

# XXIV World Allergy Congress

14-17 October, 2015, Seoul Korea

Plenary Session 3

Atopic Dermatitis : From Barrier to Inflammation

## Function and Dysfunction of Skin Barrier

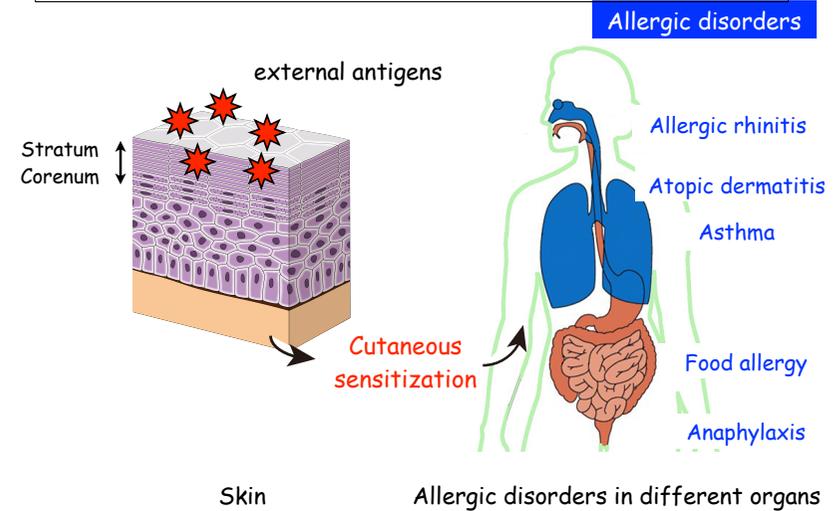


Masayuki Amagai, M.D., Ph.D.

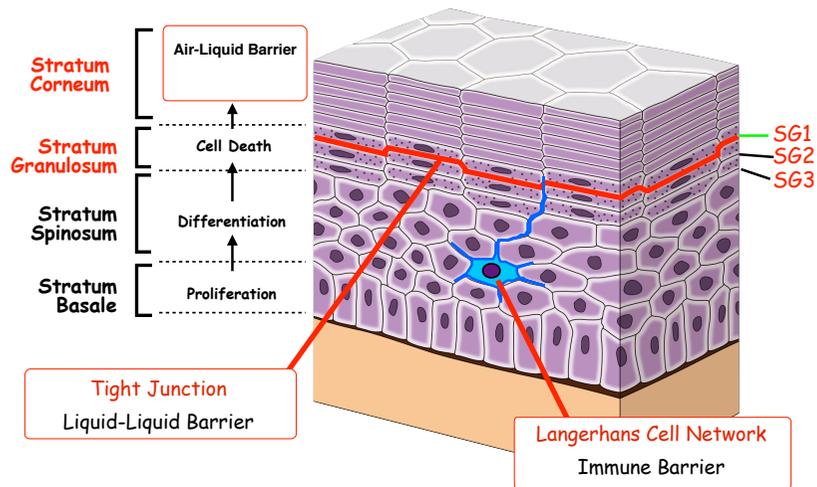
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## Cutaneous sensitization is the initial key step for many allergic disorders



