Skin barrier function in Atopic Eczema

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UCT
BASIC STRUCTURE OF THE EPIDERMIS

- Stratum corneum
- Granular layer
- Spiny layer
- Basal layer
BRICK AND MORTOR MODEL

Barrier

keratinocyte bricks
BRICK AND MORTOR MODEL

Barrier

keratinocyte *bricks*

intercellular lipid *mortar*
BRICK AND MORTOR MODEL

Barrier

keratinocyte bricks

intercellular lipid mortar

surface sebum plaster
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*Elias, Hatano and Williams*  
*J Allergy Clin Immunol*  
*June 2008*
BARRIER DYSFUNCTION
THE DRIVER OF DISEASE IN AD

“OUTSIDE-INSIDE-OUTSIDE MODEL”

BARRIER DISRUPTION
irritants, infection, inhalants
genetically predisposed individuals

↓

INFLAMMATION

↓

IMMUNE ACTIVATION

↓

BARRIER DYSRUPTION
BARRIER DYSFUNCTION
THE DRIVER OF DISEASE IN AD

BASED ON FOLLOWING OBSERVATIONS

- Filaggrin gene null mutations in Euro-American patients with AD (20%)
- The extent of disease parallels amount of barrier abnormality
- ↑ Trans-epidermal water loss in atopic skin
- ↓ Irritancy threshold
- ↑ Percutaneous absorption
- AD patients have ↓ lipid ceramide
- Emollient therapy is effective ancillary therapy
- Lipid replacement therapy corrects permeability barrier and has anti-inflammatory effects
BARRIER DYSFUNCTION IN AD

- **Physical barrier**
  - corneocyte adhesion and water retention (filaggrin)
  - corneodesmosomes

- **Chemical barrier**
  - lipid barrier
  - acid mantle
  - protease/protease inhibitor balance
  - Antimicrobial peptides (HBD-2,3 + human cathelcidin)

- **Immune barrier**
  - humoral (↑IgE) and cellular defects

The components of the physical and chemical barrier defects interact to cause a disruption of the permeability and antimicrobial functions in AD skin.
PERMEABILITY BARRIER DEFECT IN AD (INTERACTION BETWEEN GENES + ENVIRONMENT)

GENES

- **Filaggrin** null mutations
- **Serine protease** (excess cause desquamation)
  Human kallikrein related peptidases (KLK)
- **Protease inhibitors** (deficiency cause desquamation)
  Cystatin A
  LEKTI (SPINK 5 GENE)
FILAGGRIN-FUNCTIONS

- Filament Aggregating Protein = cement of the epidermis

- Aggregates and binds keratin cytoskeleton > collapse of granular cells > flattens to anucleated squames > cross linking by transglutamase > epidermal barrier effect (CCE)

- Degradation > hygroscopic aminoacids > act as osmolyte (NMF) > draw water into corneocytes

- Filaggrin > polycarboxylic acids > acid mantle

- Filaggrin > urocanic acid > chromophore > sun protection
Homozygous FLG mutations lead to complete loss of filaggrin expression in skin
(JID 2006, VOL 126)
ATOPIC ECZEMA
FILAGGRIN MUTATIONS

- Carrier of 1 null mutation 4x chance of early onset persistent eczema, 2 mutations chance increases 80x

- >½ Children with moderate to severe AD

- Major risk factor for predisposition to AD and eczema associated asthma

- Early onset infant eczema which persists into adulthood

- Correlates with severity of filaggrin associated eczema
  (↓ hydration, ↑ TEWL, ↑ SC thickness)

- Associated with elevated levels of IgE

- Filaggrin deficiency > ↑ TEWL > chronic exposure to insults > inflammation > AD
PERMEABILITY BARRIER

Lipid composition

- ceramides 50% : fatty acids 10-20% : cholesterol 25%
- ratio and composition important to keep hydrated and prevent pathogen and allergen entry
- AD skin has decreased ceramides
PERMEABILITY BARRIER

Acid mantle

- Important for optimal function of lipid processing enzymes and those involved in keratinisation
- Prevents activation of serine proteases
- Prevents pathogen invasion
- Favours adhesion of non pathogenic bacteria to the stratum corneum
- AD patients found to have ↑ pH in lesional and non lesional skin
Antimicrobial barrier

