

Atopic dermatitis: skin barrier dysfunction and inflammation

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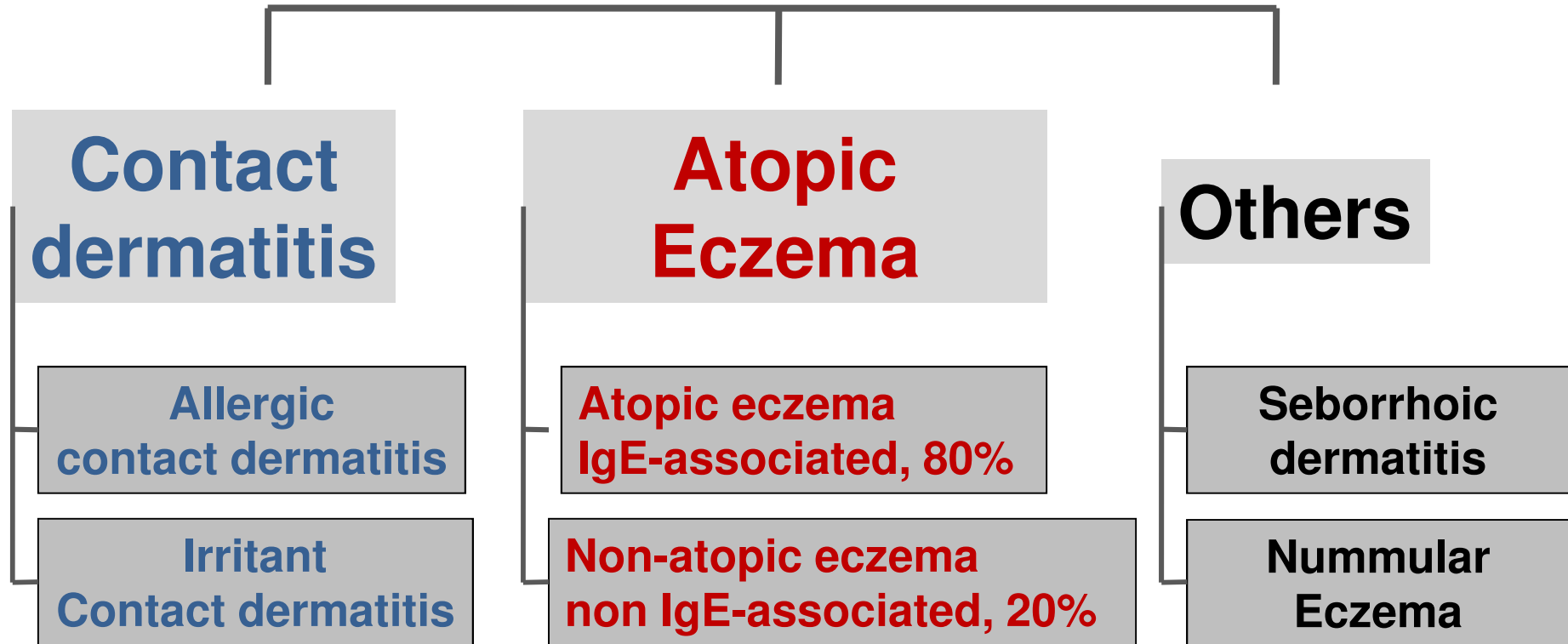
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Classification

