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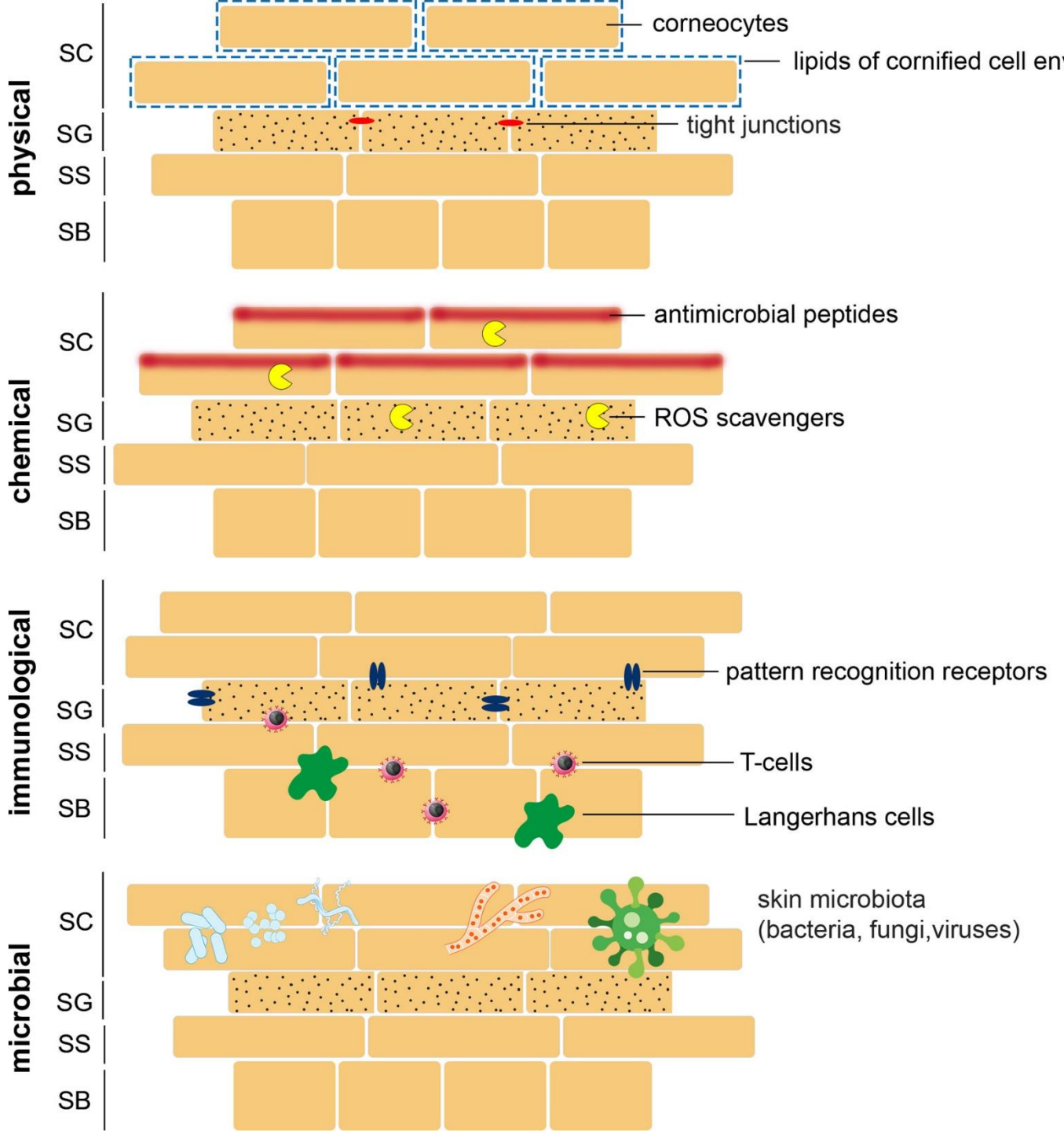
Kožní bariérové systémy ve zdraví a nemoci

Embryolog
Jaro 2024

Kožní bariéra

- Slouží jako první linie obrany mezi tělem a prostředím. Její poruchy vedou ke zvýšenému průniku mikrobů a alergenů.
- Zvýšený průnik látek s alergenním potenciálem zvyšuje riziko rozvoje přecitlivělosti, protože dochází k interakci mezi alergeny a a antigen- prezentujícími buňkami.
- Zvýšený průnik iritant podporuje rozvoj nealergických zánělivých reakcí.

