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Editorial: understanding IBS pathophysiology through "converging channels" of research – authors' reply

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We thank Dr. Elwing and Dr. Sayuk for their thoughtful comments in response to our manuscript demonstrating association between lipid-induced sensitivity in irritable bowel syndrome (IBS) and small intestinal mucosal expression of Transient receptor potential channels, of the vanilloid subtype (TRPV)[1,2]. As they highlight, studies utilizing converging and complimentary assessments are much more likely to decipher the complex and heterogenous pathophysiology of IBS. Mechanistically, most studies in IBS have assessed colonic pathophysiology[3]. Our work was motivated by the paucity of understanding of small intestinal mechanisms of symptom genesis in IBS.

Our assessments were made in a cohort of 26 IBS patients (12 constipation-predominant and 14 diarrhea-predominant) and 15 healthy volunteers. We agree that is a limited cohort and findings will need to be validated in larger cohorts. However, we believe the study provides a robust starting point for a previously uninvestigated mechanism. TRPV ion channels are established to play a role in visceral sensation in a number of complementary animal and human studies. In IBS, their role has been studied predominantly in the colon[4-6]. However, it makes plausible sense for a role of these channels to mediate pain in response to chemical and mechanical stimuli in the proximal small bowel that sees the first exposure to these stimuli. Further studies will need to determine the contribution of chemical and mechanical stimuli to the activation of various channels within the TRPV family[7,8]. Additionally, our exploratory analysis to determine sex-differences showed interestingly that TRPV1 expression associated with symptoms in males whereas TRPV3 expression associated with symptoms only in females. Further studies powered for each sex will need to validate these sex-differences. Lastly, we performed probe-based confocal laser endomicroscopy before and after administration of intraluminal lipids. Although the differences between IBS and healthy were not significant for the epithelial architecture, this study provides further demonstration that endomicroscopy is a feasible approach to study structural changes in epithelial barrier in response to dietary or other stimuli.

We concur that the examination of IBS pathogenesis through converging channels (e.g., clinical, environmental, physiologic, genetic) should be seen as the next research frontier. These studies are often cumbersome but regardless provide a significant advancement that can fuel mechanistic studies to demonstrate specific mechanisms. As an example, our study also provides a small intestinal mucosal transcriptomics database of IBS which can be of use for other investigators and drug-manufacturers.

Guarantor of Article: Madhusudan Grover

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