

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

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## BACKGROUND

- Eosinophilic gastritis (EG) and/or duodenitis (EoD) are associated with the pathologic accumulation and activation of eosinophils (Eos) and mast cells (MCs) in the stomach and/or duodenum (Figure 1)<sup>1,2</sup>
- Patients with EG and/or EoD have decreased quality of life due to chronic debilitating and often nonspecific symptoms such as abdominal pain, abdominal cramping, bloating, early satiety, loss of appetite, nausea, vomiting, & diarrhea
- Recently, a large prospective study demonstrated that a meaningful proportion of patients with chronic GI symptoms and/or history of functional GI diagnoses met histologic criteria for EG and/or EoD, suggesting EG and/or EoD may be significantly underdiagnosed<sup>3</sup>

Figure 1. Pathogenesis of EGIDs

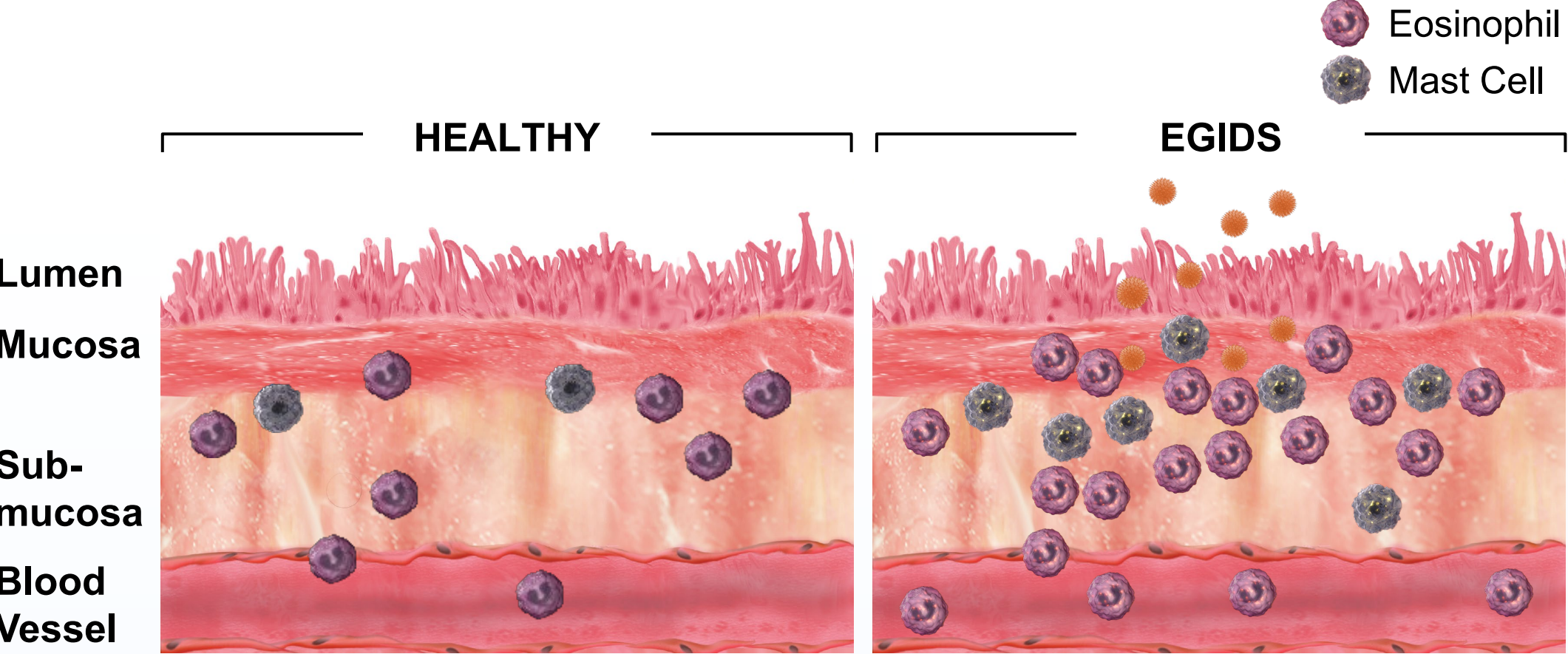
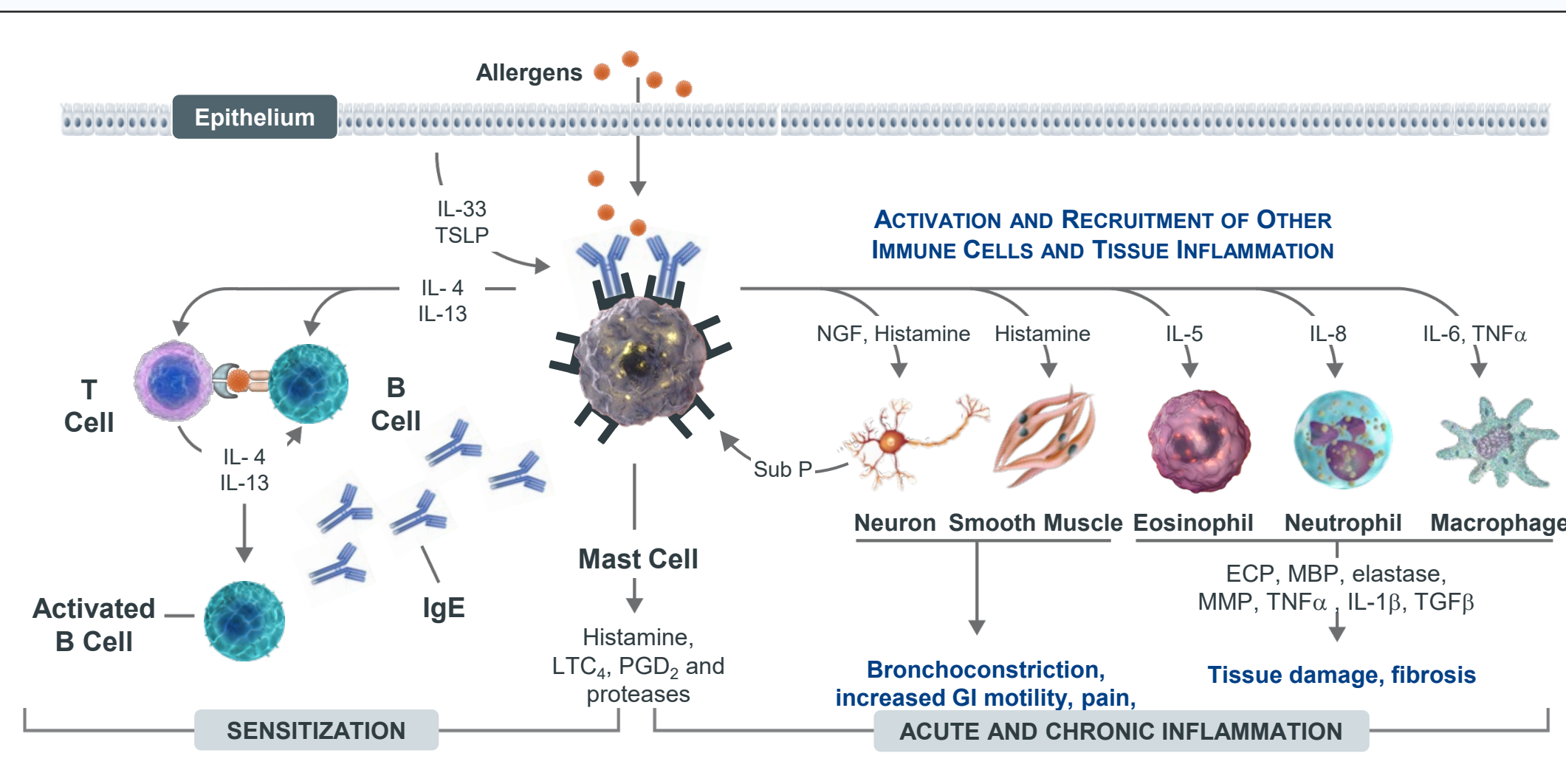


