The Atopic Dermatitis Pathogenesis, and Implications for Alopecia Areata

Emma Guttman-Yassky, MD PhD
Sol and Clara Kest Professor, and Vice Chair Dermatology, Icahn School of Medicine at Mount Sinai Medical Center, NY
President, International Eczema Council
Atopic Dermatitis

◆ Most common inflammatory skin disease (3-7% of adults, 15-25% of children)

◆ 20-30% of patients have moderate-to-severe disease

◆ Large Unmet Need for long-term disease control

The therapeutic drought is finally ending!
AD Has A Complex Multifactorial Pathogenesis

Type 2 (Th2) (IL-4, IL-13, IL-5, IL-31)
Th22 (IL-22)

"Inside-Out"

Immune Hypothesis

"Outside-In"

Barrier Hypothesis

Epithelial Defects

AD Pathogenesis

General Inflammation

Itch

Skin Barrier Defects

Microbiome

Th2 and Th22 Adaptive Immunity

Modified with Permission from Beck LA
Two Proposed Pathogenic Hypotheses

**Epidermal-based model (“Outside-in”)**

AD is a disease of fixed (genetic) epidermal barrier defects that may trigger abnormal keratinocyte hyperplasia and secondary immune activation

*Supported by the FLG gene mutation in 2006.

**Immune-based model (“Inside-out”)**

The abnormal epidermal phenotype in lesional AD skin is initiated by increased expression of cytokines that induce the epidermal abnormalities

---

Barrier Defects in AD (and Clinical Correlations)

Lichenification: Epidermal hyperplasia characterizes chronic lesional AD skin

- AD, atopic dermatitis; H&E, hematoxylin and eosin; K16, keratin 16.

Terminal Differentiation, Tight Junction, and Lipid Defects

Guttman-Yassky, et al
J Allergy Clin Immunol 2009

De Benedetto A et al JACI 2011; 127: 773-786
AD shows progressive Th2 and Th22 cytokine activation with Th1 skewing in chronic disease.
The Type 2 Cytokines IL-4 and IL-13 Downregulate Epidermal Differentiation Proteins *In Vitro*

IL-22 promotes hyperplasia and impairs terminal differentiation

Full thickness skin rafts (epidermis + fibroblasts/dermis)

Genes up/down-regulated by IL-22 in keratinocytes

<table>
<thead>
<tr>
<th>S100As</th>
<th>FCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100A7 psoriasin</td>
<td>458.87</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Terminal Differentiation</th>
<th>FCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOR Loricrin</td>
<td>0.084</td>
</tr>
<tr>
<td>FLG Filaggrin</td>
<td>0.032</td>
</tr>
<tr>
<td>CALML5 Calmodulin 5</td>
<td>0.326</td>
</tr>
<tr>
<td>KRT1 keratin 1</td>
<td>0.022</td>
</tr>
<tr>
<td>KRT10 keratin 10</td>
<td>0.499</td>
</tr>
</tbody>
</table>

Effects:
- Acanthosis of epidermis
- Keratin 16 synthesis
- S100A7 synthesis

Sa SM et al, J Immunol, 2007
A paradigm shift in pathogenesis of AD

Gittler J....Guttman-Yassky E Allergy Clin Immunol 2012
Is AD A Single Disease Across The Spectrum?

◆ All AD subtypes share robust Th2 activation

◆ But, stratification of biomarkers specific to different AD phenotypes may be important for developing a personalized medicine approach for AD

Czarnowicki T, He H, Krueger JG, Guttman-Yassky E JACI IN Press 2018
Atopic Dermatitis Emerges as a Systemic Disease

- Systemic Inflammation is well established in psoriasis
- Higher immune activation has been recently reported in peripheral blood from AD vs. psoriasis patients
  - Increased activated T cells
  - Increased circulatory cytokines and cardiovascular associated markers

Systemic Cytokine Activation in AD

Serum cytokines levels were increased in AD patients and correlated with disease severity (SCORAD).
post CsA treatment ...

Modifiable risk factors?

