

Gut microbiota-derived tryptophan metabolites improve total parenteral nutrition-associated infections by regulating Group 3 innate lymphoid cells

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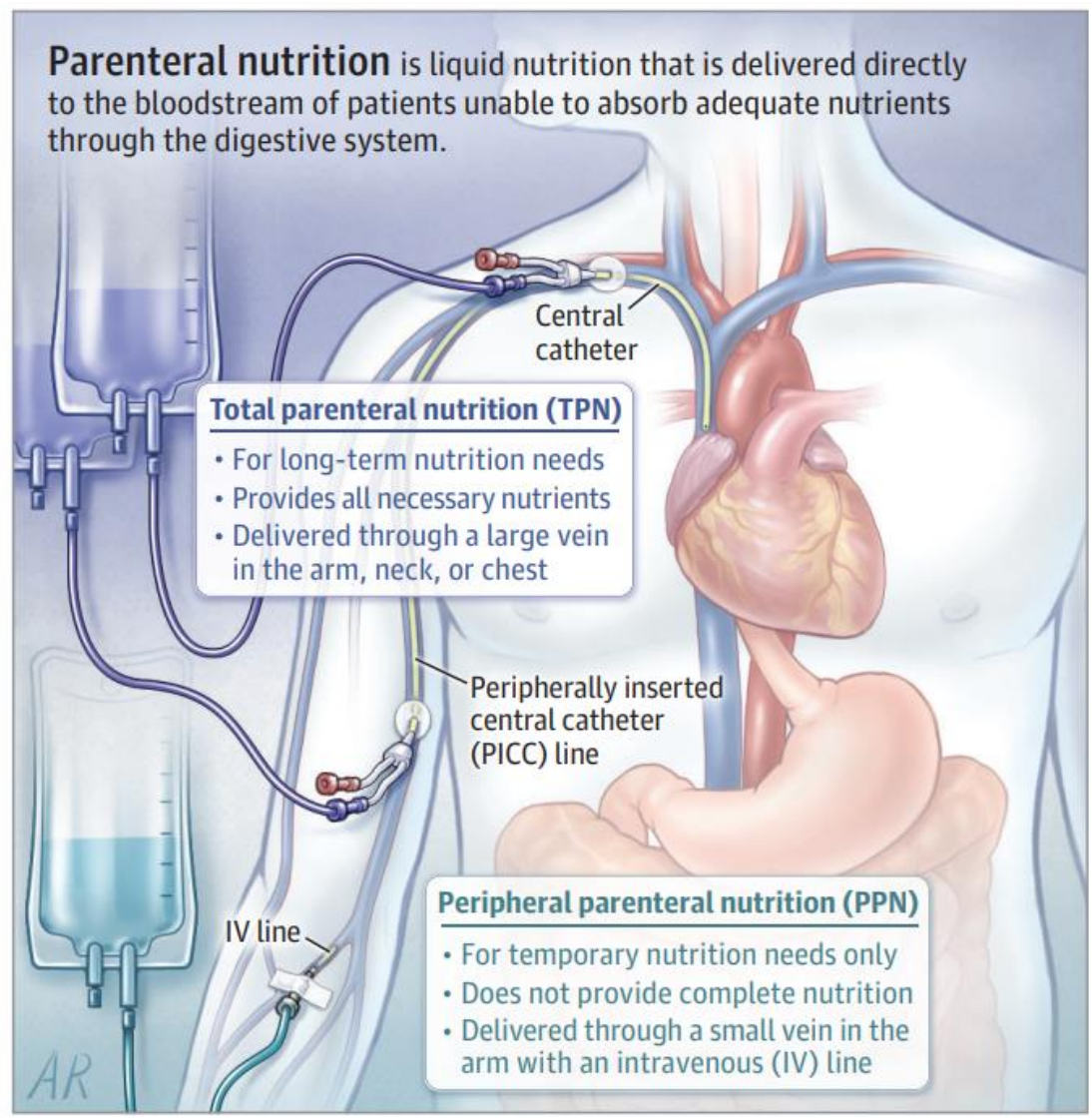
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Introduction



- ❑ Clinical nutritional support is recognized by Klinefner's Surgery as one of the four pivotal advancements in surgical practice during the 20th century;
- ❑ Total parenteral nutrition (TPN) is a key treatment method for rescuing patients with chronic intestinal failure (CIF);
- ❑ TPN can lead to a series of complications, and the incidence of TPN-related infections can reach 42.05%;
- ❑ The pathogenesis of TPN-related infections still needs further investigation.



