Role of skin-colonizing microbes in atopic dermatitis

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Bacterial colonization of the skin in atopic dermatitis

80-100% colonization by S. aureus

- defects of the innate immune system
- defects of the epidermal barrier

Higher susceptibility to skin infection by S. aureus

Defects of the innate immune system

Toll-like receptor (TLR)-2

- decreased expression and genetic polymorphisms

Dysregulation of the innate immune system

- Antimicrobial peptides: dysregulation of the production by keratinocytes
  - decreased expression of human beta defensins 2 and 3
  - decreased expression of cathelicidin LL-37
    in acute, Th2 polarized lesions

Atopic Dermatitis

30-60% of S. aureus:

- superantigens (SE-A -D)
- toxin secretion (e.g., α-toxin)

- T cell activation
- skin inflammation
- stimulation of macrophages, keratinocytes, MHC-expressing cells

Breuer K et al. J Dermatol 2002; 147:35
Triclosan
- No irritative, photoallergen, phototoxic, mutagenic side effects known
- Induction of multiresistancy mechanism in grammnegative bacteria
- Contact sensitization (rare)

Chlorhexidine
- contact allergy (type I/type IV) possible (rare)

Octinidine
- available in solutions only

Gentianaviolett
- Induction of skin irritation (when used in high concentration)

Silver (in ointments and textiles)
- safe, but expensive!

S. aureus exotoxins
- with superantigenic property (e.g. SEB)

IgE-sensitization to SEB: increased severity of AD

S. aureus exotoxins
- without superantigenic properties (e.g. α-toxin)

α-toxin and SEB
- ex-vivo stimulation of T cells and PBMC in AD patients:
  induction of IL-22
  - member of the IL-10 family
  - produced by Th17 and Th22 cells
  - unique IL-22 producing CD4+ and CD8+ T cells accumulate in lesional skin of AD patients
  - IL-22 producing CD8+ T cells correlate with the disease severity

IgE- and T cell reactivity to proteins from S. aureus in AD
- IgE-reactivity in 30% of AD patients
- more frequent in severe forms of AD

Bacterial superinfections in atopic dermatitis
- 80-100% of AD patients colonized by S. aureus
- risk factors: defects of the innate immune system, epidermal barrier
- S. aureus exotoxins induce skin inflammation in AD
- activation of T cells, macrophages, keratinocytes, iNOS expressing cells
- S. aureus exotoxins induce proinflammatory cytokines (IL-31, IL17A, IL-22)
- IgE-sensitization to SEB is associated with increased severity of AD
- IgE-reactivity and T cell reactivity to S. aureus proteins is only seen in AD patients
  - new target for diagnostic/therapeutic strategies?
Malassezia sympodialis and atopic dermatitis

- Malassezia sympodialis has been reported as the most frequent skin-colonizing yeast in AD patients.
- Sensitization to the yeast occurs almost exclusively in AD patients.
- The main cause for this specific sensitization may be the disrupted skin barrier facilitating allergen uptake.

Mala s 13 - Thioredoxin

Human homologue: HuTRX – Human thioredoxin 45% homology

Cross-reactivity at the IgE level between HuTRX and Mala s 13 has been recently reported.

Mala s 13 specific TCCs restimulated with Mala s 13 and hTRX

Study Design

- Atopy Patch Test (APT) with Mala s 13 and M. sympodialis extract
- Mala s 13 specific T-cell lines (TCLs) and T-cell clones (TCCs)
  - Blood (PBMCs)
  - Skin (biopsies from APT lesions)
- Determination of cross-reactivity of the Mala s 13 specific TCCs to hTRX
- Cytokine profile of cross-reacting TCCs
- Immunohistochemical analyses of the APT

Cytokine Profile of TCC restimulated with hTRX


Glaser et al. Allergy 2008: 63, 1617–1623

Autoantigen - Crossreactivity

FOOD ALLERGENS

Bet v 1 vs Cor a 1, Api g 1

Predominant CD 4 response
Predominant Th2 cytokines

FUNGAL ALLERGENS

Mala s 13 vs hTRX

Predominant CD 4 response
Predominant Th1 cytokines
Th17 & Th22 response

The role of microbial allergens in the skin in atopic dermatitis

Werfel, J Invest Dermatol 2009