National Institute of Arthritis and Musculoskeletal and Skin Diseases

Mechanisms of Foreign Antigen Recognition in Skin

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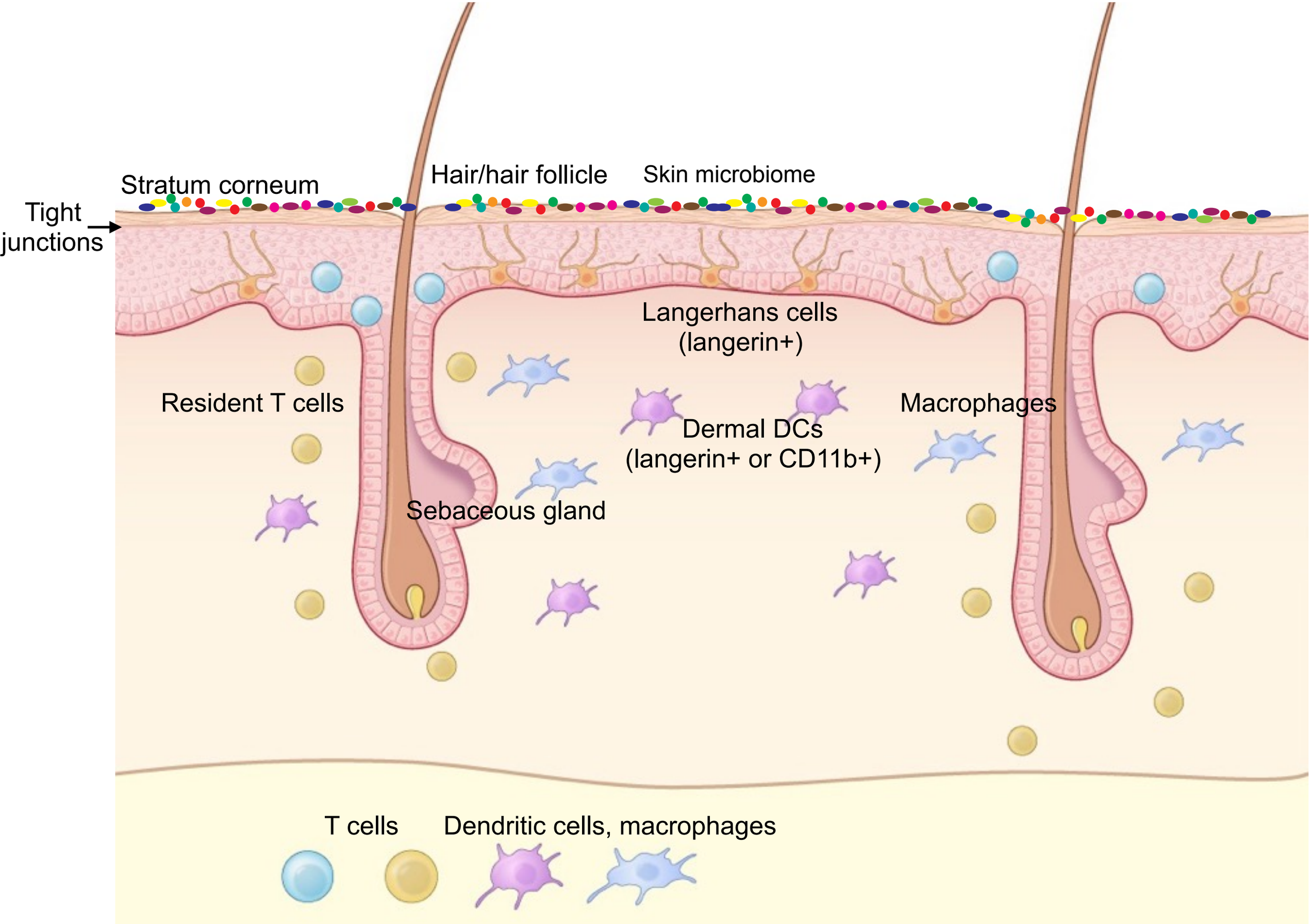
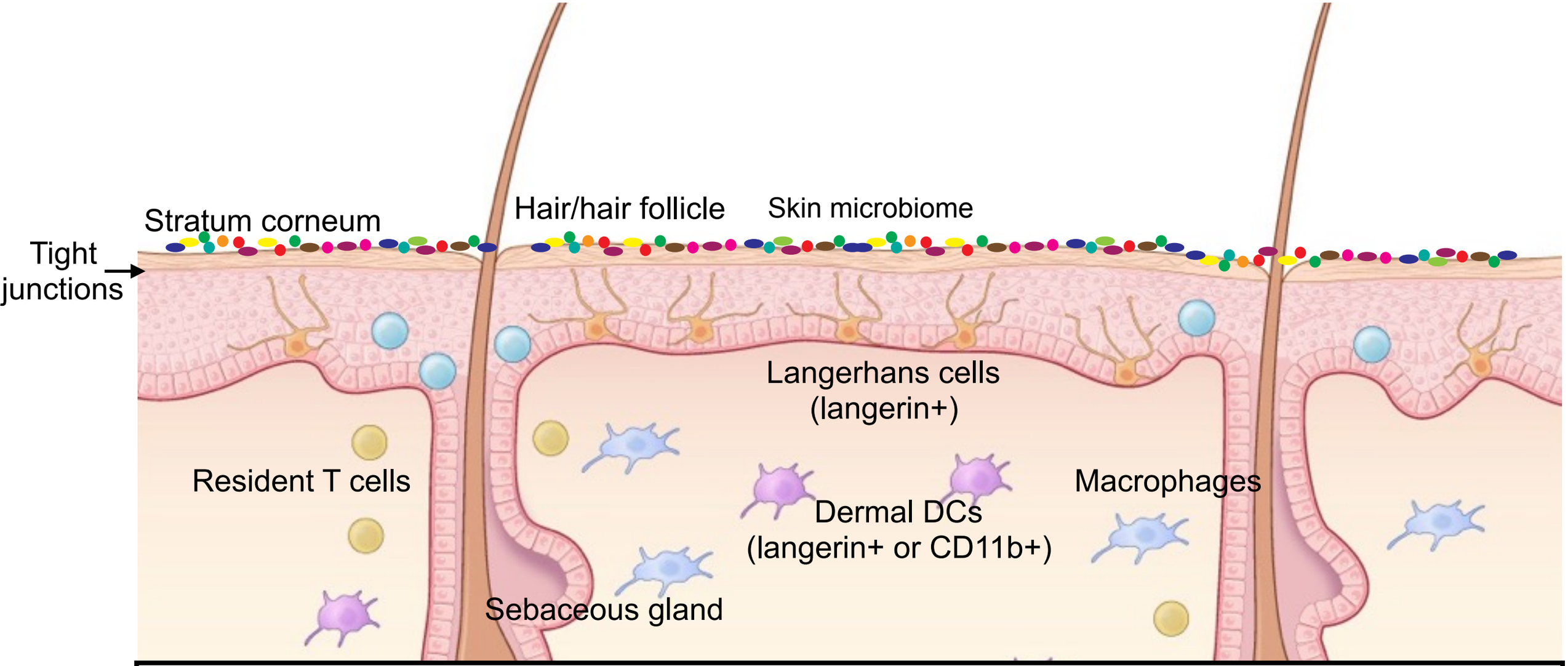
Complexity of the skin and its immune system



Importance of skin immunity beyond skin

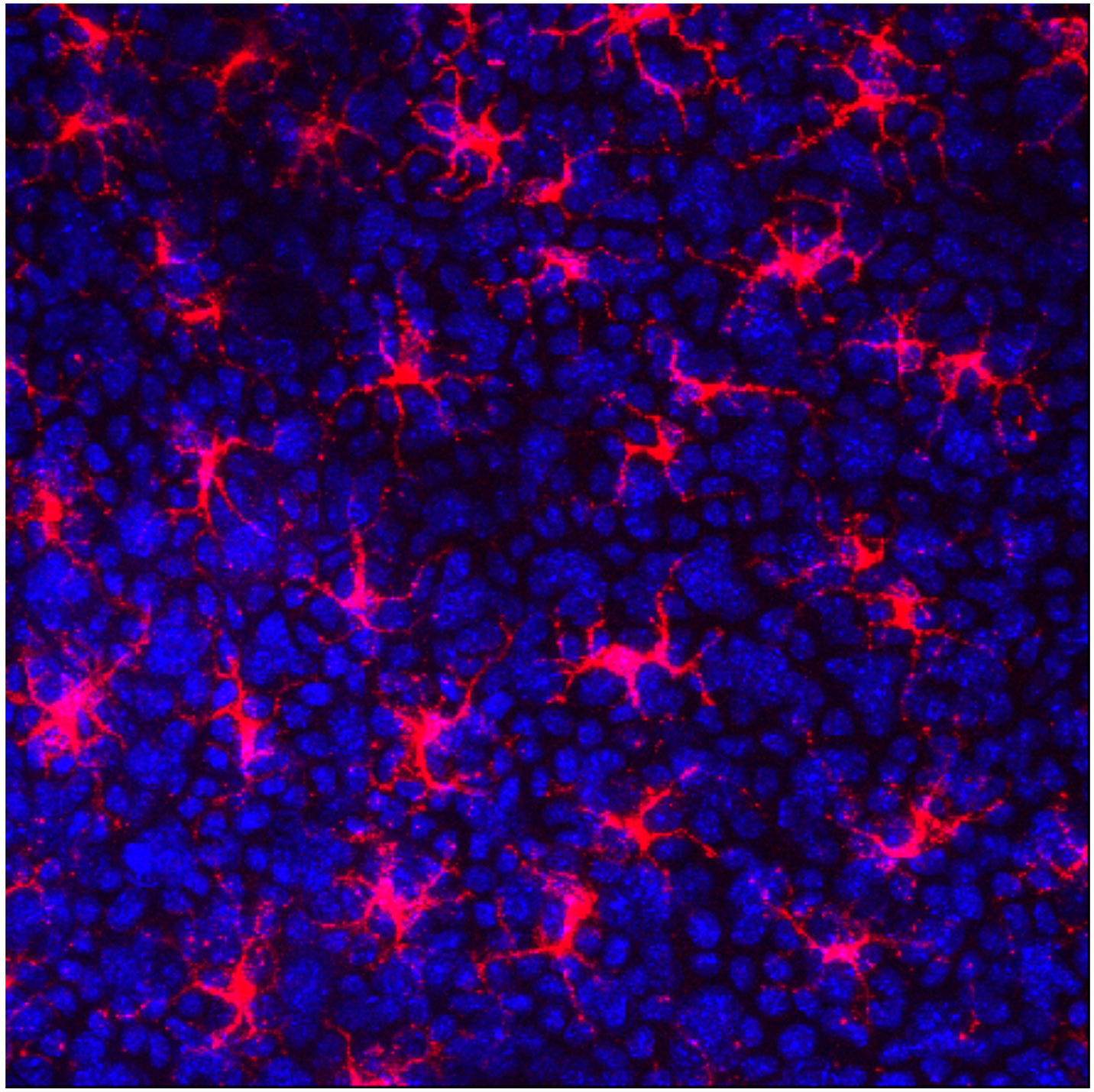


Vaccination → **Systemic immunity**

Atopic dermatitis → **Asthma**
Food allergy

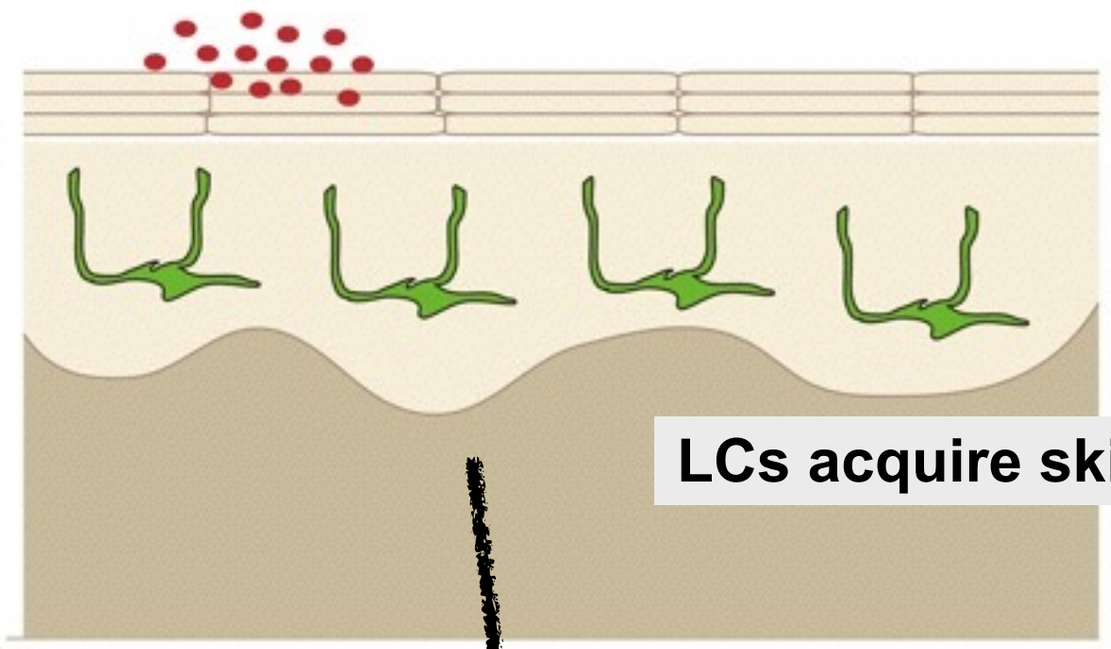
Psoriasis → **Cardiovascular diseases**
Metabolism

Langerhans cells as immunological sentinels



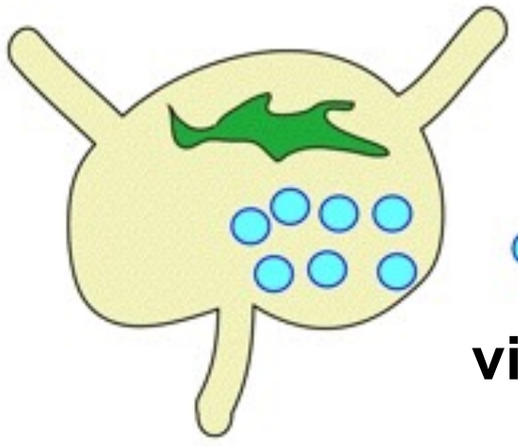
Epidermal sheet (mice)

