

Skin microbiome and skin allergies

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CIRI – INSERM U1111

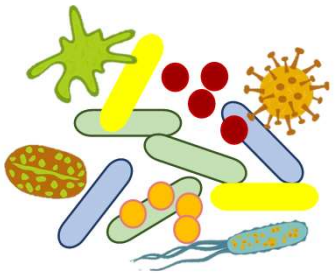
Team Leaders: **M.VOCAISON- J-F.NICOLAS**

LYON - France



Microbial dysbiosis – immune responses & allergic diseases

Microbiome

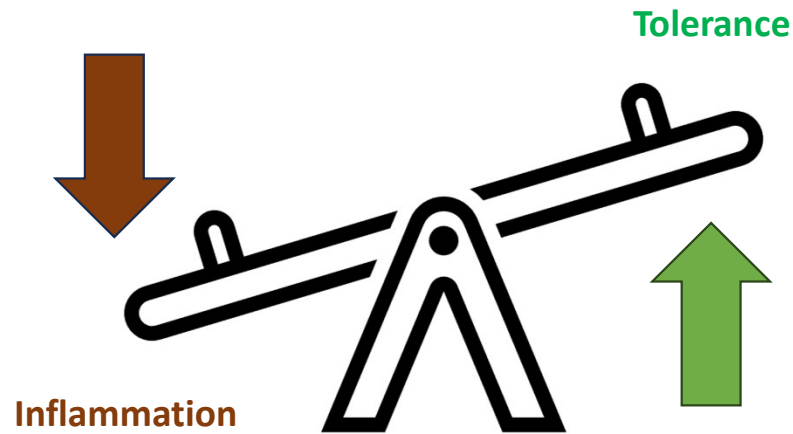


Microbial dysbiosis



Microbial molecules & metabolites

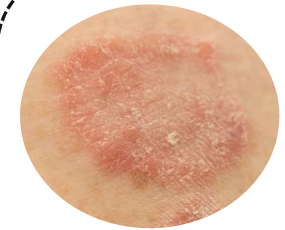
Immune response



Inflammation

Tolerance

Allergic diseases

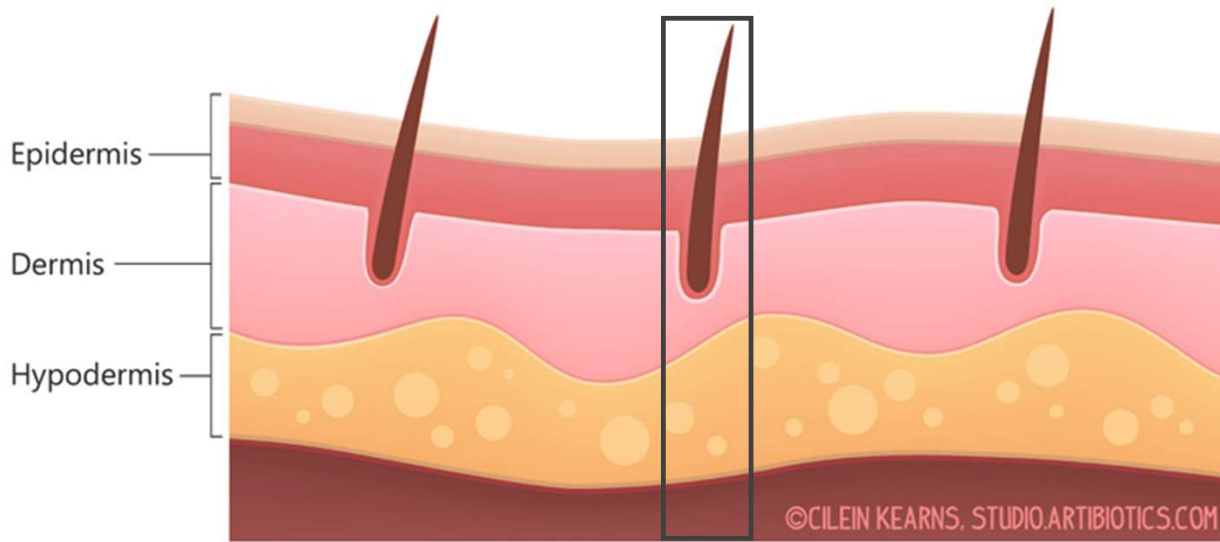


Allergic eczema

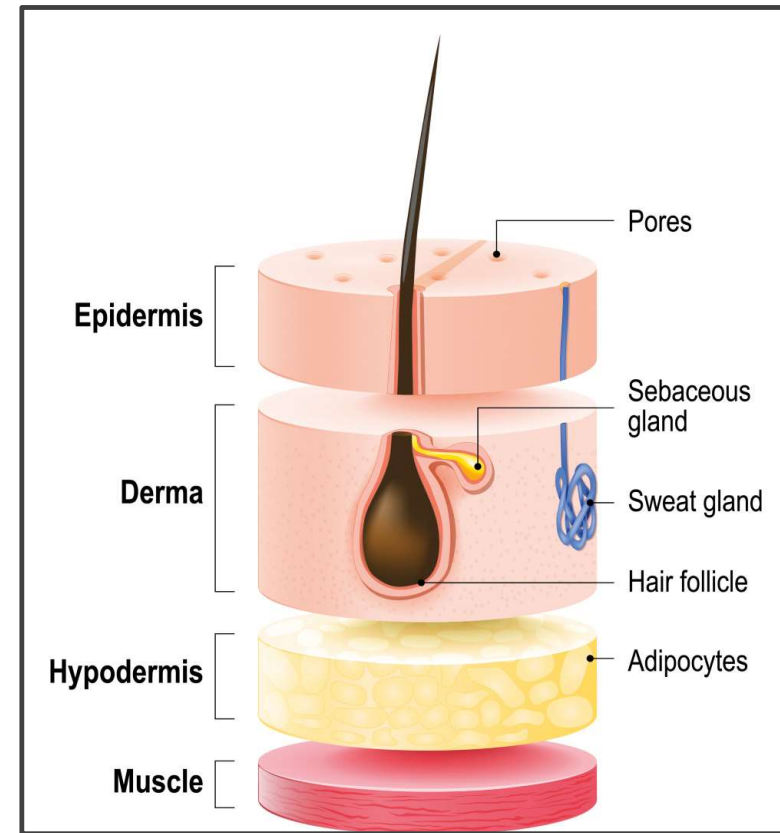
Sun allergy (PLE)



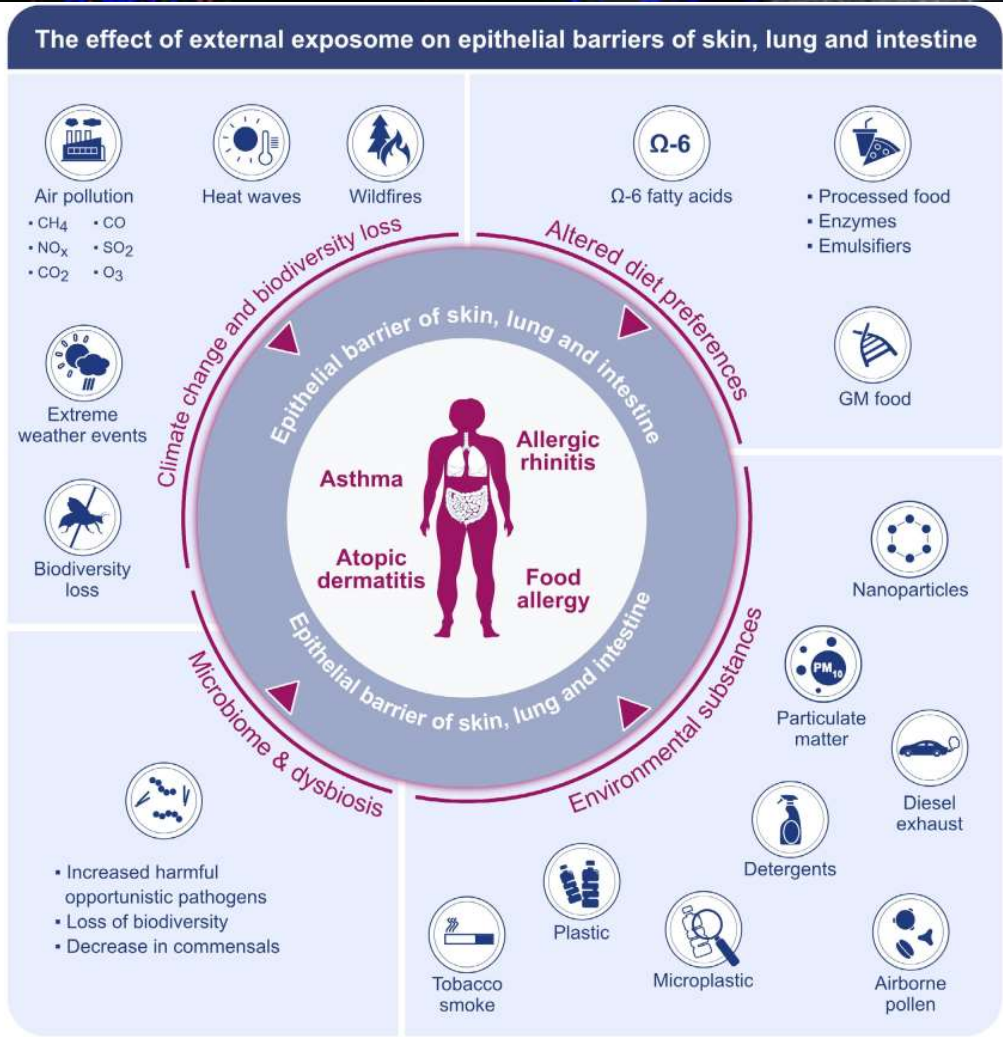
The skin: not just a barrier!



