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The Science of Atopic Dermatitis

UHealth
UNIVERSITY OF MIAMI HEALTH SYSTEM

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Conflicts of interest:

None to disclose

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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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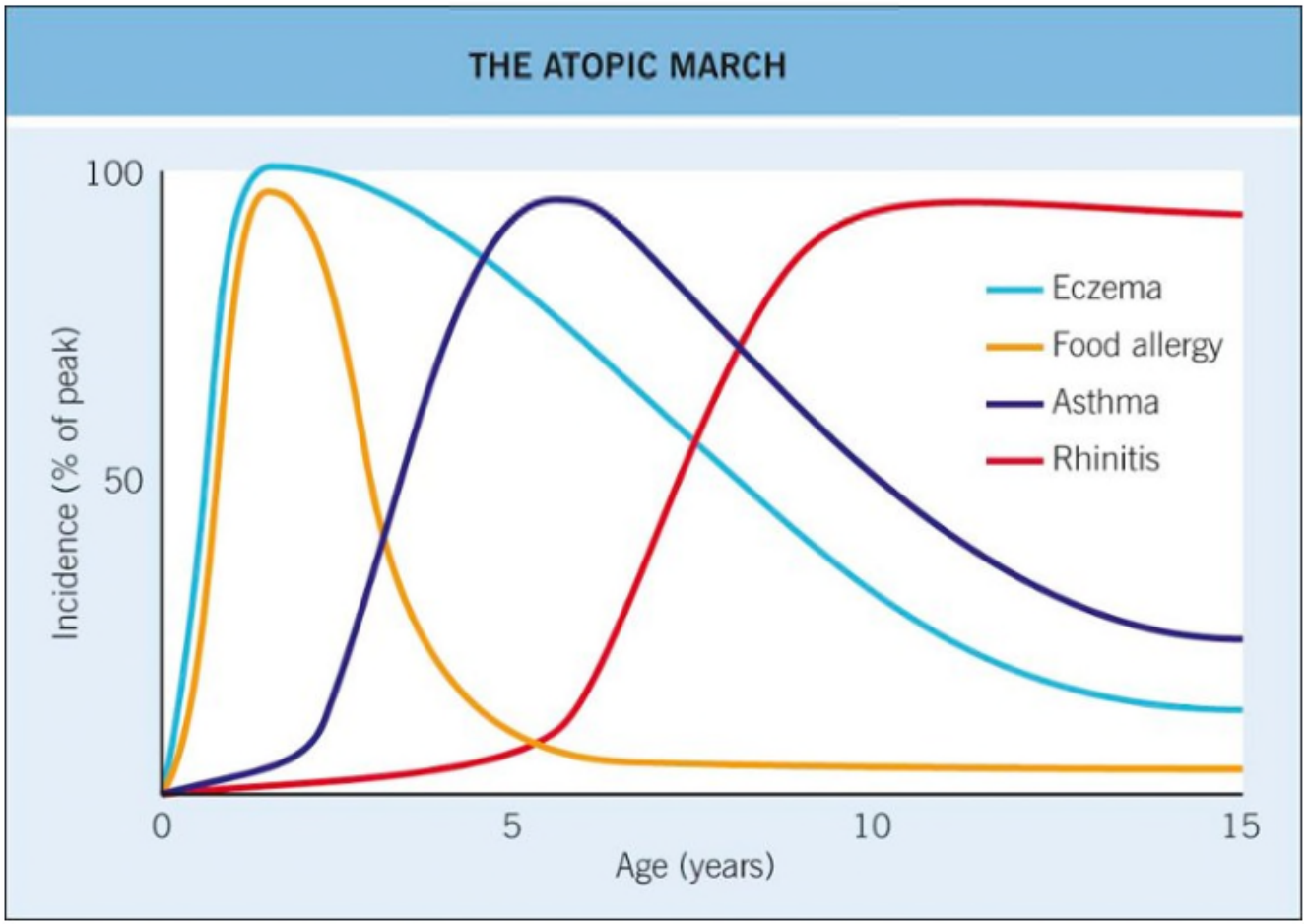
1. Kay J, Gawkrodger DJ, Mortimer MJ et al.
2. Wan J, Takeshita J, Shin DB et al.
3. Spergel JM, Mizoguchi E, Brewer JP et al.



