ECCO Pioneer Award

GLYCANTALK: Glycans as the crosstalk between gut microbiome and immune response: mechanisms and potential therapeutic applications in Inflammatory Bowel Disease

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AIM OF THE RESEARCH

The goal of this proposal was to unlock the role of gut mucosa glycome as a novel pathway that regulates host–microbiome interactions in IBD.

METHODOLOGY THAT WAS USED IN THE RESEARCH

We started task 1 by using different glycoengineered mouse models as platforms to model specific changes in the gut mucosa glycome, aiming to investigate how the host glycocalyx composition affects gut microbiota and immune response.

Then, in task 2 and in collaboration with the Gastroenterology departments of Porto University Centre Hospital (a long-term collaborator of Pinho lab) and Saint Antoine Hospital, Paris (Sokol), a cohort of paraffin and fresh colonic biopsies from IBD patients (UC and CD, stratified into active versus inactive disease) and controls was used to test for a correlation between changes in host mucosa glycocalyx and the presence of dysbiosis associated with inflammation. Paraffin colonic samples, fresh/frozen colonic biopsies and frozen stools are readily available at both labs.

Finally, in task 3, a preclinical assay (in animal models from task 1) was conducted as the proof-of-principle for the therapeutic/preventive efficacy of metabolic supplementation with glycans in restoring a healthy microbiota and gut homeostasis in IBD.

MAIN FINDINGS/RESULTS OF THE RESEARCH

We revealed that alterations in the expression of complex branched N-glycans at the gut mucosa surface, modelled in glycoengineered mice, resulted in dysbiosis, with a deficiency in Firmicutes bacteria. Concomitantly, this mucosa N-glycan switch was associated with a downregulation of type 3 innate lymphoid cell (ILC3)-mediated immune response, leading to the transition of ILC3 towards an ILC1 proinflammatory phenotype and increased TNFα production. In addition, we demonstrated that the mucosa glycosylation remodelling through prophylactic supplementation with glycans at steady state was able to restore microbial-derived short-chain fatty acids and microbial sensing (by NOD2 expression) alongside the rescue of the expression of ILC3 module, suppressing intestinal inflammation and controlling disease onset. In a complementary approach, we further showed that IBD patients, often displaying dysbiosis, exhibited a tendency toward decreased MGAT5 expression at epithelial cells that was accompanied by reduced ILC3 expression in gut mucosa. Taken together, these results unlock the effects of alterations in mucosa glycome composition in the regulation of the bidirectional crosstalk between microbiota and gut immune response, revealing the host branched N-glycans/microbiota/ILC3 axis to be an essential pathway in gut homeostasis and in the prevention of transition from intestinal health to inflammation.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

Our results reveal host glycocalyx and specifically mucosa branched N-glycans to be master regulators at the frontier of microbiome and ILC3/ILC1-mediated immune response, bringing to light the power of glycosylation reprogramming of gut mucosa as a promising interventional strategy to prevent IBD onset, with clinical applications.

PLAN OF PUBLICATION

The results of this study were published in:
- Alterations in mucosa branched N-glycans lead to dysbiosis and downregulation of ILC3: a key driver of intestinal inflammation. Rodrigues CS, Gaifem J, Pereira MS, Alves MF, Silva M, Padrão N, Cavadas B, Moreira-Barbosa C, Alves I, Marcos-Pinto R, Torres J, Lavelle A, Colombel JF, Sokol H, Pinho SS.
Gut Microbes. 2025 Dec;17(1):2461210. doi: 10.1080/19490976.2025.2461210.
URL:

- T-cell branched glycosylation as a mediator of colitis-associated colorectal cancer progression: a potential new risk biomarker in inflammatory bowel disease.
Leite-Gomes E, Silva MC, Dias AM, Fernandes Â, Faria G, Nogueira R, Santos-Pereira B, Fernandes-Mendes H, Azevedo CM, Raposo J, López Portero J, de Alda Catalá T, Taxonera C, Lago P, Fernandez-Aceñero MJ, Rosa I, Marcos-Pinto R, Pinho SS.
J Crohns Colitis. 2025 Apr 4;19(4):jjaf043. doi: 10.1093/ecco-jcc/jjaf043.
PMID: 40087977

A review manuscript, based in part on these results is also planned.