The Langerhans cell paradigm

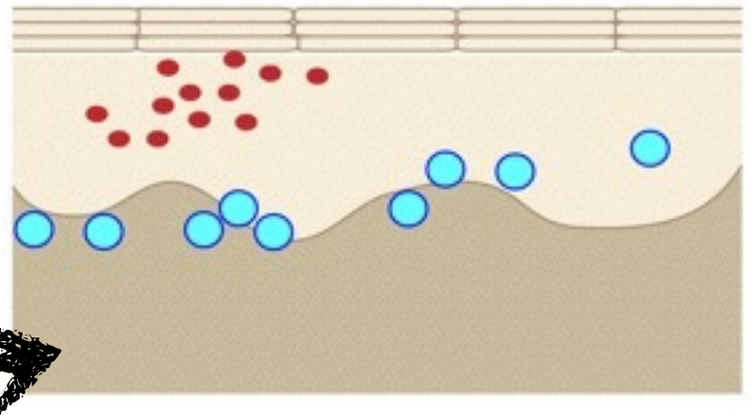


LCs acquire skin-associated antigens

Migration to LN



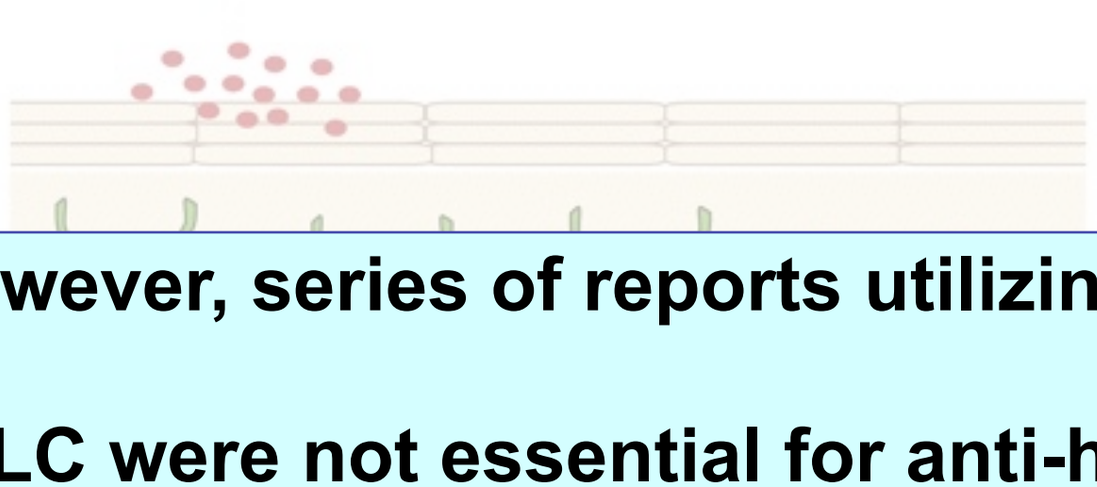
via circulation



Inflammation in skin

anti-microbial response
contact dermatitis

The Langerhans cell paradigm



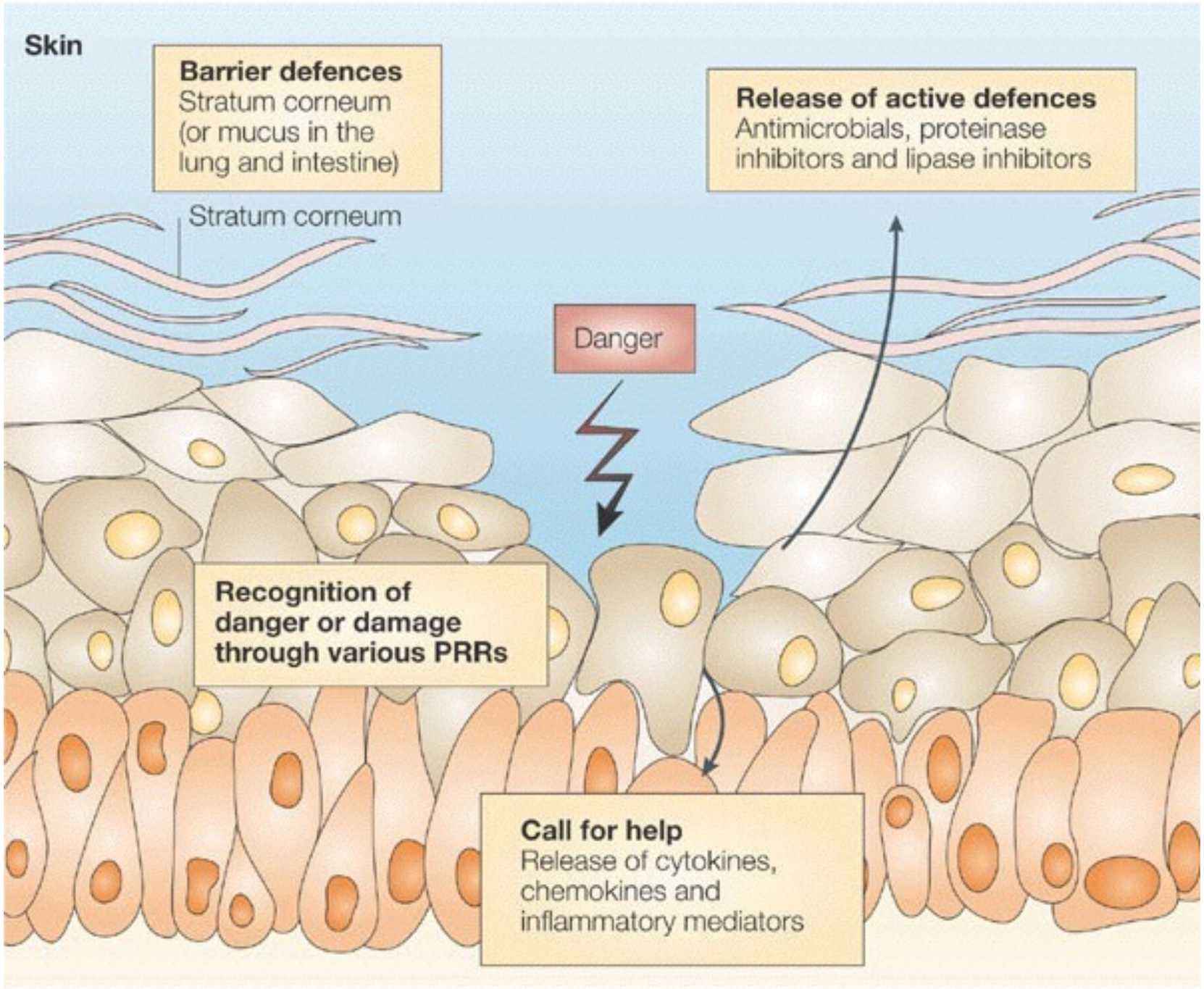
However, series of reports utilizing Tg mice revealed that:

1) LC were not essential for anti-herpes simplex virus responses

2) Mice that were depleted of LC exhibited hapten-induced contact hypersensitivity

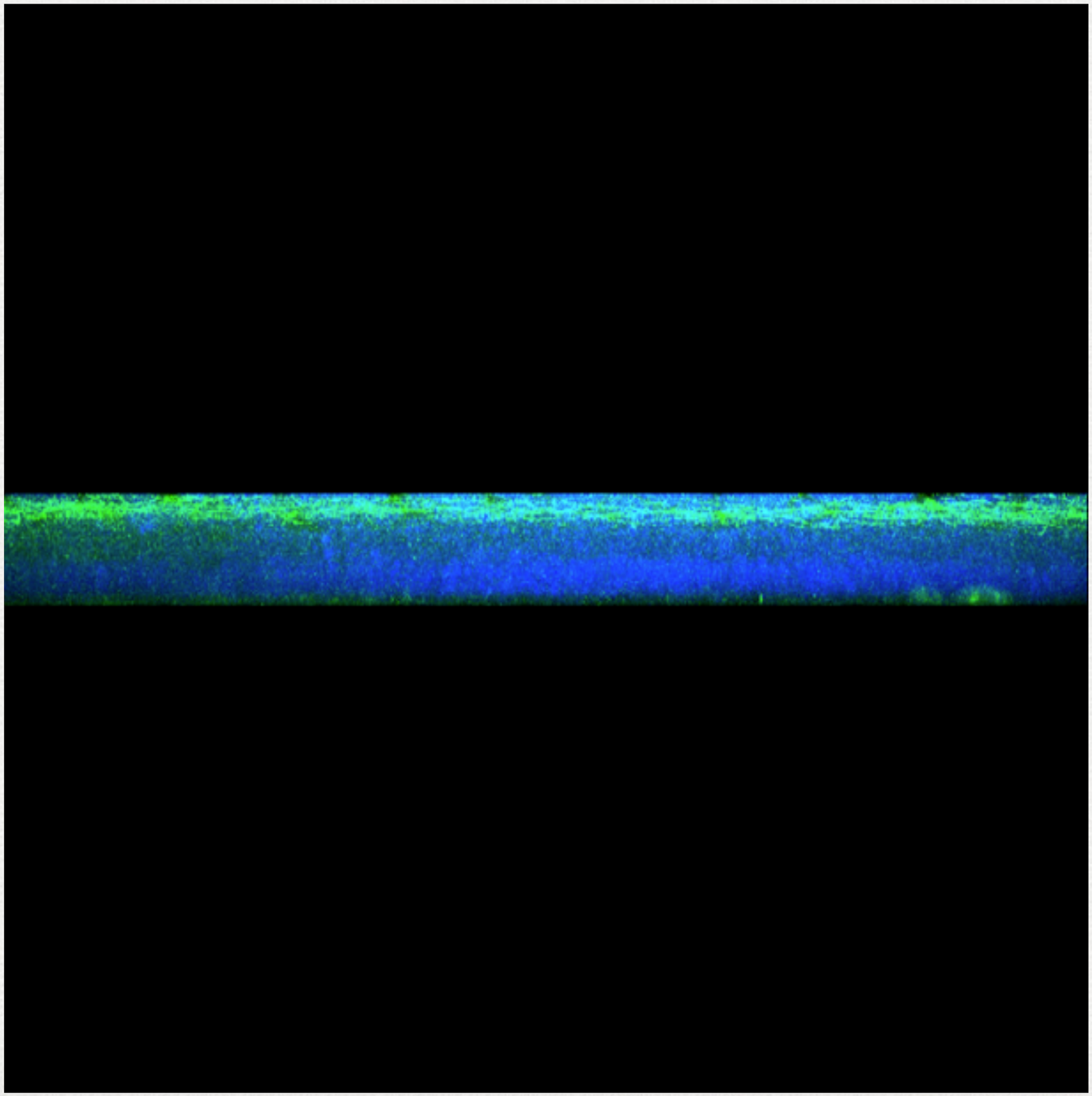
Thus, the role of LC still remains enigmatic

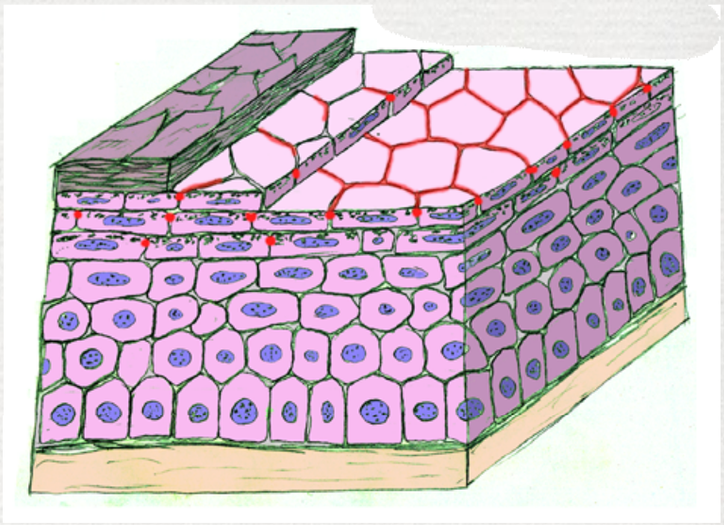
Past studies have neglected the two epidermal barriers



Nature Reviews | Immunology

Tight junction barriers cover skin surface



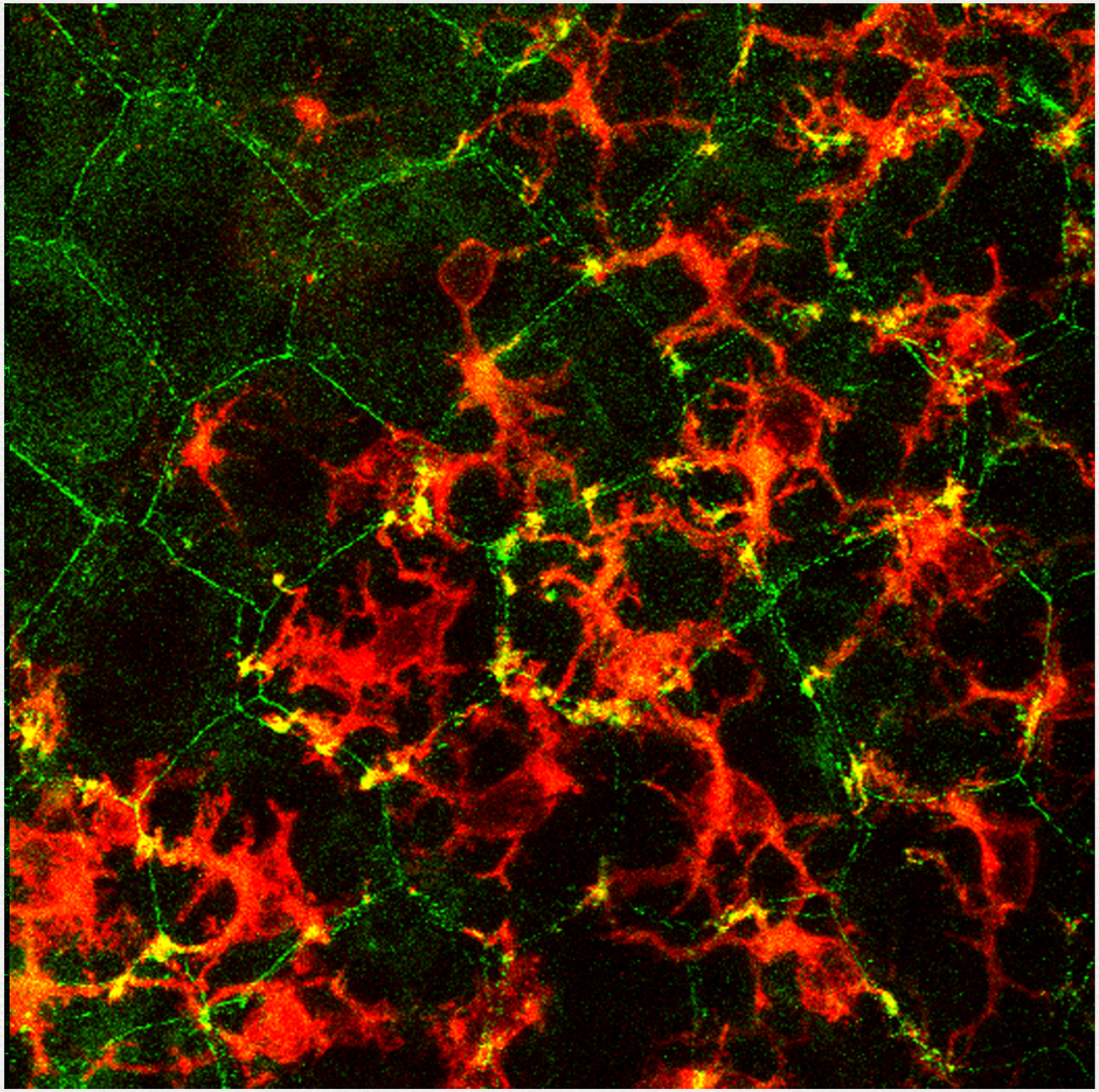


ZO-1 (TJs)
DAPI (nucleus)

ZO-1: zonula occludens 1
(a scaffold protein of TJs)

(Kubo, Nagao et al, JEM 2009)

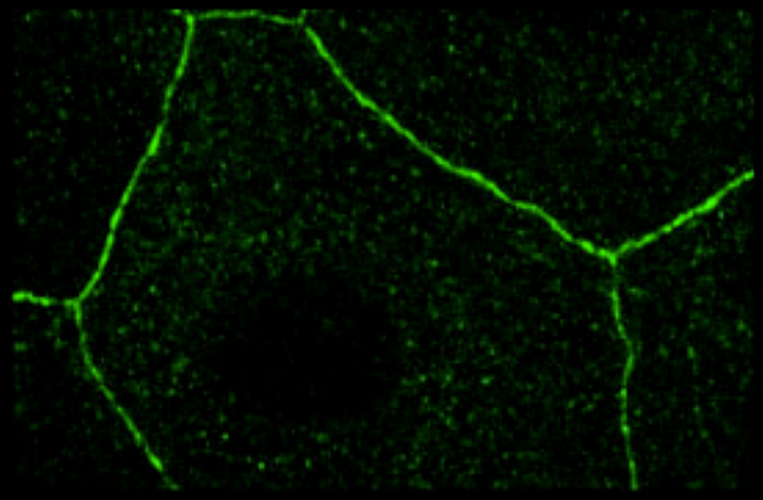
Tape stripping induces activation of Langerhans cells



