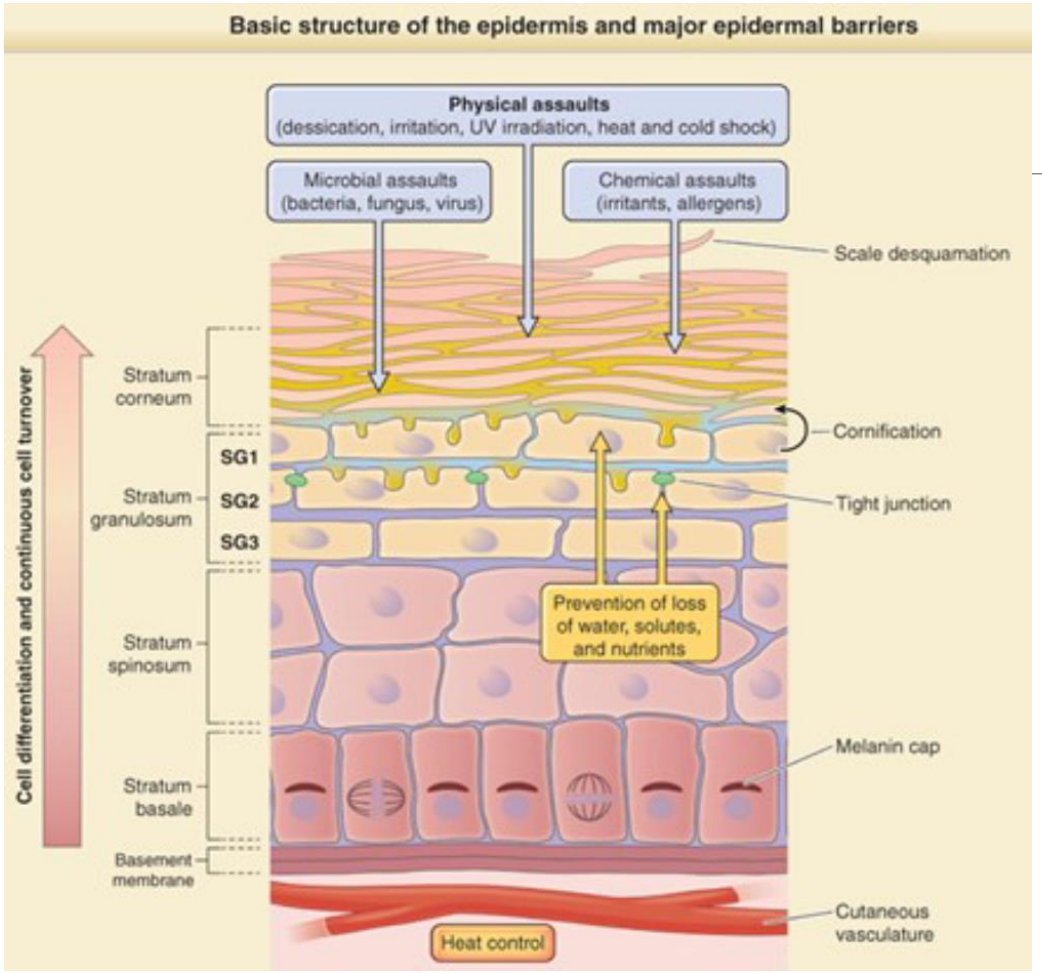
Clinical Relevance of Cornification

HEIDE M. NEWTON DVM, DACVD



Cornification and skin lesions

Keratinocytes have 2 actions when barrier is challenged

- Increase proliferation
- Stimulate inflammation

Lesions are signs of these actions

Understanding cornification allows better

- Interpretation of lesions
- Recommendations of diagnostics and treatments
- Prediction of outcomes

Figure 14-2 from Kubo A, Amagai M. Skin Barrier. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS. eds. Fitzpatrick's Dermatology, 9e. McGraw Hill; 2019.

Epidermal lesions

Primary lesion – develops spontaneously as a direct reflection of the underlying disease	Secondary lesions - evolve from primary lesions or are artifacts induced by patients or external factors	Primary or secondary
• **Papule, plaque, pustule,** macule, patch, vesicle, bulla, **nodule**	• Epidermal collarette, **erosion, ulcer,** excoriation, fissure, **lichenification,** callus, scar	• Alopecia, hyper/hypopigmented macules/patches, **scale, crust**, follicular casts, comedo

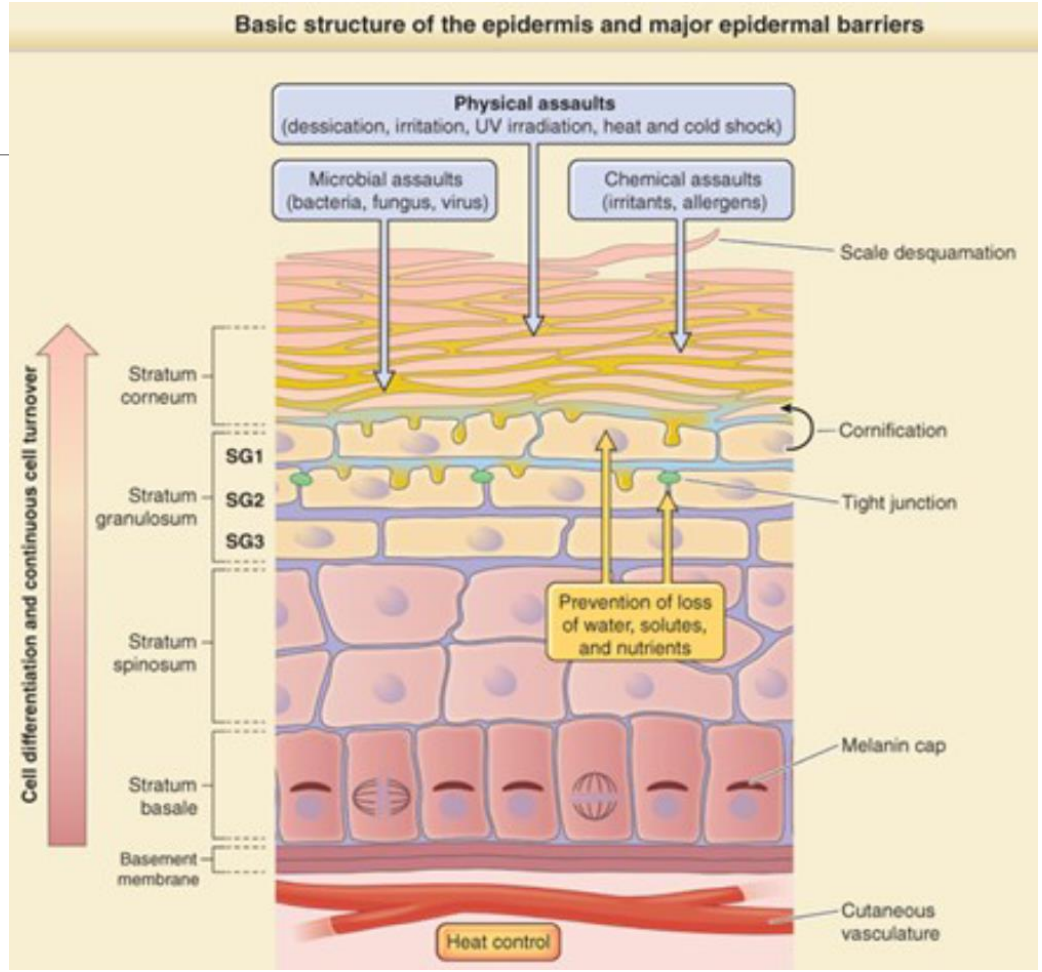
Solid elevated lesions

Papule - up to 1 cm diameter

Nodule - over 1 cm diameter

Plaque – flat, circumscribed, over 1 cm

Result from keratinocyte proliferation or other cell proliferation or infiltration



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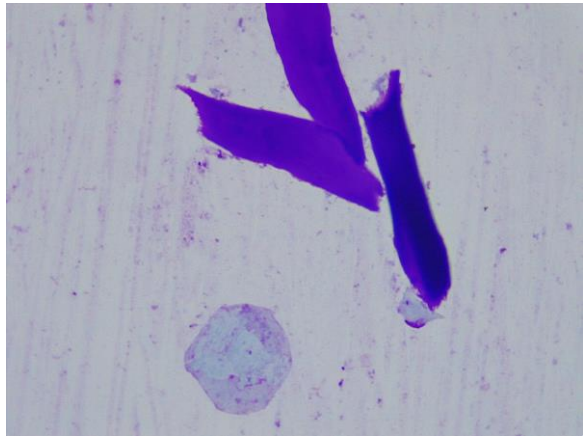
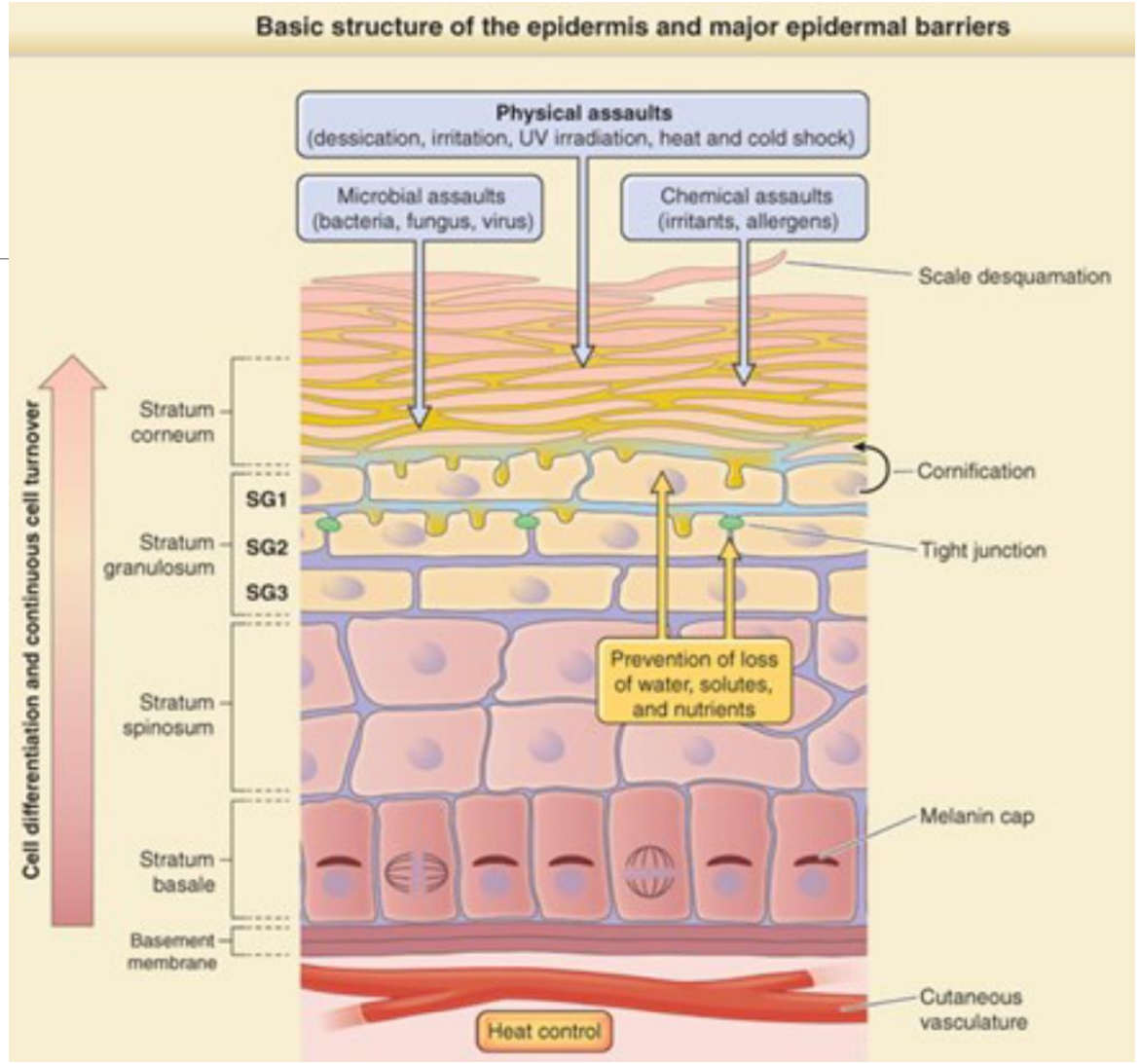
Scale

Scale – corneocytes

- Normal desquamation or disease





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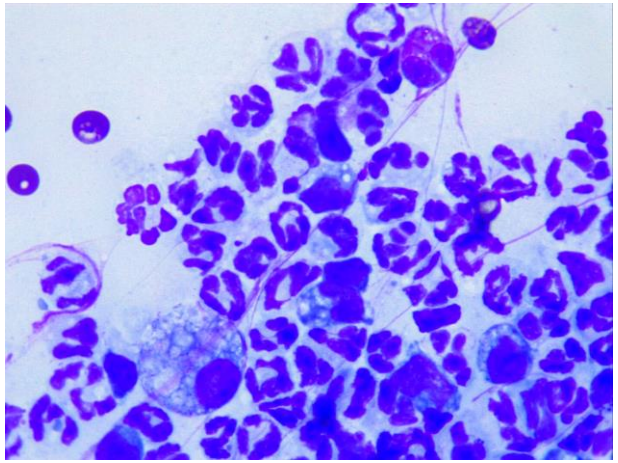
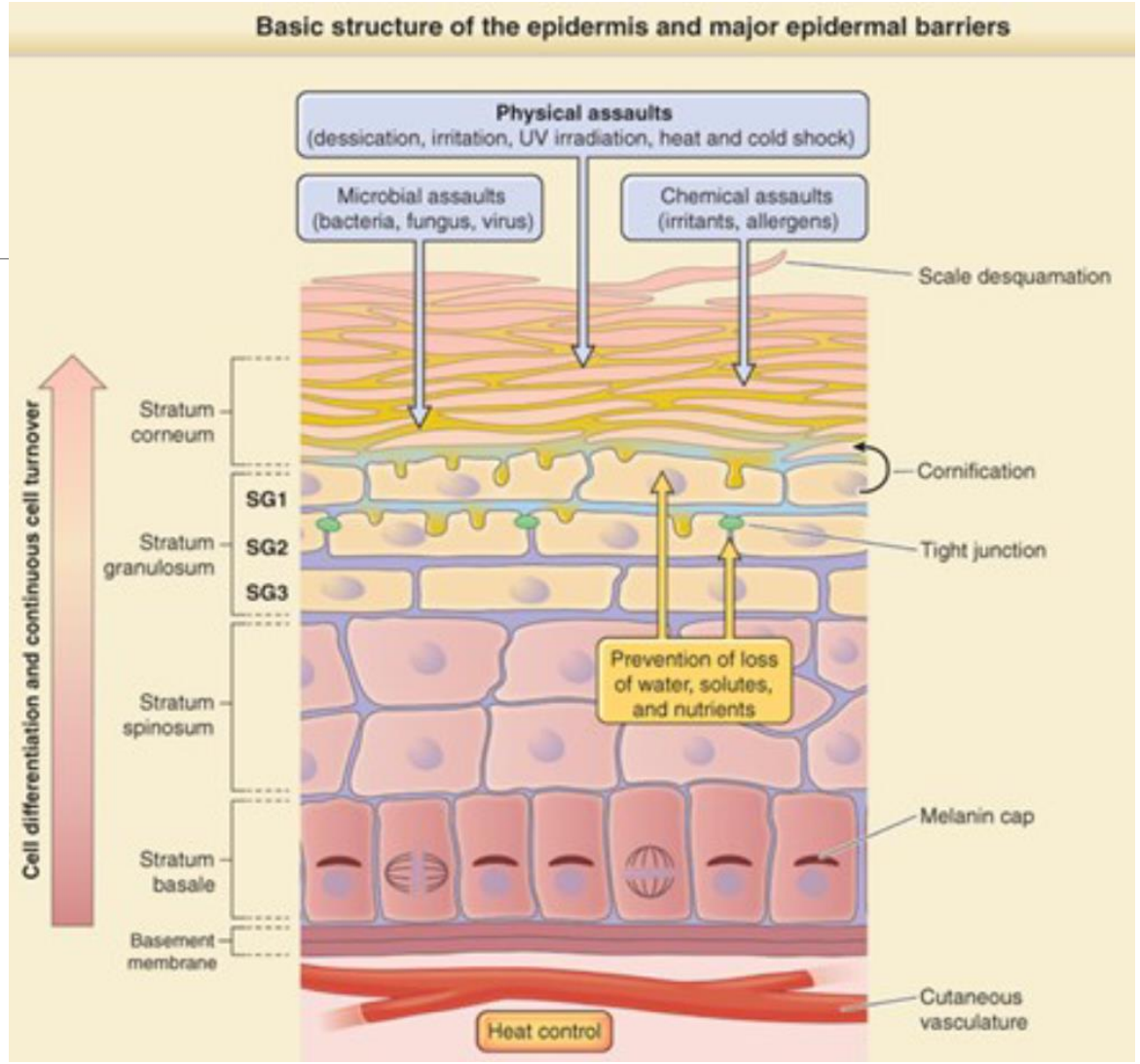
Crust