Kožní bariéra



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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Kožní bariérové sytémy

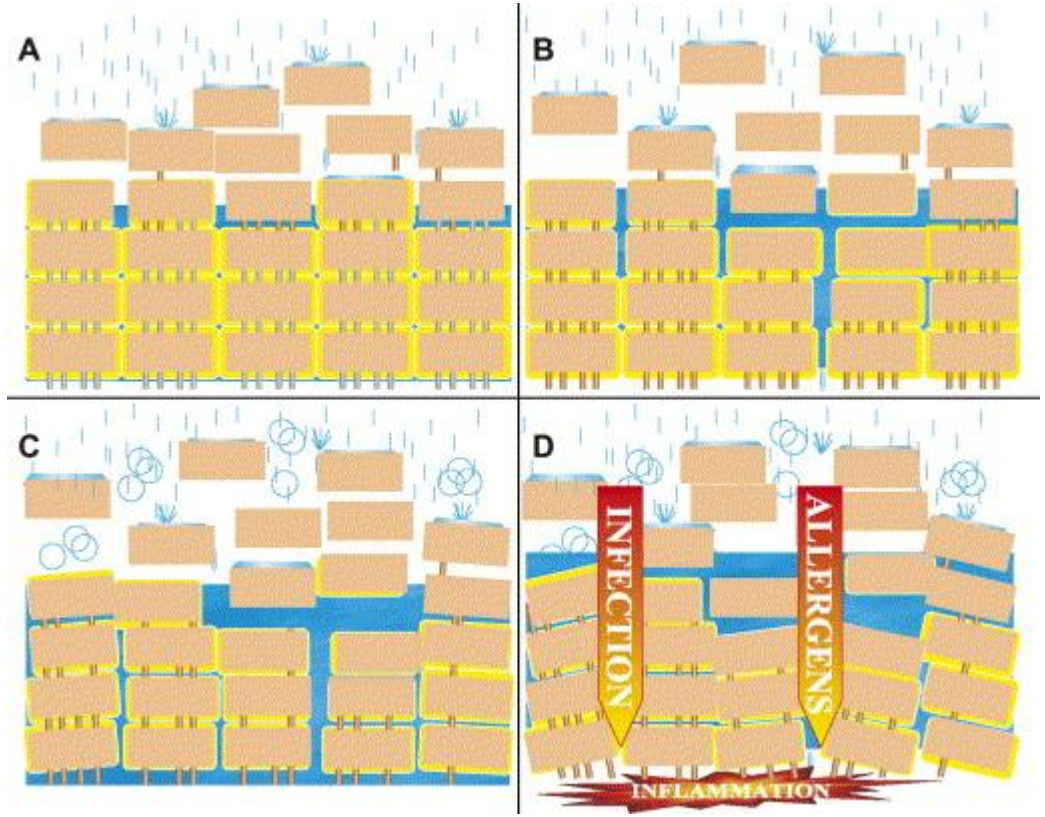
Typ bariéry	Funkce	Podklad	Lokalizace
Fyzikální bariéra	Odolnost mechanická Odolnost proti tření	Struktura/kolagen Desmosomy	Epidermis a dermis Epidermis
Epidermální vodní bariéra/permeabilita	Pohyb vody	Lipidy	Stratum corneum
Bariéra proti UV	Prevence poškození DNA, struktur v dermis apod.	Melanin Enzymy reparující DNA Karotenoidy Další pigmenty	Melanocyty Epidermis Dermální chromatofory
Oxidativní bariéra	Prevence peroxidace a poškození volnými radikály	Antioxidanty - vitamin C, E, další	Epidermis Mazové žlázy