Eczema / Dermatitis

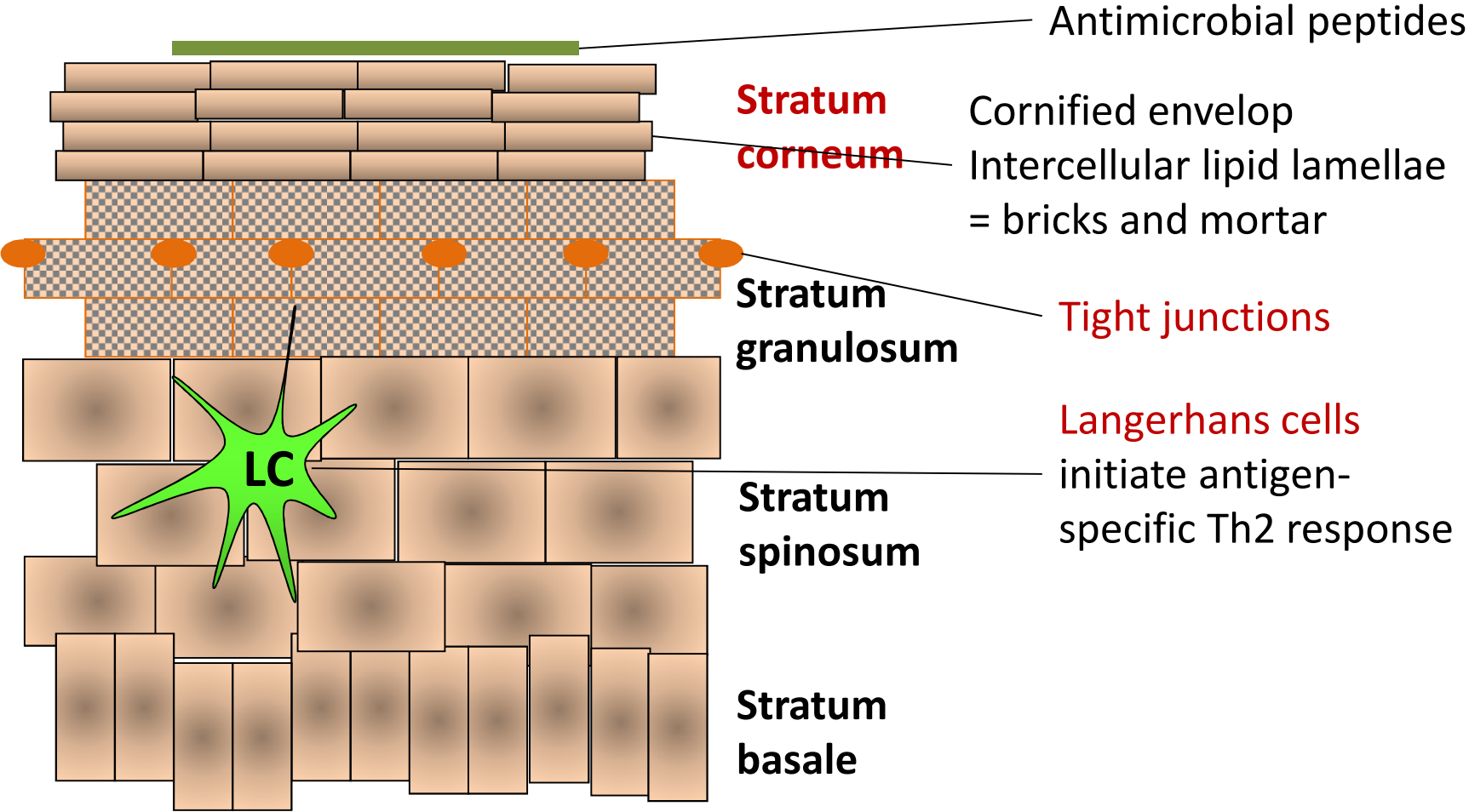


Atopic dermatitis (AD)

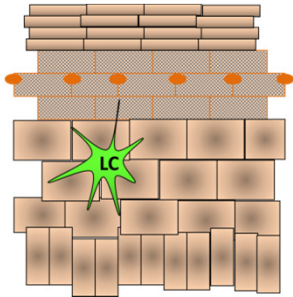
- Chronic inflammatory skin disease
- Typical morphology and localisation of skin lesions depending on age
- Itch (pruritus)
- Runs in families
- Association with other atopic diseases (AR, AB)



The skin barrier: physical, chemical, immunological



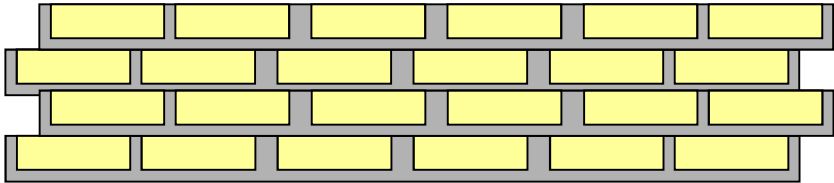
Brick-mortar wall



Normal skin

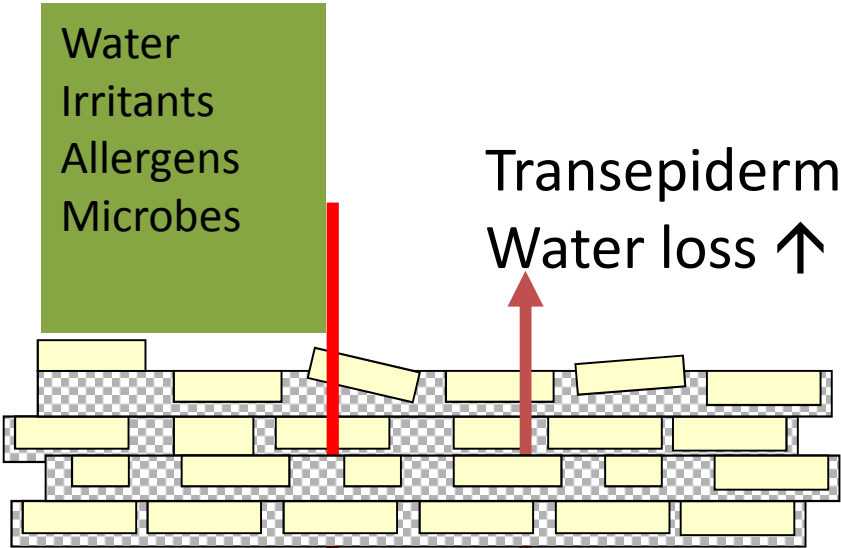
Disturbed skin barrier

Water
Irritants
Allergens
Microbes



Water

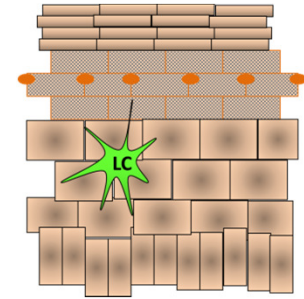
Water
Irritants
Allergens
Microbes



Transepidermal
Water loss ↑

Water

Impaired skin barrier: Filaggrin



- Profilaggrin in keratohyalin granules - cleavage into filaggrin protein - aggregates with keratin cytoskeleton – to form the **cornified cell envelope**
- Filaggrin monomers degraded into natural **moisturizing** factor (NMF) – maintain hydration, reduce pH
 - Increase of pH promotes colonization with S.aureus
- Loss-of-function mutations (R5 10X; 2282del4) associated with Ichthyosis vulgaris, AD
- FLG mutations are associated with early onset AD, bronchial asthma (with eczema), food (peanut) and nickel allergy

