Gut-Derived *Lactobacillus* from Exceptional Responders Mitigates Chemoradiotherapy-Induced Intestinal Injury through Methionine-Driven Epigenetic Modulation

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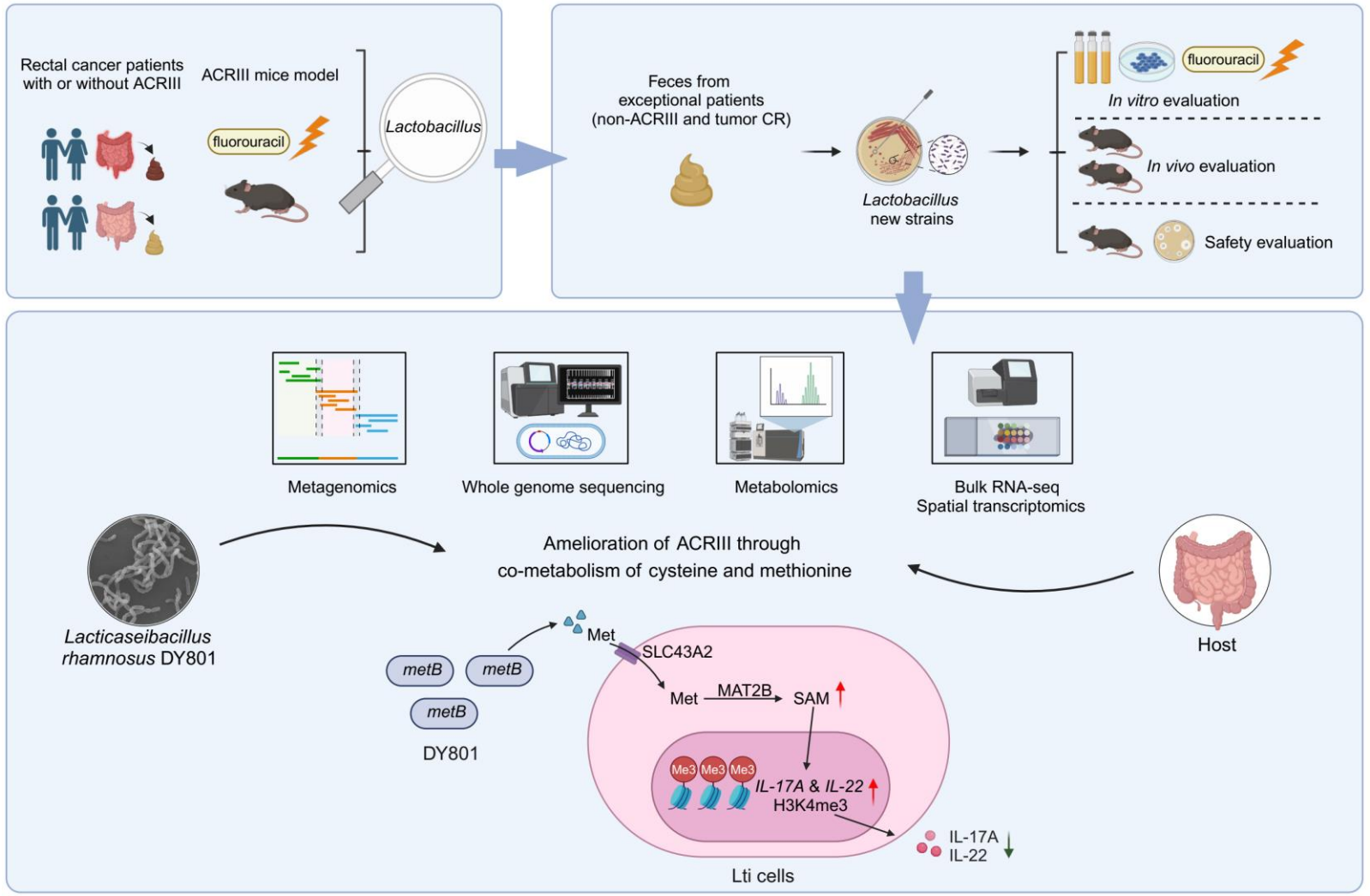
Introduction

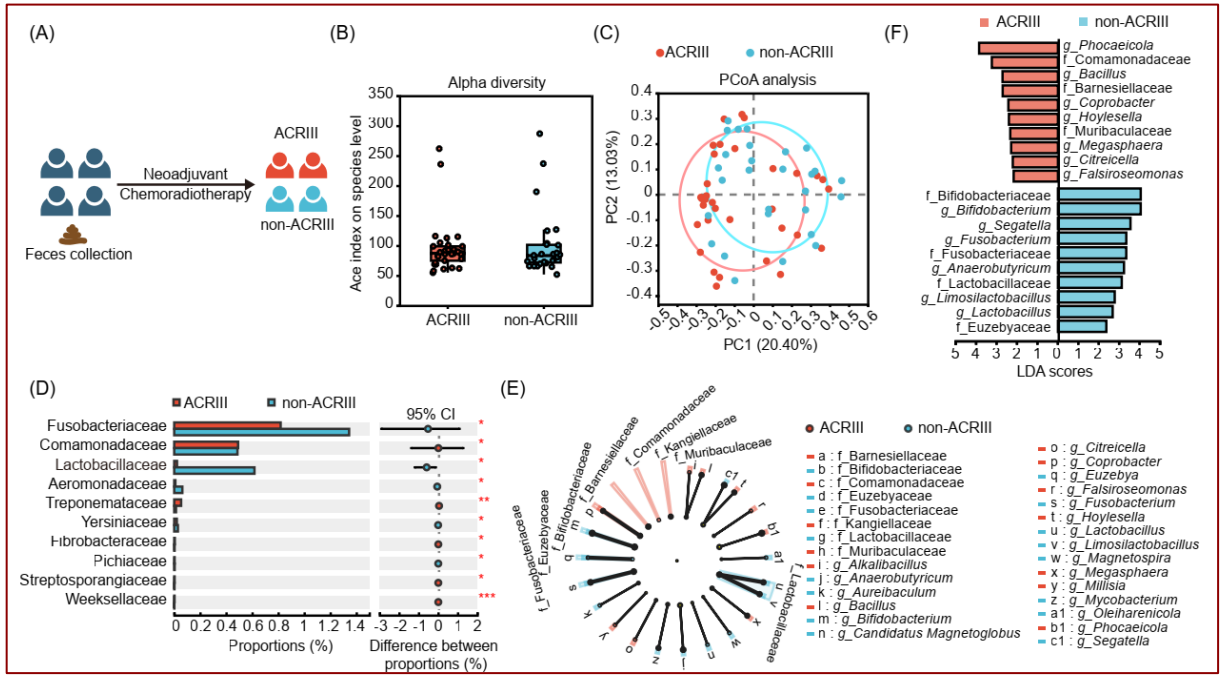
- **Clinical Problem**: Acute chemoradiotherapy-induced intestinal injury (**ACRIII**) represents a prevalent yet challenging complication, significantly impairing life quality, causing treatment interruption and prolonged therapeutic courses.
- **Therapeutic Gap**: No standardized treatment exists; current management is empirical.
- **Limited Solutions**: Gut microbiome modulation (FMT, conventional probiotics, and prebiotics) attenuates intestinal damage by suppressing excessive immune activation; their efficacy against ACRIII remains limited.
- **Urgent need for innovative microbiome-based interventions for ACRIII.**
- **Research Objectives:**
  - **Clinical Specimen Analysis:** Fecal metagenomics + Random Forest machine learning, to identify key gut microbiota associated with ACRIII; Isolate novel *Lactobacillus* strains from exceptional responders; Validation through patient-derived fecal and blood samples.
  - **Model Validation:** Evaluate therapeutic effects of novel strains, methionine, and SAM in ACRIII murine models.
  - **Mechanistic Investigation:** Integrate multi-omics analyses (metagenomics, metabolomics, transcriptomics, comparative genomics, and pan-genomics) to elucidate bacterial-host methionine co-metabolism.
  - *L. rhamnosus* DY801 alleviates ACRIII, providing novel therapeutic targets and strategies.

