Exploring Microbiota-Immune Interactions in Short Bowel Syndrome and Crohn's Disease in a model of human microbiota associated mice

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Background and aim. Short bowel syndrome (SBS) is a malabsorptive condition mostly caused by massive surgical resection of the small intestine and is associated with significant morbidity and mortality, reduced quality of life, and high healthcare costs[1]. Crohn's disease (CD) represents a potential cause leading to an increased risk of SBS with considerable clinical consequences[2]. Human microbiota-associated (HMA) mice represent a model to establish human fecal microbiota in preclinical models[3-4]. Here, for the first time, we tried to conduct a "humanized" model of SBS, using faeces from patients affected by this disease. The aim of the current study is to determine the functional role of the gut microbiota of CD patients with or without SBS.

Methods. A dextran sodium sulphate model of colitis on C57BL/6 mice was employed to assess immune and metabolic signatures following faecal transplantation from patients affected by SBS/IF, CD with high or low risk for SBS/IF. Lymph node samples were collected to examine differences in T cell populations, and disease activity index and bronchoscopy were used to evaluate the activity of the disease.

Results. Fecal microbiota transplantation (FMT) from CD patient with a low risk of SBS/IF was associated with worse disease activity and endoscopic scores in colitis mice. Additionally, an increase in the percentages of Treg, Tnaive, Th1, and Th17 cells was observed in mice that received FMT from CD patient with a low risk of SBS/IF, compared to controls and those that received FMT from patient with SBS/IF or from CD patient with a high risk of SBS/IF.

Conclusion. Our data underscore the complex interactions between gut microbiota and host immunity and highlight the importance of careful donor selection in FMT applications, particularly for inflammatory conditions. Further research is warranted to characterize specific microbial and immunological factors that drive these effects and to identify microbiota profiles that could potentially confer therapeutic benefits.

References

1. *Massironi S, Cavalcoli F, Rausa E, Invernizzi P, Braga M, Vecchi M. Understanding short bowel syndrome: current status and future perspectives. Dig Liver Dis. 2020;52(3):253-261. doi:10.1016/j.dld.2019.11.013*
2. *Aksan A, Farrag K, Blumenstein I, Schröder O, Dignass AU, Stein J. Chronic intestinal failure and short bowel syndrome in Crohn's disease. World J Gastroenterol. 2021;27(24):3440-3465. doi: 10.3748/wjg.v27.i24.3440.*
3. *Staley C, Kaiser T, Beura LK, Hamilton MJ, Weingarden AR, Bobr A, Kang J, Masopust D, Sadowsky MJ, Khoruts A. Stable engraftment of human microbiota into mice with a single oral gavage following antibiotic conditioning. Microbiome. 2017;5(1):87. doi: 10.1186/s40168-017-0306-2.*
4. *Zhu Z, Kaiser T, Staley C. Antibiotic Conditioning and Single Gavage Allows Stable Engraftment of Human Microbiota in Mice. Methods Mol Biol. 2021;2327:281-291. doi: 10.1007/978-1-0716-1518-8_17.*