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Bolognia JL, Jorizzo JL, Schaffer JV

A multifactorial disease

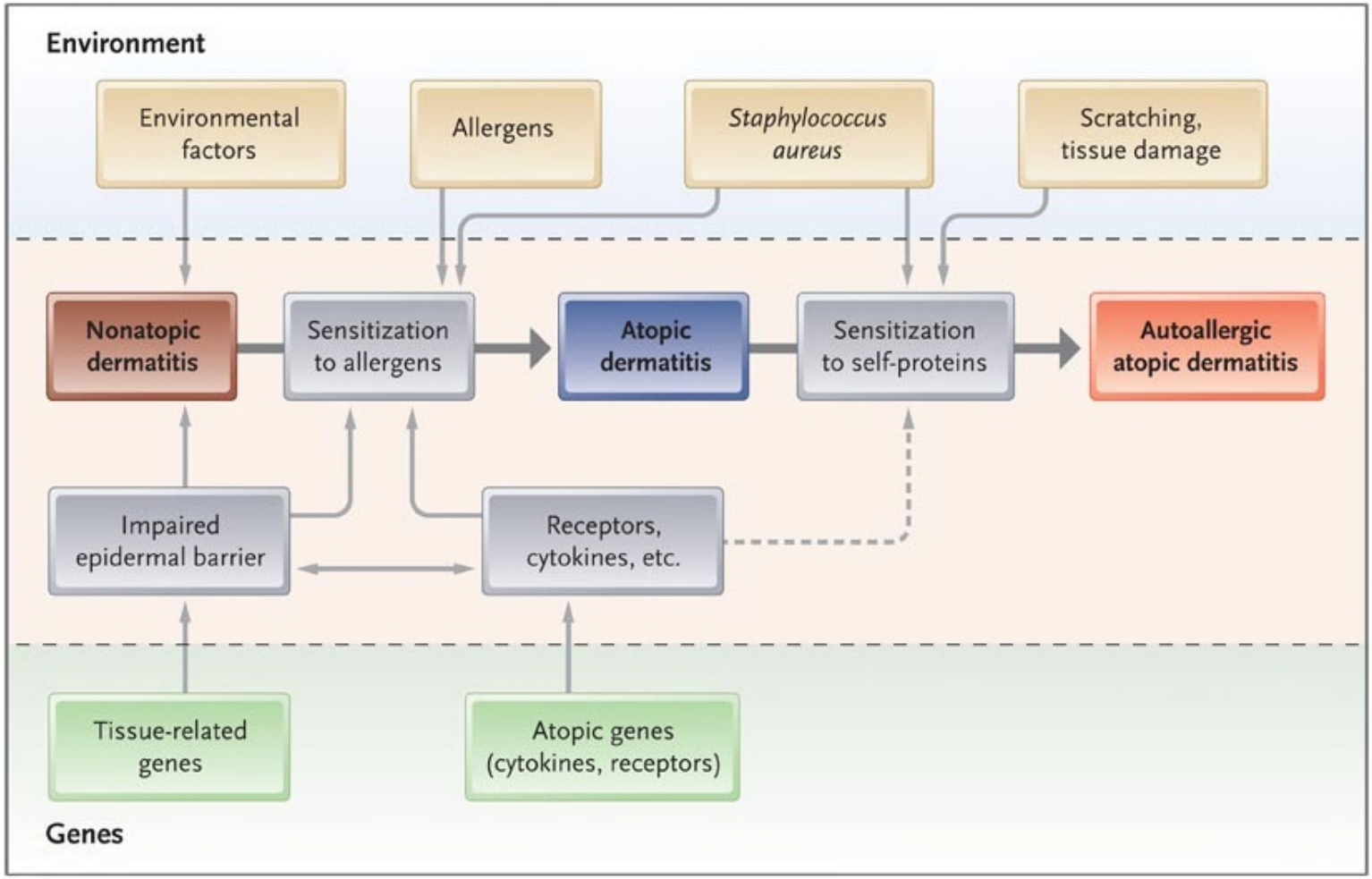
- Numerous factors causing, aggravating and perpetuating AD
- Two main hypothesis concerning mechanism:

