Allergic Skin Disease: Immunologic Consequences of Playing Host to Pathogenic Microbes

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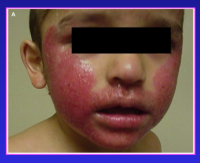
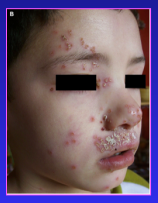
Recent insights into atopic dermatitis and implications for management of infectious complications

Increased susceptibility to infections or colonization with microbial organisms: *Staphylococcus aureus*, *Herpes simplex*

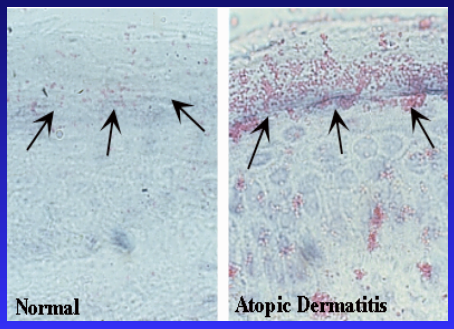




Boguniewicz M, et al. J Allergy Clin Immunol 2010;125:4

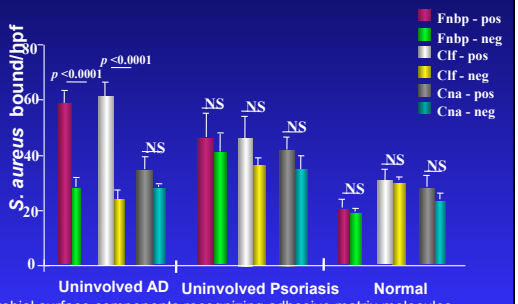
1980 Hanifin & Rajka criteria for AD included tendency toward cutaneous infections

S. aureus adherence to normal healthy skin and uninvolved AD skin



Cho S-H et al. J Allergy Clin Immunol 2001;108:269

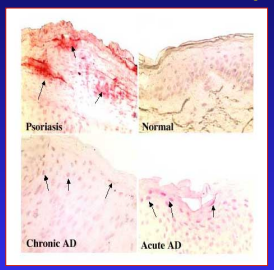
Quantification of MSCRAMM* mutant *S. aureus* strains to uninvolved AD vs normal skin



*microbial surface components recognizing adhesive matrix molecules

Cho S-H, et al. J Allergy Clin Immunol 2001;108:269

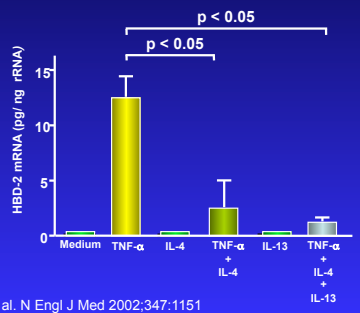
A deficiency in antimicrobial peptide* (H-β-defensin-2) expression may allow *S. aureus* to colonize and infect skin of AD patients



**** keratinocytes are the major source of AMPs in the skin***

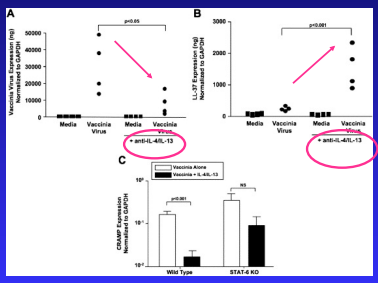
Ong PY, et al. N Engl J Med 2002;347:1151

Effects of IL-4 and IL-13 on TNF-α-induced H-β-defensin-2 expression in HaCat cells



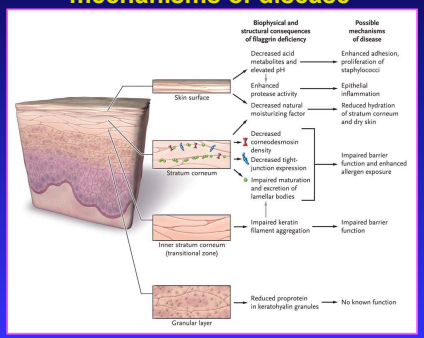
Ong PY, et al. N Engl J Med 2002;347:1151

IL-4 and IL-13 inhibit cathelicidin expression through STAT-6 and can be reversed by neutralizing antibodies



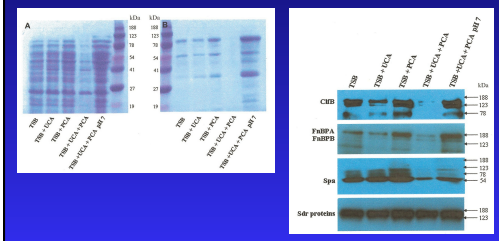
Howell MD, et al. Immunity 2006;24:341

Filaggrin deficiency and possible mechanisms of disease



Irvine AD, et al. N Engl J Med 2011;365:1315

Effect of filaggrin breakdown products on growth of and protein expression by *Staphylococcus aureus*