Highlights

Gut microbiota-derived tryptophan metabolites improve total parenteral nutrition-associated infection by regulating Group 3 innate lymphoid cells (ILC3s)

Total parenteral nutrition

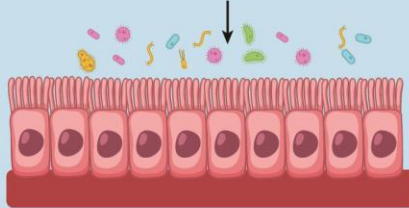


↓ *Lactobacillus murinus*

Treatment with *Lactobacillus murinus*

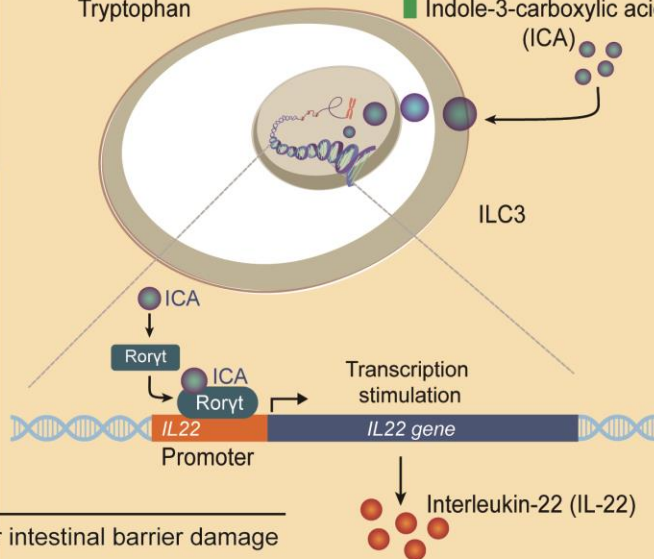
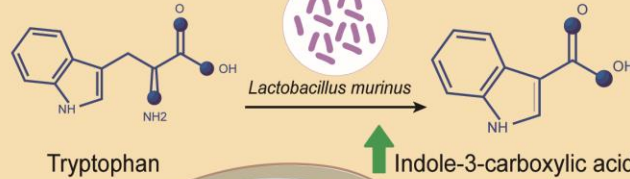