- **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



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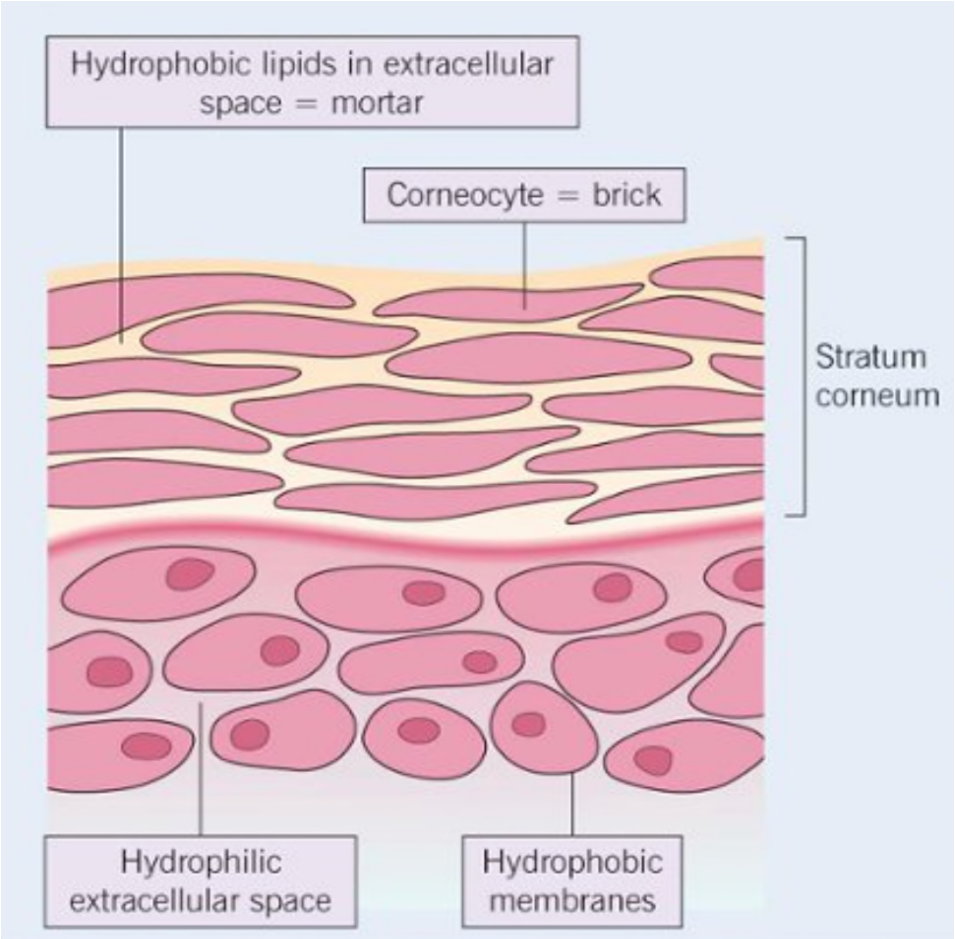
Bieber T.

Skin barrier – more than just “mortar and brick”