Kožní bariérové systémy

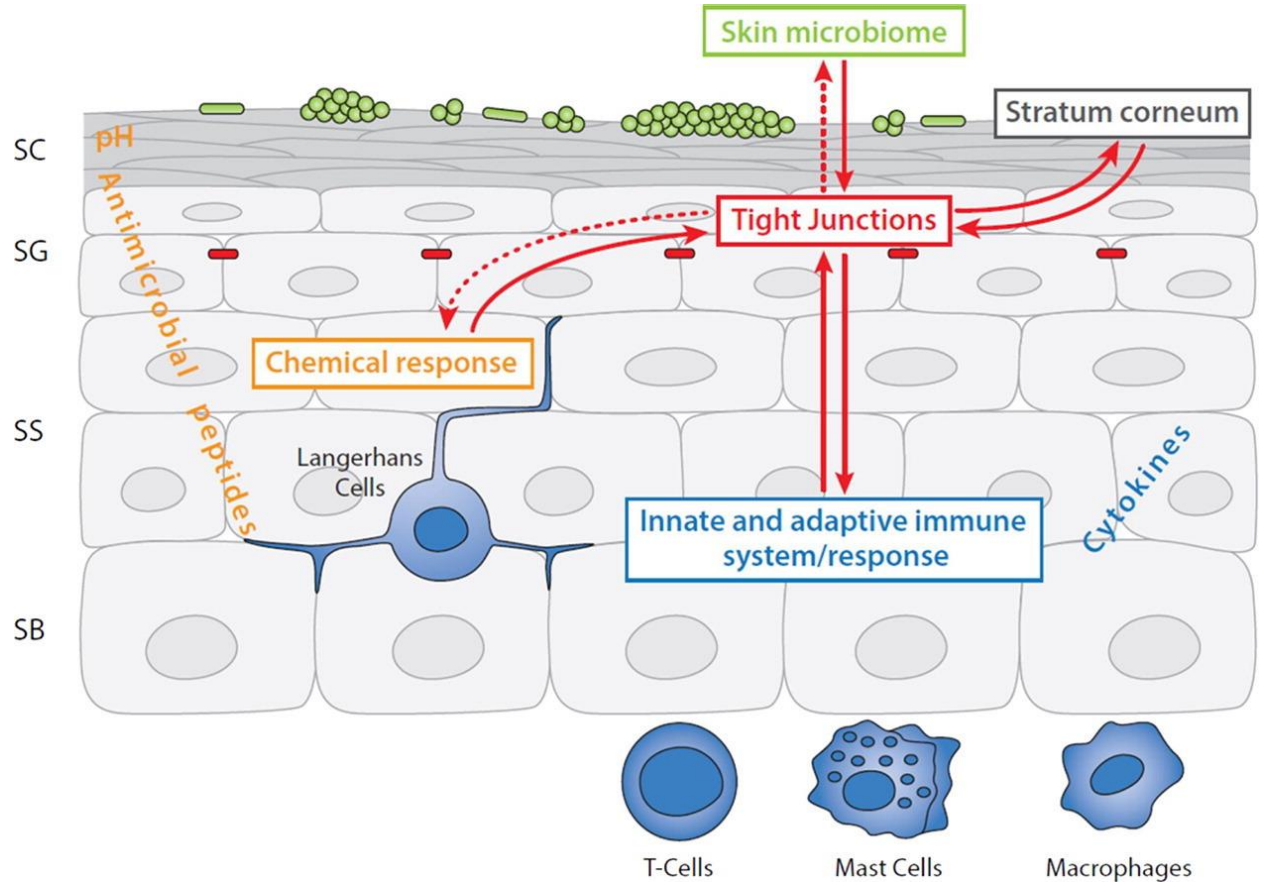
Typ bariéry	Funkce	Podklad	Lokalizace
Tepelná bariéra	Ochrana před poškozením teplem/chladem	Proteiny tepelného šoku	Epidermis
		Anti chladové proteiny	Dermis
Imunitní bariéra	Zajištění imunity	Langerhansovy buňky	Epidermis
	buňky	Jiné dendritické	Dermis,
		potní žlázy	
		Jiné buněčné typy	
		Imunoglobuliny	
Mikrobiální bariéra	Ochrana před patogeny	Defenziny	Stratum corneum
		Sfingozin	
		Symbiotická mikroflóra	Epidermis