Highlights

- Exceptional patient-derived *Lactobacillus* strains, notably *Lacticaseibacillus rhamnosus* DY801, effectively alleviate acute chemoradiotherapy-induced intestinal injury (ACRIII).
- *Lacticaseibacillus rhamnosus* DY801 modulates host gut cysteine and methionine metabolism.
- Lti cells are crucial proinflammatory mediators in the pathogenesis of ACRIII.
- Microbial-derived methionine promotes histone methylation in Lti cells and reduces ACRIII-associated inflammatory responses.



High abundance of *Lactobacillus* in the gut correlates with absence of ACRIII in patients



- Post-treatment non-ACRIII patients exhibited higher relative abundances of *Lactobacillaceae* and *Lactobacillus*.
- Through the application of the Random Forest machine learning algorithm and evaluation using mean decrease in accuracy, *Lactobacillus* was identified as the most important genus in predicting ACRIII.

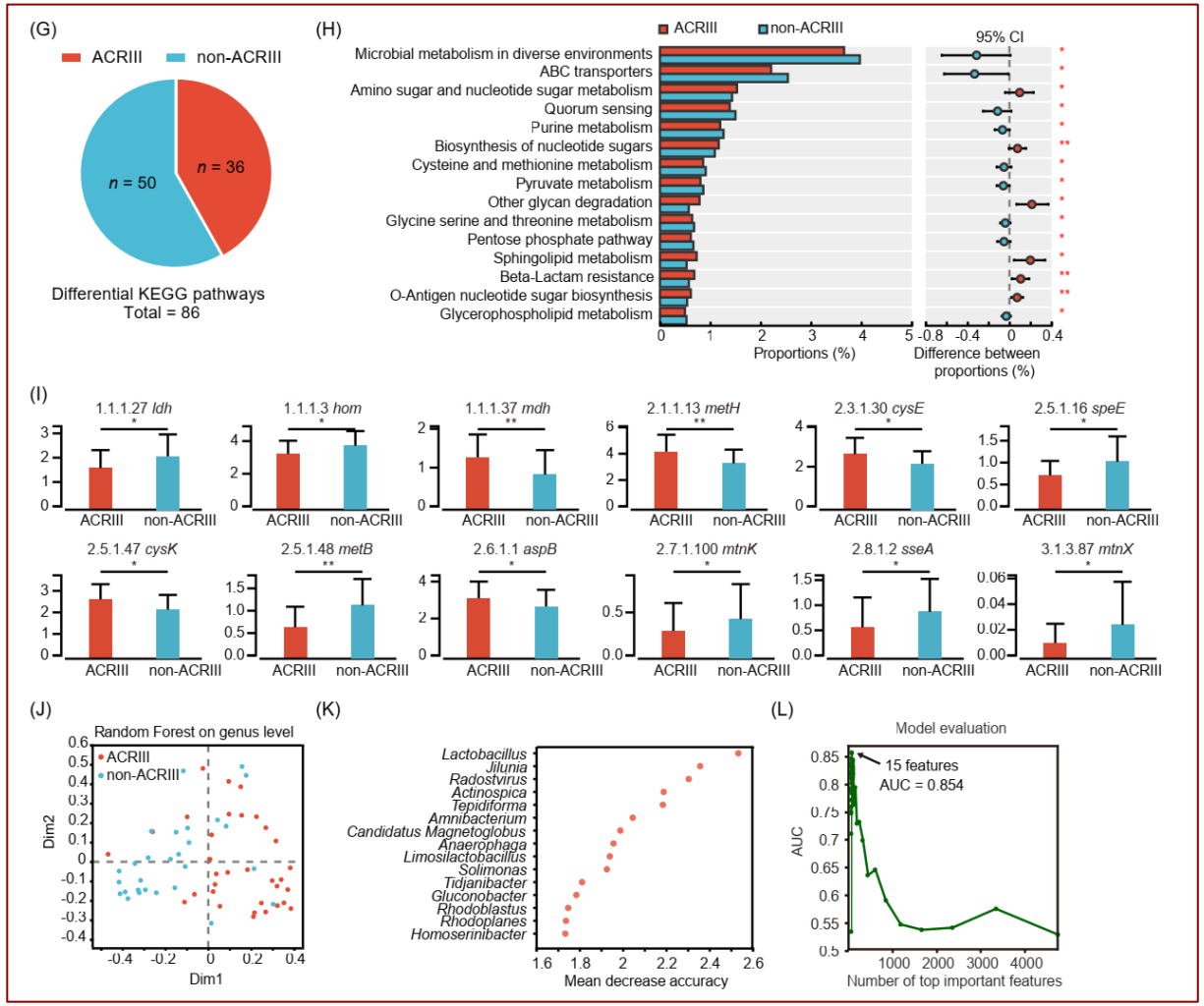
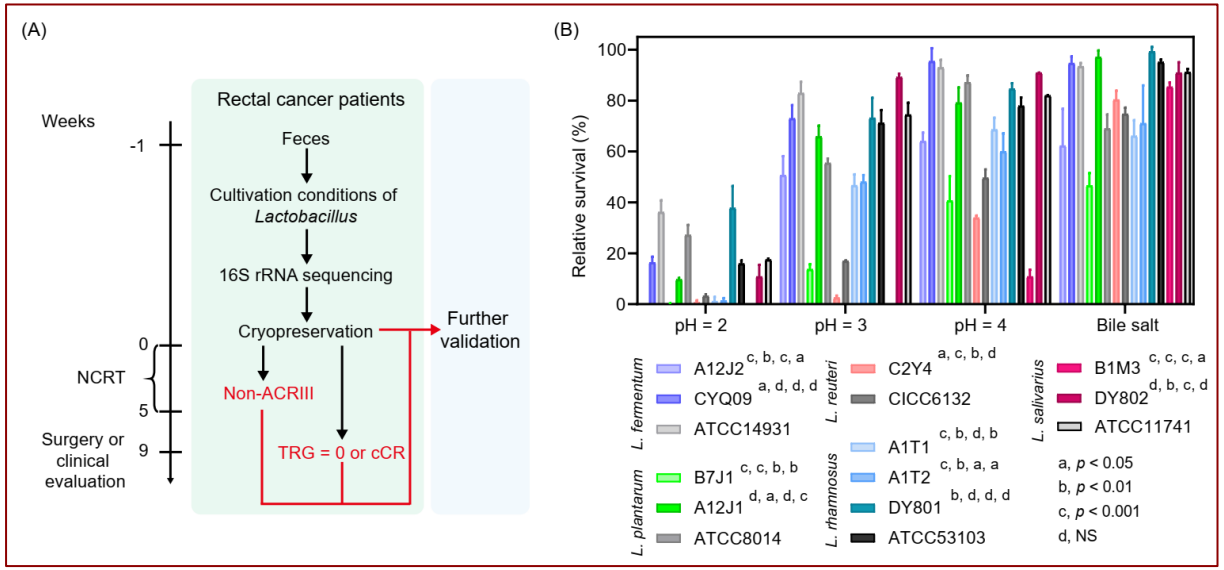


Figure 1. Fecal metagenomics links pretreatment gut *Lactobacillus* depletion to ACRIII.