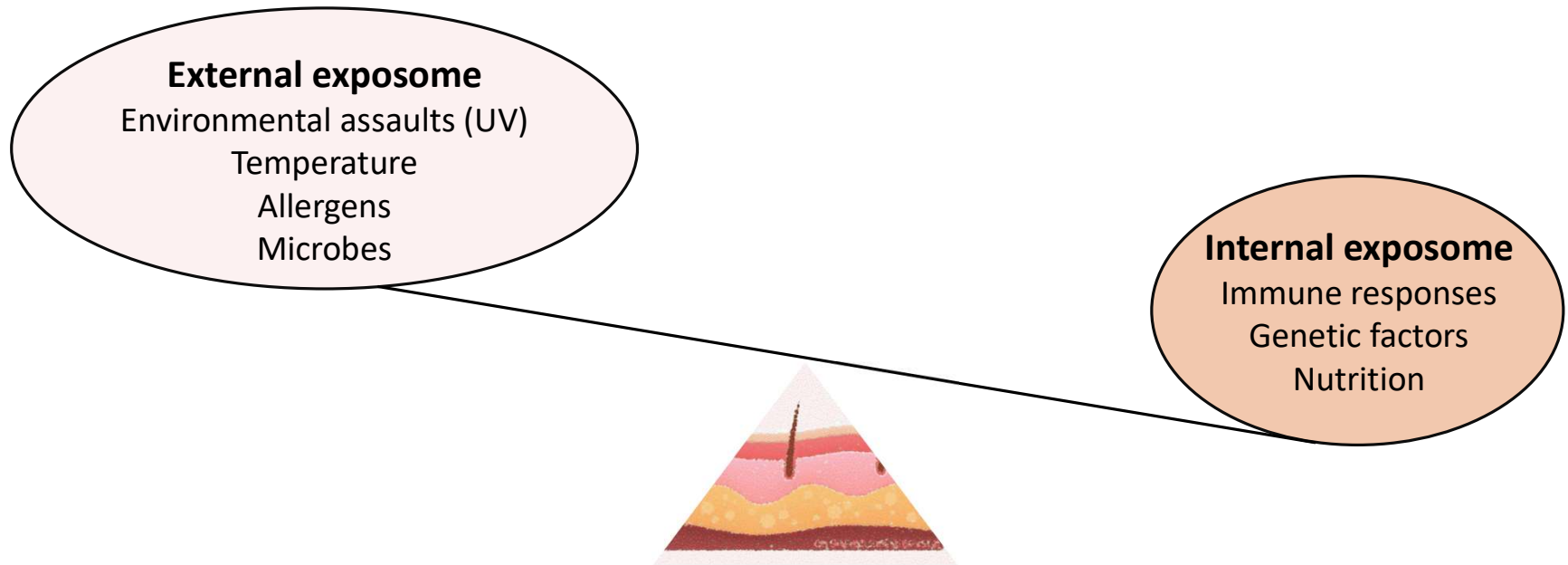
- 0.5- 4 *mm* in thickness
- 25m² surface area



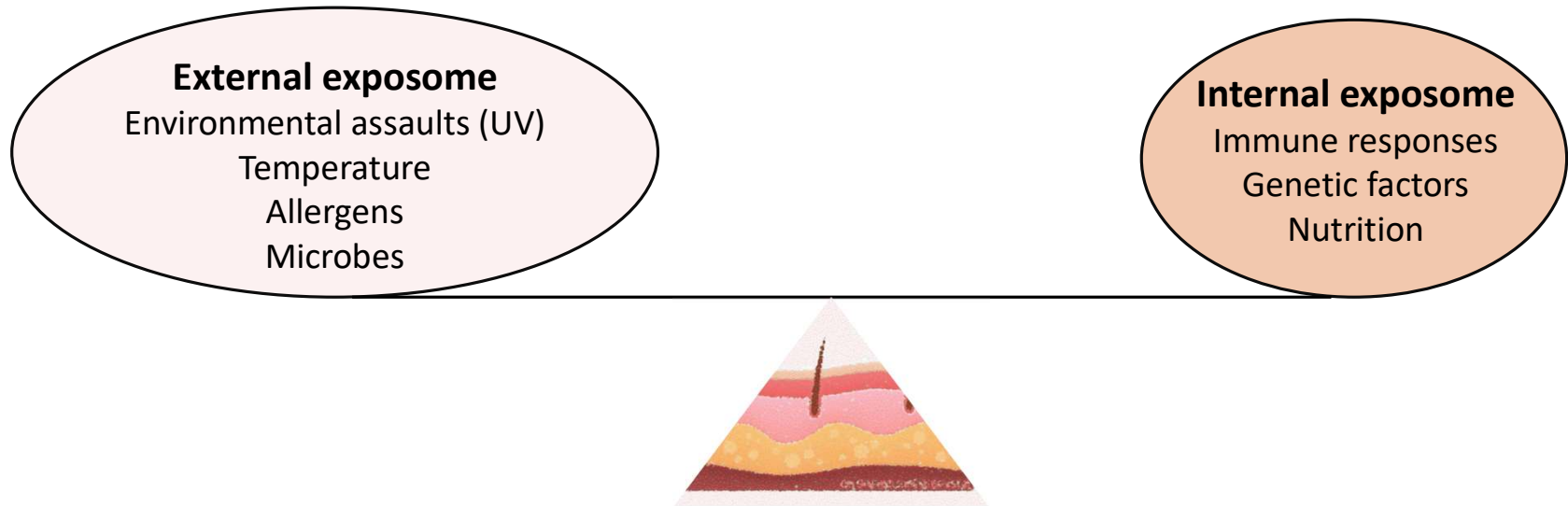
Exposome



Skin homeostasis: an essential balance



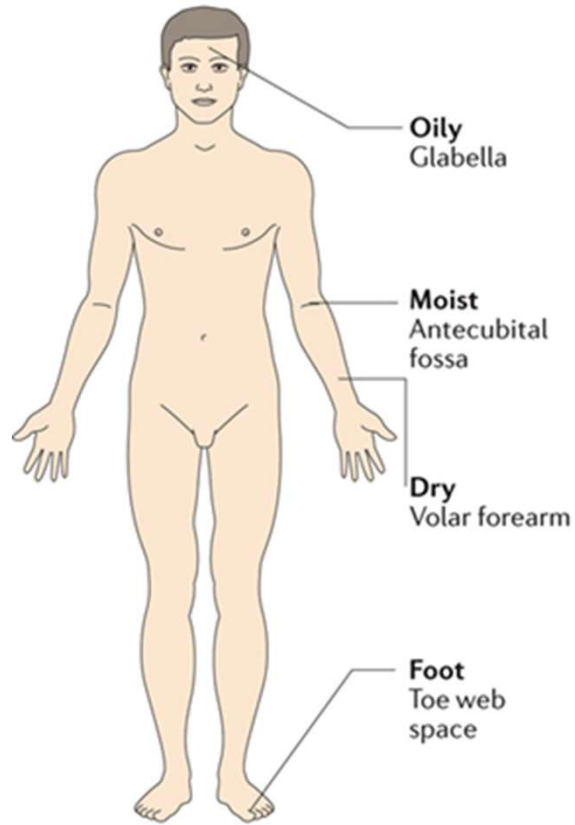
Skin homeostasis: an essential balance



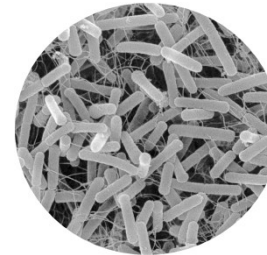
The Skin microbiome

Commensal microbes'
resident microbes that live
in harmony with skin cells

Pathogenic microbes present on
skin or acquired, that evade
immune system causing
inflammation



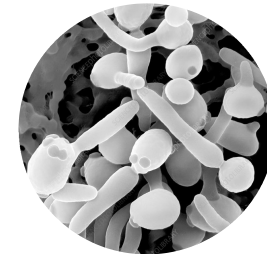
Byrd A et al., 2018
Pausan M et al., 2019