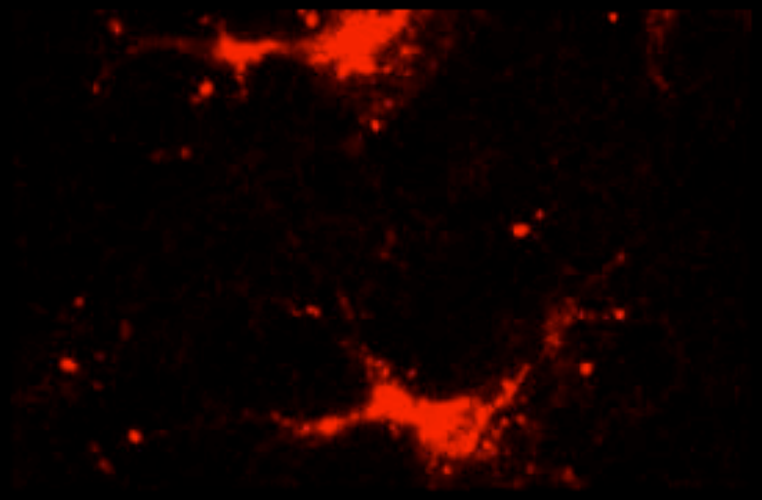
12 hours after tape stripping of mouse ear skin

ZO-1 (TJ)
MHC class II (LC)

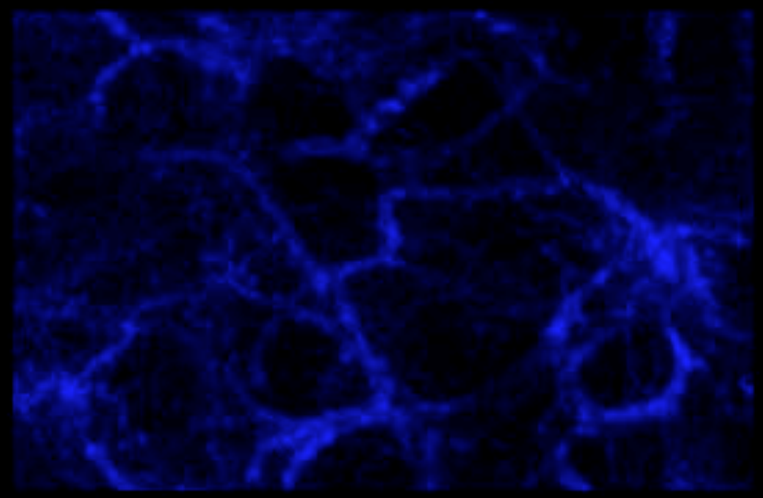
Langerhans cells in resting state



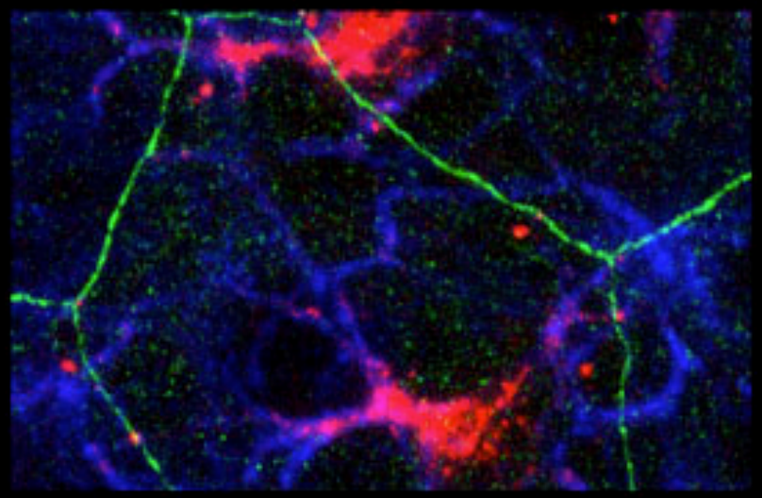
ZO-1



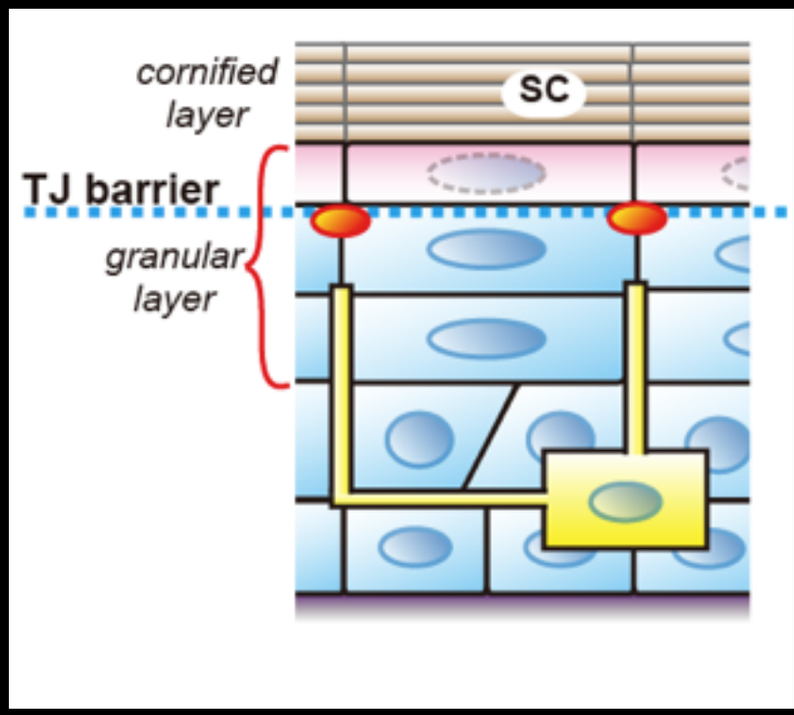
MHC class II



Claudin-1

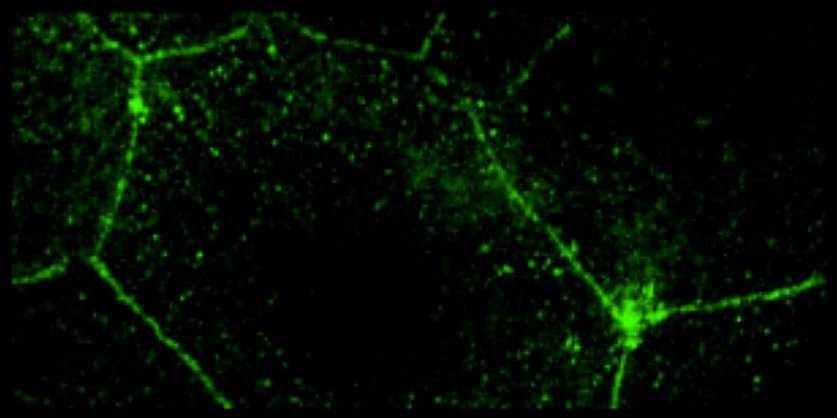


merged

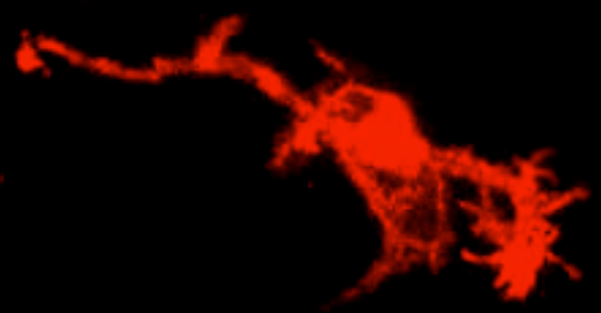


Resting LCs stay under the TJ barrier

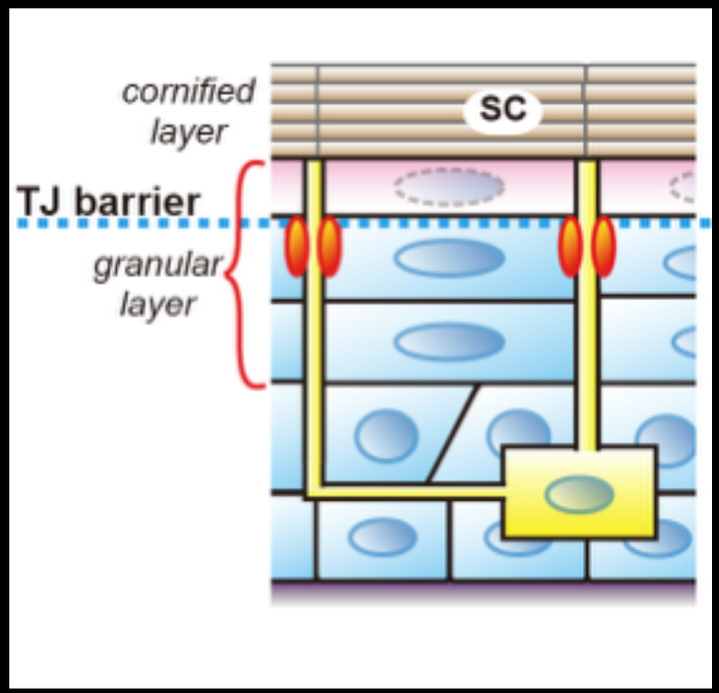
Langerhans cell in an activating state

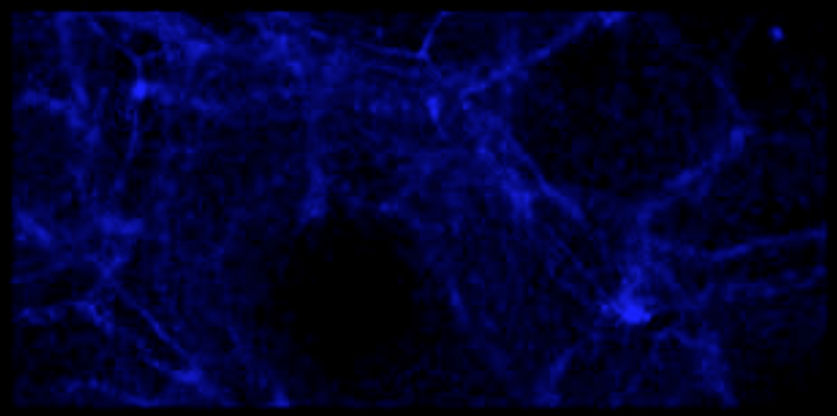


ZO-1

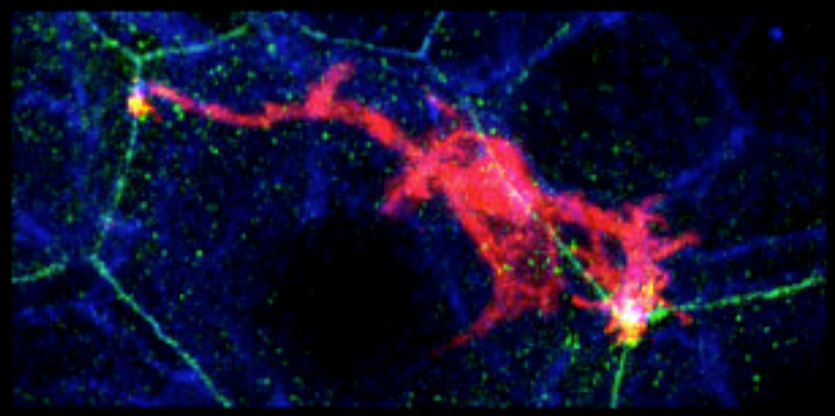


MHC class II





Claudin-1



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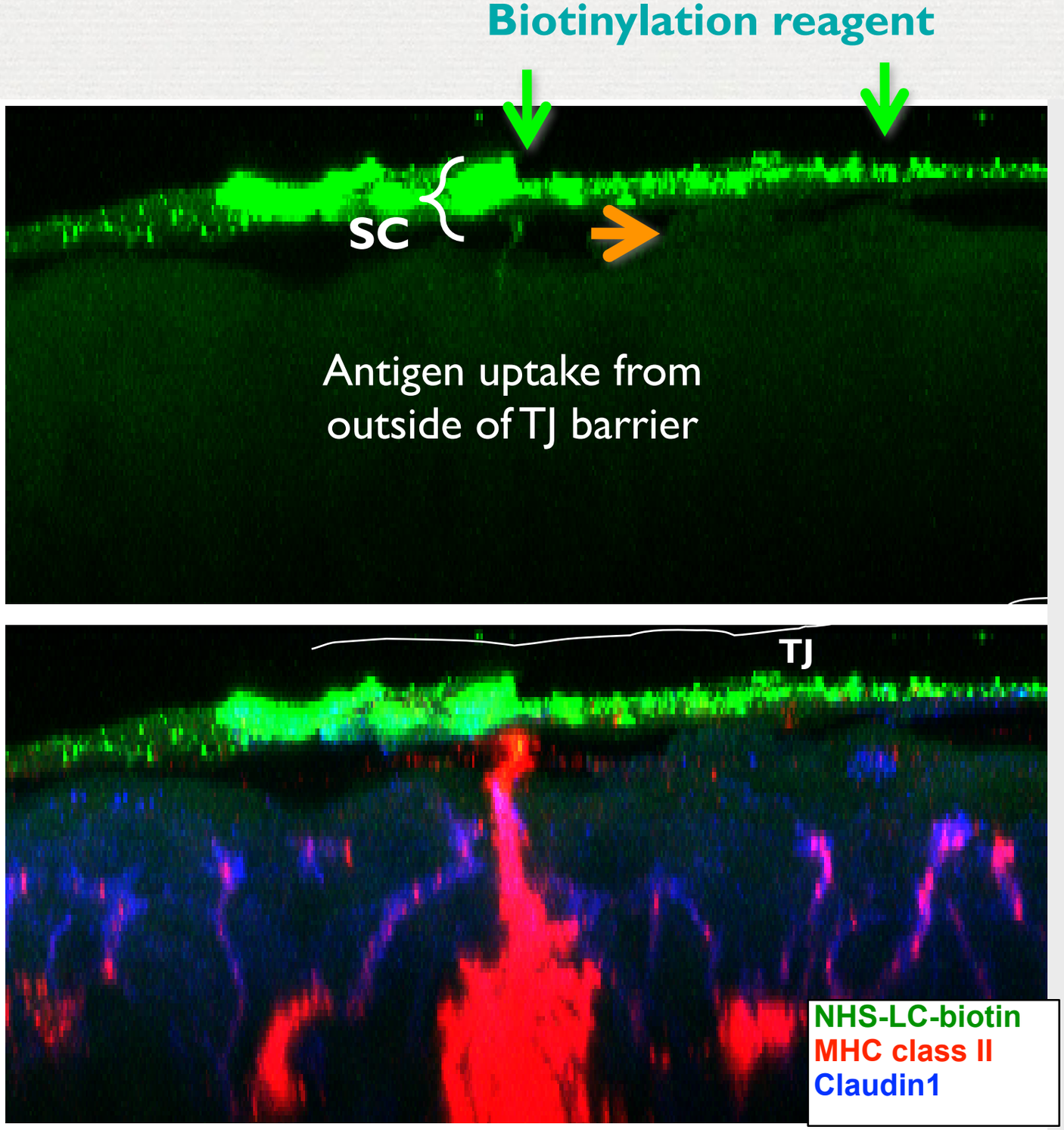
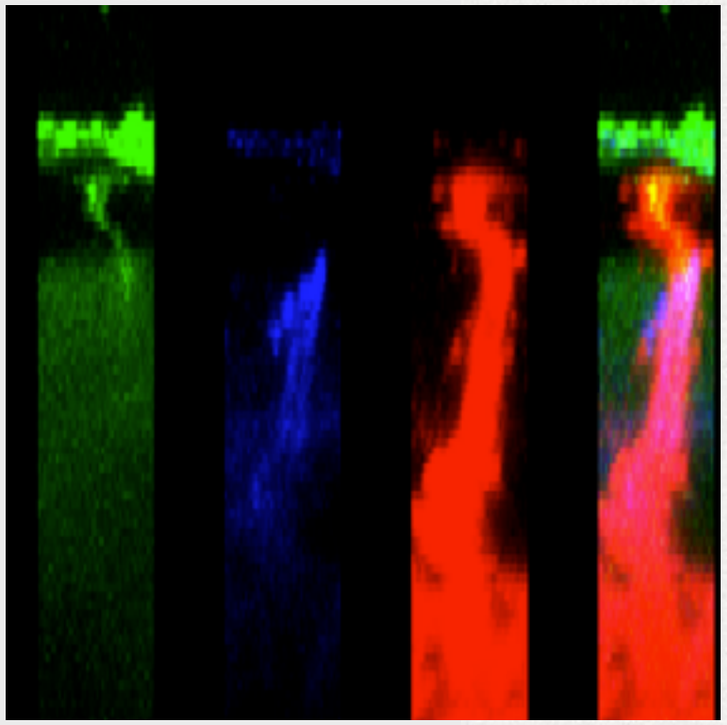
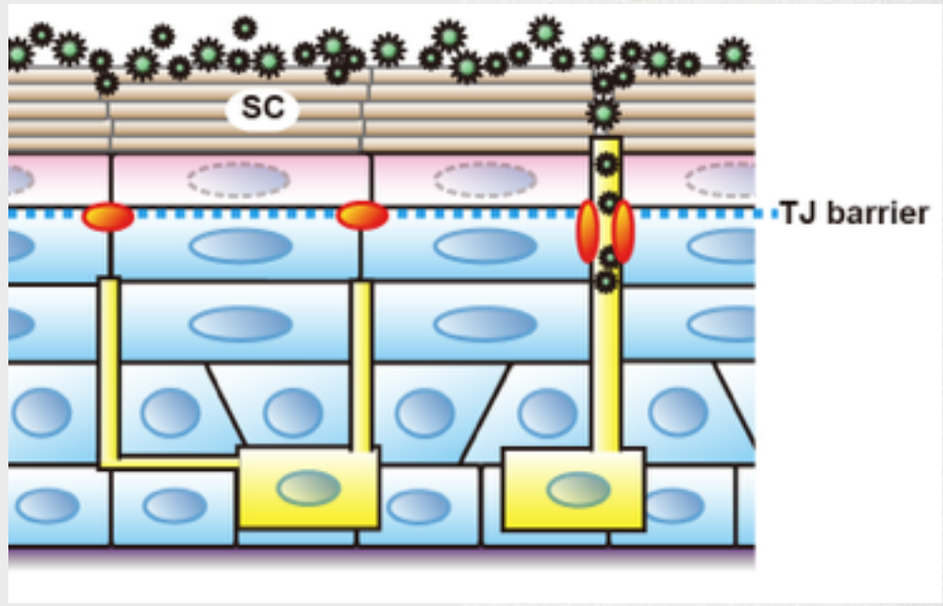
Activated LCs elongate their dendrites through TJ barrier