Isolation and screening of gut-derived *Lactobacillus* from exceptional rectal cancer patient cohorts



- Ten novel *Lactobacillus* strains with stable genetic characteristics were successfully isolated.
- Wild-type Lactobacillus strains (*Lacticaseibacillus rhamnosus* DY801, *Limosilactobacillus fermentum* CYQ09, and *Ligilactobacillus salivarius* DY802) demonstrated robust overall performance in the *in vitro Lactobacillus* screening experiments.

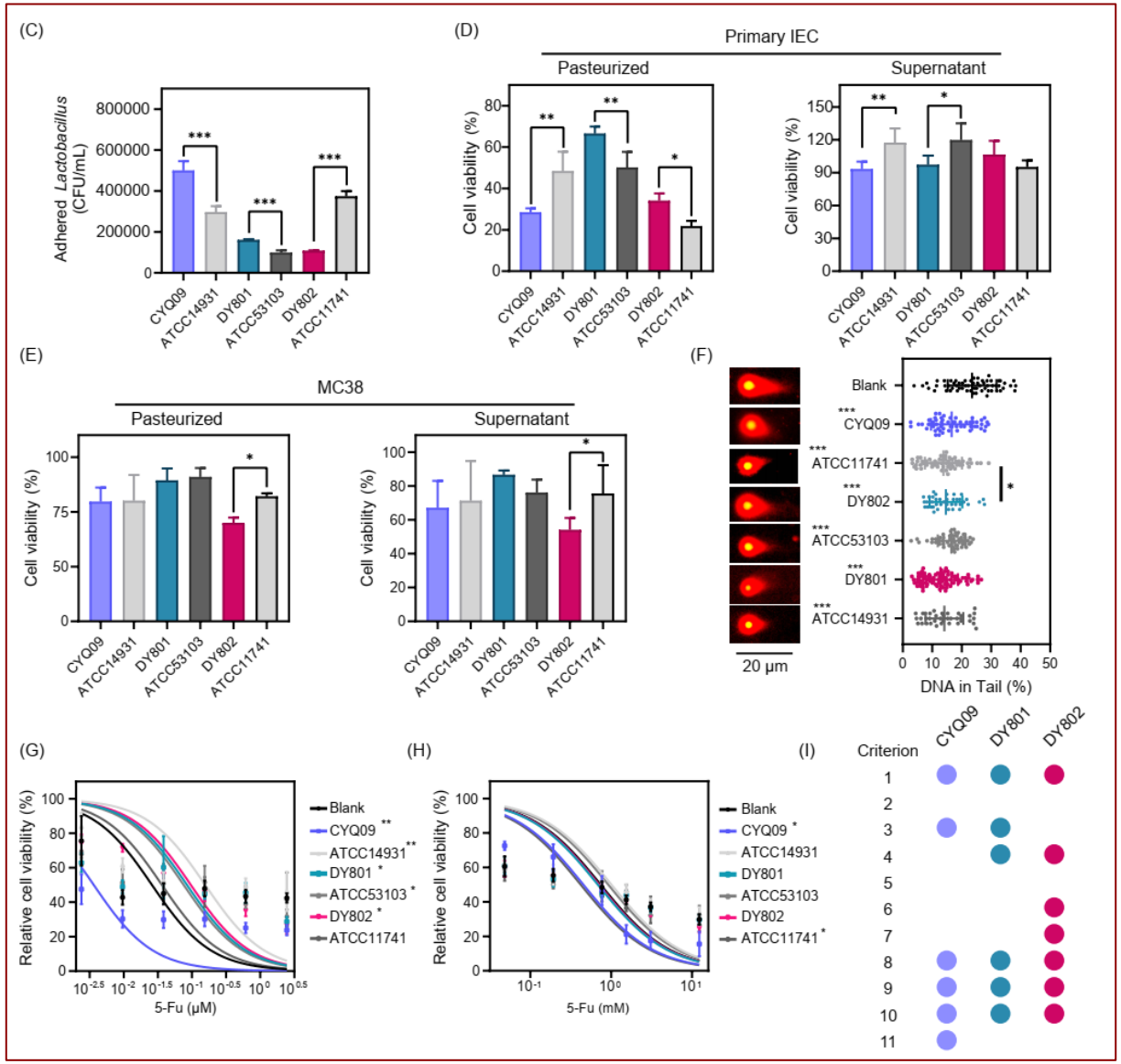
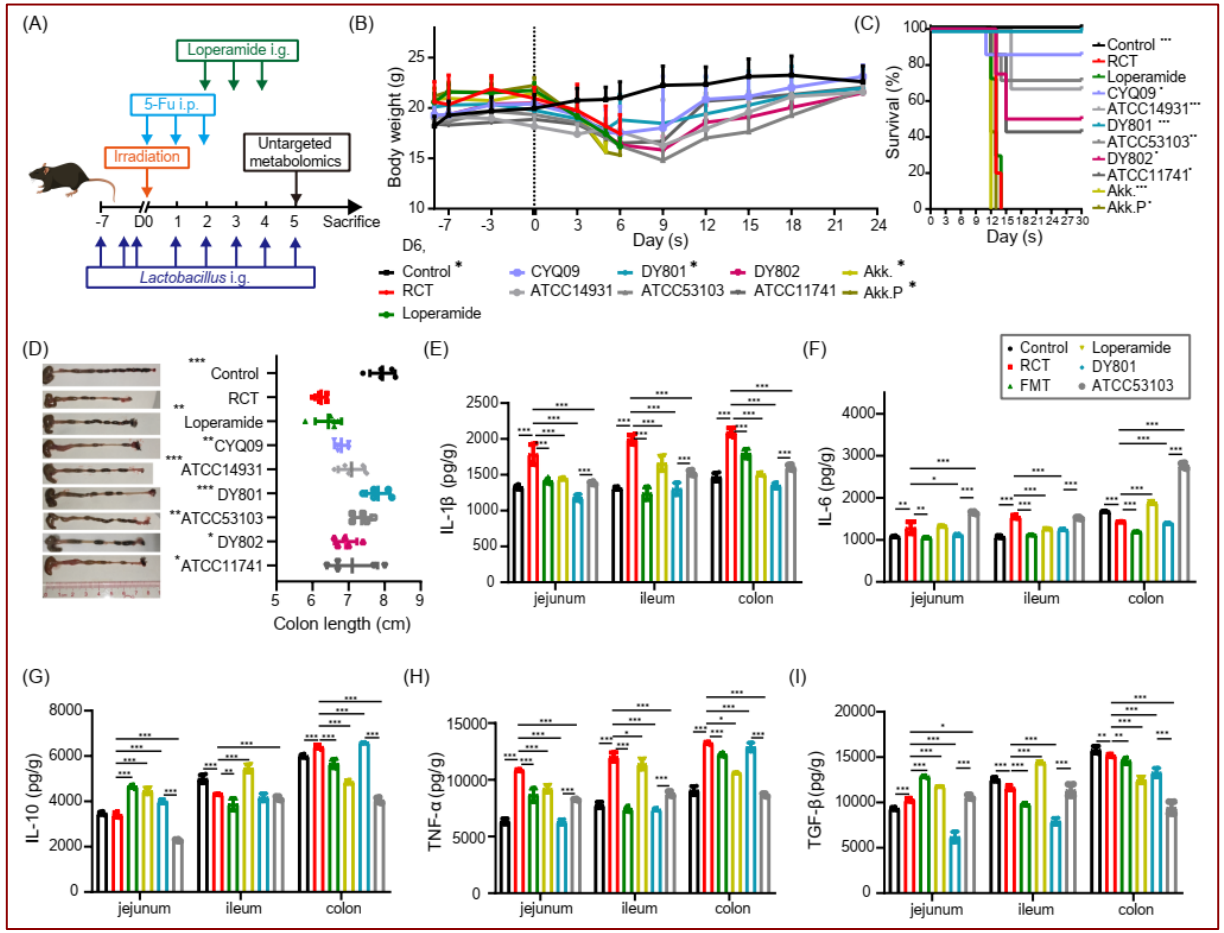