Figure 2. Mast Cells and Eosinophils Are Key Drivers of Inflammatory Disease

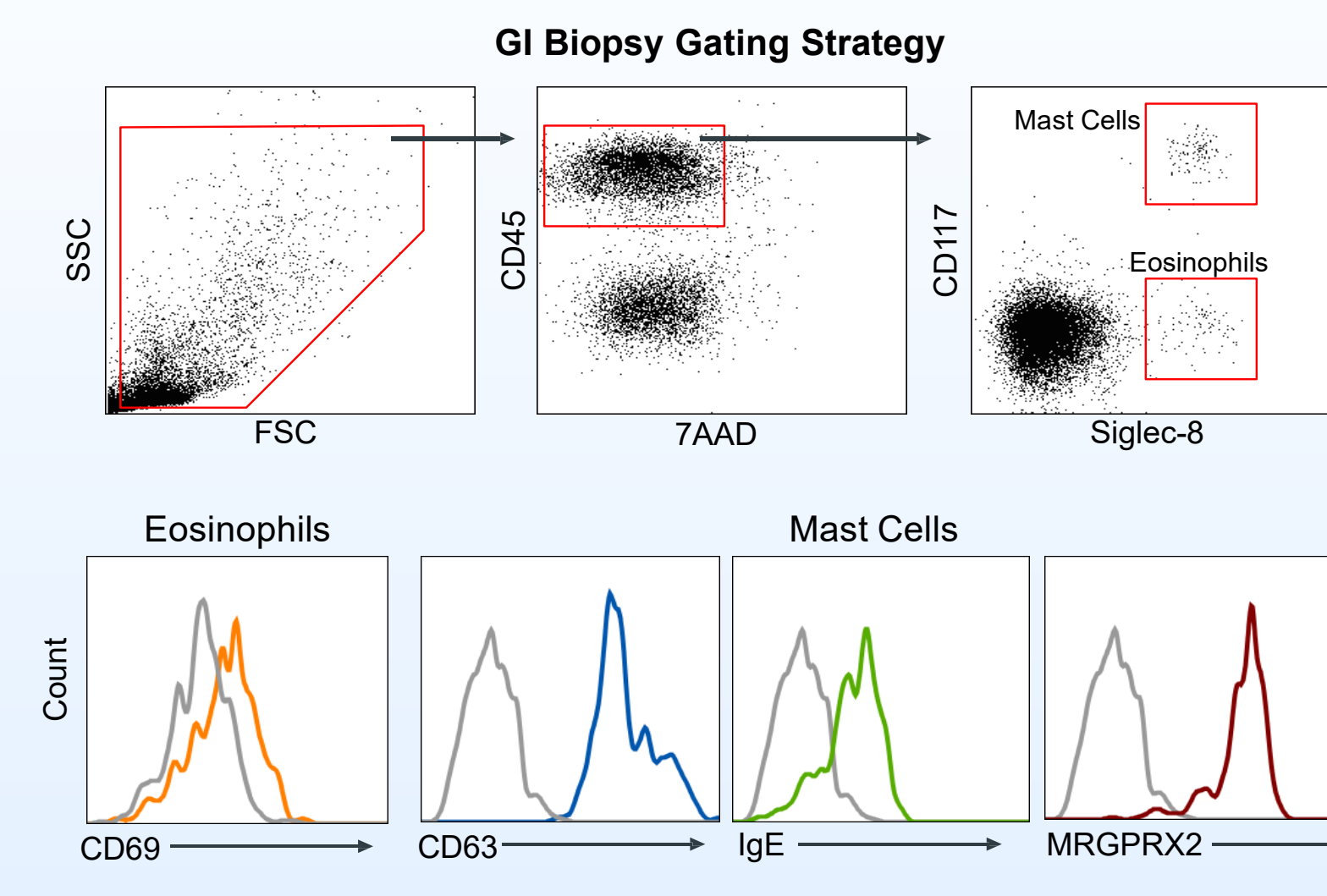


- MCs are tissue-resident immune cells that regulate acute and chronic inflammation through IgE-dependent and -independent mechanisms (Figure 2)
- IgE-dependent MC activation through FcεR1 is a known driver of allergic diseases, however, IgE-independent activation, particularly via MRGPRX2, is now recognized as an important regulator of pain and allergic inflammation
- Although Eos are recognized as key effector cells in EG and/or EoD, the immunological mechanisms that contribute to eosinophilic inflammation and non-specific GI symptoms are unknown

## 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
- Flow cytometry and bulk RNA-sequencing were used to phenotype tissue MCs and eosinophils in GI biopsies
- Levels of inflammatory mediators were measured in whole GI tissue ex vivo biopsy supernatants after overnight culture

