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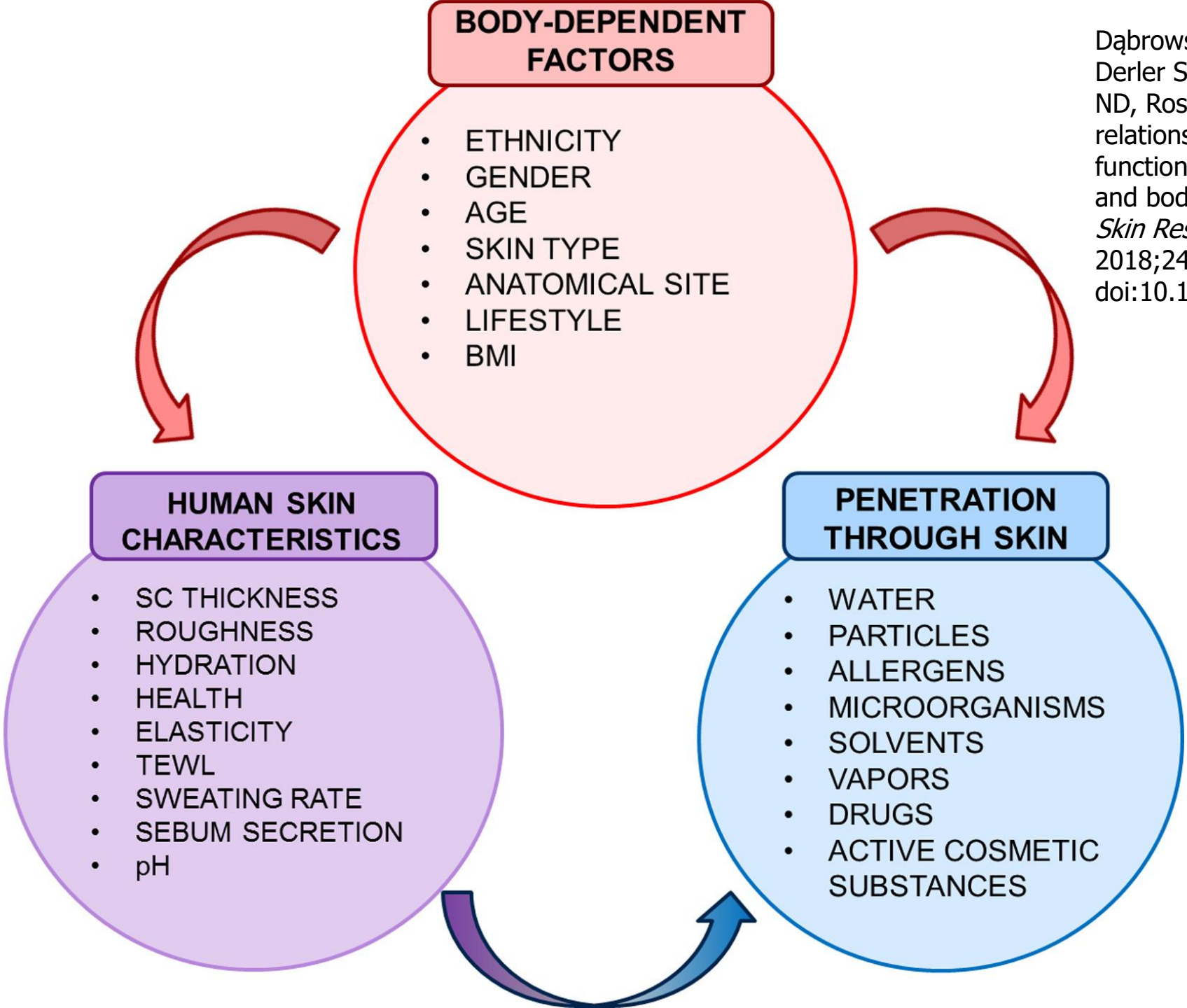
Skin barrier.
Skin barrier disorders

May 2020



Dąbrowska AK, Spano F, Derler S, Adlhart C, Spencer ND, Rossi RM. The relationship between skin function, barrier properties, and body-dependent factors. *Skin Res Technol*. 2018;24(2):165-174. doi:10.1111/srt.12424

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Body-dependent factors influencing human skin. Ethnicity

- Skin tone varies among ethnic groups due to different levels of the four chromophores responsible for skin color: hemoglobin and oxyhemoglobin (pinkish tones), melanin (brownish shades), and carotenoids, responsible for yellow-orange tones.
- Ethnicity also influences the natural hydration level of the skin as well as the decrease in hydration level with age. It has been reported that Caucasians and African-Americans have slightly drier skin, compared to Chinese, due to the lower levels of SC natural moisturizing factors.

Ethnicity

- Caucasians exhibit higher dryness with age than Chinese, which may be caused by different eating habits and avoidance of sun exposure among Chinese. It has been shown that darker skin is more resistant to photo aging processes. Also, the thickness of the SC was found to be greater for darker skin. Some studies have also indicated differences in the number of layers within comparable SC thickness, suggesting that African-Americans have more cell layers within the SC than do Caucasians (16 and 9 layers, respectively), the skin thus being more resistant to chemicals and damage. Most studies demonstrated higher transepidermal water loss (TEWL) for African-Americans than for Caucasians as well as larger gland pore sizes and a higher level of sebum secretion.

Age

- Overall, the hydration level of the skin decreases significantly with age, mainly because of the decrease in the amount of natural moisturizers present in the skin.
- The influence of the skin-aging processes on skin hydration can vary between different ethnic groups, being the most significant for Caucasians.
- The elasticity of the skin is also known to decrease, predominantly due to the decreasing collagen production in the dermis and reduction in the resilience of existing collagen and elastin fibers.
- The thickness of skin initially increases with age, showing a maximum value for women at around 30-40 years of age and for men at around 40-50 years, and then significantly decreases with age.
- The amount of sebum secretion has been reported to be either independent or slightly decreasing with age. The sweating rate slightly decreases with age.
- Skin pH has been found to be higher for older subjects, due to an age-related decrease in the amount of acidic natural moisturizing factors present in the skin.
- Skin roughness, the dimensions of the primary lines and anisotropy were all found to increase with age.

Gender

Some researchers found that TEWL is higher for men, explaining this by the fact that they spend more time outdoors and their skin is more damaged and therefore more prone to transepidermal water loss.
Sebum secretion is considered to be either independent of gender or slightly higher in males due to a higher testosterone level.
The sweating rate was found to be 30%-40% higher in males than in females (taking the difference in body surface area into consideration). Results show no clear relationship between gender and SC thickness, but it was also found that the cellular *epidermis* is slightly thicker in males than in females.
Measurements have shown no clear and statistically significant difference between the elastic properties and pH of the skin in females and males for the same anatomical sites.

Skin type

- Skin type, its pigmentation, hydration, roughness, and many other parameters are very individual. Significant variations can be observed between people from the same ethnic groups, living in the same environment and sharing the same lifestyle, but having different complexions.

Anatomical sites

- Skin differs not only between different people but also between anatomical sites for the same person.
- The SC thickness varies significantly with the investigated anatomical site. It was found that the thickest SC layer is to be found in heels, having 86 ± 36 cell layers, whereas the smallest number of cell layers (6 ± 2) has been observed for genital skin. The thickness of the *epidermis* depends on the body site in a similar way. The SC thickness is related to many other phenomena, such as surface morphology, hydration level, and permeability to various substances. Since the SC acts as a barrier layer, penetration through the skin is higher on body sites with thinner SC. The roughness (Ra) of the index finger lies within the range of 19-33 μm, whereas it is lower (12-20 μm) for the volar forearm. Also, sebum secretion varies between different anatomical regions, not only as far as the amount is concerned, but also the chemical composition.

Anatomical sites

- Due to many reasons, such as exposure to harsh environmental conditions or the frequency of washing with detergents, certain body parts, eg, hands, are more prone to having a lower hydration level of the superficial *stratum corneum* (SSC). The highest density of sweat glands can be found on the soles of the feet (620 ± 20 sweat glands per cm^2), whereas the lowest density of sweat glands is found on the upper lips (16 sweat glands per cm^2). In general, the SC thickness is directly related to the TEWL and anatomical sites characterized by the thickest SC display the lowest TEWL values. However, TEWL levels are also dependent on other factors, such as SC lipid content, blood flow, or skin temperature. This explains the fact, that the TEWL of the palm (characterized by a thick SC layer but a low level of barrier lipids) is higher than that of the leg.
- The elastic properties of skin depend on the collagen structure in the *dermis*, the local thickness of the skin and other parameters that depend on the anatomical site. For example, facial skin was found to be less elastic than the skin on the arm and on the back. As the properties of human skin are rarely independent of each other but work as a system, a variation in one property is generally coupled with a variation in others. For example, the frictional behavior of human skin varies with body site because it depends on SC roughness, elastic properties, thickness, hydration level, sweating rate as well as on the presence of hair and sebum.

Lifestyle and body-mass index

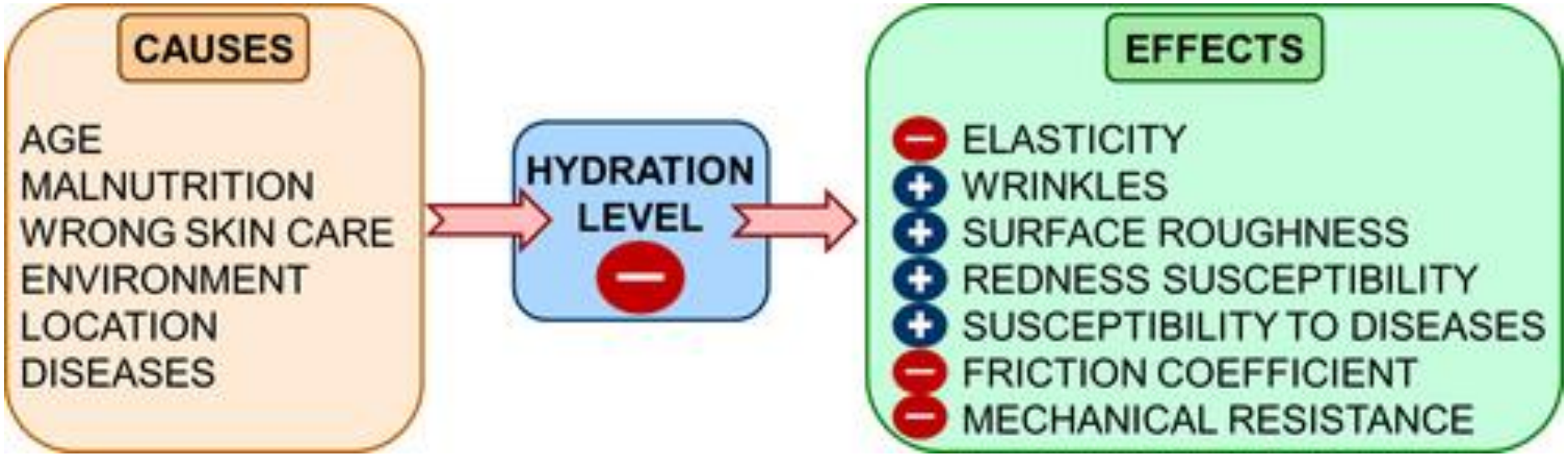
- Lifestyle is considered to be one of the factors influencing the extrinsic aging process, which is related to visible aging caused by the exposure to external factors.
- Proper sun protection prevents accelerated skin aging and the risk of skin cancer and other skin damage.
- A healthy diet, containing significant amount of fruits and vegetables, as well as a calm, low-stress lifestyle, leads to a higher concentration of carotenoids and may result in a slower rate of skin aging. Higher daily vitamin C intake has been connected to a decreased formation of wrinkles, while a higher linoleic acid dose has been associated with a lower level of dryness.
- Smoking is associated with an altered skin condition (wrinkling, larger pores, rougher skin surface, and presence of discoloration). It also significantly increases the risk of skin diseases, as it decreases the self-healing abilities of the skin.

Lifestyle and body-mass index

- Skin properties are also dependent on the body-mass index (BMI).
- TEWL is usually higher for obese people.
- Obesity is also correlated to elevated sweat gland activity and higher skin blood flow.
- Obesity can also increase the risk of various skin disorders and impaired wound healing. For example, 74% of examined obese people have been found to suffer from *acanthosis nigricans*, also related to insulin resistance. In another study, 40% of obese children were diagnosed with striae disease.

Skin hydration

- As skin hydration is a very important parameter responsible for skin homeostasis, all deviations from a normal hydration level can result in significant changes in human skin properties and functions. Among the main causes of dry skin, one can list skin aging, the wrong or no skin care or malnutrition.
- Skin hydration can also be influenced by environmental factors or by anatomical location (eg, skin on the palms and legs is drier than on the forehead).
- Skin dryness can also be a consequence of various diseases, not only directly related to the skin, such as atopic dermatitis, but also other health problems, eg, hypothyroidism. A lower hydration level results in a lower elasticity of the skin, faster skin aging and wrinkle creation, higher surface roughness, and lower mechanical resistance.
- Dry skin is also more susceptible to skin diseases and more prone to redness and itchiness. The frictional behavior of human skin also depends on hydration. It was reported that moist skin shows higher friction-coefficient values than dry or completely wet skin. Drier skin is more prone to mechanical failure, flakiness, irritation, and other problems. Irritated skin leads to difficulties in achieving and maintaining an adequate hydration level. This results in drier skin and may lead to more severe skin conditions, if untreated.



Cause and effect chain for the example of the decrease in skin hydration level. "+" and "-" symbolize positive and negative correlation

Dąbrowska AK, Spano F, Derler S, Adlhart C, Spencer ND, Rossi RM. The relationship between skin function, barrier properties, and body-dependent factors. *Skin Res Technol*. 2018;24(2):165-174. doi:10.1111/srt.12424

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Penetration through skin

- Our skin is constantly in contact with various substances that are either present in the environment or deliberately applied to the surface of the skin. Numerous substances have been applied to the skin surface for medical or religious reasons since the beginning of humanity, which provides a hint that the absorption properties of the skin were already known a long time ago. Depending on the circumstances, the barrier properties of human skin, given mainly by its horny layer (SC), may be perceived as being either an advantage or an obstacle. In everyday life, the skin can be exposed to various substances in the solid, liquid, or gaseous states. Some of them, such as harmful chemicals, allergens, pathogens etc. can be dangerous and lead to irritation, rashes, burns, or other health problems following the topical application or penetration of these substances into deeper layers of the skin.

