Scientists propose therapeutic approach for inflammatory bowel disease

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In a study published in *Cell Host & Microbe*, a research team has demonstrated the causal link between microbial factors and dysfunction of intestinal stem cells (ISCs) in colitis. On the basis of this mechanism, they proposed a possible approach to restore ISC function in colitis.
Inflammatory bowel disease (IBD) is a chronic disease characterized by microbial dysbiosis and dysfunction of ISCs in the gut. However, how these two factors are directly communicated remains poorly understood.

In this study, researchers first revealed that $\alpha_{2A}$-adrenergic receptor (ADRA2A) is a highly expressed G-protein-coupled receptor (GPCR) in ISCs. Through PRESTO-Tango and BRET2 GPCR assays against ADRA2A using a customized library of 88 microbial metabolites, they identified that a microbial metabolite, tyramine, directly activates ADRA2A in ISCs.

Tyramine is mainly produced by human gut commensal Enterococcus bacteria via tyrosine decarboxylase (tyrDC). Additionally, Enterococcus, tyramine and ADRA2A are enriched in geographically distinct IBD cohorts.

The researchers subsequently investigated the effect of Enterococcus-derived tyramine. They used an engineered tyrDC-deficient Enterococcus faecalis strain and intestinal epithelial cell-specific Adra2a knockout mice, and demonstrated that Enterococcus-derived tyramine suppresses ISC proliferation (and thus epithelial regeneration), thereby impairing epithelial regeneration and exacerbating DSS-induced colitis through ADRA2A.

The researchers came up with a possible treatment for colitis by blocking the Enterococcus–tyramine–ADRA2A axis to restore ISC-driven epithelial regeneration. They applied yohimbine, an antagonist of ADRA2A, to mice with DSS-induced colitis. Compared with the non-treatment controls, yohimbine treatment significantly ameliorated the phenotypes of DSS-induced colitis, suggesting a helpful therapy.
The study reveals a causal link between microbial regulation of ISCs and colitis exacerbation, and provides new ways for treating colitis. The research team was led by Prof. Pan Wen from the University of Science and Technology of China (USTC) of the Chinese Academy of Sciences, in collaboration with research teams led by Prof. Zhu Shu and Prof. Song Xinyang


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