Crust - corneocytes plus dried exudates

- Serous, sanguineous, purulent, mixed
- Sometimes microorganisms
- Always signifies something abnormal





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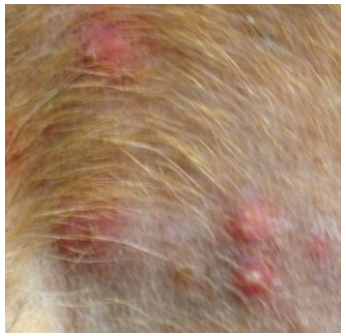
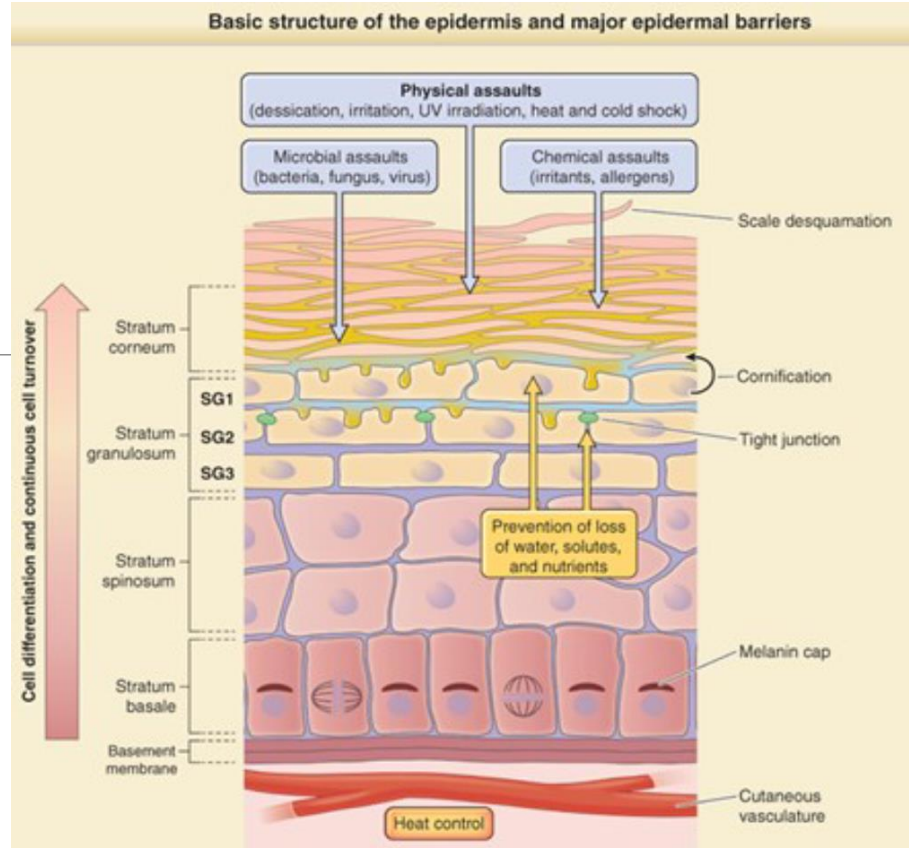
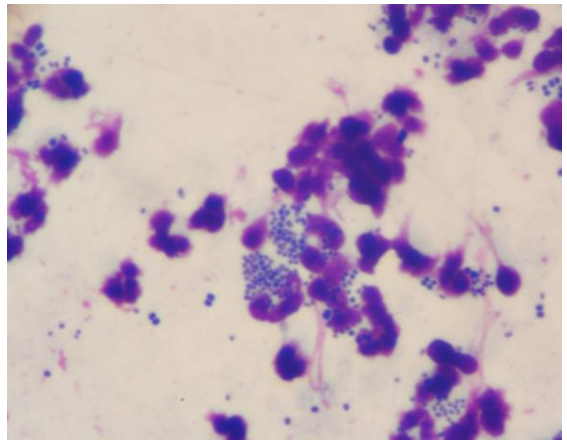
Pustule

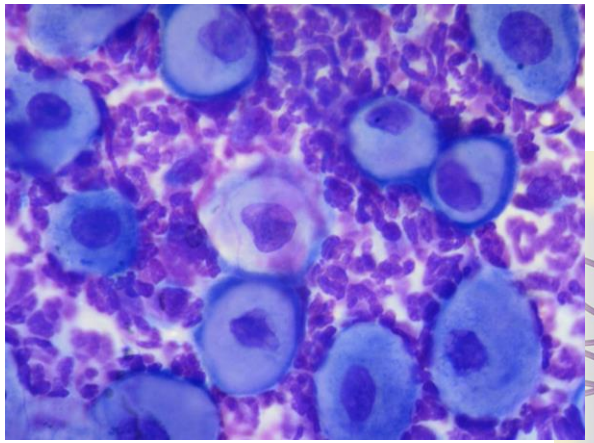


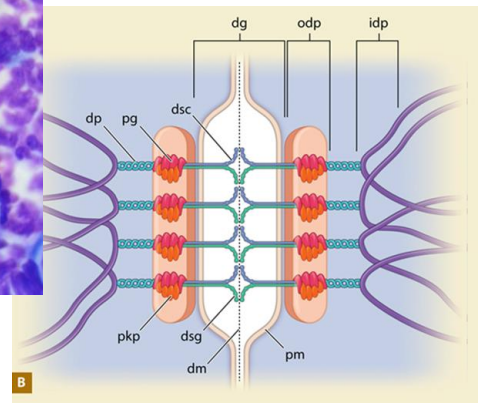
Pustule – circumscribed lesion containing purulent material

- Neutrophils, other inflammatory cells
- Sometimes microorganisms and/or acantholytic cells









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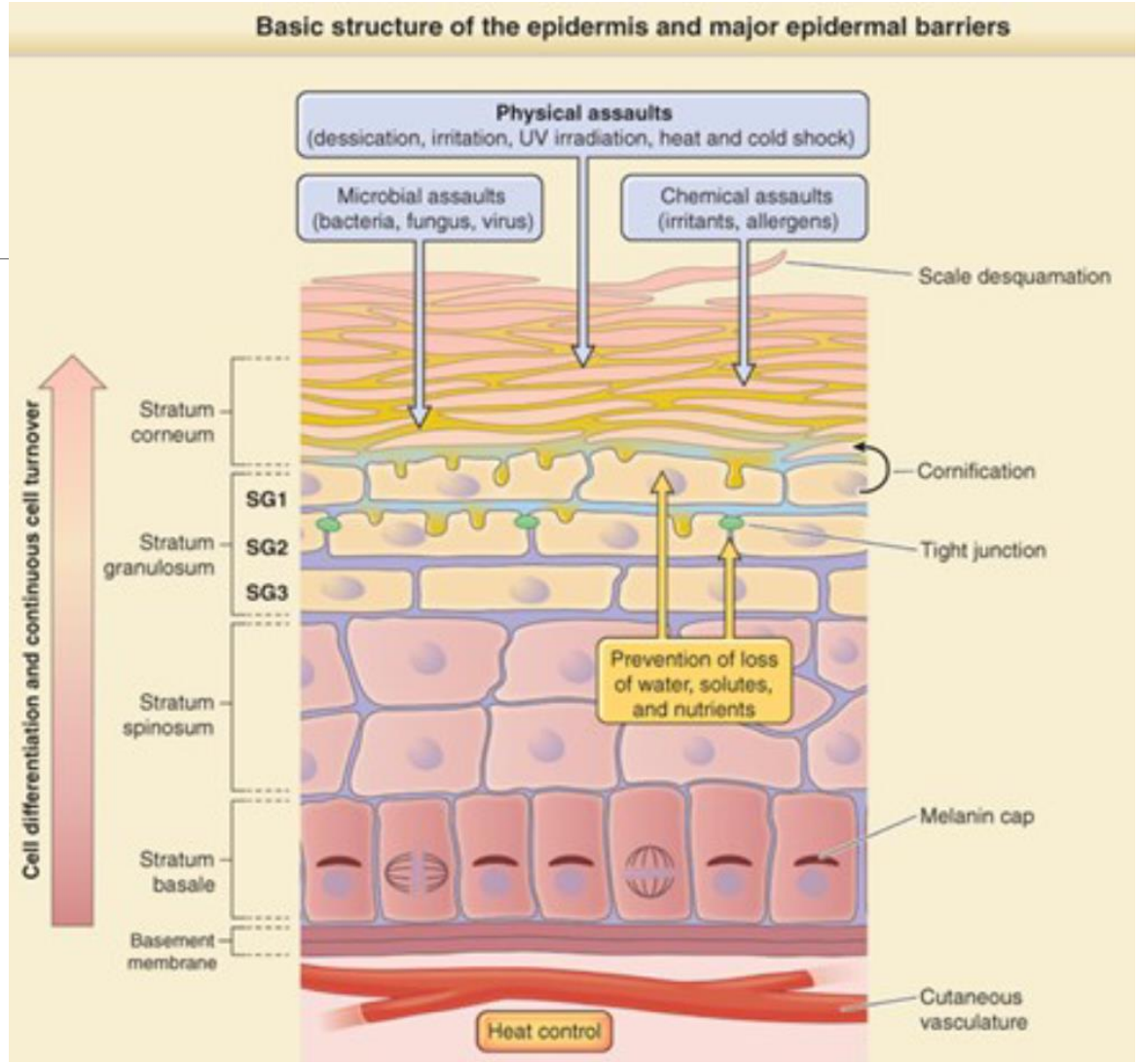
Loss of epidermis

Erosion – loss of part of epidermis

Ulcer - loss of epidermis extending beyond basement membrane

Can result from rupture of pustule and dried exudates become crusts

Barrier is removed and repair requires keratinocyte proliferation leading to desquamation and scale



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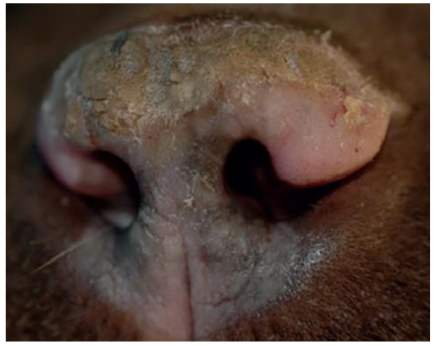
Thickening of epidermis

Hyperkeratosis – thickening of stratum corneum



Lichenification – thickening of stratum spinosum

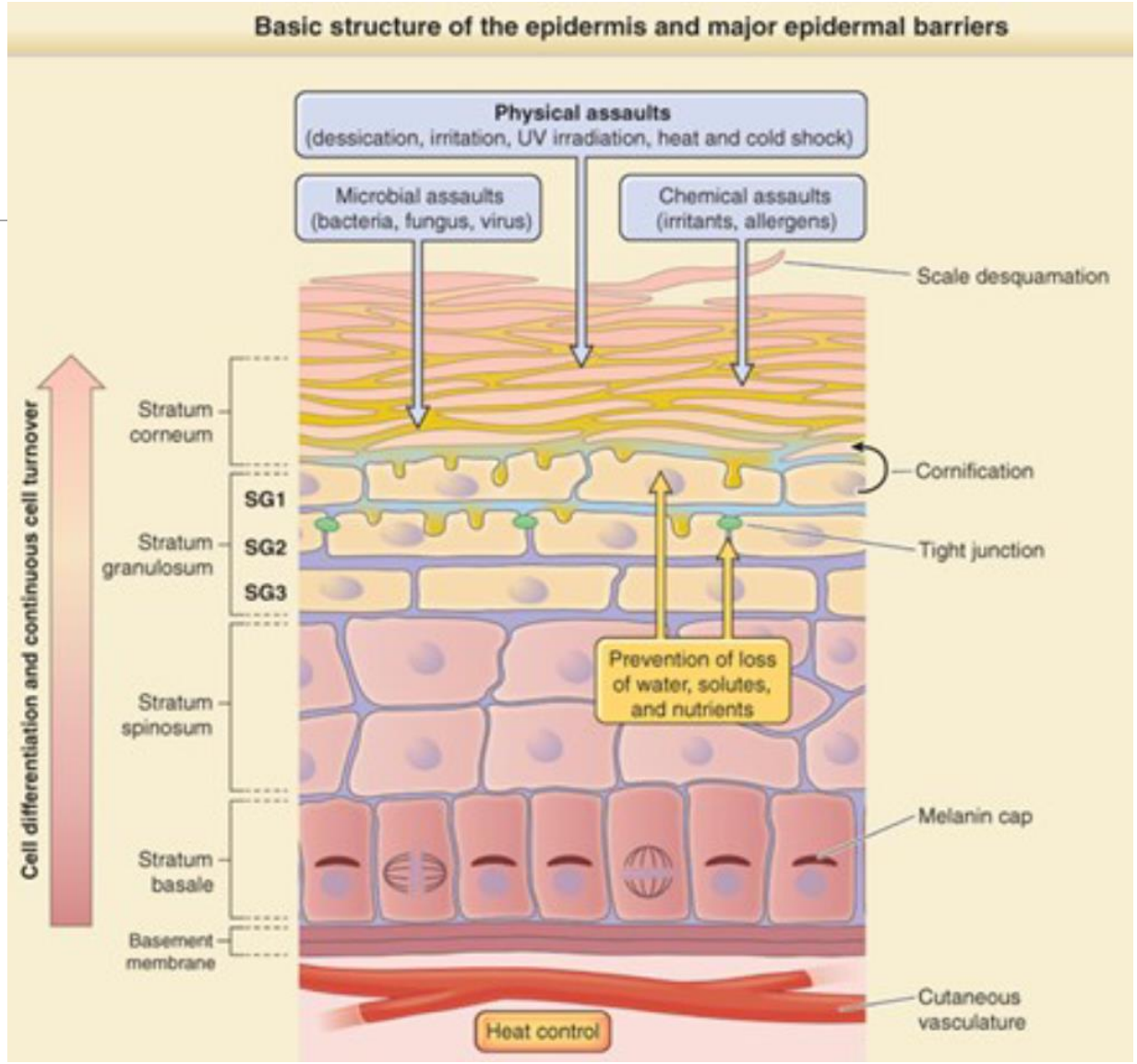


Fig 14-2 from Kubo A, Amagai M. Skin Barrier. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS. eds. Fitzpatrick's Dermatology, 9e. McGraw Hill; 2019 & Fig 1 from Bannoehr J, Balmer P, Stoffel MH, Jagannathan V, Gaschen V, Ku¨hni K, et al. (2020) Abnormal keratinocyte differentiation in the nasal planum of Labrador Retrievers with hereditary nasal parakeratosis (HNPK). PLoS ONE 15(3): e0225901