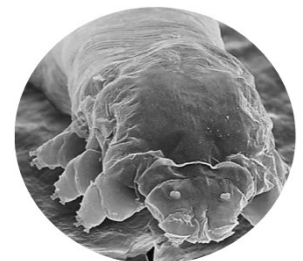
Bacteria



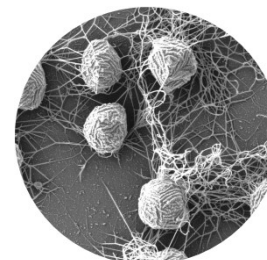
Virus



Fungi



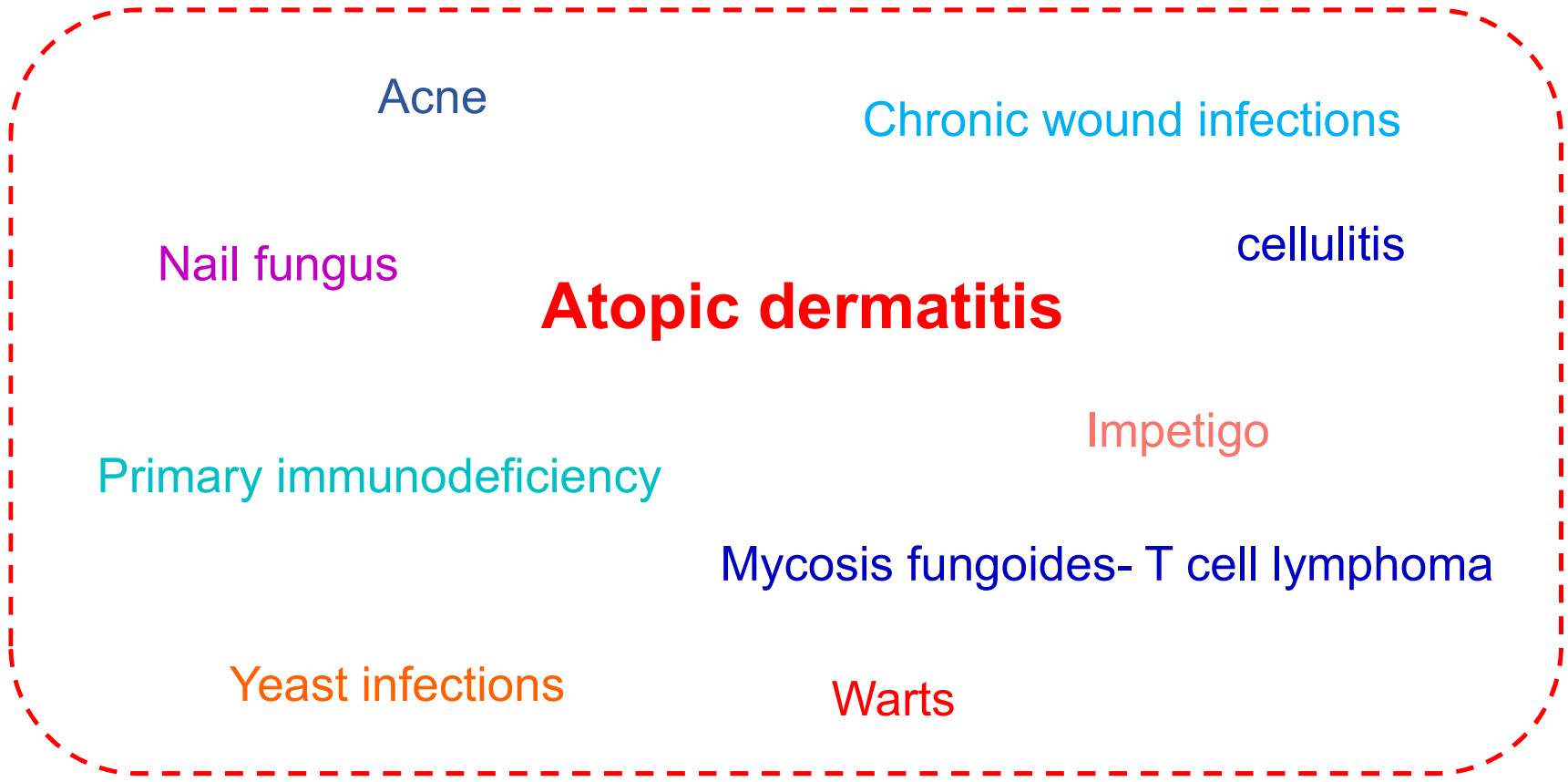
Mites



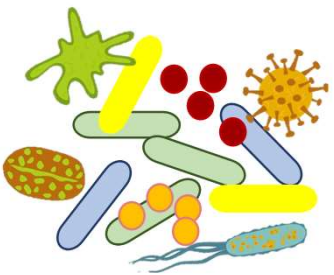
Archaea

Skin microbiome and association with diseases

Microbial dysbiosis <--> skin diseases



Skin microbiome: Functions and therapeutic potential



Microbes

Molecular

Modulate gene expression ¹

- *Innate immune genes*
- *Cytokine related genes*

Produce antimicrobial peptides ²

- *Production of Lantibiotics*

Cellular

Regulatory T cell migration ²

- *CCL20-CCR6 pathway*

Commensal specific T-cell response ³

- *Induction of IL-17A+ CD8+ cells*

Before

After

Staphylococcus hominis A9



Nakatsuji et al., Nat Med 2021

Allergic eczema

Roseomonas mucosa



Myles et al., Sci. transl. med 2020

¹ Meisel JS et al., Microbiome 2018

² Scharshmidt TC et al., Cell Host Microbe 2017

³ Naik S et al., Nature 2015

Hygiene hypothesis and its evolution



Hygiene hypothesis

A lower incidence of infections in early childhood may increase the risk of developing allergic and autoimmune diseases.

Infection history, number of siblings and close contact with farm animals or pets may alter the health status.



'Old friends' hypothesis

Sustained exposure to immunoregulatory microbes (old friends) facilitates swift immune activation and prevents immune-related diseases.

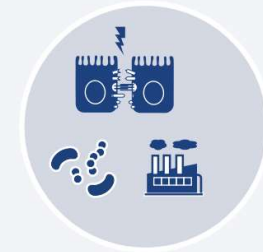
Farm and rural environments, breastfeeding, farm milk and food diversity may have favorable effects.



Biodiversity hypothesis

A reduction in the diversity and richness of the microorganisms can increase the risk of impaired immune balance and inflammatory diseases.

Increasing exposure to greenness, farms, vegetation and high microbe diversity is associated with beneficial health outcomes.



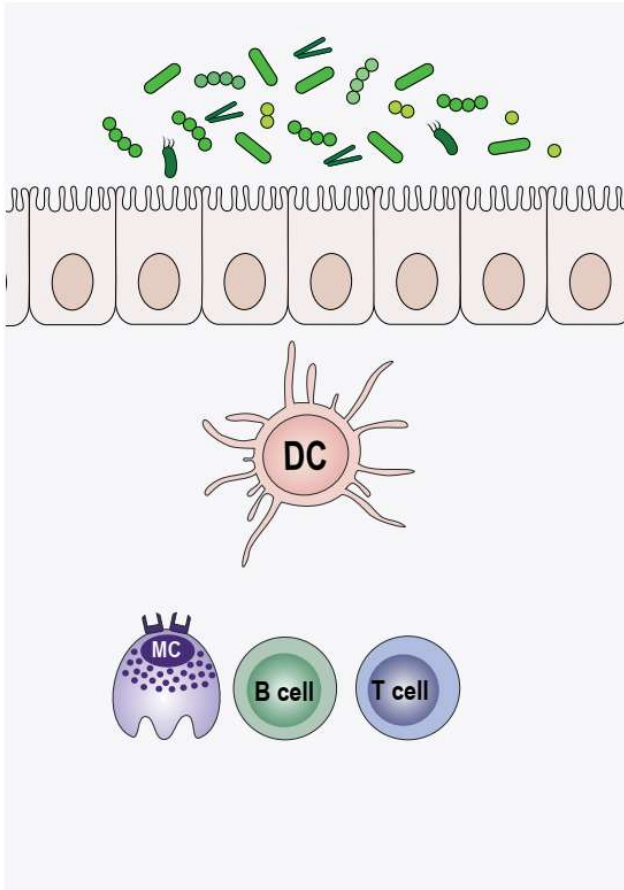
Epithelial barrier theory

Exposure to harmful substances in the environment can undermine the integrity of the protective epithelial barriers, causes microbial dysbiosis and immune system activation.

