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

1980 Hanifin & Rajka criteria for AD included tendency toward cutaneous infections
**S. aureus** adherence to normal healthy skin and uninvolved AD skin


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

*microbial surface components recognizing adhesive matrix molecules


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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

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

\[ p < 0.05 \]


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


Filaggrin deficiency and possible mechanisms of disease

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


**Genes contributing to skin barrier breakdown**

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

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

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

Staphylococcal Superantigens

Virulence factor production by *S. aureus*

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


Thymic stromal lymphopoietin: Master switch for allergic inflammation

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


FLG mutations and Th2 polarization (Genetic variants in thymic stromal lymphopoietin are associated 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

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


Translating lessons from research to patient care

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

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