Clinical relevance of cornification

Lesion interpretation

Atopic dermatitis

Ichthyosis and other hereditary disorders of cornification

Atopic dermatitis (AD)

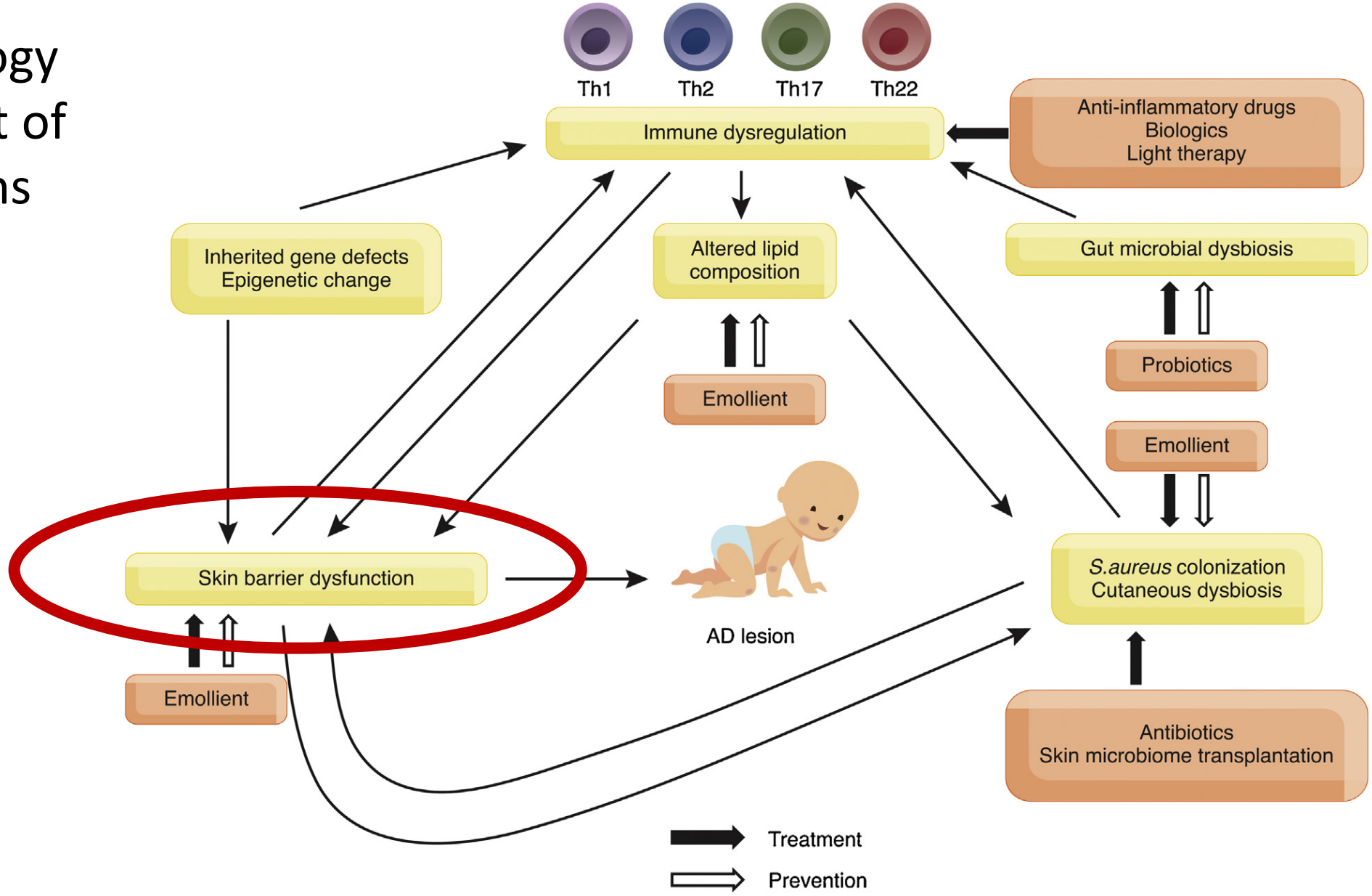
AD – inflammatory, pruritic skin disorder with complex etiology

- Impaired skin barrier
- Immune dysregulation (Th2, IgE)
- Genetic mutations
- Cutaneous dysbiosis
- Environment

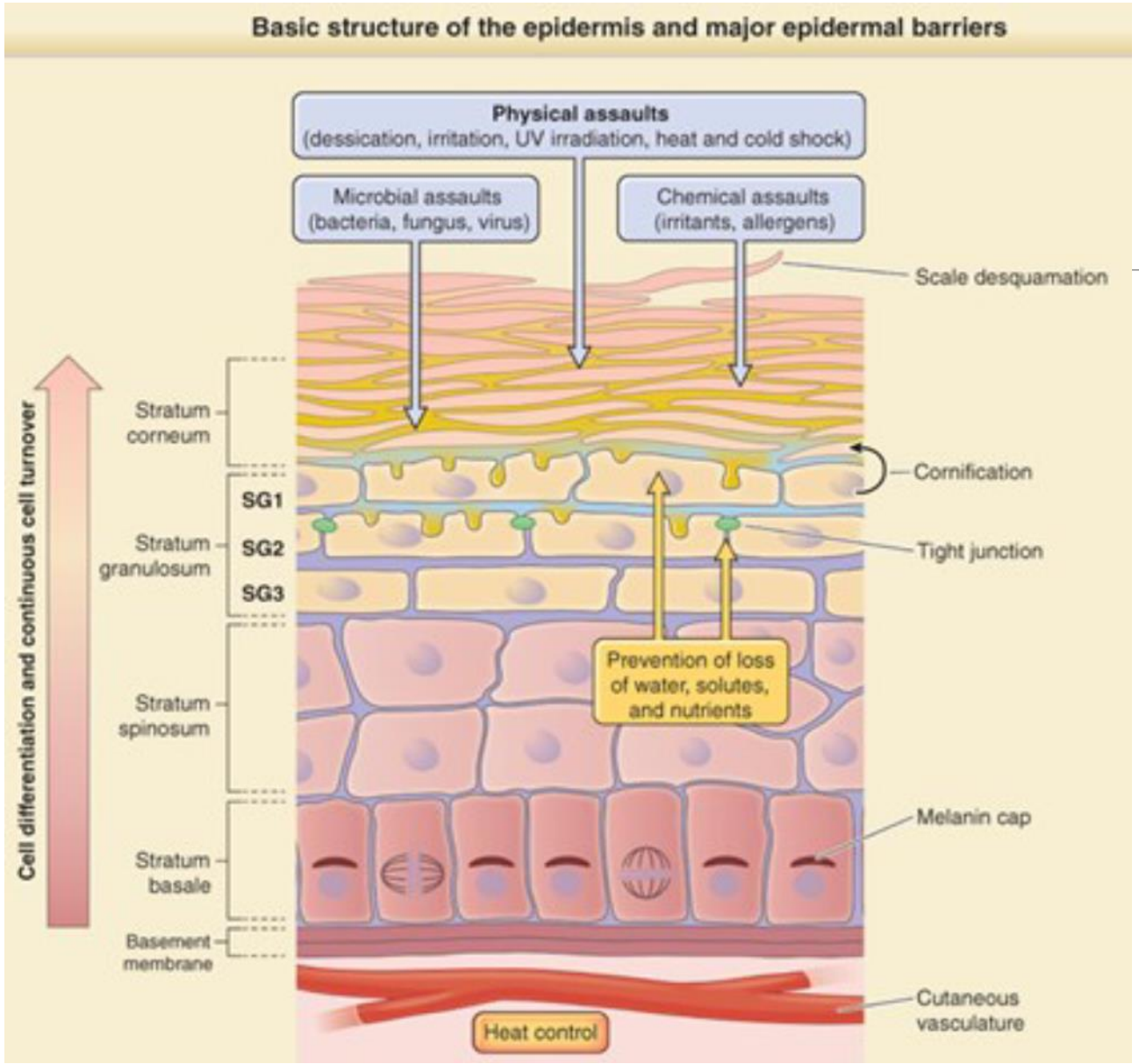
Similarities of AD clinical features and treatment response in dogs and humans

https://nationaleczema.org/wp-content/uploads/2020/07/eczema_atopic_dermatitis.jpg

Pathophysiology and treatment of AD in humans



Luger T, Amagai M, Dreno B, Dagnelie MA, Liao W, Kabashima K, Schikowski T, Proksch E, Elias PM, Simon M, Simpson E, Grinich E, Schmuth M. Atopic dermatitis: Role of the skin barrier, environment, microbiome, and therapeutic agents. J Dermatol Sci. 2021 Jun;102(3):142-157. doi: 10.1016/j.jdermsci.2021.04.007.



Epidermis in humans with AD

Decreased expression

- Filaggrin
- Loricrin
- Involucrin
- Corneodesmosin

Increased

- Desquamation
- TEWL and percutaneous penetration

Figure 14-2 from Kubo A, Amagai M. Skin Barrier. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS. eds. Fitzpatrick's Dermatology, 9e. McGraw Hill; 2019.

Filaggrin metabolism

Filaggrin functions

- Aligns KIFs and flattens corneocyte
- Contributes to hydration once degraded to NMF

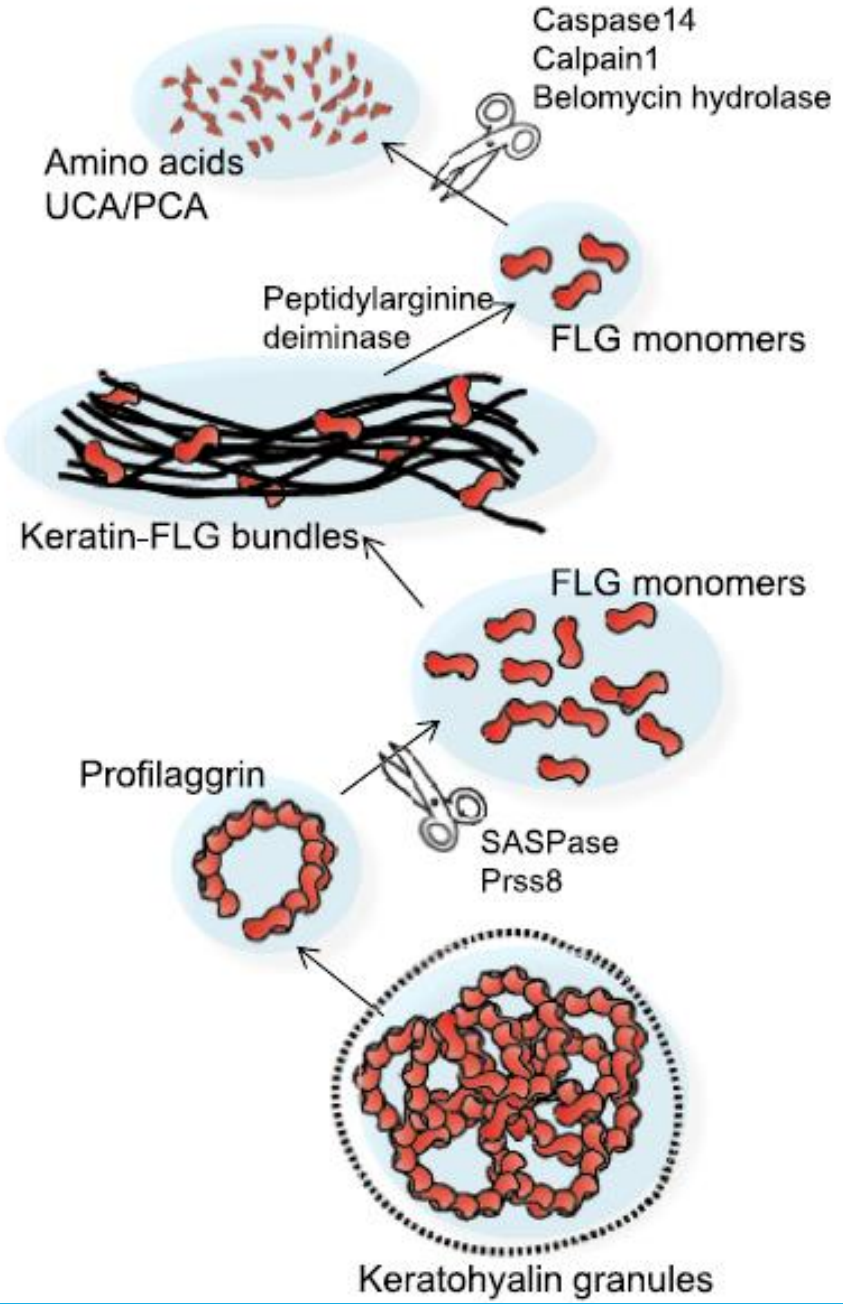


Figure 2 from Egawa, G. and Kabahima K. Barrier dysfunction in the skin allergy. *Allergology International* 2018; 67: 3-11.