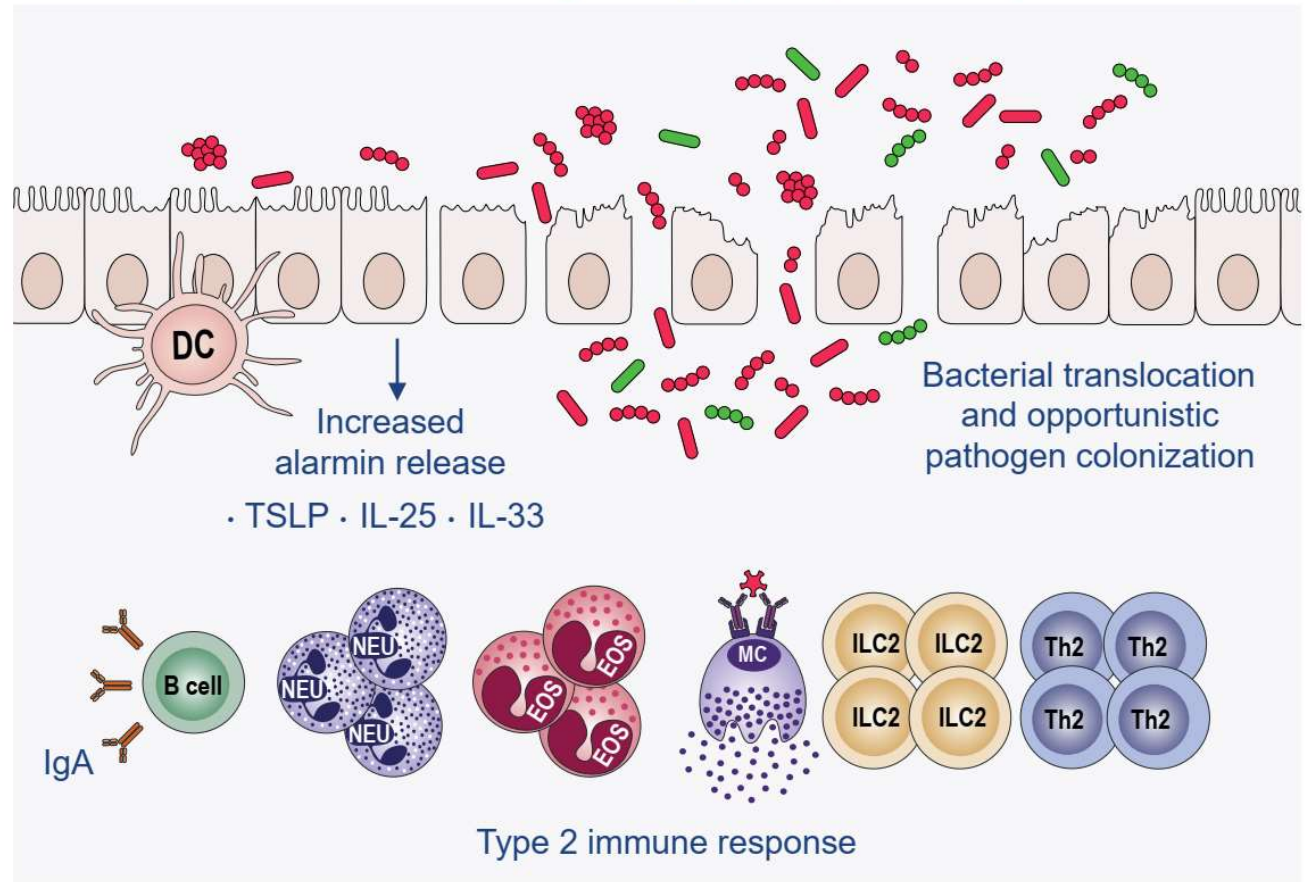
Epithelial barrier defects by toxic substances, colonization of opportunistic pathogens, decreased expression of commensals, bacterial translocation and tissue inflammation have been linked to many chronic, autoimmune and neuropsychiatric diseases.

Mechanisms of epithelial barrier theory - gut

Healthy gut

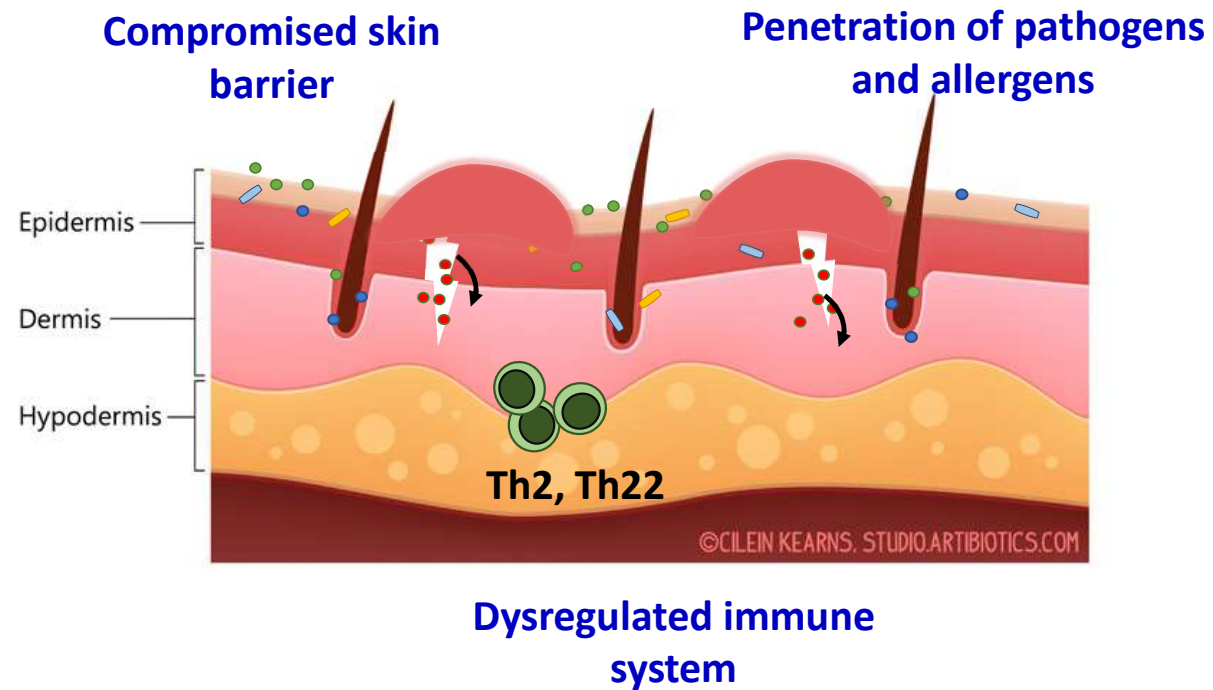


Perturbed gut integrity and permeability

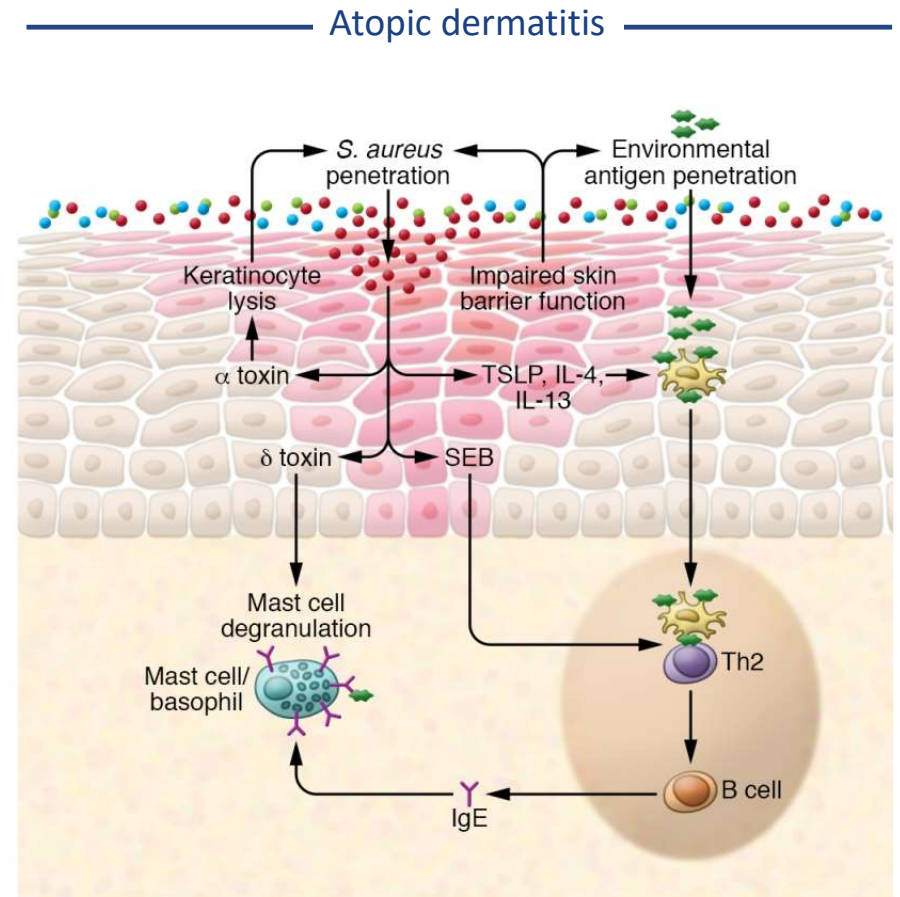
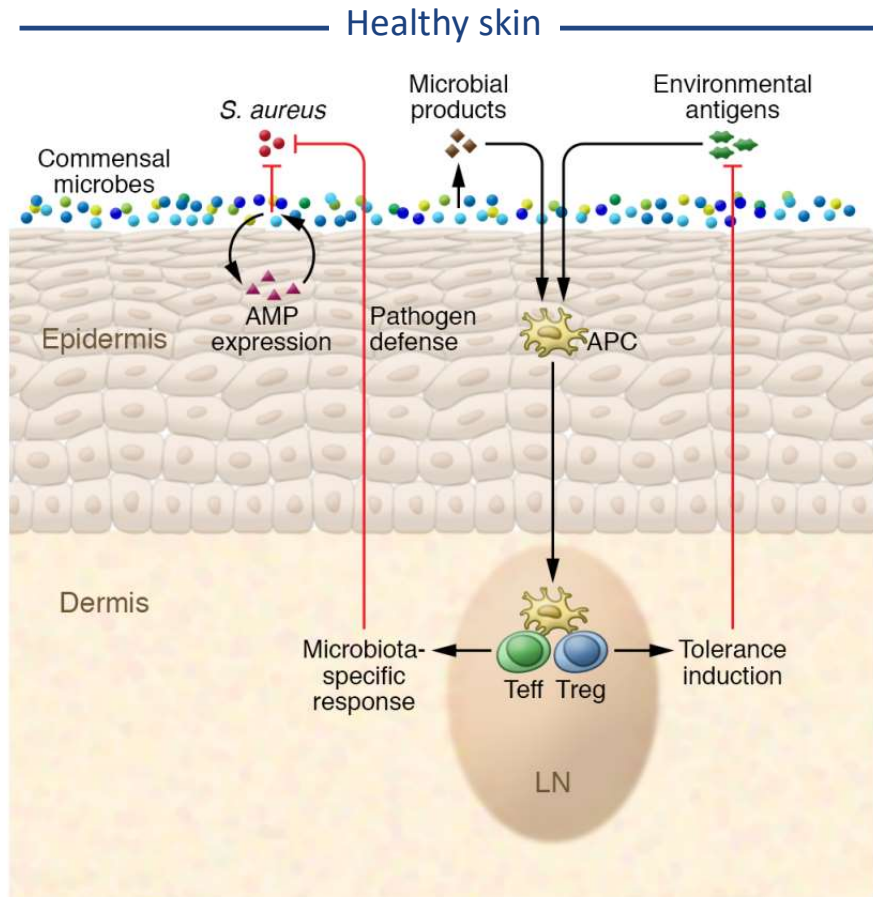