Penetration through skin

- The *epidermis* and *dermis* are the skin layers involved in the penetration processes, but the SC composition and properties are mainly responsible for the barrier function of human skin. Skin protects the body from penetrating substances through various mechanisms, either mechanically blocking particles from further migration into the skin or neutralizing, attacking, or degrading them. Substances that penetrate through the SC barrier layer still have to overcome many other obstacles, such as the antimicrobial barrier and immunological or enzymatic systems.There are three different pathways that can be used by substances penetrating the skin mentioned in the literature: **intercellular**, **transcellular,** and **transappendageal**.

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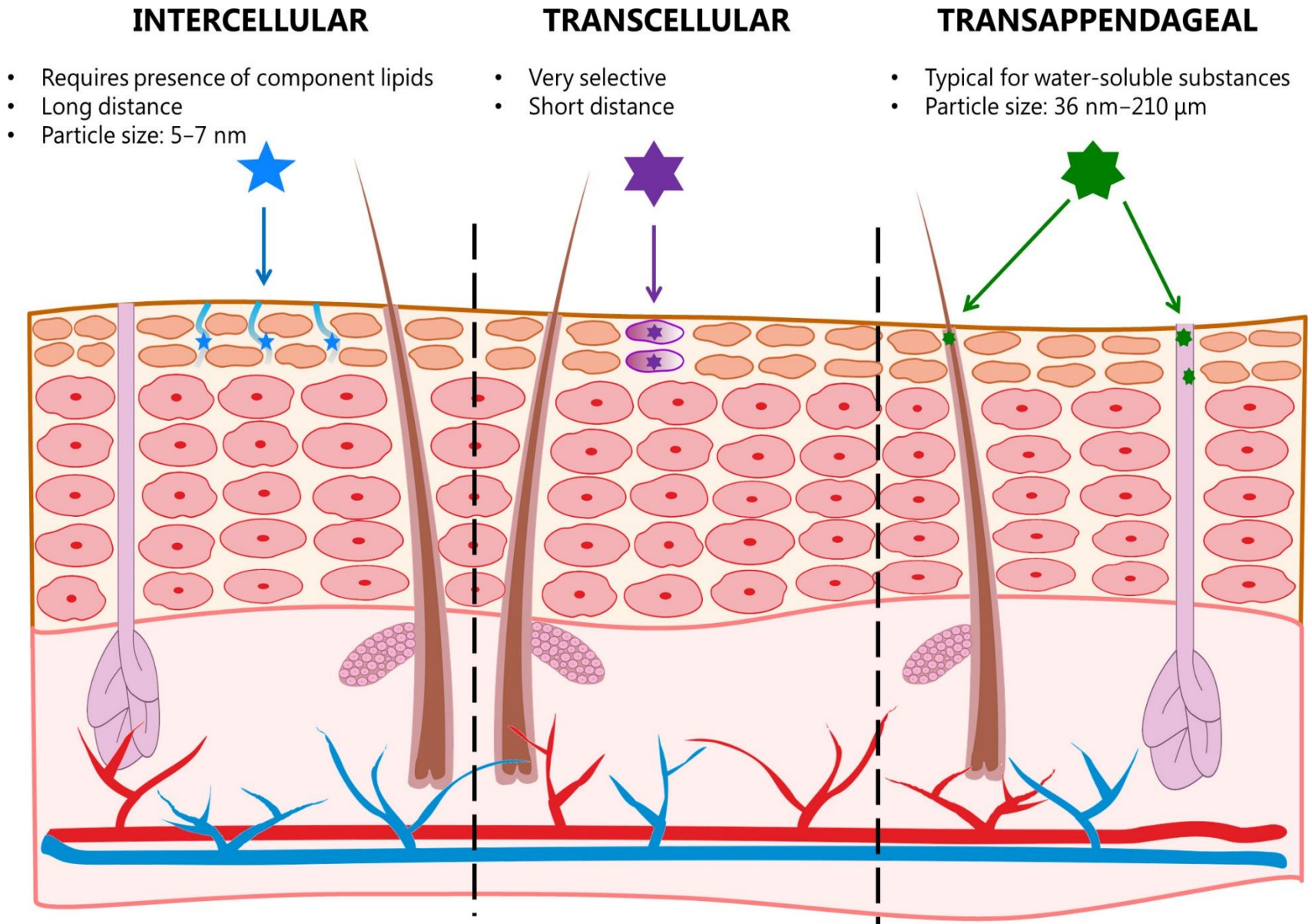

Three penetration pathways for the skin: intercellular, transcellular, and transappendageal

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The intercellular pathway

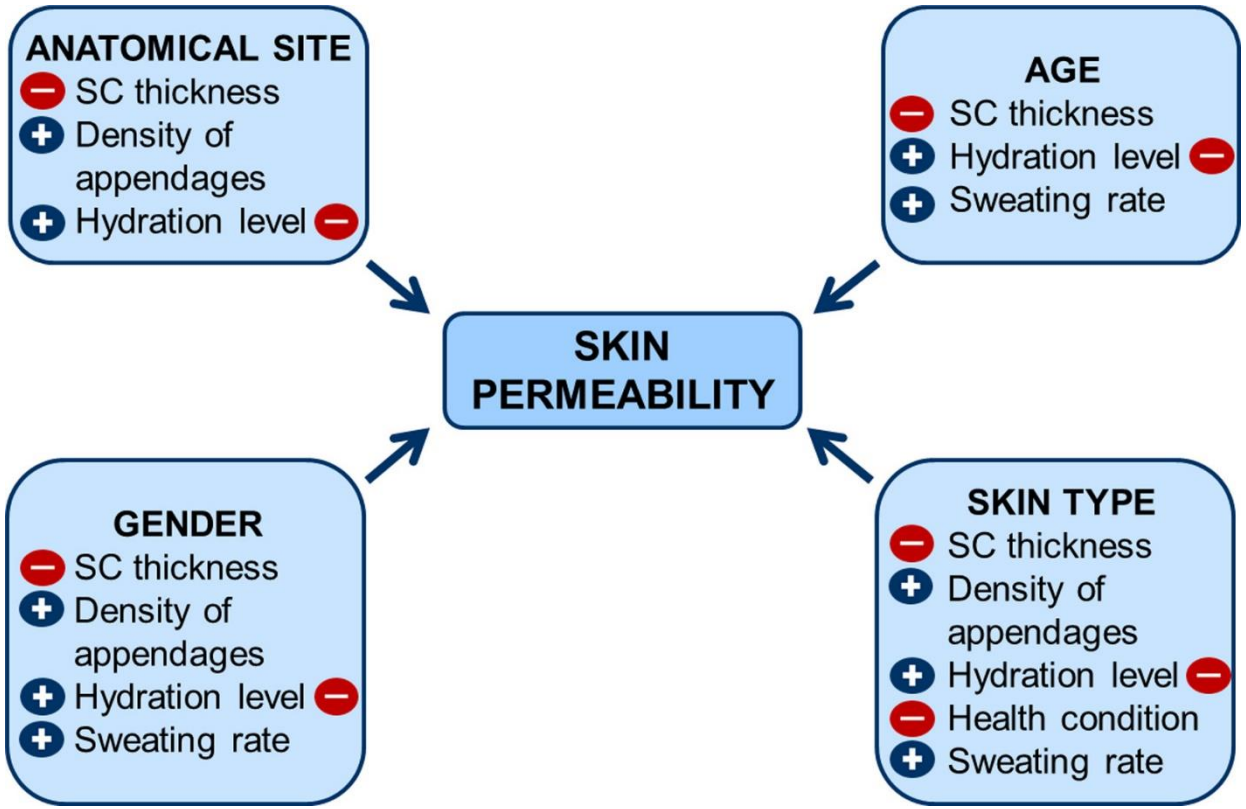
- involves the transport of substances between the cells of the SC layer. This mechanism plays a major role in skin permeability and requires the presence of component lipids, such as ceramides, that allow free lateral water diffusion by forming nanometric spaces via short range repulsive forces.
- The diffusion rate depends on the properties of penetrating particles, such as volume, weight, solubility, lipophilicity, or hydrogen-bonding ability. It is assumed that particles with a size of 5-7 nm can be efficiently transported through the intercellular pathway. Although the SC is a thin layer, reaching a thickness of some 20 μm for the volar forearm, the intercellular pathway is much longer and reaches 400 μm, which reduces penetration rate significantly.

The transcellular pathway

- involves keratinocytes in the transport of substances. Despite the seemingly short distances involved, this pathway is very selective. Penetrating particles have to overcome various barriers that are repeated many times in the skin structure; lipophilic cell membranes, hydrophilic cellular contents with keratin, and phospholipidic cell barriers.

The transappendageal pathway

- involves appendages, such as sweat and sebaceous glands and hair follicles and is a typical route for the penetration of water-soluble substances.
- The size of particles penetrating the skin through aqueous pores can be around 36 nm, whereas trans-follicularly penetrating particles may potentially have a diameter of up to 210 μm (this being the maximum size of the follicular openings). However, other researchers have argued that only particles with sizes up to 40 nm or even as small as 20 nm can effectively penetrate through follicles into deeper skin layers, whereas bigger particles will only be transported deep into the hair follicle.
- The transappendageal pathway used to be considered as the least significant penetration passage, as the appendages cover only 0.1% of the skin surface. On the other hand, it is the only penetration pathway for particles larger than few nm. In addition, appendages may play a role as reservoirs for topically applied substances and therefore could potentially be an efficient penetration path.



Body-dependent factors influencing skin permeability. "+" and "-" symbolize positive and negative correlation between single factors and skin permeability

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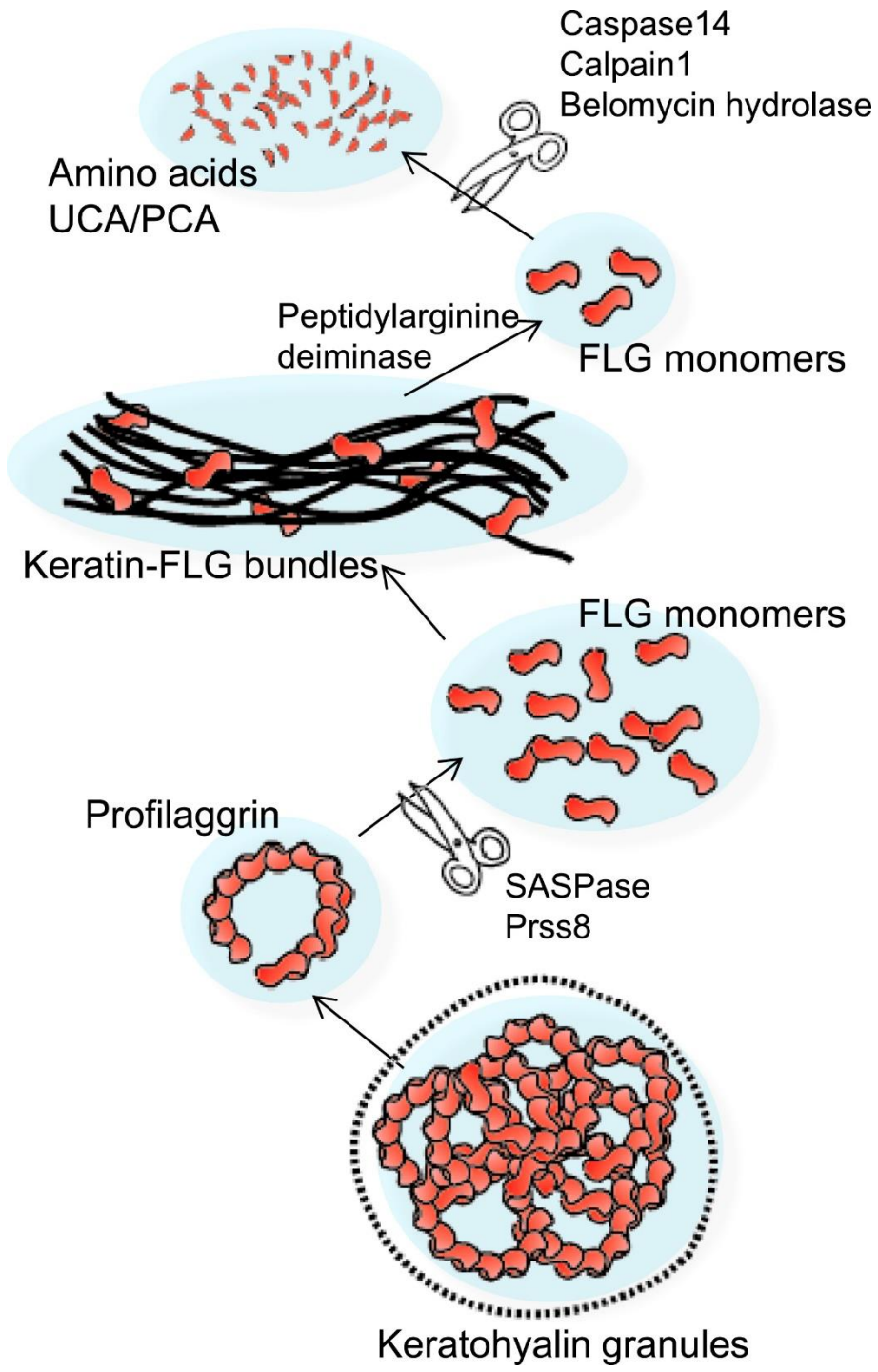
Barrier function of the skin

- The barrier function of the skin is largely dependent on the stratum corneum (SC), the outermost layer of the epidermis. The SC is formed through a course of tightly regulated processes of keratinocyte differentiation called keratinization. Keratinization is achieved by keratinocytes passing through four cell layers of the epidermis: the stratum basale, the stratum spinosum, the stratum granulosum (SG), and the SC.
- In the SG, keratinocytes start to produce two membrane-circumscribed granules: keratohyalin granules and lamellar bodies. Keratohyalin granules contain intracellular components of the SC (such as filaggrin [FLG], loricrin, and keratin filaments), whereas lamellar bodies contain extracellular components (such as lipids, corneodesmosin, and kallikreins).
- In the SC, keratinocytes are flattened and denucleated (which are then called as corneocytes) and simultaneously, corneocyte cell membranes are replaced by a specific barrier structure called a cornified envelope (CE). At the transition from the SG to the SC, lamellar bodies are secreted into the intercellular space of corneocytes and fill it up with lipids. These structures are often described as bricks (corneocytes) and mortar (intercellular lipids).



Egawa G, Kabashima K. Barrier dysfunction in the skin allergy. *Allergol Int*. 2018;67(1):3-11. doi:10.1016/j.alit.2017.10.002

Schema of the FLG metabolic process. In the stratum granulosum, profilaggrins are stored in keratohyalin granules and then cleaved into FLG monomers. FLG monomers bind to keratin filaments in corneocytes. At the upper layer of the SC, FLG monomers are released from keratins and cleaved into free amino acids, followed by conversion into pyrolidin carboxilic acid (PCA) and urocanic acid (UCA). UCA significantly reduced costimulatory molecule expression on dendritic cells and increased their ability to induce a regulatory T cells. In contrast, PCA is a major constituent of natural moisturizing factors (NMFs), which are responsible for retaining water in the SC.