LC dendrites engage in endocytic activity

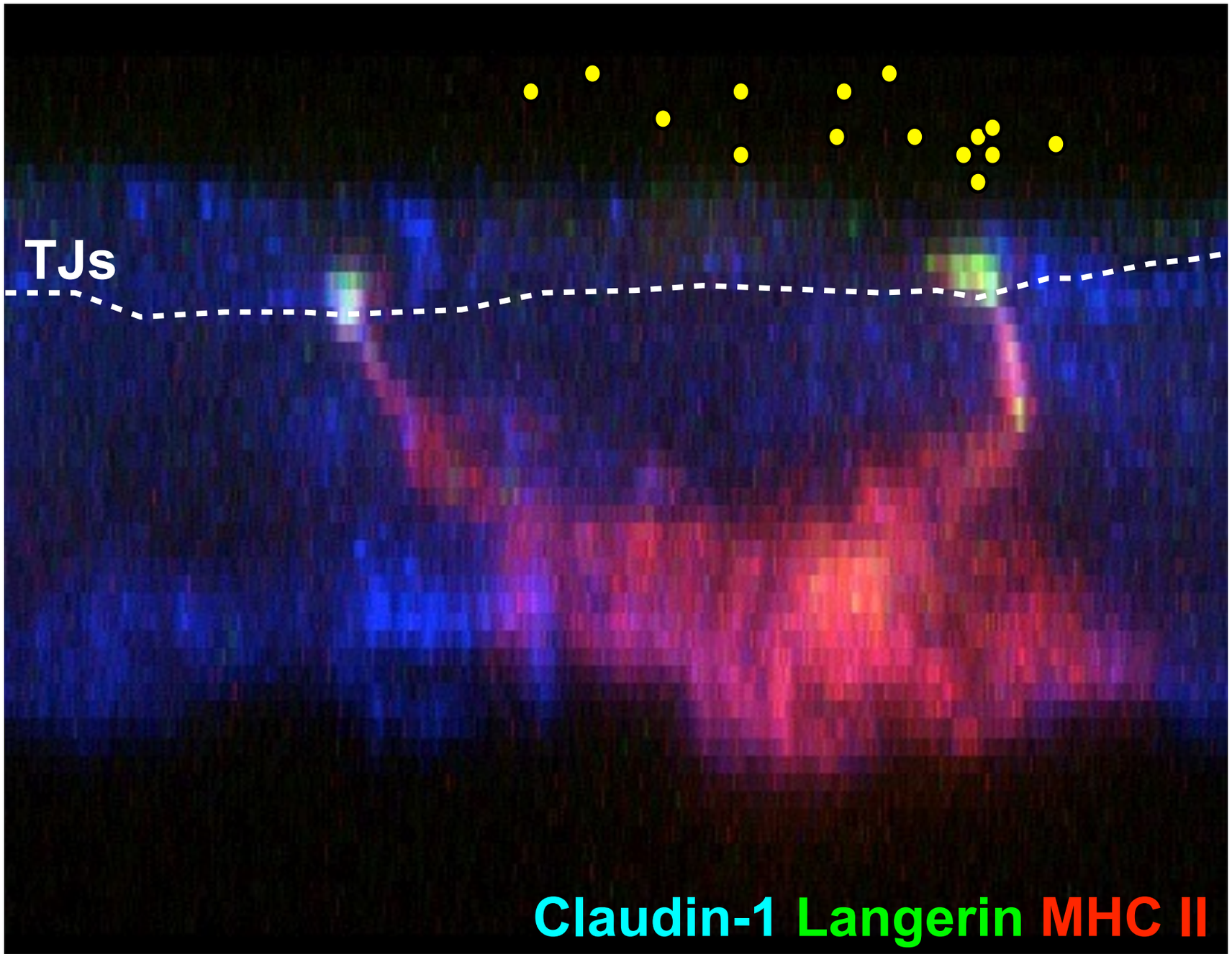






(Kubo, Nagao et al, JEM 2009)

Why should LCs acquire foreign antigens that exist outside of TJs?



LCs might uptake skin-surface microbes that are potentially pathogenic...

One such bacteria is *Staphylococcus aureus*

Staphylococcal Scalded Skin Syndrome (SSSS)

Dermatology Image Bank

Skin infection of exfoliative toxin (ET)-producing *S. aureus*

ET circulates to distal skin sites where it cleaves desmoglein1, resulting in loss of keratinocyte adhesion, manifesting as severe blistering disease

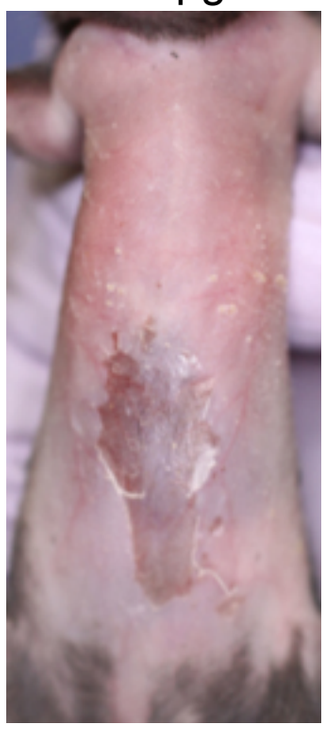
(Amagai et al, Nat Med 2000)

rETA induces experimental SSSS

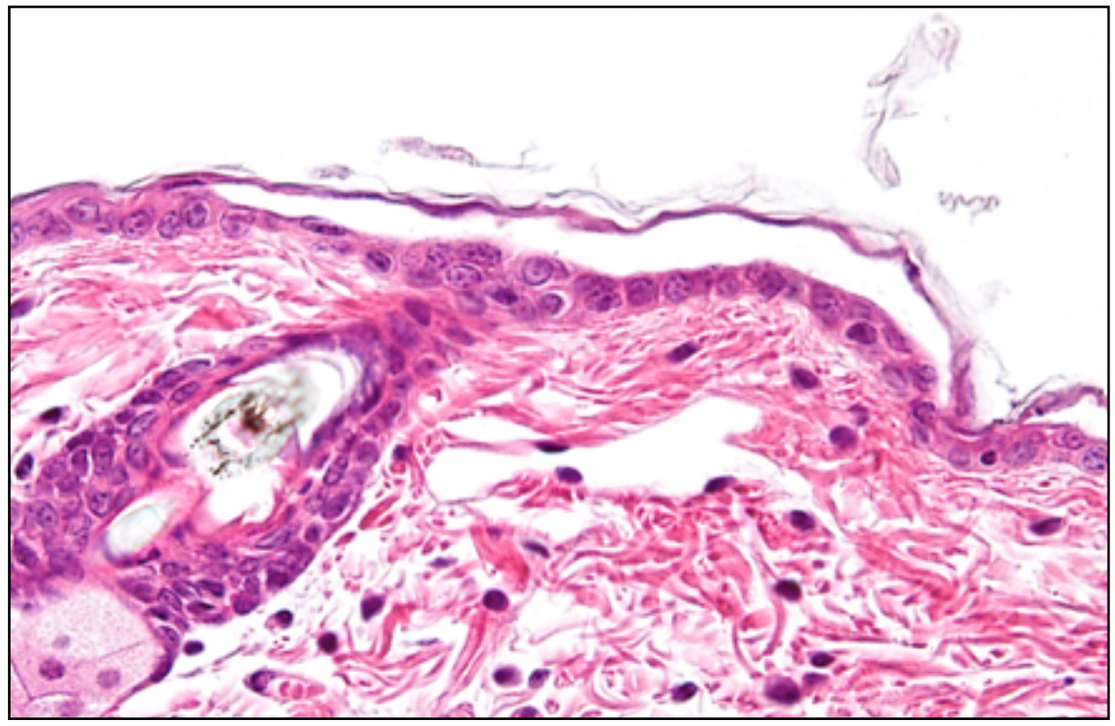
800µg

400µg

200µg

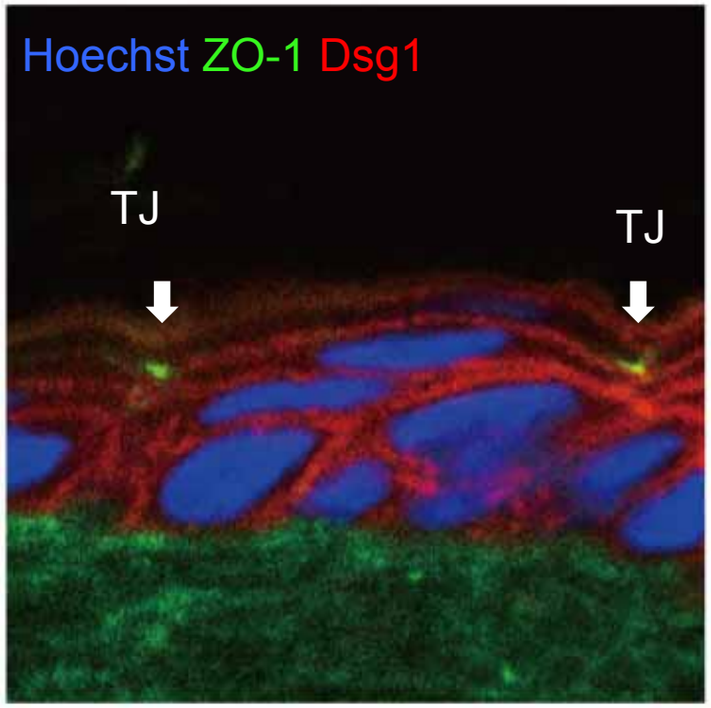


3 hrs post ETA i.p.

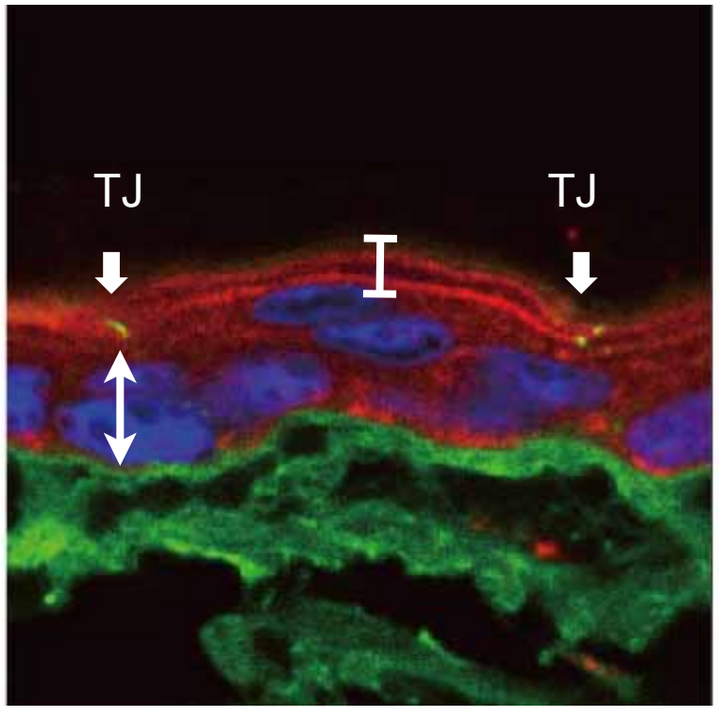


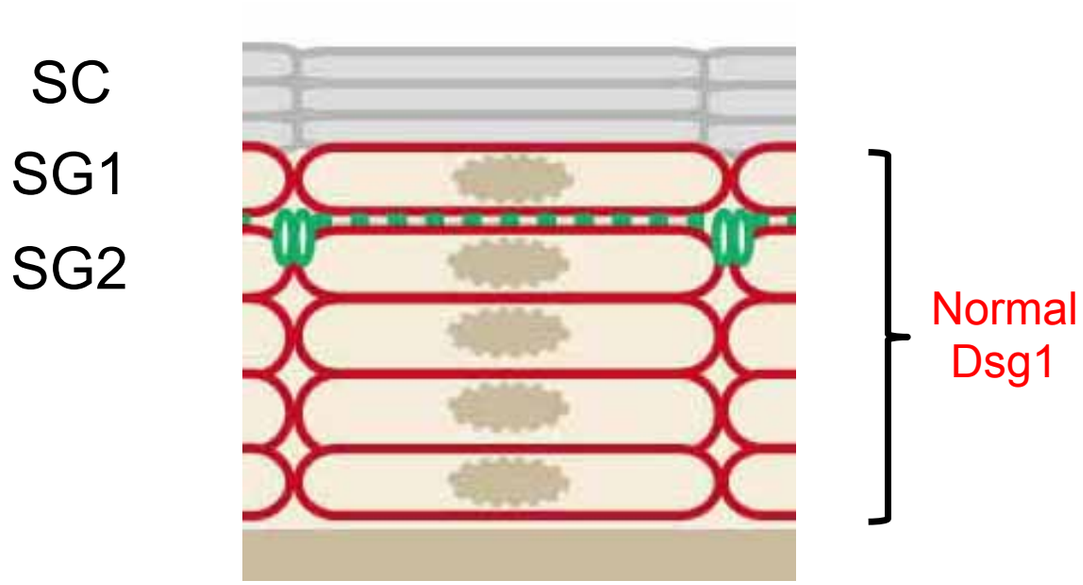
ETA fails to penetrate TJs

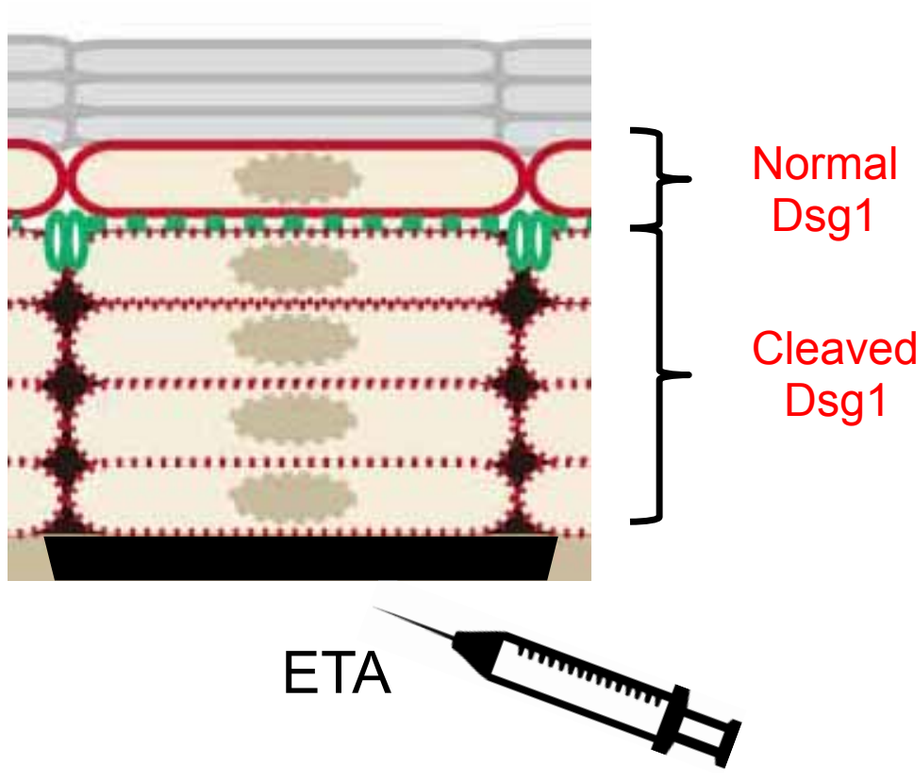
PBS i.d.