Bariérová funkce kůže

- Je nejvíce závislá na funkci stratum corneum (SC). SC se tvoří během striktně regulované diferenciace keratinocytů, zvané keratinizace. Během keratinizace se keratinocyty pohybují os stratum basale přes stratum spinosum a stratum granulosum do stratum corneum.
- Ve SG keratinocyty začínají produkovat dvě membránou obklopená tělíska: keratohyalinová granula a lamelární tělíska.
- Keratohyalinová granula obsahují intracelulární složky SC (filagrin [FLG], loricrin, a keratinová filamenta), zatímco lamelární tělíska obsahují extracelulární komponenty (lipidy, korneodesmosin a kalikreiny).
- Ve SC se keratinocyty oplošťují a denukleují a jejich buněčná membrána je nahrazena speciální strukturou, zvanou kornifikovaná obálka (CE). Během přesunu z SG do SC jsou lamelární tělíska exportována do intercelulárního prostoru. Vzniká struktura „cihel a malty“.



Analogie stratum corneum s cihlovou stěnou jako model epidermální bariéry. Korneodesmozomy zdravé kůže jsou v celé vrstvě stratum cornemu intaktní (železné tyče, A). Směrem k povrchu epidermis se začínají korneodesmozomy štěpit jako součást procesu fyziologické deskvamace, což je proces analogický rezivění železných tyčí **(A)**. Pokud je jedinec predisponován k atopické dermatitidě, předčasné štěpení korneodesmosomů vede k podpoře deskvamace, což vede k rezavění železných tyčí dolů podél cihlové stěny **(B)**. Pokud jsou už železné tyče oslabené (zrezivělé), faktory prostředí , jako je mýdlo, je budou dále korodovat mnohem snadněji. Cihlová stěna se začně hroutit **(C)** a umožní průnik alergenů **(D)**.