- Atopic skin found to have decreased human beta defensin 2,3 which makes them susceptible to staphylococcal and fungal infections

- Also decreased human cathelcidin LL-37 predisposes to eczema herpeticum and eczema vaccinatum

- Decreased recruitment of innate immunity cells

- TLR2 defects

- Reduced levels of sphingosine predisposes to staph infection

- Reduced levels of dermcidin from eccrine glands predisposes to bacterial and viral infections
Environmental stressors that affect barrier function in AD patients

**Infections**

*staphylococcus and malassezia*

*S. Aureus*

- chronicity and severity of AD
- direct barrier damage
- secretes proteases > desquamation
- sphingosine deacylase and glycerophosphylase interfere with lipid formation
Environmental stressors that affect barrier function in AD patients

Irritants

- Physical - tape stripping, rough fabric, etc.
- Chemical - detergents, soaps, alcohol, water, preservatives
SOAPS!!!!!!

- Emulsify skin surface lipids
- Act as surfactants - scaly, dry, tight, inflamed skin
- ↑ TEWL
- ↑ pH
- Alters protease activity - ↓ SC thickness
- Pro inflammatory cytokines
- Activates PAR-2 receptors thereby mediating inflammation and pruritus
Environmental stressors that affect barrier function in AD patients

ALLERGENS

HOUSE DUST MITE
- provokes IgE
- secretes protease
- direct skin irritation

COAKROACH ALLERGENS
- barrier break down
- activate PAR-2
OTHER ENDOGENOUS AND EXOGENOUS STRESSORS

- Prolonged exposure to decreased environmental humidity accelerates TEWL over a defective stratum corneum
  (radiant heated homes in temperate climates)

- Hard water

- Psychological stress $\rightarrow$ glucocorticoids $\rightarrow$ ↓ lipids

- IL-4 (TH2 cytokine) delays barrier recovery, ↓ ceramide secretion in vitro, inhibits FLG and Dsg expression
CLINICAL IMPLICATIONS

Mainstay of AD treatment and control

- **Restoration of barrier**
  - correcting barrier abnormality is anti-inflammatory:
    - decreases ingress of hapten, ↓ Th2
    - lipid restoration decreases the PH
    - FFA is antimicrobial
    - down regulates signaling mechanisms

- **Avoiding triggers**
When used under supervision, moisturizers have been shown to reduce topical steroid use (Cork at al; 2003)

- **What?**
  
  *Choice of moisturizers*
  
  Composed of 3 physiological lipids in the right ratios
  
  Humectant effect
  
  Occlusive
  
  ↓ pH
  
  Irritant free (no color, no smell)

- **How often?**
  
  *Use frequently 4x*

- **When?**
  
  After bath, or with bath (liquid paraffin, milk)
ANTI-STAPH MEASURES

Use when obvious infection or trial when encountered with nonresponsive eczema and prophylactic treatment for recurrent staphylococcal infection

- Topical antiseptics
  Betadine scrub as soap and shampoo, or diluted hypochlorite baths
  nasal cream
- Antibiotic if obvious infection
- Soaps (use emollient wash products)
- Bubble baths
- Woolen or rough fabric clothes
- Fragrances
- Aggressive antiseptics
- Shampoos with high content sodium lauryl sulphate
- ?cats
- Sweat (use wet wraps)
- Dry climates (increase frequency of moisturizing)
CONCLUSION

- Atopic eczema is due to breach of barrier as a result of interplay between environment and genes.
- Strong genetic predisposition + environmental insults = AD
- Early avoidance of environmental triggers and barrier maintenance leads to early resolution of AD.
- Dry skin is the first sign to start preventive measures.
**Pathogenesis of AE:**

**Impaired skin barrier and altered immune reaction**

**Environment**
- Mutations of structural proteins (FLG)
- Reduced/disturbed lipids (ceramides)
- High protease activity (loss of inhibitors)
- Decrease of antimicrobial peptides

**Skin inflammation**
- CD4, CD8
  - IL-4
  - IL-5
  - IL-13
  - IFN-γ
- B cells
- IgE
- DC
- Eosinophils
- Mast cells

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