Intestinal barrier damage



↑ Improved protective intestinal barrier

Repair intestinal barrier damage

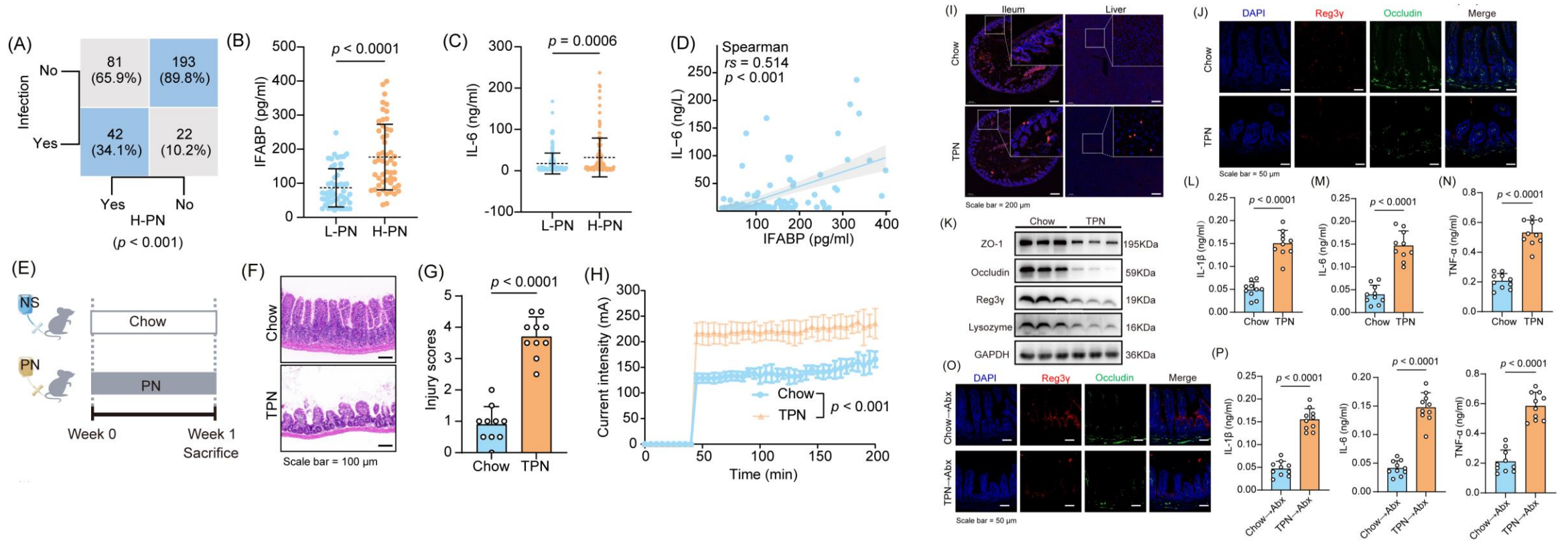


- Dysbiosis caused by total parenteral nutrition (TPN) reduces the response of intestinal Group 3 innate lymphoid cells (ILC3s), thereby increasing susceptibility to infections;
- *Lactobacillus murinus* (*L. murinus*) is reduced in patients with chronic intestinal failure (CIF) using TPN, and *L. murinus* and its metabolite, indole-3-carboxylic acid (ICA), can modulate ILC3s and mitigate infections;
- ICA enhances the secretion of IL-22 in ILC3s through activation of Ror γ t.



