Mucosal microbiota modulate host intestinal immune signatures in Inflammatory Bowel Disease

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Published in:
Journal of Crohn's and Colitis

DOI:
10.1093/ecco-jcc/jjab232.215

Publication date:
2022

Figure 1a

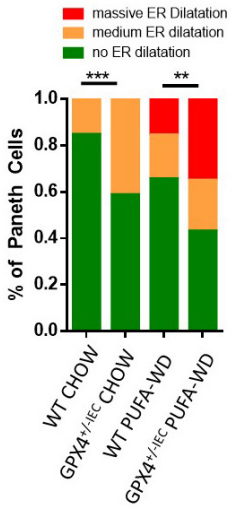


Figure 1b

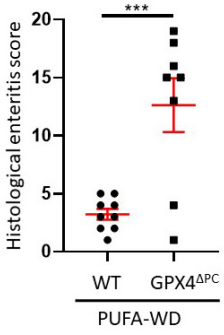
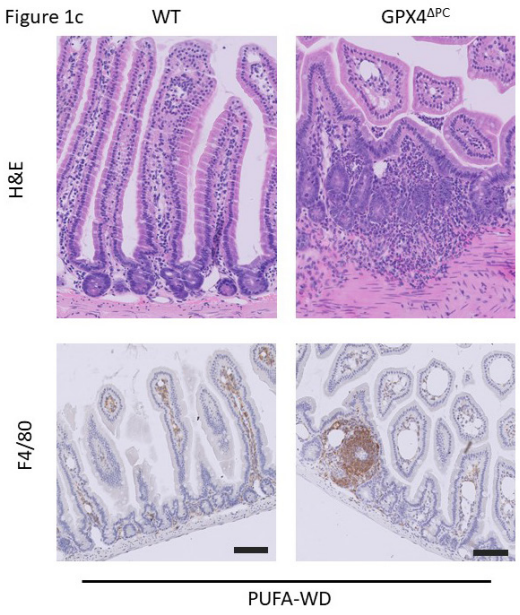


Figure 1c



enriched with PUFAs for 12 weeks. Intestinal inflammation was assessed by histology and immunohistochemistry. Further we analyzed small intestinal whole tissue cultures and evaluated cytokine production by ELISA.

Results: Paneth cells of mice lacking one allele of *Gpx4* showed morphological signs of ER-stress at baseline and after exposure to a PUFA-WD for 12 weeks when compared to WT mice (Fig 1a). Based on these results, we dissected a role for PC in GPX4-restricted gut inflammation. When fed a PUFA WD for 12 weeks GPX4$^{\Delta PC}$ mice developed a CD like enteritis while WT controls did not (Fig 1b). A WD did not induce this inflammatory response in GPX4$^{\Delta PC}$ or WT mice. The infiltrating leukocytes contained mainly neutrophils and macrophages (indicated by positive F4/80 staining, Fib 1c). Whole tissue cultures derived from GPX4$^{\Delta PC}$ mice fed a PUFA WD produced more Interleukin-6 and CXCL-1, the murine homologue of the human Interleukin-8, compared to whole tissue cultures derived from WT mice fed the same diet (Fig 2).

Figure 2

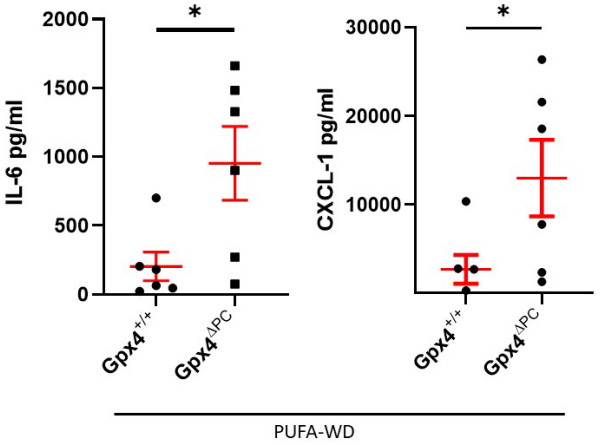


Figure legend 1a) % of PC showing massive, medium or no ER dilatation 1b&c) enteritis score and representative H&E and F4/80 staining 2) IL-6 and CXCL-1 in supernatant of whole tissue jejunal samples

Conclusion: The presented data identify Paneth cells to be crucially involved in the development of PUFA induced enteritis in genetically susceptible hosts.