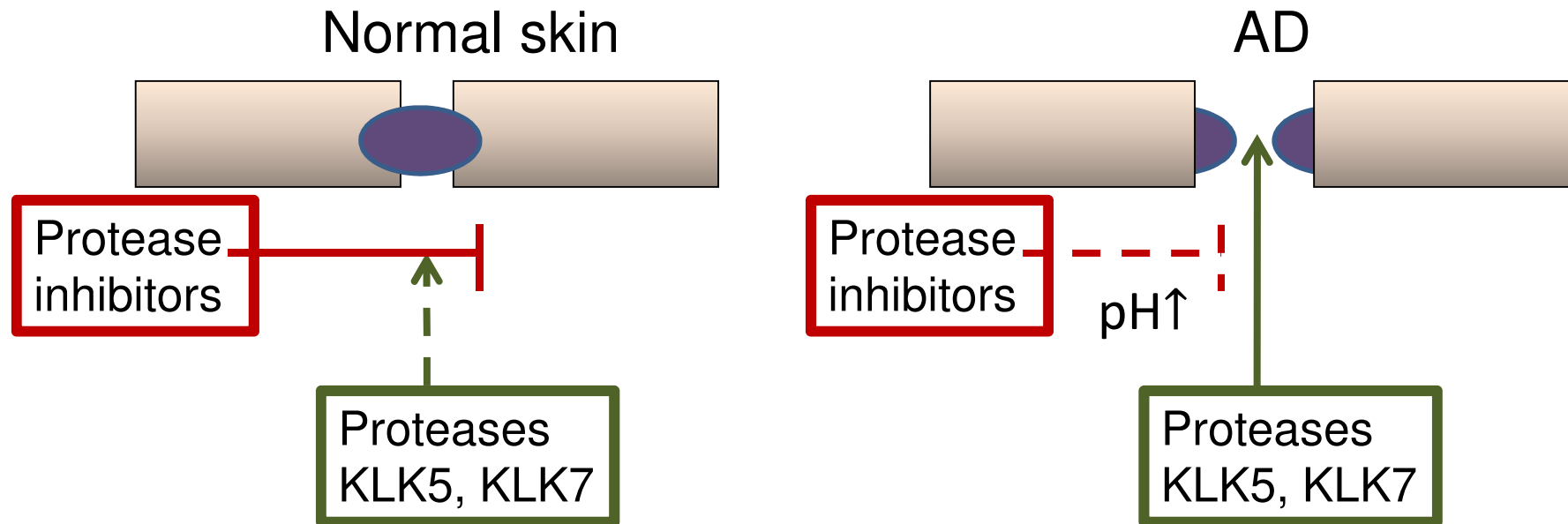
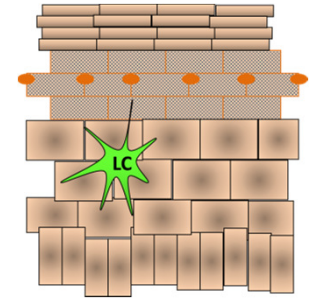
Palmer CNA et al; Nat Genet 2006; 38:441-6.

Morar N et al; J Invest Dermatol 2007;127:1667-72.

Rogers AJ et al; JACI 2007;120:1332-7.

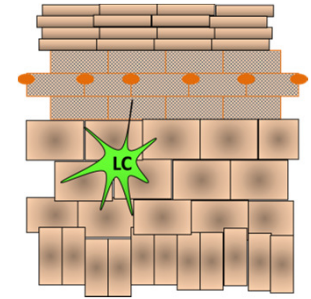
Howell MD et al. J Allergy Clin Immunol 2007;120:150-5.

Impaired skin barrier: Proteases-protease inhibitors



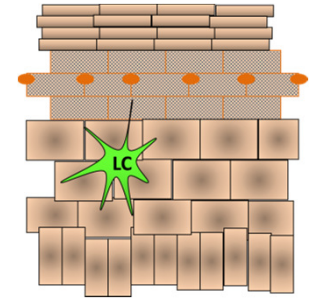
- Essential for epidermal homeostasis, desquamation
- Increase of pH inhibits LEKTI

Impaired skin barrier: Proteases-protease inhibitors



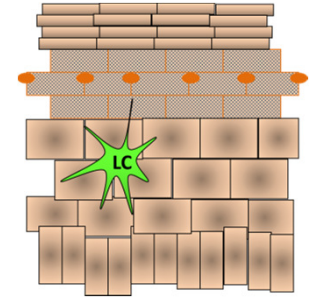
- Lymph-epithelial Kazal type inhibitor (**LEKTI**), serine protease inhibitor, coded by SPINK5 gene (Netherton's S., 5q31-q32)
 - Polymorphisms with mis-sense function associated with AD
 - Proteinase inhibitor ↓ → Proteases activated → PAR → TSLP
- Skin-derived antileukoprotease (**SKALP**, elafin), inducible after skin injury, detergents
- Exogenous proteases: house dust mites, S.aureus

Impaired skin barrier: Antimicrobial peptides



- Endogeneous small molecular weight proteins
- Produced by keratinocytes
- Human β -defensins (HBD-1 -4), cathelicidin (LL-37)
- AMPs
 - Cationic, interact with anionic components of microbes to permeabilize membrane, cell lysis
 - Modulate immune function:
 - recruit T cells, DC, monocytes, neutrophils
 - induce cytokine (IL-6, IL-10) and chemokine (MCP-1, MIP-3, RANTES) production by keratinocytes
- Th2 cytokines decrease IL-17-mediated AMP production

Impaired skin barrier: Tight junctions



- TJ consist of claudins, occludins, junctional adhesion molecules, zonula occludens, regulate paracellular permeability
- HBD-3 increases expression of claudins

In AD:

