Barrier function and immunology of the skin: skin health and skin disease

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Barrier function

Why does it matter?
Childhood eczema

- Eczema is common
- Mild, moderate or severe
- 20% under one year olds
- Big impact on families
- Recent research shows importance of barrier function
- Relevant to eczema of all types in all ages
Barrier function and atopic eczema
A Healthy Skin Barrier

- Swelled corneocytes
- Cornified envelope
- Intact corneodesmosomes
- Lipid lamellae (pH 5.5)

**Components:**
- NMF
- H₂O
- Filaggrin
- Profilaggrin
- Degradatory proteases
- Protease inhibitors
- Lipid processing
- Lipid delivery
A Healthy Skin Barrier

Swelled corneocytes

\[ \text{pH 5.5} \]

Intact corneodesmosomes

Lipid Lamellae
Ceramide: cholesterol: fatty acids

Natural moisturizing factor
Urocanic acid, Pyrrolidone carboxylic acid, lactic acid, urea

Filaggrin

Degradatory proteases

Protease inhibitors

Lipid delivery & processing

Cornified envelope

NMF
H\(_2\)O

NMF
H\(_2\)O

NMF
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NMF
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Allergens & Irritants

Water

pH 5.5

NMF
H₂O

NMF
H₂O

NMF
H₂O

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Brick $\Rightarrow$ Corneocyte

Mortar $\Rightarrow$ Lipid Lamellae
Mortar $\Rightarrow$ Lipid Lamellae

Ceramides + Fatty acids + Cholesterol
The Normal Skin Barrier
What goes wrong in childhood eczema?
Infant skin has a low epidermal barrier reserve


When is the skin barrier not optimum?
A Defective Skin Barrier in AD

- Defective lipid lamellae
- Degraded corneodesmosomes
- Abnormal cornified envelope

- Reduced levels of ceramides
- pH 7.0

- NMF
- H₂O

- Filaggrin
- Profilaggrin

- Degradatory proteases
- Protease inhibitors

- Lipid processing
- Lipid delivery

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PAR = Proteinase-activated Receptor-2

**Increased pH**

**Acute disruption**

**Environmental Factors**
- Soap & detergents
- Bodily excretions
- Excessive hydration/occlusion
- Exogenous proteases

**Genetic Factors**
- FLG
- KLK7
- SPINK5 CYSTA

**Serine proteases**

**PAR2**

Skin barrier breakdown, inflammation & pruritus
An allergic response is elicited

Allergens

NMF

H₂O

NMF

H₂O

NMF

H₂O

Th1

?  Th2

Cork, Danby et al (2009) In Skin Moisturization. Academic Unit of Dermatology Research, The University of Sheffield
Allergens & Irritants

Water

pH 7.0

↓NMF
↓H₂O

↓NMF
↓H₂O

↓NMF
↓H₂O

↓NMF
↓H₂O

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Irritants & allergens
What do we mean by irritants?
Identifying irritants: ask about skin care regime

• Bath or shower
• How often, per day, per week
• Products used for washing/showering, added to bath
• Products used for laundry
Common irritants
Common cause of irritancy!

TOO MUCH WASHING!!!!
Itching: some simple tips

STOP ALL IRRITANTS:

• Shower gels
• Soaps
• Biological washing powders
• Fabric conditioners
• Leave on moisturiser
• NOT AQUEOUS CREAM
The effect of topical products/treatments on pH and protease activity
A Healthy Skin Barrier

Swelled corneocytes → Cornified envelope → Intact Corneodesmosomes → Lipid Lamellae

NMF → H₂O

Filaggrin → Protease Inhibitors → Lipid processing

Profilaggrin

Lipid delivery → pH 5.5

Degradatory Proteases
A Defective Skin Barrier in AD

Defective lipid lamellae

(Reduced levels of ceramides)

(NMF ↓ H₂O)

Filaggrin ↓

Profilaggrin ↓

Degraded Corneodesmosomes

(Degradatory Proteases)

Protease Inhibitors

(Reduced levels of ceramides)

Abnormal cornified envelope

Lipid delivery

Lipid processing

pH 7.0
Protease activity in the skin barrier

Protease Activity
(in the stratum corneum - no red stain)

Nucleated layers
(nuclear material stained red)

Dermis

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The effect of pH on skin barrier protease activity: clinical relevance

pH 8.5  pH 7.0  pH 5.0

Acute AD pH 7.3  Current AD pH 5.7  Normal skin pH 5.0

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The Effect of Washing with Liquid Soap on Skin Surface pH

* $p = <0.05$;  *** $p = <0.001$;  n = 3

The Effect of Washing with Liquid Soap on Skin Surface pH

* $p = <0.05$; *** $p = <0.001$; n = 3

**Clinical relevance**

Aqueous cream – first appeared in the BNF in 1958

Its formulation containing SLS remains largely unchanged today.
Aqueous Cream Leave-On compared with No Treatment for 4 weeks

Skin Barrier Integrity: End Point

$p = 0.0002 \ (n = 9)$
Atopic eczema and domestic water hardness.

“Living in a hard water area is significantly associated with an increased lifetime prevalence of AD”

Confirmed by 2 replicate studies (in Japan and Spain)
A Randomised Controlled Trial of Ion-Exchange Water Softeners for the Treatment of Eczema in Children

Kim S. Thomas, Tara Dean, Caroline O'Leary, Tracey H. Sach, Karin Koller, Anthony Frost, Hywel C. Williams, and the SWET Trial Team

To summarise
Atopic eczema: pathophysiology

**BRICK WALL THEORY**
The Brick Wall theory

Irritants penetrate and trigger inflammatory response

Leads to dry skin

Irritants penetrate and trigger inflammatory response
Brick wall theory: correct barrier function

Correcting barrier function reduces dry skin and penetration of irritants and inflammation
EMOLLIENTS
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