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Mucosal microbiota modulate host intestinal immune signatures in Inflammatory Bowel Disease

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Background: Host intestinal immune gene signatures and microbial dysregulations expose potential mechanisms in the pathogenesis of inflammatory bowel diseases (IBD). Profiling of mucosa-attached microbiota allows the understanding of locally present microbial communities and their immediate impact on the host. This study evaluated interactions between host mucosal gene expression and intestinal mucosa-attached microbiota in IBD.

Methods: Intestinal mucosal bulk RNA-sequencing data was combined with mucosal 16S rRNA gene sequencing data from 696 intestinal biopsies derived from 337 patients with IBD (181 with Crohn's disease [CD] and 156 with ulcerative colitis [UC]) and 16 non-IBD controls. Hierarchical all-against-all associations testing (HAllA) was used to assess factors affecting host gene expressions and microbiota. Mucosal cell enrichments were predicted by deconvolution. Linear mixed interaction models were used to investigate host-microbiota interactions, adjusting for age, sex, BMI and batch effects. Variation explanation analysis was performed by Lasso regression.

Results: In total, 15,934 intestinal genes and 113 microbial taxa were identified and included in subsequent analyses. Host intestinal gene expressions were characterized by tissue- and inflammation-specificity, whereas intraindividual variability of the mucosal microbiota dominated over disease location and inflammation effects. We observed forty associations between the mucosal expression of genes and the abundance of specific microbes independent of dysbiosis (FDR<0.05). Examples include a positive association between aryl hydrocarbon receptor (*AHR*) and *Bifidobacterium*, and a negative association between interleukin 18 receptor 1 (*IL18R1*) and *Lachnoclostridium*. Furthermore, 112 gene-microbiota interactions changed in patients with microbial dysbiosis compared to non-dysbiosis (FDR<0.05). These interactions were enriched in immune-related and extracellular matrix organization pathways. For example, the *IL1R1* gene was positively associated with *Collinsella* abundance in non-dysbiotic patients, whereas an inverse association was observed in high dysbiosis. Finally, the presence of mucosal microbial taxa explained up to 10% of the variation in cell type enrichment, affecting epithelial cells, macrophages and regulatory T-cells.
Conclusion: Interactions between host intestinal gene expressions and mucosa-attached microbiota are disrupted in patients with IBD. Furthermore, mucosal microbiota are highly personalized and potentially contribute to intestinal cell type alterations. Our study unravels key immune-mediated molecular pathways and relevant bacteria in intestinal tissue, which may guide drug development and precision medicine in IBD.

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Communicating Needs and Features of IBD Experiences (CONFIDE) Survey: Impact of Ulcerative Colitis Symptoms on Daily Life