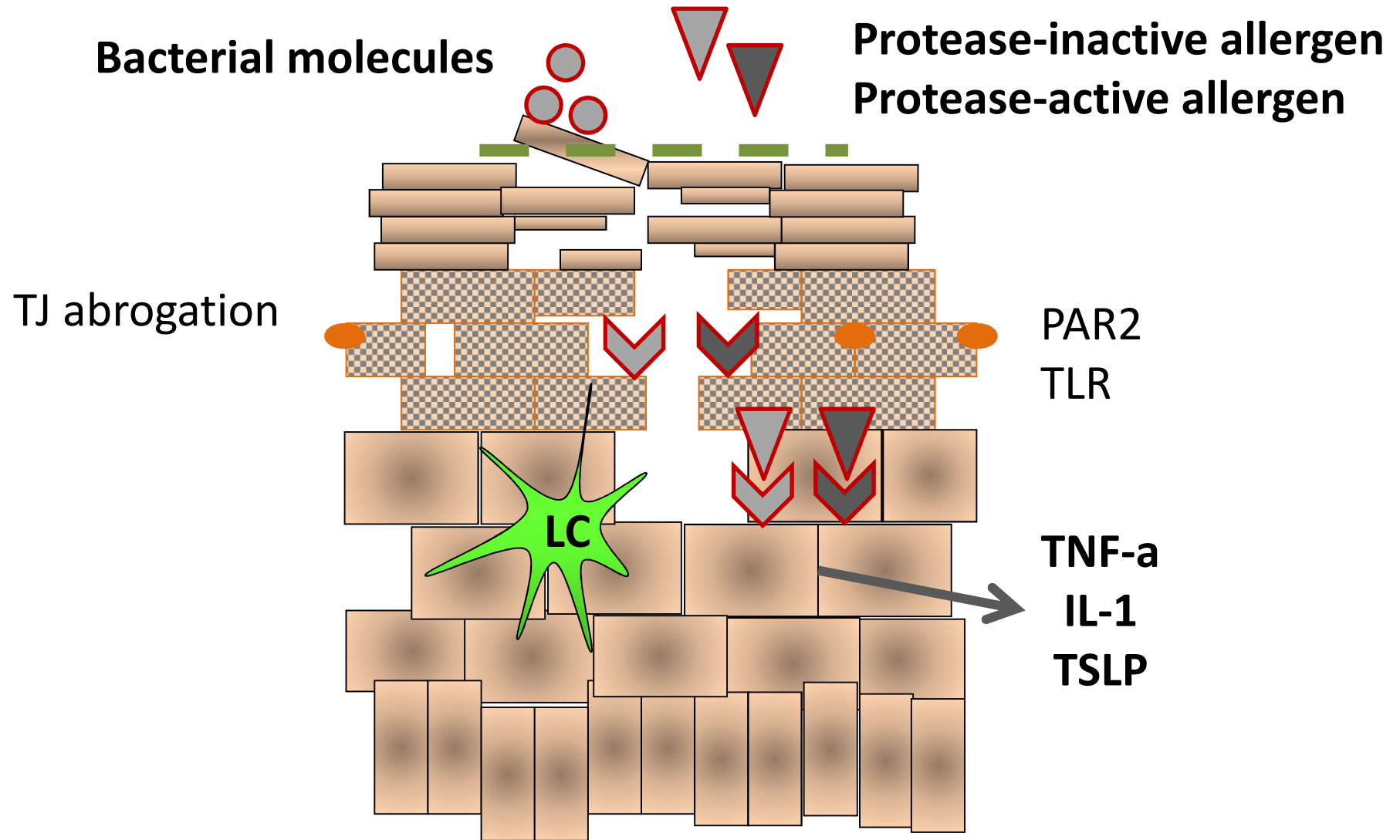
- Polymorphisms of claudin-1 gene
- Deficiency of claudin-1:
 - Keratinocyte proliferation, diminished TJ function
- Langerhans cells penetrate TJ

De Benedetto A et al. J Allergy Clin Immunol 2011;127:773-786.

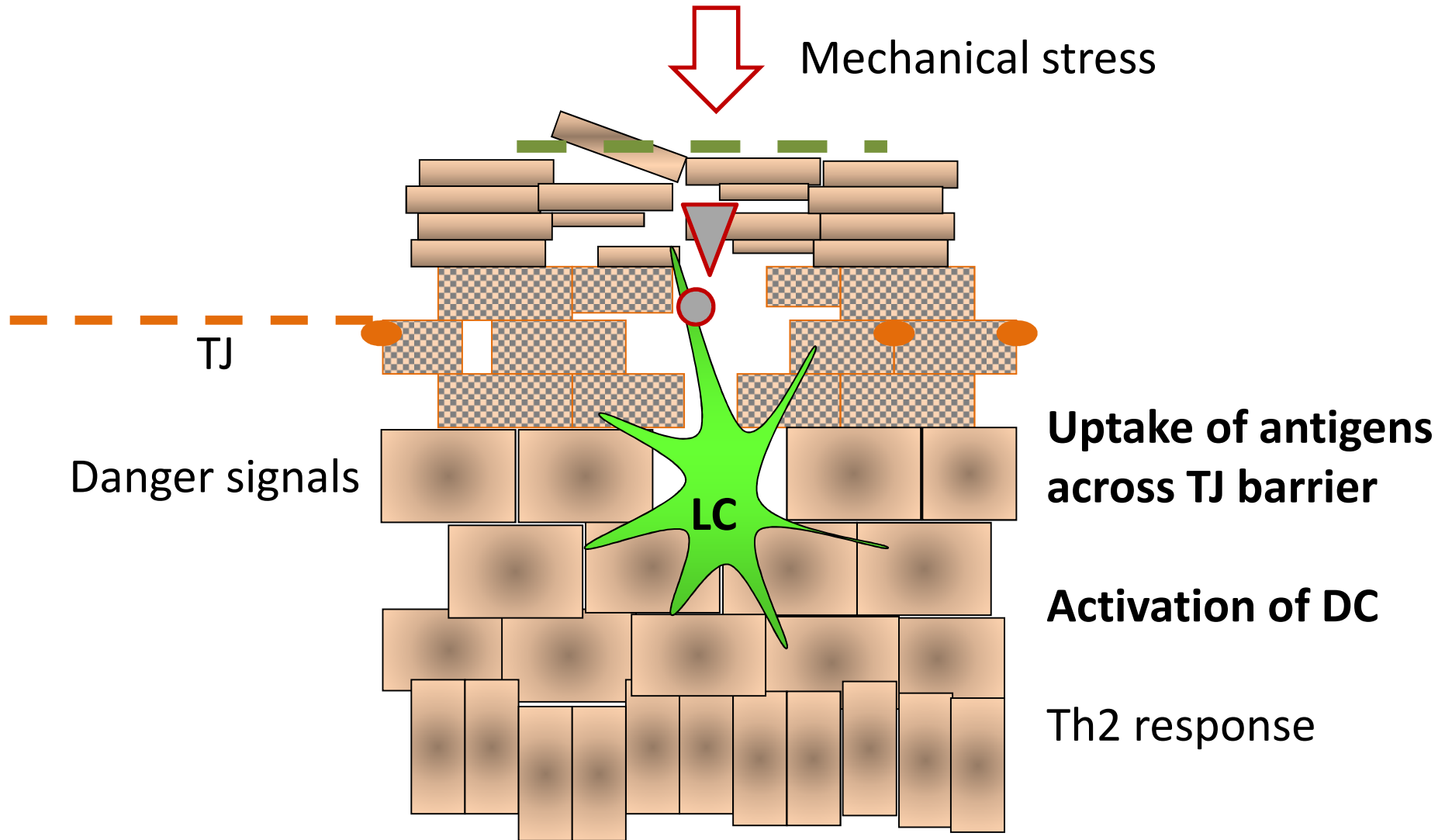
Kiatsurayanon C et al. J Invest Dermatol 2014;134:2163-2173.