ETA i.d.



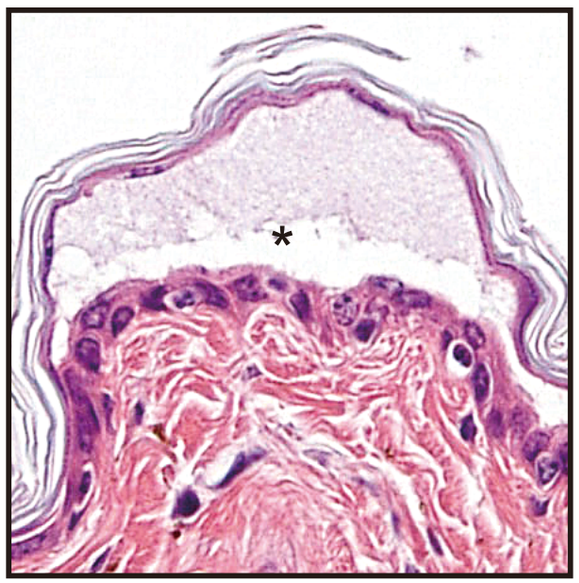




ETA patch-immunization does not alter epidermal integrity

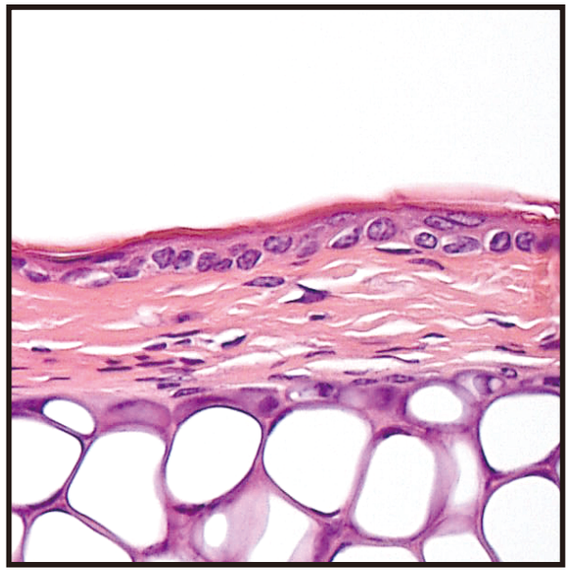
ET i.d.

1hr

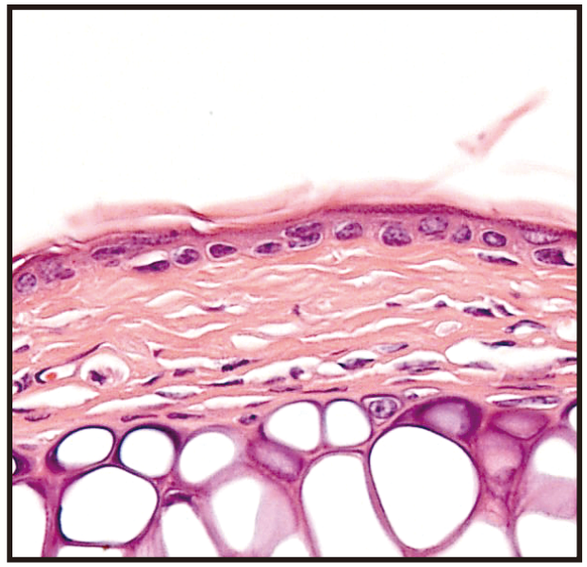


ET patch-immunization

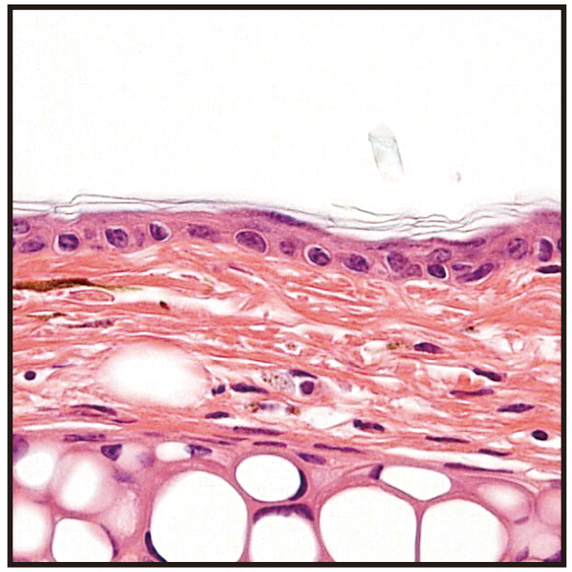
1hr



3hr

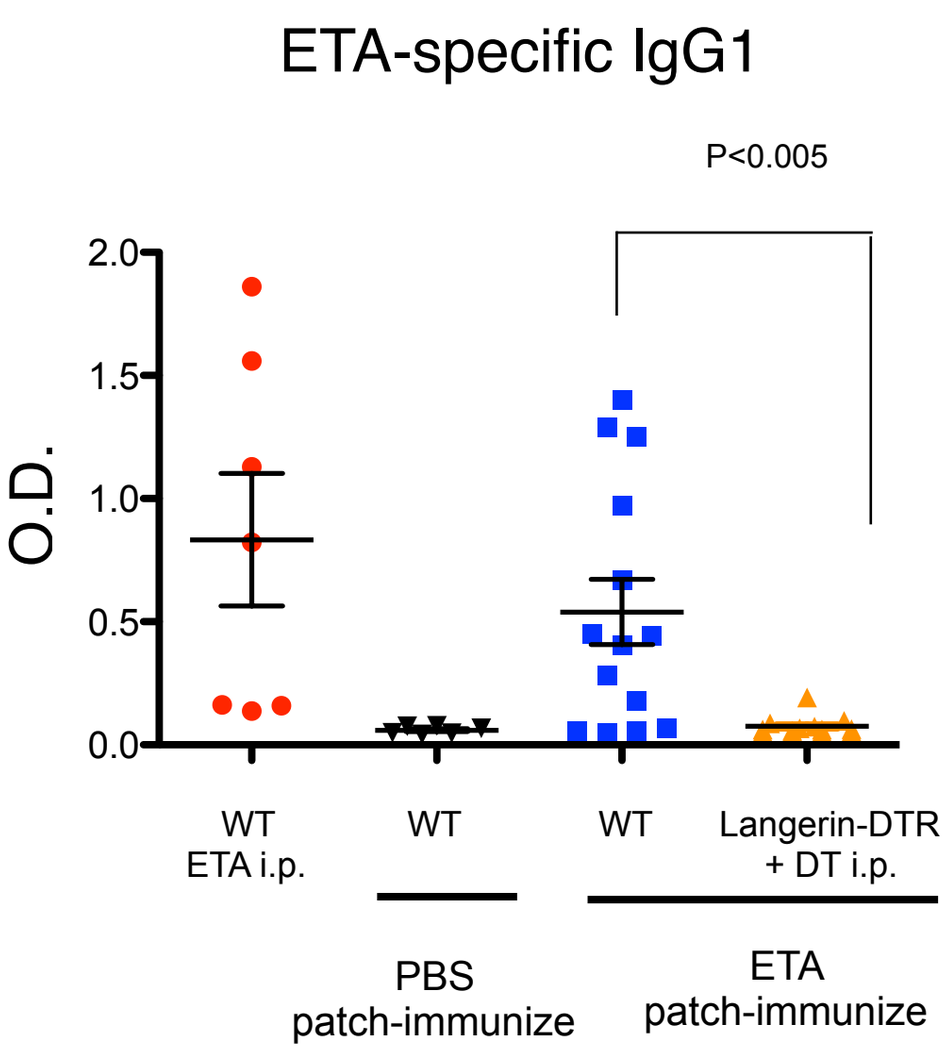


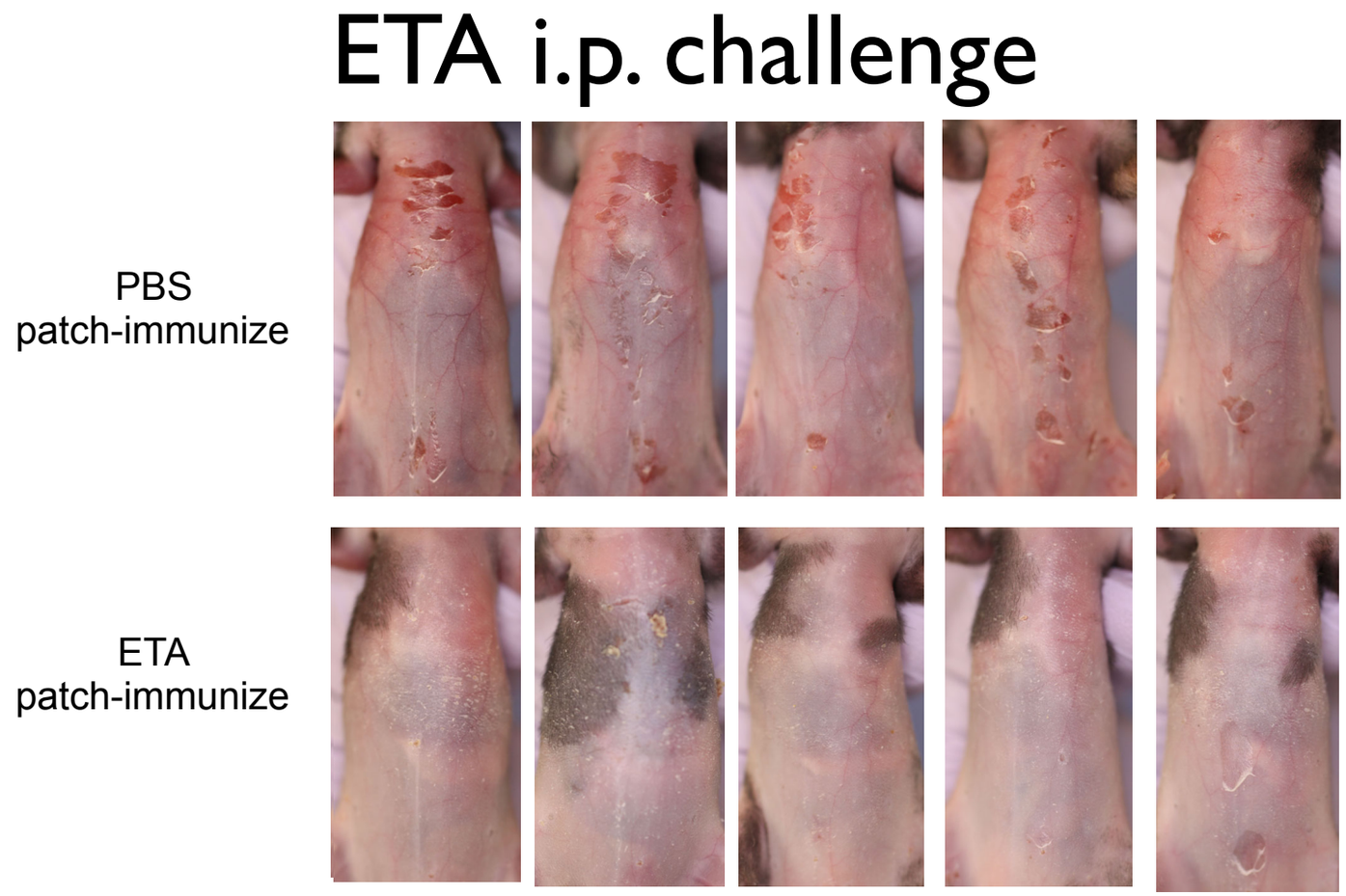
24hr



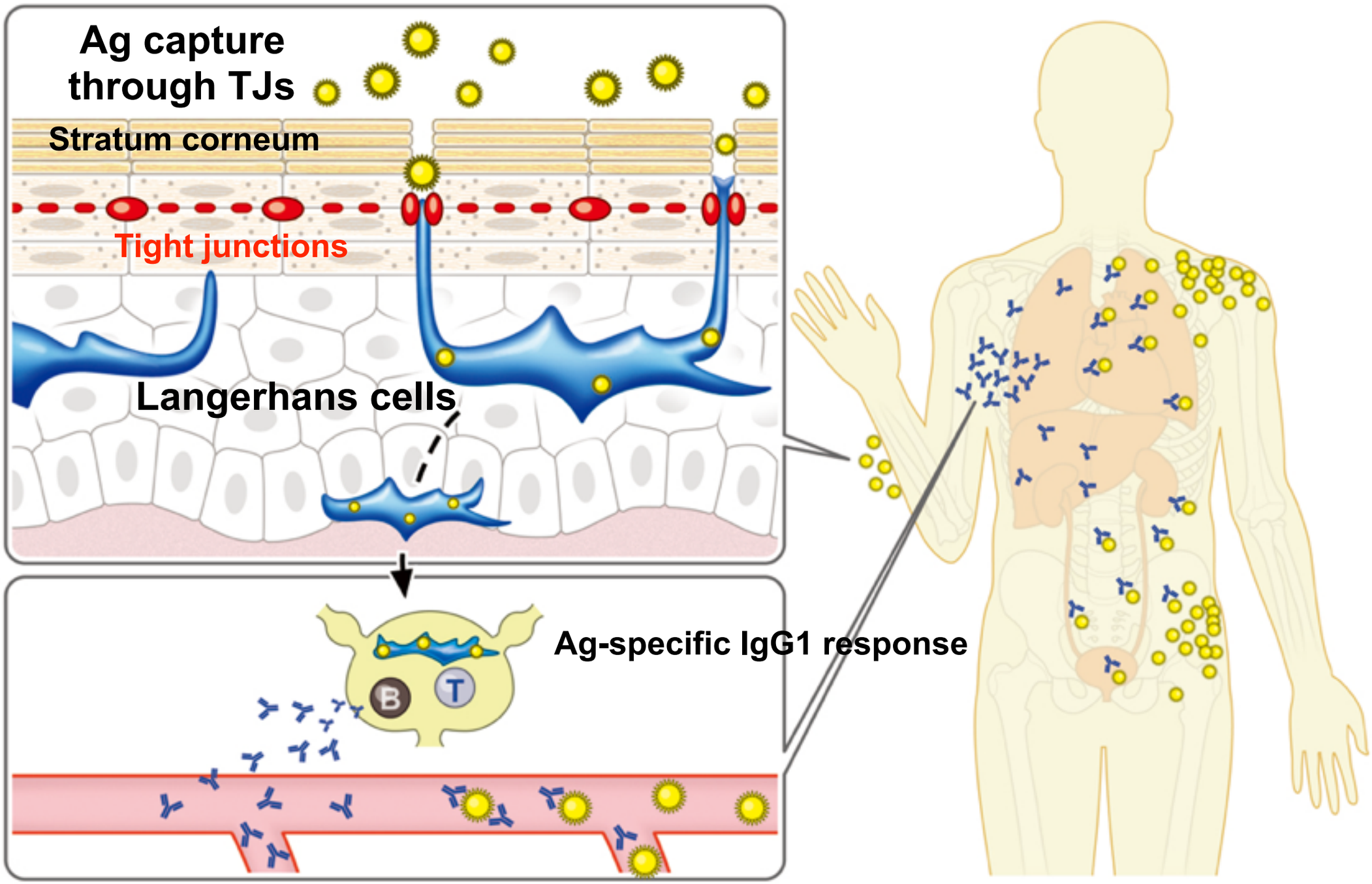
Therefore, any responses acquired via patch-immunization is attributable to Ag capture via TJ by LC

