Farnesoid X receptor activation by the novel agonist TC-100 (3α, 7α, 11β-Trihydroxy-6α-ethyl-5β-cholan-24-oic Acid) preserves the intestinal barrier integrity and promotes intestinal microbial reshaping in a mouse model of obstructed bile acid flow

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Background:

Bile acids (BA) act as signaling hormones, via the farnesoid X receptor (FXR), and interact with gut microbiota (GM). Obstruction of bile flow leads to intestinal mucosal injury. The effect of the FXR agonist TC-100 on the mucosa and GM in a mouse model of obstructed bile flow was investigated.

Methods and Results:

Pharmacological FXR activation was accomplished by daily oral gavage with TC-100 for 5 days starting 2 days before bile duct ligation. BA measurement was carried out and the 16S rDNA (V5-V6 regions) extracted from the cecal content was sequenced. TC-100 activated FXR in the gut-liver axis, inducing a significant reduction of serum and bile BA pool size and preventing signs of intestinal mucosal damage. In terms of microbial signature, TC-100 shaped a different microbial population sustaining beneficial effects compared to control mice. Indeed, the species *Akkermansia muciniphila*, recognized for improving gut homeostasis and immune functions, resulted strongly associated to TC-100.

Conclusions and Significance:

These data show that, in the absence of bile flow, FXR activation by the novel agonist TC-100 prevents early signs of mucosal damage by modulating BA homeostasis and GM composition. The GM signature associated to BA profile emphasizes the importance of both components as co-metabolic assets in the same organism.

Keywords:

Bile acids, Gut microbiota, *Akkermansia muciniphila,* Intestinal Barrier Integrity, Gut-liver axis

References:

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Piancone E, Fosso B, Marzano M, De Robertis M, Notario E, Oranger A, Manzari C, Bruno S, Visci G, Defazio G, D'ErchiaAM, Filomena E, Maio D, Minelli M, Vergallo I, Minelli M, Pesole G (2022). Natural and after colon washing fecal samples: the two sides of the coin for investigating the human gut microbiome. SCIENTIFIC REPORT, ISSN: 1479-0378, doi: https://doi.org/10.1038/s41598-022-20888-z

Krieg C, Weber LM, Fosso B, Marzano M, Hardiman G, Olcina M, Domingo E, El Andy S, Mallah K, Robinson MD, Guglietta S (2022). Complement downregulation promotes an inflammatory signature that renders colorectal cancer susceptible to immunotherapy. JOURNAL FOR IMMUNOTHERAPY OF CANCER, ISSN: 2051-1426

Marzano, M.; Fosso, B.; Piancone, E.; Defazio, G.; Pesole, G.; De Robertis, M. Stem Cell Impairment at the Host-Microbiota Interface in Colorectal Cancer. Cancers 2021, 13, 996. https://doi.org/ 10.3390/cancers13050996

Serrano D., Pozzi C., Guglietta S., Fosso B., Suppa M., Gnagnarella P., Corso F., Bellerba F., Macis D., Aristarco V., Manghi P., Segata N., Trovato C., Zampino M.G., Marzano M., Bonanni B., Rescigno M., Gandini S. Microbiome as Mediator of Diet on Colorectal Cancer Risk: The Role of Vitamin D, Markers of Inflammation and Adipokines. Nutrients 2021; 13(2) 363; https://doi.org/10.3390/nu13020363

Thematic Area:

- Microbiome: from Research to Clinics

Infrastructures:

This project took advantage of the omics and computational facilities provided by the Italian Node of ELIXIR (ELIXIR-IT), the European Research Infrastructure for Life Science, including the advanced equipment acquired by the CNRBiOmics infrastructural project (PIR01_00017) for carrying sequencing and subsequent bioinformatics analysis.