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Background: Bowel urgency is the symptom described by patients as having the most impact on quality of life but is missing from most disease activity indices (Carpio et al., 2016). The Communicating Needs and Features of IBD Experiences (CONFIDE) study aims to increase understanding of patients' experiences and the impact of IBD on their lives in the United States (US), Europe, and Japan. These data focus on US patients with moderately-to-severely active ulcerative colitis (UC).
Methods: An online, quantitative, cross-sectional survey was conducted with patients with moderately-to-severely active UC in the US in July 2021. Data included patient perspectives on their UC symptoms and the impact on their social life, work/school life, and ability to participate in sports/physical activities. Moderately-to-severely active UC was defined based on treatment, steroid use, and/or hospitalization history. Descriptive statistics (frequencies, percentages) summarise the data.
Results: 200 (of 756 total contacted) patients (61.5% male, mean age 40.4, mean disease duration 7.9 years) completed the survey in the US, with 77% (n=153) of patients receiving advanced therapies (biologic or novel oral therapy). Patients declined participation in social events due to bowel urgency (43%), fear of urge incontinence (40%), increased stool frequency (29%), and blood in stool (15%) in the last three months (Fig. 1). Patients declined participation in sports/physical exercise due to bowel urgency (38%), fear of urge incontinence (36%), increased stool frequency (24%), and blood in stool (10%) in the last three months (Fig. 2). Patients declined participation in work/school due to bowel urgency (37%), fear of urge incontinence (42%), increased stool frequency (25%), and blood in stool (16%) in the last three months (Fig. 3). Out of 123 patients who have ever suffered from bowel urgency, in the last three months 42% stopped working for the day sooner than planned and 41% worked fewer hours. Notably, 76% of patients reported wearing a diaper/pad/protection at least once in the last three months due to fear of urge incontinence. Bowel urgency had no impact on work/school for 22% (n=27) of patients who had ever experienced bowel urgency (Fig. 4).

Figure 1. Participation in social events declined due to UC symptoms in the last three months (% of patients).

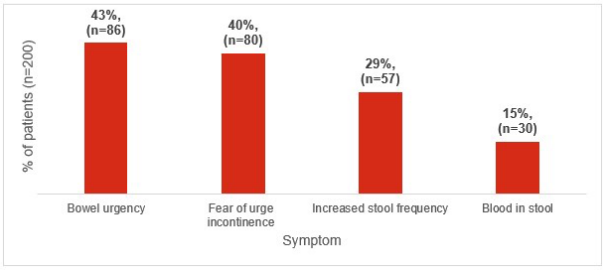


Figure 2. Participation in sports/physical exercise declined due to UC symptoms in the last three months (% of patients).

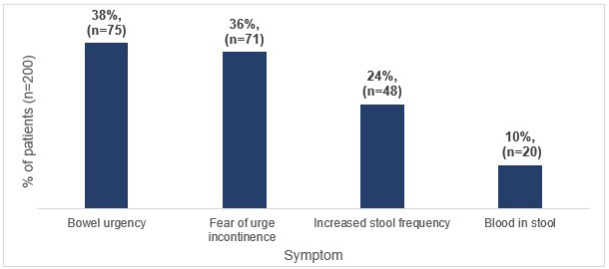


Figure 3. Participation in work/school declined due to UC symptoms in the last three months (% of patients).

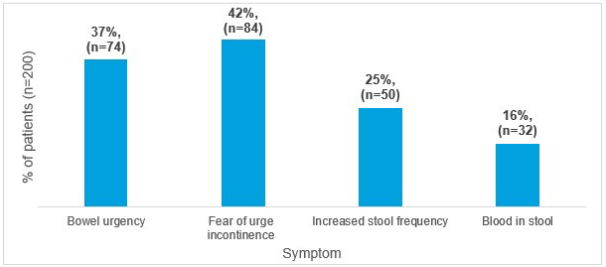
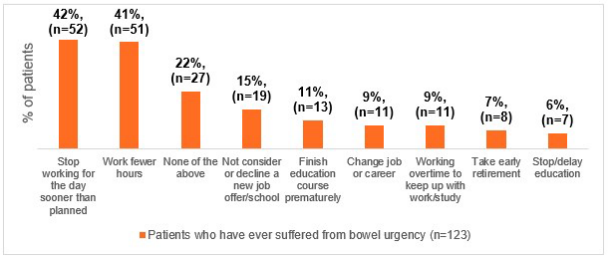


Figure 4. Consequences of bowel urgency on work/school of patients with UC (% of patients who have ever suffered from bowel urgency).



Conclusion: Bowel urgency and fear of urge incontinence are the most reported symptoms leading to patients with UC declining participation in work/school, social events, and sports/physical exercise. Over three quarters of the surveyed patients reported wearing diapers/pads/protection in the past three months due to fear of urge incontinence and only 22% of patients who had ever suffered from bowel urgency reported that it had no impact on work or school.