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INSIGHTS

Antibiotics unleash neuroinflammation

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The gut microbiome limits neuroinflammation and neurocognitive decline in acute graft-versus-host disease by modulating microglial activation via a mechanism mediated by the microbial metabolite TMAVA (Chatterjee et al. https://doi.org/10.1084/jem.20242180).

How much of a role does the gut microbiome play in protecting the brain against immune-mediated injury? Over the past decade, accumulating research has revealed diverse mechanisms used by the commensal microbiome to shape brain development, function, and susceptibility to disease via the gut–brain axis (Kadowaki and Quintana, 2020; Loh et al., 2024; Morais et al., 2021). Yet, despite these advances, little is known about the contribution of the gut–brain axis to central nervous system (CNS) acute graft-versus-host disease (GVHD). In a new study, Chatterjee et al. (2025) demonstrate that disruption of the gut microbiota promotes neuroinflammation and cognitive decline through the loss of microbiome-derived metabolites (see figure). This exciting work offers new insights into disease pathogenesis as well as potential strategies for therapeutic intervention.

GVHD is a serious complication of allogeneic hematopoietic cell transplantation (allo-HCT), most commonly affecting the gastrointestinal tract, skin, and liver. However, in addition to the well-established effects of GVHD on those tissues, mounting evidence suggests that GVHD can also affect the CNS, resulting in immune cell infiltration into the brain (Unger et al., 1993), microglial activation (Mathew et al., 2020), and neurologic symptoms (Hümmert et al., 2021; Shortt et al., 2006). Several studies have linked a reduction in commensal microbiota diversity to increased severity and mortality in GVHD (Peled et al., 2020; Taur et al., 2014). However, antibiotics are regularly employed in allo-HCT, and their use is associated with reduced GVHD incidence, suggesting that the role of the microbiome in GVHD is nuanced and requires further study (Fredricks, 2019). Moreover, the contribution of the gut microbiome and the effect of antibiotics on CNS manifestations of GVHD are not completely understood.

Using a combination of antibiotic treatment, germ-free (GF) mice, and wild-derived (wildling) mouse models, Chatterjee et al. (2025) interrogated the consequences of microbial loss on immune responses in the CNS following allo-HCT. They found that microbiota depletion in specific pathogen–free (SPF) mice leads to significant CNS infiltration by IFN-γ–producing $CD4^+$ and $CD8^+$ T cells, along with robust activation of microglia via the TLR4/p38 MAPK signaling axis. This inflammatory response was accompanied by neurocognitive deficits, recapitulating certain aspects of the neurological symptoms seen in patients after allo-HCT.

Chatterjee et al. (2025) identified microglia as central effectors of GVHD-associated CNS pathology. Indeed, expression analysis detected a pro-inflammatory transcriptional profile in microglia following antibiotic-induced microbiota loss. Moreover, microglial depletion was sufficient to recover cognitive function in antibiotic-treated SPF GVHD mice. This mechanistic link between microbiota and microglial pro-inflammatory states in GVHD is consistent with previous observations on the regulation of microglial responses by metabolites derived from the intestinal microbiome (Erny et al., 2015; Rothhammer et al., 2018).

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Further evidence for the role of the gut microbiome in shaping microglial activation in GVHD came from studies using gnotobiotic mouse models. Wildling mice, which have a natural gut microbiota composition and display immune responses more similar to humans than those detected in laboratory SPF strains (Rosshart et al., 2019), exhibited increased microglial activation following antibiotic treatment and allo-HCT. Similarly, GF mice also displayed exacerbated microglial responses following allo-HCT. However, allo-HCT in both wildling and GF mouse models was linked to increased microglial activation, but no increase in CNS T cell infiltration, suggesting that different microbiome-linked factors control specific aspects of the CNS inflammatory response in GVHD. Subtle changes in key microbial

