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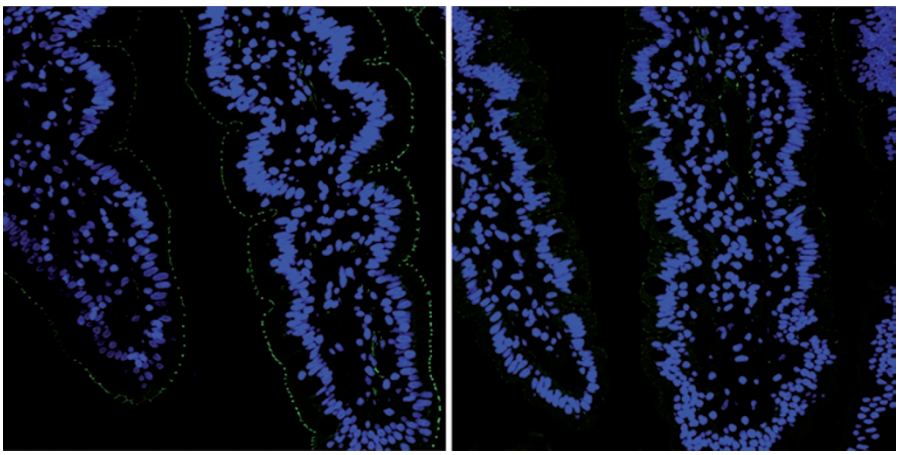
IBS

New insights into pathogenesis of diarrhea-predominant IBS

A recent study has demonstrated that alterations in tight junction proteins in the jejunal mucosa of patients with diarrhea-predominant IBS (IBS-D) are associated with activation of mast cells and with clinical features of bowel dysfunction.

"Previous work indicates the relevance of low-grade inflammation and immune activation in the intestinal mucosa for the development of visceral hypersensitivity and bowel dysfunction in IBS," say Maria Vicario and Javier Santos, two of the authors of the study. "However, the ultimate mechanisms underlying these alterations and their connection to clinical readouts are still ignored."



Micrographs of the jejunal epithelium of healthy controls (left) and patients with IBS-D (right). Zonula occludens 1 is labeled by immunoflourescence in green; nuclear staining with DAPI is in blue. Courtesy of M. Vicario and J. Santos.

Vicario, Santos and colleagues decided to focus on the small bowel, as some evidence indicates that IBS symptoms might originate from this region. 25 patients with IBS-D and 23 healthy controls were enrolled in the study. The researchers performed microarray analysis of RNA isolated from the jejunal mucosa. Results from this step demonstrated that the jejunum of patients with IBS-D displays a distinctive gene transcriptional profile—286 genes were found to be differentially expressed in patients with IBS-D compared with healthy controls.

Pathway and network analysis was then performed to identify the biological functions of the differentially expressed genes in IBS-D. The expression of genes and proteins involved in tight junction signaling (for example, zonula occludens) and mast cell activation were identified as having a major role in biological function in IBS and were, therefore, studied further using quantitative real-time PCR and immunoflourescence. Alterations in the expression of zonula occludens proteins in patients with IBS-D were found to be associated with mast cell activation, frequency of bowel movements and stool consistency.

The investigators write that these findings challenge the traditional view of IBS as a model functional disorder, and also show the importance of the upper small bowel in the pathogenesis of IBS-D.

"We are interested in further elucidating the role of gender and environmental-related factors in determining the altered expression of structural tight junction proteins and the mechanisms of its disassembly," conclude Vicario and Santos. "We also plan to pursue the identification of reliable disease biomarkers for diagnosis, treatment and monitoring disease activity."

Isobel Franks

Original article Martinez, C. *et al.* The jejunum of diarrhea-predominant irritable bowel syndrome shows molecular alterations in the tight junction signaling pathway that are associated with mucosal pathobiology and clinical manifestations. *Am. J. Gastroenterol.* doi:10.1038/ajg.2011.472