The Science of Atopic Dermatitis

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Conflicts of interest:

None to disclose
Objectives:

1. Review the epidemiology and relevance of atopic dermatitis

2. Discuss the key factors that contribute to the physiopathology of the disease

3. Create a foundation for rationale clinical management of atopic dermatitis
Relevance

• Prevalent
  • Affects up to 20% of children in developed countries \(^1\)
  • 25% develop AD in the first 6 months of life, 60% in the first year of life \(^1\)

• Burden
  • Significant impairment in quality of life, sleep, conduct, emotions, peer relationships, attention \(^2\)

• Intervention
  • **Atopic march** often starts with AD
  • **Epicutaneous sensitization** as a driver of other atopic manifestations \(^3\)

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1. Kay J, Gawkrodger DJ, Mortimer MJ et al.
2. Wan J, Takeshita J, Shin DB et al.
A multifactorial disease

- Numerous factors causing, aggravating and perpetuating AD
- Two main hypothesis concerning mechanism:
  - **Inside-out**
    Primary immunologic disturbance ➔ IgE-mediated sensitization ➔ consequent epithelial barrier dysfunction caused by local inflammation
  - **Outside-in**
    Intrinsic defect in the epithelial cells leading to barrier dysfunction ➔ secondary immunologic disturbance and IgE sensitization
Skin barrier – more than just “mortar and brick”
Filaggrin

Adapted from Brown S, Irwin McLean WH
Skin barrier – more than just “mortar and brick”

- **Not a static** physical structure

- Filaggrin: maintain cornified envelope, promotes keratin aggregation, regulation of skin pH, breakdown products have water-binding capacity (natural moisturizing factor)

- **Inflammation** can decrease expression of filaggrin

- Changes in **external humidity** regulate proteolysis of filaggrin, epidermal DNA/lipid synthesis, and initiation of inflammation

- **Changes in pH** can alter maturation of lamellar bodies
### The infant skin

<table>
<thead>
<tr>
<th>Structural and functional differences between infant and adult skin</th>
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<tbody>
<tr>
<td><strong>Infant</strong></td>
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<tr>
<td>Structural differences</td>
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<tr>
<td>Epidermal thickness</td>
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<tr>
<td>Cell attachments and epidermal cellularity</td>
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<tr>
<td>Dermoepidermal junction</td>
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<td>Lipids</td>
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<td>Melanin</td>
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<td>Functional differences</td>
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<td>Sweat</td>
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<td>Water content</td>
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<tr>
<td>Natural moisturizing factor concentration</td>
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<td>pH</td>
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<td>TEWL</td>
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<tr>
<td>Higher</td>
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<tr>
<td>No significant differences</td>
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</tbody>
</table>
Genetics

• Odds ratio of affected offspring when mother and father have atopic dermatitis is 4.7

• Concordance in dizygotic twins 15% vs. monozygotic twins 77%

• Several candidate genes identified - epithelial **structural proteins** and major **elements of the immune system**¹

  • 5q31-33: IL-4, IL-5, IL-12, IL-13

  • 1q21.3: (epidermal differentiation complex²) – **Filaggrin**

    • Early onset AD, AD with asthma, ichthyosis vulgaris

¹ Bieber T.  
² Cookson W.
The Th2 polarization

**Physiologic role:**
Clearance of parasitic worms

**Pathologic role:**
Allergic diseases

**Physiologic role:**
Clearance of intracellular pathogens

**Pathologic role:**
Autoimmunity

Interleukin-12
Interleukin-18

Dendritic cell

Interleukin-4

Naive T cell

Th0

Interleukin-4

Interleukin-5

Th1

Interleukin-4

Interleukin-18

Th2

B cell

IgE

B cell
Non-IgE mediated inflammation

TSLP: thymic stromal lymphopoietin
Chronic and acute phases of AD

MCP-1: monocyte chemotactic protein 1
IDEC: inflammatory dendritic epidermal cells

Bieber T.
Infections

- Toll-like receptors on skin ➔ induce the production of defensins and cathelicidins (antimicrobial peptides)

- Decreased cathelicidins ➔ viral infections such as eczema herpeticum

- IL-4, IL-13 downregulate production of antimicrobial peptides in AD ➔ infections

- “Non-pathologic microbial stimulation” ➔ induces regulatory T cell–mediated anti-inflammatory cytokines (IL-10 and TGF-β)
Staphylococcus aureus

• 90% of AD patients are colonized with *Staphylococcus aureus* \(^1\)

• Colonization ➔ increased TEWL, increased IgE, peripheral eosinophilia, more severe disease

• *S. aureus* **worsens barrier dysfunction** through various mechanisms: superantigens, enterotoxin (recruit T-cells), increased **serine protease** (degradation of desmoglein-1 and filaggrin and compromise of barrier integrity)\(^2\), production of ceramidases, induce the competing glucocorticoid receptor in mononuclear cells (resistance to topical steroid treatment).

• *Staphylococcus epidermidis* increases tight junctions and antimicrobial peptide production

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1. Bieber T
2. Williams MR, Nakatsuji T, Sanford JA
The microbiome, probiotics and prebiotics

- **Decrease microbial skin diversity** and an increased *S. aureus* compared to healthy controls, even on non-lesional skin ➔ more severe AD phenotypes

- Treatment with topical steroids improves microbial diversity

- Topical application of commensal bacteria (*S. hominis, S. epidermidis*) has shown clinical improvement in erythema, scaling and pruritus

- Oral probiotics - inconclusive data, not enough evidence to recommend

- Inconclusive data on prebiotics for AD

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1. Shaker M, Murray RGP, Mann JA
2. Gonzalez ME, Schaffer JV, Orlow SJ et al
Scratching and behavior

- **Mechanical injury** induced by scratching can recruit Th17 cells\(^1\), upregulates IL-13 receptors on keratinocytes \(^2\).

- **Repeated scratching** caused decrease of PGD2, which has an inhibitory role against pruritus \(^3\).

- **Psychological stress** can increase scratching and exacerbate AD \(^4\).

1. Furue K, Ito T, Tsuji G et al
2. Ulzii D, Kido-Nakahara M, Nakahara T et al
Conclusion

• AD is a prevalent, complex and multifactorial disease

• Multifaceted interactions of skin barrier, environment, immune and nervous systems

• Multiple avenues to intervene clinically

• Can we halt the atopic march by repairing the skin?