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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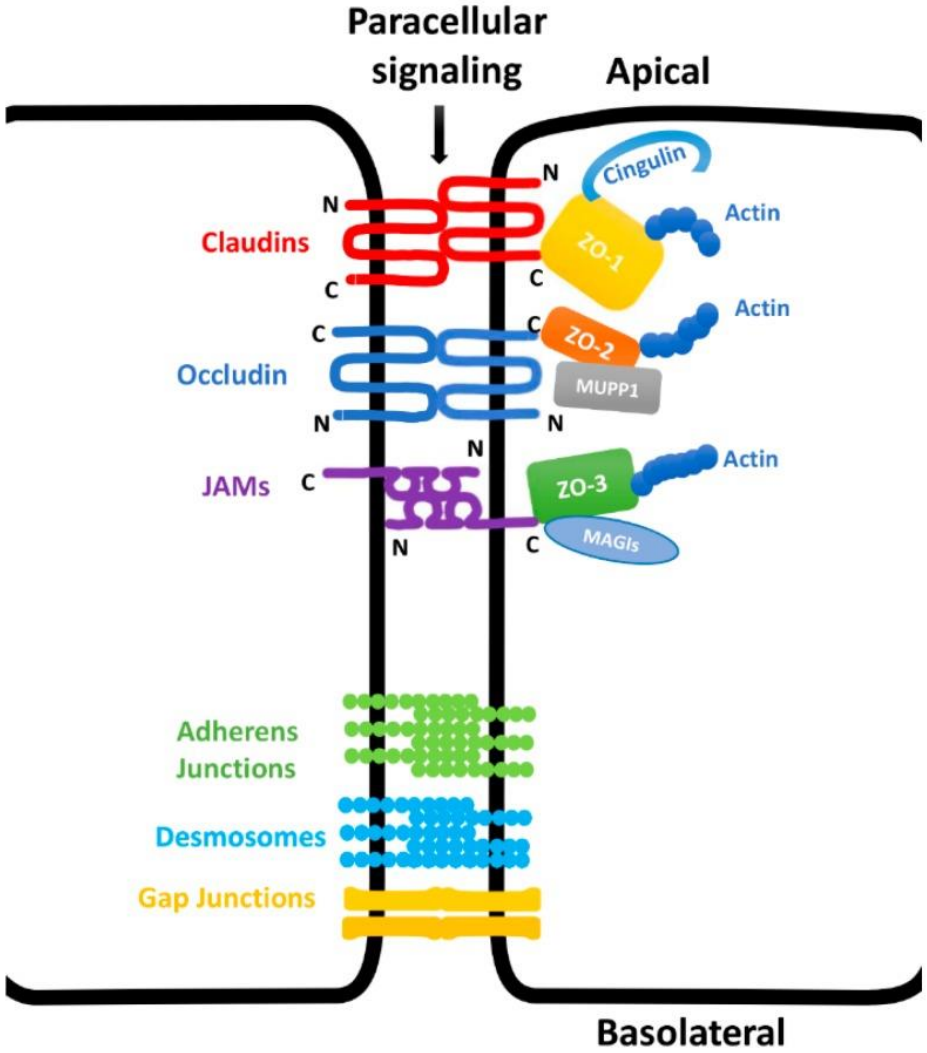

Shi J, Barakat M, Chen D, Chen L. Bicellular Tight Junctions and Wound Healing. *Int J Mol Sci*. 2018;19(12):3862. Published 2018 Dec 4. doi:10.3390/ijms19123862

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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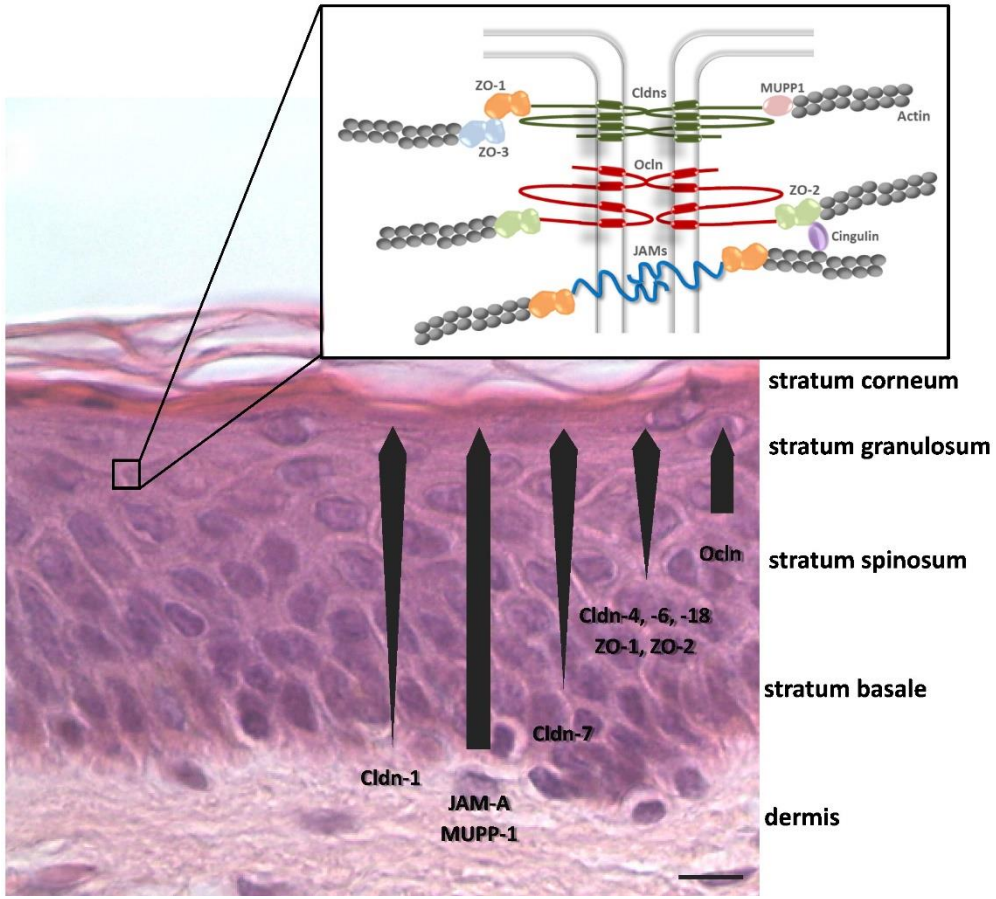

