taxonomic and functional resolution through shotgun metagenomics and culturomics approaches will be essential to refine our understanding of fungal biology[10]. The development of comprehensive fungal genomes and functional annotation resources is also needed to address current gaps. Critically, mechanistic validation through animal models and interventional studies is needed to establish causal links and assess the translational potential of gut fungi. Ultimately, if host genetics can reliably predict individual gut fungal configurations, genotype-informed fungal interventions may become feasible.

In sum, this study extends the scope of host–microbiome research from bacteria to fungi, reveals distinct immunological signatures across microbial kingdoms, and proposes a new conceptual framework for fungal involvement in the gut–brain axis. It also highlights the need for careful interpretation of association signals and for continued efforts to bridge the gap between genetic discovery and biological mechanism.

COMPETING INTERESTS

The authors declare no competing interests.

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ADDITIONAL INFORMATION

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