Atopic dermatitis disease biomarkers strongly correlate with IL-13 levels, are regulated by IL-13, and are modulated by tralokinumab in vitro

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Introduction

• Atopic dermatitis (AD) is a chronic, pruritic skin disease characterized by type 2 immune-mediated inflammation and skin barrier dysfunction.

• In a recent large-scale RNA-seq–based transcriptomic study of AD, psoriasis, and matched control samples, it was found that the type 2 cytokine interleukin 13 (IL-13) was the most distinctive marker for AD:
  - Increased expression levels of IL-13 were found in both lesional and nonlesional AD skin
  - Expression levels of IL-13 in lesional AD skin correlated with disease severity.

• In contrast, expression of the type 2 cytokine IL-13 could be detectable in 40% of the AD skin samples and at very low expression levels.

• IL-13 has been shown to modulate the expression of inflammatory mediators, such as chemokines, and skin barrier markers related to the pathophysiology of AD. 3

• Tralokinumab is a fully human IgG4 monoclonal antibody in Phase 3 development for AD that specifically neutralizes IL-13. 4

Objectives

• To examine the correlation of IL-13 expression with AD disease biomarkers by use of RNA-seq–based analysis from AD lesional skin samples.

• To investigate IL-13–mediated regulation of AD disease biomarkers and their modulation by tralokinumab in primary cultures of human keratinocytes and dermal fibroblasts.

Methods

• RNA-seq analysis of Affymetrix datasets to examine the correlation between IL-13 expression and AD disease biomarkers.

• Study population

  - Adult patients with a history of AD for at least 3 years
  - The same AD cohort as reported by Tsoi et al from their large-scale transcriptomic study of AD
  - Adult volunteers without personal or familial history of allergic atopic and chronic inflammatory diseases

• Inclusion criteria

  - Dermatologist–confirmed diagnosis of AD (diagnosed on the basis of a skin examination by experienced dermatologists according to standard criteria for AD [American Academy of Dermatology consensus criteria]).

• Exclusion criteria

  - Any other chronic skin disease
  - Systemic treatment with immune–efficient medication
  - Topical treatment within 1 week prior to material sampling

Study population

Participants

• Adult patients with a history of AD for at least 3 years
  - The same AD cohort as reported by Tsoi et al from their large-scale transcriptomic study of AD
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Inclusion criteria

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Exclusion criteria

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Results

Table 1. Patient samples included in the study

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>Control (healthy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of individuals (male/female)</td>
<td>27 (12/15)</td>
<td>38 (16/22)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>34.07 (10.94)</td>
<td>32.63 (11.64)</td>
</tr>
<tr>
<td>Objective SCORAD, mean (SD)</td>
<td>31.11 (10.94)</td>
<td>-</td>
</tr>
<tr>
<td>FLG mutation carriers</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
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*Objective SCORAD does not include the subjective items daily pruritus and sleeplessness.

Figure 1. Study design

In silico transcriptomics analysis of RNA-seq–based data to examine the correlation between IL-13 expression and AD disease biomarkers.

Figure 2. IL-13 expression strongly correlates with key AD disease biomarkers:

A) Positive correlation between IL-13 expression and inflammatory mediators; and
B) Negative correlation between IL-13 expression and skin barrier markers.

Figure 3. Tralokinumab inhibits IL-13–induced expression of the chemokines CCL-2 and CCL-5 in human dermal fibroblasts:

A) CCL-2 protein concentration in supernatant; B) Percentage inhibition of IL-13-induced CCL-2 protein secretion; C) CCL2 mRNA expression; and D) Percentage inhibition of IL-13–induced CCL2 mRNA expression.

Figure 4. Tralokinumab inhibits IL-13–induced expression of inflammatory mediators in human keratinocytes:

A) CCL-2 protein concentration in supernatant; B) Percentage inhibition of IL-13–induced CCL-2 protein secretion; C) CCL2 mRNA expression; D) Percentage inhibition of IL-13–induced CCL2 mRNA expression; E) NTRK1 mRNA expression; and F) Percentage inhibition of IL-13–induced NTRK1 mRNA expression.

Figure 5. Tralokinumab restores expression of skin barrier markers decreased by IL-13 in human keratinocytes:

A) LOR mRNA expression; B) Percentage inhibition of IL-13–induced LOR mRNA expression; C) FLG mRNA expression; D) Percentage inhibition of IL-13–induced FLG mRNA expression; E) FGF2 mRNA expression; and F) Percentage inhibition of IL-13–induced FGF2 mRNA expression.

Figure 6. Tralokinumab inhibits IL-13–induced expression of inflammatory mediators in human keratinocytes:

A) CCL-2 protein concentration in supernatant; B) Percentage inhibition of IL-13–induced CCL-2 protein secretion; C) CCL2 mRNA expression; D) Percentage inhibition of IL-13–induced CCL2 mRNA expression; E) NTRK1 mRNA expression; and F) Percentage inhibition of IL-13–induced NTRK1 mRNA expression.

Figure 7. Tralokinumab restores expression of skin barrier markers decreased by IL-13 in human keratinocytes:

A) LOR mRNA expression; B) Percentage inhibition of IL-13–induced LOR mRNA expression; C) FLG mRNA expression; D) Percentage inhibition of IL-13–induced FLG mRNA expression; E) FGF2 mRNA expression; and F) Percentage inhibition of IL-13–induced FGF2 mRNA expression.

Conclusions

• IL-13 expression levels correlate strongly with disease severity and with biomarkers related to the pathophysiology of AD.

• The expression of several AD disease biomarkers is regulated by IL-13 and is normalized in a dose–dependent manner by tralokinumab in cultures of human keratinocytes and dermal fibroblasts.

• These findings support the rationale for neutralizing excessive levels of IL-13 in AD by utilizing monoclonal antibodies targeting IL-13, such as tralokinumab.

References

1. Weidinger S et al. Nat Rev Dis Primers 2018;4:1
4. Berdyshev E et al. JCI Insight 2018;3:pii 98006

Disclosures

• Stephan Weidinger is a speaker, advisory board member, and/or investigator for: AbbVie, Galapagos, Kyorin, Kyowa Kirin, LEO Pharma, UCB, Anadys, Pillar, and Regeneron and Sullivan–Getzen.

• Maxim A.X. Tollenaere, Thomas Litman, and Hanne Norsgaard are employees of LEO Pharma.

• Katharina Drerup has nothing to disclose.

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