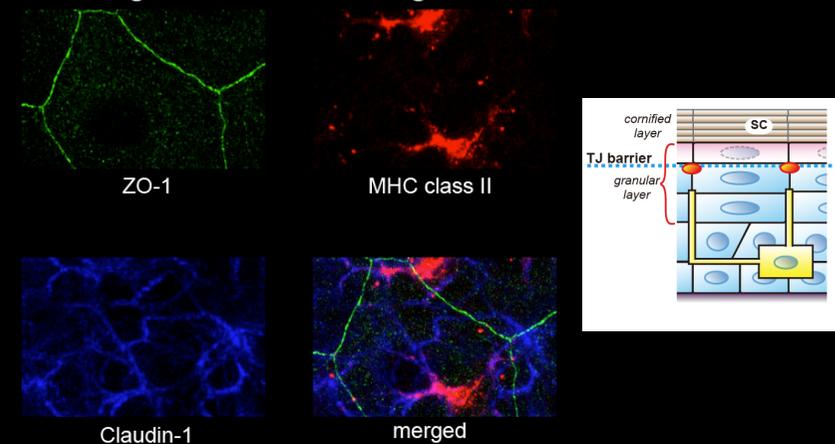
## Epidermal Structure of Mammals



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

## Resting Langerhans cells stay under the TJ barrier

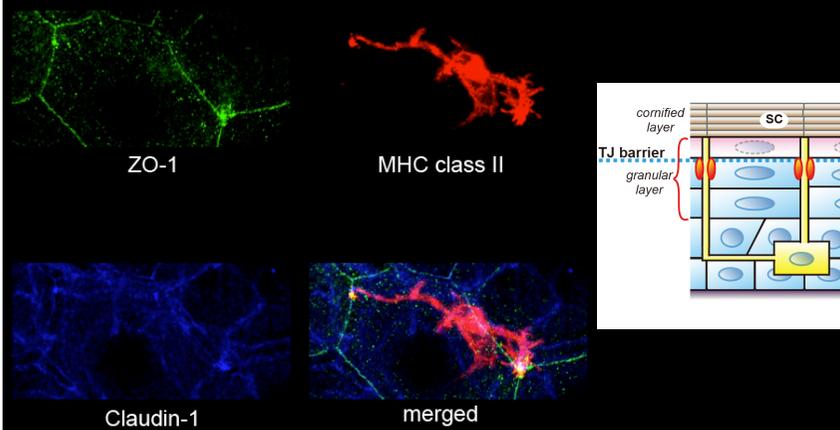
### Langerhans cells in resting state



Kubo et al, JEM 2009

Activated Langerhans cells elongate their dendrites through TJ barrier

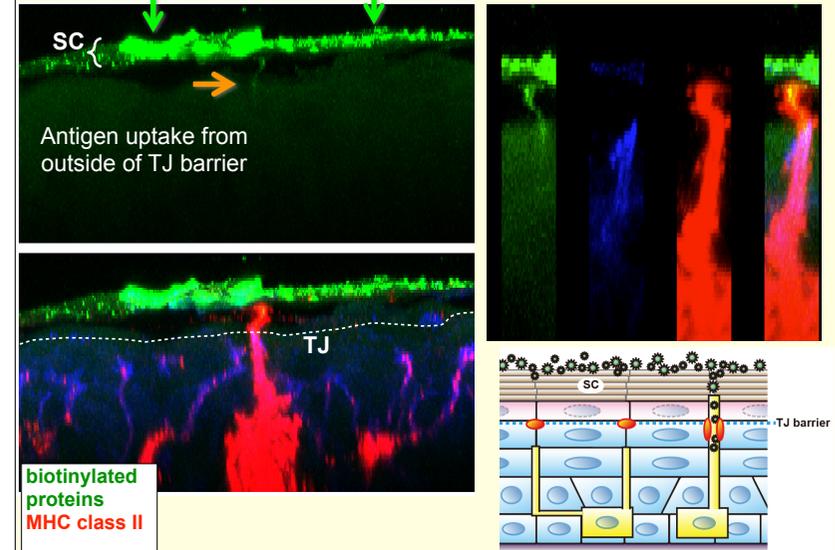
Langerhans cell in an activating state



Kubo et al, JEM 2009

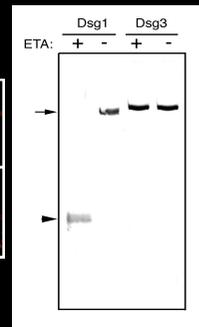
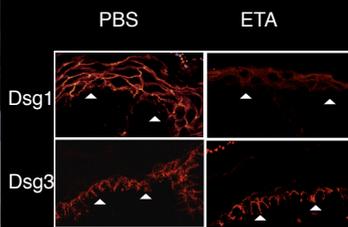
TJ-penetrated Langerhans cells sample antigens from their dendrite tips

Sulfo-NHS-LC-biotin (a TJ impermeable reagent) was topically applied



### Staphylococcal Scalded Skin Syndrome (SSSS)

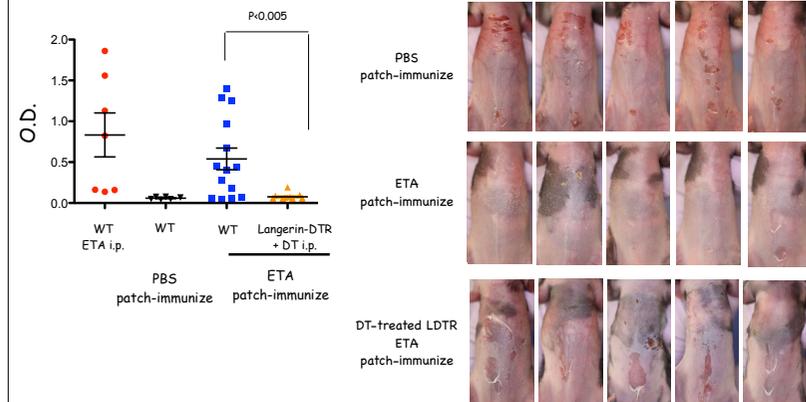
Exfoliative toxin (ET, 26-32 kDa) produced by *S. aureus* cleaves Dsg1 with resultant blister formation.



