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THE ENTERIC VIROME IN INFLAMMATORY BOWEL DISEASE

Norman JM, Handley SA, Baldridge MT, et al. Disease-specific alterations in the enteric virome in inflammatory bowel disease. Cell 2015;160:447–460.

The etiology of inflammatory bowel disease (IBD) is owing to a complex interplay between environmental factors and genetics. Environmental factors implicated include cigarette smoking, antibiotics use in childhood, and dysbiosis of the bacterial microbiome, which have been documented in cigarette smoking, antibiotics use in childhood, and dysbiosis owing to a complex interplay between environmental factors.

This study undertook metagenomics sequencing of stool filtrates from 18 Crohn’s disease (CD) patients, 42 ulcerative colitis (UC) patients, and 12 household controls from 3 geographically disparate sites including Cambridge UK, Los Angeles, and Chicago. They obtained 32,591 sequences and assigned these to either host or bacterial populations. Consistent with current literature, the most abundant viral sequences were for Caudovirales and Microviridae taxa, which in the UC cohort in the UK had a statistically significant inverse correlation with each other (P = .0033), less so in the Los Angeles UC cohort (P = .02), and not observed in the Chicago cohort.

In the second stage of the study, the authors purified virus-like particles from the feces of 17 UK households with IBD patients and healthy cohabitees. The samples were collected both at times of flare (n = 24) and inactive disease (n = 28) contributed by 36 UC and 16 CD patients together with 21 household control samples. The sequences from the virus-like particles that were obtained were mapped to a custom virus protein database, a technique that aims to identify the virus taxonomy from the sequences. Using this database, the authors were able to assign 15% of the sequences to viral taxa.

The authors highlighted an increase in richness (number of taxa per sample) of Caudovirales in CD (n = 16) patient samples and to a lesser extent in the UC (n = 36) patient samples compared with household controls. Although the individual subgroups of viruses within Caudovirales were different between UC and CD samples, the authors were able to show that 5 specific subtypes of Caudovirales were associated with disease, these were Lactococcus, Lactobacillus, Enterococcus, Clostridium, and Strepotococcus bacteriophages.

The documented increase in bacteriophage richness in IBD was associated with a parallel change in bacterial diversity highlighted using 16sRNA gene sequencing on fecal samples. Eighteen bacterial taxa were associated significantly with disease or disease activity. Consistent with the current literature the majority of operational taxonomic units were from the Bacteroidetes and Firmicutes phyla. An inverse relationship was observed in CD samples between Caudovirales diversity and bacterial richness (number) and diversity (type). More specifically, using the Spearman correlation Bacteriodaceae bacterial families were correlated inversely with several Caudovirales taxa in CD, but Caudovirales were positively correlated with Enterobacteriaceae, Pasteurellaceae, and Prevotellaceae in CD. These correlations were not present in UC samples.

To confirm this was not a finding specific to Cambridge, UK, 2 validation cohorts were used from Chicago (18 UC, 7 CD, 23 healthy matched control), and Boston (11 UC, 14 CD, and 10 healthy matched controls). Although there was a significant expansion of Caudovirales across the validation cohorts, the specific relationship between distinct members of the Caudovirale taxa and disease varied between the cohorts. The authors were unable to identify specific bacterial taxa as being associated with disease, and therefore the bacteriophage–bacteria correlation was not validated.

The authors concluded that disease-specific changes in the enteric virome occur in both UC and CD, with the primary change being an expansion of the richness of Caudovirales bacteriophages. They speculate on the role of the bacteriophages in IBD as to whether during the normal lifecycle of a bacteriophage, the lysis of bacteria would lead to the release of pathogen-associated molecular patterns that trigger inflammatory cascades, or whether the bacteriophages are inducing a humoral immune response in the host.
They also speculate as to whether the bacterial microbiome changes are secondary to changes in temperate bacteriophages or the introduction of new bacteriophages from diet or through human or animal contact.

Comment. This landmark study indicates that the intestinal virome, specifically in bacteriophages, is enriched in IBD and that there is a positive correlation between bacteriophage enrichment and disease activity. Bacteriophages are one of the most common and abundant biological entities on Earth whose genomes are largely unannotated despite advances in viral metagenomics (Nat Rev Microbiol 2005;3:504–510; Curr Opin Virol 2012:2;63–77).