Miajlovic H, et al. J Allergy Clin Immunol 2010;126:1184

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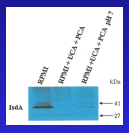
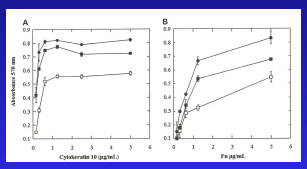
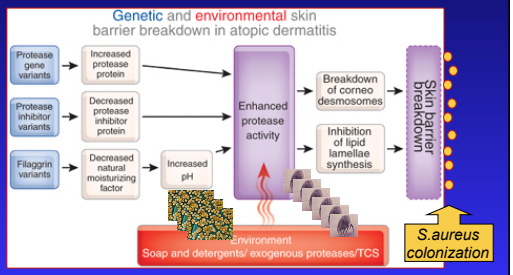




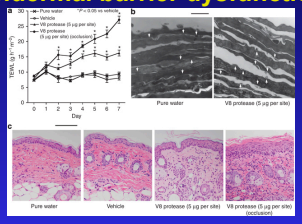
Miajlovic H, et al. J Allergy Clin Immunol 2010;126:1184

Genes contributing to skin barrier breakdown



Cork MJ, et al. J Invest Dermatol 2009;129:1892

S. aureus extracellular protease causes epidermal barrier dysfunction



** V8 protease induced structural disturbance of the SC, including loss of corneodesmosome integrity & loss of corneocyte cohesion, arrows indicate corneodesmosomes ***V8 protease without occlusion induced increase in epidermal thickness, with occlusion, greater increase in epidermal thickness and inflammatory infiltrate in the dermis

Hirasawa Y, et al. J Invest Dermatol 2010;130:614

S. aureus, toxins & AD

- Most AD pts colonized by toxin producing *S. aureus*
- Both MSSA & MRSA produce alpha-toxin critical for enhanced survival on skin
- ~ 10% of *S. aureus* isolates from AD pts shown to produce 2 superantigenic toxins (SEB & TSST) (coproduction not seen in isolates from >5000 pts with TSS)
- Use of topical steroids and TCIs may select for *S. aureus* strains that adapt to their "new" skin surface niche by increasing virulence capabilities
- AD pts make serve as an important reservoir for evolving *S. aureus* strains

Schlievert PM, et al. J Allergy Clin Immunol 2010;125:39

T regulatory cells in atopic dermatitis and subversion of their activity by superantigens

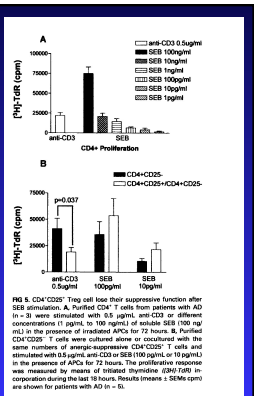
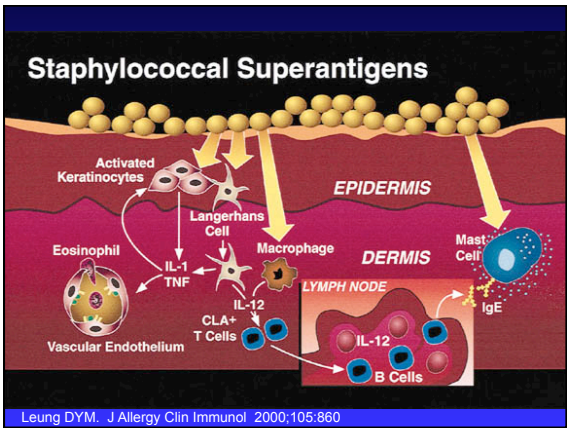


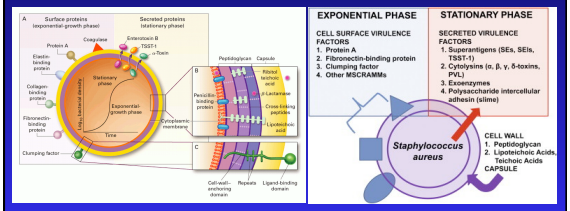
FIG 5. $CD4^+CD25^+$ Treg cell lose their suppressive function after SEB stimulation. A, Purified $CD4^+$ T cells from patients with AD (n = 9) were stimulated with 0.5 μg/mL anti-CD3 or different concentrations (1 pg/mL to 100 ng/mL) of soluble SEB (100 ng/mL) in the presence of irradiated APCs for 72 hours. B, Purified $CD4^+CD25^-$ T cells were cultured alone or cocultured with the same numbers of anergic-suppressive $CD4^+CD25^+$ T cells and stimulated with 0.5 μg/mL anti-CD3 or SEB (100 pg/mL or 10 pg/mL) in the presence of APCs for 72 hours. The proliferative response was measured by means of tritiated thymidine ([3H]-TdR) incorporation during the last 18 hours. Results (means ± SEMs cpm) are shown for patients with AD (n = 5).