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



## RESULTS

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

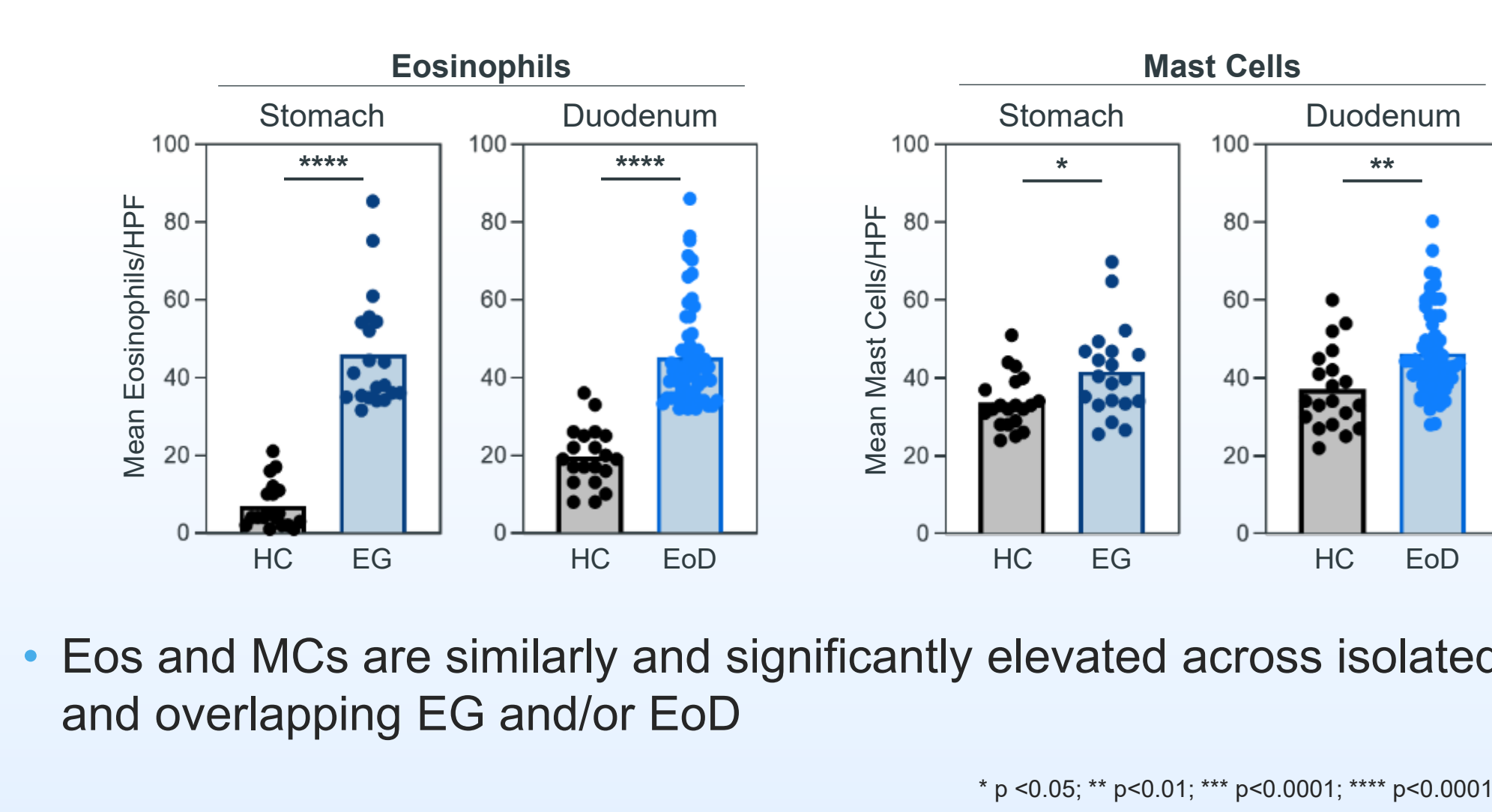


Figure 5. Eos and MCs are Activated in EG and/or EoD