

Background: Purinergic receptor activation is known to play an important role in immune responses to intestinal inflammation and infection. However, less is known about the role of intestinal epithelial purinergic signaling during inflammation. As inflammation impacts epithelial function, we hypothesized that active inflammation in ulcerative colitis alters intestinal purinergic receptors expression and signaling. **Methods:** To assess the distribution of the 19 purinergic receptors in the human gut epithelium and immune cells, we queried single-cell RNA sequencing data from the Human Protein Atlas. Using publicly available RNA seq data from individuals with ulcerative colitis and non-IBD controls, we assessed alterations in purinergic receptors across histological severity scores (GSE109142). We also analyzed RNA seq data from human intestinal organoids to identify potential inflammatory cytokines responsible for altered purinergic receptor expression (GSE289072). To evaluate functional P2 receptor signaling, we used human intestinal organoids expressing the calcium indicator GCaMP6s to measure epithelial calcium responses as a read out of receptor activation. **Results:** Single-cell analysis revealed limited P1 receptor expression in the intestinal epithelium, with greater expression across immune cell populations. In contrast, P2RY1, P2RY2, and P2RX4 were broadly expressed across epithelial cell types in the healthy small and large intestine. Analysis of ulcerative colitis transcriptomic data revealed significant reductions in epithelial-associated P2RY1, P2RY2, and P2RX4 expression with increasing inflammation, while P1 receptor expression remained unchanged. Several immune-associated purinergic receptors were increased in ulcerative colitis patients. Exposure to pro-inflammatory cytokines decreased P2Y1 and P2Y2 expression in ulcerative colitis organoids. Functionally, inhibition or knockout of P2Y1 significantly reduced epithelial calcium signaling in human intestinal organoids, consistent with impaired purinergic communication. P2Y1 inhibition, but not P2Y2 inhibition, delayed wound healing in epithelial scratch assays, suggesting P2Y1 signaling contributes to repair. **Conclusions:** These findings reveal an imbalance in epithelial and immune cell purinergic signaling during ulcerative colitis. This highlights distinct roles for purinergic receptors in intestinal epithelial function and repair.