Barrier effects of filaggrin mutations

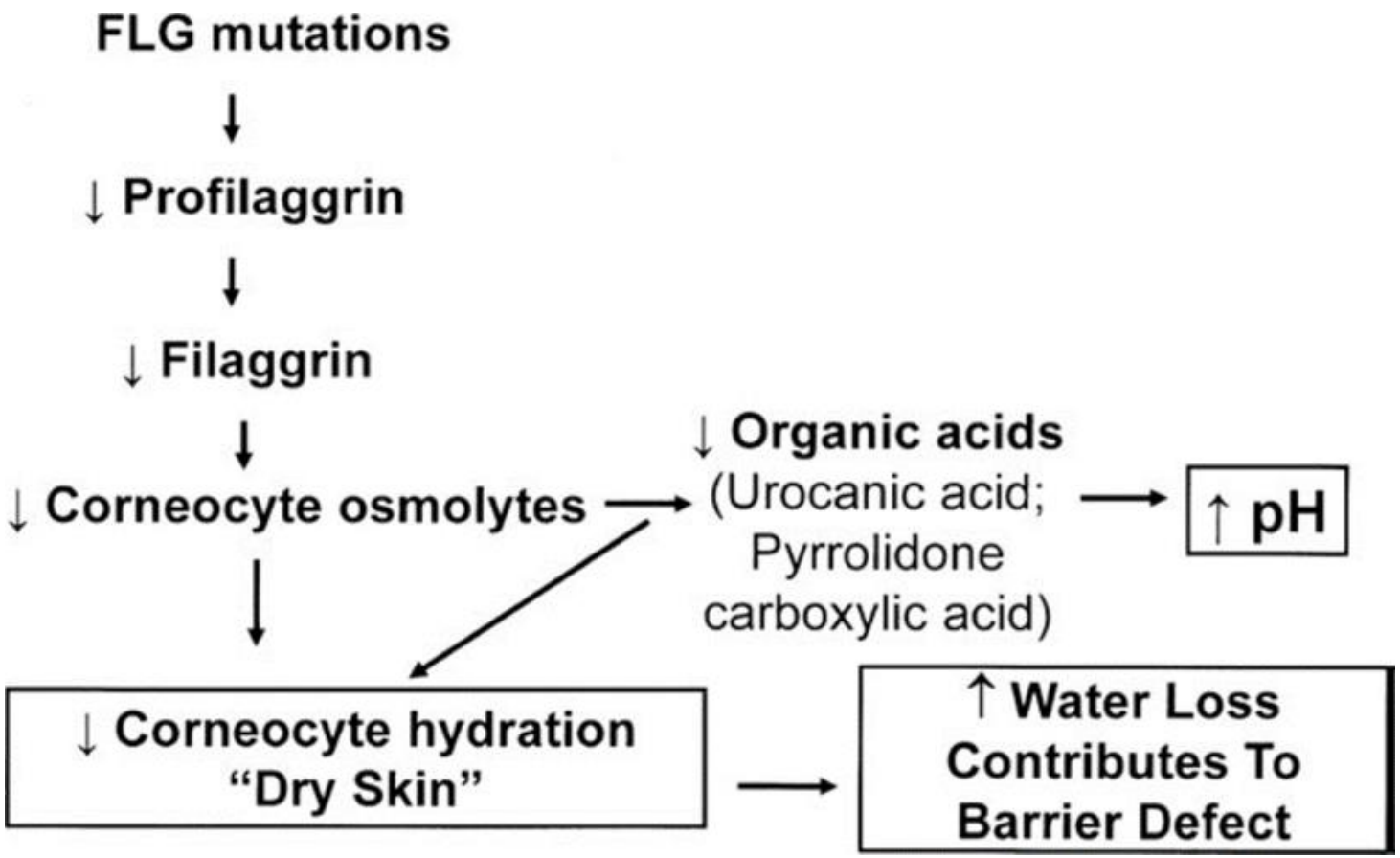


Figure 1 from Elias PM. Primary role of barrier dysfunction in the pathogenesis of atopic dermatitis. *Experimental Dermatology* 2018; 27:847-851.

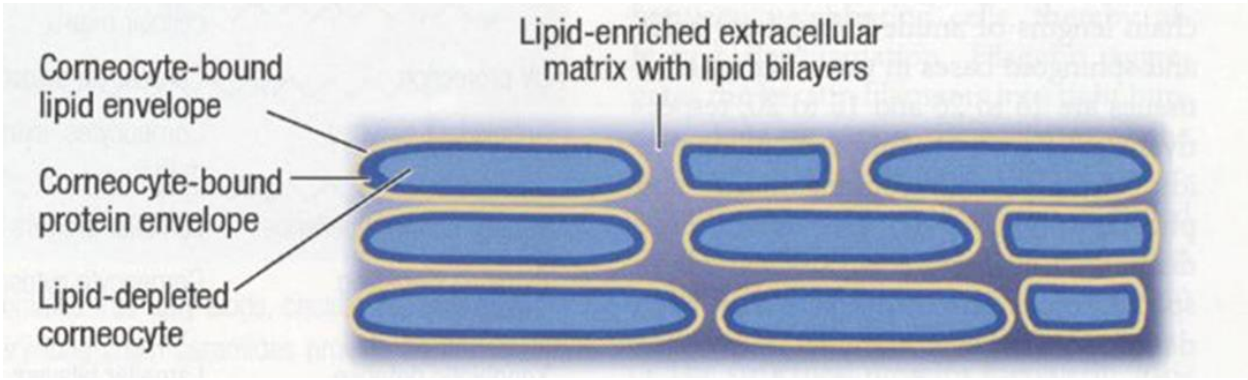
Filaggrin and AD

In humans

- Filaggrin loss of function mutations strongly associated with AD
  - Barrier impairment precedes and predicts AD development and progression
- Most AD patients show markedly reduced filaggrin regardless of mutations
  - Th2 cytokines downregulate filaggrin expression

In dogs, role of filaggrin mutations in CAD unclear

Extracellular lipid matrix



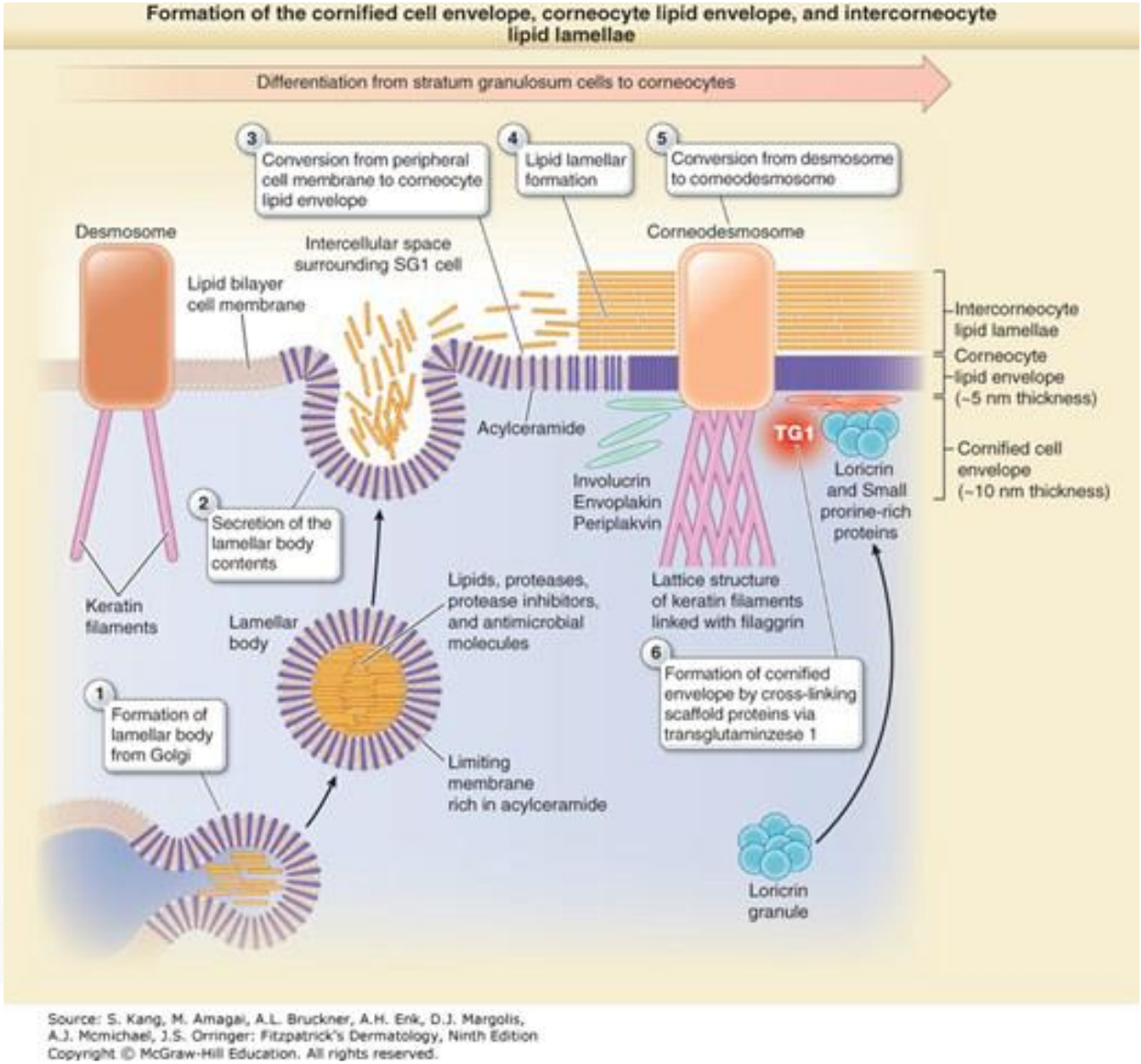


Figure 45-4 from Proksch E, Jensen JM. Skin as an organ of protection. In: Wolff K et al, editors, Fitzpatrick's Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill Companies, Inc. 2008. p. 385 and Fig 14-6 from Kubo A, Amagai M. Skin Barrier. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS. eds. Fitzpatrick's Dermatology, 9e. McGraw Hill; 2019.

Extracellular lipids and AD

Composition and architecture are disrupted

- Lamellar body secretion abnormal and some retained in corneocytes
- Reduction in
  - Total lipids in stratum corneum
  - Proportion of long chain ceramides
  - Chain length of fatty acids in ceramides and free fatty acids

In CAD, findings are similar to humans

- Decreased total lipids, fatty acids, and ceramides in AD
- Abnormal, disorganized, and reduced intercellular lipid lamellae

Tight junctions (TJ) impaired in AD

Downregulation of claudin-1 by Th2 cytokines

- Decreased TJ expression

Keratinocytes drive inflammation following barrier disruption

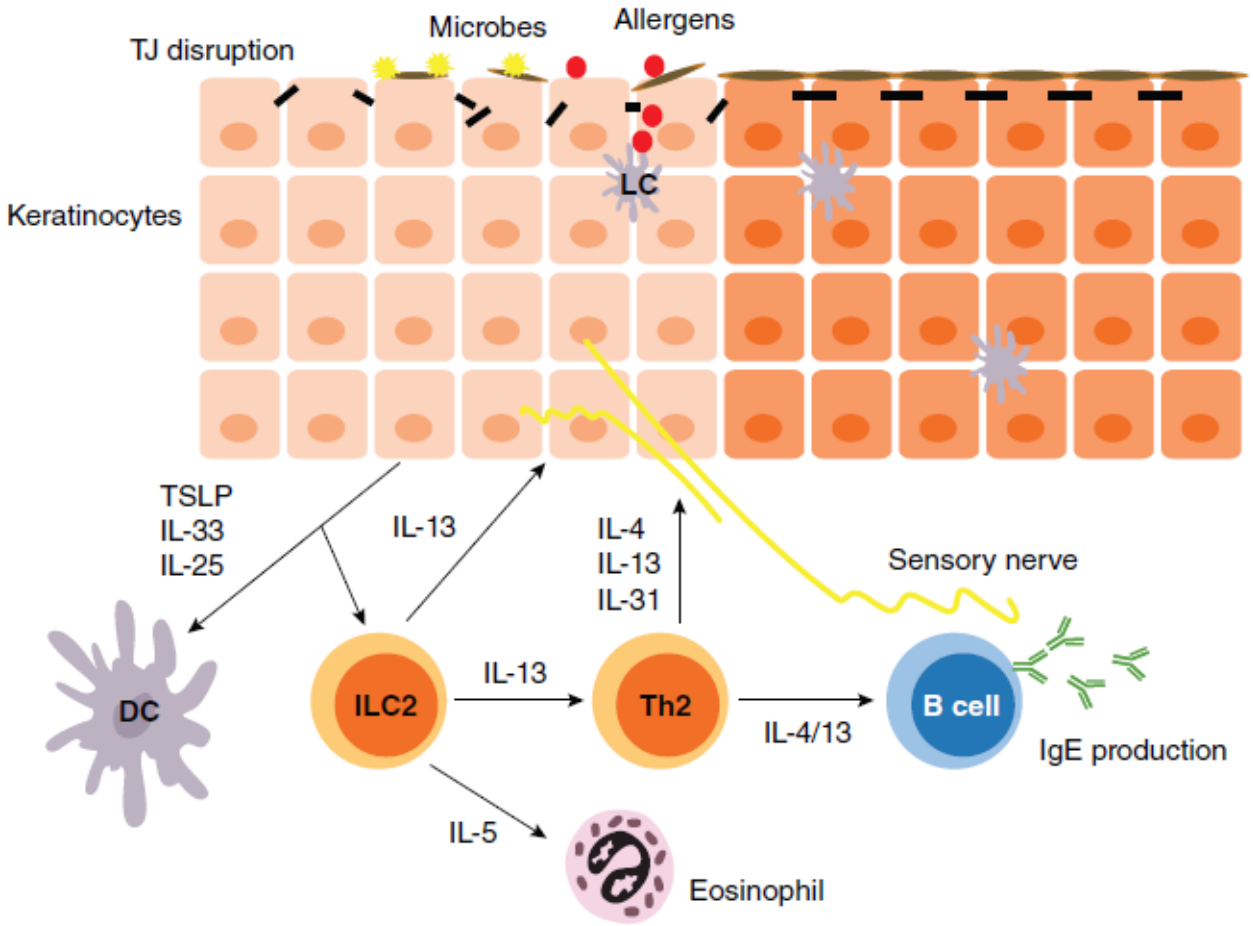


Fig 3 from Sugita K, Kabashima K. Tight junctions in the development of asthma, chronic rhinosinusitis, atopic dermatitis, eosinophilic esophagitis, and inflammatory bowel diseases. J Leukoc Biol. 2020 May;107(5):749-762. doi: 10.1002/JLB.5MR0120-230R. Epub 2020 Feb 28. PMID: 32108379.