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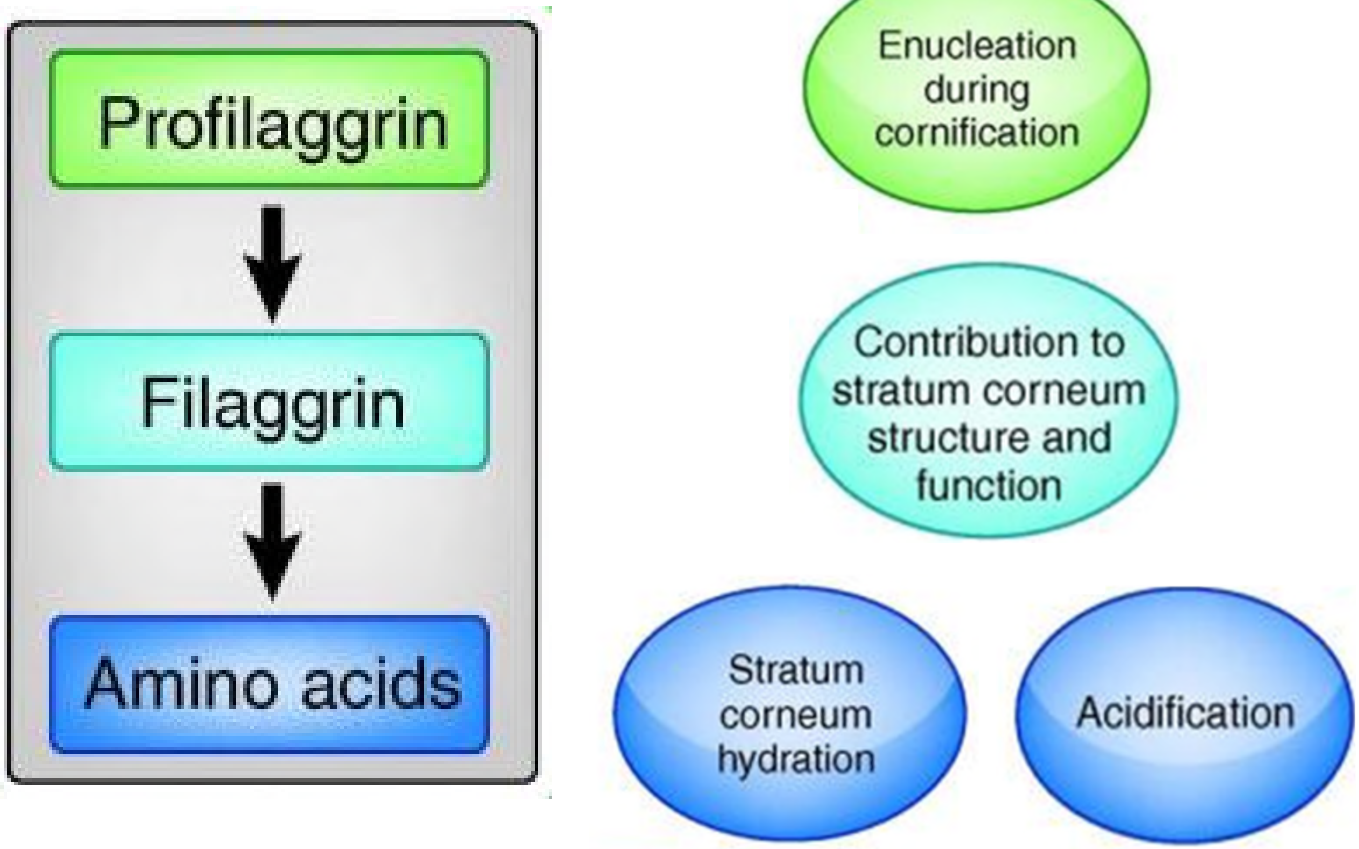
Filaggrin



