Discussion: Patients with UC and response to therapy had a significantly different pre-treatment microbiome and methylation of genes related to intestinal barrier function, including BAG4/LNTI. Larger studies will be needed to validate these findings, but these results suggest the microbiome and DNA methylation changes may be effective biomarkers of response to therapy and warrant further study.

8

ROLE OF THE HOST IMMUNE RESPONSE TO ENTERIC PROKARYOTIC VIRUSES IN INFLAMMATORY BOWEL DISEASE
Julia Angkiew, Daniel Monaco, Scott Handley, H.B. Larman
Background: Gut microbiota comprise important environmental exposures that influence human immune systems and may alter the clinical course of inflammatory bowel disease (IBD). Little is known about the role of gut bacteriophages (viral components that infect prokaryotic bacteria) and their interactions with the host’s immune responses. We tested the hypothesis that (1) immune responses of individuals with IBD to phages differ from those without IBD and (2) immune responses to phages are associated with disease type (i.e. those with Crohn’s disease have different responses than those with ulcerative colitis).
Methods: We have constructed the first bacteriophage peptidome library (“phageome”), based on sequencing of environmental phages and large-scale metagenomic sequencing of virus-like particles isolated from stool samples from IBD patients and their non-IBD household contacts. Using Phage ImmunoPrecipitation Sequencing (PhIP-Seq) technology, we generated complete serum antibody binding profiles of 48 IBD patients (16 ulcerative colitis, 11 Crohn’s, and 11 indeterminate), 9 of their non-IBD household contacts, and an independent non-IBD cohort of 674 volunteers collected by the Vaccine Research Center (VRC) at the National Institutes of Health. Antibody binding profiles were compared among groups using nonparametric statistics.
Results: IBD patients as a group had lower antibody responses to specific phages compared to both non-IBD household contacts and the non-IBD VRC controls; this difference was significant and remained after control for unequal sample sizes (Figure 1). Patients with Crohn’s disease compared to those with ulcerative colitis had similar antibody responses. Particularly for phages of the genera Philfelvirus, the immune responses of Crohn’s patients were significantly reduced compared to their non-IBD household contacts, while the immune responses of patients with ulcerative colitis did not significantly differ from non-IBD household contacts (Figure 2). IBD disease type comparisons to the VRC controls yielded similar results. Conclusion: PhIP-Seq with a phageome library can be used to study the relationship between immune responses and gut bacteriophages in IBD. Our results suggest that IBD patients may have lower antibody responses to specific phages compared to non-IBD individuals. Differential antibody reactivities in Crohn’s disease vs. ulcerative colitis compared to their household contacts and VRC controls suggest disease-specific response to the gut phageome that warrant further study.

Figure 1. Violin plots showing antibody enrichments (hits) to four phage genera for each individual in the healthy control (VRC) cohort (n=674) compared to enrichments for each individual in the IBD cohort (n=48). Hits to these four phage genera showed the most statistically significant differences in immune responses between the VRC and IBD cohorts. Mann-Whitney statistics used for comparisons.

Figure 2. Violin plots showing antibody enrichments (hits) to three phage genera for each individual with Crohn’s disease (n=11) compared to each individual with ulcerative colitis (n=16) and each non-IBD household control (n=9). Hits to these three genera showed the most statistically significant differences in immune responses between these three cohorts. Kruskal-Wallis and Mann-Whitney statistics used for comparisons. * denotes p ≤ 0.05, while ** denotes p ≤ 0.01.

10

THE ROLE OF DIETARY L-SERINE IN THE REGULATION OF INTESTINAL MUCUS BARRIER DURING INFLAMMATION
Kohel Sugihara, Nobuhiko Kamada
Background: Recent accumulating evidence suggests that amino acids have crucial roles in the maintenance of intestinal homeostasis. In inflammatory bowel disease (IBD), amino acid metabolism is changed in both host and the gut microbiota. Among amino acids, L-serine plays a central role in several metabolic processes that are essential for the growth and survival of both mammalian and bacterial cells. However, the role of L-serine in intestinal homeostasis and IBD remains incompletely understood. In this study, we investigated the effect of dietary L-serine on intestinal inflammation in a murine model of colitis.
Methods: Specific pathogen-free (SPF) mice were fed either a control diet (amino acid-based diet) or an L-serine-deficient diet (SDD). Colitis was induced by the treatment of dextran sodium sulfate (DSS). The gut microbiome was analyzed by 16S rRNA sequencing. We also evaluated the effect of dietary L-serine in germ-free mice and gnotobiotic mice that were colonized by a consortium of non-mucolytic bacterial strains or the consortium plus mucolytic bacterial strains.
Results: We found that the SDD exacerbated experimental colitis in SPF mice. However, the severity of colitis in SDD-fed mice was comparable to control diet-fed mice in germ-free condition, suggesting that the gut microbiota is required for exacerbation of colitis caused by the restriction of dietary L-serine. The gut microbiome analysis revealed that dietary L-serine restriction fosters the blooms of a mucus-degrading bacterium Akkermansia muciniphila and adherent-invasive Escherichia coli in the inflamed gut. Consistent with the expansion of mucolytic bacteria, SDD-fed mice showed a loss of the intestinal mucus layer. Dysfunction of the mucus barrier resulted in increased intestinal permeability, thereby leading to bacterial translocation to the intestinal mucosa, which subsequently increased the severity of colitis. The increased intestinal permeability and subsequent bacterial translocation were observed in SDD-fed gnotobiotic mice that colonized by mucolytic bacteria. In contrast, dietary L-serine restriction did not alter intestinal barrier integrity in gnotobiotic mice that colonized only by non-mucolytic bacteria.
Conclusion: Our results suggest that dietary L-serine regulates the integrity of the mucosal mucous barrier during inflammation by limiting the expansion of mucolytic bacteria.