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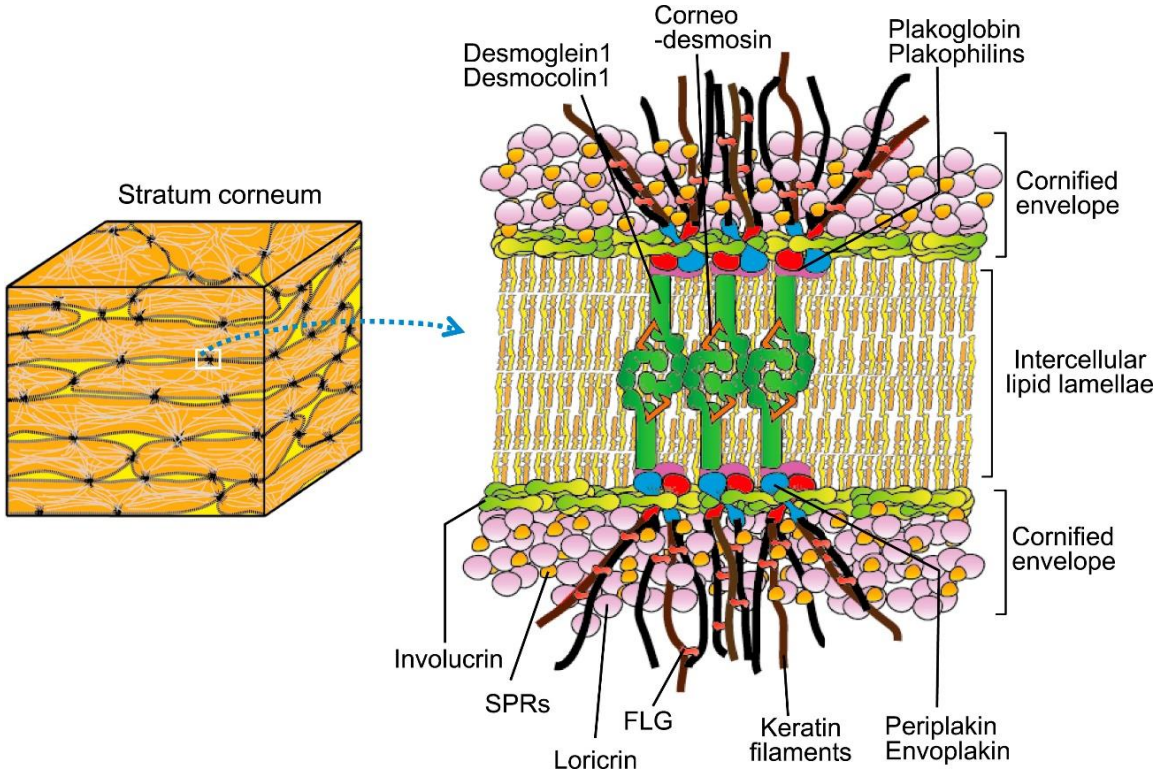

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The cornified envelope (CE) is a specific barrier structure formed beneath the cell membrane of corneocytes.
The CE consists of highly crosslinked insoluble proteins and the extracellular lipids anchoring on it. This structure acts as a vital physical barrier to the SC. The structures of the cornified envelope and corneodesmosome.
Involucrin forms the scaffold and is reinforced by loricrin and SRRs.
Envoplakin-periplakin heterodimers conjugate keratin filaments.

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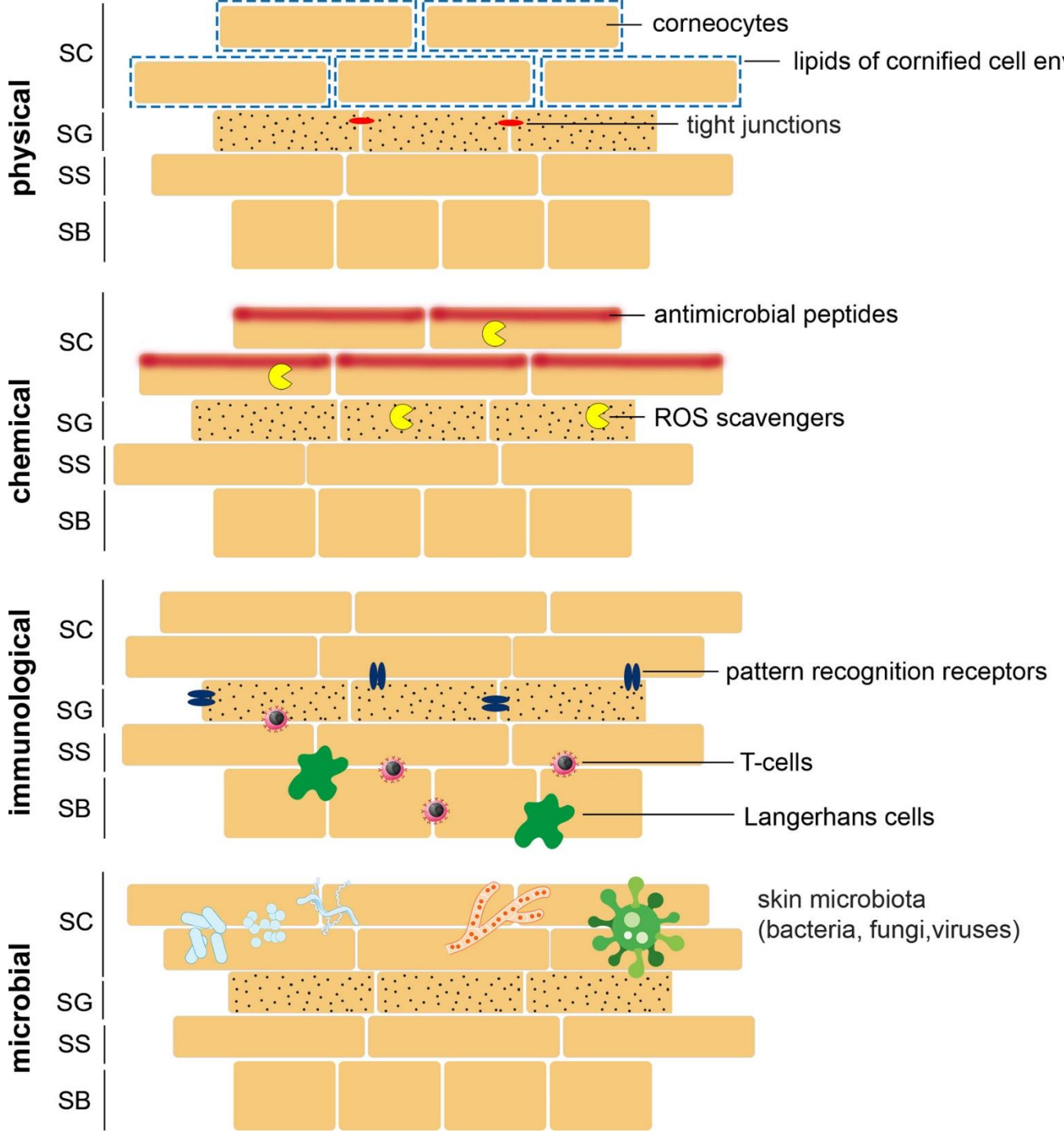
Skin Barrier



Niehues H, Bouwstra JA, El Ghalbzouri A, Brandner JM, Zeeuwen PLJM, van den Bogaard EH. 3D skin models for 3R research: The potential of 3D reconstructed skin models to study skin barrier function. *Exp Dermatol*. 2018;27(5):501-511. doi:10.1111/exd.13531

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Skin barrier

- The structural integrity of the stratum corneum is maintained by the presence of corneodesmosomes. Corneodesmosomes lock the together and provide tensile strength for the stratum corneum to resist shearing forces.
- Elias visualized the stratum corneum as being similar to a brick wall, with the analogous to bricks and the lamellae acting as cement. Extending this model, the corneodesmosomes can be thought of as analogous to iron rods that pass down though holes in the bricks to give the wall its tensile strength.

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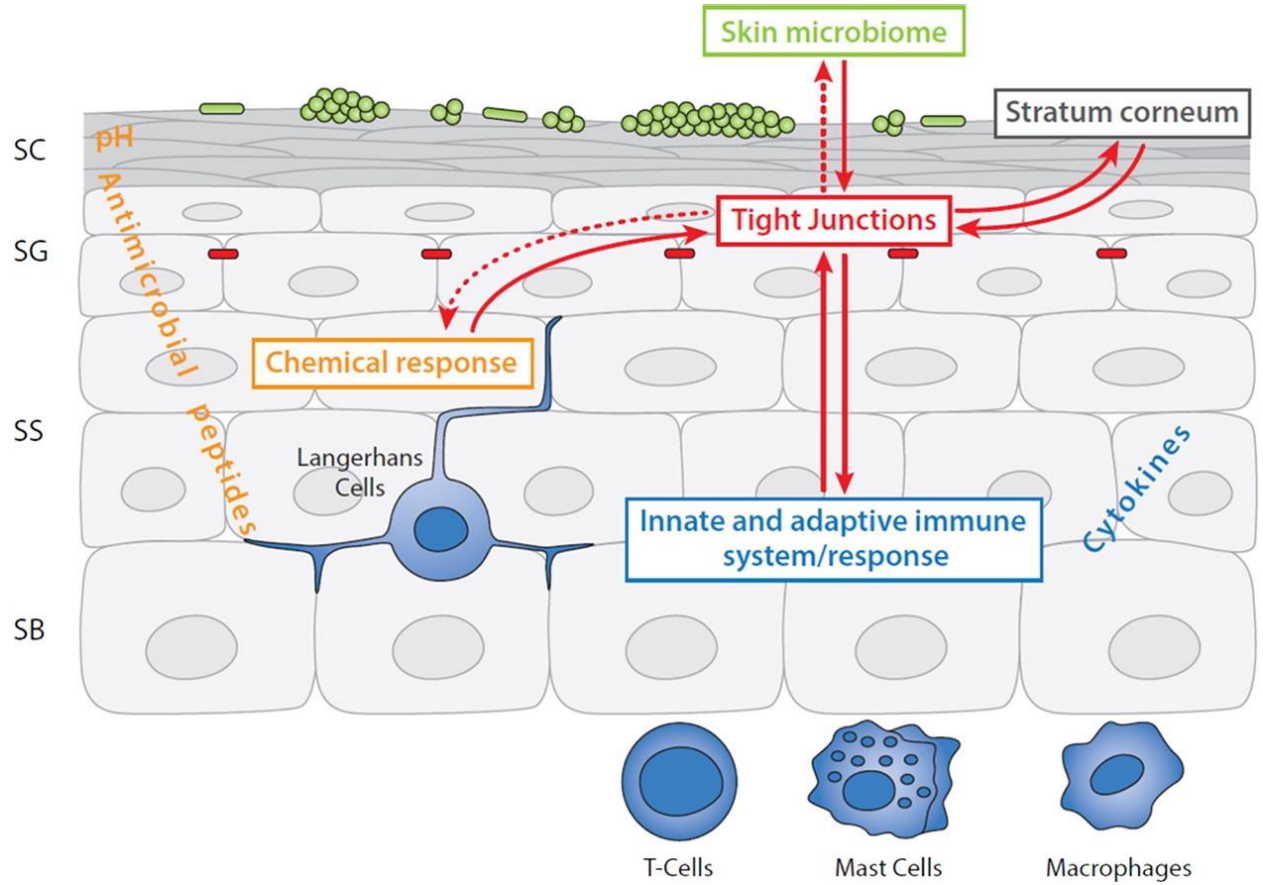

Schematic drawing denoting the different barriers in the epidermis and their interaction with the TJ barrier. Lilac spheres: desmosomes, grey spheres: corneodesmosomes. SB: *stratum basale*, SC: *stratum corneum*, SG: *stratum granulosum*, SS: *stratum spinosum.* Continous arrows denote interactions already experimentally shown. Dotted arrows denote hypothetical interactions.

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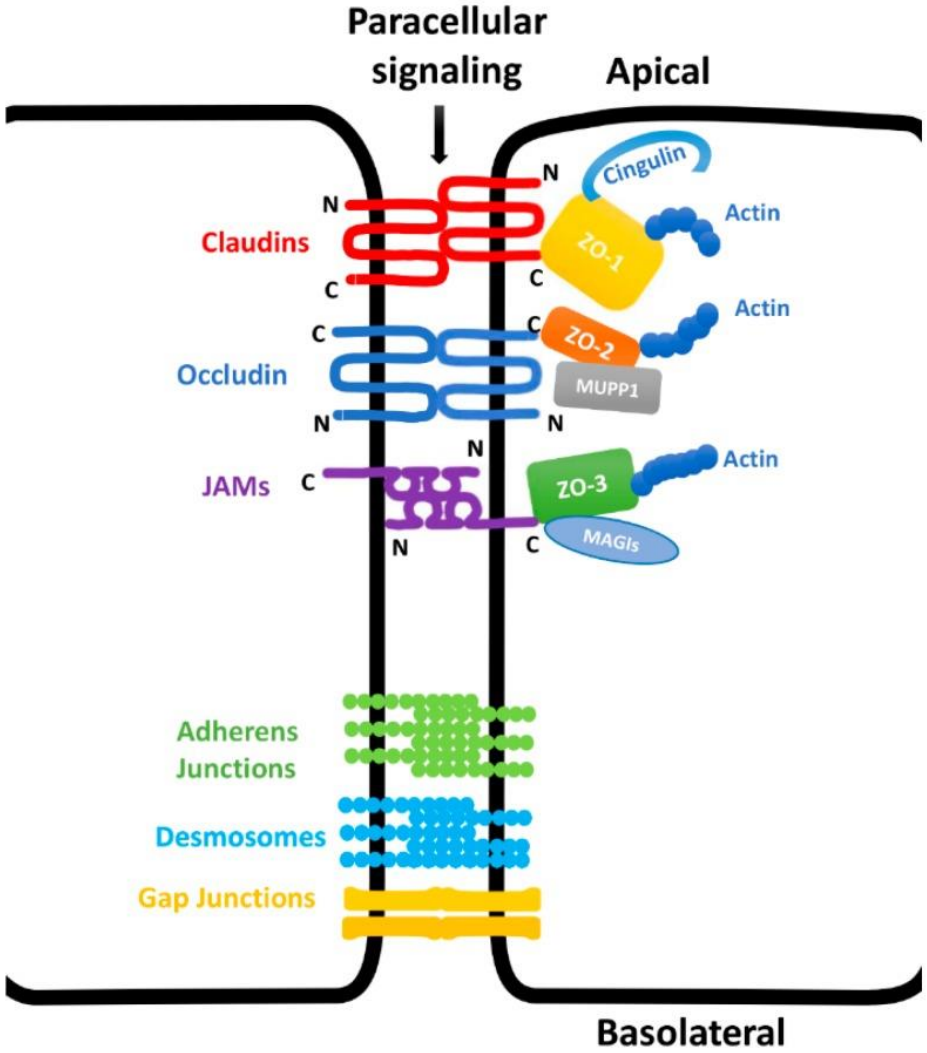

Shi J, Barakat M, Chen D, Chen L. Bicellular Tight Junctions and Wound Healing. *Int J Mol Sci*. 2018;19(12):3862. Published 2018 Dec 4. doi:10.3390/ijms19123862

Schematic structures of major bicellular tight junction proteins. The tight junction (TJ) is part of cell-cell junction complex. Major bicellular TJ proteins include three transmembrane protein families: occludin, claudins, and junctional adhesion molecules (JAMs) and a few families of peripheral intracellular membrane proteins such as zonula occludens (ZOs), which connect the transmembrane TJ molecules to the actin filament cytoskeleton.

