Spatial Localization and Functional Role of IL-13Rα1 Signaling in Atopic Dermatitis

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Introduction

- Atopic dermatitis (AD) is a chronic inflammatory skin disease that is associated with significant pruritus.[1]
- The IL-4/IL-13 receptor system serves as a clinically validated therapeutic target for AD and consists of the type I (IL-4Rα and the common γ chain) and II (composed of IL-4Rα and IL-13Rα1) receptors.[2]
- To date, therapeutics targeting this system have focused on IL-4Rα and IL-13[3,4,5], however, IL13Rα1 has recently garnered significant interest as a novel therapeutic target for AD.
- *Eblasakimab* is a novel biologic agent that binds to IL-13Rα1, inhibiting the formation of the type II receptor, and is currently progressing through clinical trials (NCT05158023).
- The purpose of this study is to better understand the role of IL-13Rα1 in AD using special localization with immunohistochemistry (IHC) and to delineate the function of the type I and II receptors using comparative transcriptomics.

Materials and Methods

- IHC was performed on lesional (L) and non-lesional (NL) skin from 14 AD patients and 10 matched healthy controls (HC).
- Skin samples were double-stained using immunofluorescence for IL-13Rα1 and either tryptase or major basic protein to determine the distribution of IL-13Rα1 in AD and its relation to mast cells and eosinophils.
- U937 cells were used to evaluate the function of the type I and II receptors as these cells express both receptors.
- Cells were incubated with *eblasakimab* to block type II or anti-common γ chain to block type I receptors.
- After 24 hour incubations, cells were stimulated with vehicle or a mixture of IL-4 + IL-13 and subjected to RNA sequencing.
- IHC data were quantified using ImageJ Fiji.
- A differential expression analysis was conducted on RNA sequencing data using the *DESeq2* package for R.

Results

- IHC showed increased IL-13Rα1 staining in L (P<0.001) and NL (P=0.045) AD skin compared to HCs (Figure 1).
- The average IL-13Rα1 staining intensity of mast cells was increased in L (P=0.034) and NL (*p*=0.031) AD samples compared to HCs (Figure 2).
- The average IL-13Rα1 staining intensity of eosinophils was also increased in L (*p*=0.024) and NL (P=0.046) AD skin compared to HCs (Figure 2).
- Blockade of IL-4 stimulation of the type I receptor in U937 monocytes with an anti-common γ chain antibody resulted in upregulation of genes such as MMP9 (P<0.001).
- Similarly, the type II receptor blockade with *eblasakimab* resulted in suppression of genes such as XBP1 (P<0.001) and CXCL8 (P=0.046) (Figure 3).