Patch-immunization leads to ETA-specific IgG1 response





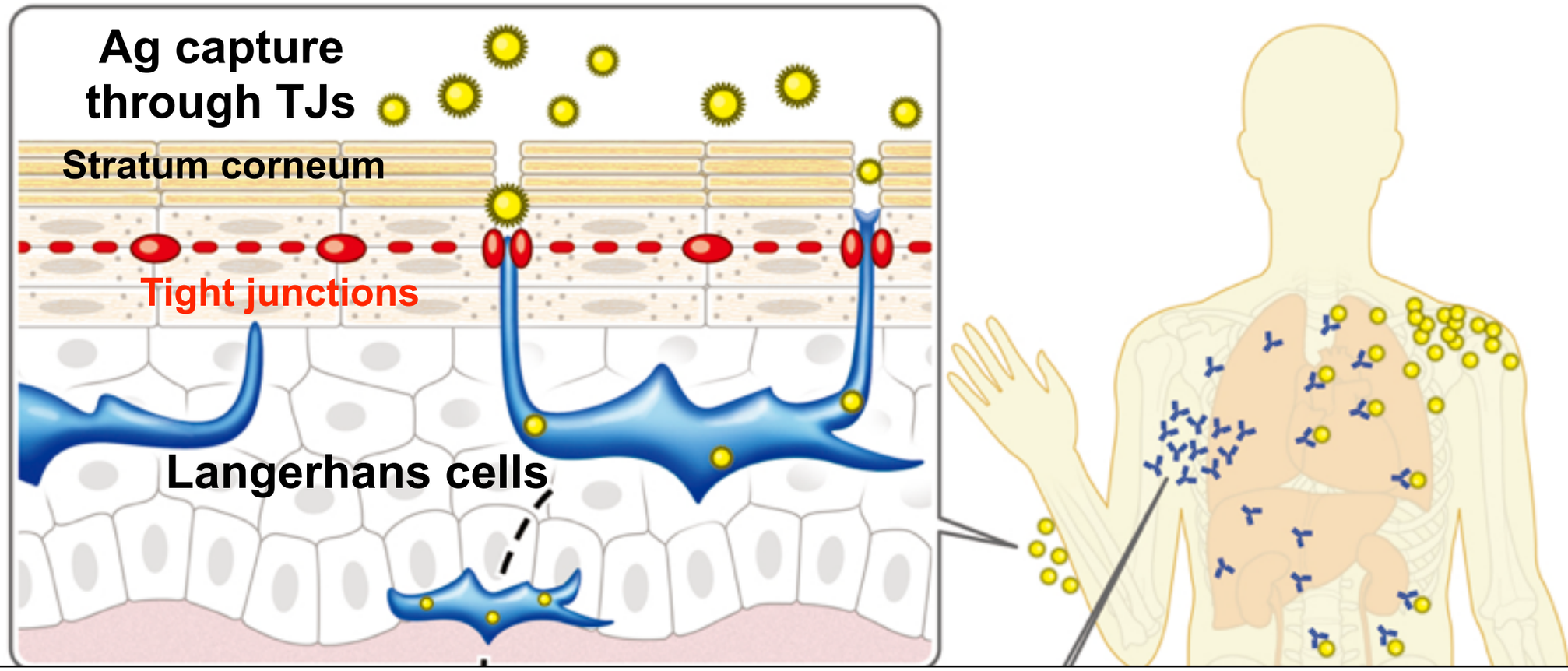
Langerhans cells confer “preemptive immunity” to skin surface antigens



Nagao et al, PNAS 2009, Kubo et al, JEM 2001, Ouchi et al., JEM 2011

Systemic immunity in the absence of breeched barriers

Langerhans cells confer “preemptive immunity” to skin surface antigens



- Consider preemptive immunity during percutaneous sensitization to protein antigens

- In barrier-perturbed skin, topical application of protein antigens will induce IgE responses

Atopic Dermatitis & *S. aureus*

Symptoms

- Dry skin
- Eczematous dermatitis
- Strong itch

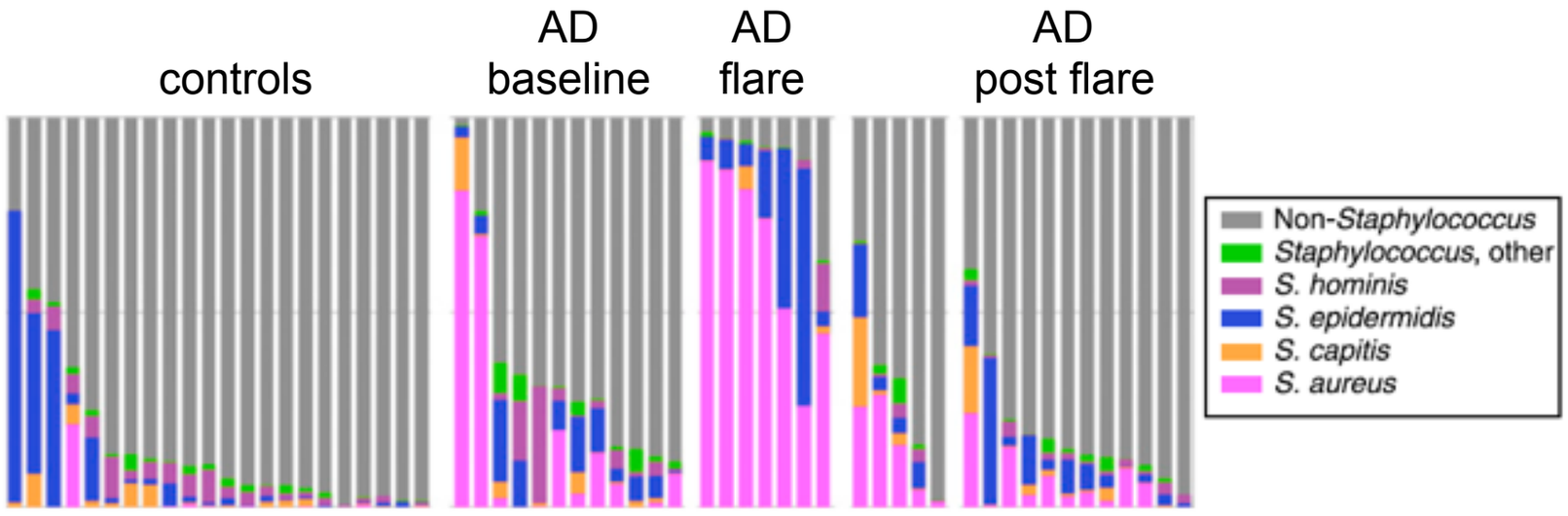
Complications (atopic march)

- Food allergy
- Asthma
- Allergic rhinitis

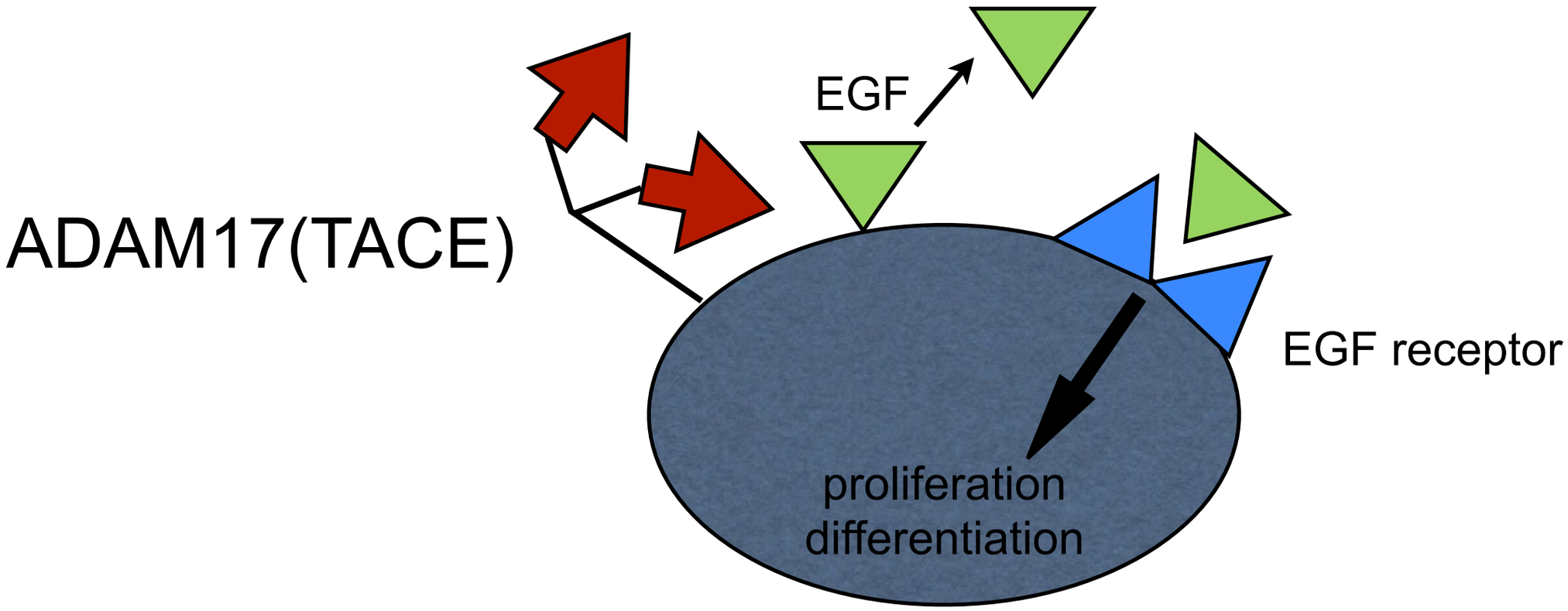
Staphylococcus aureus colonization of atopic dermatitis (AD) skin

- *Staphylococcus aureus* in the lesions of AD (*BJD* 1974)

- Temporal shifts in the skin microbiome associated with disease flares and treatment in children with AD (*Genome Research* 2012)



What is the cause-and-effect relationship of *S. aureus* and eczema?

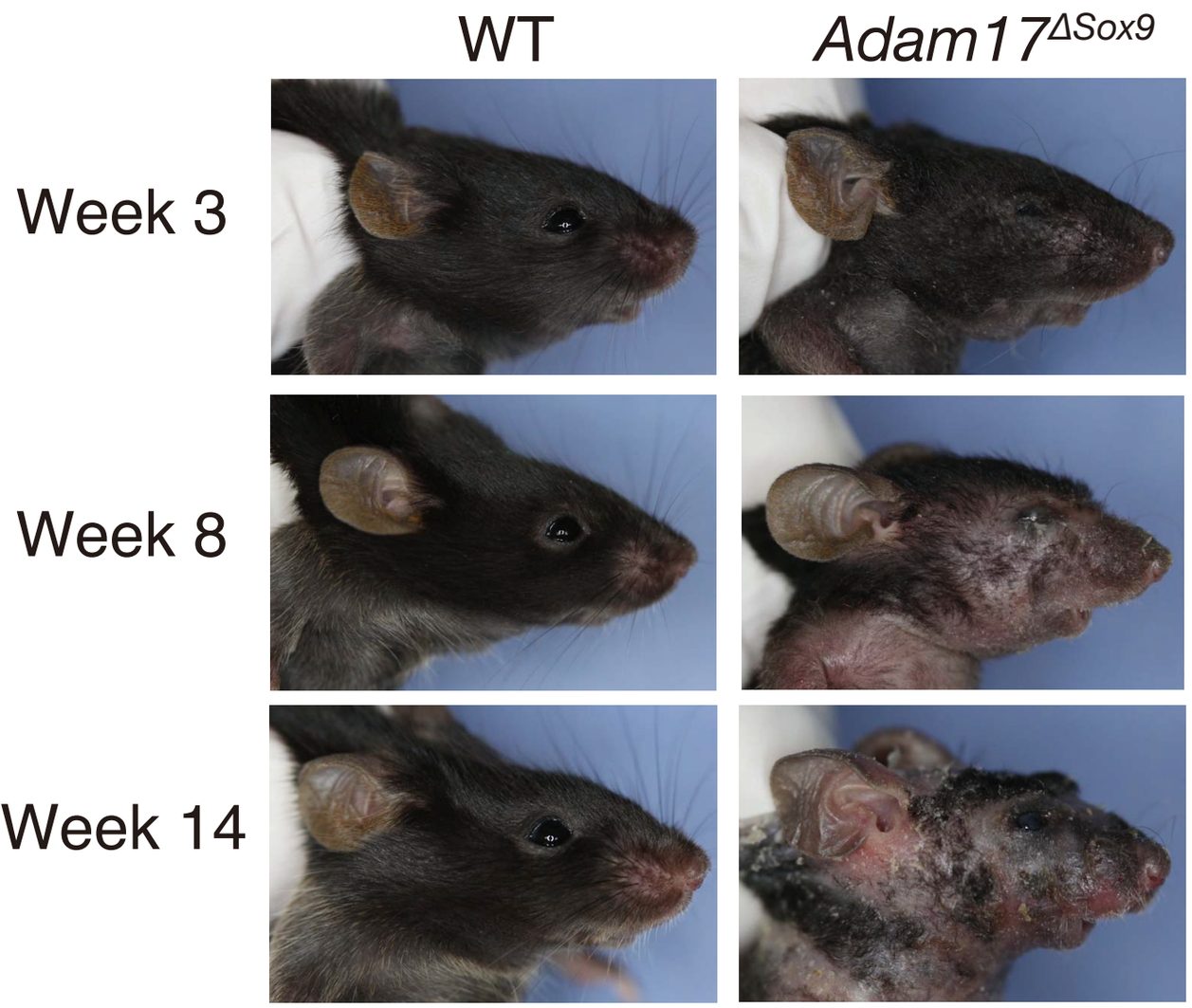


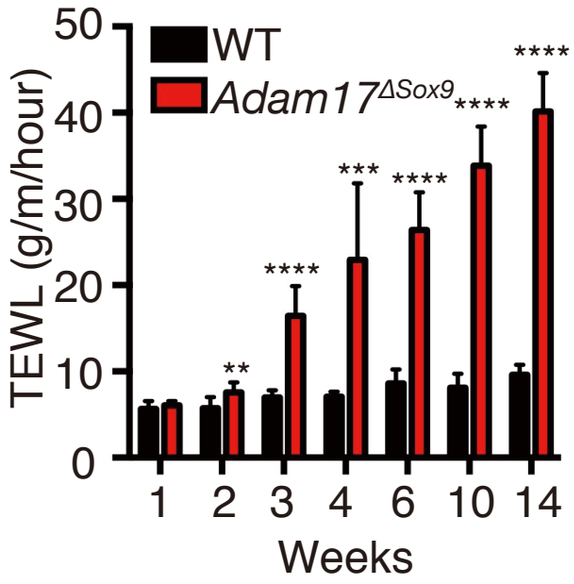
(*N Engl J Med* 2011)

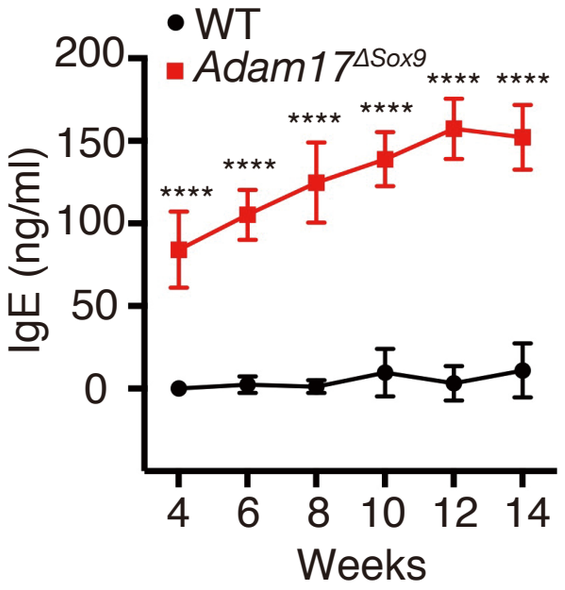
- ADAM17 (TACE) cleaves cell surface molecules including EGF and TNF-α.