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

Structural and functional differences between infant and adult skin

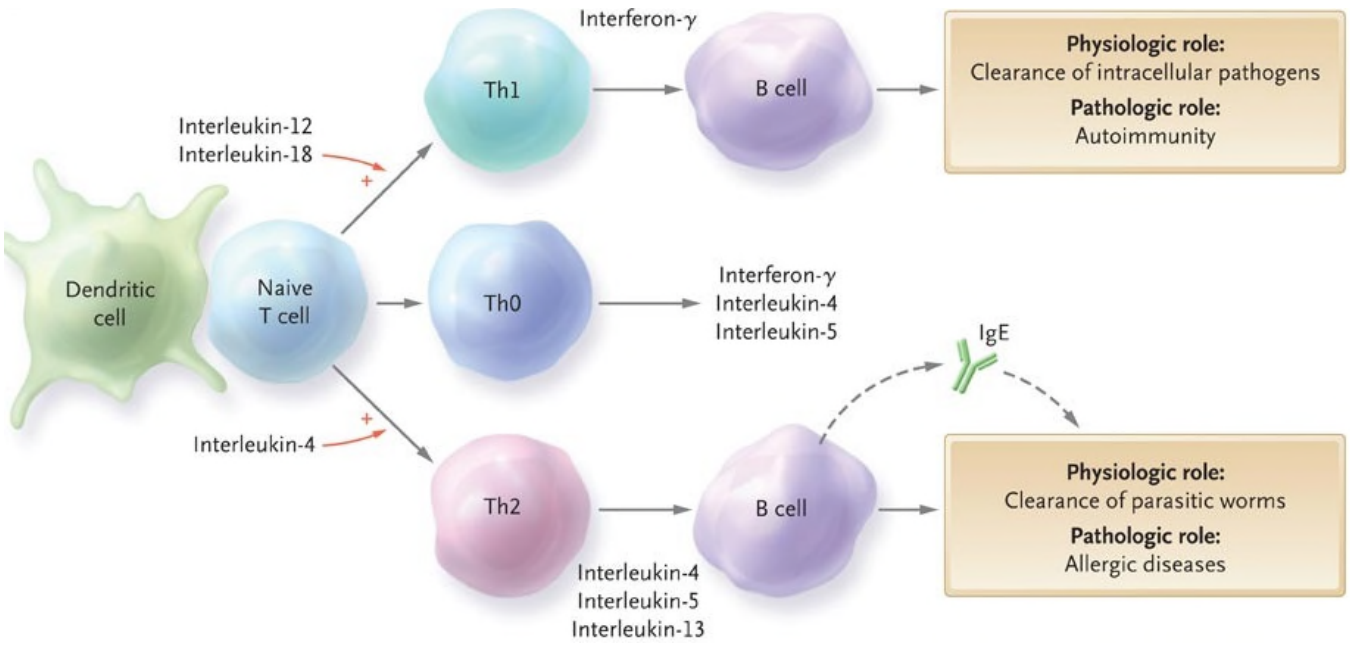
	Infant	*Adult*
Structural differences		
Epidermal thickness	Thinner	Thicker
	No significant differences	
Cell attachments and epidermal cellularity	Less	More
Dermoepidermal junction	Flat	Undulating
Lipids	Less	More
Melanin	Less	More
Functional differences		
Sweat	Less	More
Water content	Higher	Lower
Natural moisturizing factor concentration	Lower	Higher
pH	Higher	Lower
TEWL	Lower	Higher
	Higher	Lower
	No significant differences	

Genetics

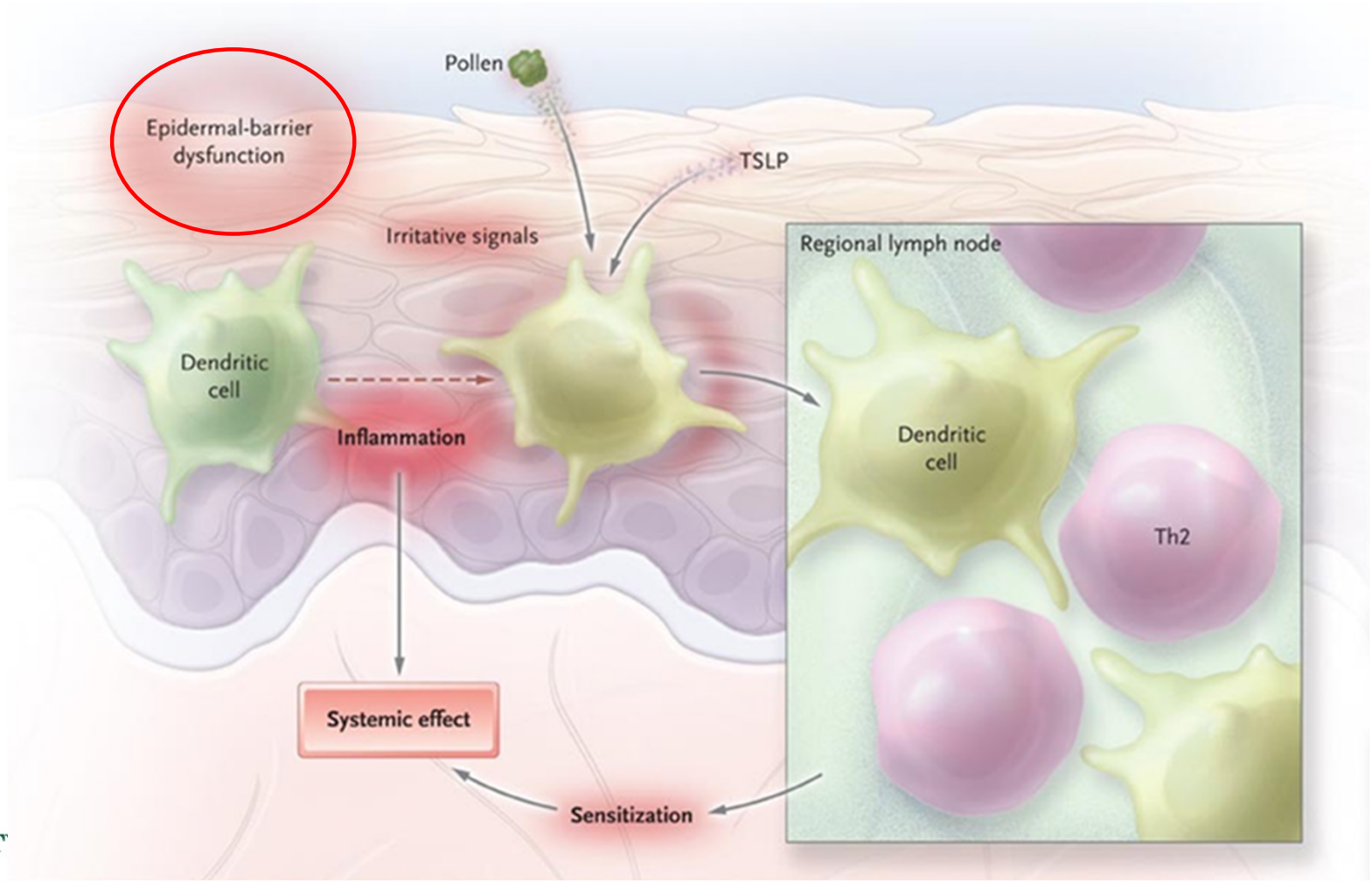
- Odds ratio of affected offspring when mother and father have atopic dermatitis is 4.7
- Concordance in dizygotic twins 15% vs. monozygotic twins 77%
- Several candidate genes identified - epithelial **structural proteins** and major **elements of the immune system** [1]
  - *5q31-33*: IL-4, IL-5, IL-12, IL-13
  - *1q21.3*: (epidermal differentiation complex[2)] – **Filaggrin**
    - Early onset AD, AD with asthma, ichthyosis vulgaris