Gastric & Duodenal Biopsies Compared to Controls

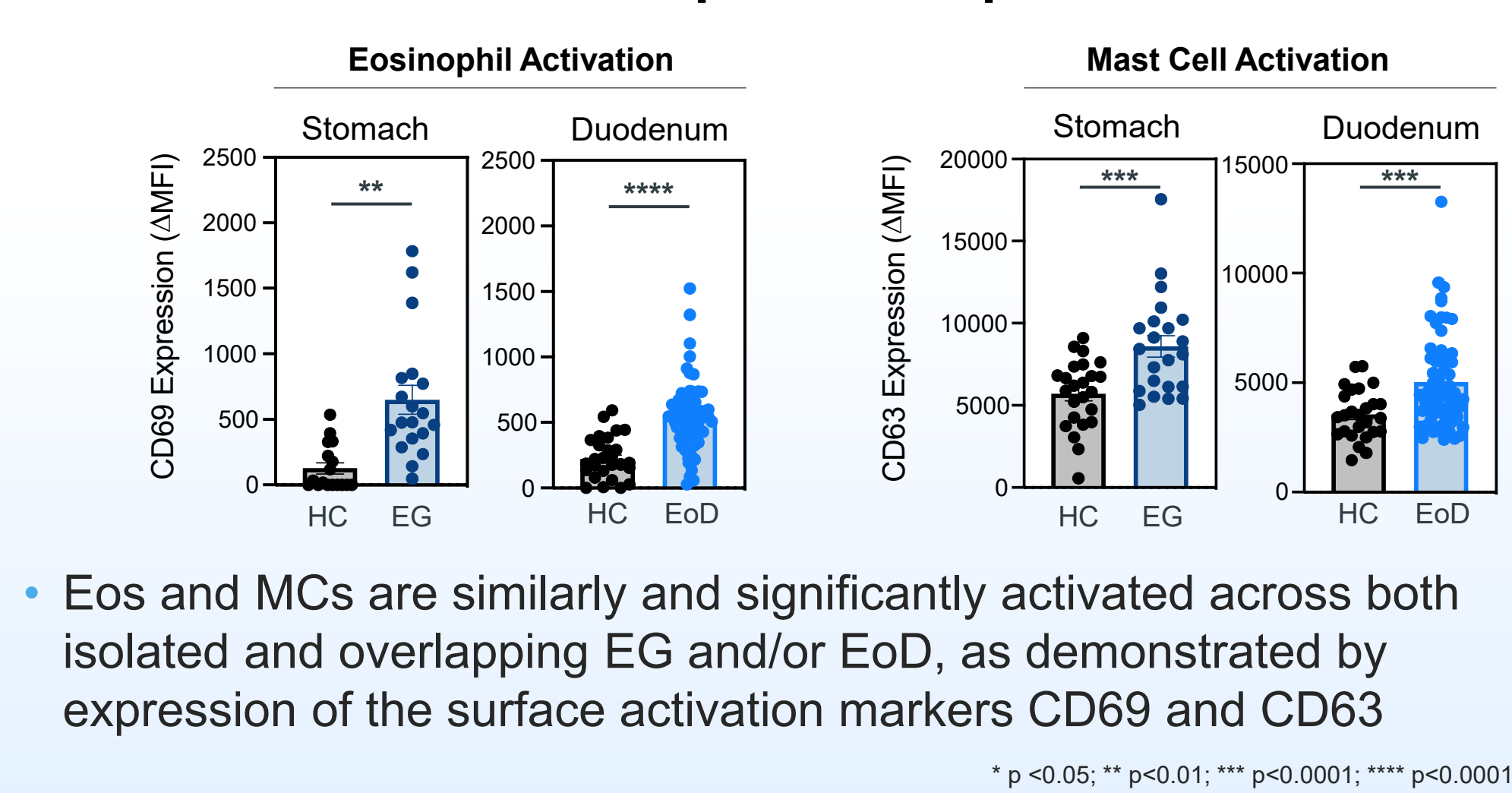


Figure 6. Eosinophil and MC Mediators are Locally Elevated in EG and/or EoD Biopsy Supernatants compared to Healthy Controls

