Accumulation and activation of mast cells and eosinophils have been implicated in the pathogenesis of several chronic inflammatory gastrointestinal (GI) diseases, including eosinophilic gastrointestinal diseases (EGIDs) and inflammatory bowel disease (IBD).

Despite the strong association of mast cells and eosinophils in IBD, no further characterization of these cells has been performed. Here, we aimed to quantify and evaluate the activation state of mast cells and eosinophils in colon tissue from IBD or non-diseased control patients as well as quantify the production of cytokines from human colonic tissue mast cells.

Figure 1. Mast Cells and Eosinophils are Key Drivers of Acute and Chronic Inflammation

Single-cell suspensions were prepared by enzymatic digestion of fresh colon biopsies from patients with IBD or non-diseased control colon tissue.

Figure 2. Antolimab (AK002) Mechanism of Action

- Siglec-8 is an inhibitory receptor selectively expressed on human eosinophils and mast cells and represents a novel target for the treatment of IBD.
- Antolimab (AK002) is a novel, humanized, non-fucosylated IgG1 monoclonal antibody to Siglec-8 that depletes blood eosinophils by antibody dependent cellular cytotoxicity (ADCC) and induces apoptosis of tissue eosinophils.
- In addition, antolimab inhibits both IgE-dependent and independent modes of mast cell activation.
- Antolimab has recently demonstrated significant symptomatic and histological improvement in a randomized, double-blind placebo-controlled Phase 2 study in patients with eosinophilic gastritis and/or gastroenteritis.

Figure 3. Study Design

- The expression of the mast cell degranulation marker CD107a was significantly increased on mast cells from UC biopsy tissue compared to CD and non-diseased colon tissue mast cells.
- However, unlike mast cells in allergic disease, IgE expression was unchanged between UC, CD, and non-diseased colon mast cells which suggest a non-IgE-driven mechanism of mast cell activation in IBD.

Figure 4. Flow Cytometry Gating Strategy for Mast Cells and Eosinophils in IBD Biopsy Tissue

- CD107a was significantly increased on mast cells from UC biopsy tissue compared to CD and non-diseased colon tissue mast cells.

Figure 5. Mast Cells and Eosinophils are Significantly Elevated in Ulcerative Colitis Biopsies

- In addition, the percentage of eosinophils was significantly increased in UC and nominally elevated in CD biopsy tissue compared to non-diseased colon tissue.

Figure 6. Mast Cells in Ulcerative Colitis Tissue Display an Increased Degranulation and Activation State

- The expression of the eosinophil activation markers CD11b was significantly increased on both UC and CD tissue eosinophils compared to non-diseased colon tissue eosinophils.

Figure 7. Eosinophils in Ulcerative Colitis and Crohn’s Disease Tissue Display an Increased Activation State

- CD66b was significantly increased on both UC and CD tissue eosinophils compared to non-diseased colon tissue eosinophils.

Figure 8. Siglec-8 is Highly Expressed on Mast Cells and Eosinophils in IBD Tissue

- Antolimab reduces cytokines associated with driving the pathogenesis of ulcerative colitis through the production of inflammatory mediators.
- Siglec-8 is highly expressed on mast cells and eosinophils in IBD tissue, thus antibodies that target the Siglec-8 receptor, such as antolimab (AK002), represent a potential novel targeted approach to IBD treatment.

Figure 9. Human GI Tissue Mast Cells Produce Multiple Pro-inflammatory Cytokines Associated with IBD

- Mast cells and eosinophils may play a significant role in driving the pathogenesis of ulcerative colitis through the production of inflammatory mediators.

Figure 10. Antolimab (AK002) Suppresses Cytokine Production from Human GI Tissue Mast Cells

- Antolimab reduces cytokines associated with driving IBD through mast cell inhibition.

CONCLUSIONS/DISCUSSION

- Mast cells and eosinophils may play a significant role in driving the pathogenesis of ulcerative colitis through the production of inflammatory mediators.
- Siglec-8 is highly expressed on mast cells and eosinophils in IBD tissue, thus antibodies that target the Siglec-8 receptor, such as antolimab (AK002), represent a potential novel targeted approach to IBD treatment.

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