Results

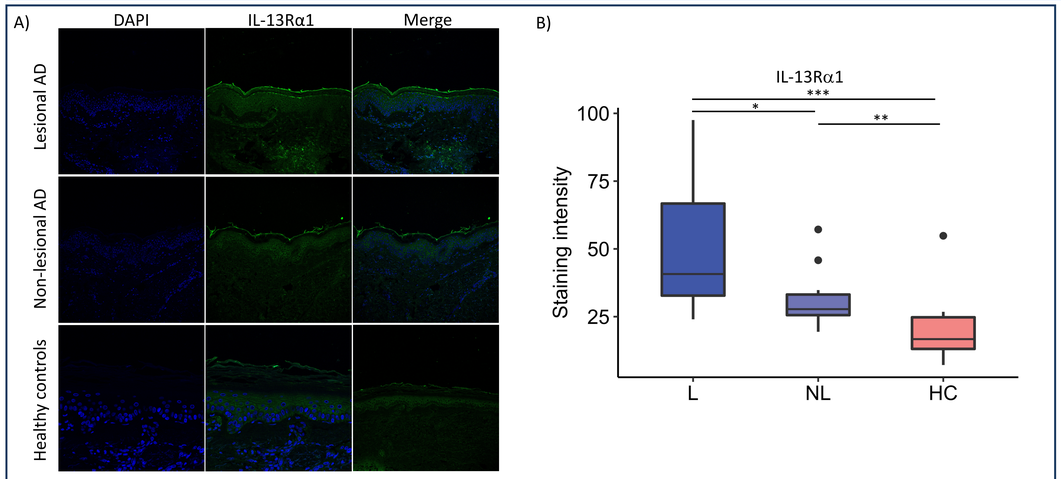

Figure 1. IL-13Rα1 expression is increased in AD. A) Representative images of IL-13Rα1 staining in lesional AD, non-lesional AD, and healthy control skin. B) IL-13Rα1 staining intensity in lesional and non-lesional AD skin and HCs. *- P<0.05; ***- P<0.01; ***- P<0.001; AD, atopic dermatitis; L, lesional; NL, non-lesional; HC, healthy control.

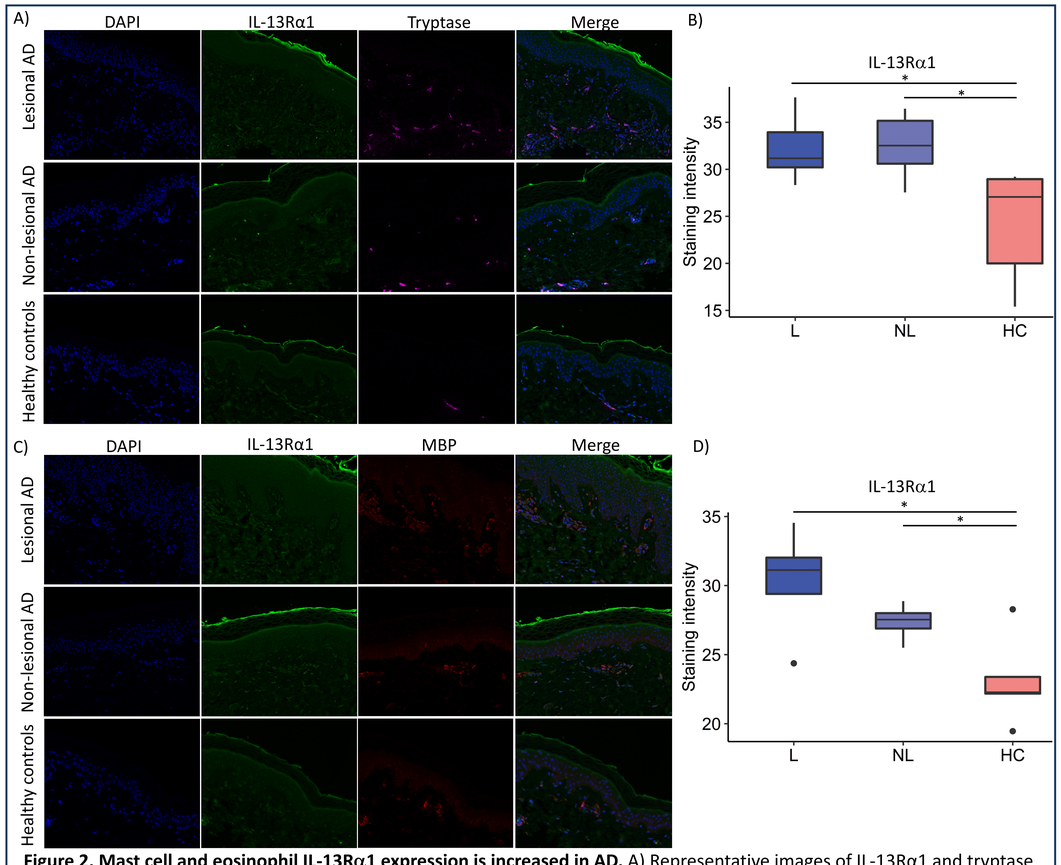

Figure 2. Mast cell and eosinophil IL-13Rα1 expression is increased in AD. A) Representative images of IL-13Rα1 and tryptase staining in lesional AD, non-lesional AD, and healthy control skin. B) Mast cell IL-13Rα1 staining intensity in lesional and non-lesional AD skin and HCs. C) Representative images of IL-13Rα1 and MBP staining in lesional AD, non-lesional AD, and healthy control skin. D) Eosinophil IL-13Rα1 staining intensity in lesional and non-lesional AD skin and HCs. *- P<0.05; AD, atopic dermatitis; MBP, major basic protein; L, lesional; NL, non-lesional; HC, healthy control.

