

## Interleukin-1 Receptor 9 Gene Deletion Worsens Murine Colitis

**Introduction/Aim:** Inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis, are characterized by chronic inflammation in the gastrointestinal tract. The pivotal role of the immune system in driving IBD pathogenesis is underscored by the current therapies which are designed to modulate immune responses. Several key immune cell subtypes, including macrophages, B cells, and T cells, have been implicated in disease progression. These cells employ intricate cytokine signaling networks to drive inflammation in IBD. Interleukin-38 (IL-38), a member of the interleukin-1 (IL-1) family, is an anti-inflammatory cytokine that has been demonstrated to contribute to the resolution of inflammation in ulcerative colitis. Previous research by our lab revealed that the genetic deletion of the *Il38* gene (*Il1f10*) exacerbates colitis in a mouse model, however, the precise mechanism through which IL-38 acts to control inflammation in IBD has remained elusive. In this study, we aimed to characterize the role of an IL-38 ligand binding receptor, interleukin 1 receptor 9 (IL-1R9; IL1RAPL1) in regulating the severity of murine colitis.

**Methods:** In this study, we induced colitis in IL1-R9 knockout mice and littermate wild-type controls by supplementing drinking water with 3% dextran sodium sulfate (DSS) for 5 days. After 5 days, we allowed them to recover with fresh water for 4 days before sacrifice. To quantify the disease activity index (DAI), we obtained body mass measurements, assessed stool consistency, and scored rectal bleeding during each day of the study. Upon sacrifice, colons were isolated, and inflammation was assessed through histologic analysis and colon length measurements. In addition, we measured inflammatory gene and protein expression through quantitative PCR and ELISA, respectively.

**Results:** We observed a more severe colitis phenotype in the IL1-R9 knockout mice compared to the wild type mice ( $P < .01$ ). Gene and protein analysis in the colon revealed a prominent Th17 signature as indicated by heightened IL-6 and IL-17A expression.

### Conclusions:

Here we show novel data that suggests a critical role for IL-1R9 in preventing pathogenic bowel inflammation, possibly through modulating Th17 function. These findings shed light on the intricate interplay of cytokines and receptors of the interleukin-1 family in the regulation of IBD-related inflammation and suggests potential targets for future therapeutic interventions.