Figure 2. Isolation and screening of *Lactobacillus* strains from patients with rectal cancer *in vitro.*

L. rhamnosus DY801 significantly ameliorates ACRIII without compromising tumor treatment efficacy



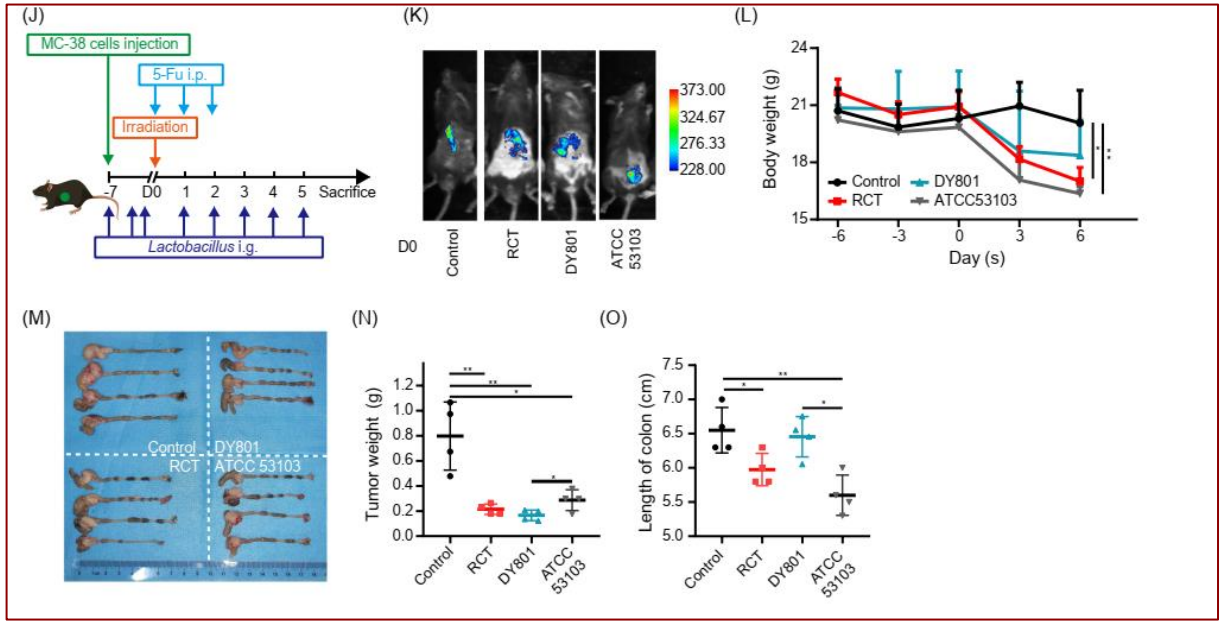
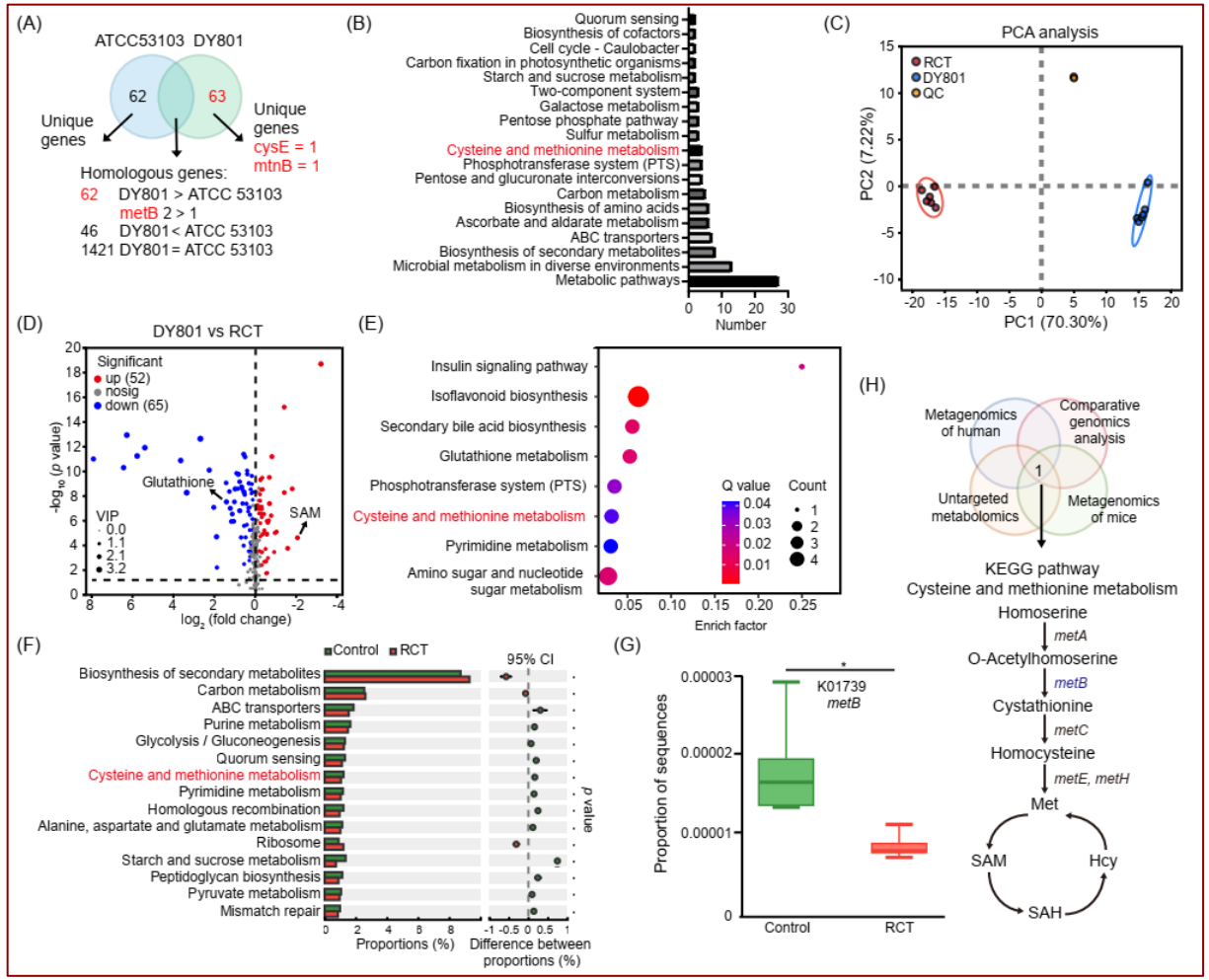


Figure 3. *Lactobacillus* strains derived from exceptional rectal cancer patients alleviate ACRIII without affecting tumor treatment efficacy *in vivo*.