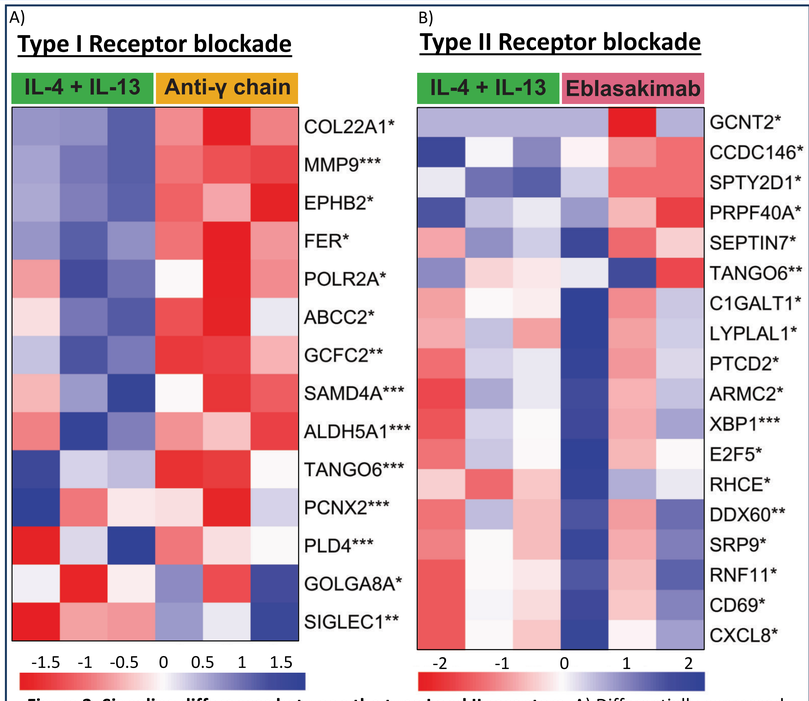

Figure 3. Signaling differences between the type I and II receptors. A) Differentially expressed genes with type I receptor blockade using an anti-common γ chain antibody. B) Differentially expressed genes with type II receptor blockade using *eblasakimab*.

Conclusion

- IL-13Rα1 expression is increased in AD skin and in mast cells and eosinophils, important mediators of allergic inflammation, in AD patients.
- Type I receptor inhibition with anti-common γ chain resulted in increased MMP9 expression, which is a collagenase that is elevated in AD patients and may exacerbate inflammation-promoting tissue edema.[6,7]
- Type II receptor inhibition with *eblasakimab* resulted in decreased expression of XBP1, which is required for leptin-mediated Th2 survival and cytokine production[8], and CXCL8, levels of which correlate with AD severity.[9]
- These findings suggest that the Type II receptor, and IL-13Rα1, play an important role in AD pathogenesis and serve as promising therapeutic targets for the treatment of this disease.

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Disclosures

Dr. Shawn G. Kwatra is an advisory board member/consultant for Abbvie, ASLAN Pharmaceuticals, Arcutis Biotherapeutics, Celldex Therapeutics, Galderma, Genzada Pharmaceuticals, Incyte Corporation, Johnson & Johnson, Novartis Pharmaceuticals Corporation, Pfizer, Regeneron Pharmaceuticals, and Sanofi and has served as an investigator for Galderma, Incyte, Pfizer, and Sanofi. Dr. Ferda Cevikbas is an employee of ASLAN Pharmaceuticals.