Ou LS, et al. J Allergy Clin Immunol 2004;113:756



Leung DYM. J Allergy Clin Immunol 2000;105:860

Virulence factor production by *S. aureus*



Lowy FD. N Engl J Med 1998;339:520;
Schlievert PM, et al. J Allergy Clin Immunol 2010;125:39

Staphylococcal toxins and protein A differentially induce cytotoxicity and release of tumor necrosis factor-alpha from human keratinocytes

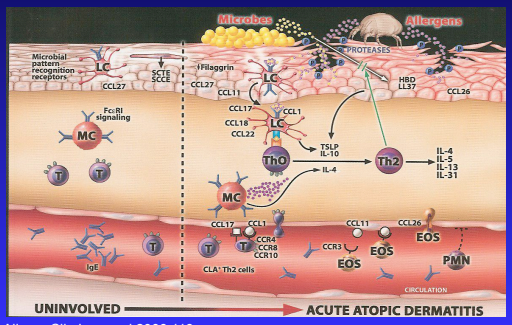
Table II. α-Toxin Induces Cytotoxicity in the HaCaT Cell Line, in Contrast to Superantigenic Toxins and SpA[*]

Toxin (ng/ml)	MTT/ESTA (% viability) 1 h	6 h	22 h
α-Toxin			
1,000	66.3 ± 4.7	47.8 ± 4.7	32.6 ± 4.5
100	82.2 ±1.7	69.7 ± 4.1	63.4 ± 3.6
TSST-1			
100	101.3 ± 0.5	106 ±3.6	121 ± 12.5
50	98.3 ± 2.8	102 ± 2.3	115 ± 1.5
SEA			
100	101 ± 1.0	103 ± 3.6	99.9 ± 1.13
50	101 ± 1.0	101 ± 1.0	100 ± 9.9
SEB			
100	100 ± 0.5	112 ± 2.6	113 ± 3.6
50	100.6 ± 0.5	110.3 ± 1.5	113 ± 5.3
ExT-A			
100	101 ± 1.0	112.3 ± 2.5	116.3 ±3.2
50	101 ± 1.0	106 ± 4.58	113.6 ± 4.16
SpA			
10,000	103 ± 3.6	115 ± 4.5	125 ± 2.9
100	99.1 ± 2.8	111 ± 5.1	116.2 ± 3.1

[*] The studied components (α-toxin, TSST-1, SEA, SEB, ExT-A, and SpA) were added in 0.1 ml to the keratinocyte HaCaT cell line in 24-well plates. After cultivating for the indicated time, cytotoxic effects were determined by MTT/ESTA. Control cells were treated with PBS alone and represented the 100% values in each experiment. The values represent mean ± SD of triplicate determinations.

Ezepchuk YV, et al. J Invest Dermatol 1996;107:603

Thymic stromal lymphopoietin: Master switch for allergic inflammation



J Allergy Clin Immunol 2006;118

Phenotype of atopic dermatitis subjects with a history of eczema herpeticum

- AD patients with more polarized Th2-type disease with allergies and asthma and increased biomarkers including serum IgE, TSLP and cutaneous T cell-attracting chemokine more likely to have severe skin disease complicated by eczema herpeticum, *S. aureus* or molluscum infections

Beck LA, et al. J Allergy Clin Immunol 2009;124:260

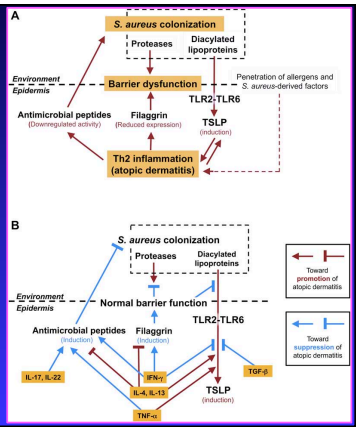
FLG mutations and Th2 polarization (Genetic variants in thymic stromal lymphopoietin are assocated with AD & EH)

- A critical link between barrier defect in AD patients with *FLG* mutations and Th2 polarization could be explained in part by enhanced allergen penetration through the damaged epidermis accompanied by increased production of TSLP* by keratinocytes leading to a Th2-type milieu

* significant associations for TSLP and IL7R tagging SNPs and AD and ADEH in European Americans with replication of associations between TSLP and IL7R SNPs in an independent African American sample

Gao P-S, et al. J Allergy Clin Immunol 2010;125:1403

***Staphylococcus aureus* membrane and diacylated lipopeptide induce thymic stromal lymphopoietin in keratinocytes through the Toll-like receptor 2–Toll-like receptor 6 pathway**



Vu AT, et al. J Allergy Clin Immunol 2010;126:985

Translating lessons from research to patient care

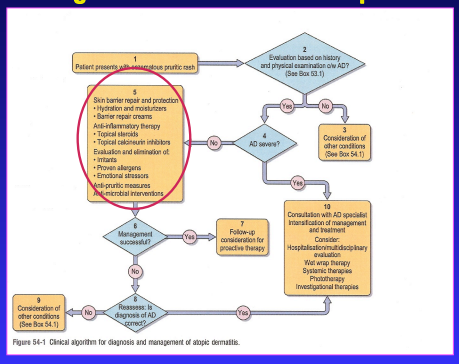


Figure 54-1 Clinical algorithm for diagnosis and management of atopic dermatitis.

Boguniewicz M, et al. In Pediatric Allergy 2010; 566

NIAID Atopic Dermatitis Research Network