Association between adult atopic dermatitis, cardiovascular disease, and increased heart attacks in three population-based studies

J. I. Silverberg\textsuperscript{1,2}

\textsuperscript{1}Departments of Dermatology, Preventive Medicine and Medical Social Sciences, Northwestern University Feinberg School of Medicine; \textsuperscript{2}Northwestern Medicine Multidisciplinary Eczema Center, Chicago, IL, USA

- **NHANES**
  - Flexural eczema in the past year was associated with significantly higher odds of CAD (P ≤ 0.04), heart attack (P ≤ 0.01), and congestive heart failure (P ≤ 0.02), but not with stroke (P ≥ 0.37), in survey-weighted multivariate logistic regression models that controlled for socio-demographics, comorbid asthma, and hay fever.

- **NHIS 2010 and 2012**
  - 1-year history of eczema was associated with significantly higher odds of CAD (P ≤ 0.02), angina (P ≤ 0.02), heart attack (P ≤ 0.047), other heart disease (P < 0.0001), stroke (P ≤ 0.02), and PVD (<0.0001) in multivariate models.
Abnormal Cytokine Profile Already Exists in Non-Lesional AD Skin (Unlike Psoriasis)

The high level systemic immune activation in AD emphasizes the need for systemic treatment approaches for moderate-to-severe AD.

An Integrated Model of Therapeutic Response Biomarkers shows much Higher Correlations with Clinical Responses to CsA

Ungar B...and Guttman-Yassky E. J Invest Dermatol 2017
How Are We Testing the Contribution of Cytokine Pathways to AD?

Through Clinical Trials with Targeted Treatments in AD Patients
Dupilumab, a fully human IL-4Rα mAb potently inhibits both IL-4 and IL-13 signaling

- 4 week study with weekly injections of dupilumab 75mg, 150mg, 300mg and placebo
- A total of 67 patients, 18 participated in the biopsy study

Beck L….Guttman-Yassky E et al, NEJM 2014
Dose dependent EASI-50 results in Phase 1B

No differences in responses were seen between AD patients based on IgE or FLG mutation status

* $p<0.05$; † $p=0.003$

Beck L....Guttman-Yassky E et al, NEJM 2014
Changes in the Atopic Dermatitis Molecular Disease Profile in Phase 1B

<table>
<thead>
<tr>
<th>Keratin 16</th>
<th>CCL20</th>
<th>IL-1β</th>
<th>CXCL1</th>
<th>S100A7</th>
<th>S100A8</th>
<th>IFNγ</th>
<th>IL-17A</th>
<th>IL-12/IL-23p40</th>
<th>CXCL10</th>
<th>CCL13</th>
<th>CCL18</th>
<th>CCL26</th>
<th>MMP12</th>
<th>CCL17</th>
<th>IL-23A</th>
<th>ELAFIN</th>
<th>S100A12</th>
<th>K16</th>
</tr>
</thead>
<tbody>
<tr>
<td>19***</td>
<td>1.1</td>
<td>-1</td>
<td>-4.1</td>
<td>-3.7</td>
<td>-3*</td>
<td>-1.2</td>
<td>-2.6</td>
<td>-3</td>
<td>-2.6</td>
<td>-6**</td>
<td>-7.6***</td>
<td>-6.3**</td>
<td>-1.3</td>
<td>-14**</td>
<td>-9.2**</td>
<td>-12.8***</td>
<td>-18.5**</td>
<td>-10.4*</td>
</tr>
<tr>
<td>3.7</td>
<td>-1</td>
<td></td>
<td>-4.1</td>
<td></td>
<td></td>
<td>-3.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-3.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-3*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.9</td>
<td></td>
<td></td>
<td>-7.1</td>
<td>-2.6</td>
<td></td>
<td>-2.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.7</td>
<td></td>
<td></td>
<td>-1.2</td>
<td>-3</td>
<td></td>
<td>-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.4</td>
<td></td>
<td></td>
<td>-2.5</td>
<td>-2.6</td>
<td></td>
<td>-2.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>-2.1</td>
<td>-6**</td>
<td></td>
<td>-6**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>-4.2***</td>
<td>-7.6***</td>
<td></td>
<td>-7.6***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.6</td>
<td></td>
<td></td>
<td>-3.1*</td>
<td>-6.3**</td>
<td></td>
<td>-6.3**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>-1.3</td>
<td>-14**</td>
<td></td>
<td>-14**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td></td>
<td></td>
<td>1.6</td>
<td>-9.2**</td>
<td></td>
<td>-9.2**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td></td>
<td></td>
<td>1.1</td>
<td>-12.8***</td>
<td></td>
<td>-12.8***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4</td>
<td></td>
<td></td>
<td>-1.9</td>
<td>-18.5**</td>
<td></td>
<td>-18.5**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.9</td>
<td></td>
<td></td>
<td>-1.8</td>
<td>-10.4*</td>
<td></td>
<td>-10.4*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.7</td>
<td></td>
<td></td>
<td>-2</td>
<td>-10.7***</td>
<td></td>
<td>-10.7***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In a larger 16wk study Dupilumab progressively reversed the AD transcriptome

