Activated Mast Cells and Eosinophils Are Associated with Increased Inflammatory Mediators in Mucosal Biopsies from EG and/or EoD Patients with Chronic Gastrointestinal Symptoms

Melina Butuci PhD, Simon Gebremeskel PhD, Alan Wong, Kathryn Peterson MD, Julia Schanin PhD, Henrik S. Rasmussen MD PhD, Bhupinder Singh MD, Amol P. Kamboj MD and Bradford A. Youngblood PhD

1Allakos, Inc., Redwood City, CA; 2University of Utah, Salt Lake City, UT


METHODS

• Gastric and duodenal biopsies were obtained from EG and/or EoD patients meeting pre-defined symptom severity criteria and non-diseased subjects with minimal or no symptoms.

• Levels of inflammatory mediators were measured in whole GI tissue obtained from symptomatic EG and/or EoD, and non-diseased controls using ELISA.

• Biopsies from symptomatic EG and/or EoD patients produced significantly elevated levels of Eos chemokines and inflammatory cytokines, consistent with local tissue inflammation.

• In addition, levels of the MRGPRX2 ligand, LL37, were elevated in biopsies from EG and/or EoD patients compared to Healthy Controls.

RESULTS

1. Eos and MCs are similarly and significantly elevated across isolated and overlapping EG and/or EoD patients compared to Healthy Controls.

2. Eos and MCs are similarly and significantly activated across isolated and overlapping EG and/or EoD biopsies.

3. Eos and MCs are similarly and significantly activated across isolated and overlapping EG and/or EoD biopsies.

CONCLUSIONS/DISCUSSION

• Eos and MCs in gastric and duodenal biopsies from EG only, EoD only, and EG/EoD patients with moderate-severe GI symptoms are significantly activated and globally activated.

• Symptomatic EG and/or EoD patients display significant local gastric and duodenal inflammation characterized by elevated levels of Eos chemokines and inflammatory cytokines.

• The MC-specific neuropeptide receptor, MRGPRX2 is elevated and functional on EG and/or EoD MCs, and activation via endogenous ligands induces eosinophilic inflammation, suggesting IgE-independent MC activation may contribute to EGID pathogenesis.

Figure 1. Pathogenesis of EGIDs

Figure 2. Mast Cells and Eosinophils Are Key Drivers of Inflammatory Disease

Figure 3. Strategy to Identify and Phenotype Eos and MCs in Gastric and Duodenal Biopsies

Figure 4. Eos and MCs Are Elevated in Symptomatic EG and/or EoD patients compared to Healthy Controls

Figure 5. Eos and MCs Are Activated in EG and/or EoD Gastric & Duodenal Biopsies Compared to Controls

Figure 6. Eosinophil and MC Mediators are Locally Elevated in EG and/or EoD Biopsy Supernatants compared to Healthy Controls

Figure 7. MCs from EG and/or EoD Biopsies are Transcriptionally Activated and Distinct Compared to Non-Diseased MCs

Figure 8. MRGPRX2 is Elevated and Functional on MCs from EG and/or EoD Biopsies

Figure 9. Eosinophil Chemokines and Cytokines, and MRGPRX2 Ligands are Locally Elevated in EG and/or EoD Biopsy Supernatants

Figure 10. LL37 Induces MC Activation and Production of Eosinophil and Inflammatory Cytokines in EG and/or EoD Biopsies

REFERENCES