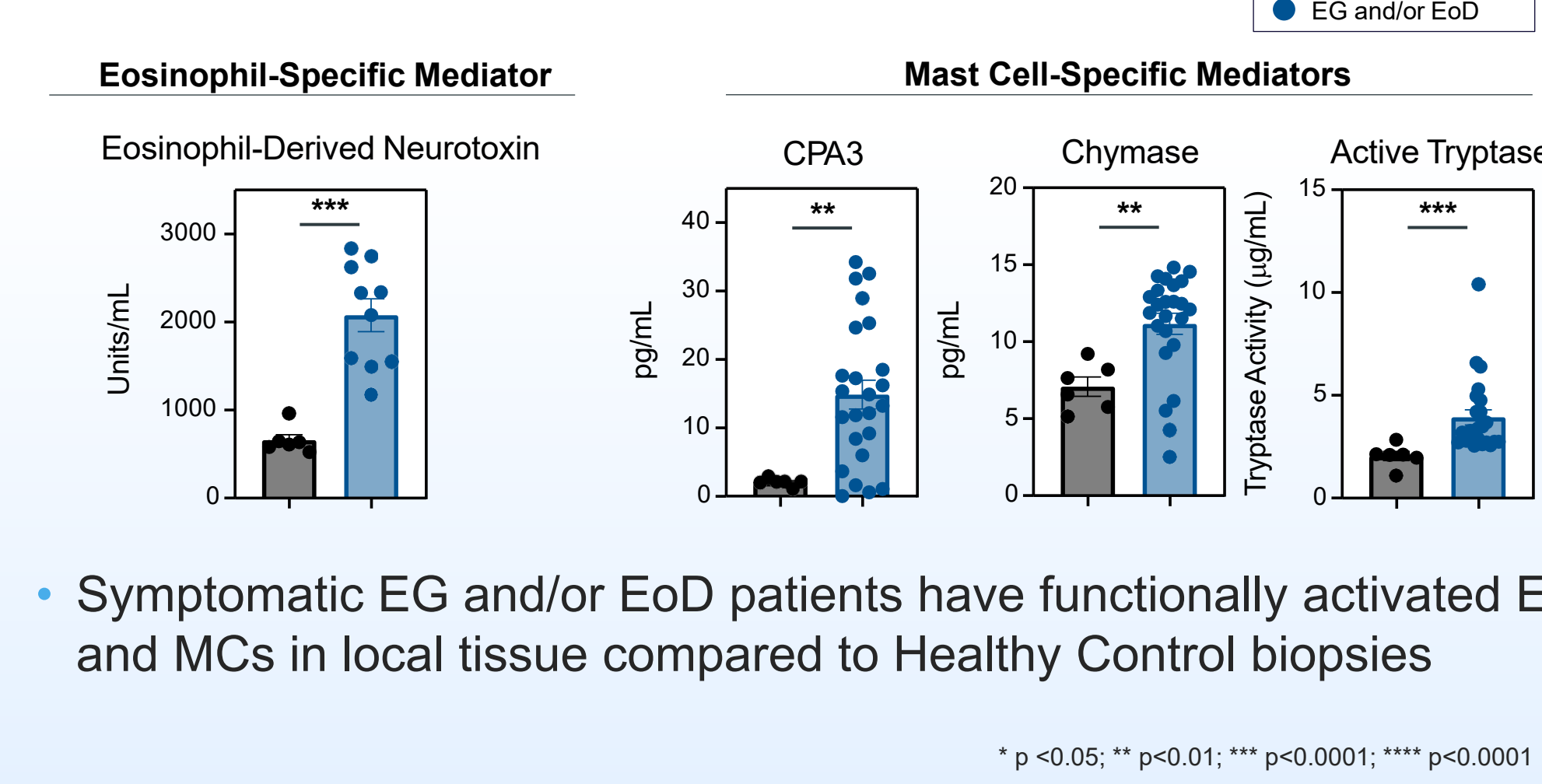


Figure 7. MCs from EG and/or EoD Biopsies are Transcriptionally Activated and Distinct Compared to Non-Diseased GI MCs