Tight junctions (TJ) impaired in AD

Activation of PAR2 (protease-activated receptor 2)

- Disrupts claudin-1 and occludins
- Reduces TJ barrier integrity
- Promotes Th2 inflammation and pruritus

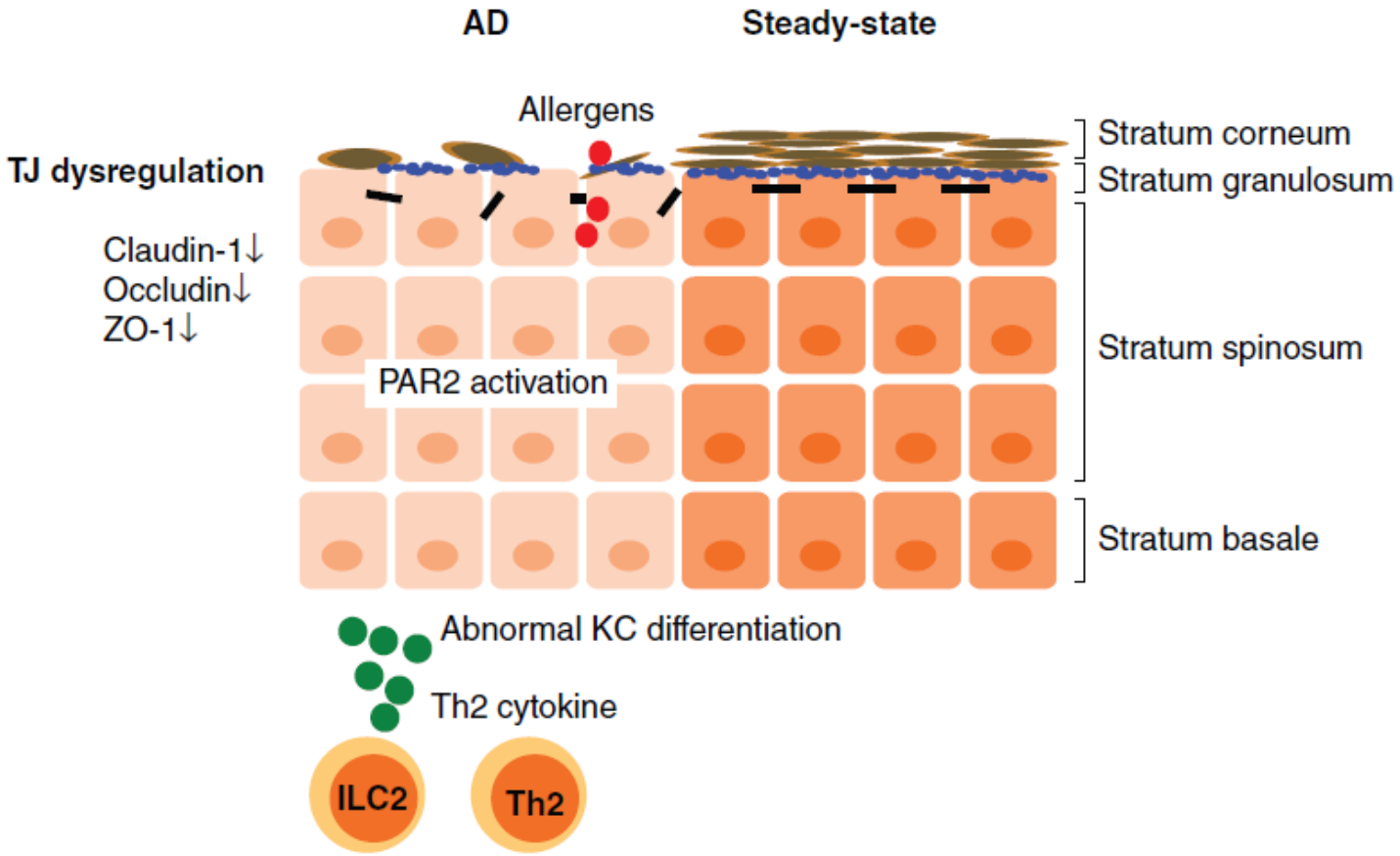


Fig 4 from Sugita K, Kabashima K. Tight junctions in the development of asthma, chronic rhinosinusitis, atopic dermatitis, eosinophilic esophagitis, and inflammatory bowel diseases. J Leukoc Biol. 2020 May;107(5):749-762. doi: 10.1002/JLB.5MR0120-230R. Epub 2020 Feb 28. PMID: 32108379.

Original Article

CED
Clinical and Experimental Dermatology

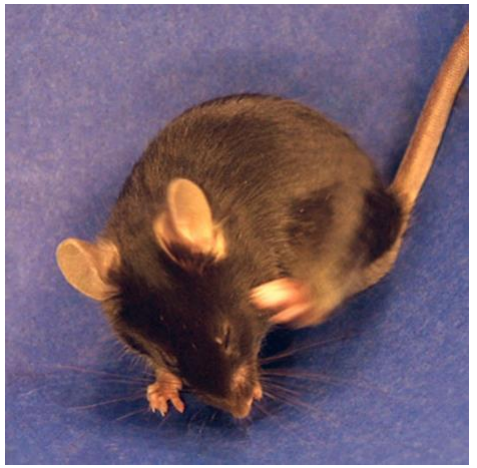
Scratching damages tight junctions through the Akt–claudin 1 axis in atopic dermatitis

X. Q. Hu,[1,2] Y. Tang,[1,2] Y. Ju,[1,2] X. Y. Zhang,[1,2] J. J. Yan,[1,2] C. M. Wang,[1] Y. Yang,[2] C. Zhu,[2] Z. X. Tang,[2] Y. Zhou[1,2] and G. Yu[1,2]

[1]*School of Medicine and Holistic Integrative Medicine, Nanjing University of Chinese Medicine, Nanjing, China; and* [2]*Key Laboratory for Chinese Medicine of Prevention and Treatment in Neurological Diseases, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China*

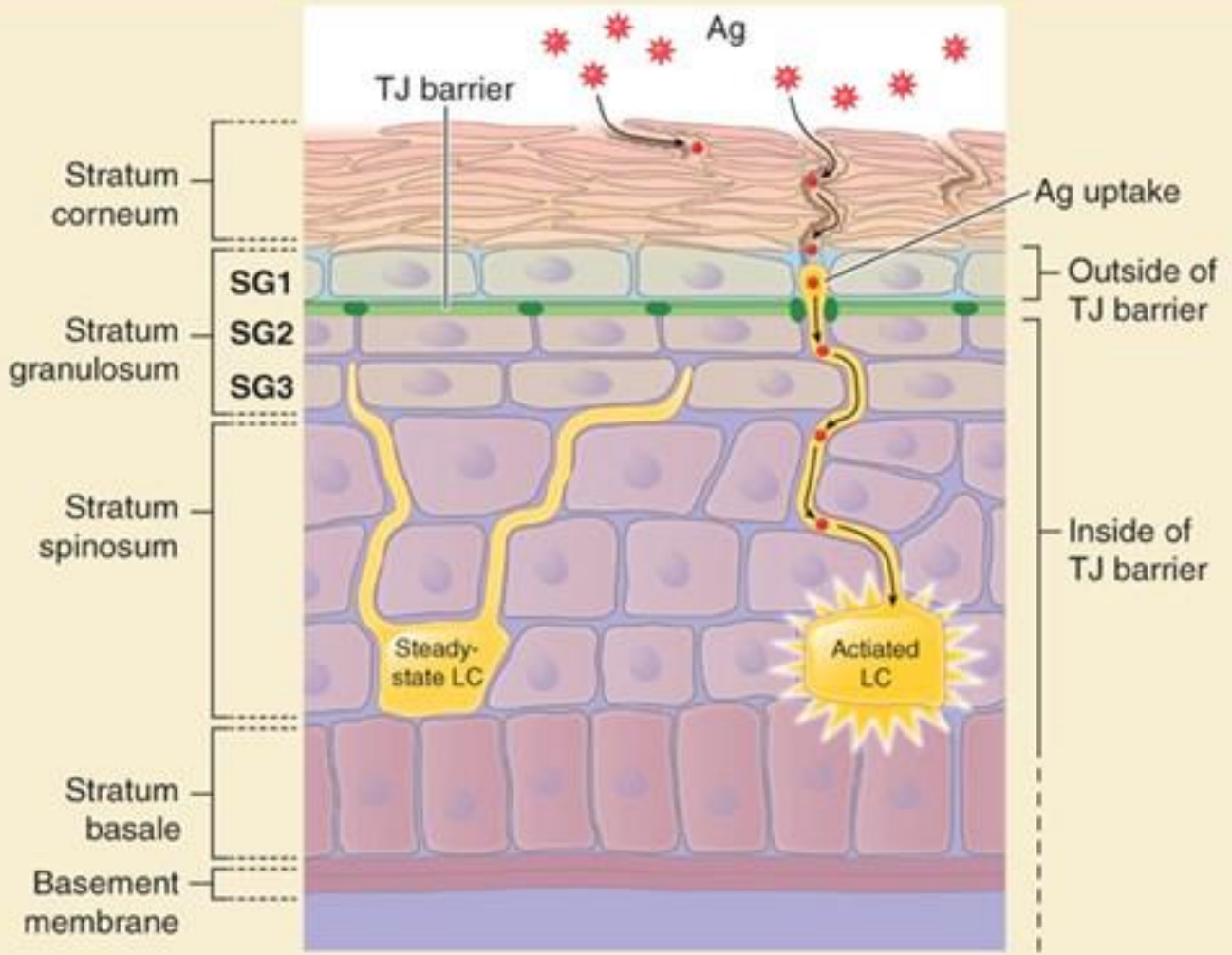
doi:10.1111/ced.14380

"Our results show that TJ damage is an important component of the itch–scratch cycle, and inhibition of Akt phosphorylation can rescue CLDN1 expression and decrease scratching behaviour."



Hu XQ, Tang Y, Ju Y, Zhang XY, Yan JJ, Wang CM, Yang Y, Zhu C, Tang ZX, Zhou Y, Yu G. Scratching damages tight junctions through the Akt-claudin 1 axis in atopic dermatitis. Clin Exp Dermatol. 2021 Jan;46(1):74-81. doi: 10.1111/ced.14380. Epub 2020 Sep 5. PMID: 32668051 and https://www.sciencenews.org/article/scratching-catching-mice

Spatial location of the stratum corneum, tight junctions, and Langerhans cells



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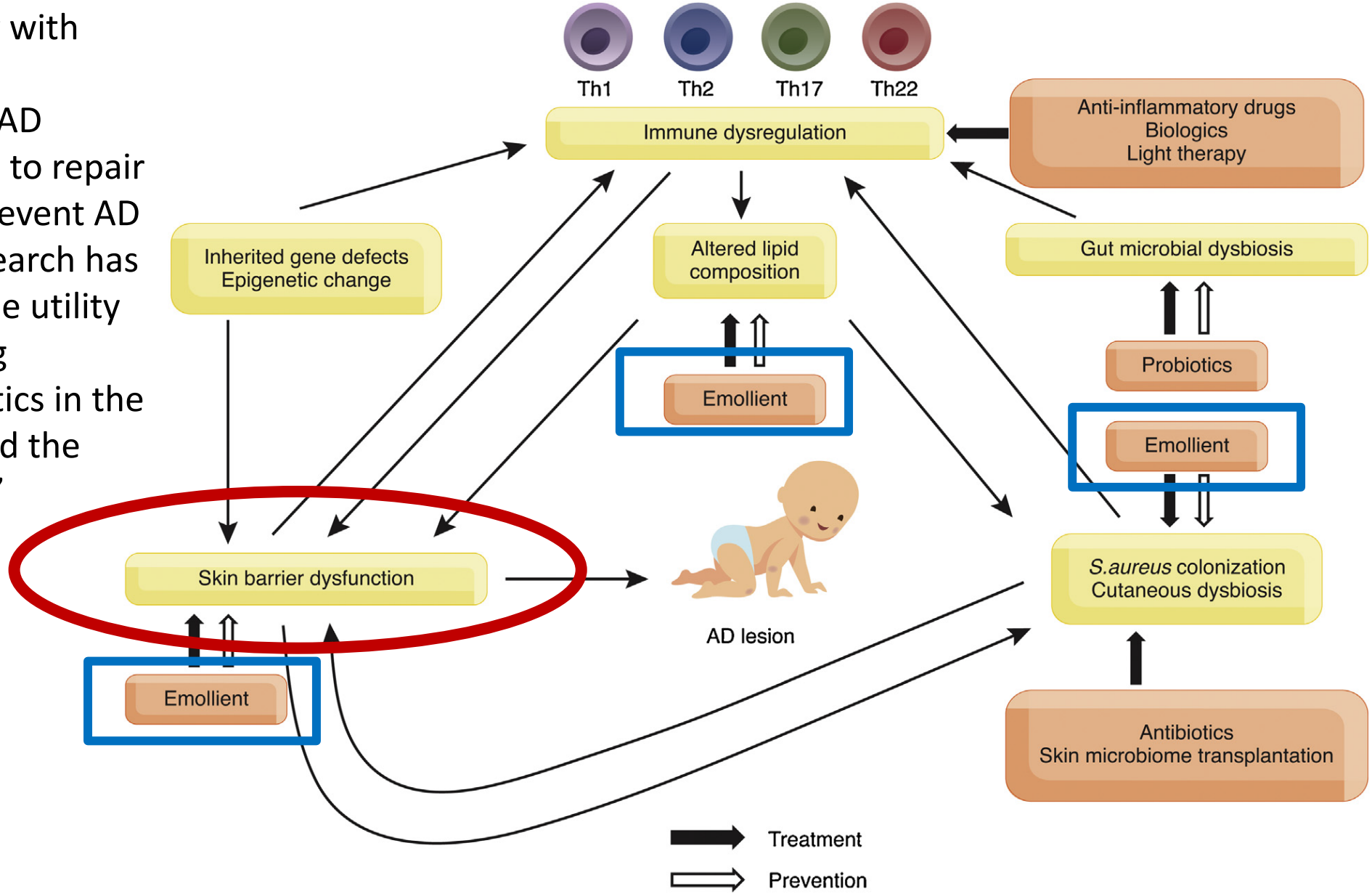
"Maintenance therapy with emollients is the main underlying strategy in AD treatment, and is used to repair the skin barrier and prevent AD relapse. … Recent research has highlighted the possible utility of ceramide containing emollients and probiotics in the management of AD and the prevention of relapse."



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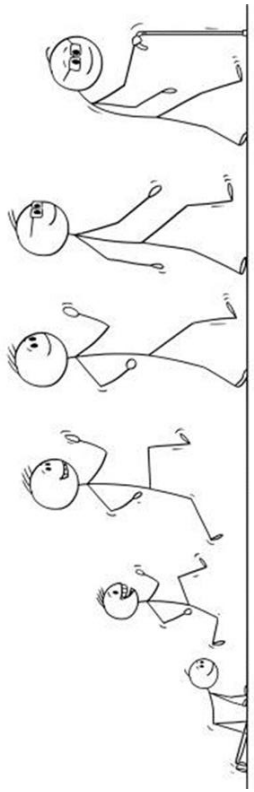