- *L. rhamnosus* DY801 significantly ameliorated ACRIII and suppressed both local and systemic inflammatory responses.
- DY801 effectively alleviated ACRIII without compromising the efficacy of *in situ* tumor treatment.

Regulation of host intestinal cysteine and methionine metabolism by *metB* gene mitigates ACRIII



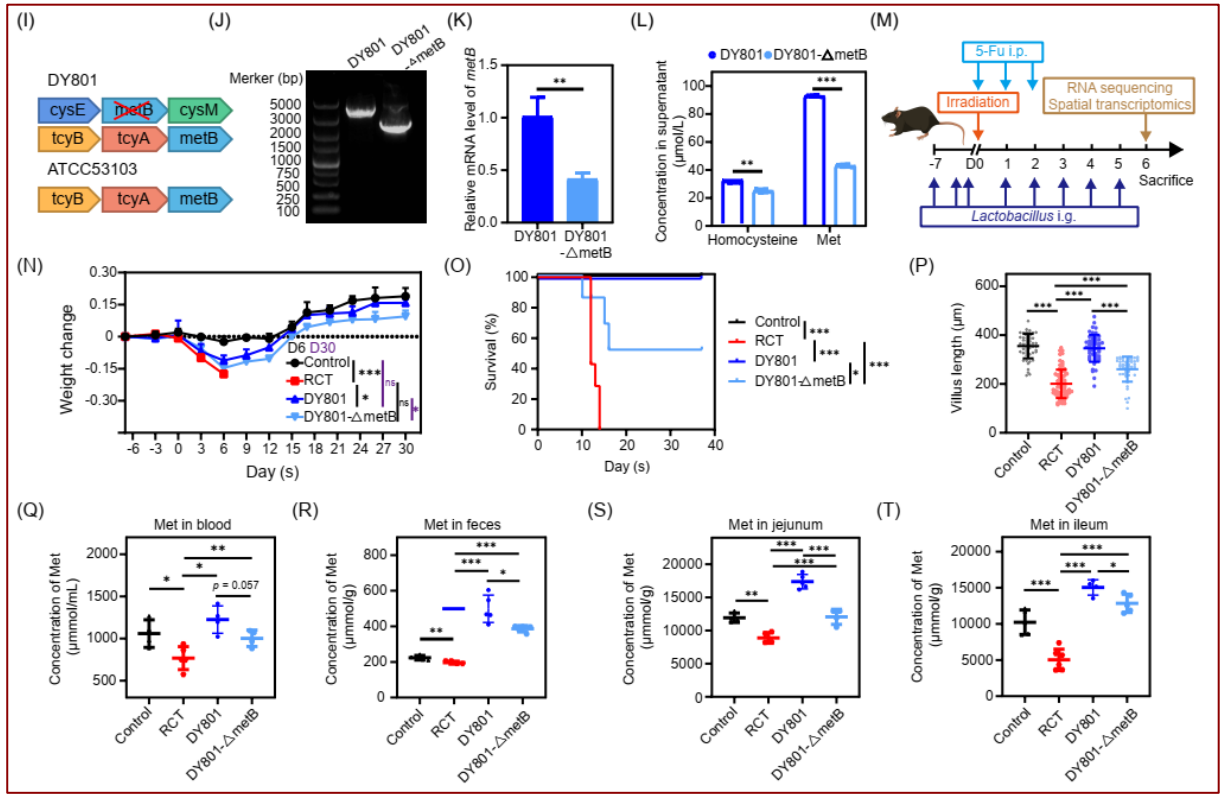
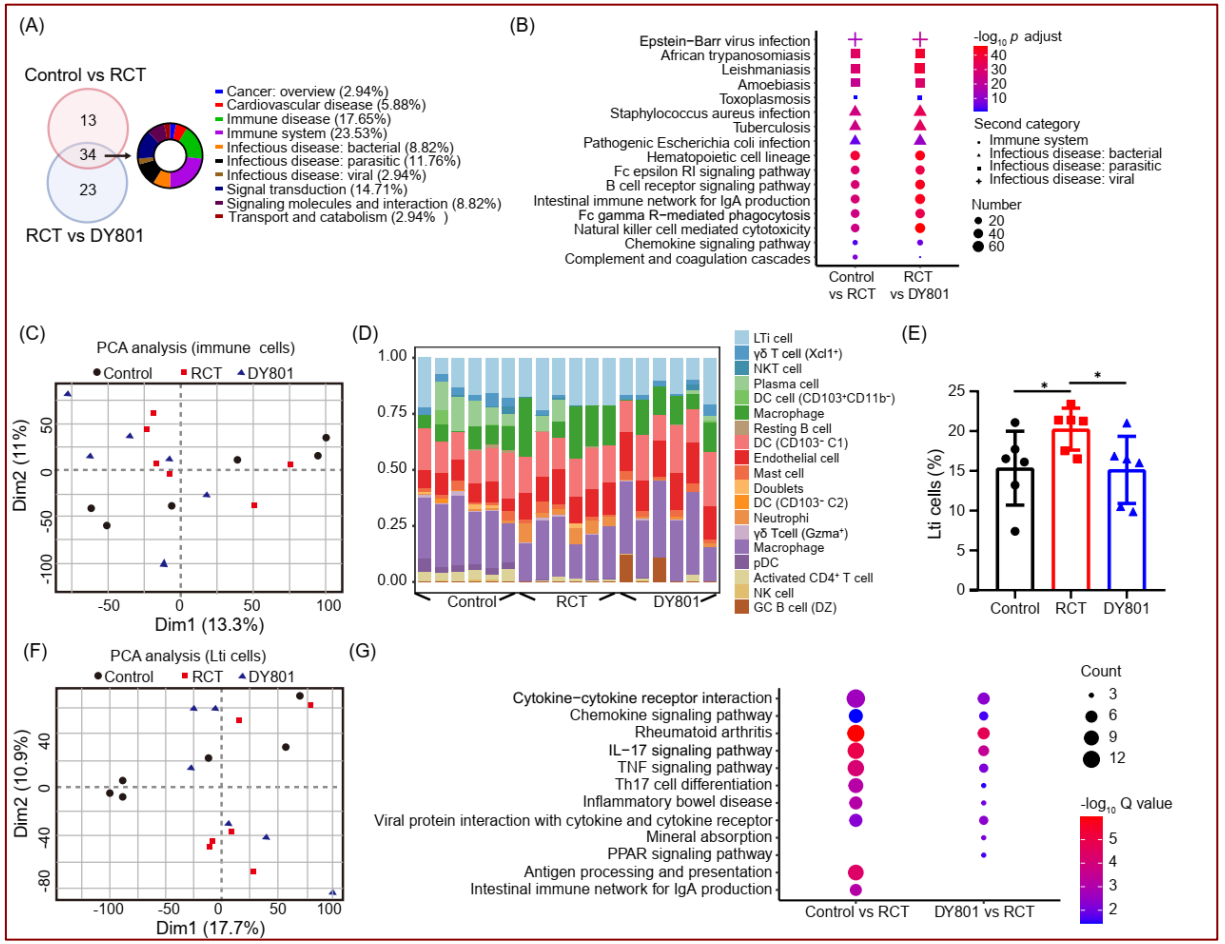


Figure 4. *Lacticaseibacillus rhamnosus* (*L. rhamnosus*) DY801 improves ACRIII activity by regulating cysteine and methionine metabolism.

