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IBS

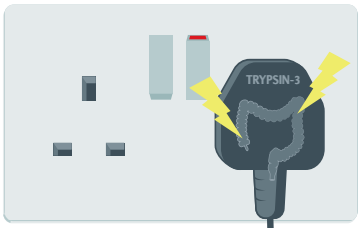
The power of protease activity in IBS

New research unravels the role of the protease trypsin-3 in IBS, demonstrating that, in the context of IBS, the intestinal epithelium releases trypsin-3, which can signal to submucosal enteric neurons and induce visceral hypersensitivity. "This project comes from a previous study in which we have identified that strong trypsin activity was associated with IBS in patients," explains author Nathalie Vergnolle. "Here, we wanted to investigate the nature and the origin of this activity in order to define potential new targets for the treatment of IBS symptoms."

Vergnolle and colleagues used a variety of techniques, including *in situ* zymography, imaging and animal models, to delineate the role of trypsin-3. First, they demonstrated that lipopolysaccharide-stimulated intestinal epithelial cells (Caco-2 cells) *in vitro* released trypsin-like proteolytic activity from the basolateral compartment. Moreover, in human colon tissue samples, increased trypsin activity was observed in samples from patients with IBS (across all IBS subtypes: constipation-predominant, diarrhoea-predominant and mixed) versus those from healthy individuals used as controls. This activity was predominantly observed in the epithelium, as well as at the base and tip of the intestinal crypts.

Examining the expression of all three human trypsin genes, the researchers found that only mRNA levels for *PRSS3* (encoding trypsin-3) were upregulated in stimulated Caco-2 cells *in vitro* and in tissue samples from patients with IBS (most dramatically in samples from patients with constipation-predominant IBS). Western blot analysis confirmed the presence of the trypsin-3 protein, and confocal microscopy showed that trypsin-3 co-localized with actin at the plasma membrane in Caco-2 cells and epithelial expression of trypsin-3 was polarized towards the basolateral side in tissue samples from patients with IBS.

Finally, *in vitro* assays confirmed that trypsin-3 increased epithelial permeability and excitability of dorsal root ganglion neurons, signalling to mouse sensory and human enteric neurons and invoking calcium transients. Moreover, colorectal administration of trypsin-3 induced visceral hypersensitivity in a rat model in response to colorectal distention.



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The researchers postulate that trypsin-3 could be used as a marker of epithelial dysfunction in patients with IBS, and as a potential new therapeutic target. "The future is to develop specific inhibitors of trypsin-3 and to test them for their potential beneficial effects in IBS," explains Vergnolle.

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ORIGINAL ARTICLE Rolland-Fourcade, C. *et al.* Epithelial expression and function of trypsin-3 in irritable bowel syndrome. *Gut* http://dx.doi.org/10.1136/gutjnl-2016-312094 (2017)