Yoshida K et al. J Allergy Clin Immunol 2014;134:856-864.

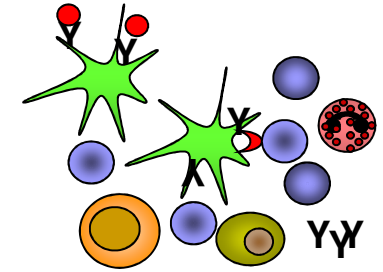
Activation of keratinocytes



Activation of DCs

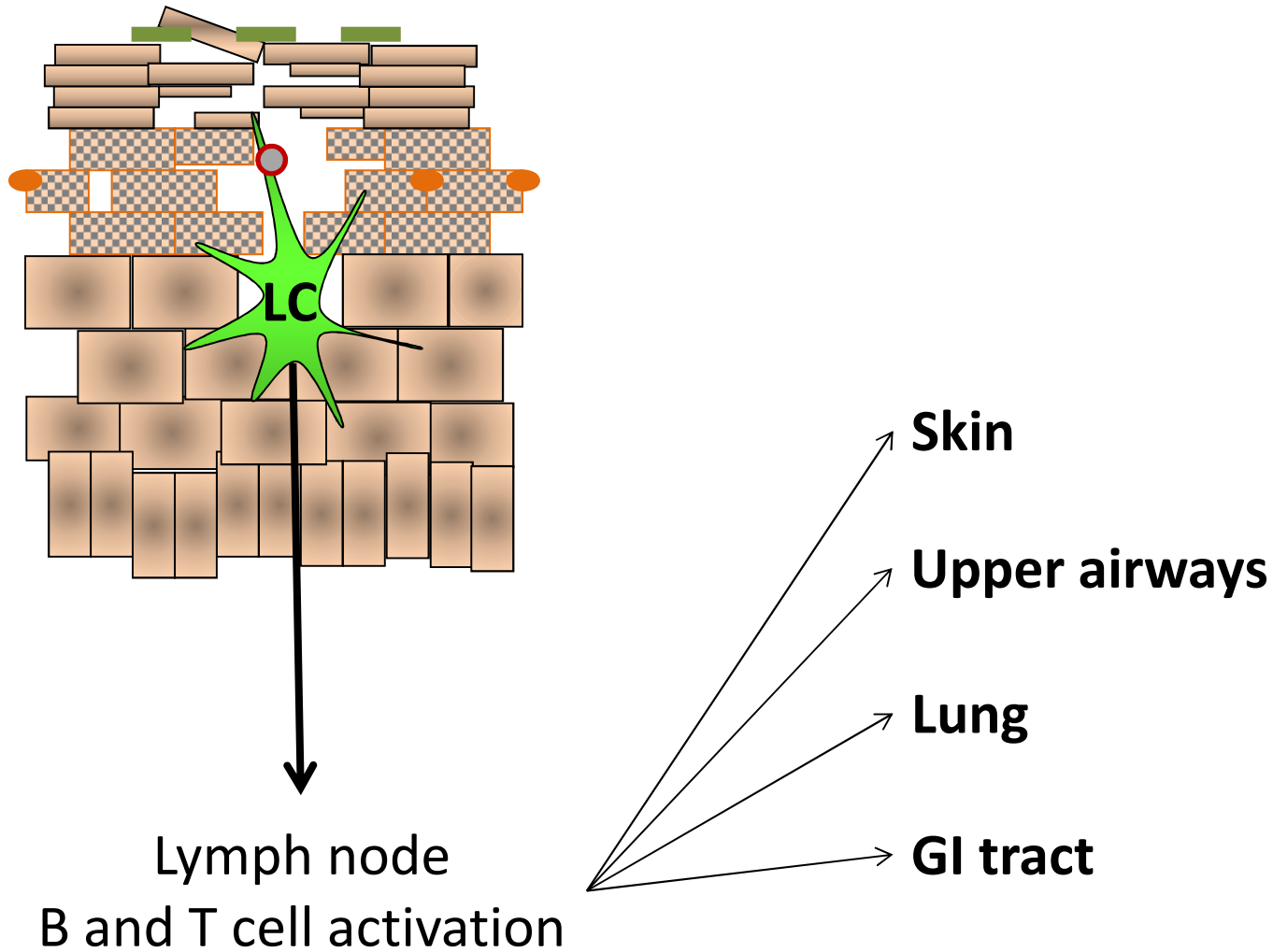


Epidermal dendritic cells



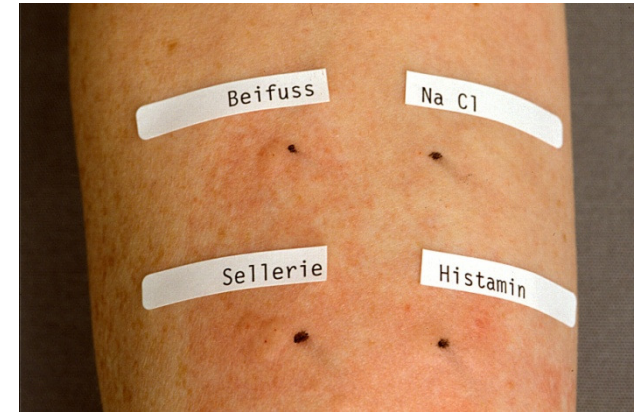
- Two kinds of APC: Langerhans cells and inflammatory dendritic epidermal cells (IDEC)
- Bear IgE on their surface, increased expression of the FcεR1 receptor