1. Bieber T.
2. Cookson W.

The Th2 polarization



Non-IgE mediated inflammation



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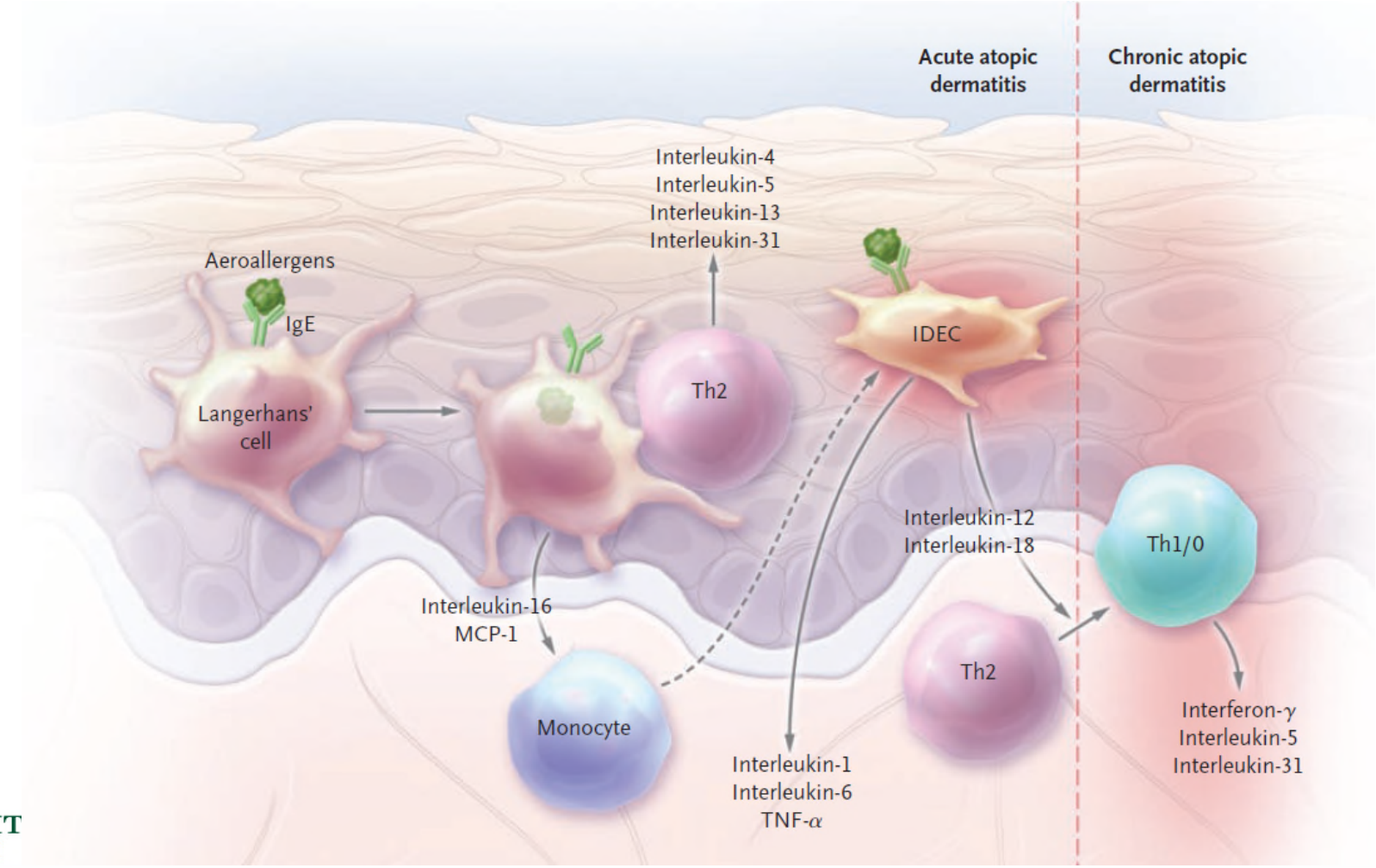
TSLP: thymic stromal lymphopoietin