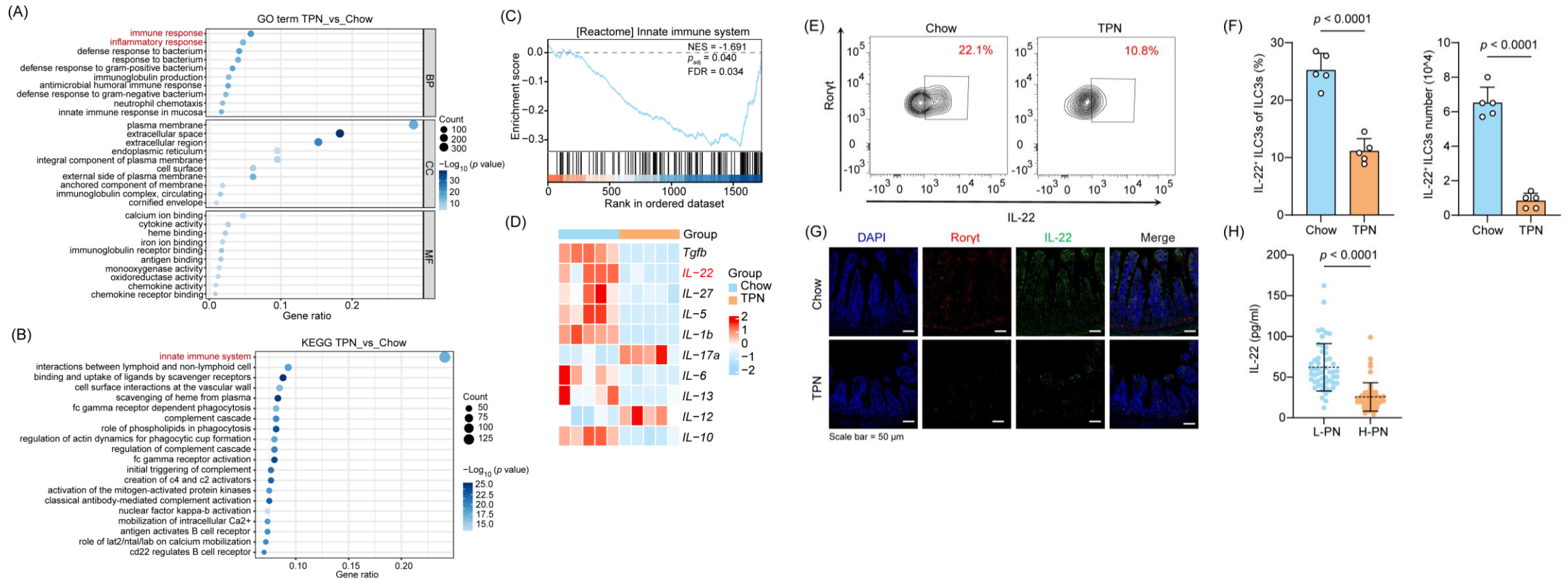
Main text

Results—Dysbiosis caused by TPN induces intestinal barrier damage and infection



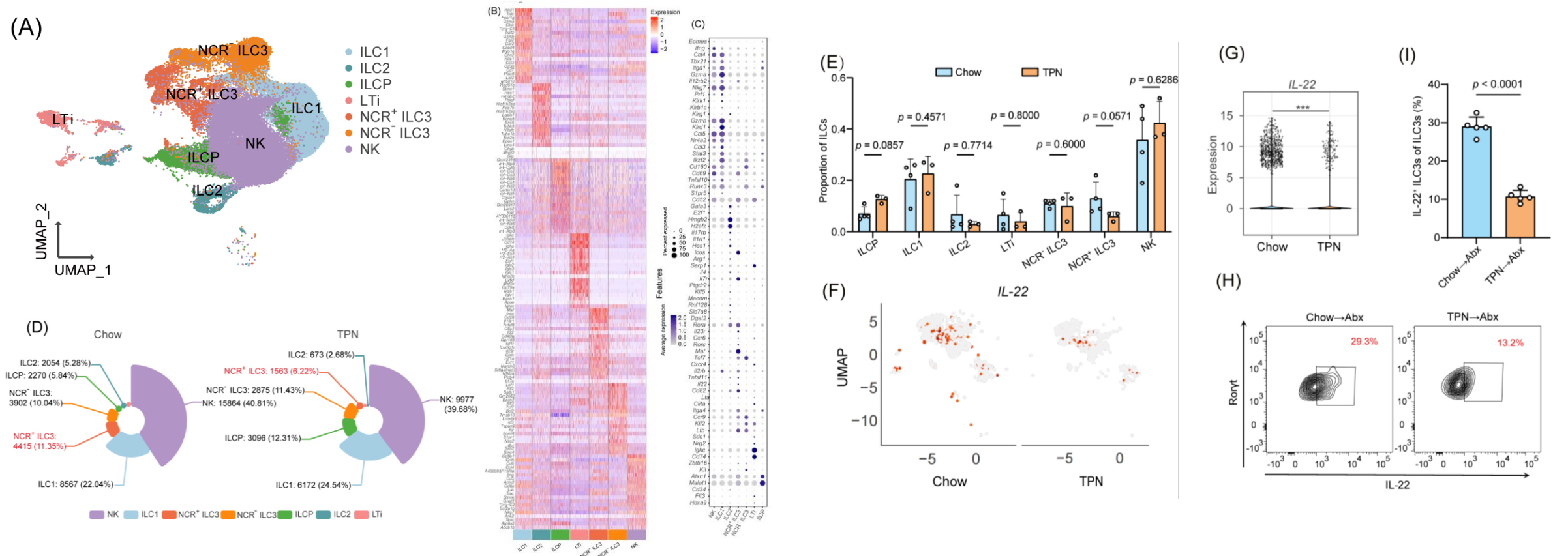
- TPN caused intestinal barrier damage and increased infection rates in 338 patients with CIF;
- TPN caused intestinal injury, increased intestinal permeability, reduced expression of tight junction proteins and antimicrobial peptides, and elevated levels of inflammatory factors in mice;
- Fecal microbiota transplantation (FMT) from TPN-treated mice exhibits the same damage of TPN.