Atopic Dermatitis / Eczema

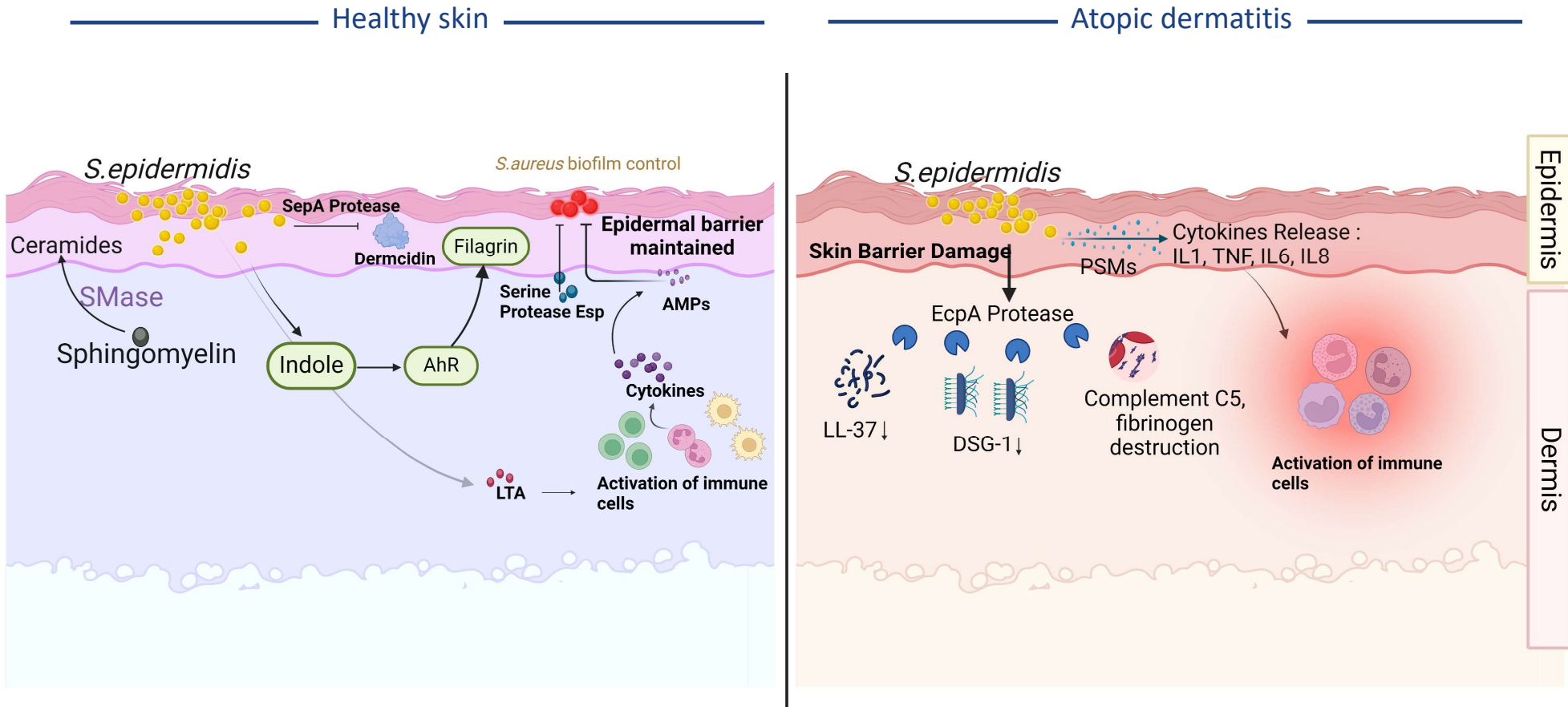
- Chronic, relapsing inflammatory skin disease
- 15-30% of children; 2-10% adults
- Eczematous lesions, intense itch and discomfort
- Complex interrelationship of genetic, environmental, immunologic (Th2/Th17) and epidermal factors



Mechanisms of epithelial barrier theory – Atopic dermatitis

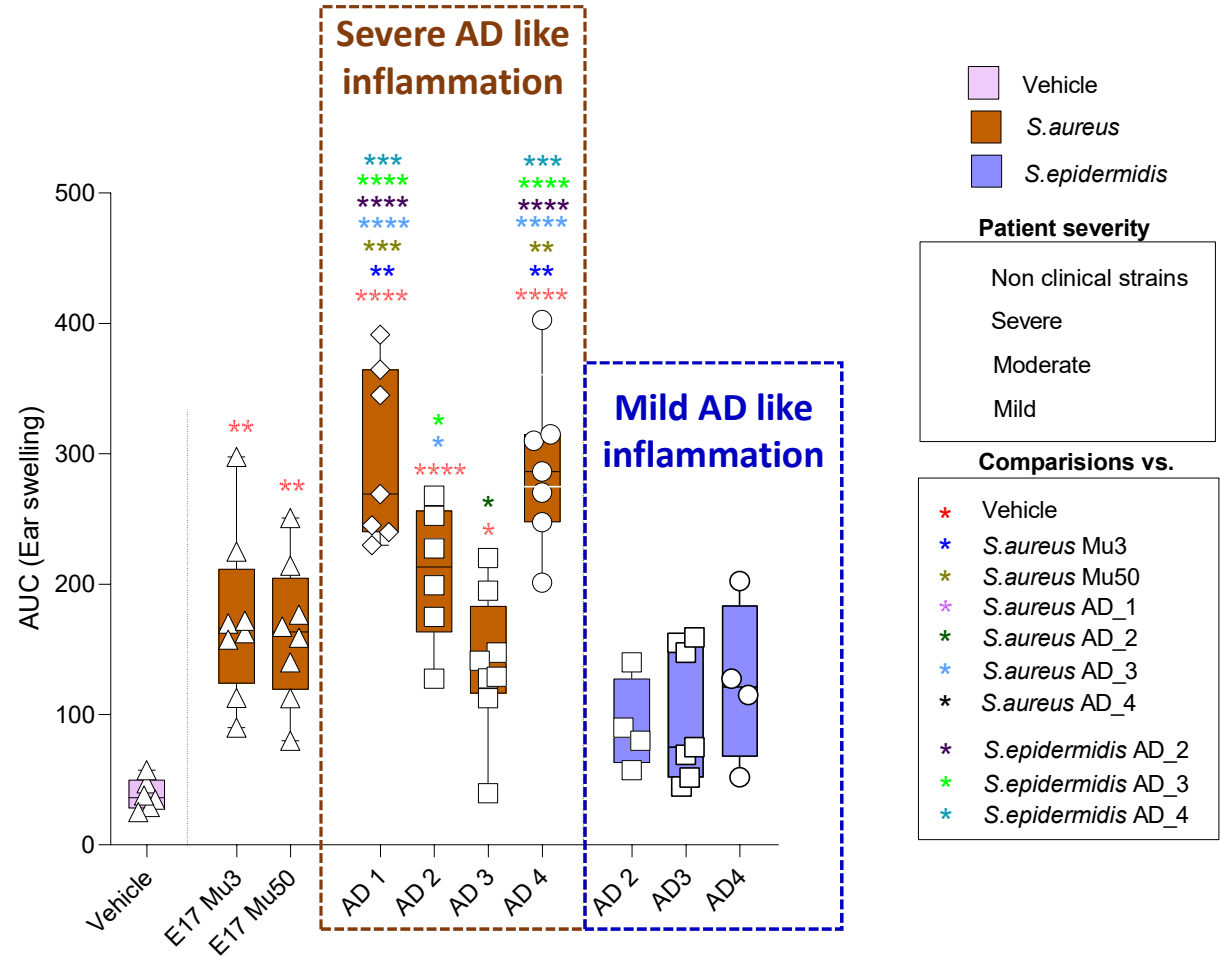
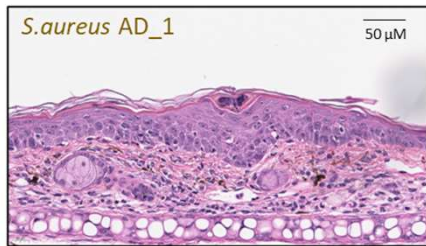
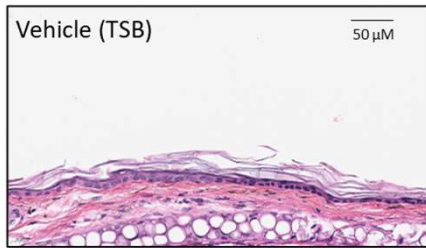
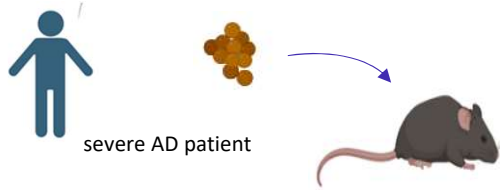


