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EDITORIAL

When Pathobiont-Carbohydrate Interaction Turns Bittersweet!

Inflammatory bowel diseases (IBDs) are characterized by an exacerbated immune response to the normally well-tolerated and beneficial intestinal microbiota. Etiologically, accumulating evidence demonstrate a central role played by select microbiota members in genetically predisposed individuals in driving chronic intestinal inflammation. Moreover, various dietary components, such as some food additives, artificial sweeteners, and purified soluble fibers, are now suspected to play a role in these chronic diseases through their detrimental impact on the intestinal microbiota.[1,2] However, the exact mechanisms beyond diet-induced alterations in microbial homeostasis remain largely unknown and correlative, mostly owing to the complexity of these interactions. In an elegant new study led by Fan et al,[3] highly trackable gnotobiotic approaches were used in order to study the role played by *Enterococcus faecalis* glucosamine metabolism in chronic intestinal inflammation.

In this study aiming to understand mechanism by which select microbiota members can drive chronic intestinal inflammation, the authors decided to use a simplified but highly relevant gnotobiotic model. Indeed, mice genetically prone to develop chronic intestinal inflammation ($IL10^{-/-}$) were colonized with a consortium of 8 nonpathogenic bacteria representing the 4 major phyla present in the human intestine and with high relevance to the IBD pathophysiology, with for example the presence of *Escherichia coli* and *Faecalibacterium prausnitzii*, suspected to play detrimental and beneficial roles in IBD, respectively.[4,5] Interestingly, while alterations in microbiota composition between wild-type (WT) and $IL10^{-/-}$ were modest in this gnotobiotic model, pretty dramatic alterations in the metatranscriptome were observed, as revealed through massive sequencing of bacterial messenger RNAs. Such alterations were not driven by all members of the consortium, with for example *E. coli*, *F. prausnitzii*, and *Bifidobacterium longum* harboring no significantly differentially expressed genes between genotypes, while *E. faecalis* presented 10% of its genes with an altered expression in $IL10^{-/-}$ mice compared with WT. Importantly, $IL10^{-/-}$ mice colonized with the consortium lacking *E. faecalis* demonstrated that this bacterium not only harbors an altered transcriptomic profile, but is also required to promote intestinal inflammation in $IL10^{-/-}$ mice. Interestingly, bacteria belonging to the *Enterococcus* genus are frequently observed within the ileal mucosa of IBD patients (unpublished data), and it will be of interest to evaluate the level of glucosamine metabolism in *Enterococcus*-colonized patients, as well as to which extent these parameters correlate with disease activity.

The authors next identified that among the genes significantly upregulated by *E. faecalis* during colitis, 7 belong to an operon predicted to encode for a phosphotransferase system (PTS), used by various bacteria to import and phosphorylate extracellular carbohydrates.[6] Through *in vitro* approaches, this operon was observed to encode for an import system for the monosaccharide glucosamine. Next, going back to their in vivo models, the authors observed an increased concentration of glucosamine in the gastrointestinal tract of $IL10^{-/-}$ mice compared with WT mice. While this observation remains mechanistically unknown, it however perfectly aligned with *E. faecalis* increasing the expression of its PTS-glucosamine system in order to benefit from such high glucosamine environment during intestinal inflammation. Even more importantly, using an isogenic mutant, the PTS-glucosamine system was found to be required for *E. faecalis*–induced intestinal inflammation. Hence, not only does *E. faecalis* benefit from an inflamed environment through its PTS-glucosamine system, but it also promotes chronic inflammation in a PTS-glucosamine-dependent mechanism! While the exact mechanism beyond the later remains to be elucidated, it nonetheless suggests that select carbohydrates can initiate vicious cycles within the intestine, with select microbiota members—such as *E. faecalis*—both benefiting from and nourishing chronic intestinal inflammation. Measuring glucosamine concentration in the gastrointestinal tract of IBD patients according to their *Enterococcus* colonization level or their disease activity appears as an important next step in order to investigate the potential of this metabolic pathway to be modulated through innovative therapeutics. It importantly appears that such approach will need to be cautiously envisioned in preselected or prestratified patients, as glucosamine also appears to be beneficial in other pathological conditions patients,[7] suggesting that targeted approach in patients harboring glucosamide-stimulated *E. faecalis* strains with pathogenic potential will need to be developed.

To conclude, the authors demonstrated here that *Enterococcus faecalis* is proinflammatory in $IL10^{-/-}$ mice and upregulates a phosphotransferase system important for glucosamine uptake. Mechanistically, such operon is needed for *Enterococcus faecalis* promotion of colitis in a way that implicates other microbiota members.[3] These results perfectly highlight the importance of intestinal symbiosis in order to avoid chronic inflammation, as well as that the intestinal microbiota should always be studied from an ecosystem point of view instead of focusing on select bacterial species whose relative abundance correlates with inflammatory level. Moreover, this study further highlights that investigating intestinal microbiota through 16S or metagenomic approaches can fail in identifying members playing a role in an inflammatory phenotype, as it would have been the case in this recent work by Fan et al, while the use of metatranscriptomic approach was key in identifying

mechanism beyond *E. faecalis*–mediated promotion of intestinal inflammation.[3]

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References

1. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, Israeli D, Zmora N, Gilad S, Weinberger A, Kuperman Y, Harmelin A, Kolodkin-Gal I, Shapiro H, Halpern Z, Segal E, Elinav E. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature 2014;514:181–186.
2. Chassaing B, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE, Gewirtz AT. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. Nature 2015;519:92–96.
3. Fan T-J, Goeser L, Lu K, Faith JJ, Hansen JJ. *Enterococcus faecalis* glucosamine metabolism exacerbates experimental colitis. Cell Mol Gastroenterol Hepatol 2021;12:1373–1389.
4. Chervy M, Barnich N, Denizot J. Adherent-Invasive E. coli: Update on the Lifestyle of a troublemaker in Crohn's disease. Int J Mol Sci 2020;21:3734.
5. Cao Y, Shen J, Ran ZH. Association between Faecalibacterium prausnitzii reduction and inflammatory bowel disease: a meta-analysis and systematic review of the literature. Gastroenterol Res Pract 2014;2014:872725.
6. Deutscher J, Ake FM, Derkaoui M, Zebre AC, Cao TN, Bouraoui H, Kentache T, Mokhtari A, Milohanic E, Joyet P. The bacterial phosphoenolpyruvate:carbohydrate phosphotransferase system: regulation by protein phosphorylation and phosphorylation-dependent protein-protein interactions. Microbiol Mol Biol Rev 2014;78:231–256.
7. Yuan X, Zheng J, Ren L, Jiao S, Feng C, Du Y, Liu H. Glucosamine ameliorates symptoms of high-fat diet-fed mice by reversing imbalanced gut microbiota. Front Pharmacol 2021;12:694107.

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