No major change at Week 4
Some change at Week 16
Further shift at Week 16

At Week 16 the LS phenotype simulates the NL molecular phenotype

Z-score = no. of SD's removed from the mean.

Dupilumab reversed the dysregulation of the AD transcriptome

Both groups showed similar dysregulation at baseline

At Week 4, dupilumab already showed reversal of dysregulation while placebo had increased dysregulation

Dupilumab showed major reversal of dysregulated genes at Week 16

Dupilumab Also Reversed the AD Barrier Defects in the 16 week study

**Epidermal Thickness**

- **Placebo**
- **200 mg dpl**

**Study week**

- **Baseline**
- **Week 4**
- **Week 16**

Dupilumab impacts both the inflammation and the barrier dysfunction of AD

This establishes the Th2 axis and IL-4 and IL-13 cytokines as pathogenic in AD and cements AD as a reversible, immune-driven disease, like psoriasis.

Th22/IL-22 targeting
A monotherapy study with ILV-094/anti-IL-22 in AD

Methods:
N=60 (2:1 to placebo)
Primary endpoint: week 12, 8 week follow up
6 IV doses until week 10

---

Guttman-Yassky E el. JAAD January 2018 (Online)
Much Greater Transcriptome Improvement in the High IL-22 Group

**High IL-22**

**Low IL-22**

**Placebo**  
**ILV-094**

Week 4  
Week 12

**Week 4**  
54%  
49.9%  
82.9%  
139.4%

**Week 12**  
-54.6%  
-117.7%  
-29.9%  
-34.5%

*Brunner P, Pavel B. Ana......and Guttman-Yassky E. JACI 2018*
Summary

- AD is increasingly recognized as a systemic disease, suggesting the need for systemic treatment approaches for severe AD patients.
- The $T_{H}2$ axis is central to the pathogenesis of AD but is not solely responsible.
- The therapeutic pipeline for AD is robust with many promising new targets and drugs in development.
- Specific cytokine targeting (with mechanistic correlates) helps to shed light into their relative contributions to AD.
Extending the translational revolution to AA

AA is highly associated with Atopy

Comorbidities of AA:

38.2%  Atopy (allergic rhinitis, asthma, and/or eczema)
25.5%  Depression or anxiety
24.5%  Hyperlipidemia
21.9%  Hypertension
17.3%  Gastroesophageal reflux disease
14.6%  Thyroid disease
11.1%  Diabetes mellitus
6.3%   Psoriasis and psoriatic arthritis
4.3%   Systemic lupus erythematosus
3.9%   Rheumatoid arthritis
2.0%   Inflammatory bowel disease

Huang KP et al. JAMA Dermatol 2013
Genetic Associations

**GWAS studies**: IL-13, CTLA4, IL-2RA, IL-2/IL-21, ULBP3/ULBP6, PRDX5, STX17, and IKZF4/ERBB3 identified in the 1st North American study

Authors concluded that IL-13 is also a susceptibility loci for other atopic diseases, supporting the hypothesis of shared pathways of susceptibility

Genetic polymorphisms of **IL-4, IL-16, ICOS, IL-18, FAS/FASL** were also associated with AA

AA is a highly inflammatory skin disease with increased Th1, IL-23 and Th2 cytokine circuits

Suarez-Farinas, M....Guttman-Yassky, E. JACI August 2015.