Mechanisms of epithelial barrier theory – Atopic dermatitis

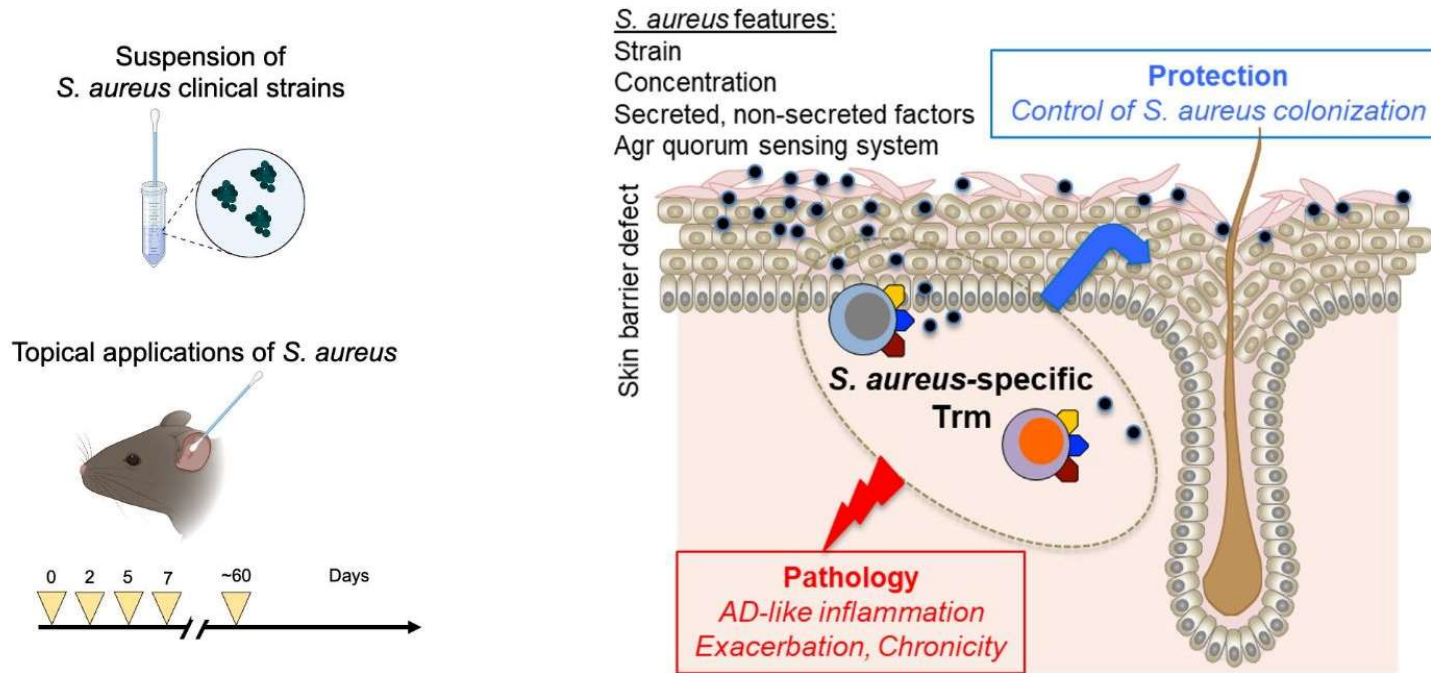


S. aureus from AD lesions induce inflammation in mouse skin

S. aureus clinical strains



Staphylococcus aureus-specific skin resident memory T cells protect against bacteria colonization but exacerbate atopic dermatitis-like flares in mice

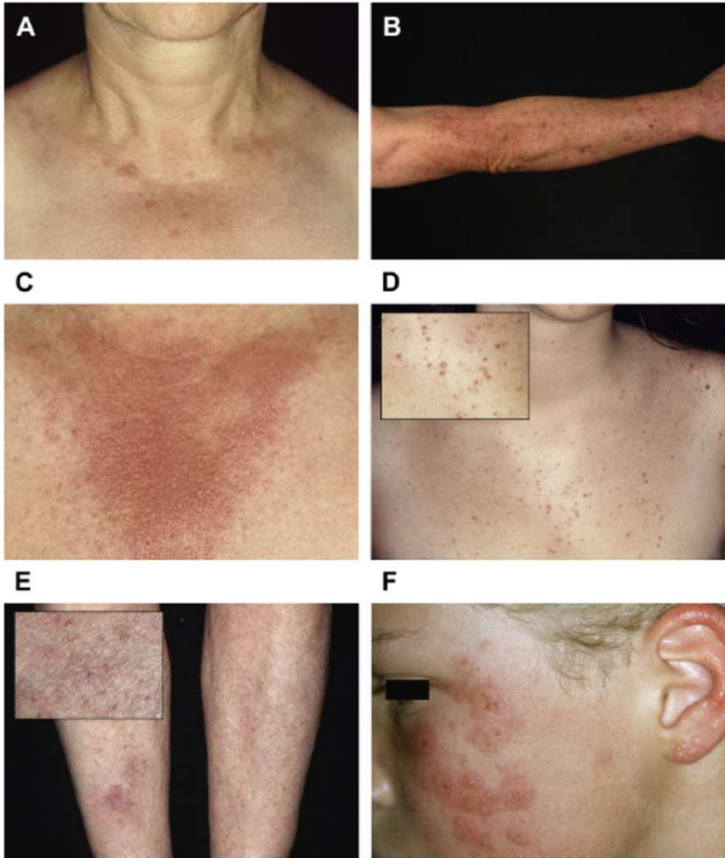


 $\gamma\delta$ Trm
  CD4+ Trm
 • *S. aureus*

AD: Atopic Dermatitis; *S. aureus*: *Staphylococcus aureus*; Trm: Resident memory T cell