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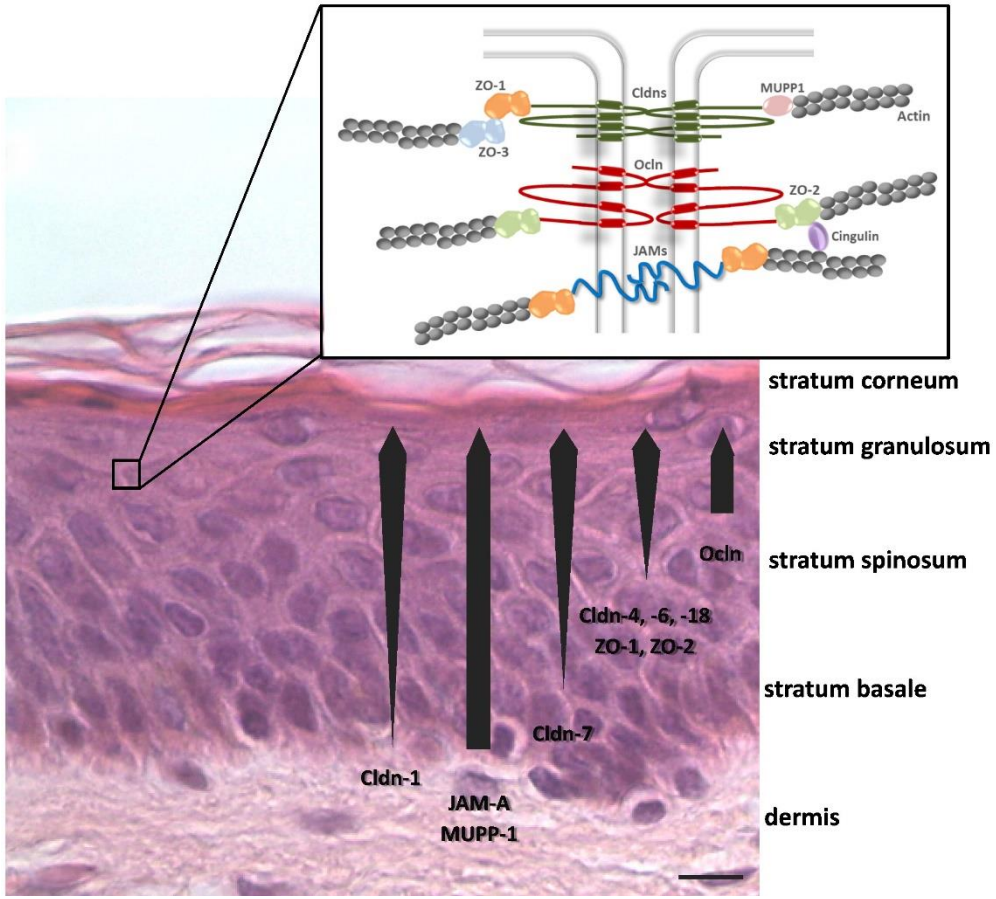

Localization of TJs and TJ proteins in the epidermis and molecular composition of TJs. Cldn: claudin; JAM: junctional adhesion molecule, MUPP1: Multi-PDZ domain protein 1, Ocln: occludin. Bar:20 μm.

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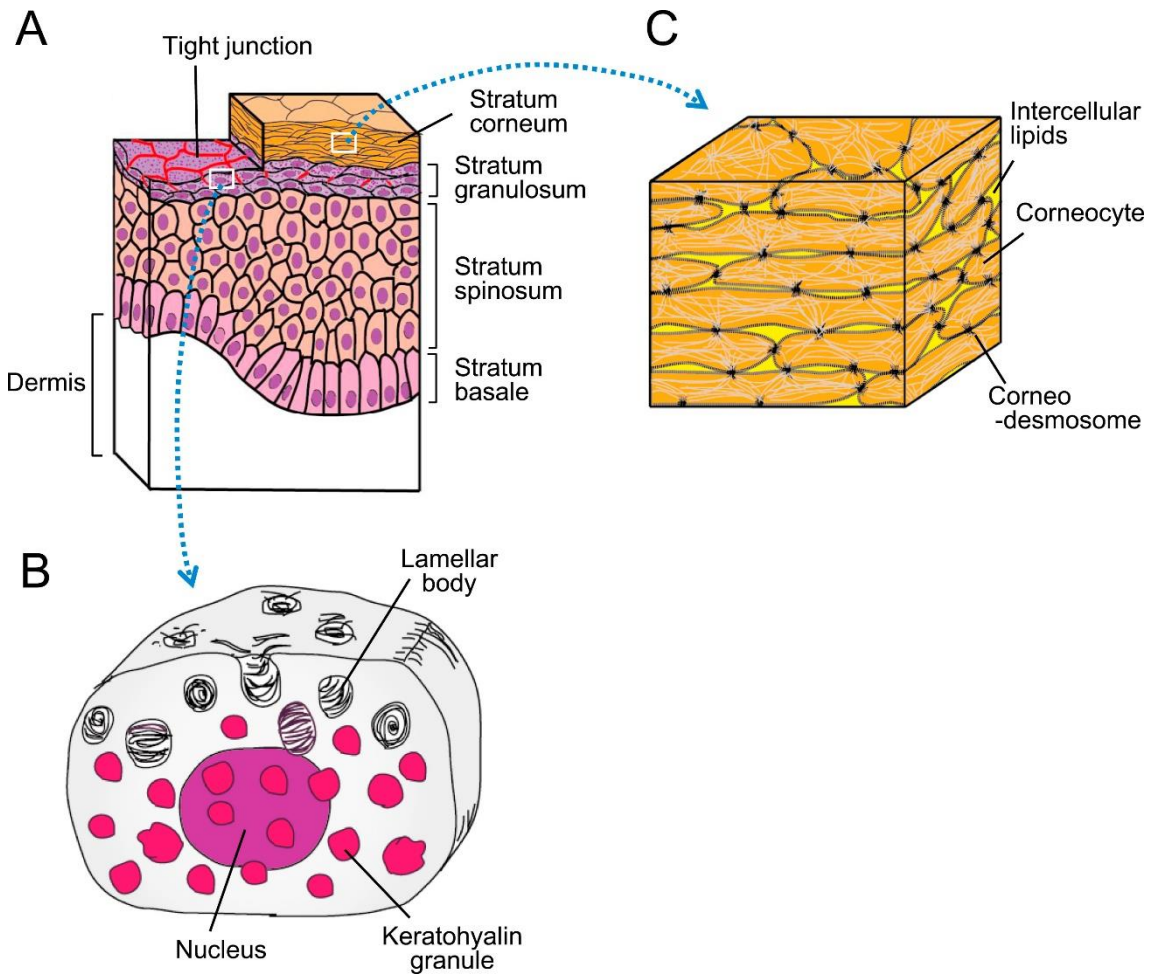

The structure of the epidermis. The red line represents tight junctions in the stratum granulosum. **B**, Magnified view of the cell in the stratum granulosum. **C**, The "bricks and mortars" structure of the stratum corneum.

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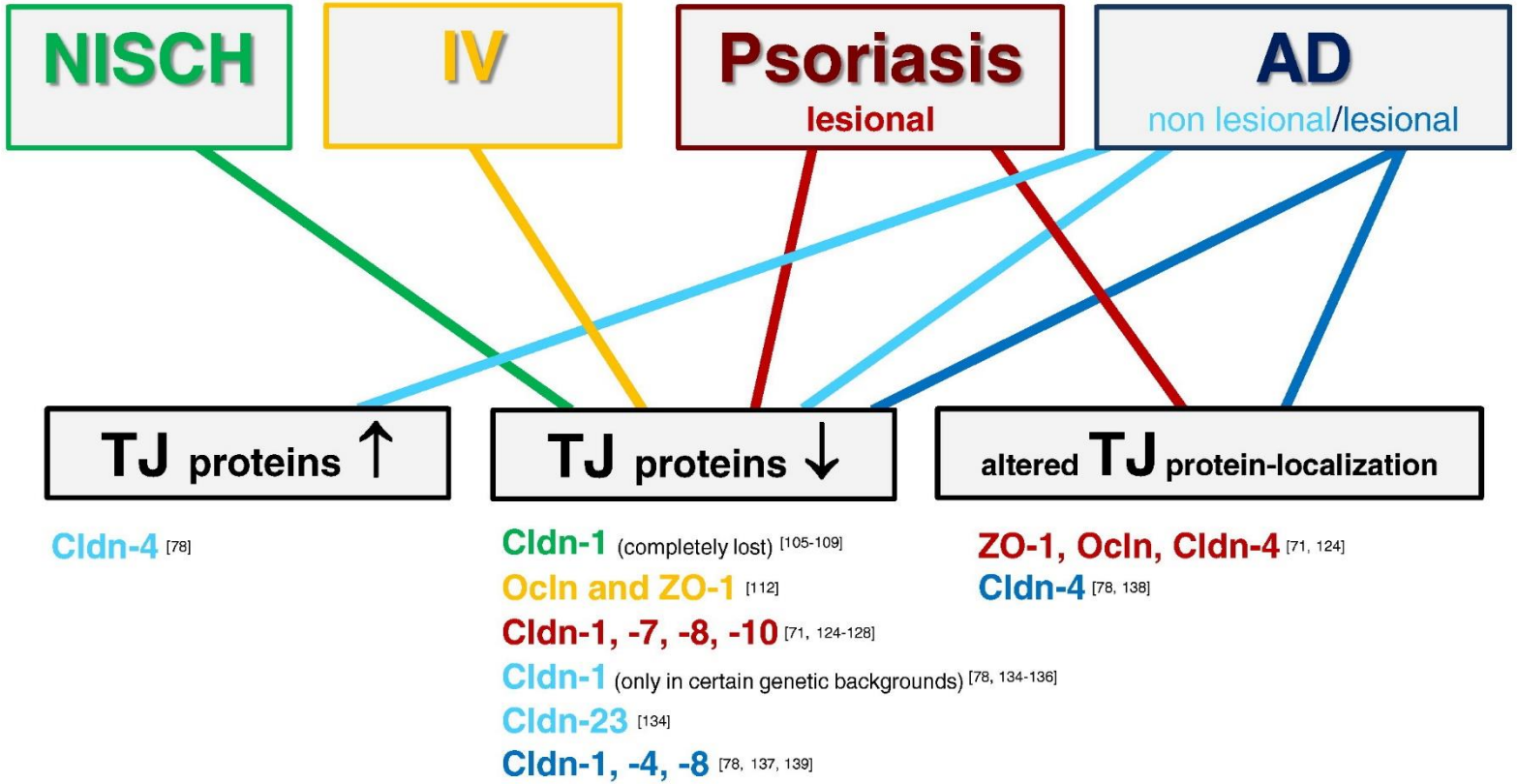
Impaired epidermal barrier

- The skin covers the entire body and protects us from various kinds of external stimuli. An impaired epidermal barrier allows the enhanced penetration of external antigens and readily induces skin inflammation. This facilitates the interaction of external antigens with local immune cells and may lead to systemic immune responses. This is called the “outside-to-inside” hypothesis, and it explains the association between skin barrier dysfunction and an increased risk of developing allergic diseases, including atopic dermatitis (AD), asthma, food allergies, and allergic rhinitis. In addition, it is evident that persistent skin inflammation, in turn, causes further attenuation of the skin barrier, suggesting the existence of an exacerbation loop between the skin barrier and skin immunity (the “outside-to-inside-and-back-to-outside” hypothesis). These observations suggest that maintaining the skin barrier function is important not only for effective management of allergic diseases but also for preventing their development.

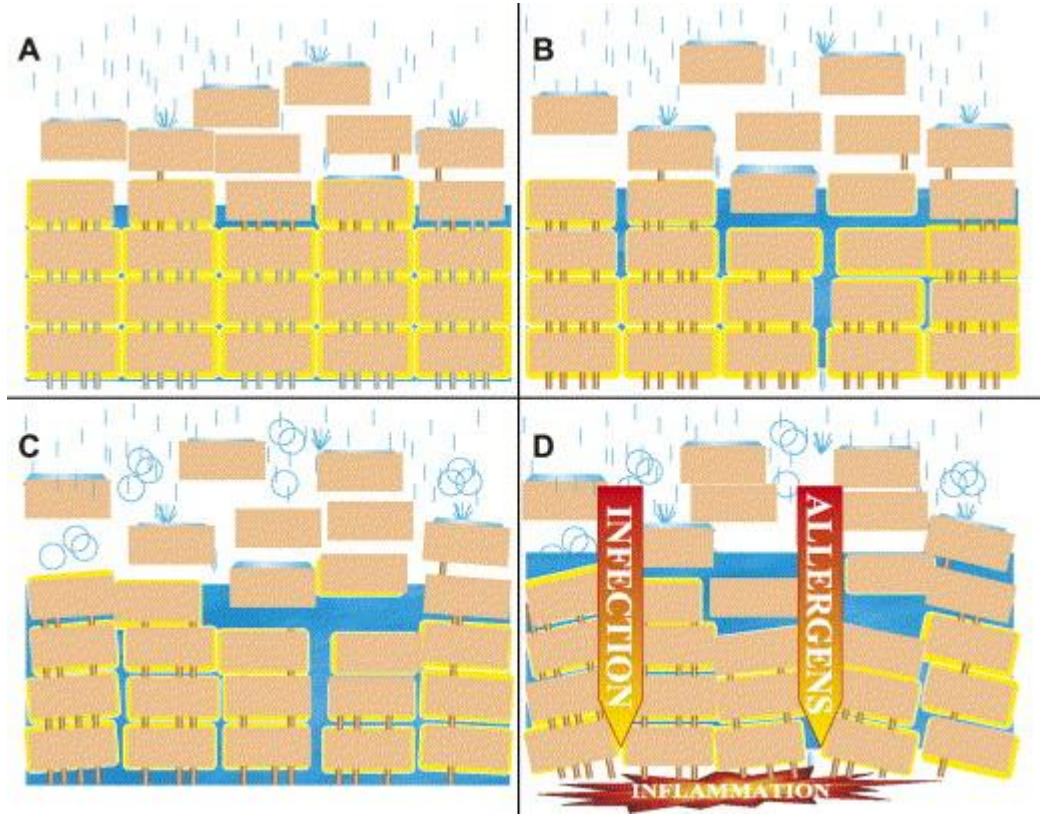
Immunological modulation of skin barriers

- Accumulating evidence suggests that immune cells influence skin integrity through the production of cytokines. Although complex interaction of immune cells creates AD skin lesions, the immunopathogenesis of AD is characterized by Th2-skewed responses.
- IL-4 and IL-13, the two major Th2 cytokines, downregulate the production of 1) FLG and keratins, 2) the CE components (loricrin and involucrin), 3) cell adhesion molecules (desmogleins, ZO-1), and 4) ceramide lipids.
- IL-31, another Th2 cytokine dominantly produced by Th2 cells, also downregulates FLG expression. Furthermore, a recent study has shown that IL-33, an alarmin that is abundantly stored in keratinocytes, has the potency to downregulate FLG expression as well.
- The original purpose of these immunological modulations against skin integrity may be to facilitate the desquamation and replacement of damaged corneocytes; however, to achieve this, dysregulation of the skin barrier is essential. A series of these modulations may cause problems, particularly in AD patients. The exacerbation loop between congenital barrier deficiency and immunogenic barrier deficiency leads to the formation of chronic, persistent skin inflammation in AD.

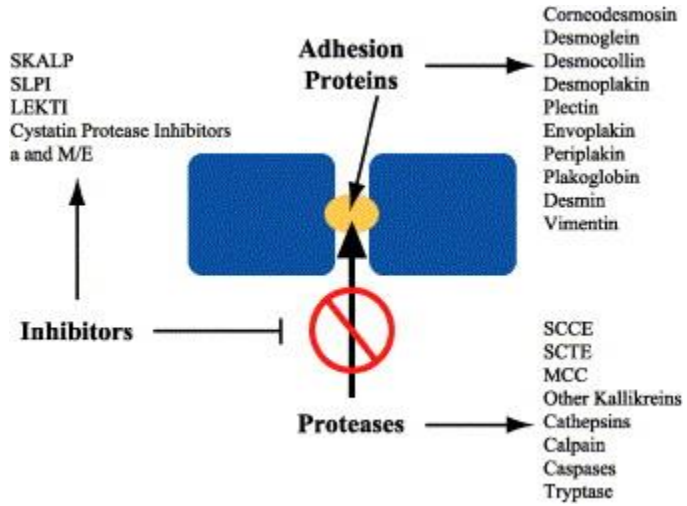


Alteration of tight junction proteins in skin diseases. The different colors denote the different diseases and the corresponding TJ protein alterations. AD: atopic dermaitits Cldn: claudin; IV: ichthyosis vulgaris; NISCH: neonatal ichthyosis sclerosing cholangitis; Ocln: occludin, ZO-1: zonula occludens 1.

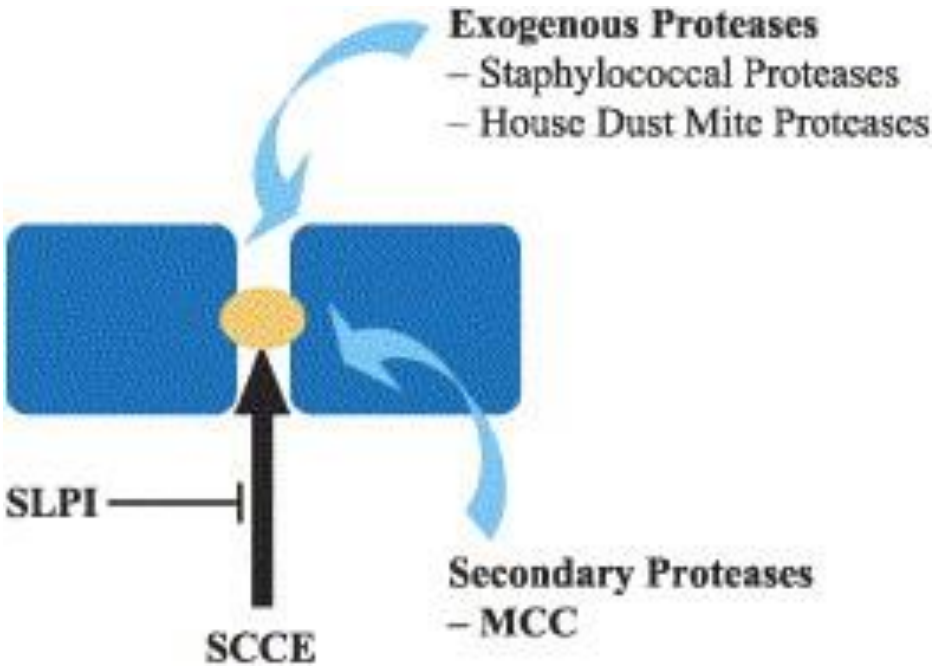
Bäsler K, Bergmann S, Heisig M, Naegel A, Zorn-Kruppa M, Brandner JM. The role of tight junctions in skin barrier function and dermal absorption. *J Control Release*. 2016;242:105-118. doi:10.1016/j.jconrel.2016.08.007



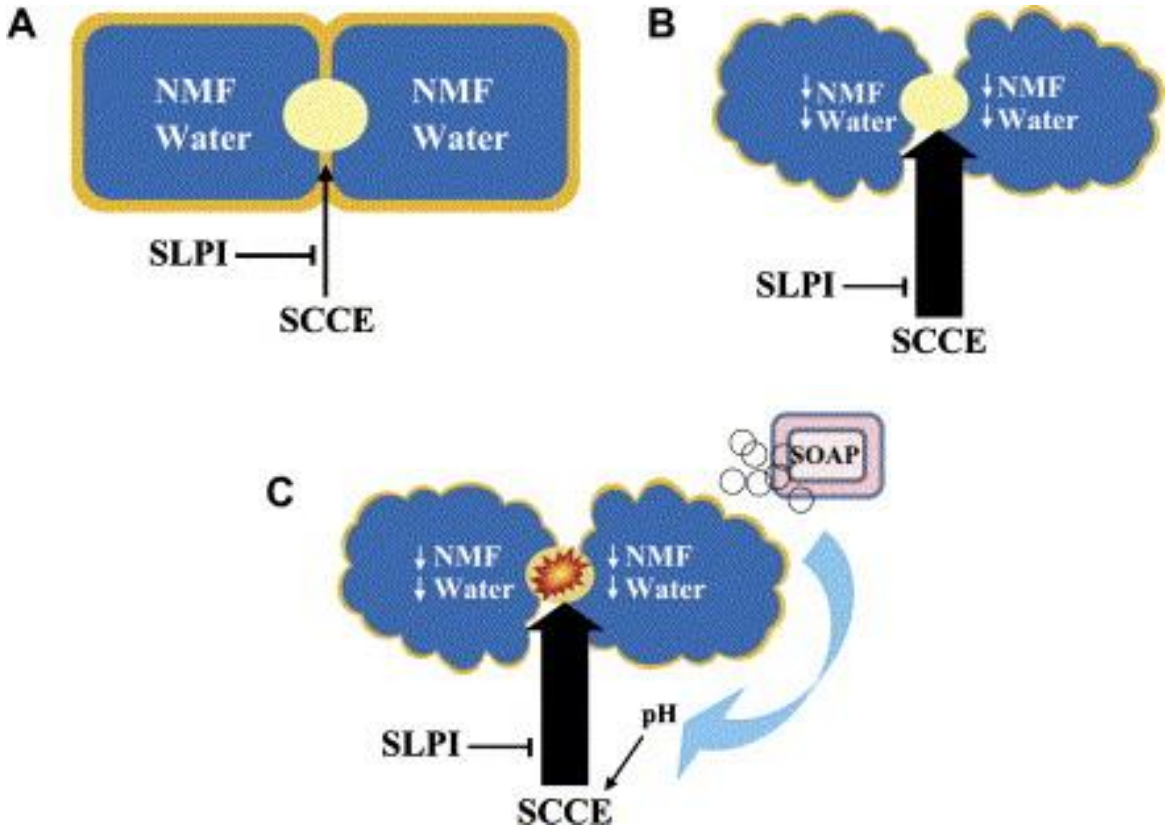
The brick wall analogy of the stratum corneum of the epidermal barrier. In healthy skin the corneodesmosomes (iron rods) are intact throughout the stratum corneum. At the surface, the corneodesmosomes start to break down as part of the normal desquamation process, analogous to iron rods rusting **(A)**. In an individual genetically predisposed to AD, premature breakdown of the corneodesmosomes leads to enhanced desquamation, analogous to having rusty iron rods all the way down through the brick wall **(B)**. If the iron rods are already weakened, an environmental agent, such as soap, can corrode them much more easily. The brick wall starts falling apart **(C)** and allows the penetration of allergens **(D)**.



The corneocytes of the skin barrier are locked together by corneodesmosomes comprising several adhesion proteins. Desquamation of corneocytes can only occur once the corneodesmosome has been broken down by skin-specific proteases, such as the SCCE. The proteases are kept under control by specific protease inhibitors, such as the skin-derived antileukoprotease *(SKALP)*. *SLPI*, serine leukoprotease inhibitor; *LEKTI*, lymphoepithelial Kazal-type 5 serine protease inhibitor.



Corneodesmosomes are not only broken down by endogenous serine proteases, such as SCCE (SCCE – stratum corneum chymotryptic enzyme) and SCTE (stratum corneum tryptic enzyme). Once a flare of AD has been triggered, cells within the inflammatory infiltrate produce secondary proteases, which can also break down the skin barrier (eg, MCC). The stratum corneum is also exposed to many exogenous proteases from the environment, such as *Staphylococcus aureus* and house dust mites. *SLPI*, serine leukoprotease inhibitor.



In the stratum corneum from healthy , there is a balance between the structural integrity of the corneodesmosomes and the level of proteases and protease inhibitors **(A)**. In individuals genetically predisposed to , increased protease activity leads to premature breakdown of the corneodesmosomes and thinning of the stratum corneum (**B** and **C**). Soap use increases the pH from 5.5 to the optimal value for activity (≥7.5), further increasing the breakdown of the corneodesmosomes and desquamation (**C**). , leukoprotease inhibitor

Barrier dysfunction is leading pathogenesis of skin allergy

It is now evident that epicutaneous antigens are strong sensitizer of allergic disorders.
In human, sequential acquisition of allergic diseases (atopic march) are frequently observed in both AD and some genodermatoses, such as Netherton syndrome (mutation in *SPINK5*), peeling skin syndrome 1 (*Corneodesmosin*) and SAM syndrome (*Desmoglein1*), which strongly suggests that skin barrier deficiency contributes to the development of atopic march.
Eosinophilic esophagitis is another chronic immune disorder that is associated with hypersensitivity to food, and has recently been linked to the mutations in *Calpain* 14 (*CAPN14*), a protease specifically expressed in the esophagus.
The barrier deficiency in mucosal epithelium also contribute to the induction of allergic disorders.
Recent clinical trials have shown that epicutaneous antigen exposure induces sensitization while oral antigen consumption induces immune tolerance.

Egawa G, Kabashima K. Barrier dysfunction in the skin allergy. *Allergol Int*. 2018;67(1):3-11. doi:10.1016/j.alit.2017.10.002

Different combinations of genetic and environmental factors

contribute to the development of multifactorial diseases, such as AD. Focusing on the skin barrier, severe barrier breakdown could be caused by a combination of functional variants in adhesion protein, protease, and protease inhibitor genes **(A)** or by a single major environmental insult. Alternatively, major functional changes in the skin barrier–related genes could produce a defective skin barrier. Exposure of this defective barrier to an environmental insult, such as soap and detergents, breaks it down further, allowing penetration of irritants and allergens **(B)**. A third possibility is the combination of several changes in skin barrier genes, resulting in small functional changes **(C)**. Other combinations of both genetic and environmental factors can also lead to the development of AD (**C**). A combination of repeated environmental insults might, alone, also produce sufficient barrier breakdown to lead to the development of eczematous lesions (**C**).