- Cysteine and methionine metabolism was the crucial pathway for DY801 to alleviate ACRIII.
- DY801 alleviates ACRIII by regulating intestinal methionine levels in a *metB*-dependent manner.

Lti cells function as key proinflammatory mediators in the progression of ACRIII



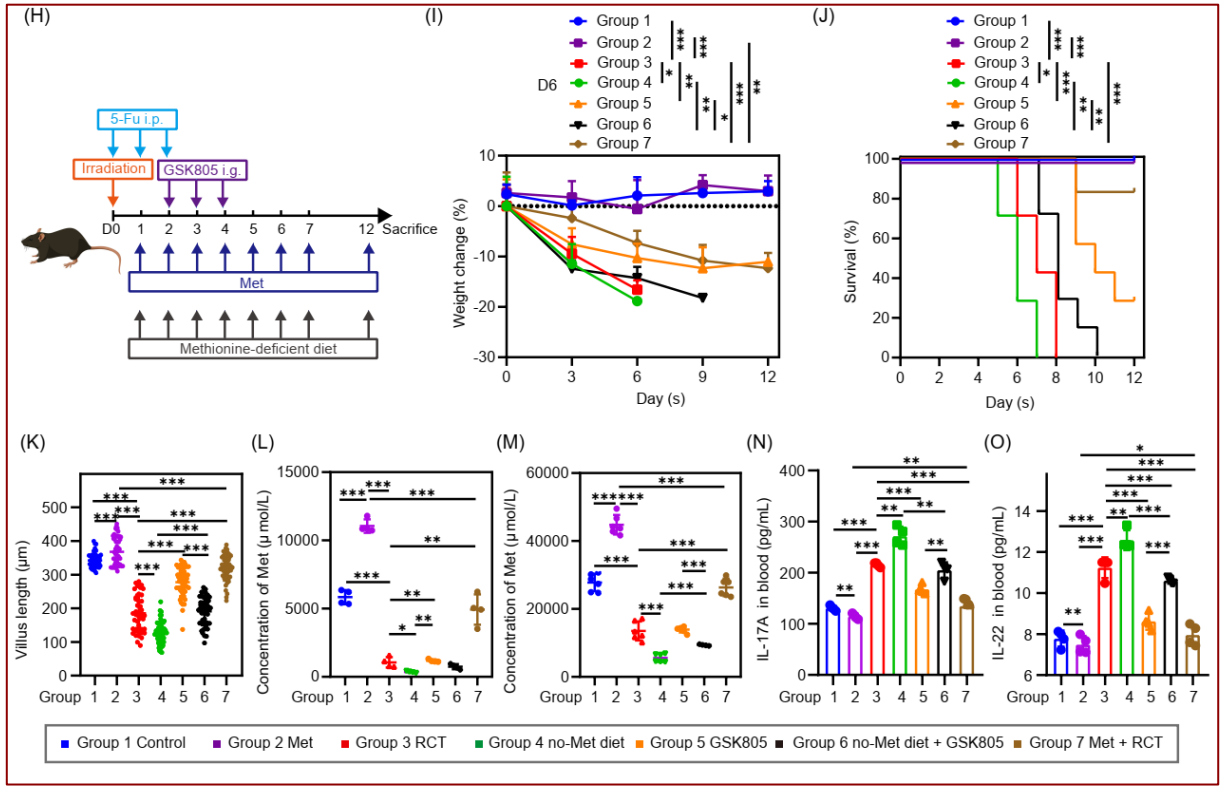
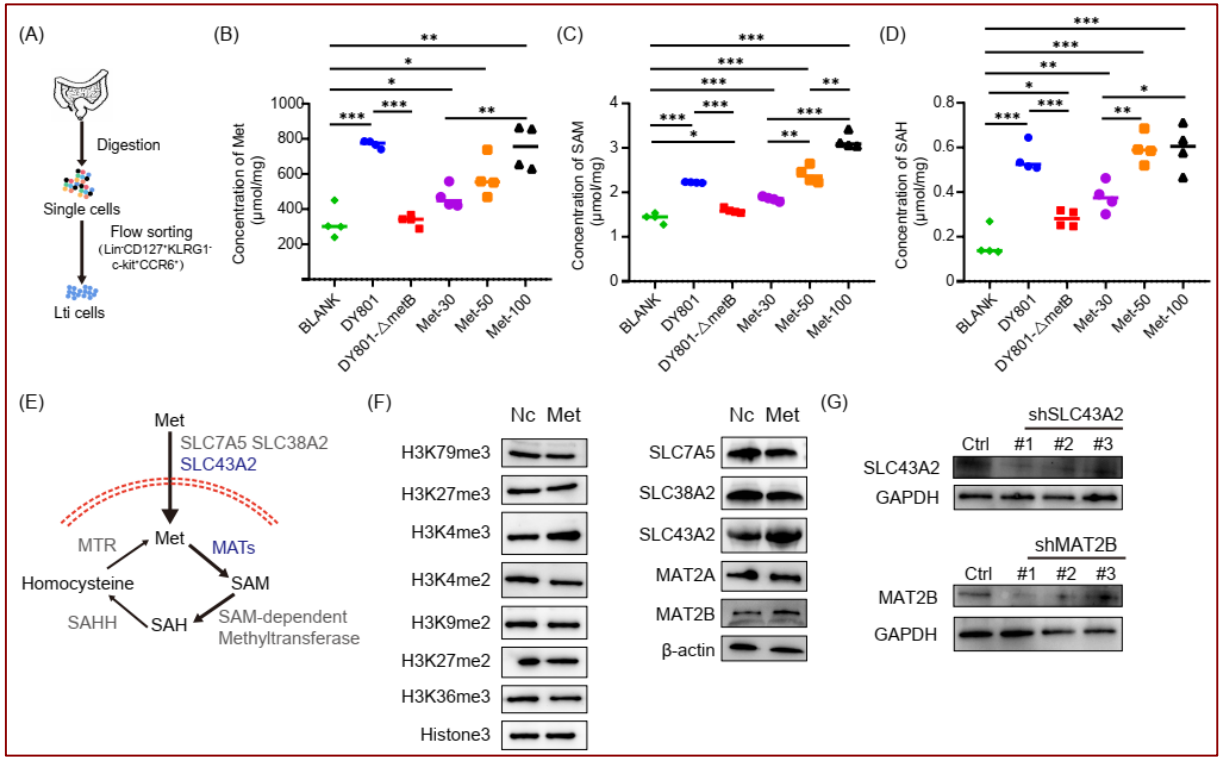


Figure 5. Lymphoid tissue inducer (Lti) cells are important proinflammatory effector cells of ACRIII, and methionine inhibits Lti cells.