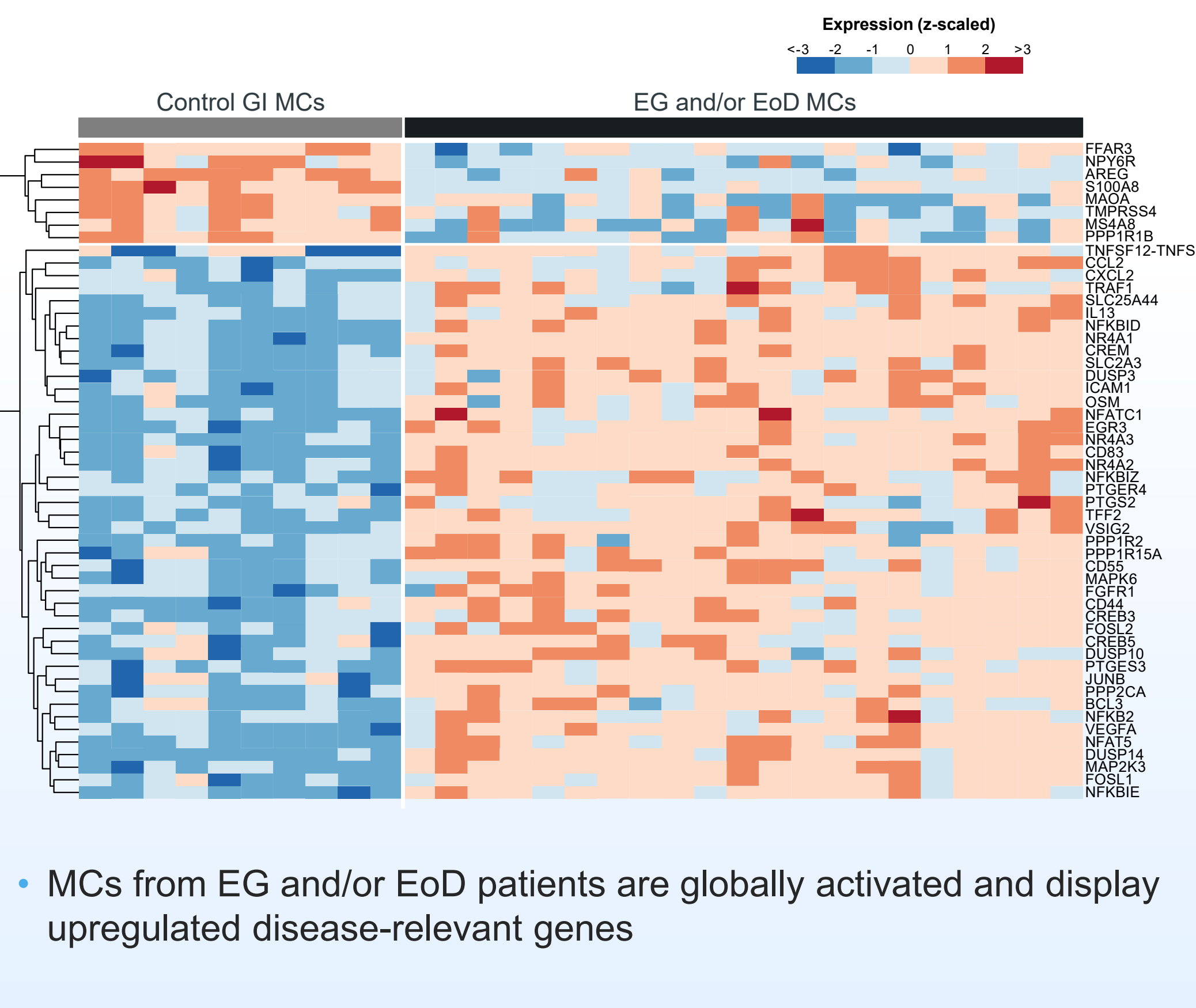


Figure 8. MRGPRX2 is Elevated and Functional on MCs from EG and/or EoD Biopsies

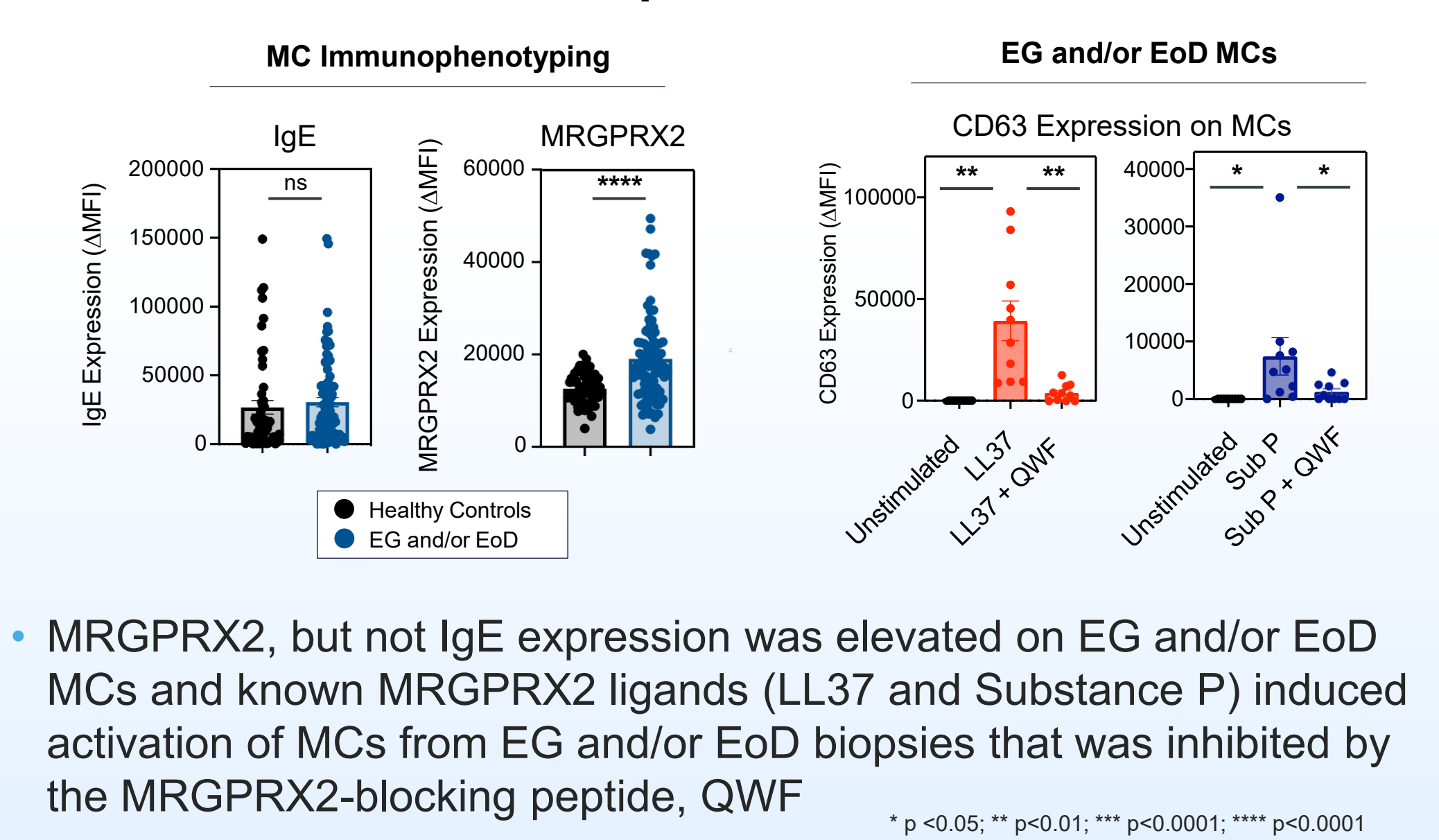


Figure 9. Eosinophil Chemokines and Cytokines, and MRGPRX2 Ligands are Locally Elevated in EG and/or EoD Biopsy Supernatants

