

## **Distinguishing immunomodulatory capacity of the enteric virome in healthy and diseased intestine**

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Although the microbiome has been established as an important regulator of homeostasis, the role of commensal viruses that inhabit human intestine (collectively, the virome) is largely unknown. The fecal virome is altered in inflammatory bowel disease (IBD) suggesting a role for virome dysbiosis. How the virome contributes to host homeostasis or how changes in virome composition impacts gut inflammation is unknown. To advance our knowledge of the virome-intestine relationship, a critical step is to move beyond correlation and toward identifying specific immunoregulatory viruses and mechanisms of virome immunomodulation. Mammalian cells detect viral nucleic acids via receptors RIG-I and MDA-5, triggering canonical antiviral defense pathways. How host viral sensors distinguish from, and achieve divergent responses toward pathogenic viruses and viral symbionts is a fundamental and unanswered question in mucosal immunity. We recently demonstrated interaction between certain commensal viruses with RIG-I in mouse intestine. The overall objective of the present proposal is to identify immunomodulatory virome constituents of healthy and diseased human intestine and elucidate the host immune response that ensues. We will elucidate global RIG-I/MDA-5-virome interaction maps in healthy and diseased intestinal tissue using a crosslinking immunoprecipitation (CLIP) technique in fresh intestinal resections from non-IBD and IBD patients. As a second aim, we will determine the immunomodulatory capacity of viruses isolated from healthy versus IBD intestinal tissue or ileostomies. Determination of the precise viral components that interact with the host will help in understanding the role of the virome in regulating immune homeostasis and how commensal viruses may contribute to IBD.