- Lti cells played a pivotal role in the pathogenesis of ACRIII.
- DY801 and its metabolites affected both Lti cell quantity and function.
- DY801 and methionine inhibited the production of intestinal IL-17A and IL-22 through *in vivo* experiment.

Increased methionine enhances SAM-mediated H3K4 trimethylation, inhibiting Lti cell activation and cytokine secretion



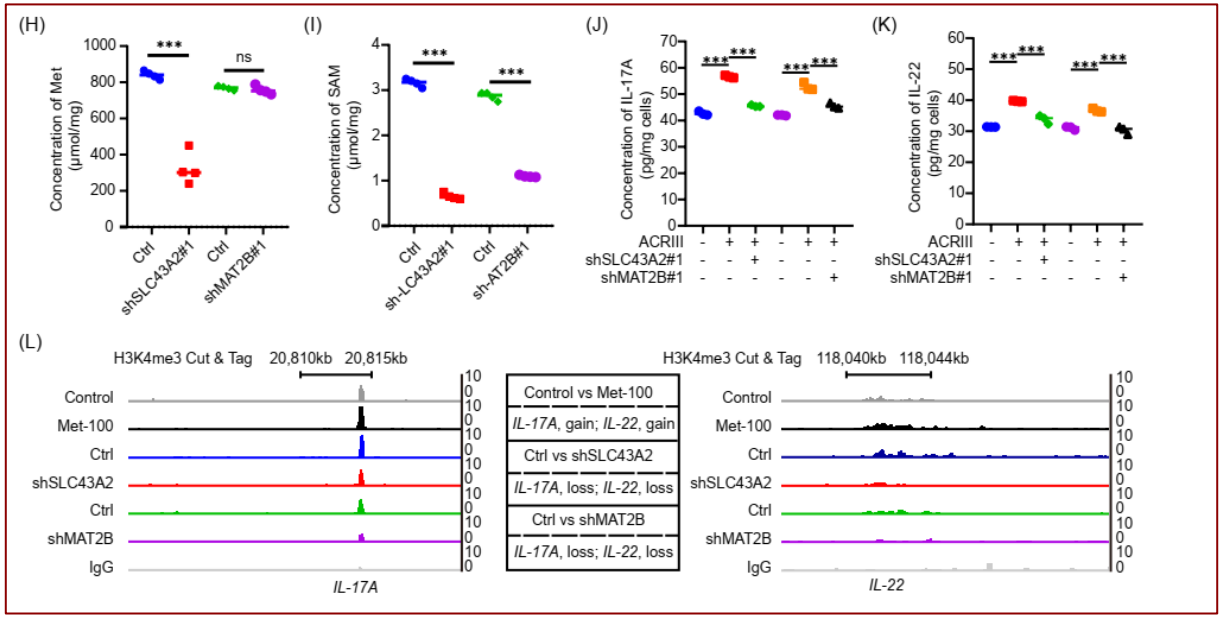
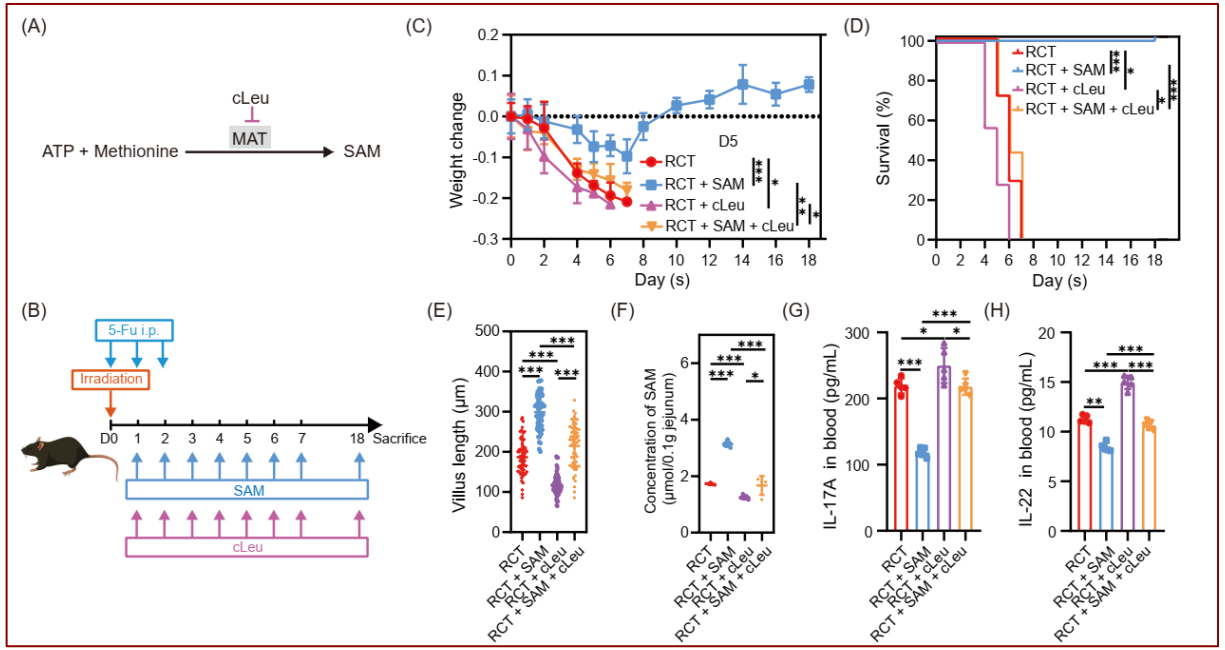


Figure 6. Methionine increases histone H3 lysine 4 trimethylation (H3K4me3) of *IL-17A* and *IL-22* in Lti cells and inhibits the release of proinflammatory cytokines.

- DY801-derived methionine was taken up via SLC43A2 and converted to SAM by MAT2B, regulating Lti cells.
- This process increased H3K4me3 levels at the *IL-17A* and *IL-22* gene loci, directly suppressing their transcription and reducing cytokine secretion.

Increased methionine enhances SAM-mediated H3K4 trimethylation, inhibiting Lti cell activation and cytokine secretion



- The SAM-induced alleviation of ACRIII was reversed by cLeu treatment.
- Clinical samples across three independent cohorts confirmed the association between low baseline fecal abundance of *Lactobacillus*, reduced blood levels of methionine and SAM, elevated IL-17A and IL-22, and the occurrence of ACRIII.

