Gasdermin B in IBD and epithelial barrier repair

Gasdermin B (encoded by GSDMB) has been associated with genetic susceptibility to inflammatory bowel disease (IBD), but its precise role in disease is unknown. In a new study, researchers investigate gasdermin B expression in patients with IBD and establish a novel mechanism by which gasdermin B restores epithelial barrier function.

“One of the most compelling arguments that gasdermin B plays an important role in the pathogenesis of IBD comes from prior genome-wide association studies, indicating that carriage of polymorphic single-nucleotide polymorphisms (SNPs) in GSDMB confers an increased susceptibility to IBD,” say Nitish Rana and Theresa Pizarro, first author and corresponding author of the study, respectively. To investigate the role of gasdermin B in IBD, the researchers first demonstrated increased expression of gasdermin B in gut biopsy samples from patients with active Crohn’s disease and ulcerative colitis compared with healthy controls. They then pinpointed inflamed colonic crypts and crypt top colonocytes as the sites of highest expression of gasdermin B in patients with IBD.

Interestingly, single-cell RNA-sequencing analysis as well as in vitro experiments in intestinal epithelial cell (IEC) lines suggested a lack of gasdermin B-dependent pyroptosis (a form of programmed cell death) in IECs. “This finding was particularly novel since it was thought that GSDMB was mainly a mediator of pyroptosis,” say Rana and Pizarro. Instead, gasdermin B translocated to the plasma membrane and regulated IEC proliferation and migration — and a lack of gasdermin B impeded IEC wound healing in vitro.

Next, the researchers investigated the effect of IBD-associated GSDMB SNPs on epithelial barrier function. In vitro functional assays comparing human IECs expressing wild-type GSDMB or a mutated GSDMB (GSDMBR529S) demonstrated that mutated GSDMB dampened proliferation and migration but increased adhesion, thereby impeding epithelial repair. Finally, analysis of key focal adhesion molecules involved in epithelial restitution revealed a decrease in focal adhesion kinase (FAK) phosphorylation in GSDMB−/− versus wild-type GSDMB cells, and further observations implicated gasdermin B in regulating FAK phosphorylation in a platelet-derived growth factor A (PDGFA)-mediated process.

Taken together, the findings implicate gasdermin B, which has increased expression in patients with IBD, in restoring intestinal epithelial barrier function. However, in patients carrying GSDMB mutations, these processes can be impaired. “Future studies investigating potential downstream targets of gasdermin B will be important to better understand the molecular mechanisms of these processes, especially differences attributed to disease-associated GSDMB SNPs,” say Rana and Pizarro.

“Our findings provide the foundation to develop novel therapeutic strategies that target gasdermin B to potentially improve epithelial restitution and repair and the resolution of inflammation, with the goal of more effectively treating disorders affecting mucosal barrier function, such as IBD.”

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A representative confocal image of 2D monolayers transformed from 3D colonic epithelial organoids co-localizing EpCAM (red) and GSDMB (green) to the plasma membrane (yellow) after stimulation with methylxanthine (right) compared with untreated control (left). Image courtesy of N. Rana and T. Pizarro, Case Western Reserve University School of Medicine.