Localization of TJs and TJ proteins in the epidermis and molecular composition of TJs. Cldn: claudin; JAM: junctional adhesion molecule, MUPP1: Multi-PDZ domain protein 1, Ocln: occludin. Bar:20 μm.

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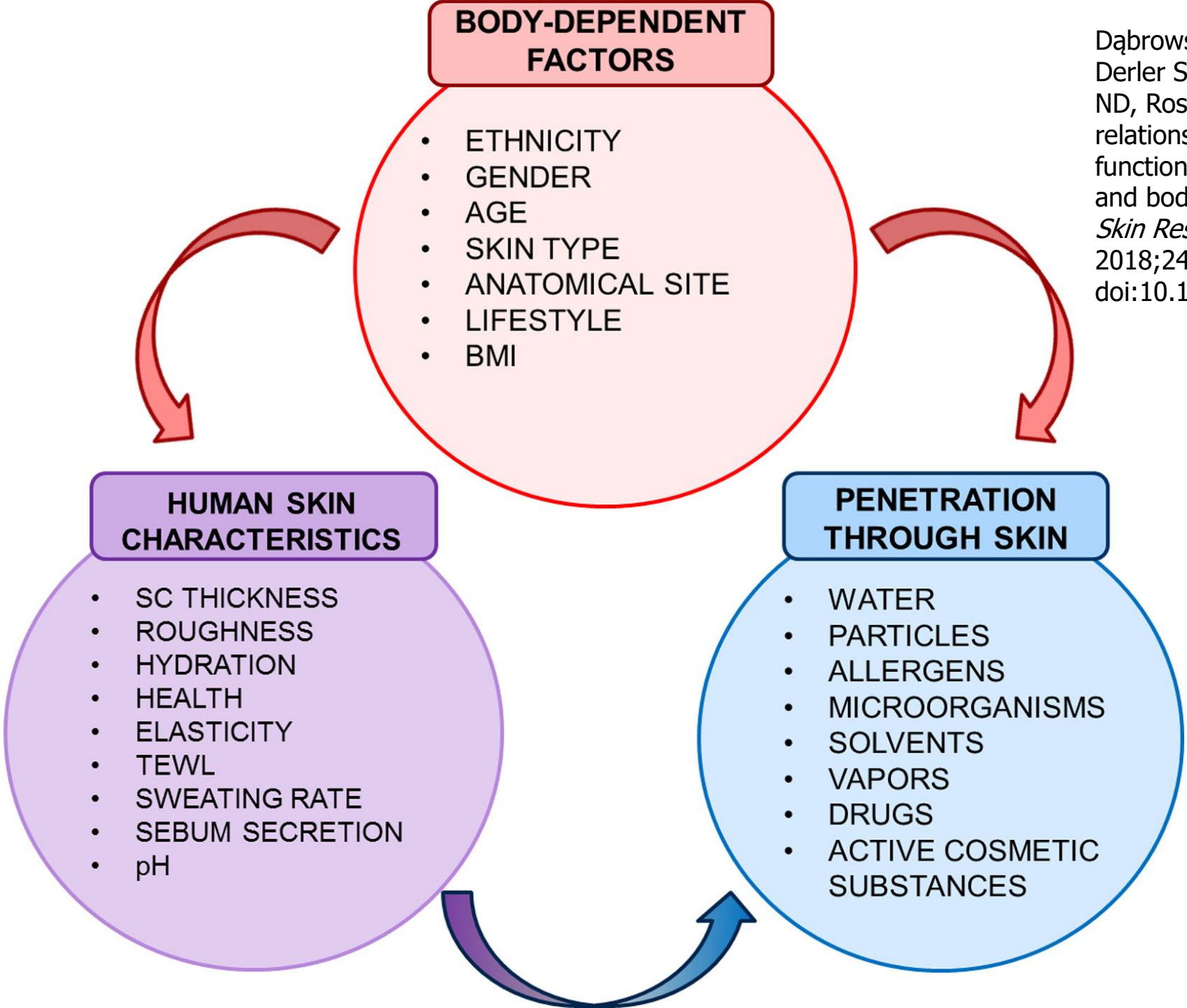