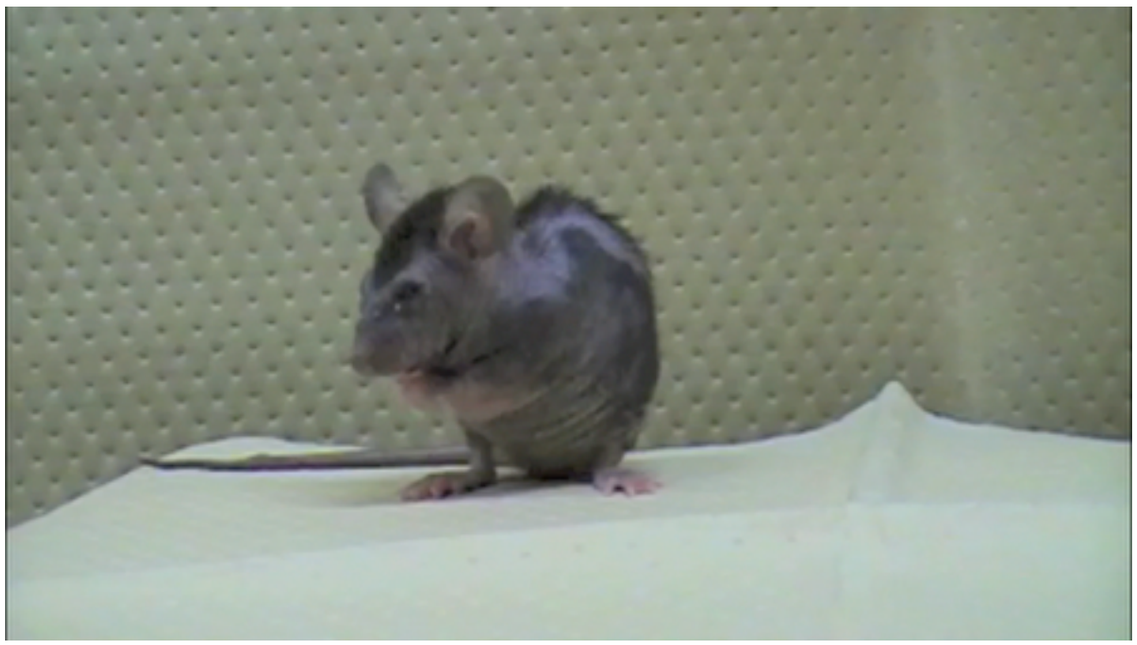
- ADAM17 deficiency results in eczematous inflammation in human and mice (*N Engl J Med* 2011, *Immunity* 2012, *JEM* 2012)

Adam17$^{flox/flox}$ *Sox9-Cre* (*Adam17*$^{\Delta Sox9}$) mice exhibit eczematous inflammation



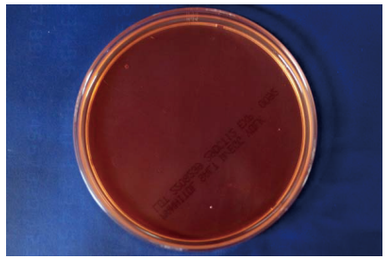




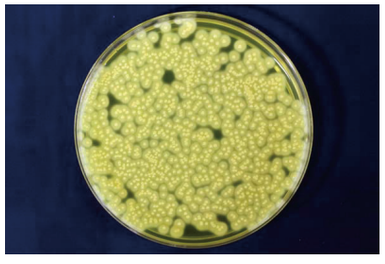


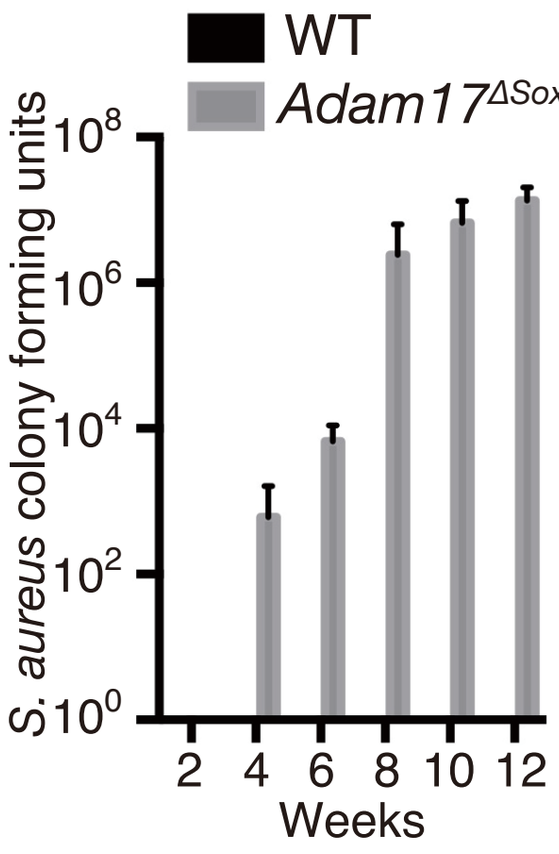
Adam17$^{\Delta Sox9}$ mice are heavily colonized by *S. aureus*

WT



Adam17$^{\Delta Sox9}$





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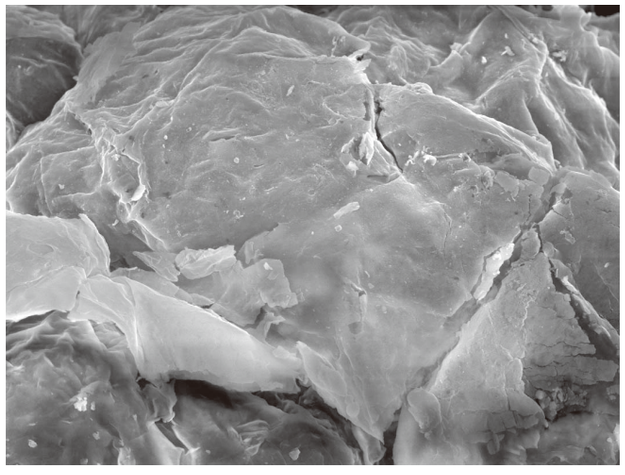
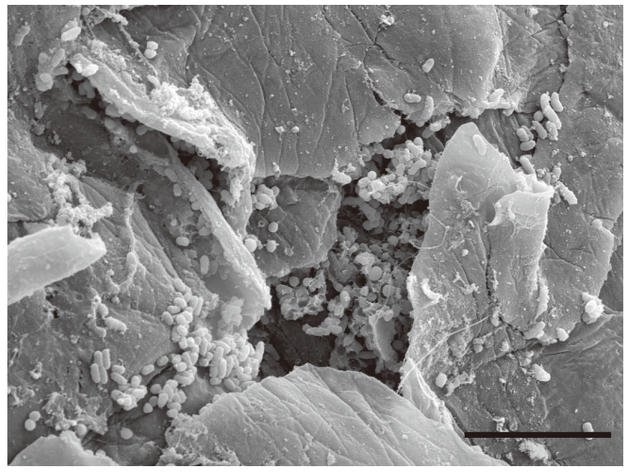
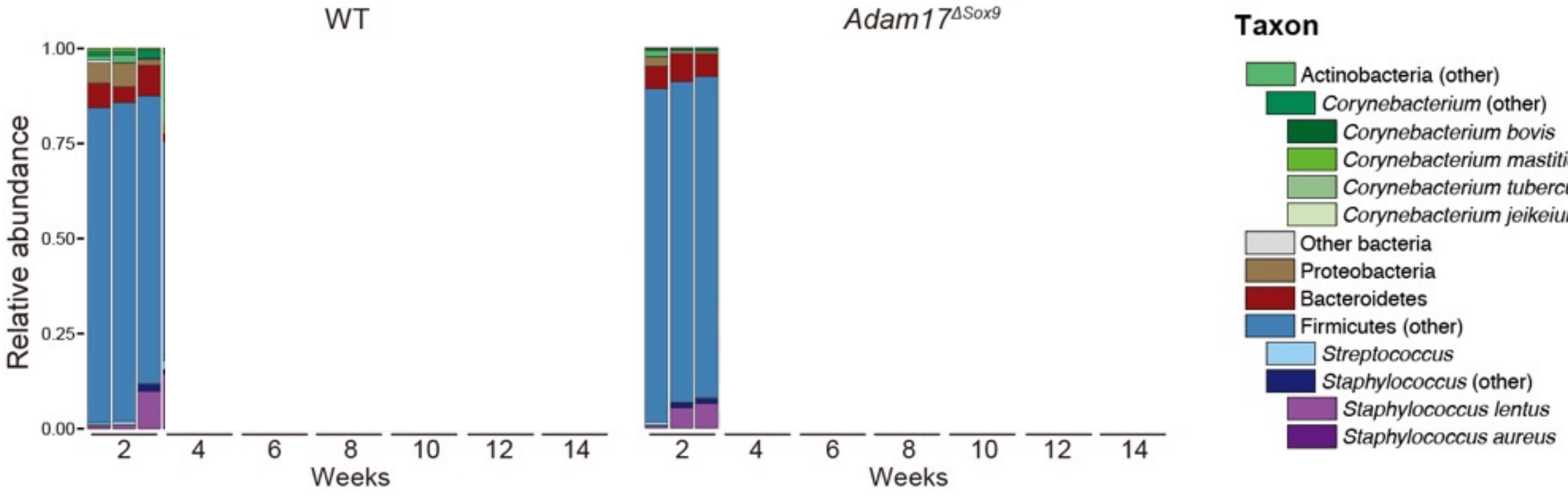


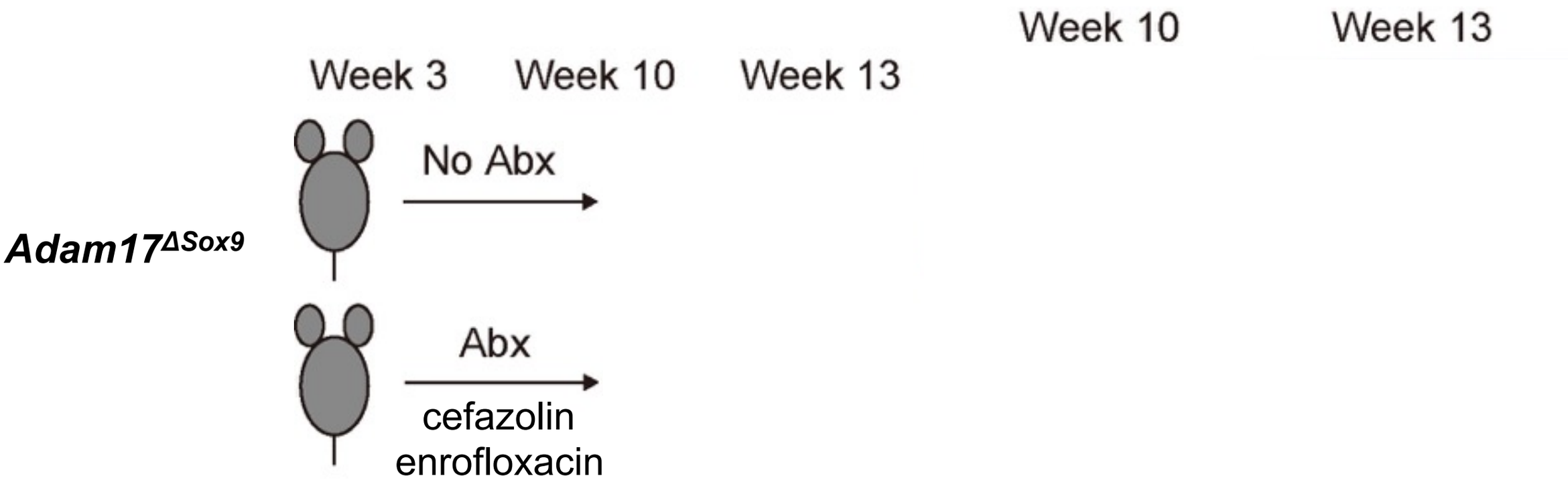
Adam17$^{\Delta Sox9}$

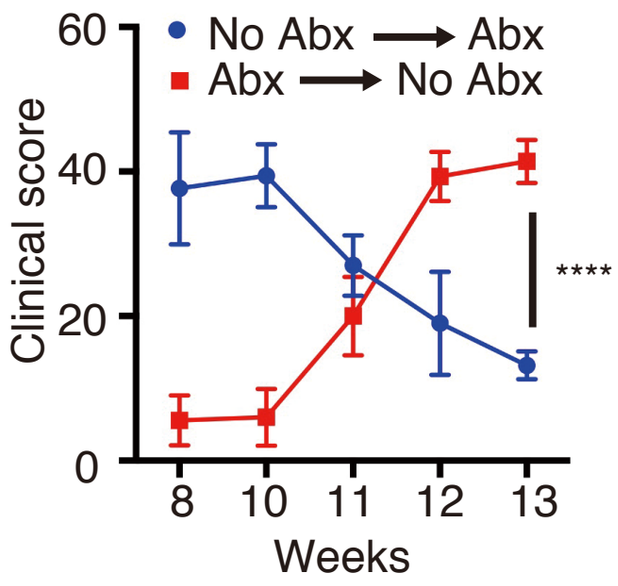


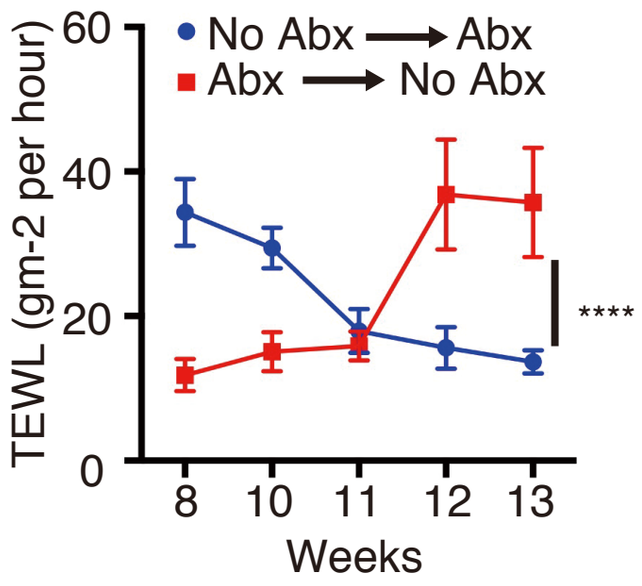
Predomination of *S.aureus* and *Corynebacterium* spp.