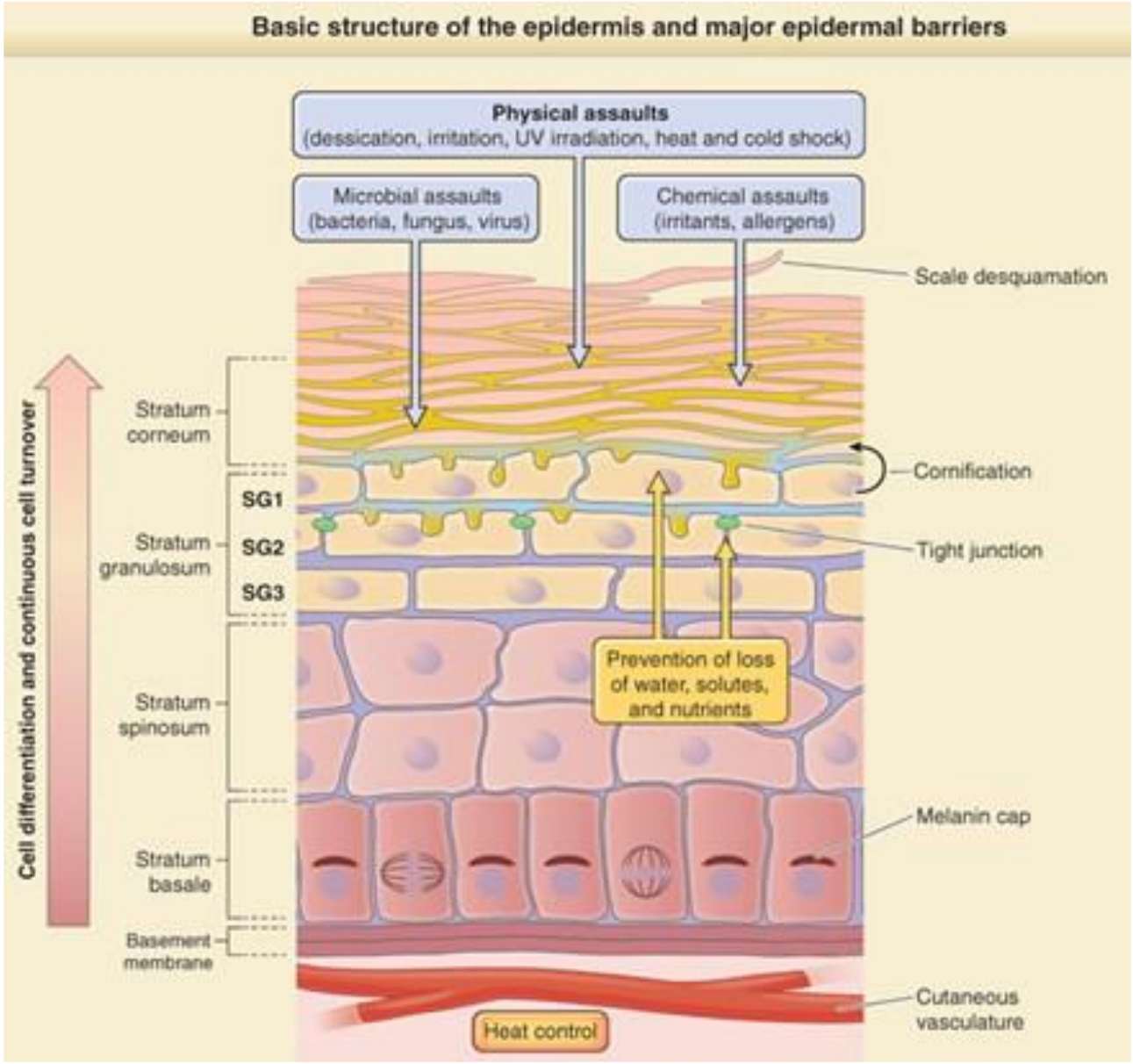

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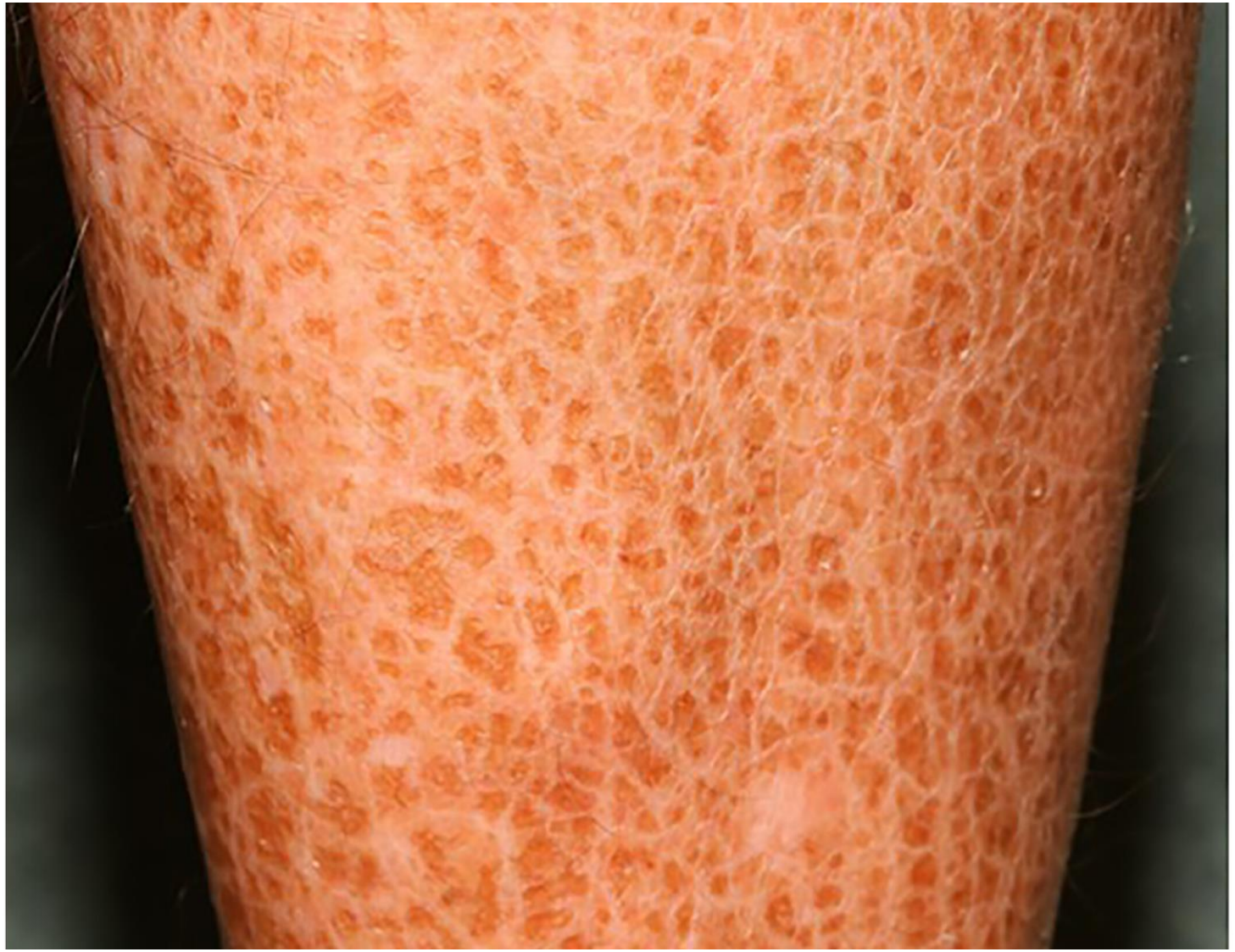
Ichthyosis and hereditary cornification disorders in dogs

Breed	Genetic variant	Impact on Cornification
American bulldog	NIPAL-4	CLE absent or attenuated. Gene encodes protein (ichthyin) involved in synthesis of very long chain fatty acids.
Golden retriever	PNPLA-1	CLE absent or attenuated. Gene encodes enzyme involved in synthesis of very long chain fatty acids.
Jack Russell terrier	TG1	CE markedly attenuated. Gene encodes enzyme transglutaminase 1 required for synthesis of CE.
Labrador retriever	SUV39H2	Hereditary nasal parakeratosis Decreased loricrin expression. Function of encoded enzyme unknown but likely involved in differentiation pathways.[2]
Norfolk terrier	KRT10	Absence of keratin 10. Mild epidermolytic hyperkeratosis.

Mauldin EA, Elias PM. Ichthyosis and hereditary cornification disorders in dogs. Vet Dermatol. 2021 Dec;32(6):567-e154. doi: 10.1111/vde.13033. PMID: 34796560.



Ichthyosis vulgaris

Humans

Loss of function mutations of filaggrin

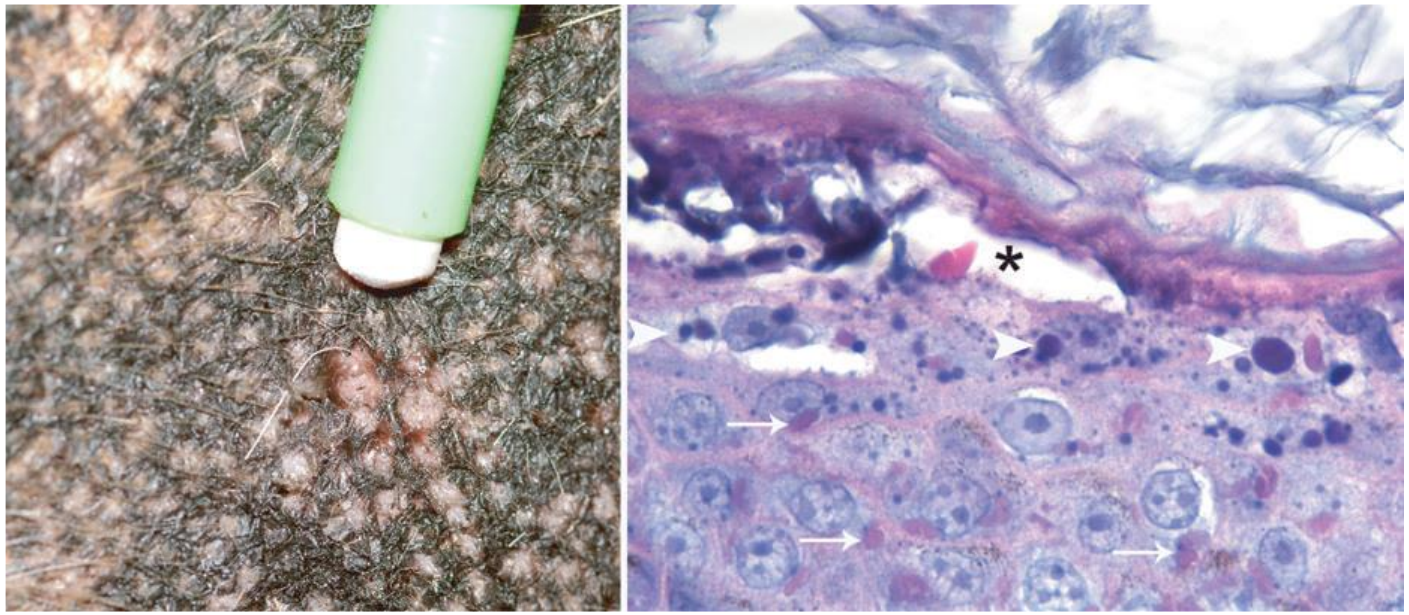
https://onlinelibrary.wiley.com/doi/full/10.1002/ski2.187

Norfolk terriers and K10

Mild form of epidermolytic ichthyosis

- Generalized, pigmented hyperkeratosis

Keratin 10 mutation



* vesicle in stratum granulosum

Arrowhead – coarse KHG

Arrows (pink) – keratin clumps

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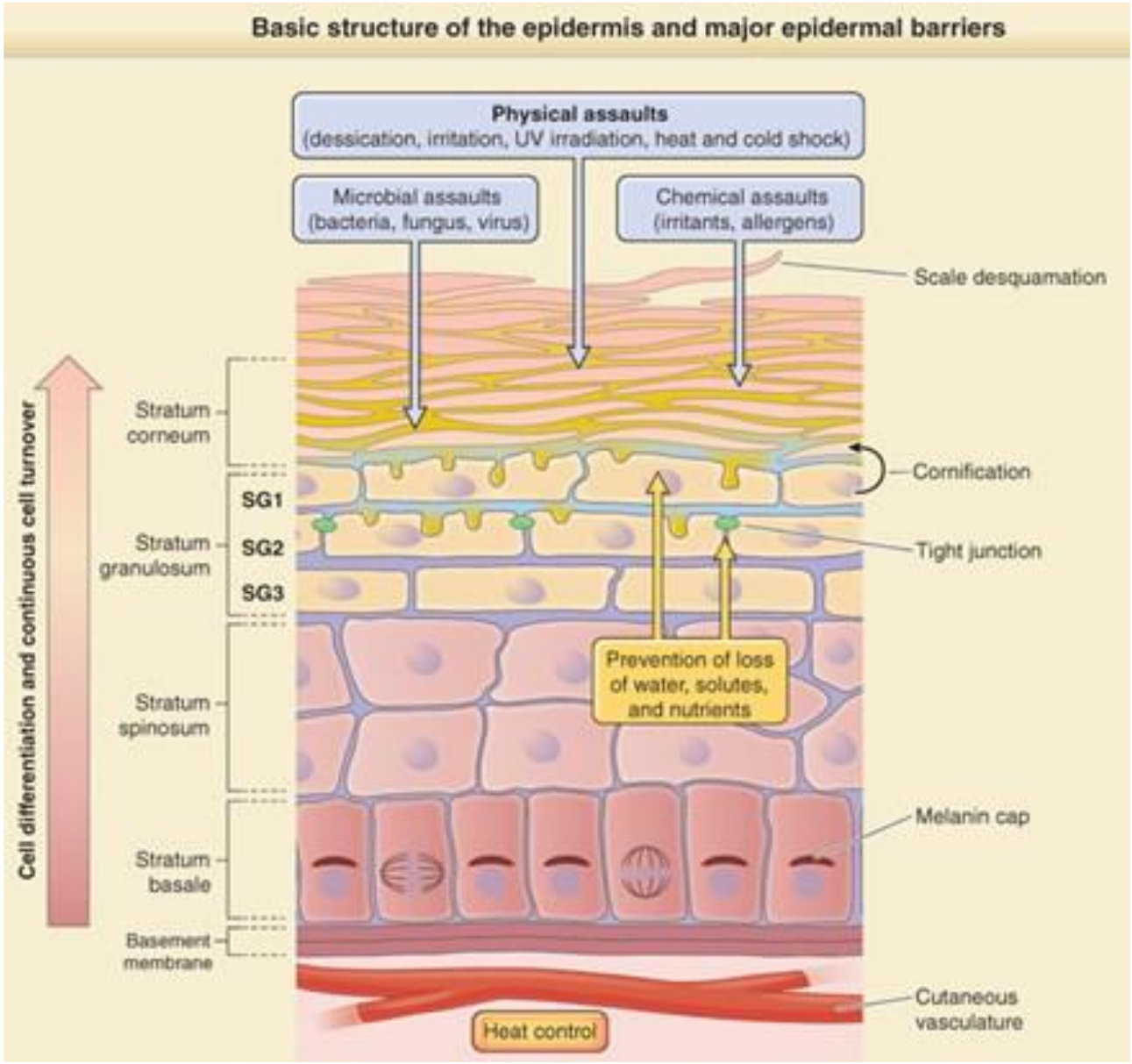
Norfolk terrier K10



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Cornified cell envelope (CE) construction

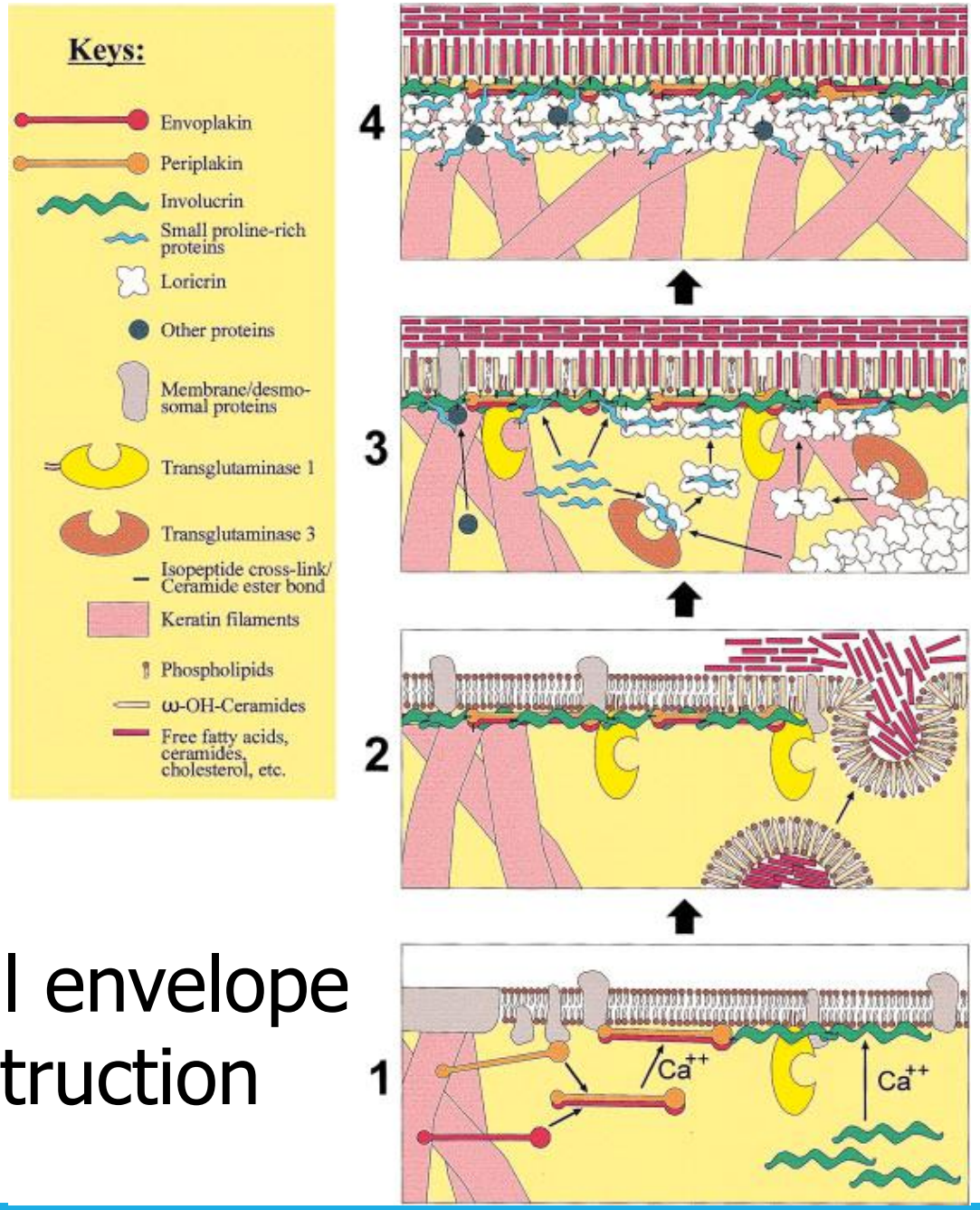


Figure 4 from Kalinin AE, Kajava AV, Steinert PM. Epithelial barrier function: assembly and structural features of the cornified cell envelope. *BioEssays* 2002; 24:796.

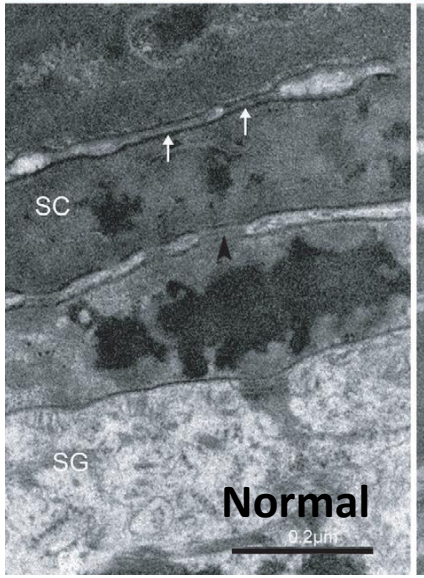
Jack Russell terriers and TG1

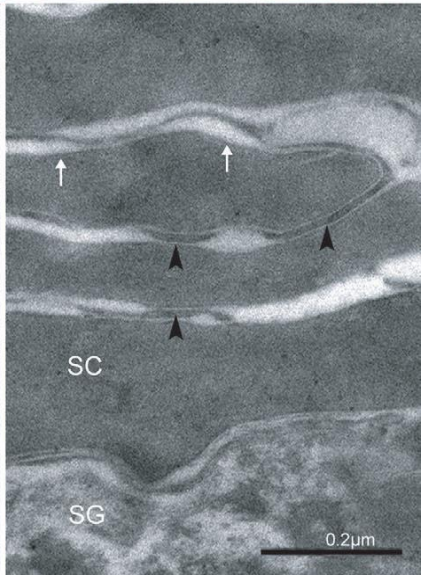
Lamellar ichthyosis phenotype

- Severe adherent “parchment paper”- like scale
- *Malassezia* overgrowth

TG1 deficiency

- Markedly attenuated/absent CE
- Leads to fragmentation of lipid lamellae





White arrows - CE

Black arrowheads - corneodesmosomes

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JRT TG1

Norfolk terrier K10

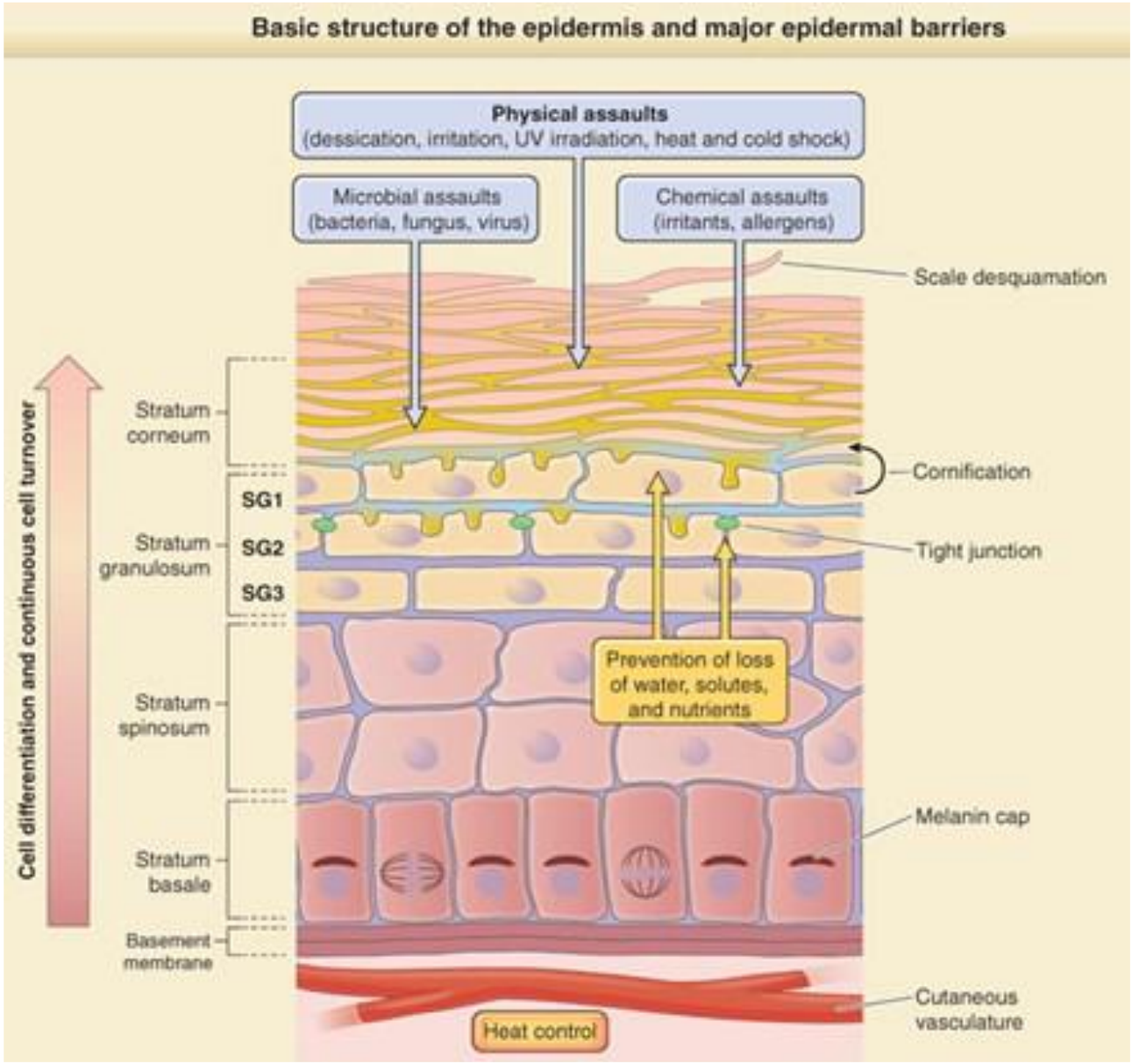


Figure 14-2 from Kubo A, Amagai M. Skin Barrier. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS. eds. Fitzpatrick's Dermatology, 9e. McGraw Hill; 2019.

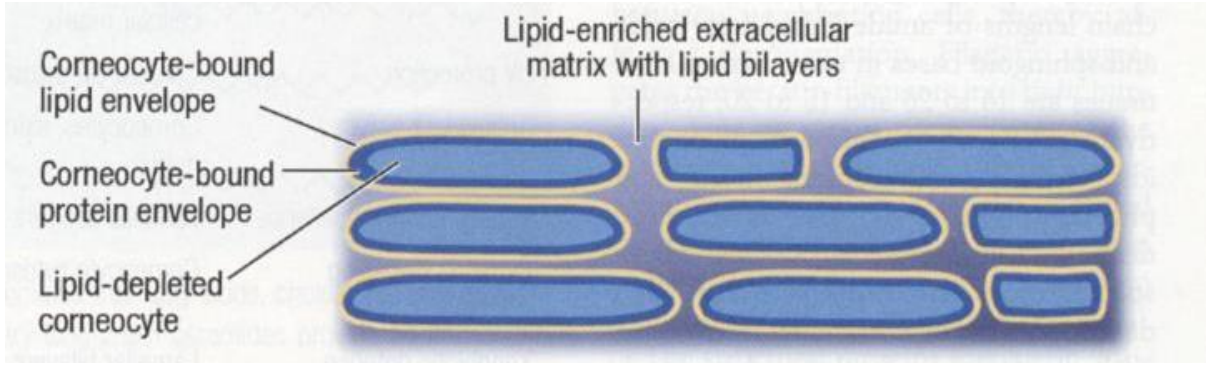
Extracellular lipid matrix

Corneocyte lipid envelope (CLE)

- ω-hydroxyceramides

Intercellular lipid lamellae

- Ceramides, free fatty acids, and cholesterol



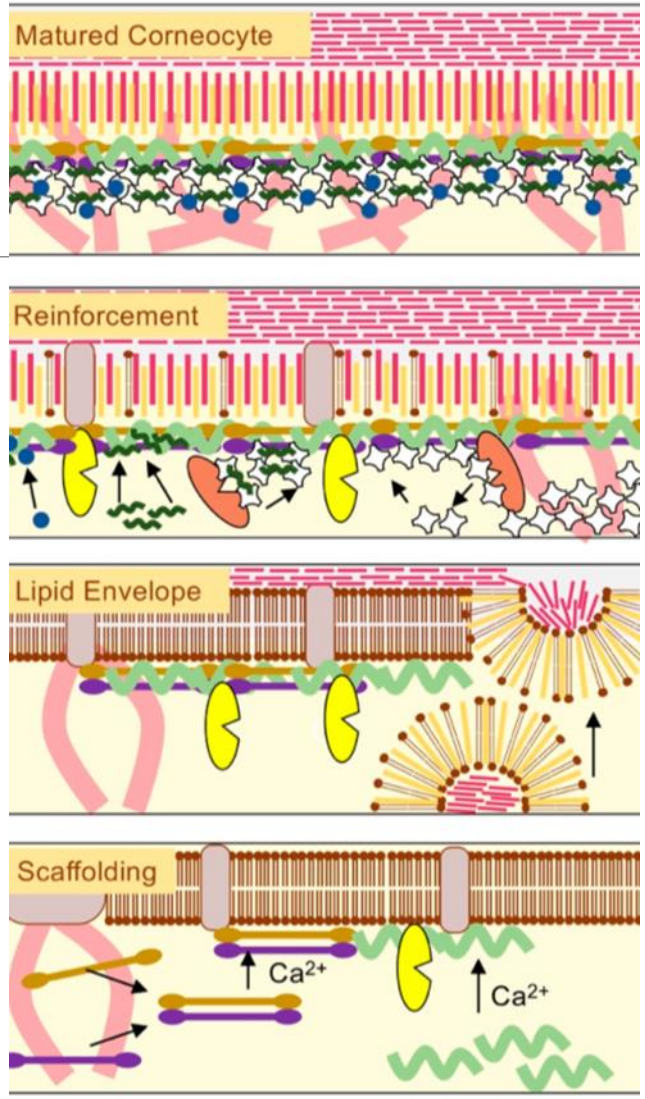


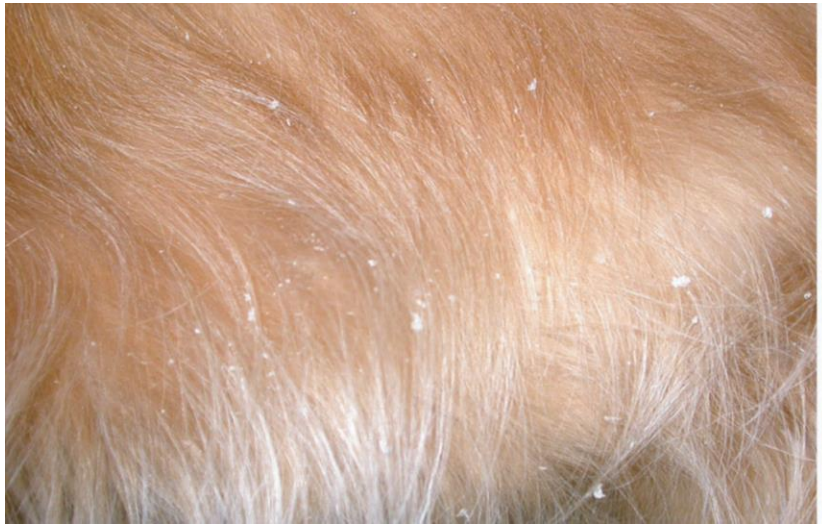
Figure 45-4 from Proksch E, Jensen JM. Skin as an organ of protection. In: Wolff K et al, editors, Fitzpatrick's Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill Companies, Inc. 2008. p. 385.

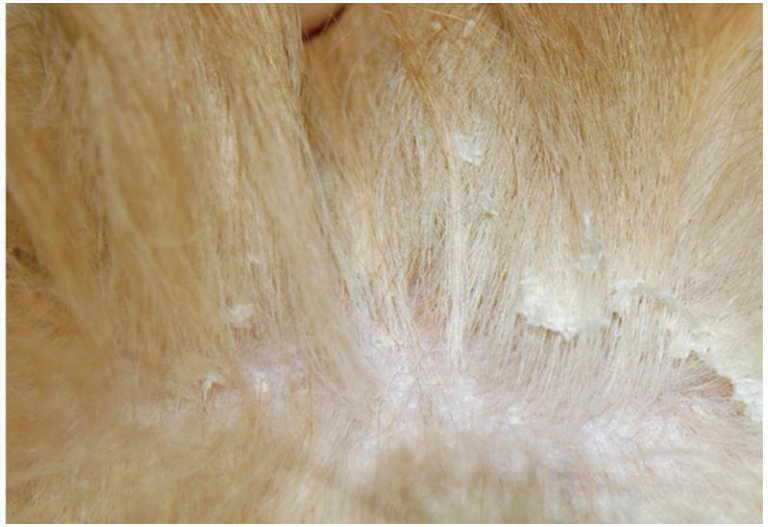
Golden retrievers and PNPLA-1

Generalized large white to grey scale, ventral hyperpigmentation

PNPLA-1 (patatin-like phospholipase domain-containing protein) mutation

- Acyltransferase which donates linoleic acid to ceramides
- CLE attenuated or absent





Mauldin EA, Elias PM. Ichthyosis and hereditary cornification disorders in dogs. Vet Dermatol. 2021 Dec;32(6):567-e154. doi: 10.1111/vde.13033. PMID: 34796560.