- LHC promote Th2 cell differentiation
- IDEC secrete proinflammatory cytokines, chemokines, promote Th1 immune reaction

DC migrate to LN, T and B cell activation



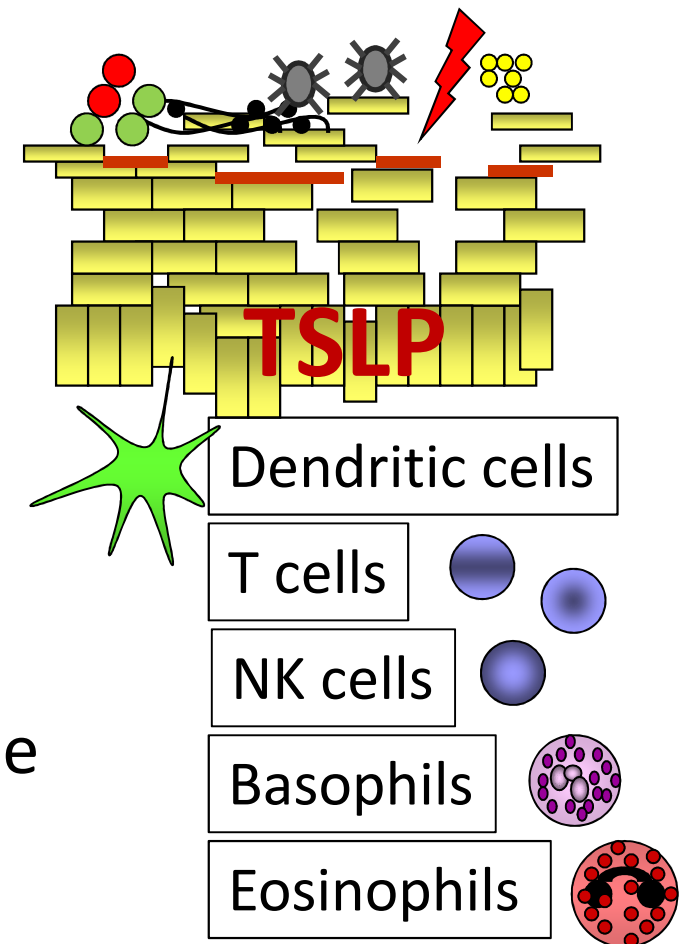
Allergens

- IgE-mediated delayed type hypersensitivity reaction
(type I + type IV)
- Pollens, house dust mites, animal dander, moulds
- Food allergy: 30% in infants, 3-5% in adults
- Diagnostics:
 - skin prick test
 - atopy patch test

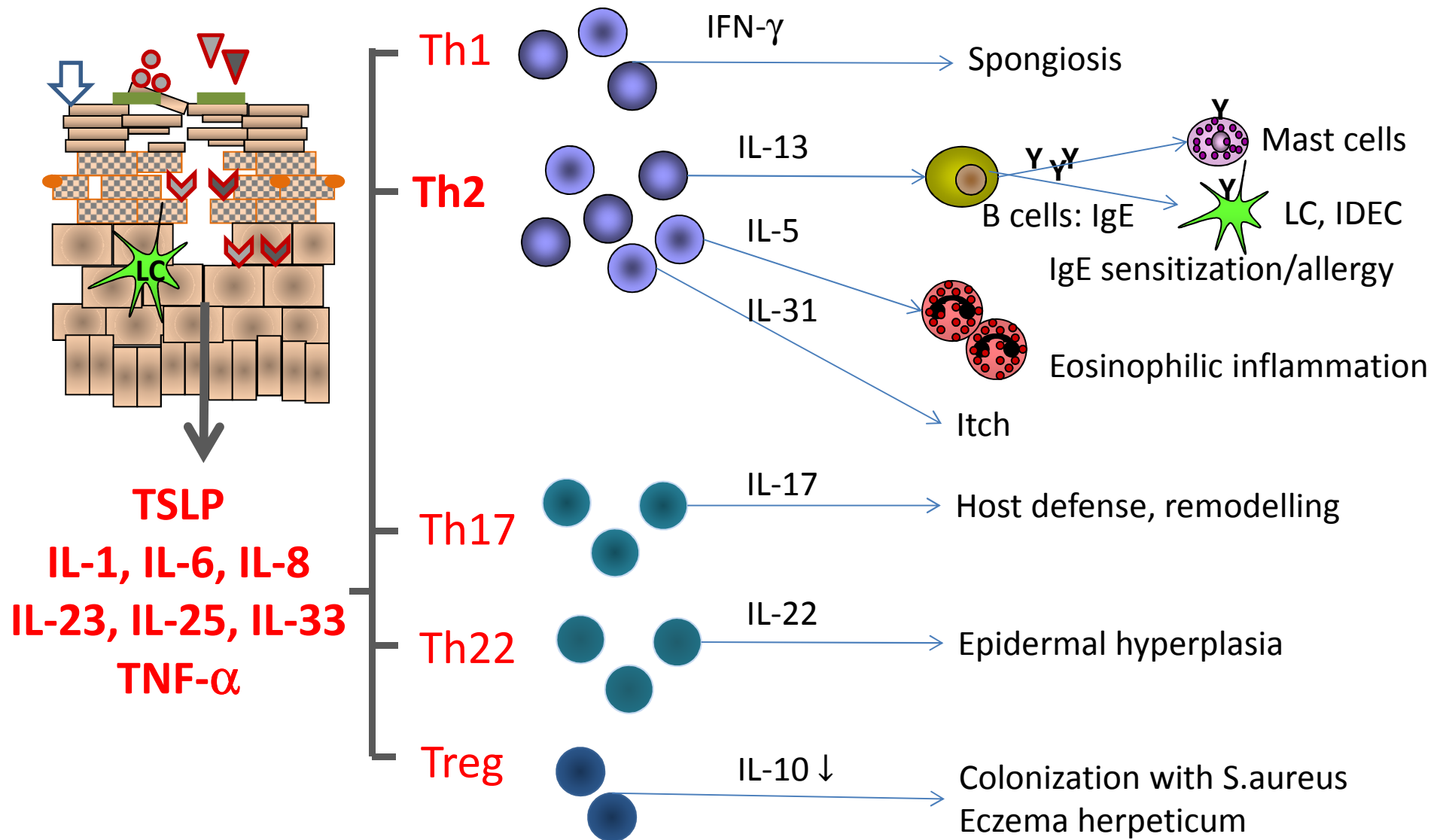


TSLP

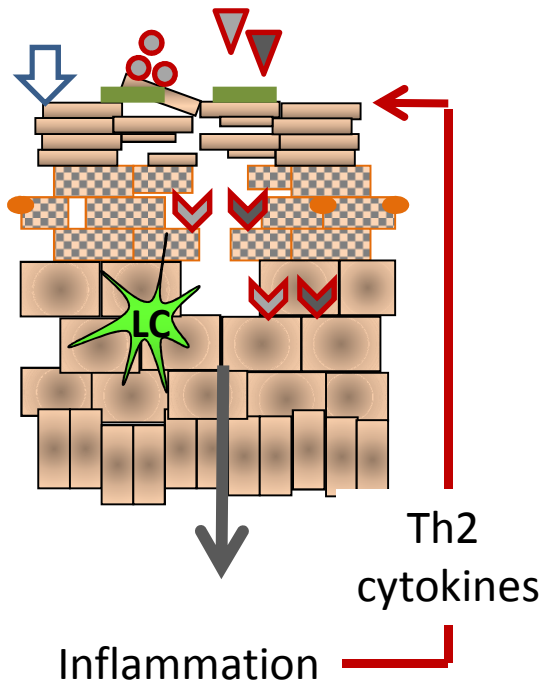
- produced by epithelial cells of intestine, airways, skin
- upon stimulation of PAR-2, TLR-2/TLR-6, TLR-3, mechanical injury
- binds to TSLP/IL-7 α receptor complex
- drives T-helper 2 immune response



T cell subsets and cytokines in AD



Inflammation further impairs skin barrier



- IL-4, IL-13 reduce filaggrin expression
- IL-31 inhibits epidermal differentiation, induces itch/scratching
- IL-4, IL-13 inhibit AMP production induced by IL-17

Howell MD et al; Clin Immunol 2006;121:332-8.

Howell MD et al; J Invest Dermatol 2005;125:738-45.

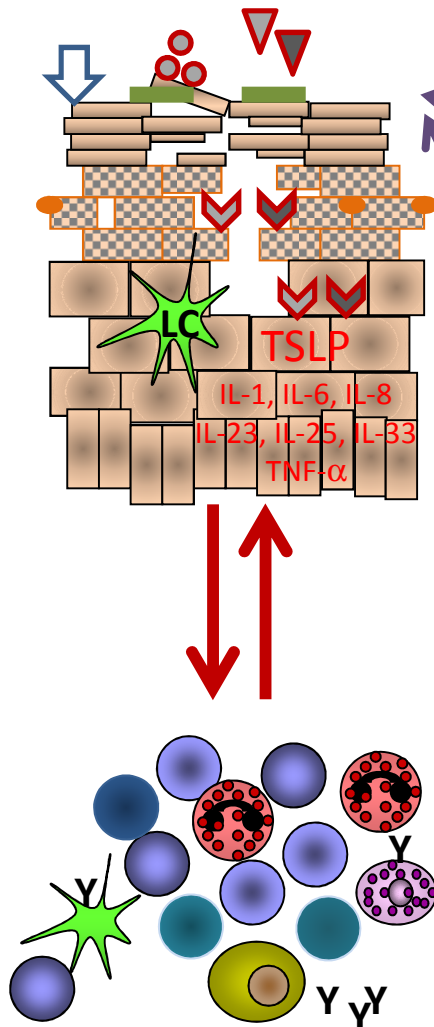
Menzies BE, Kenoyer A. Infect Immun 2005;73:5241-4.