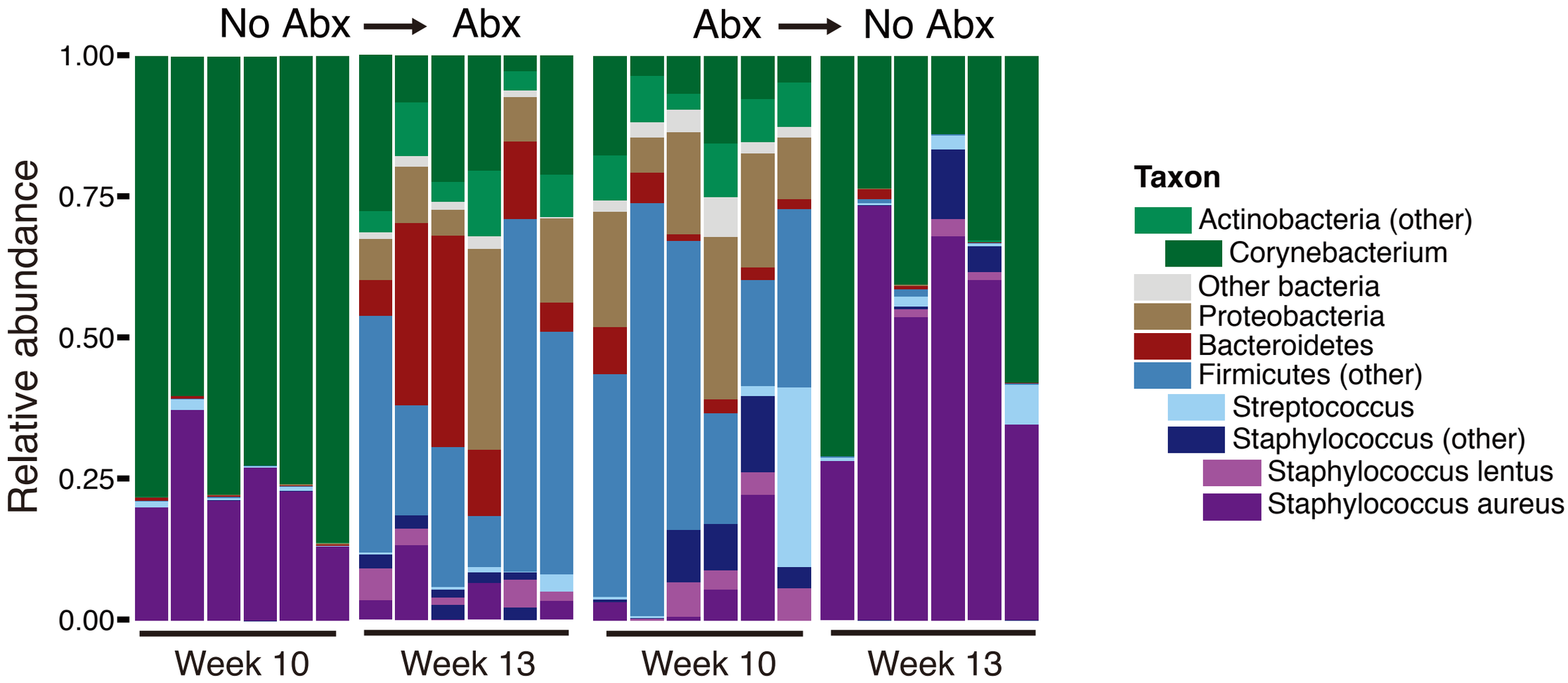
Targeting dysbiosis has preventive & therapeutic effects





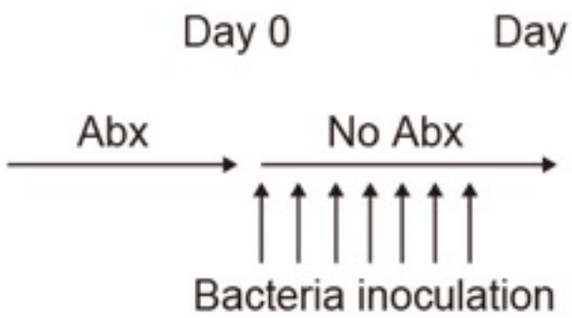


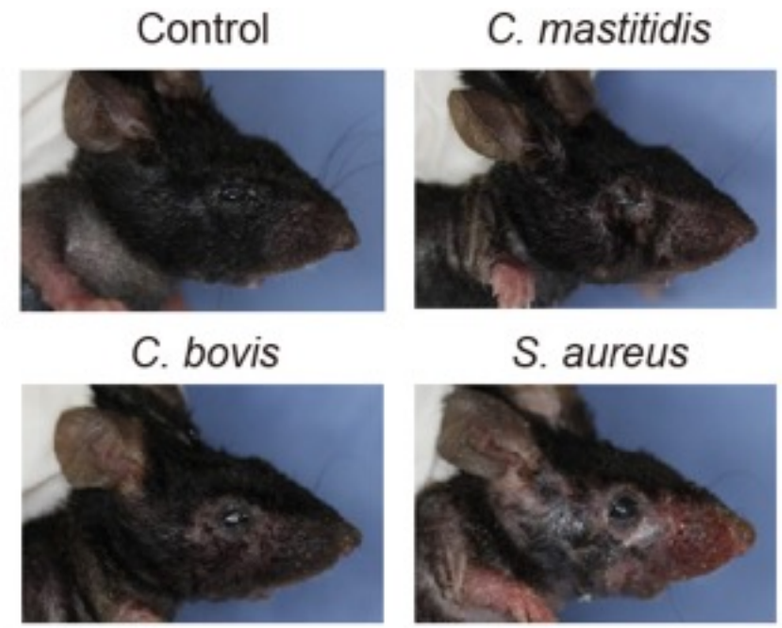
Antibiotic therapy reverses staphylococcal dysbiosis in *Adam17$^{\Delta Sox9}$* mice

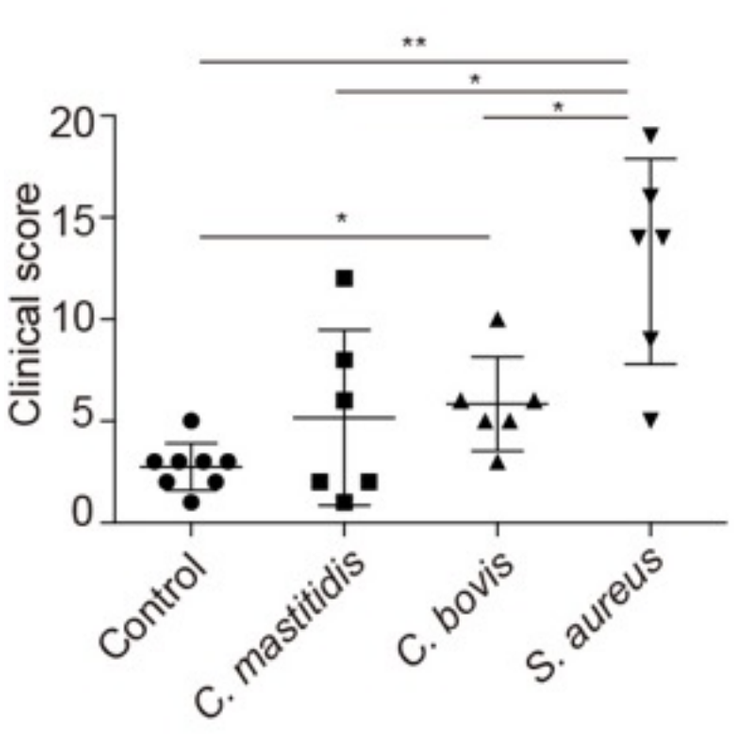


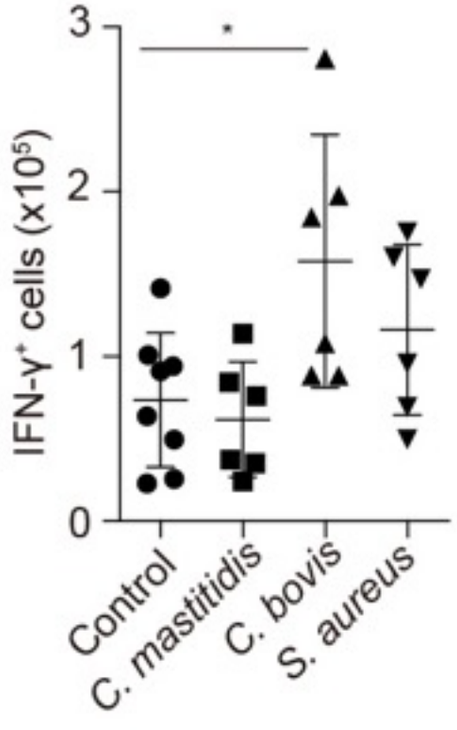
Differential contribution of dysbiotic microbiota

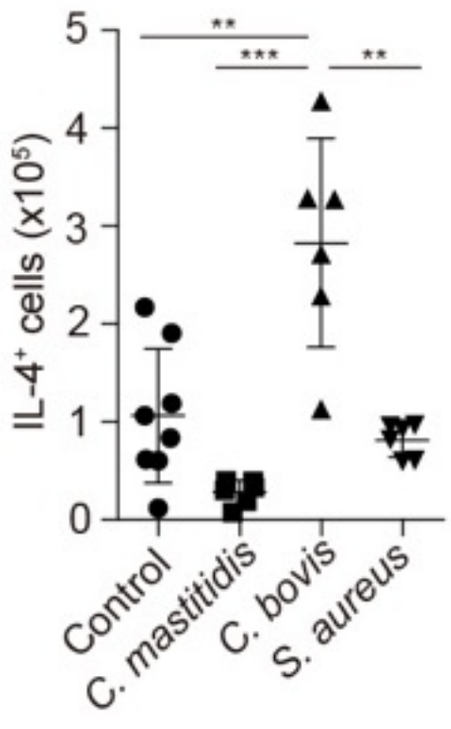
Adam17$^{\Delta Sox9}$

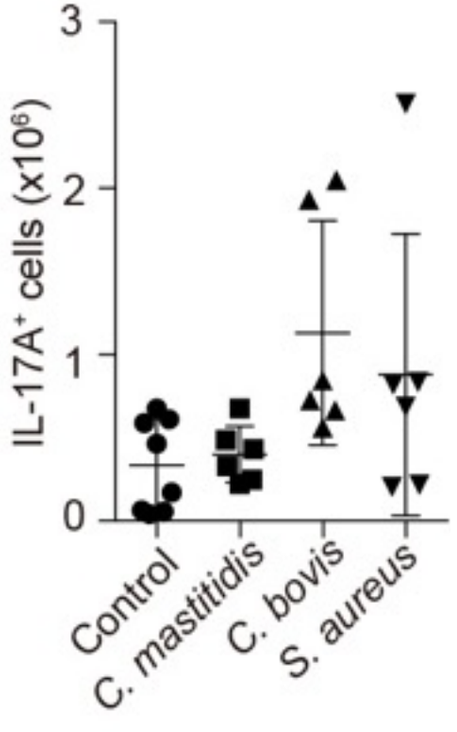






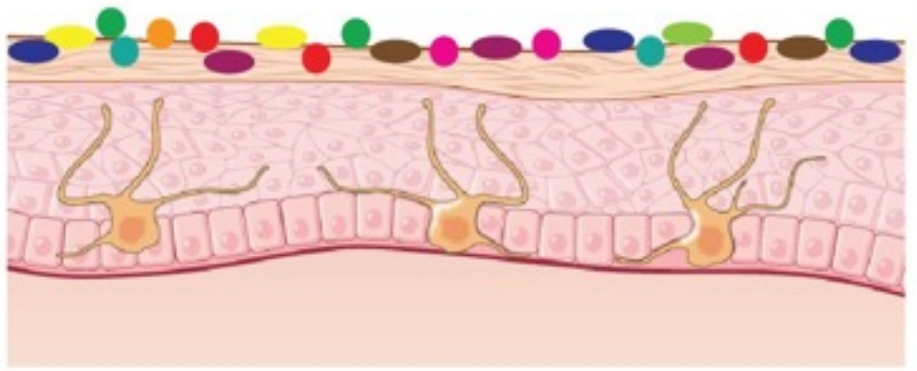






Summary

Normal skin
(High microbial diversity)



Staphylococcus aureus

Corynebacterium mastitidis
or *Corynebacterium bovis*

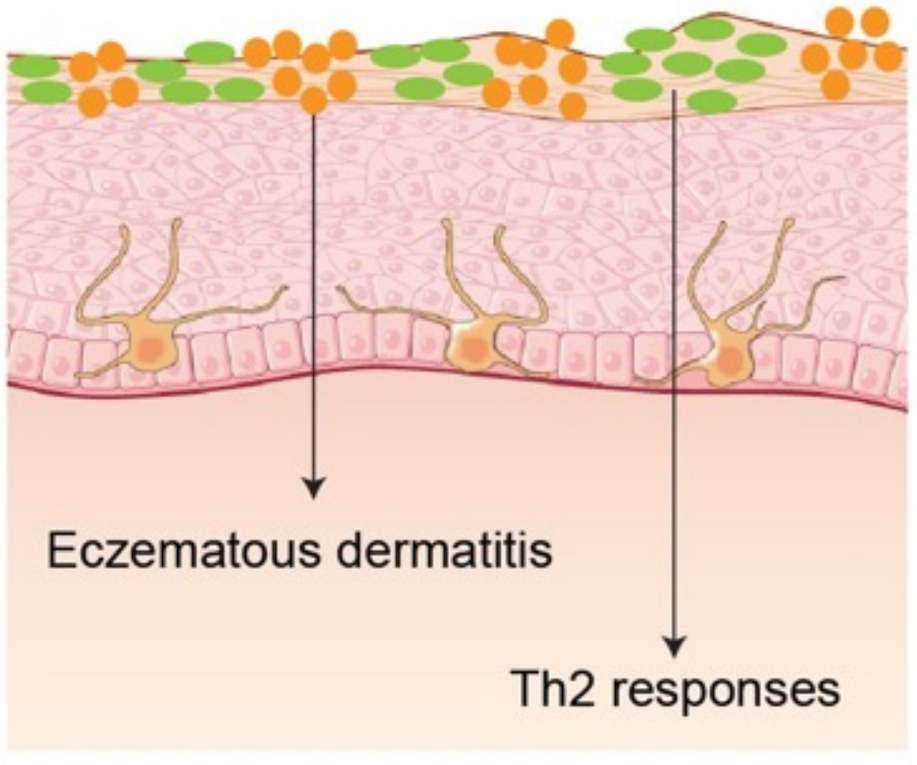
Epidermal ADAM17-deficiency

↓

Impaired EGFR signaling

↓

Dysbiosis
(Low microbial diversity)



(Kobayashi et al. *Immunity* 2015)

Conclusion

1) *S. aureus* was critical for eczema formation in our AD mouse model.

2) Although this concept needs to be validated in humans, it provides basis for novel therapeutic strategies by targeting:

a) mechanisms that lead to dysbiosis
b) immune responses down stream of dysbiosis
c) dysbiotic flora

(Kobayashi et al. *Immunity* 2015)

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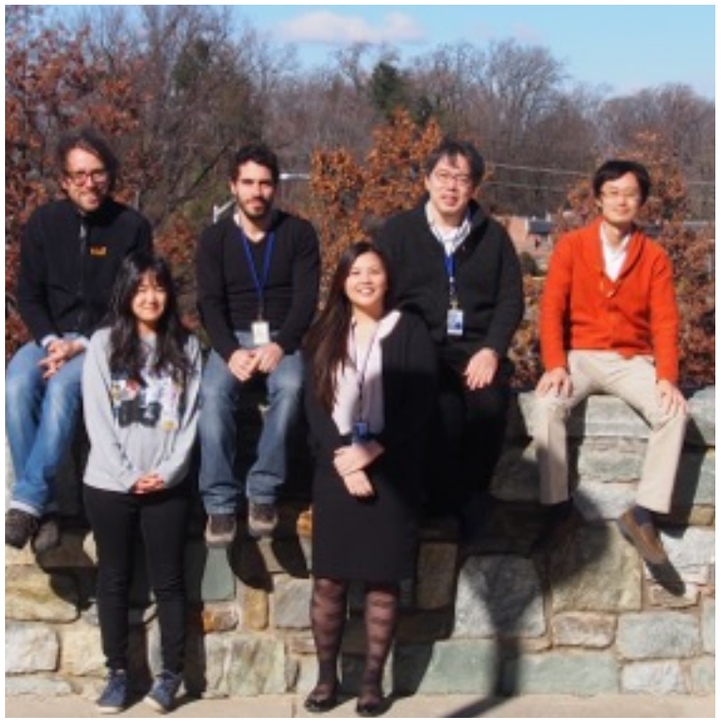

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases