

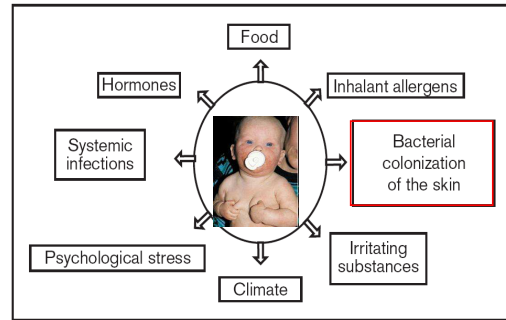
# Role of skin-colonizing microbes in atopic dermatitis

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## Trigger factors of atopic dermatitis



Werfel et al. *Curr Opin Allergy Clin Immunol* 2004;4: 379

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## Bacterial colonization of the skin in atopic dermatitis

80-100% colonization by *S. aureus*

Williams et al. *Br J Dermatol* 1990;123: 493



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

Higher susceptibility to skin infection by *S. aureus*

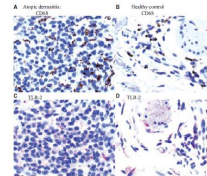
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## Defects of the innate immune system

### Toll-like receptor (TLR)-2

- decreased expression and genetic polymorphisms



Niebuhr M et al. *Allergy* 2009; 64: 1580

Ahmad-Nejad P et al. *J Allergy Clin Immunol* 2004; 113: 56  
Mrabet-Dahbi et al. *J Allergy Clin Immunol* 2008; 121:1013  
Oh et al. *Allergy* 2009; 64:1608  
Niebuhr M et al. *Exp Dermatol* 2010; 19: e296

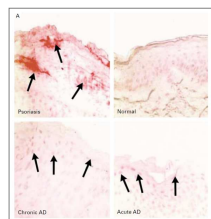
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## Dysregulation of the innate immune system

- **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

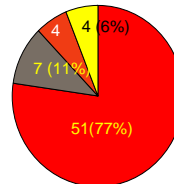


Ong PY et al. *N Engl J Med* 2002; 346: 1151  
Howell MD et al. *Curr Opin Allergy Clin Immunol*. 2007; 7: 413

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## Atopic Dermatitis



■ skin+, nose+  
■ skin+, nose-  
■ skin-, nose+  
■ skin-, nose-

- 30-60% of *S. aureus*:
- superantigens (SE-A -D)
  - toxin secretion ( $\alpha$ -toxin)

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

Breuer K et al. *J Dermatol* 2002; 147:55

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## Topical antiseptic therapy for the reduction of *S. aureus* colonization in atopic eczema

### Triclosan

- No irritative, photoallergen, phototoxic, mutagenic side effects known
- Induction of multi-resistance mechanism in gram-negative bacteria
- Contact sensitization (rare)

### Chlorhexidine

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

### Octidine

- available in solutions only

### Gentianaviolett

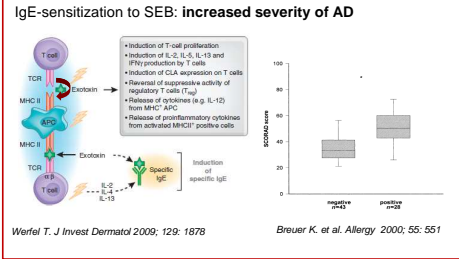
- Induction of skin irritation (when used in high concentration)

### Silver (in ointments and textiles)

- safe, but expensive!

## *S. aureus* exotoxins

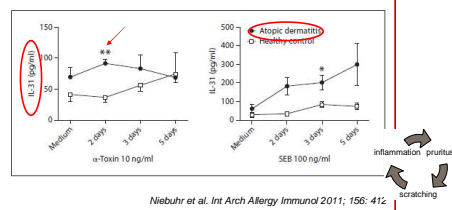
- with superantigenic property (e.g. SEB)



## *S. aureus* exotoxins

- without superantigenic properties (e.g.  $\alpha$ -toxin)

stimulation of PBMC with *S. aureus* exotoxins:  
induction of IL-31



## *S. aureus* exotoxins

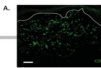
- $\alpha$ -toxin and SEB

- ex-vivo stimulation of T cells and PBMC in AD patients:  
induction of IL-22

Niebuhr et al. *J Allergy Clin Immunol* 2010; 126: 1176

### IL-22

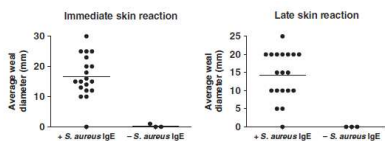
- member of the IL-10 family
- produced by Th17 and Th22 cells
- unique IL-22-producing CD4<sup>+</sup> and CD8<sup>+</sup> T cells accumulate in lesional skin of AD patients
- IL-22 producing CD8<sup>+</sup> T cells correlate with the disease severity



Nogales et al. *J Allergy Clin Immunol* 2009; 12: 1244

## 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



- Target for diagnostic strategies against superinfection in AD?

Reginald et al. *J Allergy Clin Immunol* 2011; 128: 82



## 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, MHC-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?