Bieber T.

Chronic and acute phases of AD



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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

1. Bieber T
2. Williams MR, Nakatsuji T, Sanford JA

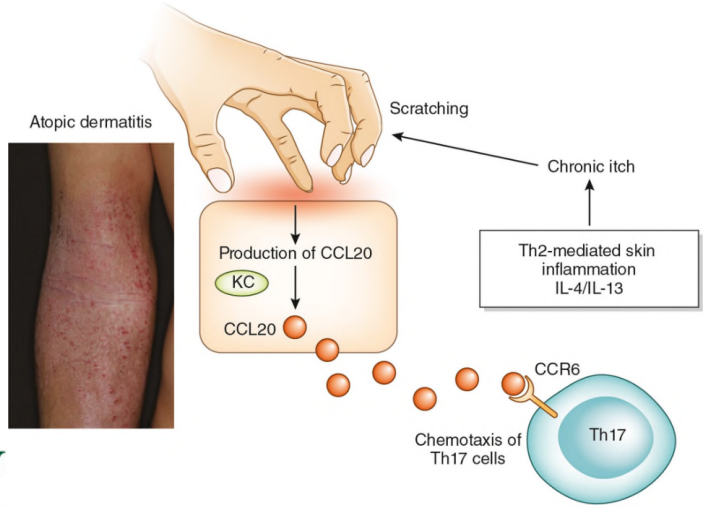
The microbiome, probiotics and prebiotics

- **Decrease microbial skin diversity** and an increased *S. aureus* compared to healthy controls, even on non-lesional skin ➔ more severe AD phenotypes [1]
- Treatment with topical steroids improves microbial diversity [2]
- Topical application of commensal bacteria (S. hominis, S. epidermidis) has shown clinical improvement in erythema, scaling and pruritus [3]
- Oral probiotics - inconclusive data, not enough evidence to recommend
- Inconclusive data on prebiotics for AD [4]

1. Shaker M, Murray RGP, Mann JA
2. Gonzalez ME, Schaffer JV, Orlow SJ et al
3. Knackstead R, Knackstead T, Gatherwritgh J
4. Navarro-Lopez V, Ramirez-Bosca A, Ramon-Vidal D 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]



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1. Furue K, Ito T, Tsuji G et al
2. Ulzii D, Kido-Nakahara M, Nakahara T et al
3. Sugimoto M, Arai I, Futaki N et al
4. Mochizuki H, Lavery MJ, Nattkemper LA 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?

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