Cell Stem Cell

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Spotlight

Microbial metabolite steers intestinal stem cell fate under stress

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https://doi.org/10.1016/j.stem.2024.04.006

Recently in *Cell Metabolism*, Wei et al.[1] unveiled a brain-to-gut pathway that conveys psychological stress to intestinal epithelial cells, leading to their dysfunction. This gut-brain axis involves a microbial metabolite, indole-3-acetate (IAA), as a niche signal that hampers mitochondrial respiration to skew intestinal stem cell (ISC) fate.

Psychological stress elicits a complex physiological response involving the brain, endocrine system, and autonomic nervous system, which can impact gut function through the bidirectional gut-brain axis. Stress-induced gut-brain communication is implicated in the pathogenesis and relapse of gut disorders. Clinically, a stressful lifestyle is critically involved in the exacerbation of gut-brain comorbidities such as irritable bowel syndrome and inflammatory bowel disease. Recently, the microbiota has emerged as a key regulator of gut-brain crosstalk.[2,3] Stress alters the diversity and composition of the gut microbiota, leading to alterations in microbial metabolites, cytokines, chemokines, and monoamine transmitters. These molecules, on one hand, regulate behavior by stimulating the peripheral and central nervous systems, and on the other hand, they influence immune homeostasis, host energy metabolism, and maintenance of mucosal integrity.

Serving as extrinsic factors, commensal microbiota and their derived metabolites are emerging as niche agents capable of influencing intestinal stem cell (ISC) behavior, which is essential for intestinal epithelial homeostatic self-renewal and regeneration upon epithelial damage. Specific classes of microbial metabolites, such as butyrate, a short-chain fatty acid, inhibit expansion of colonic ISCs via Foxo3 upon injury.[4] Microbiota-derived lactate accelerates ISC-mediated epithelial development.[5] However, whether stress-triggered microbial signals are perceived at the gut interface, regulating ISC behavior and influencing gut epithelial disturbance, remains poorly understood.

Now, Wei et al. report that microbial metabolite indole-3-acetate (IAA), induced by psychological stress, serves as a niche signal that skews ISC fate and epithelial renewal.[1] They initially found that chronic restraint stress (CRS) significantly reduced the villi length and crypt height in the distal ileum of mice. This was accompanied by a pronounced decrease in secretory cells, including goblet cells and enteroendocrine cells. They further identified that CRS elicited an ISC-intrinsic defect in secretory lineage commitment.

To seek the mechanisms relaying stress signals to secretory lineage differentiation of ISCs, the authors first ruled out the potential influences of calorie intake[6] and T helper cell cytokines[7] and the direct roles of the canonical stress hormones norepinephrine and corticosterone[8] on ISC self-renewal and differentiation. They then investigated the potential roles of microbiota through loss- and gain-of-function experiments. Antibiotic (ABX) treatment significantly alleviated stress-induced reductions in villi length, crypt height, and secretory cell populations, while fecal microbiome transplantation of CRS microbiota resulted in a transferable phenotype, indicating that gut microbial dysbiosis contributes to the stress-skewed ISC fate decision.

Given that *Lactobacillus* spp. showed a significant enrichment in chronic stress, the authors particularly examined the contribution of specific *Lactobacillus* strains for CRS-mediated ISC phenotypes. They conducted mono-colonization studies in germ-free (GF) mice, introducing a selected strain of *Lactobacillus murinus* that showed a notable increase in CRS-treated mice and a control strain, *Lactobacillus reuteri*, known for its epithelial protective properties. Under stress conditions, *L. murinus*-colonized, but not *L. reuteri*-colonized, mice showed decreased villi and crypt length and goblet cell density compared with GF mice, suggesting that specific members of the *Lactobacillus* genus can contribute to stress-induced intestinal crypt dysfunction.

Stress induces alterations in microbial metabolites within the intestine. Using metabolomics and metagenomics analysis, the authors identified that IAA, an indole derivative produced from tryptophan by gut bacteria, increased consistently throughout the intestinal sites of mice subjected to CRS. They showed that *L. murinus*, but not *L. reuteri*, could transform tryptophan into IAA. Additionally, the authors provided clinical relevance by showing that the abundance of *Lactobacillus* genus, IAA levels, and IAA biosynthetic genes were significantly enriched in patients with psychological distress, such as major depressive disorder. These findings led to the hypothesis that IAA may contribute to the stress-induced ISC phenotype.

More recently, microbial-derived indole pathways have garnered significant interest due to their diverse biological and clinical applications. Indole derivatives have been implicated in the gut-brain axis, exerting a potential role in neurological

disorders such as depression and anxiety. Additionally, indole derivatives have been found to modulate antitumor immunity, regulate inflammatory responses, and influence host-microbe interactions. However, the involvement of indole derivatives in the regulation of ISCs is less understood.

In light of this, to investigate the impact of IAA on ISC behavior, the authors treated organoids with IAA and observed a decrease in organoid budding rate, enteroid formation, and secretory lineage differentiation. To further validate the role of microbial IAA production on ISC dysfunction observed in chronic stress, the authors engineered an *Escherichia coli* strain capable of producing IAA. They then colonized ABX-treated mice with this IAA-producing *E. coli* strain or with a control strain, confirming that the IAA-producing bacteria could precipitate stress-induced ISC defects.

Given the profound impact of IAA, the authors further investigated the molecular mechanism for IAA-induced ISC defects. By conducting bulk RNA and single-cell RNA sequencing on IAA-treated intestinal organoids, they found that IAA treatment decreased mitochondrial bioenergetics in ISCs, which largely recapitulated the impact of stress on ISCs. Metabolic pathways have been reported to be critical for the regulation of stem cell function.[9] ISC differentiation requires metabolic reprogramming to fulfill the bioenergetic demands. To address how metabolic pathways in ISCs were rewired by IAA and stress, the authors performed isotope tracing analysis in IAA-treated intestinal crypts and demonstrated that both IAA and stress induce a metabolic reprogramming in intestinal crypts that is characterized by restrained glutamine.

Based on this mechanism, the authors proposed a metabolic intervention strategy involving the supplementation of α-ketoglutarate (α-KG), a key intermediate that links the glutamine metabolism pathway to the TCA cycle, to counteract the effects of IAA-induced restrained glutamine utilization on the TCA cycle. They found that supplementation of α-KG partially rescues IAA-induced impairment of organoid formation. Additionally, α-KG supplementation conferred a protective effect on toxic irinotecan-induced epithelial injury and goblet cell loss. Moreover, supplementation with α-KG improved intestinal epithelial barrier function in CRS-exposed mice.

The findings of this study reveal a pathway through which the gut microbiota relays stress signals from the brain to shape ISC behavior in mice. Specifically, the gut-brain axis involves the microbial metabolite IAA as a niche signal that hampers mitochondrial respiration, leading to a skewed fate decision in ISCs. Compared to the variability in microbiota composition observed across different neuropsychiatric cohorts, the enrichment of microbial IAA production is more consistently observed, suggesting a potentially shared metabolic trait in patients under chronic mental stress. Although the exact mechanisms for how stress induces IAA and how IAA triggers ISC defects remain to be fully investigated, the current findings provide an essential framework for targeting microbial IAA metabolism or reshaping metabolic signaling in ISCs to enable improved therapeutic interventions for gut-brain comorbidities.

DECLARATION OF INTERESTS

S.Z. is a cofounder of Ibiome, which studies microbial regulation of immune responses.

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