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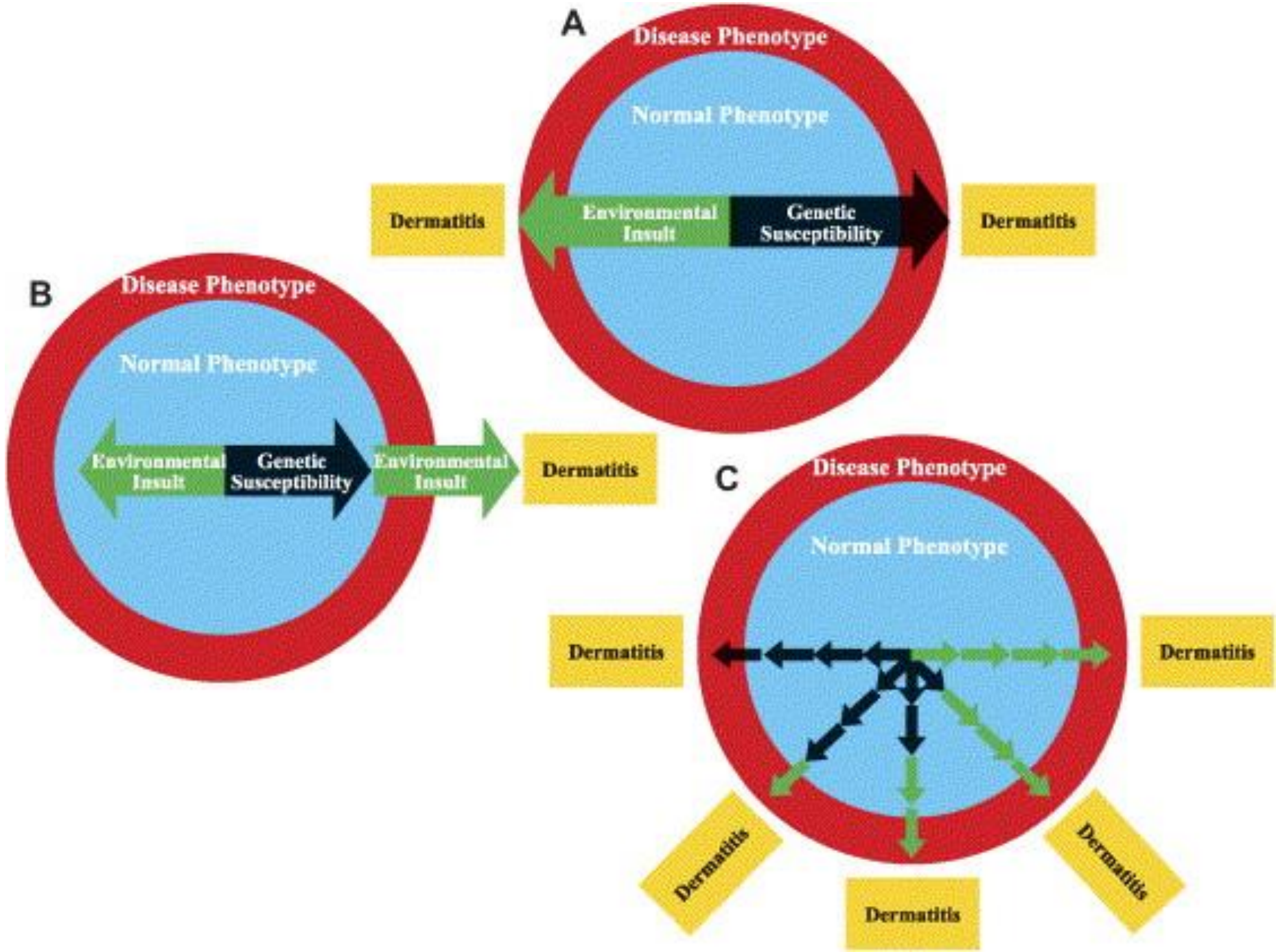
A
Disease Phenotype
Normal Phenotype
Environmental Insult
Genetic Susceptibility
Dermatitis
Dermatitis
B
Disease Phenotype
Normal Phenotype
Environmental Insult
Genetic Susceptibility
Environmental Insult
Dermatitis
C
Disease Phenotype
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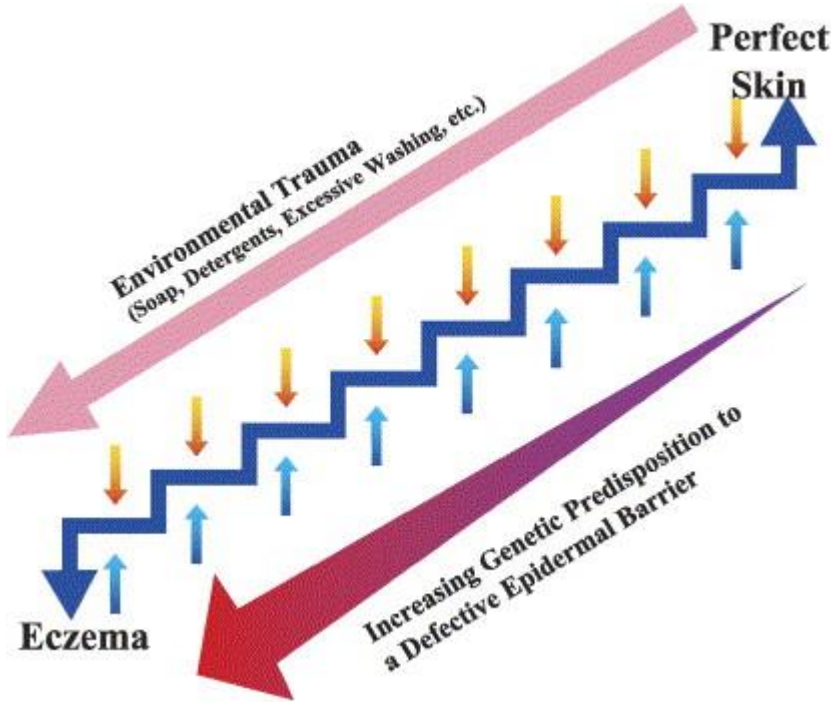
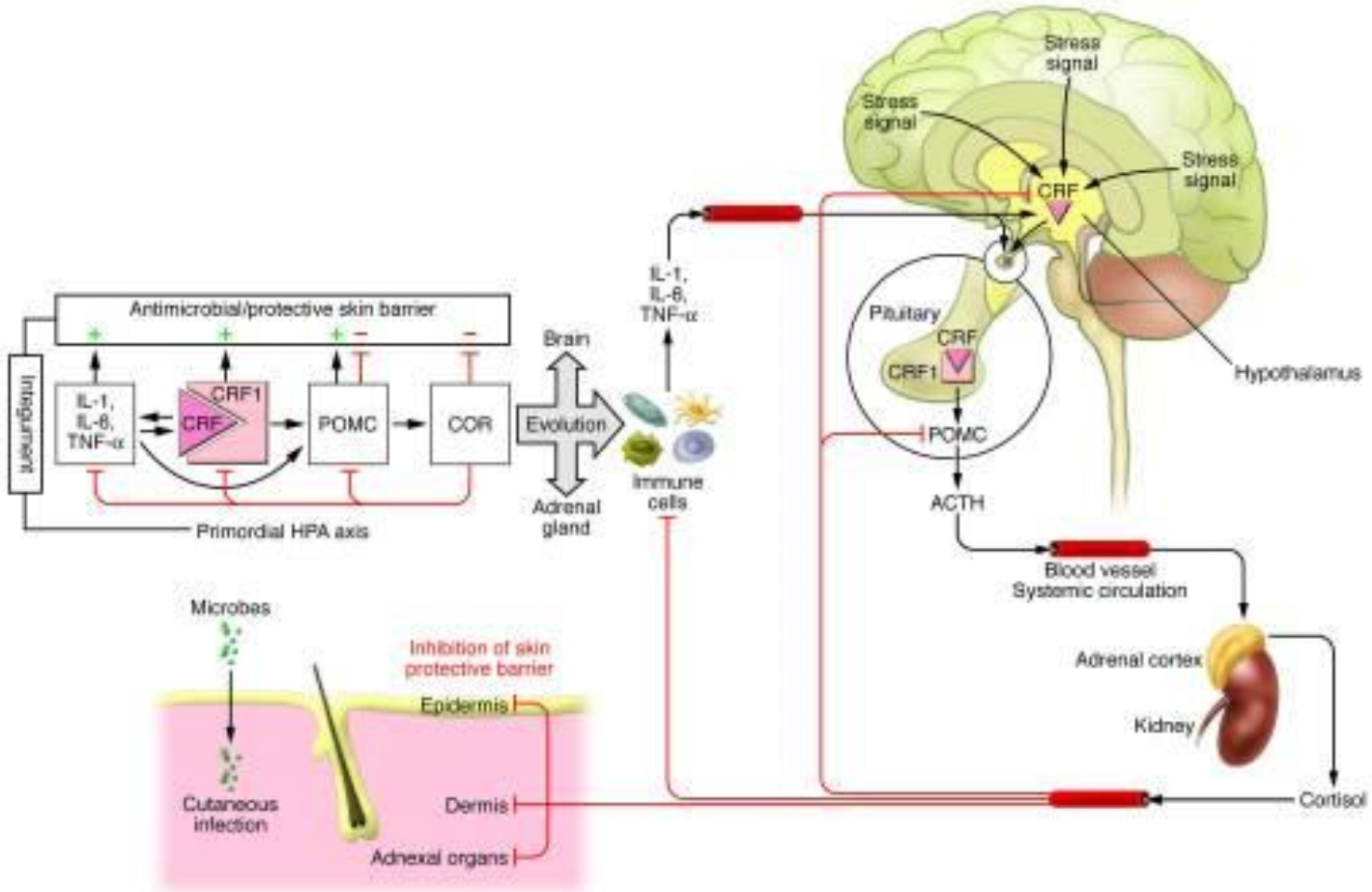
Dermatitis



The skin can be considered to be on a spectrum from perfect skin to eczematous skin. Changes in skin barrier–related genes alter the epidermal barrier function, making the skin more susceptible to the development of AD. When a genetic predisposition to barrier breakdown is combined with exposure to environmental agents, such as soap, the chance of eczema development is increased substantially.

Hypothalamic-hypophyseos axis and skin



Psoriasis: General aspects

- Psoriasis is a chronic, inflammatory, immune-mediated skin disease affecting ~2% of the European population[1]
- The disease usually occurs in individuals with genetic susceptibility in conjunction with environmental stimuli, and may involve an immune response to autoantigens[2]
- Evidence supports a central role for dendritic cells and T cells in establishing and maintaining the "vicious cycle" of psoriatic plaque development[2,3]

1. Gudjonsson JE, Elder JT. Clin Dermatol. 2007;25(6):535-46. 2. Griffiths CE, Barker JN. Lancet. 2007;370:263-71. 3. Nickoloff BJ, Nestle FO. J Clin Invest. 2004; 113:1664-75.

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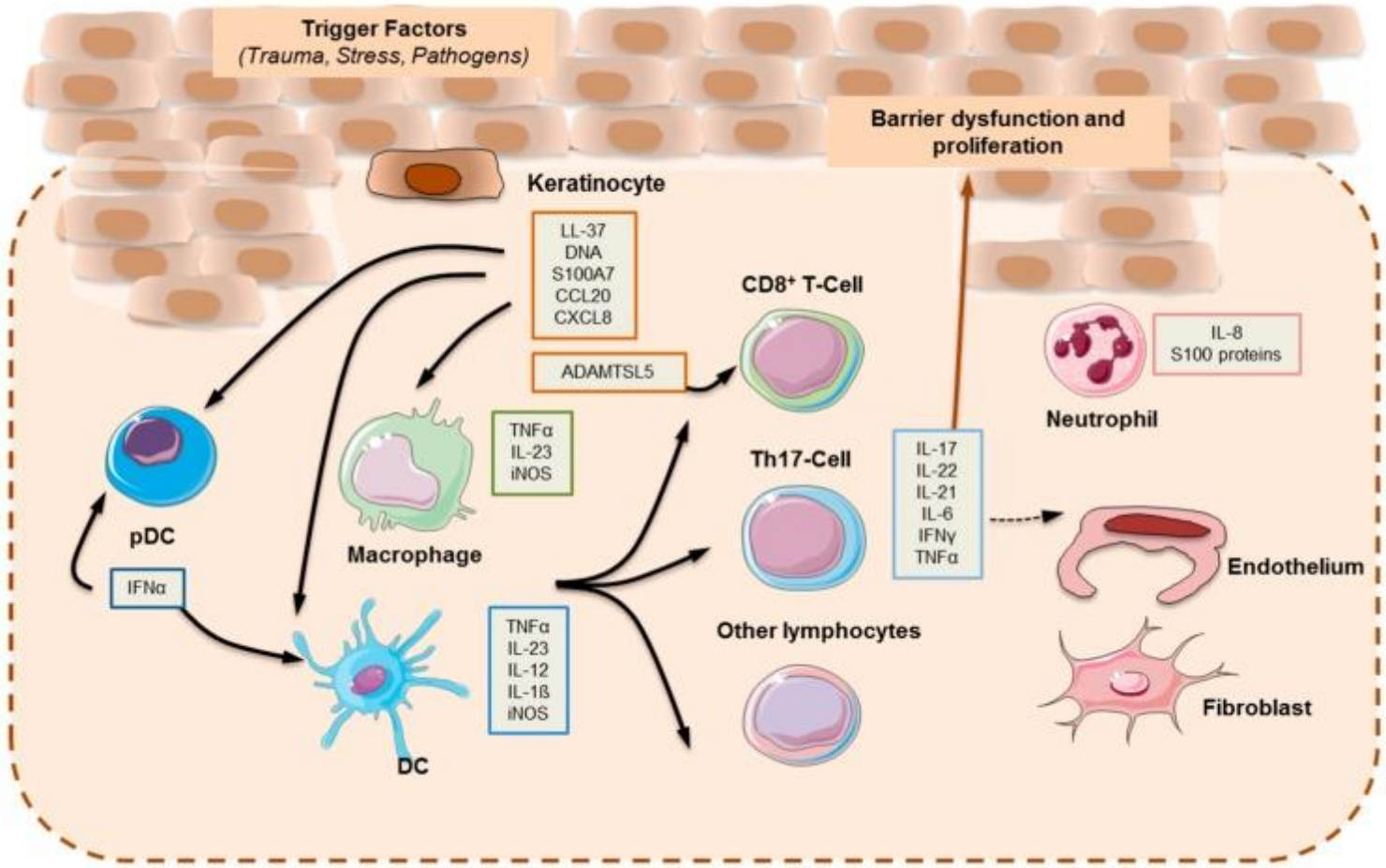

Pathophysiology of psoriasis

Rendon A, Schäkel K. Psoriasis Pathogenesis and Treatment. *Int J Mol Sci*. 2019;20(6):1475. Published 2019 Mar 23. doi:10.3390/ijms20061475

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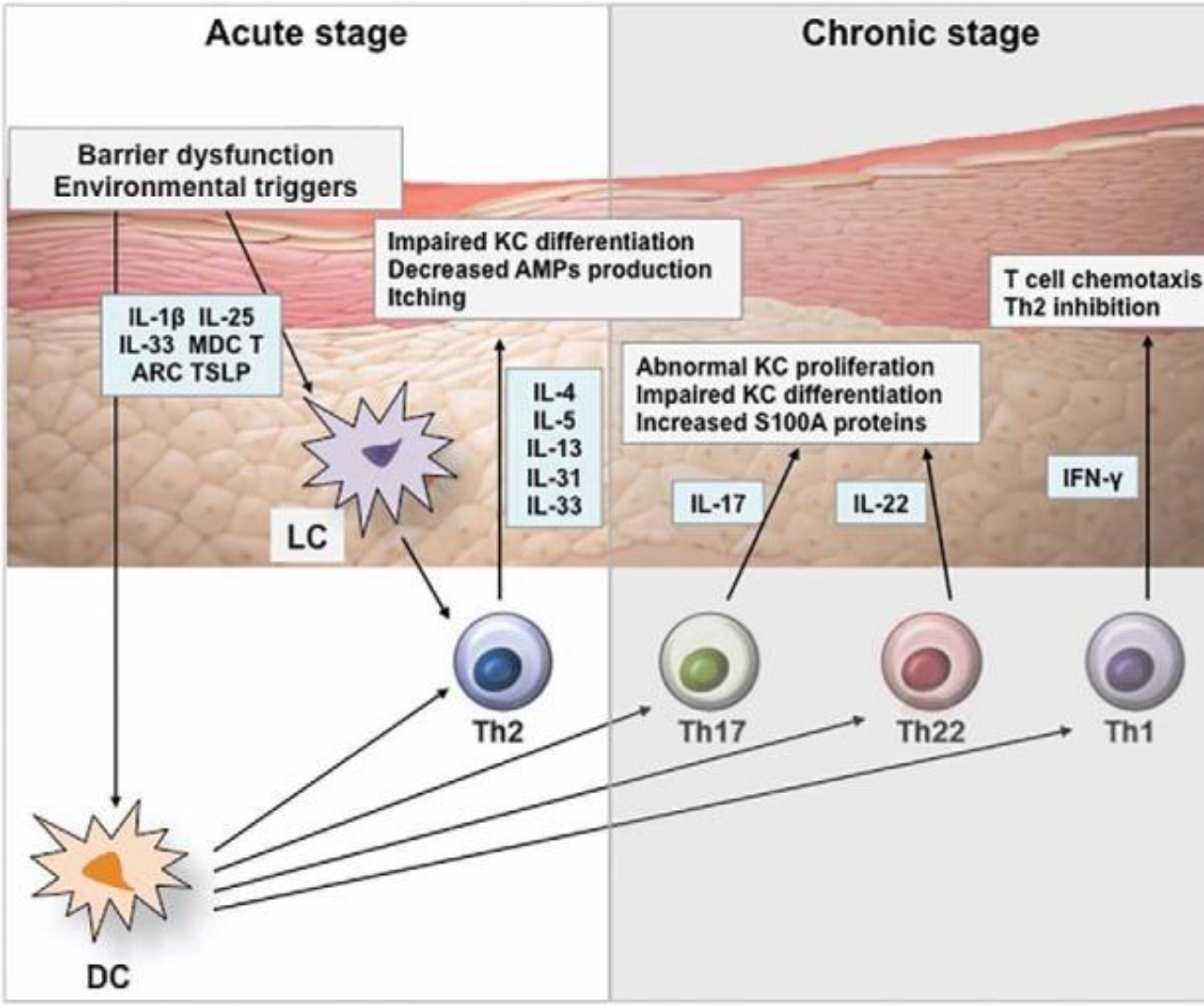
Atopic dermatitis