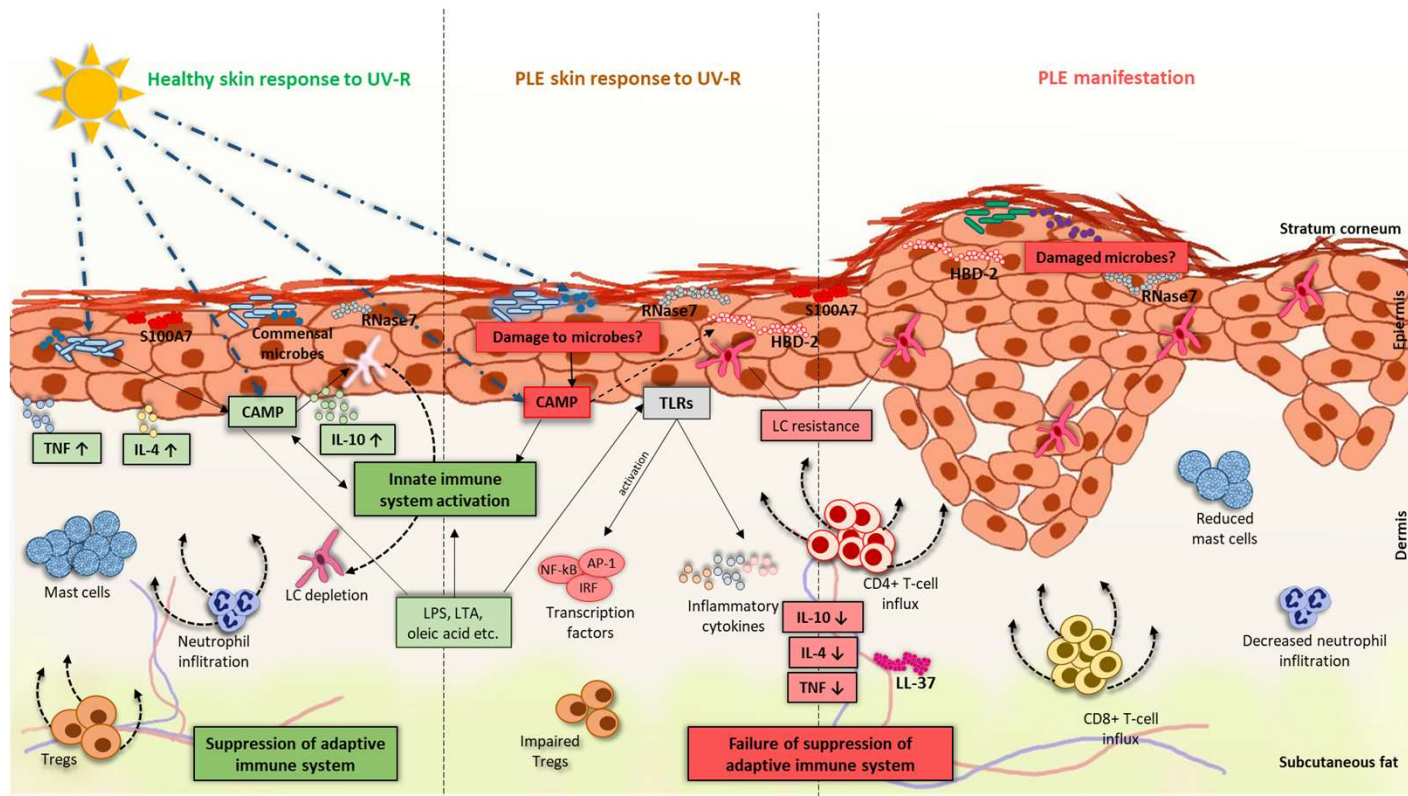


Sun allergy



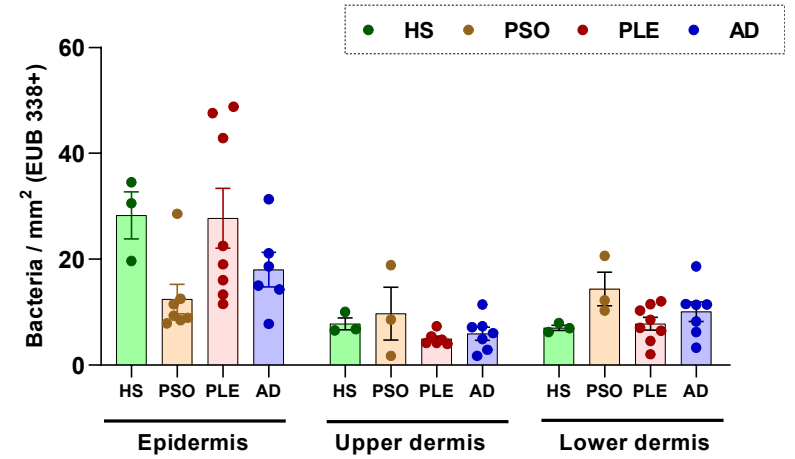
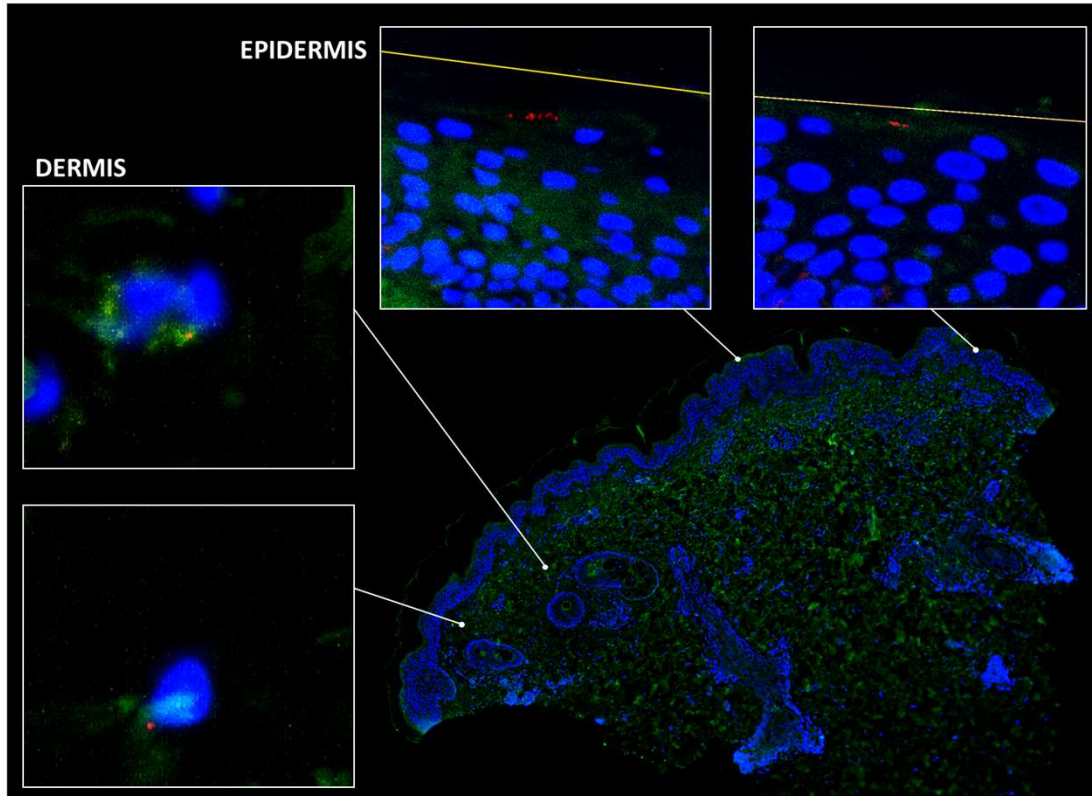
- Photosensitivity condition (sun allergy).
- Prevalence of 10-20%
- Itchy , non scarring lesions of polymorphic morphology on sun-exposed parts.
- Prophylactic treatment is done by photo (chemo)

Microbes and microbial elements in sun allergy



Patra V, Wolf P. Microbial elements as the initial triggers in the pathogenesis of polymorphic light eruption? *Exp Dermatol.* 2016 Dec;25(12):999-1001.

Microbes persist in PLE lesions; higher density in epidermis



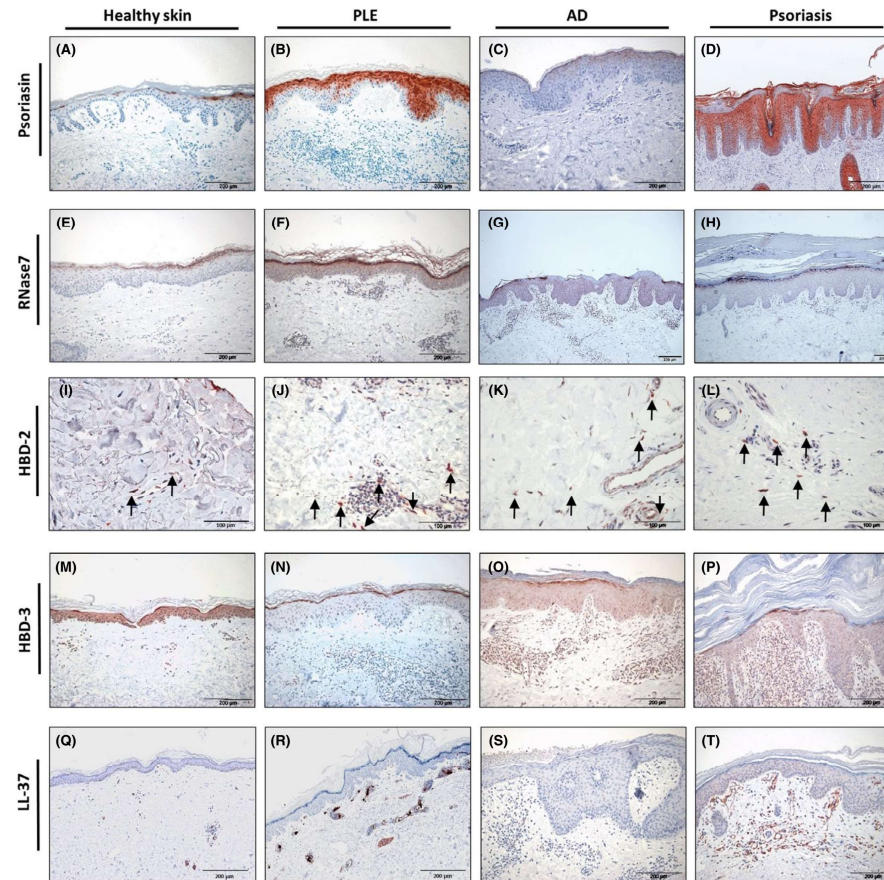
Unique profile of antimicrobial peptides in PLE vs AD

PATRA ET AL.

