Barrier Function and Microbiotic Dysbiosis in Atopic Dermatitis

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Eczema / dermatitis is an inflammatory skin reaction
Dermatitis

Atopic

Contact

Phototoxic

Photoallergic

Seborrhoeic

Irritant
Aetiopathogenesis

- Genetics
- Atopy
- Skin barrier disruption
- Environmental irritants
- Environmental allergens
- Microbes
Immune Response

Skin Barrier
Eczema is an allergy. No, it’s a skin condition.
Outside-inside / Inside-outside

- **Outside – inside hypothesis**
  - Xerosis and abnormal permeability of skin barrier drives eczema with secondary sensitisation

- **Inside – outside hypothesis**
  - Inflammatory responses to irritants and allergens drives eczema with secondary barrier disruption:
T cells in skin lesions of atopic dermatitis
Atopic eczema: A skin barrier disease
The brick wall model of the skin barrier

Bricks: cells (corneocytes)

Iron rods: hold cells together (corneodesmosomes)

Cement: around the cells (lipid lamellae)
The brick wall model of the skin barrier
Fillagrin

- Profillagrin cleaved to fillagrin
- Fillagrin aggregates the keratin skeleton and causes flattening
- Filagrin proteolysed into natural moisturising factor and acidifies the surface
- Protects against Staph toxin induced keratinocyte death
- Mutations cause dryness
- Early onset AD
- More persistent AD
- Association with asthma, FA and infection
- Enhanced expression of IL1 cytokines
Tight junctions on stratum granulosum keratinocytes

De Benedetto. 2011
JACI
- **Filaggrin-2**
- **Hornerin**
- **SPINK 5 gene (Serine protease inhibitor Kazal type 5)**
  - Encodes the protease inhibitor lymphoepithelial Kazal-type-related inhibitor (LEKTI)
  - Regulates desquamation
- **SPRR3 small proline rich protein 3**
The brick wall model of the skin barrier

Skin barrier breakdown in atopic dermatitis
The brick wall model of the skin barrier

Portal of entry
Complexity: Interrelationships!
Eczema as an entry point for allergens
Atopic dermatitis
Pruritis

Lesions

Infection

Atopic dermatitis

Dry skin

Barrier

Allergen

Irritants

Atopy

Lesions

Infection

Barrier

Atopy

Allergen

Irritants
Phases of Atopic Dermatitis

Irritants

Nonatopic dermatitis

Allergens

Sensitisation to allergens

Atopic dermatitis

Scratching → tissue damage

Sensitisation to self proteins

Auto-allergic dermatitis

Impaired epidermal barrier

Tissue-related genes

Receptors, cytokines etc

Atopic genes (cytokines receptors)

Genes
<table>
<thead>
<tr>
<th>Normal Skin</th>
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<tbody>
<tr>
<td><strong>Actinobacteria</strong></td>
</tr>
<tr>
<td>Corynebacterium</td>
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<tr>
<td>Propionibacterium</td>
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<tr>
<td>Rothia</td>
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<tr>
<td>Actinomyces</td>
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<tr>
<td><strong>Bacteroidetes</strong></td>
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<td>Prevotella</td>
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<td><strong>Proteobacteria</strong></td>
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<td>Alphaproteobacteria</td>
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<td>Betaproteobacteria</td>
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<td>Gammaproteobacteria</td>
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<tr>
<td><strong>Firmicutes</strong></td>
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<tr>
<td>Streptococcus</td>
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<tr>
<td>Staphylococcus</td>
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<tr>
<td>Granulicatella</td>
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<tr>
<td>Bacteria Group</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Actinobacteria</strong></td>
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<tr>
<td><strong>Bacteroidetes</strong></td>
</tr>
<tr>
<td><strong>Proteobacteria</strong></td>
</tr>
<tr>
<td><strong>Firmicutes</strong></td>
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</tbody>
</table>
Increased Staph at baseline and worse during flare.
Atopy → Genes → Dysbiosis
Dysbiosis

- Itch
- Infection

- Barrier dysfunction
- Immune dysfunction

- Atopy
- Genes

- Irritants

- Genes

- Infection
- Itch
Dysbiosis

Itch

Infection

Barrier dysfunction

Immune dysfunction

Genes

Irritants

Atopy

Genes

Dysbiosis

Irritants

Atopy

Immune dysfunction

Genes

Dysbiosis

Irritants

Atopy

Immune dysfunction

Genes

Dysbiosis

Irritants
Dysbiosis

Atopy

Immune dysfunction

Genes

Barrier dysfunction

Irritants

Dysbiosis

Infection

Itch

Atopy

Immune dysfunction

Genes

Barrier dysfunction

Irritants

Dysbiosis

Infection

Itch
• Endogenous antimicrobial peptides decreased

Ong 2002
NEJM
Atopy

Immune dysfunction

Genes

Barrier dysfunction

Staph

Infection

Itch

Irritants
Antigen Presenting Cell

MHC Class II

Foreign Peptide

Staph Enterotoxin

T Cell

NFkB → IL-1, IL-6, TNF-α

MHC Class II

T Cell Receptor

αV βV

αC βC

Signaling → IL-2, IFN-γ
Mast cells stimulated with Delta toxin degranulate

Delta toxin causes skin disease

Nakumura 2013 Nature
Staphylococcal extracts
Homeostasis vs. Dysbiosis

- **Pathobiont expansion**
- **Reduced diversity**
- **Loss of beneficial microbes**
Increased Staph at baseline and worse during flare
Causes marked loss of diversity

Kong et al. 2012
Genome res
Microbial diversity

Normal

Atopic dermatitis

Salava 2014
CTA
Therapeutic implications
Random fact -> Some mechanism -> Cycle

Blah Blah

Whatever

Side issue

Cause

Effect

Blah Blah
Phases and treatment of Atopic Dermatitis

- Acute phases (flare-ups): Topical steroids
- Interval (non-acute) phases: Emollient treatments

Skin with acute flare-ups

Interval (non-acute) phases:
Emollient treatments

Interval

Time

Subclinical inflammation

Interval

Flare

Flare

Severity

Interval
Restore skin barrier

• Avoid triggers and aggravators
• Avoid soap
• Use bath oils and wash with soap
  substitute: cleansing oils or creams
• “Moisturize” – use a good emollient at least twice a day
Wet Dressings

- Reduce the itch
- Cooling and soothing
- Moisturise the skin
- Protect the skin
- Help skin heal
Before emollients

Affected skin

Unaffected skin

After 2 ½ months emollients

Affected skin

Unaffected skin

Seite et al. 2014
J drugs dermatol

Genera_unassigned
Finegoldia
Prevotella
Brevibacterium
Paracoccus
Peptoniphilus
Anaerococcus
Staphylococcus
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Anti-Staph approach

- Bleach baths
- Nasal eradication
- Topical antibiotics
Future strategies?

- Direct manipulation of microbiome
- Apply bacterial products to skin