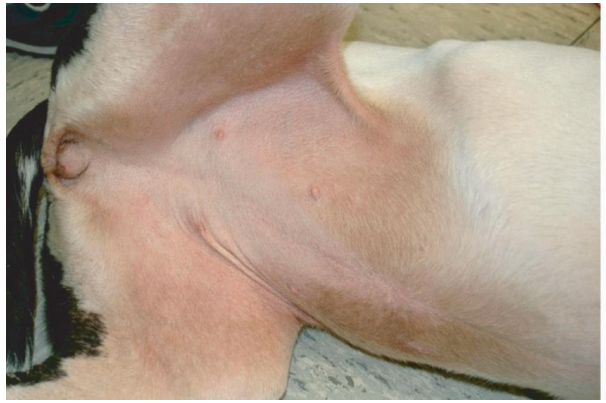
American bulldogs and NIPAL-4

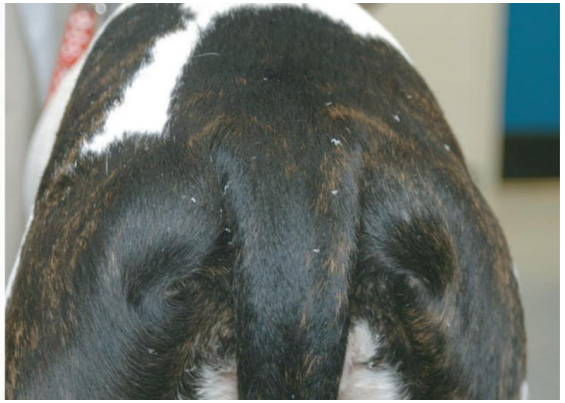
Generalized white scale, ventral adherent scale and erythema

- *Malassezia* overgrowth with pruritus

NIPAL-4 (Nipa-like Domain-Containing 4) mutation

- Encodes cofactor (ichthyin) for enzyme that synthesizes long chain fatty acids
- Markedly attenuated or absent CLE
- Toxic metabolite accumulation in stratum granulosum

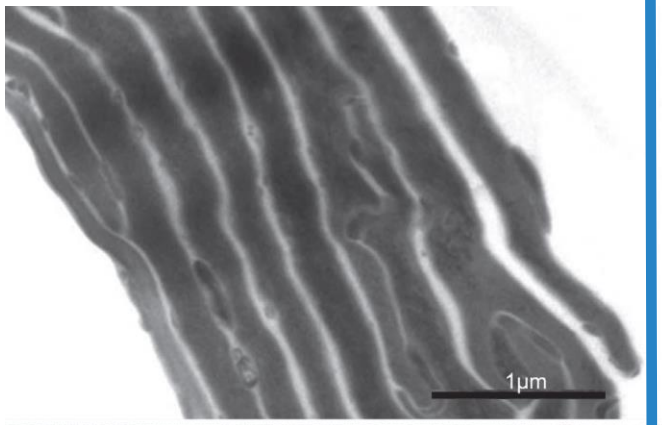


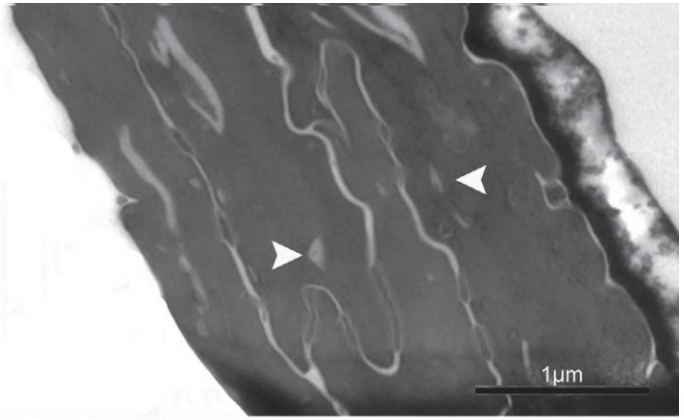


Mauldin EA, Elias PM. Ichthyosis and hereditary cornification disorders in dogs. Vet Dermatol. 2021 Dec;32(6):567-e154. doi: 10.1111/vde.13033. PMID: 34796560.

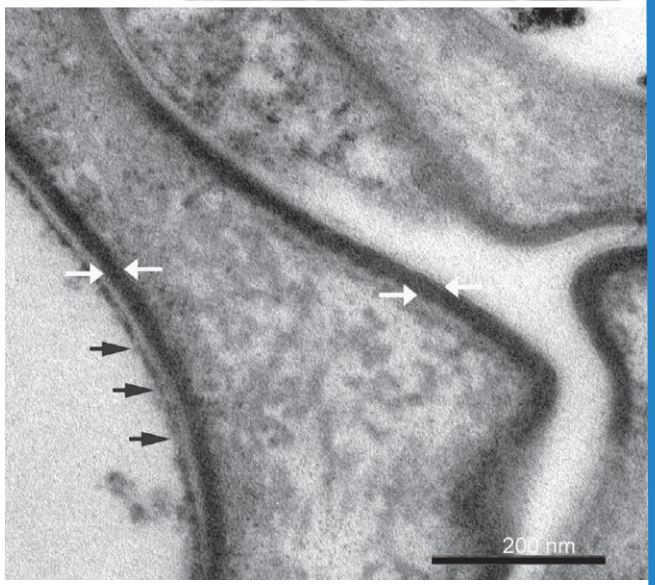
Normal American bulldog

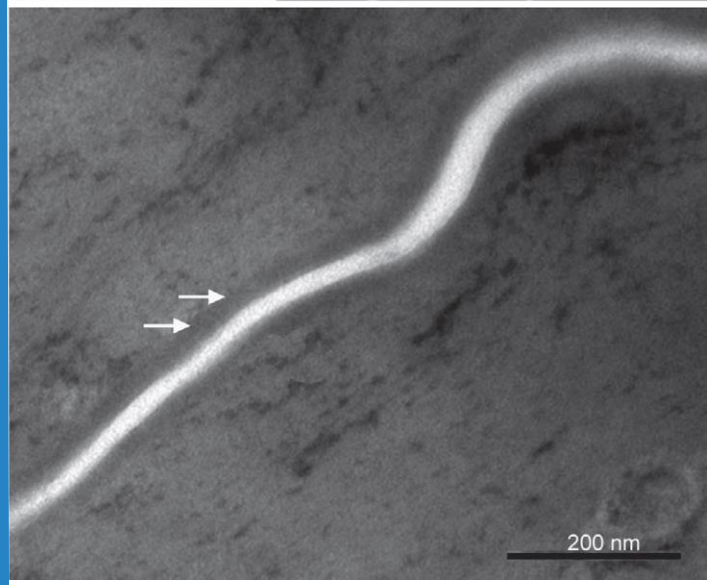
American bulldog with NIPAL-4 deficient ichthyosis





White arrowheads – lamellar body contents inside corneocytes





White arrows – CE

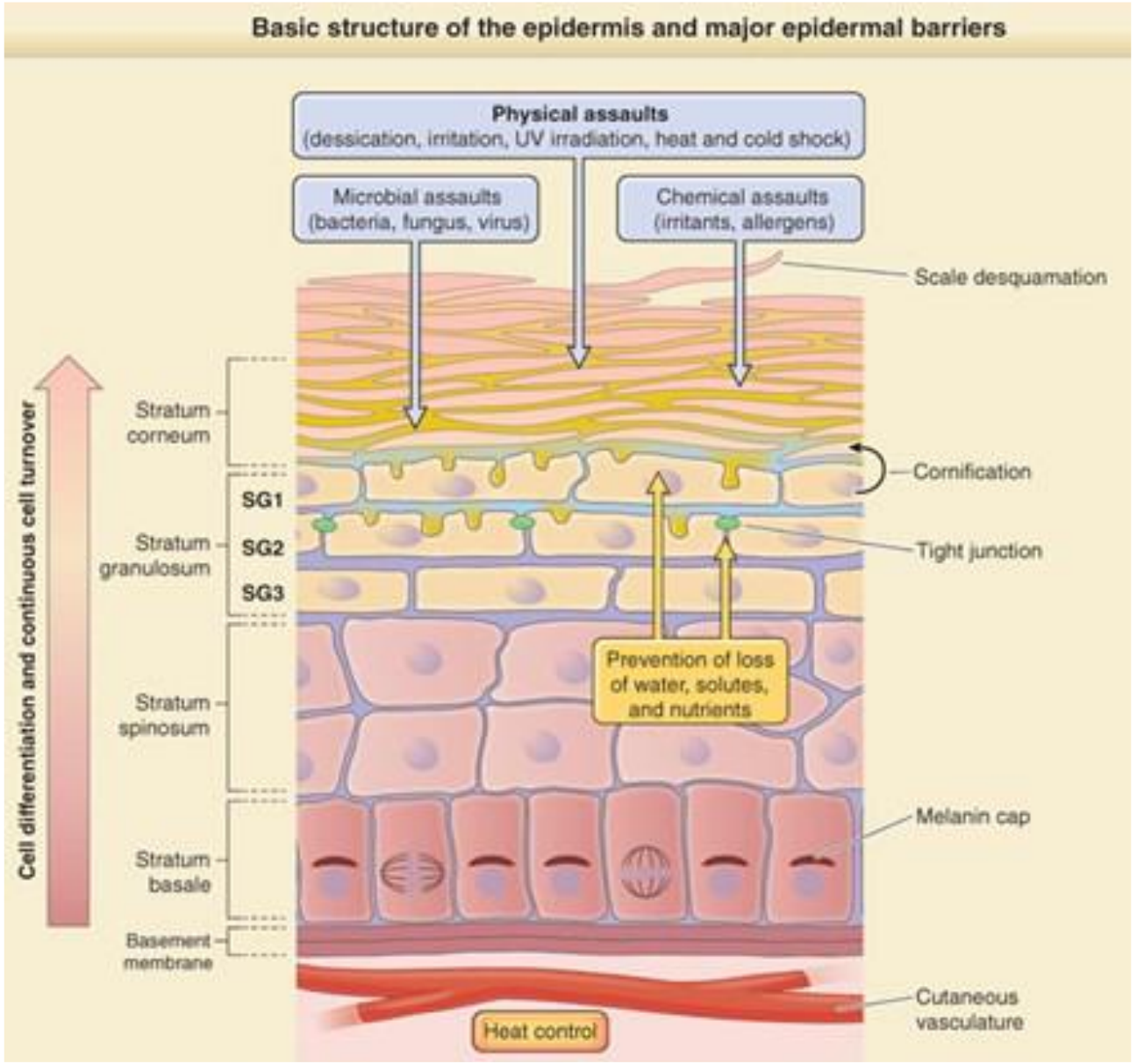
Black arrows – CLE

Mauldin EA, Elias PM. Ichthyosis and hereditary cornification disorders in dogs. Vet Dermatol. 2021 Dec;32(6):567-e154. doi: 10.1111/vde.13033. PMID: 34796560.

corneocyte

Norfolk terrier K10

JRT TG1



CLE

Golden retriever PNPLA-1
American bulldog NIPAL-4

Figure 14-2 from Kubo A, Amagai M. Skin Barrier. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS. eds. Fitzpatrick's Dermatology, 9e. McGraw Hill; 2019.

Diagnosing cornification disorders

Primary

- Genetic mutation – ichthyosis

Secondary

- Any other cause of scale or hyperkeratosis

Keratinocytes proliferate in response to threats

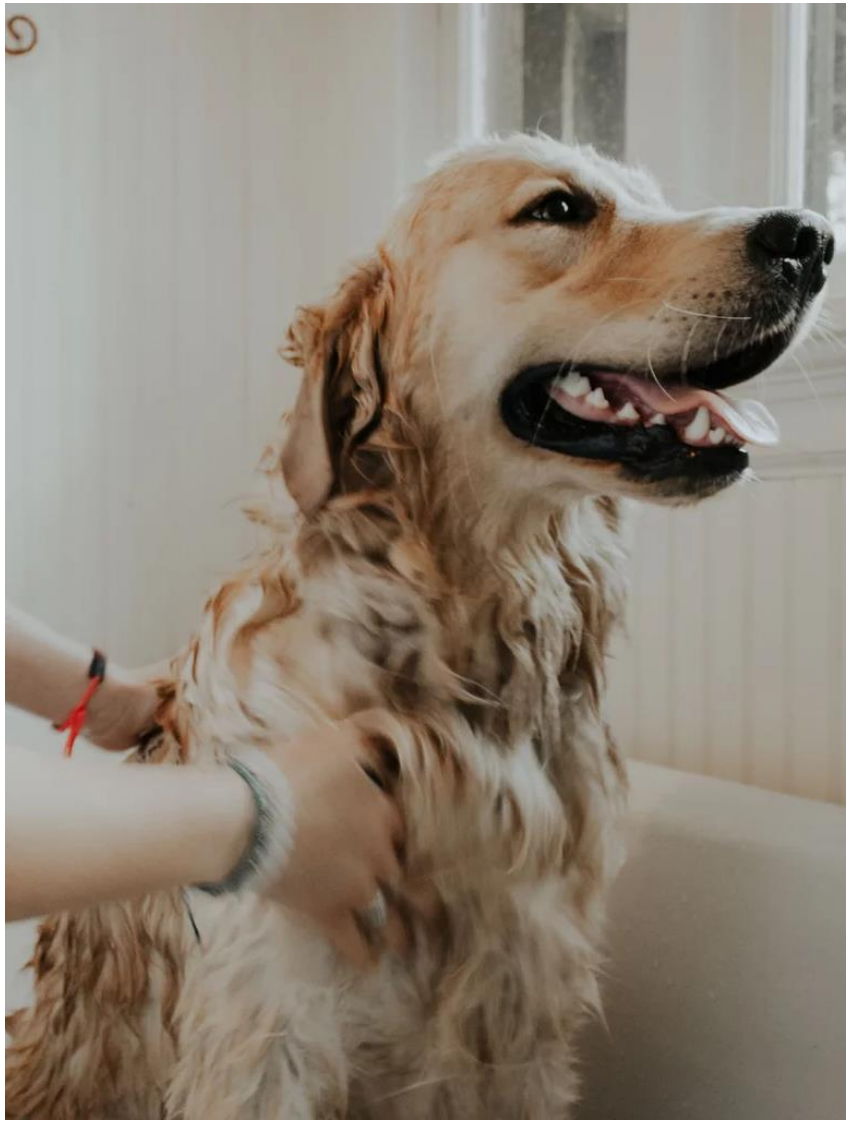
Diagnosis of ichthyosis

Signalment
- Young patient
- Breed predilections

Clinical signs
- Scale, hyperkeratosis
- Non-pruritic (unless secondary infections)

Rule out secondary disorders of cornification
- Skin scrapes, cytology, histopathology

Breeders
- DNA testing



Treatment of ichthyosis

Topical “soak and slather” regimens

- Management of barrier defects
- Lifelong treatments

Pathogenesis-based treatment

CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb deficits) syndrome

- Humans
- Mutations affect cholesterol synthesis pathway
  - Deficiency of cholesterol in intercellular lipid lamellae
  - Accumulation of toxic precursors
- Cutaneous lesions successfully managed with pathogenesis-based treatments
  - Topical cholesterol applied to stratum corneum
  - Cholesterol lowering drugs (statins) to decrease toxic metabolites

Thank you!

ANY QUESTIONS?