N Scalp, normal scalp, N Skin, normal skin; NL, non lesional; LS, lesional
An Integrated Model of Alopecia Areata Scalp and Serum Biomarkers Highlights Th1 and Th2 Biomarkers

**TABLE E3. Pearson correlations of serum and scalp markers with SALT scores**

<table>
<thead>
<tr>
<th></th>
<th>Correlation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SALT</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CCL13_NL</td>
<td>0.707950355</td>
<td>0.00312547</td>
</tr>
<tr>
<td>CCL13_LS</td>
<td>0.666522369</td>
<td>0.00665752</td>
</tr>
<tr>
<td>IL-13_LS</td>
<td>0.529054484</td>
<td>0.04257426</td>
</tr>
<tr>
<td>IL-15_Serum</td>
<td>0.521993472</td>
<td>0.04594147</td>
</tr>
<tr>
<td>IFN-γ_LS</td>
<td>0.398517514</td>
<td>0.05863321</td>
</tr>
<tr>
<td>CXCL10_LS</td>
<td>0.497940847</td>
<td>0.05890219</td>
</tr>
<tr>
<td>IL-15_NL</td>
<td>0.497009935</td>
<td>0.05939874</td>
</tr>
<tr>
<td>Eotaxin_Serum</td>
<td>0.466142606</td>
<td>0.07988072</td>
</tr>
<tr>
<td>MCP-1_Serum</td>
<td>0.431349337</td>
<td>0.10841310</td>
</tr>
<tr>
<td>MDC_Serum</td>
<td>0.398533497</td>
<td>0.1410586</td>
</tr>
<tr>
<td>CCL13_NL</td>
<td>0.354106554</td>
<td>0.19534049</td>
</tr>
<tr>
<td>IL-13_NL</td>
<td>0.300738785</td>
<td>0.27607323</td>
</tr>
<tr>
<td>IFN-γ_NL</td>
<td>0.277021665</td>
<td>0.31752173</td>
</tr>
<tr>
<td>IL-15_LS</td>
<td>0.24964435</td>
<td>0.36950431</td>
</tr>
<tr>
<td>CCL13_Serum</td>
<td>0.210507366</td>
<td>0.45141285</td>
</tr>
<tr>
<td>MIP-1α_Serum</td>
<td>0.190827577</td>
<td>0.49570896</td>
</tr>
<tr>
<td>CCL17_Serum</td>
<td>0.186925674</td>
<td>0.50472610</td>
</tr>
<tr>
<td>IFN-γ_Serum</td>
<td>0.129623548</td>
<td>0.64520932</td>
</tr>
<tr>
<td>IL-13_Serum</td>
<td>0.083101337</td>
<td>0.78843675</td>
</tr>
<tr>
<td>CXCL10_Serum</td>
<td>0.064965322</td>
<td>0.81807307</td>
</tr>
<tr>
<td>CCL17_LS</td>
<td>0.056811135</td>
<td>0.84061942</td>
</tr>
<tr>
<td>MIP-1α_Serum</td>
<td>0.038272464</td>
<td>0.89228182</td>
</tr>
<tr>
<td>Eotaxin-3_Serum</td>
<td>-0.075627877</td>
<td>0.78873459</td>
</tr>
<tr>
<td>CCL17_NL</td>
<td>-0.078498565</td>
<td>0.78093329</td>
</tr>
</tbody>
</table>

MCP, Monocyte chemoattractant protein; MDC, macrophage-derived chemokine; MIP, macrophage inflammatory protein.

**Figure**

- **IFNγ LS, IL5 LS, IL13 NL, IL10 NL**
  - $r = 0.79$, $p < 0.01$

**Score**

- **SALT**
  - Score range: 25 to 100

**Teresa Song, Guttman-Yassky E. JACI 2018**
**P<0.01, ***P<0.001 vs placebo
BL, baseline; CI, confidence interval; LS, least squares; SALT, Severity of Alopecia Tool.

Guttman-Yassky et al. ISDS 2018
The immune pathogenesis of AA is complex and still being elucidated.

- Because of more broad inhibition of multiple cytokines/pathways, JAK inhibitors cannot fully tease out the pathogenesis of AA.

- Clinical trials with targeted therapeutics against different axes are required to test their possible pathogenic contributions.
In Sum

◆ AA shares pathogenic features with AD

◆ Similar to AD, AA is also increasingly recognized as a systemic disease, suggesting the need for systemic treatment approaches for severe patients.

◆ AA might present a similar model to AD in which immune cytokines suppress formation of hair keratins.

◆ Similar to AD, AA may present different disease endotypes (subtypes) with differing immune polarizations.

◆ Specific cytokine inhibition with mechanistic correlates is needed to dissect the mechanisms underlying AA.
Thank You

We are now beginning an exciting medical and scientific path for a new treatment paradigm for our atopic dermatitis patients and beyond.