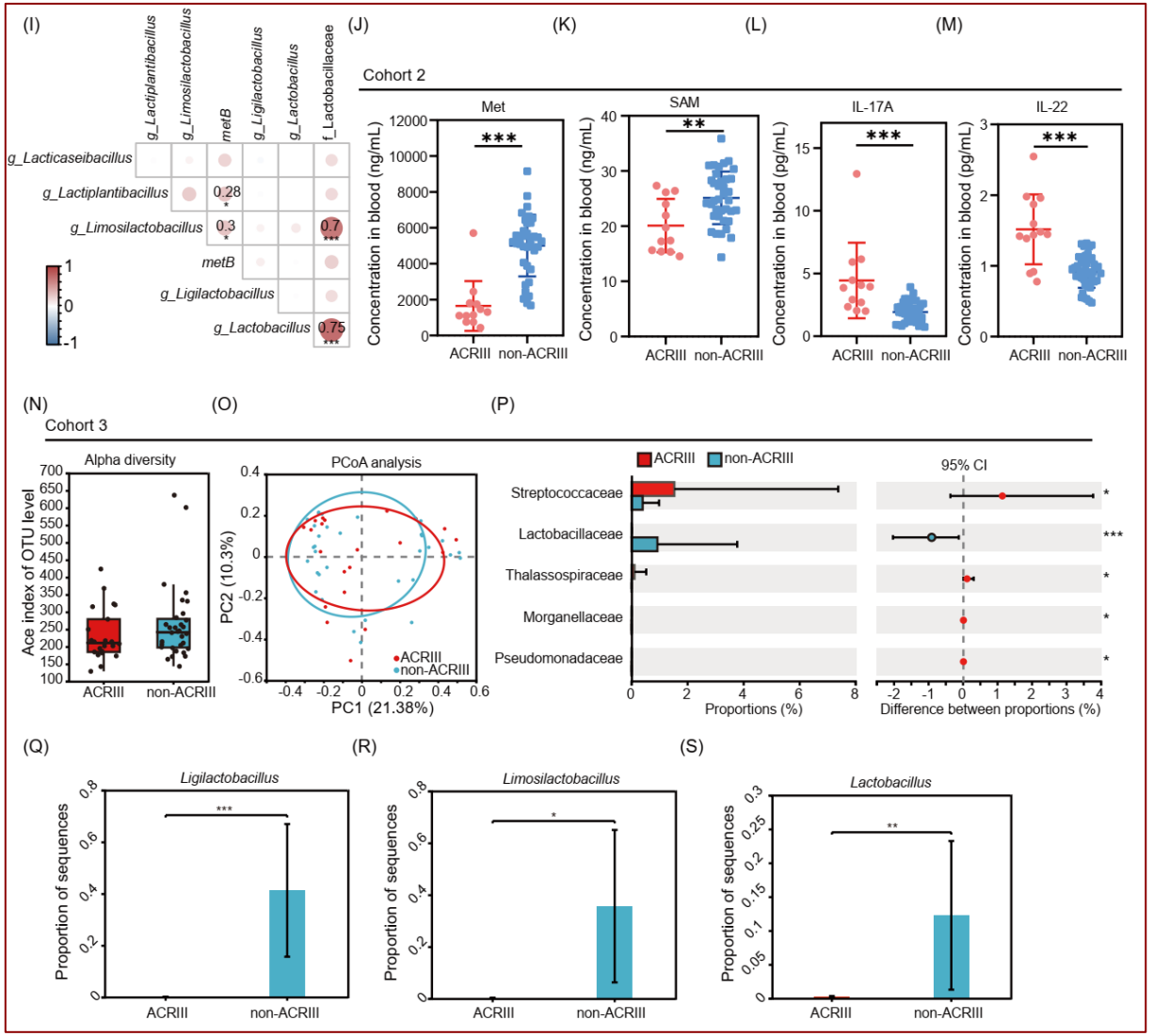


Figure 7. *In vivo* validation of methionine alleviates ACRIII.

Summary

- **Novel strains:** Ten novel *Lactobacillus* strains with stable genetics from exceptional responders patients were obtained, including three (*L. rhamnosus* DY801, *L. fermentum* CYQ09, and *L. salivarius* DY802) with outstanding ACRIII alleviation.

- **Novel mechanism:** *L. rhamnosus* DY801's *metB*-derived methionine triggers H3K4me3-mediated chromatin remodeling in Lti cells, suppressing IL-17A/IL-22 and improving ACRIII.

- **Novel strategy:** Eexceptional responders patient-derived probiotics offer a novel therapeutic approach against ACRIII.

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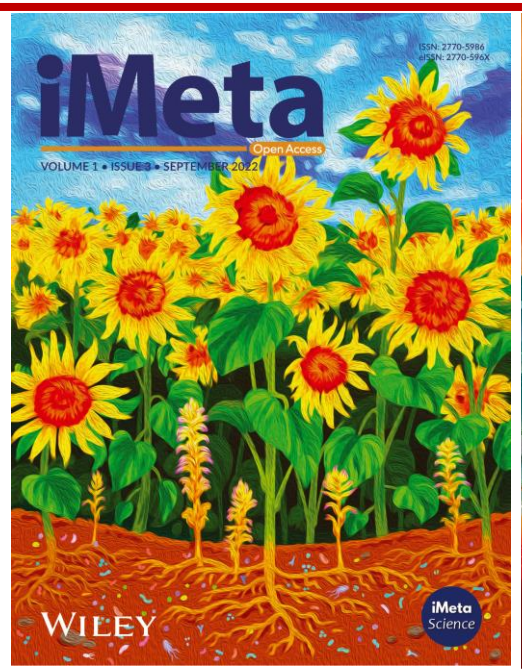

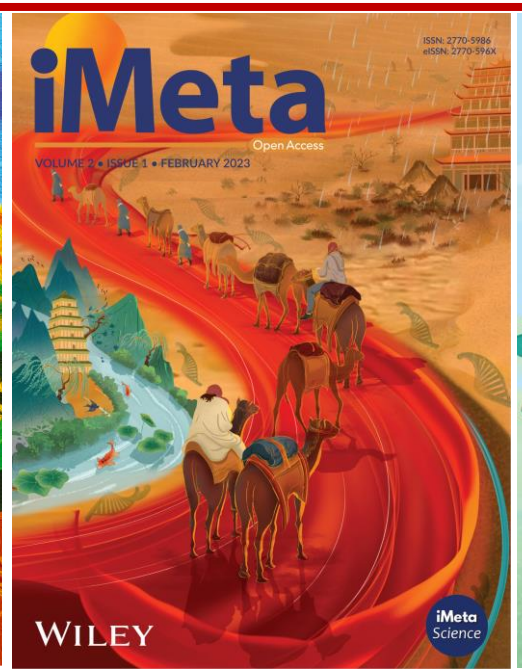

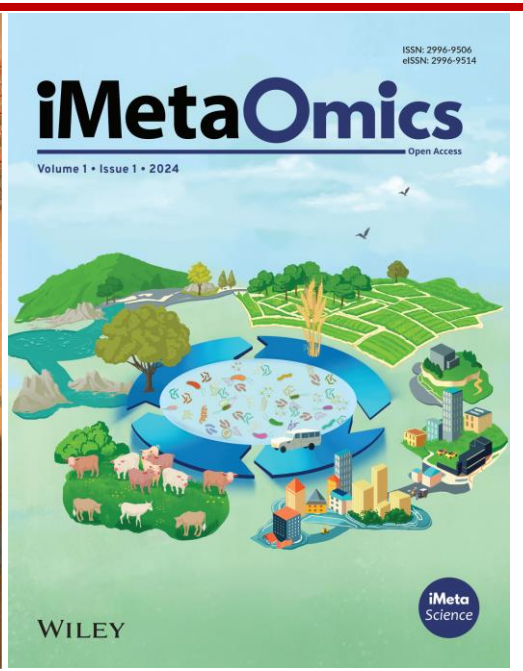

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