GENETICALLY ENGINEERED MICROBIOME AS A NEW TREATMENT OPTION FOR INFLAMMATORY BOWEL DISEASE

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Background: Inflammatory bowel disease (IBD), comprising Crohn's disease and ulcerative colitis, is a chronic, immune-mediated disorder characterized by relapsing intestinal inflammation. Its incidence continues to rise globally, including in developing countries. Current treatments such as corticosteroids and immunomodulators achieve remission in only about half of patients and cause severe side effects. Microbiome-based strategies are therefore gaining attention as safer and more targeted alternatives. The aim of this study is to develop and test a novel therapeutic approach using engineered *Kluyveromyces lactis* yeasts secreting CCL5/CCR5 axis antagonists to suppress intestinal inflammation in murine IBD models.

Materials and methods: Engineered *K. lactis* clones were generated through plasmid construction, genomic integration, and verified by Western blot for CCL5 antagonist expression and secretion. Acute colitis was induced in C57BL/6J mice using dextran sulfate sodium (DSS) or 2,4,6-trinitrobenzenesulfonic acid (TNBS). Chronic colitis was induced using DSS. After induction of IBD, mice received either antagonist-expressing yeast, wild-type yeast, or no additional treatment. Colon length, body weight dynamics, and inflammatory markers (IL-17RA, CCR5) were analyzed to evaluate the level of inflammation.

Results: Engineered *K. lactis* strains successfully expressed CCL5 antagonists. In DSS- induced acute colitis, mice treated with antagonist-expressing strain showed improved weight recovery and statistically significant, reduced IL-17RA and CCR5 markers compared to controls. Preliminary data in TNBS models indicated milder effects, reflecting model-specific immune responses. In chronic DSS colitis, the group treated with CCL5 antagonist-expressing

K. lactis preserved colon length and mitigated weight loss more effectively than the group receiving wild-type yeast or no yeast. However, results remain preliminary due to limited sample size.

Conclusion: Engineered *K. lactis* secreting CCL5 antagonists show potential to ameliorate colitis in murine models, supporting microbiome-based therapeutics as a promising avenue for IBD treatment. Larger studies are needed to validate efficacy and safety.

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Key words: Inflammatory bowel disease, microbiome, CCL5 antagonist, *Kluyveromyces lactis*, colitis

References

1. Alatab, S., et al. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: A systematic analysis for the global burden of disease study 2017. *Lancet Gastroenterol. Hepatol.* **5**, 17–30 (2020).

2. Qu, F.F., et al. The CCL5/CCR5 axis in ulcerative colitis. *Cell. Immunol.* 407, 104891 (2025). Mencarelli, A., et al. Highly specific blockade of CCR5 inhibits leukocyte trafficking and reduces mucosal inflammation in murine colitis, *Sci. Rep.* 6, 30802 (2016).

3. Mukanova, S., et al. Role of periostin in inflammatory bowel disease and synergistic effects mediated by CCL5–CCR5 axis. *Front. Immunol*. 13, 956691 (2022).