Dąbrowska AK, Spano F, Derler S, Adlhart C, Spencer ND, Rossi RM. The relationship between skin function, barrier properties, and body-dependent factors. *Skin Res Technol*. 2018;24(2):165-174. doi:10.1111/srt.12424

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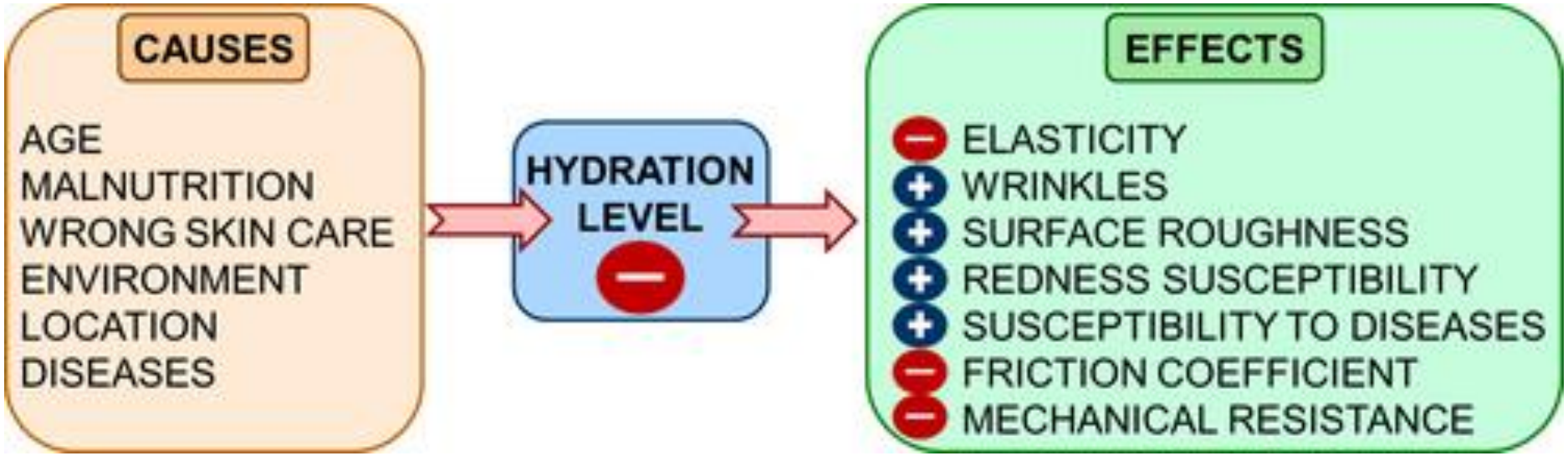
Skin hydration

- 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.