- Atopic dermatitis is a systemic disorder characterized by abnormal barrier function across multiple organ sites. Causes of epidermal barrier breakdown are complex and driven by a combination of structural, genetic, environmental and immunological factors. In addition, alteration in microflora diversity can influence disease severity, duration, and response to treatment. Clinically, atopic dermatitis can progress from skin disease to food allergy, allergic rhinitis, and later asthma, a phenomenon commonly known as the atopic march. The mechanism by which atopic dermatitis progresses towards gastrointestinal or airway disease remains to be elucidated.

Effects of cytokines on epidermis in AD. Disrupted epidermal barrier and environmental triggers stimulate keratinocytes to release IL-1β, IL-25, IL-33, MDC, TARC, and TSLP, which activate dendritic cells and Langerhans cells. Activated dendritic cells stimulate Th2 cells to produce IL-4, IL-5, IL-13, IL-31, and IL-33, which leads to barrier dysfunction, decreased AMP production, impaired keratinocyte differentiation, and itch symptoms.

Chronic AD is characterized by recruitment of Th1, Th22, and Th17 subsets, which results in epidermal thickening and abnormal keratinocyte proliferation.

AD = atopic dermatitis; AMP = antimicrobial peptide; DC = dendric cell; IFN = interferon; IL = interleukin; KC = keratinocyte; LC = Langerhans cell; MDC = macrophage-derived chemokine; S100A = S100 calcium-binding protein A; Th = T-helper type; TARC = thymus and activation-regulated chemokine; TSLP = thymic stromal lymphopoietin.



Kim J, Kim BE, Leung DYM. Pathophysiology of atopic dermatitis: Clinical implications. *Allergy Asthma Proc*. 2019;40(2):84-92. doi:10.2500/aap.2019.40.4202

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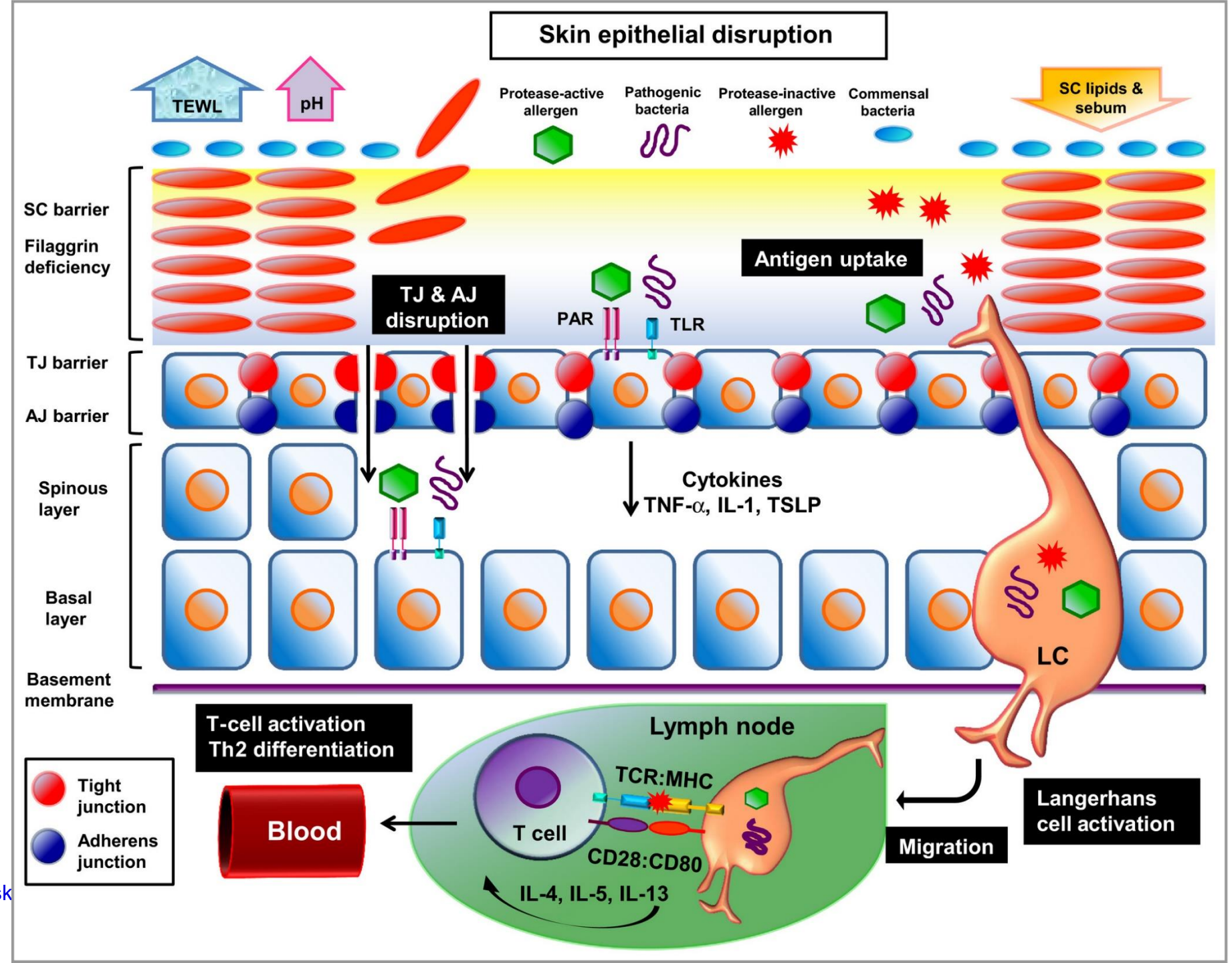
Table 1 **Epithelial skin dysfunction in atopic dermatitis**

Epithelial Dysfunction	Abnormalities	Effects
Cornified envelope proteins	Decreased expression of filaggrin, transglutaminases, keratins, loricrin, involucrin, and intercellular proteins	↓ Skin hydration ↑ Skin pH ↑ Penetration of allergens and microbes ↑ Proinflammatory cytokines ↓ Inflammatory threshold levels
Tight junctions	Reduced claudins	↓ Skin hydration ↑ TEWL ↑ Penetration of allergens and microbes
Antimicrobial peptides	Decreased cathelicidin (LL-37) and human β-defensins	↑ Skin infections ↑ Cytokine production
Microbiome	*S. aureus* colonization and decreased bacterial diversity	↓ Expression of filaggrin, loricrin, desmocollin1, and keratins ↑ Proinflammatory cytokines ↑ Skin infections
Epidermal lipids	Decreased long-chain free fatty acids and ceramides	↑ TEWL ↑ *S. aureus* infections

↓ = *decreased;* ↑ = *increased; TEWL = transepidermal water loss; S. aureus = Staphylococcus aureus.*

Kim J, Kim BE, Leung DYM. Pathophysiology of atopic dermatitis: Clinical implications. *Allergy Asthma Proc*. 2019;40(2):84-92. doi:10.2500/aap.2019.40.4202


Skin epithelial disruption
TEWL
pH
Protease-active allergen
Pathogenic bacteria
Protease-inactive allergen
Commensal bacteria
SC lipids & sebum
SC barrier
Filaggrin deficiency
TJ barrier
AJ barrier
Spinous layer
Basal layer
Basement membrane
TJ & AJ disruption
PAR
TLR
Antigen uptake
Cytokines
TNF-α, IL-1, TSLP
LC
Lymph node
T-cell activation
Th2 differentiation
TCR:MHC
T cell
CD28:CD80
IL-4, IL-5, IL-13
Blood
Migration
Langerhans cell activation
Tight junction
Adherens junction

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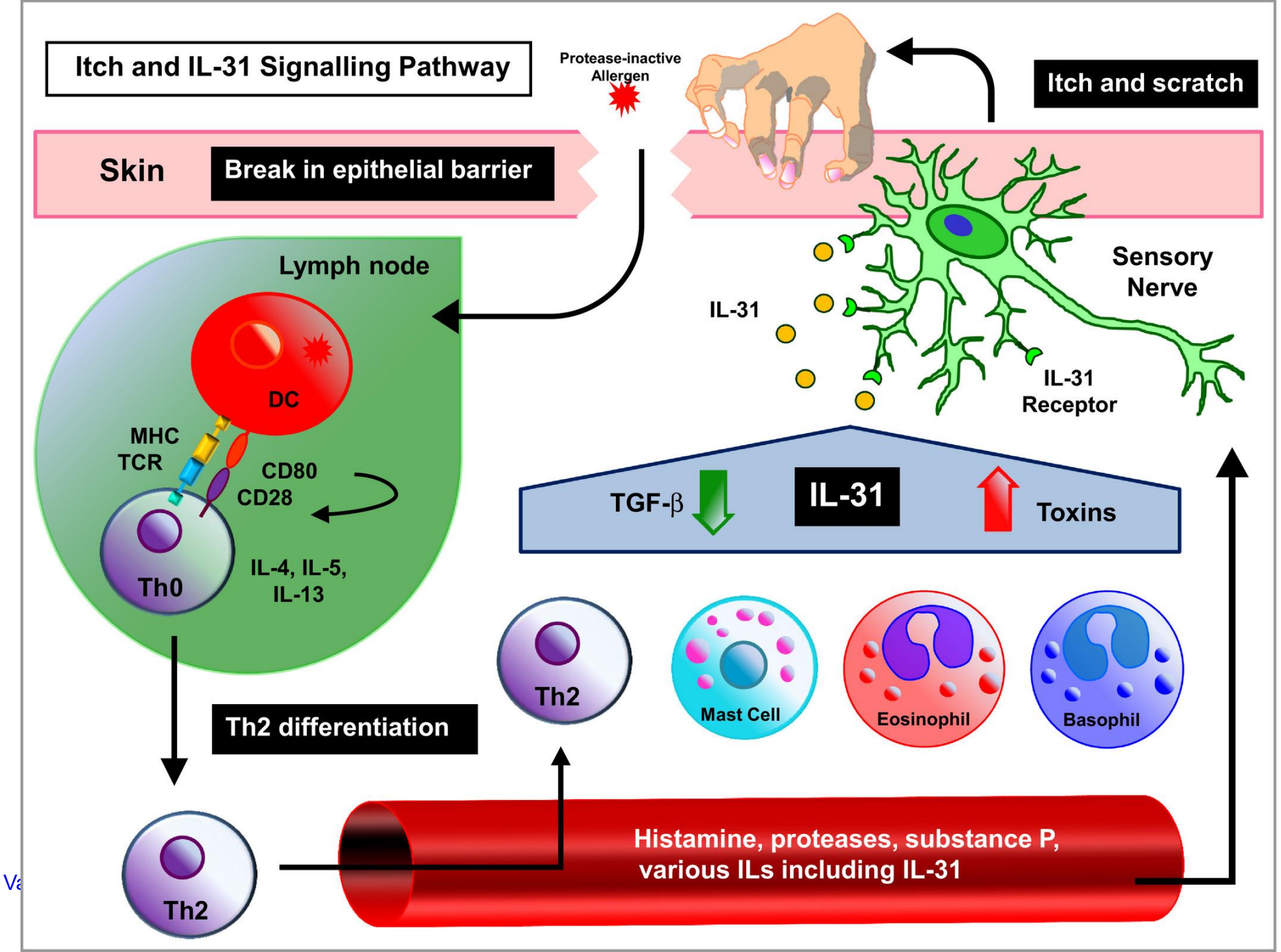
Skin barrier disruption

- Stratum corneum (SC) barrier damage often occurs as a result of a decrease in surface microbial diversity, *FLG* expression, antimicrobial peptide production and SC lipid synthesis [measured by increased skin pH and transepidermal water loss (TEWL)].
- After SC breakdown, protease-inactive allergens and bacterial molecules are taken up by resident Langerhans cells (LCs), which migrate to draining lymph nodes to trigger an adaptive immune response. Engagement of the T-cell receptor (TCR) with major histocompatibility complex (MHC) containing antigen and concomitant engagement of costimulatory complex (CD80:CD28) activate the naive T cell. Additional factors secreted by LCs include interleukin (IL)-4, IL-5 and IL-13, which induce T helper (Th)2 differentiation. Alternatively, protease-active antigens can directly cause SC breakdown and activate protease-activated receptors (PARs) and Toll-like receptors (TLRs) on keratinocytes (black arrows), triggering production of proinflammatory cytokines including tumour necrosis factor (TNF)-α, IL-1 and thymic stromal lymphopoietin (TSLP), which can mediate permeability defects at other sites, such as the intestinal and respiratory tracts. TJ, tight junction; AJ,


Itch and IL-31 Signalling Pathway
Protease-inactive Allergen
Itch and scratch
Skin
Break in epithelial barrier
Lymph node
DC
MHC
TCR
CD80
CD28
Th0
IL-4, IL-5, IL-13
Sensory Nerve
IL-31
IL-31 Receptor
TGF-β
IL-31
Toxins
Th2
Mast Cell
Eosinophil
Basophil
Th2 differentiation
Th2
Histamine, proteases, substance P, various ILs including IL-31