Amagai et al, Nat Med 2000

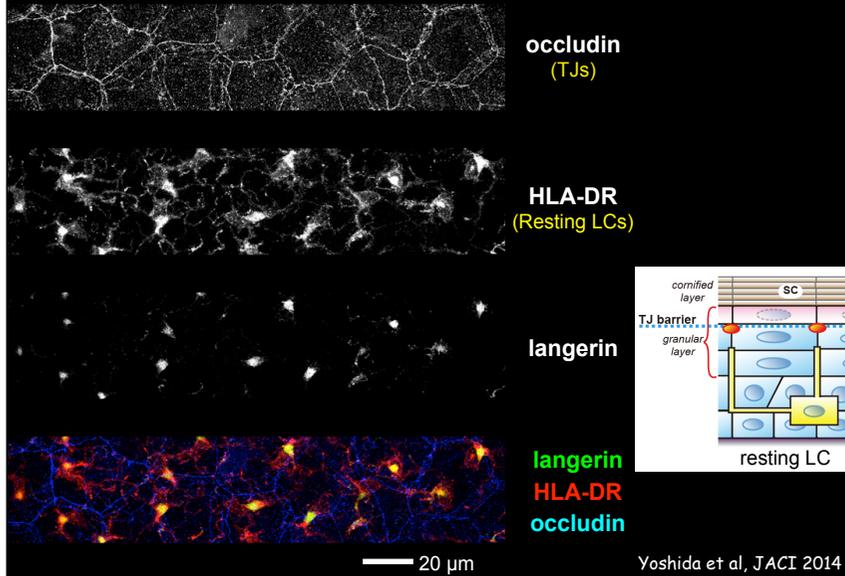
Cutaneous immunization (topical application with patch) leads to ETA-specific IgG1 response and prevents SSSS

ETA i.p. challenge

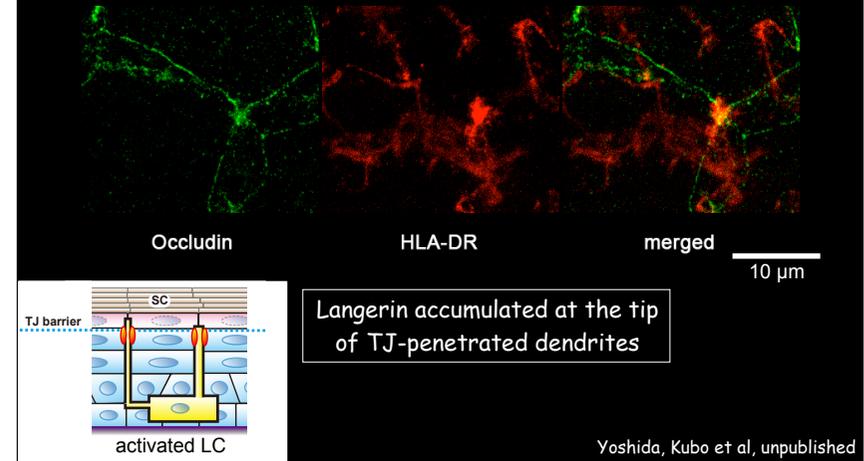


Ouchi, Nagao et al, JEM 2011

### 3D Visualization of TJs and LCs in normal human epidermis



### Activated LCs penetrated TJ barrier to send their dendrites to the extra-TJ environment in human epidermis.



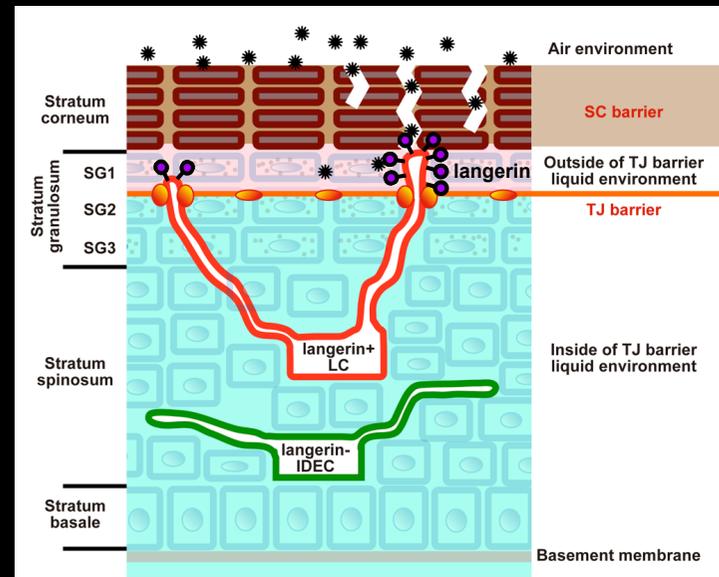
### Two sets of Intra-epidermal dendritic cells in AD