Results—Dysbiosis reduces intestinal ILC3s response



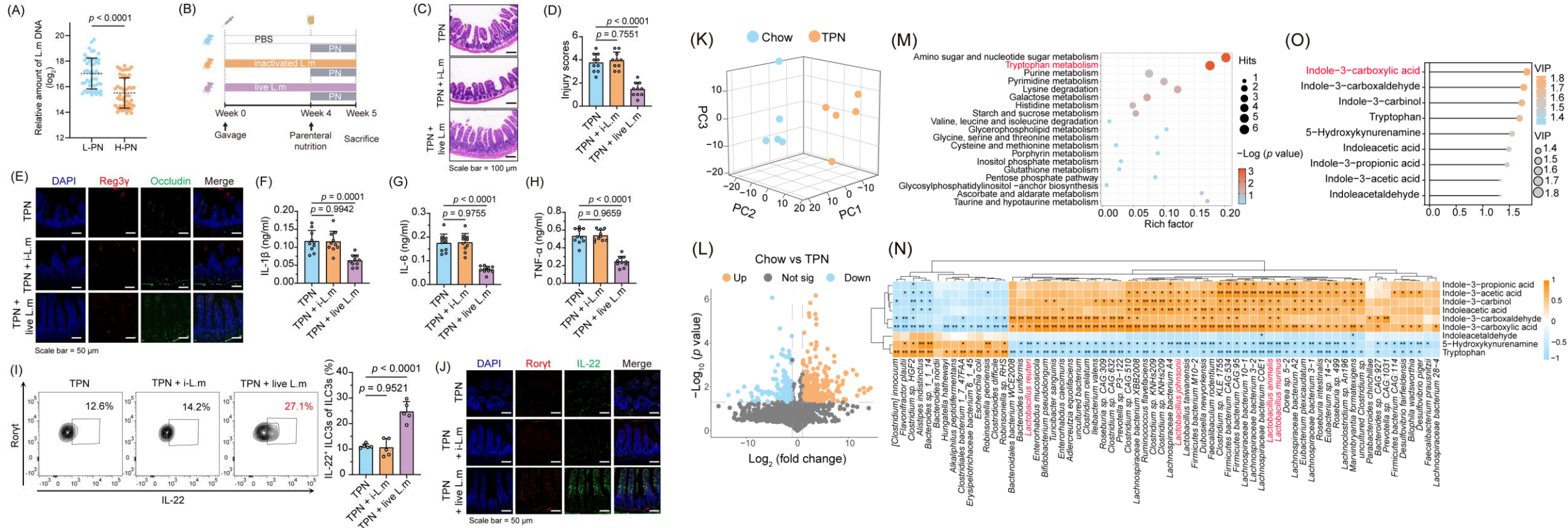
- ❑ TPN leads to a decreased innate immune function in the intestines;
- ❑ TPN leads to a decrease in intestinal *IL-22* gene expression and a reduction in the proportion and number of *IL-22*⁺ ILC3s.