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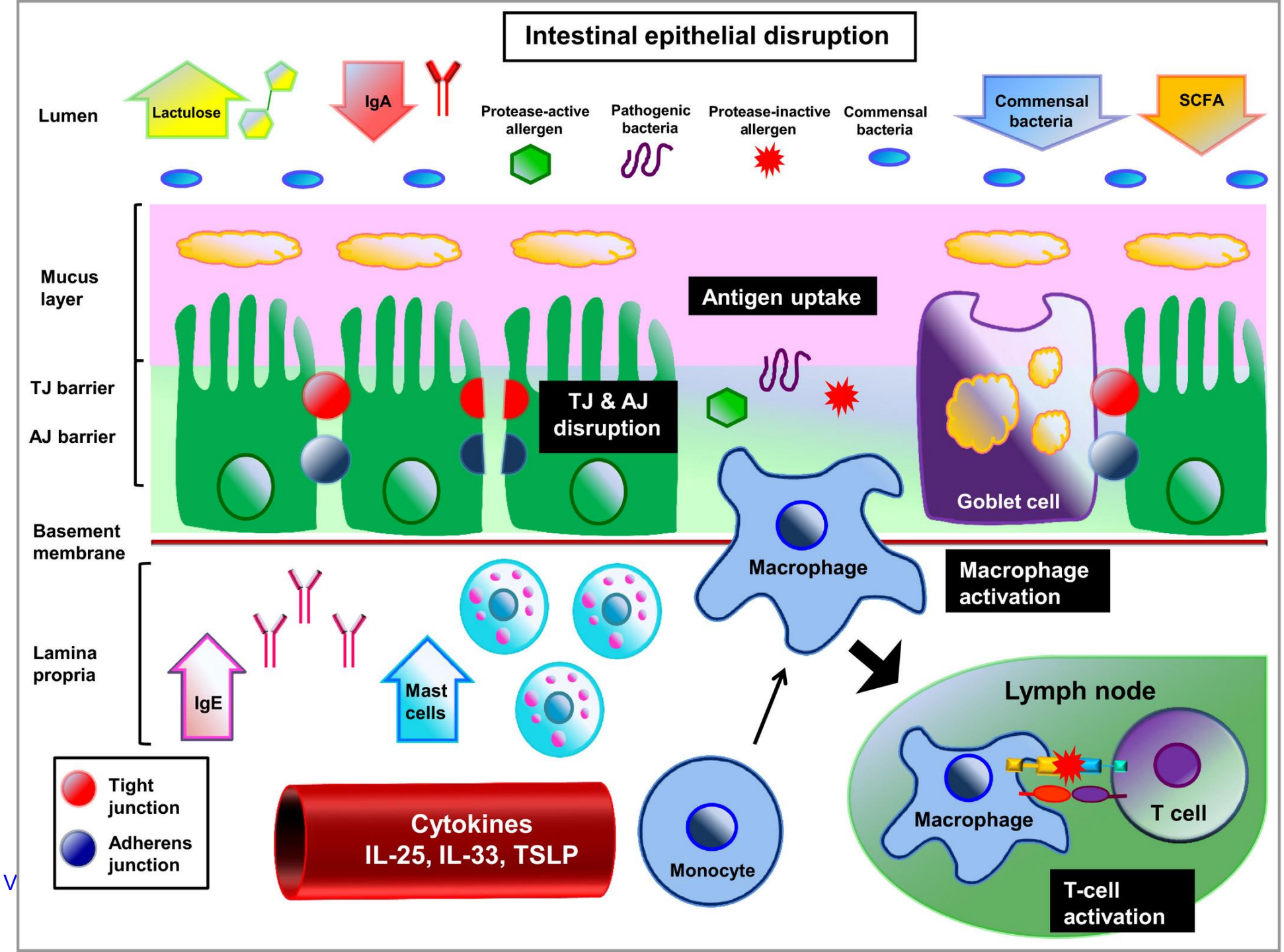
Itch and interleukin (IL)-31 signalling pathway

- The itch–scratch cycle is a common phenomenon whereby scratching behaviour induced by itch sensory transmission causes breakdown of the skin barrier. Antigen presenting cells such as dendritic cells (DCs) and macrophages are then sensitized to exogenous antigen. Subsequent processing in draining lymph nodes engages a naive T cell (Th0) with the DC. The DC also secretes IL-4, IL-5 and IL-13, which promotes induction of T helper (Th)2 differentiation and circulation to the target organs. IL-31 is secreted by activated Th2 in addition to mast cells, eosinophils and basophils. IL-31 plays a pivotal role in cell-mediated immunity in the skin, lung and intestine, and the perception of itch through binding to IL-31 receptors on nerve-fibre endings. Immunomodulating cytokines such as transforming growth factor (TGF)-β can downregulate IL-31 levels, whereas bacteria toxins such as staphylococcal α-toxin can increase IL-31 levels. The systemic allergic inflammatory response ultimately recruits additional pruritic initiators to the site of injury, which further propagates the itch–scratch cycle. TCR, T-cell receptor; MHC, major histocompatibility complex.


Intestinal epithelial disruption
Lumen
Lactulose
IgA
Protease-active allergen
Pathogenic bacteria
Protease-inactive allergen
Commensal bacteria
Commensal bacteria
SCFA
Mucus layer
TJ barrier
AJ barrier
Basement membrane
Lamina propria
TJ & AJ disruption
Antigen uptake
Goblet cell
Macrophage
Macrophage activation
IgE
Mast cells
Lymph node
Macrophage
T cell
T-cell activation
Tight junction
Adherens junction
Cytokines
IL-25, IL-33, TSLP
Monocyte

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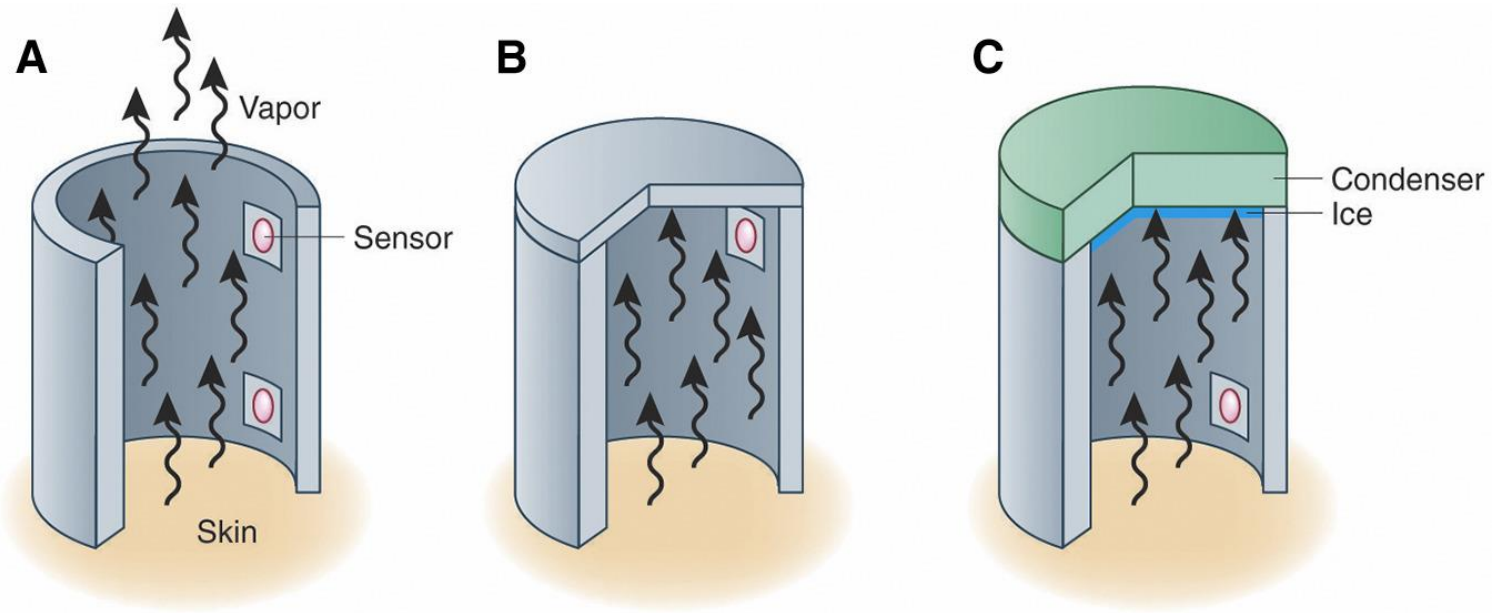
Gut barrier disruption

- Various factors can modulate gastrointestinal permeability and contribute to increased ‘gut leakiness’. Patients with atopic dermatitis have elevated luminal lactulose, decreased luminal IgA, and decreased luminal commensal bacteria and short-chain fatty acids (SCFAs). Normal gastrointestinal function and homeostasis are regulated by junctional complexes formed by tight junctions (TJs) and adherens junctions (AJs), mucosal production by goblet cells and the immune system within the intestinal laminal propria. Systemic inflammatory signals including interleukin (IL)-25, IL-33 and thymic stromal lymphopoietin (TSLP) can promote monocyte migration, diapedesis and activation into macrophage (arrow). Breaks in the barrier formed by the junctional complex allow luminal antigens access through the epithelial barrier where they are phagocytosed by macrophages and subsequently presented to T cells in draining lymph nodes (arrow head) to trigger visceral T helper 2-dominant hypersensitivity. Patients with atopic dermatitis also demonstrate elevated IgE levels in the serum and lamina propria and increased mast cell number and function, which can contribute to food allergen sensitivity.

Alexander H, Brown S, Danby S, Flohr C. Research Techniques Made Simple: Transepidermal Water Loss Measurement as a Research Tool. *J Invest Dermatol*. 2018;138(11):2295-2300.e1. doi:10.1016/j.jid.2018.09.001



TEWL devices.
(a) Open-chamber TEWL device. A hollow cylinder is placed in contact with the skin, and water vapor diffuses through the open chamber. Spatially separated temperature and relative humidity sensors detect the humidity gradient.
(b) Unventilated-chamber TEWL device. The upper end of the chamber is closed, resulting in water vapor collecting in the chamber. The temperature and relative humidity sensors detect the rate of increase of relative humidity.
(c) Condenser-chamber TEWL device. The upper end of the chamber is closed by a condenser that removes water vapor from the chamber, enabling continuous TEWL measurements to be recorded. Water vapor density is measured by sensors in the chamber and condenser. TEWL, transepidermal water loss.

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TEWL

Skin care practices also affect TEWL. Detergents such as sodium lauryl sulfate can damage the skin barrier and lead to increased TEWL, whereas emollients transiently occlude the skin and reduce TEWL.
Skin surface temperature and sweating additionally alter TEWL .
Älso seasonal variation in TEWL was shown
TEWL is affected by circadian rhythm and sun exposure.

TEWL

- TEWL has been shown to vary significantly at different anatomical sites within an individual. TEWL is high at the palms, soles, axillae, and forehead and low at the calf and forearm. The increased TEWL at sites such as the palms and soles is linked to the low sebaceous lipid content at these sites. Regional differences in TEWL may also be due to differences in sweat gland activity, occlusion, skin temperature, thickness, and microvasculature as well as corneocyte size, maturity, and shedding.

Dermotest

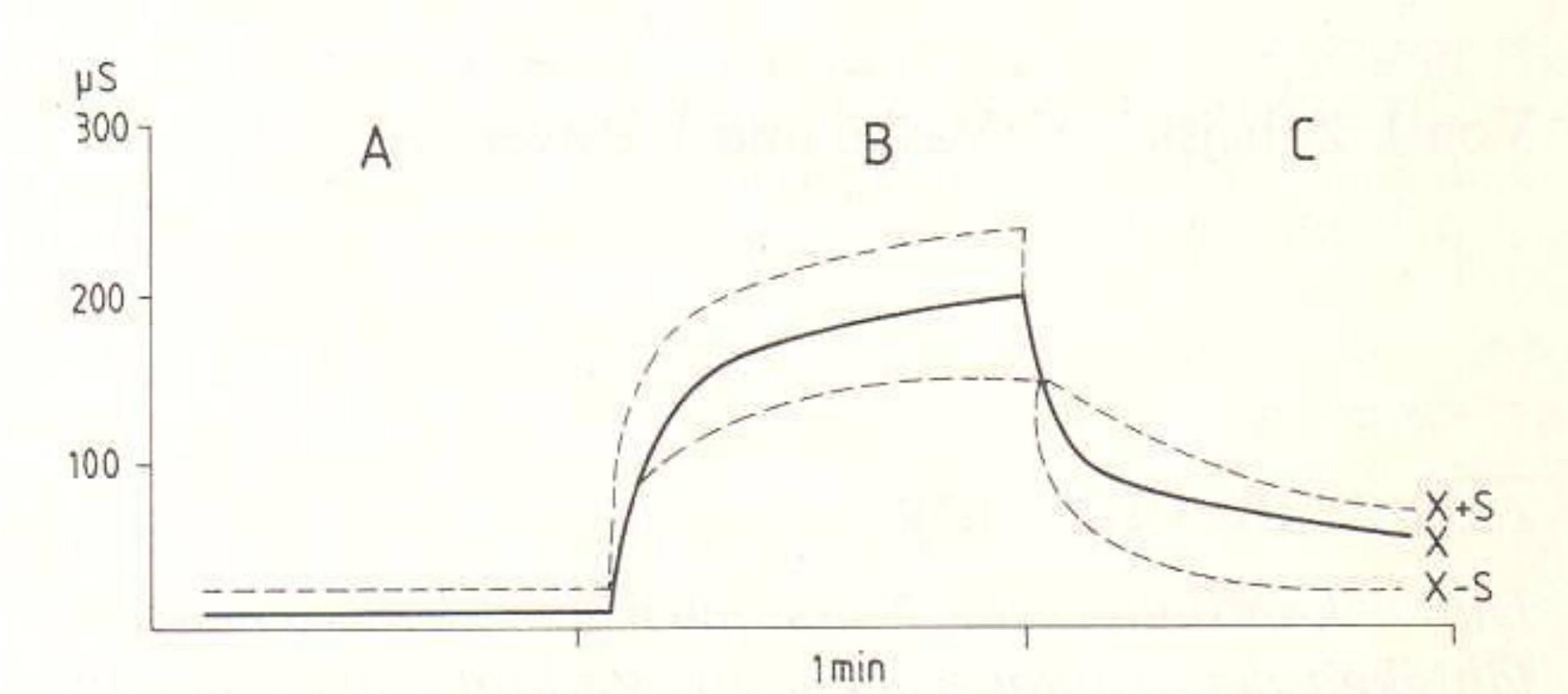

Abb. 1: Registration der elektrischen Leitfähigkeit vor (A), im Verlauf (B) und nach Beendigung der Iontophorese (C).

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