#### 1. Langerhans cells (LCs)

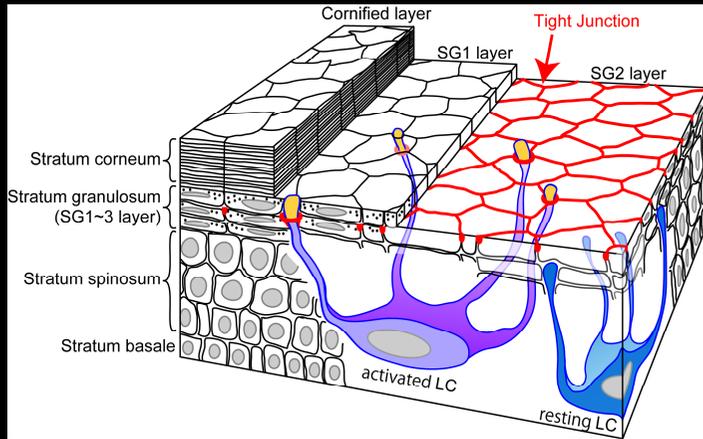
- Langerin (+) / Birbeck granules (+)
- HLA-DR (+)
- High affinity IgE receptor (Fc-epsilon receptor I) (+)
- Th2 response induction in vitro

#### 2. Inflammatory dendritic epidermal cells (IDECs)

- Langerin (-) / Birbeck granules (-)
- HLA-DR (+)
- High affinity IgE receptor (Fc-epsilon receptor I) (+)
- Th1 response induction in vitro

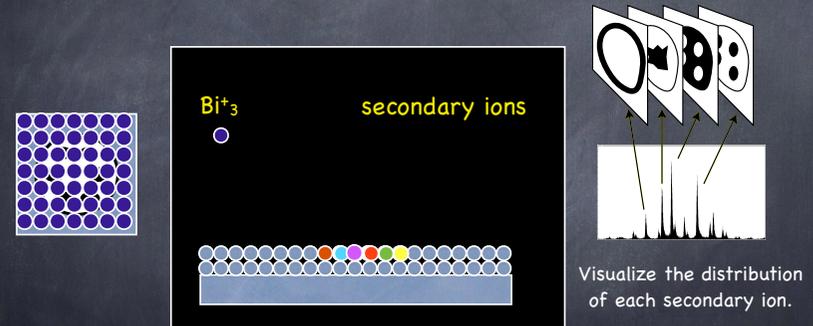


Beautiful collaboration by Tight Junction and Langerhans cells to capture external antigens without breaking barrier function



Langerhans cells (LC) extend their dendrites above tight junction and capture external antigens which penetrate through stratum corneum

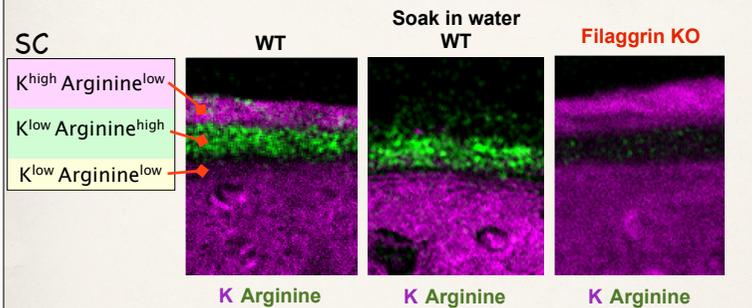
Visualize the unknown structure of the SC by Time-of-Flight Secondary Ion Mass Spectrometry (TOF-SIMS)