Skin barrier, inflammation, environment

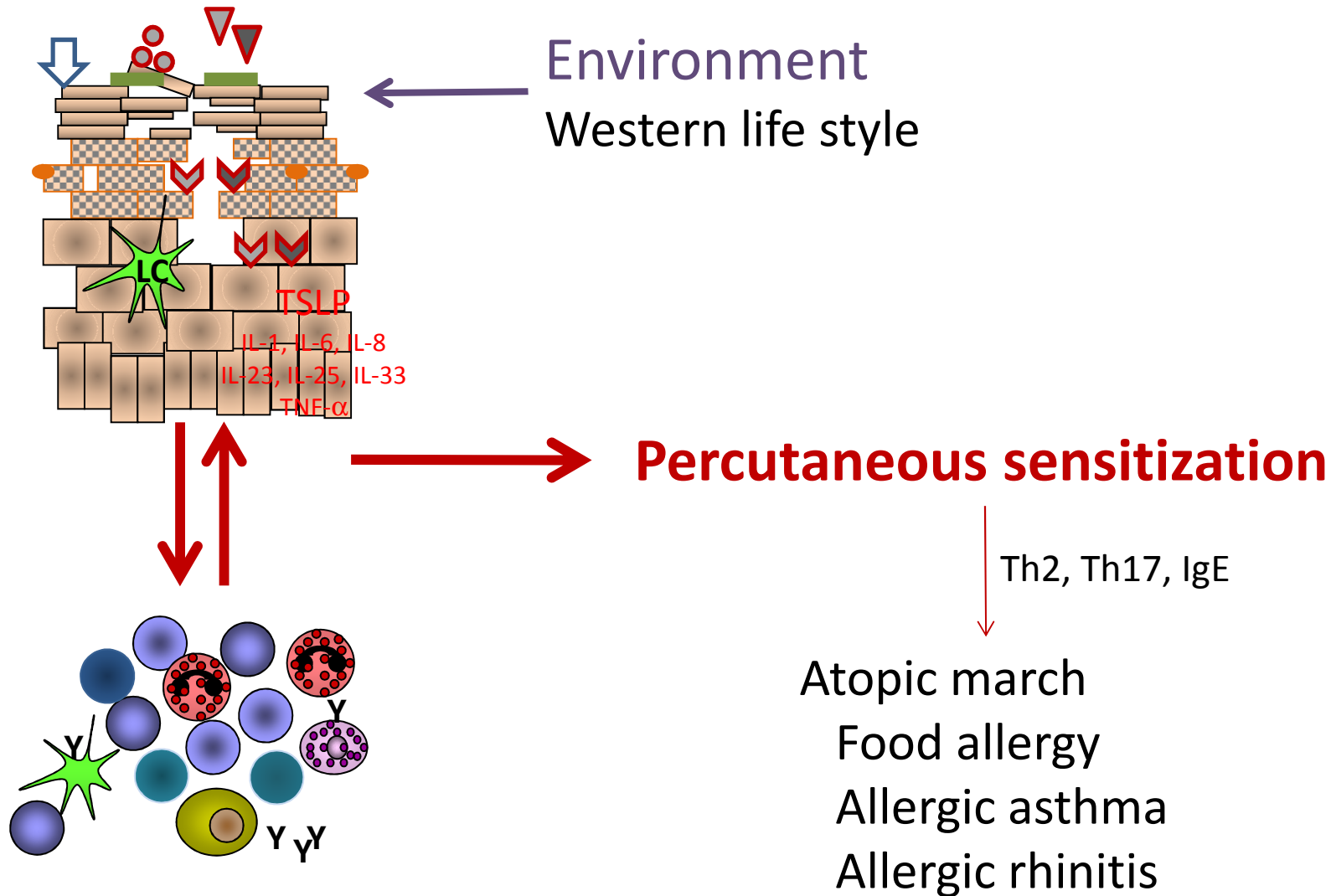
Environment

Heating, decreased ventilation, carpets
Increased house dust mite exposure

Frequent bathing, regular use of soaps
Concret houses, air conditioning, dehumidified air
Physical stress
Increase pH



Skin barrier dysfunction as starting point for the atopic march



Bacterial infections

- Staphylococcus aureus
- On lesional and non-lesional skin
- Infection (impetigo)
- Endotoxines (SEB) are superantigens
- Lipoteichoic acid
- IgE to S. aureus
- Th17 response

Eczema herpeticum

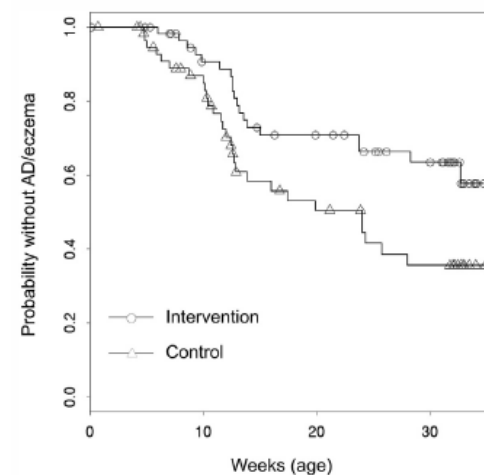
- Phenotype: severe AD, infection with Staph. aureus, molluscum contagiosum
- Impaired skin barrier
 - Filaggrin mutations
 - Claudin-1 deficiency
 - Reduced antimicrobial peptides
- Inflammation:
 - TSLP-variants, increased IL-25
 - reduced IFN-gamma production by CD8+ cells
 - Expansion of Tregs, IL-10, after withdrawal of TCS
- Aciclovir, valaciclovir + basic + antiinflammatory therapy

Mathias RA et al.; Br J Dermatol. 2013 Sep;169(3):700-3

De Benedetto A et al.; J Allergy Clin Immunol. 2011;128:242-246.

Emollient enhancement of skin barrier prevents AD

- Intervention (daily use of emollient) vs. control
 - Newborns at high risk for AD
 - US/GB: 124; Japan: 118
- US, GB: relative risk reduction of AD 50% (22% vs. 43%) after 6 months
- Japan: risk of AD/eczema lower in intervention group (hazard ratio 0.48)
- No effect on allergic sensitization (IgE to egg)
- Children with AD/eczema had higher IgE levels



Repairing skin barrier

- Recombinant filaggrin
 - Filaggrin linked to cell penetrating peptide
 - applied on reconstructed human epidermis (RHE)
 - Construct penetrates to Str.granulosum
 - Applied to flg-/- mice: internalisation and processing of construct, restoration of normal phenotype
- Inducer of filaggrin: JTC801
 - Induced mRNA of filaggrin, did not affect expression of epithelial differentiation proteins
 - suppressed development of AD-like skin inflammation in NC/Nga mice

Therapeutic approaches