Bacteriophages are viruses that are specific to the bacteria on whom they predate and they are thought to play a crucial role in maintaining the microbial balance in every ecosystem including the human intestine (Nat Rev Microbiol 2011;9:254–264). These viruses have been implicated in enteric human disease including induction of hemolytic uremic syndrome from Shiga toxin–producing Escherichia coli (Microbiology 2015;161:451–462). The ability of bacteriophages to integrate their genome into their host allows for horizontal transfer of genetic material within the microbiota as well as potentially changing the pathogenicity of commensal flora.

This study relied on metagenomics, a research technique that uses the ability to extract genomic DNA and identify the sequence regardless of source. It allows identification of the genomic diversity within the environment in question without the need for culture of the organisms under study. However, metagenomics has a number of drawbacks at its current stage of development. Analysis of the sequence outputs is highly dependent on accurately annotated databases to identify the taxa from the DNA sequences; otherwise, attrition bias is introduced as seen with this study with only 15% of reads being able to be assigned taxonomy. This metagenomics method has recently been brought into question by the identification of a highly abundant and geographically conserved bacteriophage present in human fecal samples, named CrAssphage, that was identified from the unknown sequences that are largely ignored when examining read sequences against a current ‘known’ databases (Nature Comms 2014;5:4498).

Another potential pitfall of metagenomics used in this study is that RNA viruses are not identified and yet RNA viruses such as norovirus and astrovirus have been suggested as potential precipitators or triggers of intestinal inflammation (J Pediatr Gastroenterol Nutr 2009;48:328–333; Inflamm Bowel Dis 2013;19:124–131; J Med Virol 2012;84:345–347). In should be noted that this study identified 1 eukaryotic virus (annelovirus) via metagenomics, but it was only detected in a proportion of patients and did not correlate with disease activity. A further goal for future studies should include RNA viruses, particularly those introduced from diet and the environment to fully evaluate their role in IBD disease pathogenesis. It is also worth noting that enveloped viruses (eg, coronavirus or human immunodeficiency virus) are not measured by this metagenomics approach thus their potential roles in IBD cannot be assessed.

One of the difficulties in examining the virome is controlling for the impact that changes in geographical regions, diet, gender, and medications have on the virome. This article is among the first to use household controls on the premise that these environmental confounders are controlled for. The importance of this was brought into focus when comparing the household-controlled Cambridge cohort Microvirales and Caudovirales abundance results ($P =$ .0033), to the matched controls from the Chicago cohorts, where significance was lost.

This study identified that bacterial dysbiosis (in terms of diversity) was inversely related to bacteriophage diversity. Further studies are needed to identify which comes first—whether bacterial dysbiosis promotes changes in the virome, or whether virome fluxes in a stress environment lead to changes in bacterial diversity, and indeed what role this had in the induction or perpetuation of intestinal inflammation.

Clearly, this article has opened a new area of research for IBD. From an IBD diagnosis and therapeutics perspective, it is interesting to speculate on the role of the virome, especially in the era of fecal transplantation where the donor virome may have as big a role to play in the success of the transplantation as the rest of the microbiome. Other interesting possibilities include being able to differentiate between a UC and CD diagnosis in that grey hinterland of “indeterminate colitis” using a patients virome. The role of the virome in IBD causality remains unclear, but this study comes as a timely reminder of the potential role of virus in the initiation of IBD and subsequent relapse and also reminds the clinician of the possible importance of viruses in the complications of immunosuppressive therapy and new bacterial-based therapies.

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TARGETING SMAD7 IN CROHN’S DISEASE BY MONGERSEN: THERAPEUTIC REVOLUTION UNDER WAY?

Monteleone G, Neurath MF, Ardizzone S, et al. Mongersen, an oral SMAD7 antisense oligonucleotide, and Crohn’s disease. N Engl J Med 2015;372:1104–1113.

The efficacy of currently available drugs for the treatment of Crohn’s disease remains suboptimal. Novel drugs targeting the major inflammatory pathways involved in