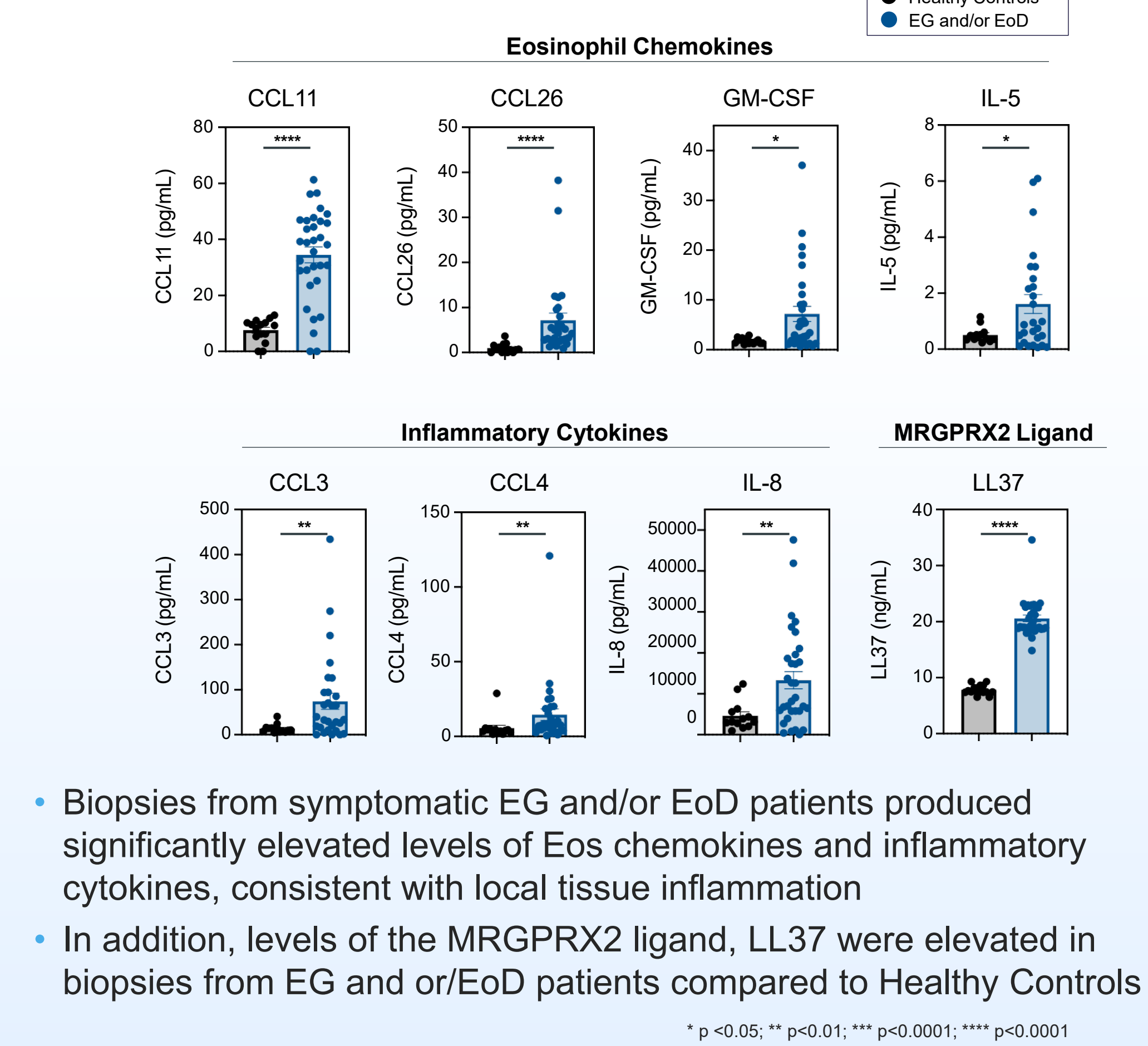
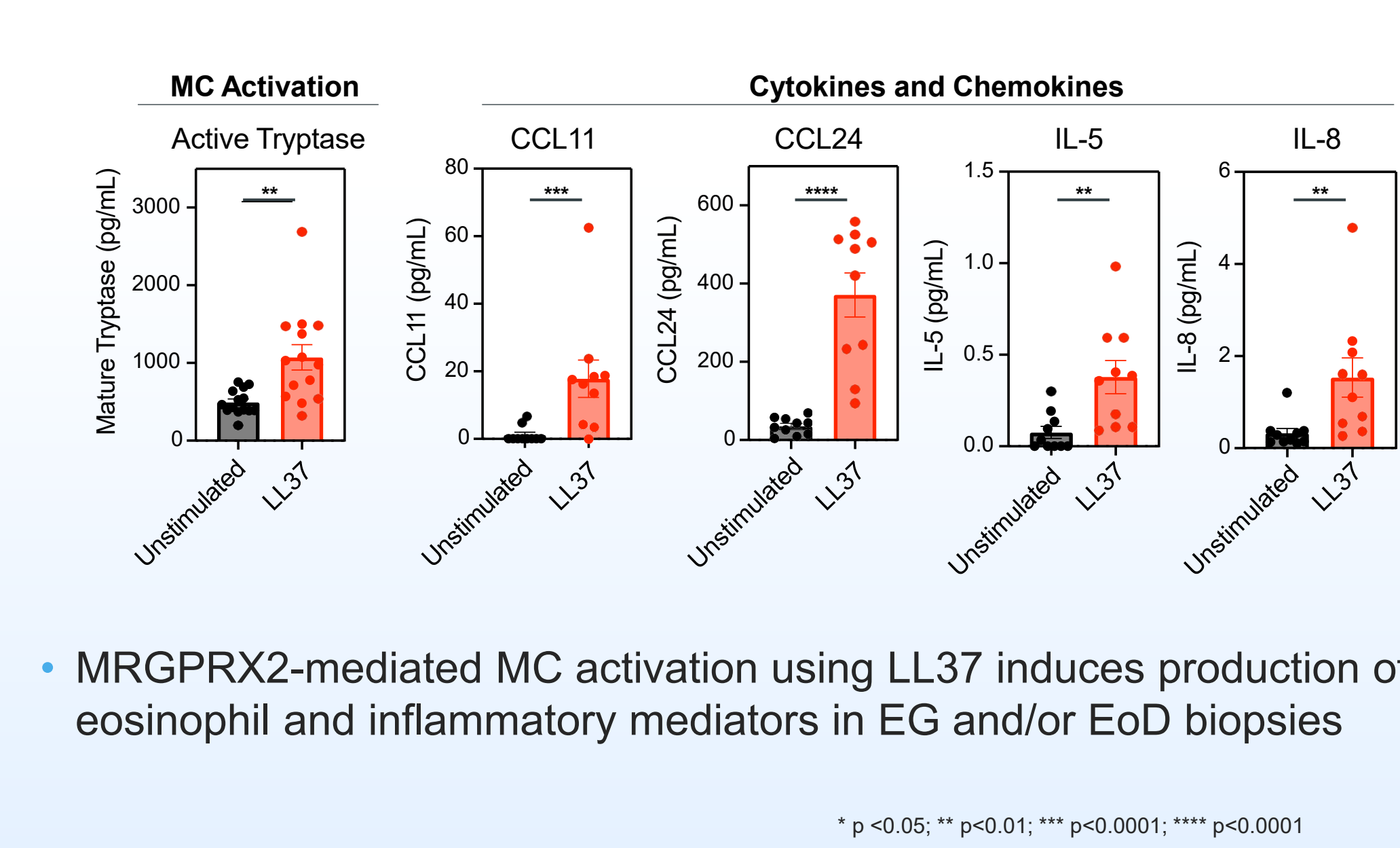


Figure 10. LL37 Induces MC Activation and Production of Eosinophil and Inflammatory Cytokines in EG and/or EoD Biopsies



## 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 elevated 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