Function and Dysfunction of Skin Barrier

Masayuki Amagai, M.D., Ph.D.
Department of Dermatology, Keio University School of Medicine
Laboratory for Skin Homeostasis, RCAI, RIKEN Center for Integrative Medical Sciences

Atopic Dermatitis: From Barrier to Inflammation

Cutaneous sensitization is the initial key step for many allergic disorders

Allergic disorders
- Allergic rhinitis
- Atopic dermatitis
- Asthma
- Food allergy
- Anaphylaxis

Skin

Allergic disorders in different organs

Epidermal Structure of Mammals

Stratum Corneum
Stratum Granulosum
Stratum Spinosum
Stratum Basale

Tight Junction
Liquid-Liquid Barrier

Air-Liquid Barrier
Cell Death
Differentiation
Proliferation

Langerhans Cell Network
Immune Barrier

Reviewed by Kubo, Nagao and Amagai, J Clin Invest 2012

Resting Langerhans cells stay under the TJ barrier

Langerhans cells in resting state

ZO-1
MHC class II
Claudin-1
merged

Reviewed by Kubo et al, JEM 2009
**Activated Langerhans cells elongate their dendrites through TJ barrier**

**Langerhans cell in an activating state**

- ZO-1
- MHC class II
- Claudin-1
- merged

Kiibo et al., JEM 2009

**Staphylococcal Scalded Skin Syndrome (SSSS)**

Exfoliative toxin (ET, 26-32 kDa) produced by *S. aureus* cleaves Dsg1 with resultant blister formation.

- Dsg1
- Dsg3

Amagai et al., Nat Med 2000

**Cutaneous immunization (topical application with patch) leads to ETA-specific IgG1 response and prevents SSSS**

> Ouchi, Nagao et al., JEM 2011
Two sets of Intra-epidermal dendritic cells in AD

1. Langerhans cells (LCs)
   - Langerin (+) / Birbeck granules (+)
   - HLA-DR (+)
   - High affinity IgE receptor (Fc-epsilon receptor I) (+)
   - Th2 response induction in vitro

2. Inflammatory dendritic epidermal cells (IDECs)
   - Langerin (-) / Birbeck granules (-)
   - HLA-DR (+)
   - High affinity IgE receptor (Fc-epsilon receptor I) (+)
   - Th1 response induction in vitro
Langerhans cells (LC) extend their dendrites above tight junction and capture external antigens which penetrate through stratum corneum.

Beautiful collaboration by Tight Junction and Langerhans cells to capture external antigens without breaking barrier function.

TOF-SIMS analyses of corneal layers revealed the three distinct layers in stratum corneum in mice and human.

Upper SC layer functions like a sponge
Middle SC layer functions for hydration
Lower SC layer functions as a barrier

Arginine of the middle-SC disappeared in filaggrin KO.

Langerhans cell repopulation in the epidermis
Langerin  MHC II

MHC II+ Langerin- EpCAM-
MHC II+ Langerin+ EpCAM+

Nagao et al, Nat Immunol 2012

Tape strip induces rapid infiltration of leukocytes to hair follicles (0.5~4.5 hrs)

GFP+ cells were mostly MHC II+ and/or CD11b+ (not shown)

Nagao et al, Nat Immunol 2012

Upregulation of CCL8 expression after tape-stripping

CCL8
No tape strip
18 hrs after tape strip

Nagao et al, Nat Immunol 2012

HFs are immunologically functional structures that differentially regulate LC/pre-LC recruitment

Mechanical stress
Interfollicular epidermis
Infundibulum
Isthmus
Basal bulge
Suprabasal bulge

CCL20
pre-LC (CCR6)
LC/pre-LC (CCR2)
CCL2
LC/pre-LC (CCR6)
CCL1
LC (CCR8)
CCL8
Stress-induced chemokine production

Nagao et al., Nat Immunol 2012