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**Characterisation of MRGPRX2+ mast cells in irritable bowel syndrome**

**Decraecker L, Cuende Estévez M, Van Remoortel S, *et al.* Characterisation of MRGPRX2+ mast cells in irritable bowel syndrome. *Gut* 2025; 74(7): 1068-1077. doi: 10.1136/gutjnl-2024-334037.**

The pathophysiological basis of irritable bowel syndrome (IBS) is yet to be elucidated. In this study, Decraecker *et al.* test the theory that mast cell activation, through a ‘pseudoallergic’ pathway distinct from the canonical IgE-mediated pathway, is implicated in a subtype of patients with IBS with visceral hypersensitivity. These pathways are mediated by the mast cell G-protein receptor coupled family (MRGPR), which are stimulated by a wide number of compounds, including drugs, toxins and endogenous molecules such as substance P.

The group has previously demonstrated a 10.7-fold increased expression of the specific receptor MRGPRX2 (Mas-related G-protein coupled receptor member X2) in colonic specimens of a subset of patients with IBS. The researchers compare the expression and functional characteristics of MRGPRX2 in rectal biopsies obtained from patients with IBS against those from healthy controls. They also undertake functional studies of MRGPRX2 in healthy colonic specimens.

In healthy colonic specimens, Decraecker *et al.* demonstrate that MRGPRX2 agonists—such as compound 48/80, substance P (SP), and MRG-733—induce significant mast cell degranulation and TRPV1 (transient receptor potential cation channel subfamily V member 1) sensitisation in the submucosal plexus, indicating a potential mechanism for nociceptor sensitisation.

Exposure to MRGPRX2 agonists in the IBS rectal specimens induced heightened mast cell de-granulation compared to the rectal specimens of healthy controls, despite no difference in MRGPRX2 frequency or receptor expression. This enhanced responsiveness suggests intracellular sensitisation mechanisms or a pre-activated mast cell phenotype in IBS. Furthermore, supernatants from the IBS biopsies showed elevated MRGPRX2 agonistic activity, particularly due to increased levels of substance P. This mechanistic insight supports the development of MRGPRX2 antagonists or modulators as treatment targets.