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Summary

THE TRYPTOPHAN-DERIVED METABOLITE 8-METHOXYKYNURENATE ACTIVATES GPR35 ON MACROPHAGES TO DRIVE EOSINOPHILIC ESOPHAGITIS THROUGH IL-18 AND EPITHELIAL BARRIER DYSFUNCTION

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Tryptophan-derived metabolite 8-methoxykynurenate activates macrophage GPR35 to drive IL-18 production and epithelial barrier dysfunction in eosinophilic esophagitis.

KEY POINTS

- GPR35 expression is elevated in active EoE versus controls or steroid-treated patients across independent datasets, and macrophage-specific deletion of Gpr35 reduced esophageal inflammation in both sodium dodecyl sulfate- and ovalbumin-driven murine EoE models with decreased eosinophil infiltration and type 2 cytokine levels.
- Molecular docking identified 8-methoxykynurenate as an endogenous GPR35 ligand with IC_{50} of 122.3 nM, and mass spectrometry revealed increased 8-MK levels in active EoE patient biopsies.
- 8-MK induces IL-18 in human and murine macrophages in a GPR35-dependent manner via Gpr35-mediated Gi signaling, intracellular calcium flux, and inflammasome activation, while 8-MK administration exacerbated disease and pharmacological GPR35 antagonism attenuated inflammation in murine models.
- Macrophage-specific deletion of Il-18 conferred similar protection with reduced eosinophil numbers, and IL-18 impaired epithelial barrier integrity in human esophageal organoids, reducing transepithelial resistance and increasing macromolecule permeability.
- Genetic ablation of Gpr35 or Il-18 confers protection across multiple EoE models, identifying a feed-forward loop linking tryptophan metabolism, macrophage-epithelial crosstalk, immunity, and barrier dysfunction in EoE pathogenesis.

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