Results—Dysbiosis reduces intestinal ILC3s response



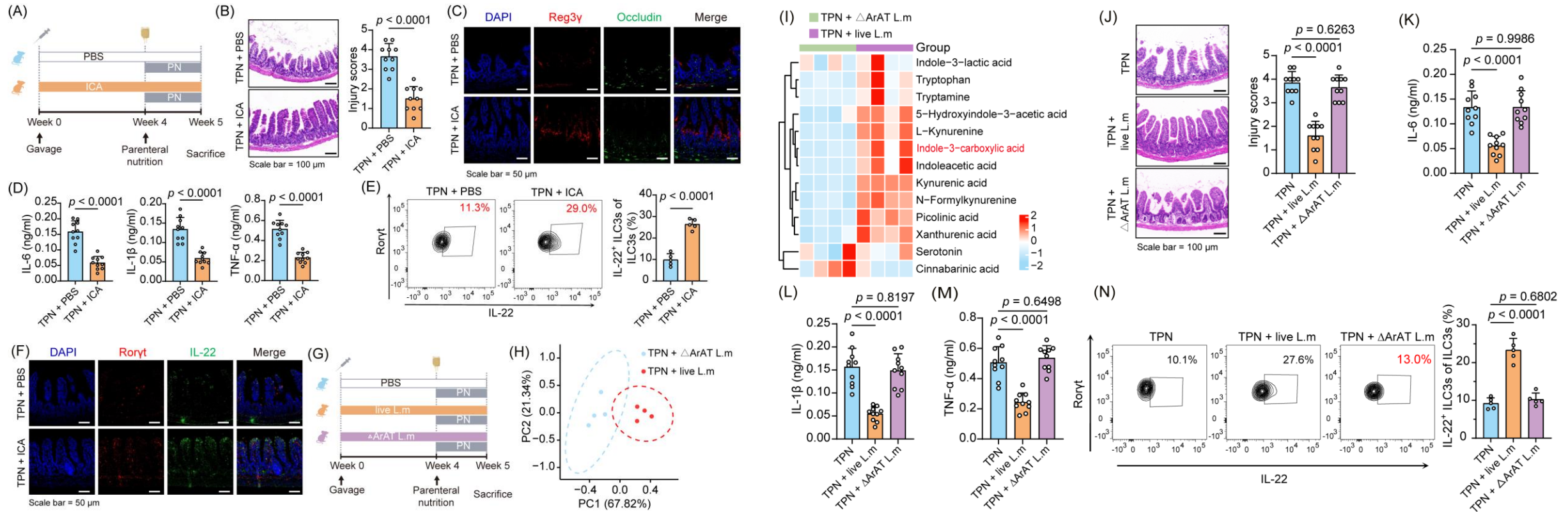
- Single-cell sequencing results show that TPN leads to a decrease in the proportion of NCR⁺ ILC3s in the intestines and a reduction in IL-22 expression;
- FMT from TPN-treated mice lead to a reduction in the proportion of IL-22⁺ ILC3s.

Results—*L. murinus* can ameliorate TPN-related infection by regulating ILC3s



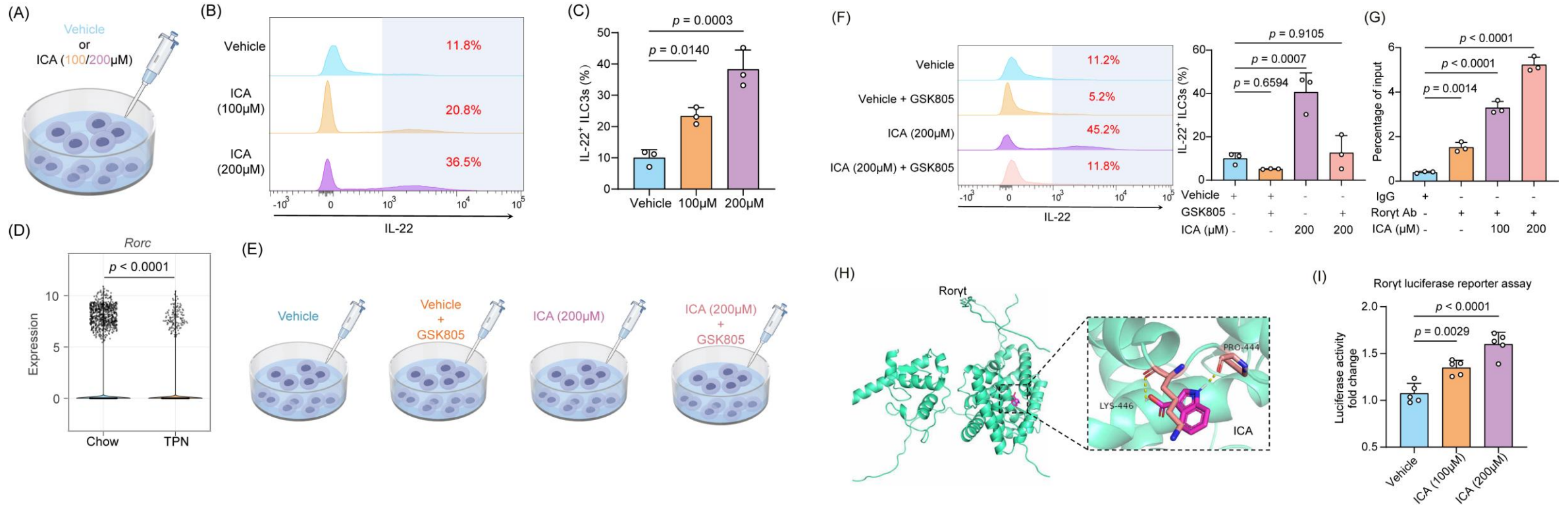
- *L. murinus* improves intestinal damage, reduces inflammatory status, and increases intestinal IL-22⁺ ILC3s proportions;
- *L. murinus* does not exhibit the above effects after inactivation;
- Non-targeted metabolomics analysis suggests that ICA may be the key metabolite of *L. murinus*.