Kubo et al, Sci. Rep. 2013

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

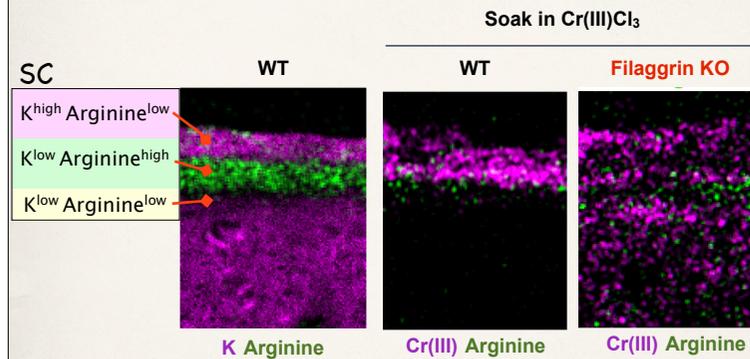


Arginine of the middle-SC disappeared in filaggrin KO

Kubo et al, Sci Rep 2013

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

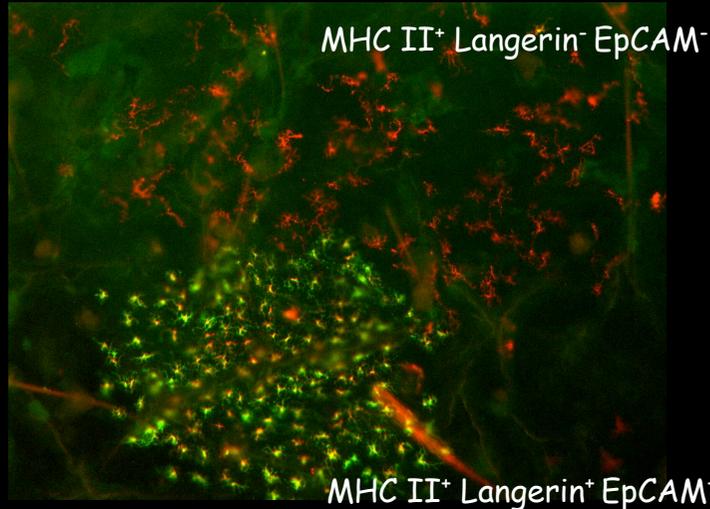
Lower SC layer functions as a barrier



Kubo et al, Sci Rep 2013

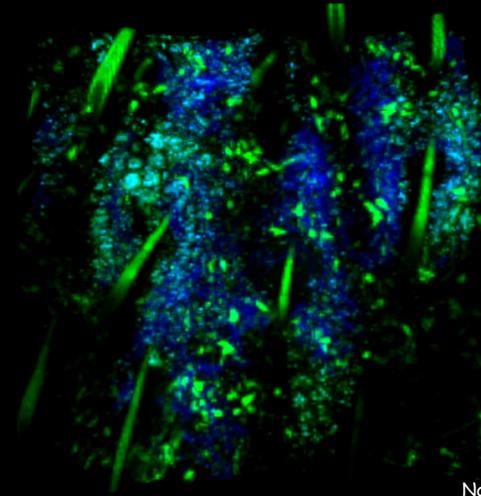
### Langerhans cell repopulation in the epidermis

Langerin MHC II



Nagao et al, Nat Immunol 2012

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



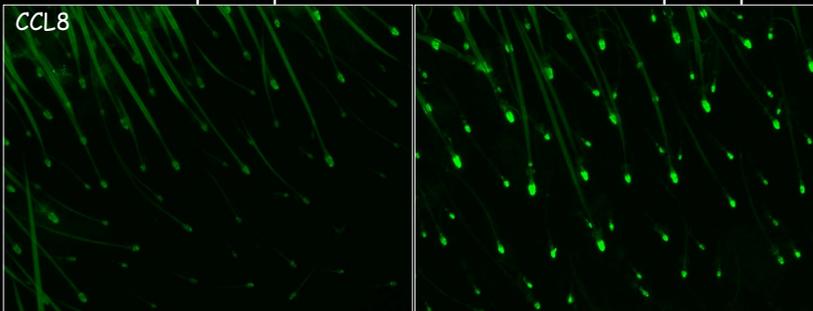
GFP+ cells were mostly MHC II+ and/or CD11b+ (not shown)

Nagao et al, Nat Immunol 2012

### Upregulation of CCL8 expression after tape-stripping

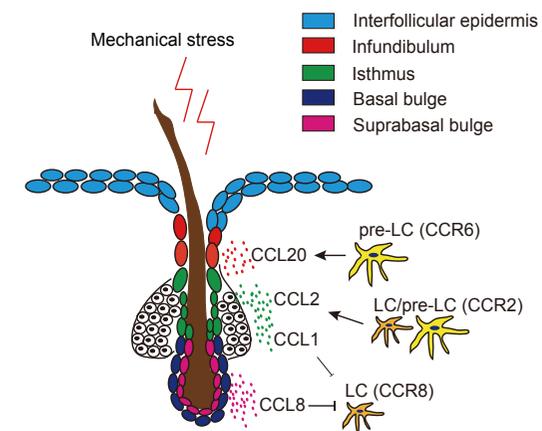
No tape strip

18 hrs after tape strip



Nagao et al, Nat Immunol 2012

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



Stress-induced chemokine production

Nagao et al., Nat Immunol 2012