Paired immunoglobulin- like receptor B inhibits eosinophil accumulation and activation in Eosinophilic esophagitis

Ben Baruch- Morgenstern N[1*], Mingler MK[2], Stuck EM[2], Besse JA[2], Reichman H[1], Wen T[2], Rothenberg ME[2^], Munitz A[1^]

[1]-Department of Clinical Microbiology and Immunology, The Sackler School of Medicine, The Tel-Aviv University, Ramat Aviv, 69978, Israel.

[2-] Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH, 45229

^- These authors contributed equally to this work

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Abstract:

Eosinophilic esophagitis (EoE) is a global emerging, Th2-mediated disease resulting in substantial eosinophilic infiltration, epithelial cell hyperplasia and tissue remodeling. Recent studies have highlighted a major contribution for IL-13 and IL-13-associated genetic pathways in EoE pathogenesis. Yet, molecular mechanisms governing IL-13-induced responses in EoE are largely unknown. Paired immunoglobulin-like receptor (PIR)-B is a cell surface immune inhibitory receptor that is expressed by and critically regulates eosinophil development and migration. We now report that PIR-B is an IL-13 regulated gene in the esophagus. Indeed, the expression of PIR-B was upregulated in the esophagus following inducible overexpression of IL-13 (e.g. in CC10-*Il13*^{Tg} mice). In these settings, PIR-B was highly overexpressed by esophageal eosinophils. CC10-*Il13*^{Tg}/*Pirb*$^{-/-}$ mice displayed markedly increased esophageal eosinophilia and showed severe EoE pathology including increased epithelial cell hyperplasia, fibrosis, collagen deposition, myofibroblast formation and angiogenesis. Global transcriptome analysis of primary sorted *Pirb*$^{+/+}$ and *Pirb*$^{-/-}$ esophageal eosinophils revealed increased expression of transcripts associated with induction of tissue remodeling and cellular activation in *Pirb*$^{-/-}$ eosinophils. These data demonstrate that PIR-B is a negative regulator of IL-13-induced esophageal pathology likely by regulating eosinophil effector functions. Specifically, our data highlights PIR-B as a key molecular checkpoint in IL-13-induced eosinophil accumulation and subsequent activation, which may serve as a novel target for future therapy in EoE.