Results—*L. murinus* exerts a protective effect through ICA



- ❑ ICA improves intestinal damage, reduces inflammatory status, and increases intestinal IL-22⁺ ILC3s proportions;
- ❑ Aromatic amino acid transaminase (*ArAT*) is the key gene for the production of ICA by *L. murinus*;
- ❑ The protective effects of *L. murinus* disappear after knocking out *ArAT*.

Results—ICA promotes ILC3s to express IL-22 by targeting Ror γ t



- ICA dose-dependently increases the proportion of IL-22⁺ ILC3s;
- ICA regulates ILC3s via Ror γ t, and the Ror γ t inhibitor GSK805 can inhibit the effect of ICA;
- Chip-qPCR, molecular docking, and dual-luciferase assays further confirmed that ICA targets Ror γ t to promote the expression of IL-22 in ILC3s.



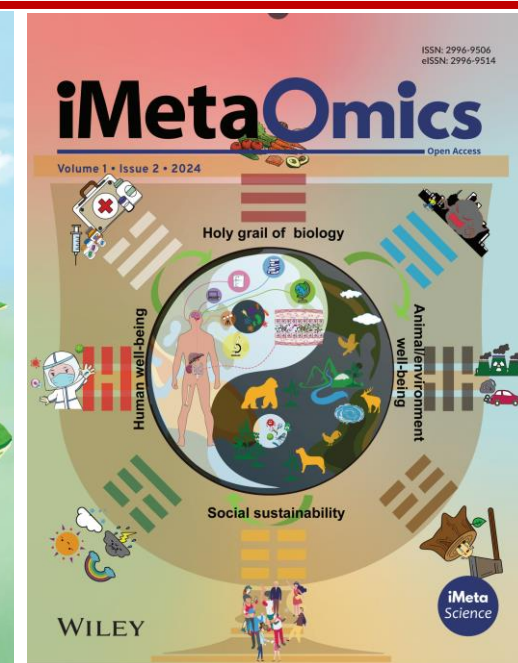
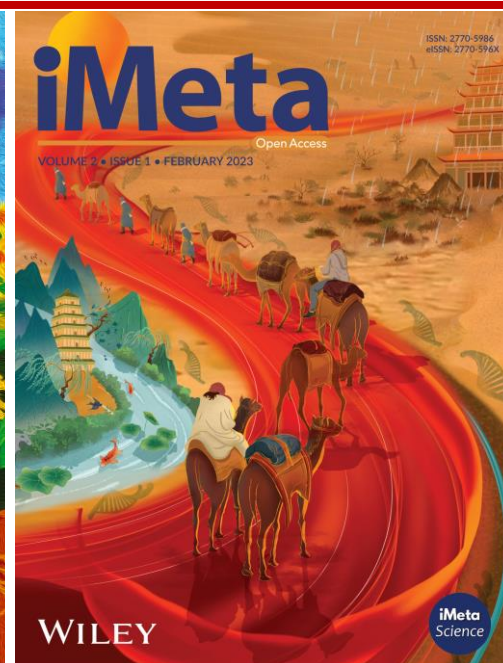
Summary

- ❑ Dysbiosis caused by total parenteral nutrition (TPN) reduces the response of intestinal Group 3 innate lymphoid cells (ILC3s), thereby increasing susceptibility to infection.
- ❑ *L. murinus* and its metabolite, indole-3-carboxylic acid (ICA), can modulate ILC3s and mitigate infections;
- ❑ ICA enhances the secretion of IL-22 in ILC3s through activation of Ror γ t;
- ❑ The “microbe-metabolism-immune” axis provides a crucial theoretical foundation for advancing intestinal rehabilitation therapies in clinical patients with CIF and for reducing susceptibility to infections.

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