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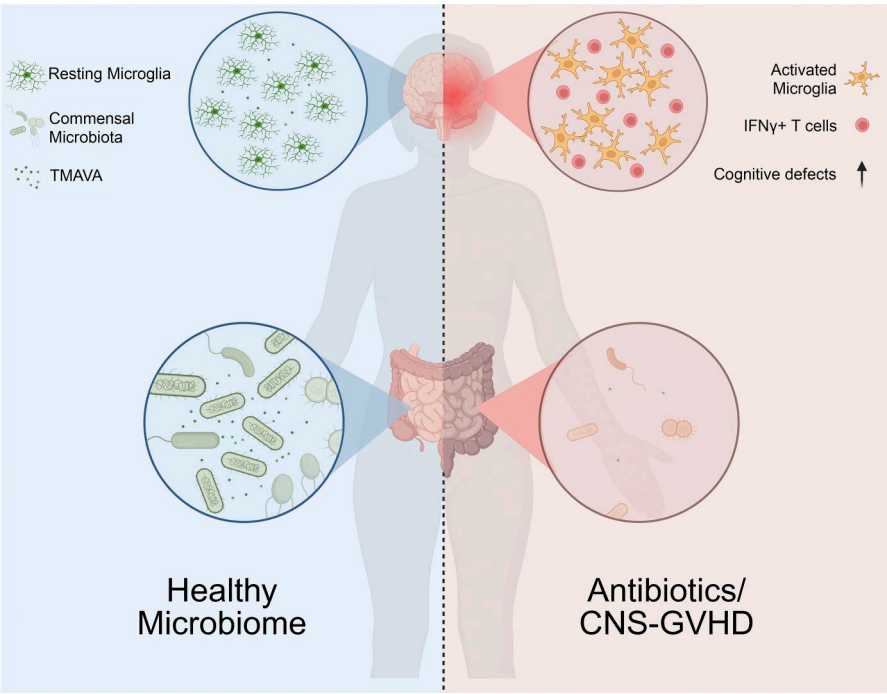

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Microbial metabolite TMAVA restrains CNS-aGVHD. Gut microbiota–derived TMAVA restrains CNS inflammation by suppressing microglial activation and T cell infiltration after allo-HCT. Antibiotic administration reduces TMAVA levels, increasing IFNγ-producing T cells in the brain and cognitive decline. Administration of exogenous TMAVA or TMAVA-producing engineered probiotics may provide new therapeutic approaches for CNS-aGVHD. Figure created using BioRender. CNS-aGVHD, CNS acute GVHD.

communities or differences in the extent of microbial depletion may explain the variations observed across mouse models, while also helping to inform differences observed across human patients undergoing allo-HCT.

A key mechanistic finding of the Chatterjee et al. (2025) study is the identification of the microbial metabolite N,N,N-trimethyl-5-aminovalerate (TMAVA) as a critical mediator at the gut–brain axis. TMAVA abundance was diminished in the serum, stool, colon, and liver from antibiotic-treated and GF mice, and also in the plasma of patients after allo-HCT and GVHD onset. Moreover, intracellular TMAVA levels were decreased in microglia from antibiotic-treated SPF allo-HCT mice. Peripheral administration of TMAVA to microbiota-depleted mice suppressed microglial TLR4/p38 MAPK signaling and alleviated neurocognitive deficits, suggesting that TMAVA may act as a direct molecular link between gut commensal bacteria and the regulation of microglial activation in GVHD.

In addition to the new mechanistic insights provided by this study, these findings by Chatterjee et al. (2025) have important translational implications. TMAVA is a metabolite produced by mammalian commensal bacteria and thus may be a promising target for the design of engineered biotherapeutics. Indeed, engineered bacterial or yeast probiotics designed to deliver specific metabolites or immunomodulatory proteins can ameliorate inflammation and alter CNS pro-inflammatory states in preclinical models (Sanmarco et al., 2023; Scott et al., 2021). Thus, probiotics engineered for the targeted delivery of TMAVA may offset complications associated with antibiotic treatment in the context of allo-HCT. Moreover, these strategies may enable the restoration of metabolic and immune homeostasis without broadly disrupting the commensal microbiome, as usually seen following broad-spectrum antibiotic treatment or untargeted metabolite supplementation.

In summary, this elegant study by Chatterjee et al. (2025) demonstrates that loss of gut microbiota–derived TMAVA is a central driver of CNS acute GVHD, linking the intestinal microbiome to CNS microglial activation and posttransplant neurocognitive decline. These findings highlight unexpected roles of the gut–brain axis in GVHD, underscoring the potential of microbiota-derived therapeutics to modify CNS disease risk. As understanding of the gut–brain–immune interface deepens, efforts to restore or engineer beneficial microbial metabolites hold considerable promise as strategies to prevent or treat neurological complications in the setting of allo-HCT.

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