Photodermatology, Photoimmunology & Photomedicine

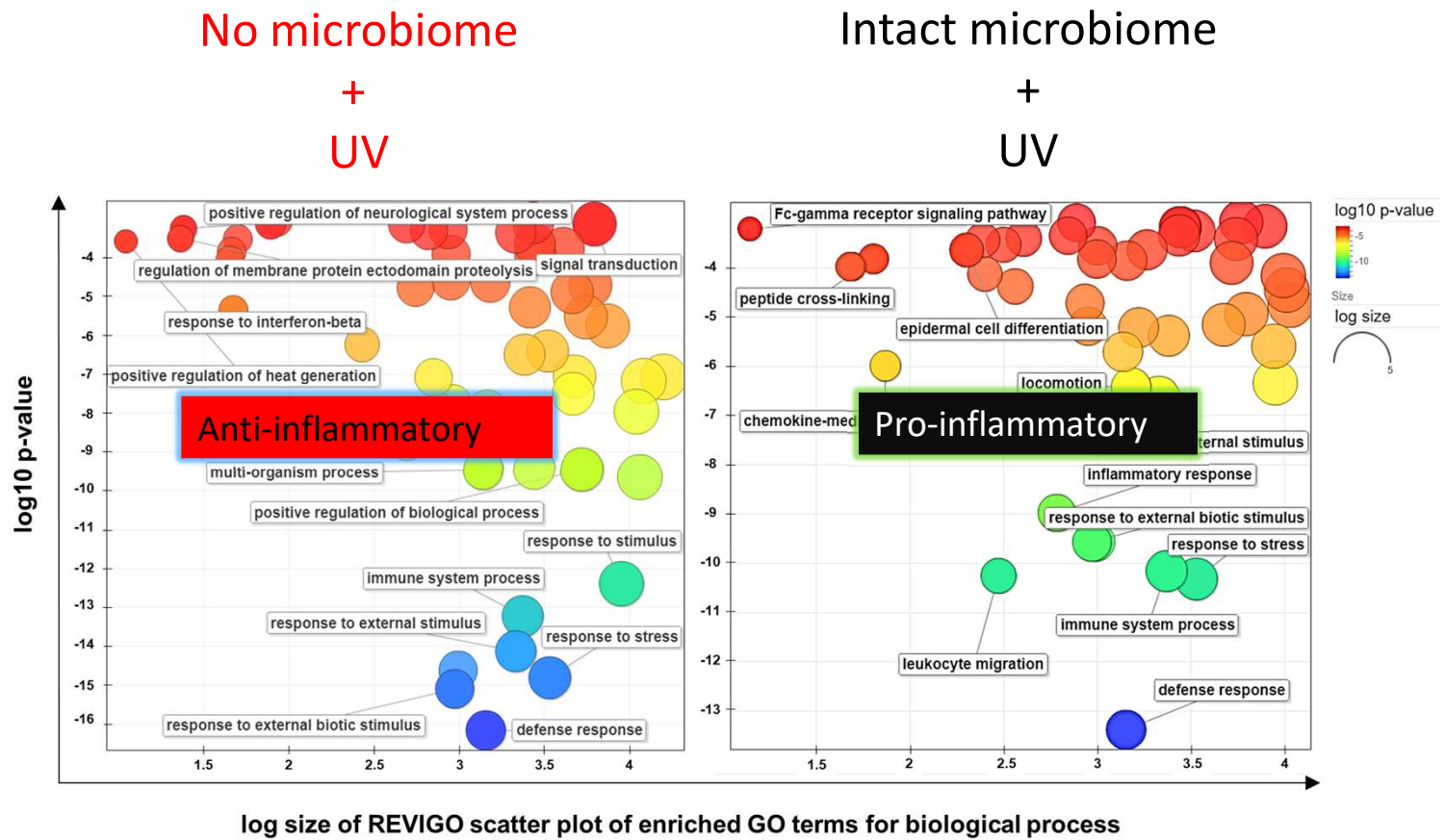
WILEY

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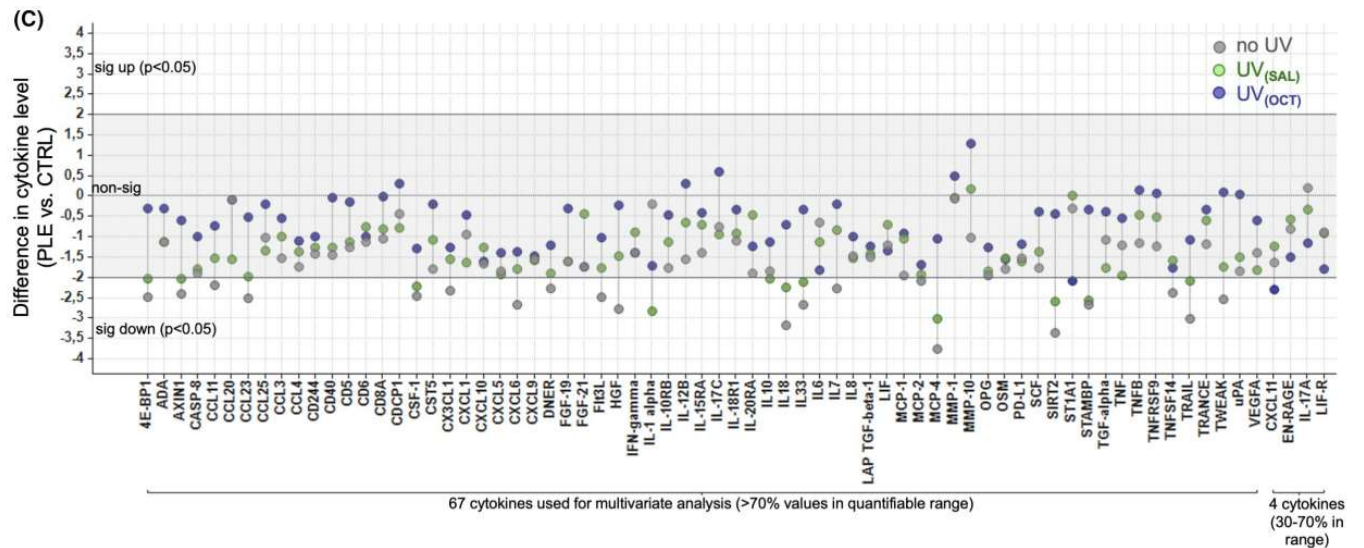
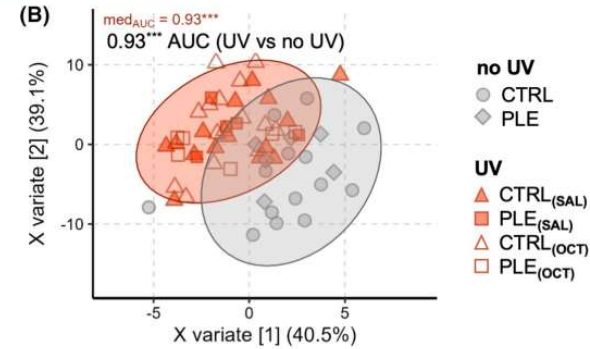
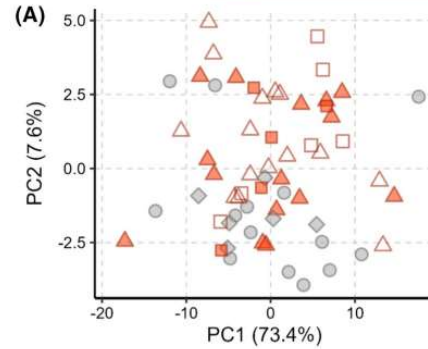
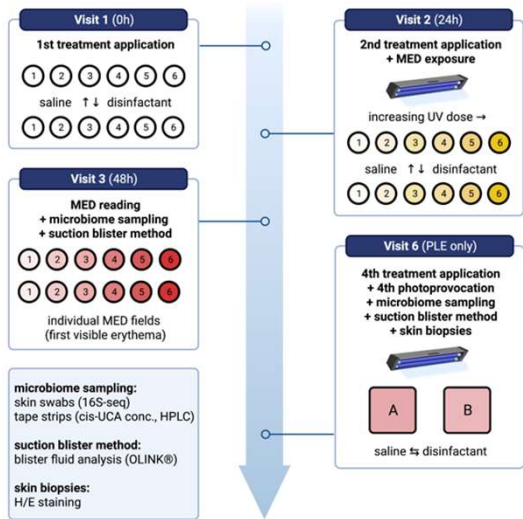
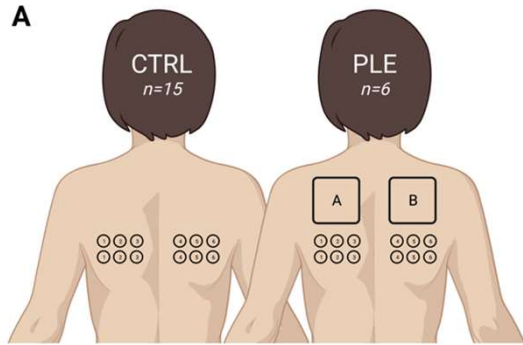
Patra V, Mayer G, Gruber-Wackernagel A, Horn M, Lembo S, Wolf P. **Unique profile of antimicrobial peptide expression in polymorphic light eruption lesions compared to healthy skin, atopic dermatitis, and psoriasis.** *Photodermatol Photoimmunol Photomed.* 2018 Mar;34(2):137-144.

Differential gene regulation with or without microbiome after UV exposure



Patra V, Wagner K, Arulampalam V and Wolf P. (2019) Skin microbiome modulates the effect of UV on cellular response and immune function. *iScience*, 2019; 15: 211-222

Differential microbiota-dependent cytokine patterns and their regulation after ultraviolet exposure





Summary

- Microbiome is an integral component of the skin's ecosystem
- Skin microbiome can shape the molecular and cellular features of the immune system
- Immune mediated allergic diseases are characterized by defective epithelial barriers
- Exposure to barrier-damaging agents causes
 - epithelial cell injury and barrier damage
 - colonization of opportunistic pathogens
 - loss of commensal bacteria/ decreased microbiota diversity
 - bacterial translocation
 - Allergic sensitization and inflammation.