Barrier dysfunction - Th2 Immunity - Microbial Dysbiosis: Determinants of Atopic Dermatitis and Implications for New Treatments

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• Introduction into atopy and AD

• Barrier dysfunction and Th2 immunity

• Microbial dysbiosis in AD pathogenesis

• Consequences for AD treatment
Genotypes (complex genetic trait) – Phenotypes (environmental triggers)

Atopic Dermatitis
Gene 1:
- Mutation → Loss of protein
- SNPs → Gain-of-function
Gene 2:
- Mutation → Loss of protein
- SNPs → Gain-of-function
Gene 3:
- Mutation → Loss of protein
- SNPs → Gain-of-function
Gene 4:
- Mutation → Loss of protein
- SNPs → Gain-of-function
Gene 5:
- Mutation → Loss of protein
- SNPs → Gain-of-function
Gene 6:
- Mutation → Loss of protein
- SNPs → Gain-of-function

Allergic Asthma

Allergic Rhinoconjunctivitis

Food allergy

Gene 1:
- Mutation → Loss of protein
- SNPs → Gain-of-function
Gene 2:
- Mutation → Loss of protein
- SNPs → Gain-of-function
Gene 3:
- Mutation → Loss of protein
- SNPs → Gain-of-function
Gene 4:
- Mutation → Loss of protein
- SNPs → Gain-of-function
Gene 5:
- Mutation → Loss of protein
- SNPs → Gain-of-function
Gene 6:
- Mutation → Loss of protein
- SNPs → Gain-of-function
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Atopic Dermatitis

- Dry skin
- Reduced barrier
Mutation of the gene `Filaggrin´ associated with atopic dermatitis

- Impermeable proteolipids
- Low surface pH
- Antimicrobial activity
- `Natural moisturizing factor´ (NMF)

Palmer CN et al.. Nat Genet. 2006;38:441-6
Smith FJ et al.. Nat Genet. 2006;38:337-4
Atopic Dermatitis

Signals for Immune system

Initiation of Th2 immune response
Sensitized host
Clinical outcomes: atopy and asthma

Barrier ↓↓↓

Anti-microbial peptides ↓↓↓


Palmer CN et al.. Nat Genet. 2006;38:441-6
Smith FJ et al.. Nat Genet. 2006;38:337-4

Adaptive immunity and atopic dermatitis

- Epidermis
- Antimicrobial peptides
- Barrier

- Th1
- Interferon-γ
- Interleukin-23
- Interleukin-17

- Th17

- Th2
- IL-4

- Guenova E et al.. Proc Natl Acad Sci U S A 2015:112: 2163-8
Atopic Dermatitis

- Dry skin
- Reduced barrier

- "Allergy"
- Th2-disease
**Microbiome and atopic dermatitis**

**Figure 3.** Bacterial taxonomic classifications in the AD skin microbiome. (A) Mean relative abundance of the 14 major phyla-order in the antecubital (Ac) and popliteal creases (Pc) for controls and AD disease states: baseline, flare (no-treatment [trt] and intermittent-trt), and postflare (Supplemental Table S13 for order of subjects). (B) Mean relative abundances for Ac and Pc of species-level classifications of staphylococcal species. Order of subjects follows A.
Microbiome and atopic dermatitis

Kong-HH et al. Genome Res 2012
Atopic Dermatitis

- Dry skin
- Reduced barrier
- “Infections“
- Cutaneous microbiome

- “Allergy“
- Th2-disease
Barrier dysfunction - Th2 immunity - microbial dysbiosis in atopic dermatitis

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Consequences of innate immune signaling

Innate immunity

Adaptive immunity

‘Immunity’
Triggers of chronic atopic dermatitis

- *Staphylococcus aureus*
- *Malassezia species*
- *Herpes simplex*

→ Hypothesis: TLR2 ligands trigger atopic dermatitis
Pathogenesis of chronic atopic dermatitis

Interplay

Th2 inflammation

innate immune sensing of *S. aureus*
One single exposure to one TLR2 ligand

- Th2 + OVA
- Th2 + OVA + Pam2Cys
- OVA
- Pam2
- Th2

Pathogenesis of chronic atopic dermatitis

- Dependent on IL-4

Skabytska et al. Immunity 2014

EADV/AAD Joint Symposium
New York, 27.07.2017
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• Consequences for AD treatment
Rapid first response
Immediate `relief´
Complete response at about day 30
Side effects: Conjunctivits

Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial


Blaauvelt et al. The Lancet 2017;389:2288
`Good´ microbes as therapeutic strategy?

Inflammation

Tolerance

Inflammation

Tolerance
`Good´ microbes as therapeutic strategy?

**Vitreoscilla filiformis**

- Double-blind, prospective, randomized trial
- 75 patients with mild atopic dermatitis

Randomized in 2 groups (1:1)

- Glycerylmono-/distearate, Polyethyleneglycol-stearat, 5% Isoparaffin, 15% Cyclopentadi-methylsiloxan, 3% Glycerin and 2% Vaseline (Vehicle)
- Vehicle plus 5% Vitreoscilla filiformis lysate

Evaluation, SCORAD, TEWL on days 0 / 15 / 29
`Good´ microbes as therapeutic strategy?


* p<0.0001
* p=0.004
n.s.
Nonpathogenic Bacteria Alleviating Atopic Dermatitis Inflammation Induce IL-10-Producing Dendritic Cells and Regulatory Tr1 Cells

Thomas Volz¹, Yuliya Skabytska¹, Emmanuella Guenova¹, Ko-Ming Chen¹, Julia-Stefanie Frick², Carsten J. Kirschning³, Susanne Kaesler¹, Martin Röcken¹ and Tilo Biedermann¹

[Graph showing cytokine release from DCs treated with TLR2 ligands]
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**Conclusion**

• Th2 bias prerequisite for AD development
  – Antimicrobial peptides down
  – Barrier function down
  – Antimicrobial immunity down

• Cutaneous *S. aureus* overgrowth

• *S. aureus*: Transition from acute to chronic AD

• Targeting the Th2 pathway – revolution for AD

• Further patient stratification (responder – non-responder analyses)
Barrier dysfunction - Th2 Immunity - Microbial Dysbiosis in AD

Conclusion

• `Hen and egg´ problem
  – Barrier down first?
  – Dysbiosis first?
  – Th2 first?

• Ecosystem `cutaneous microbiota´

• Immune regulation by non-pathogenic bacteria

• Perspective for the `microbiome´
Barrier dysfunction - Th2 Immunity - Microbial Dysbiosis: Determinants of Atopic Dermatitis and Implications for New Treatments

Thank you for your attention!!

- Susanne Kaesler
- Yuliya Skabytska
- Thomas Volz