Příčina a následky poklesu kožní hydratace. "+" a "-" symbolizují pozitivní a negativní korelace

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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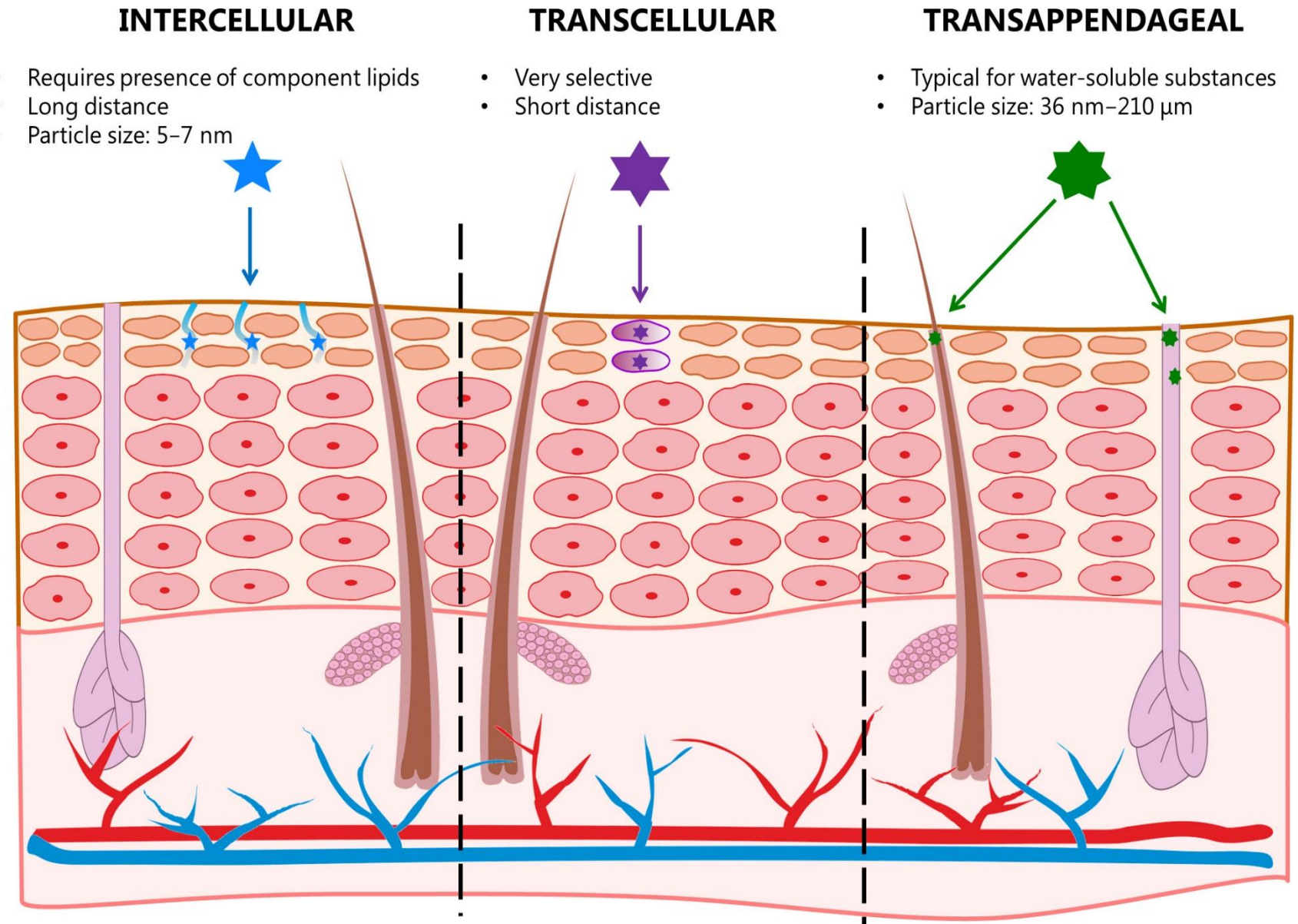
Penetration through skin

- 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**.

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



Tři průnikové cesty do kůže: intercelulární, transcelulární a transadnexální

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The intercellular pathway

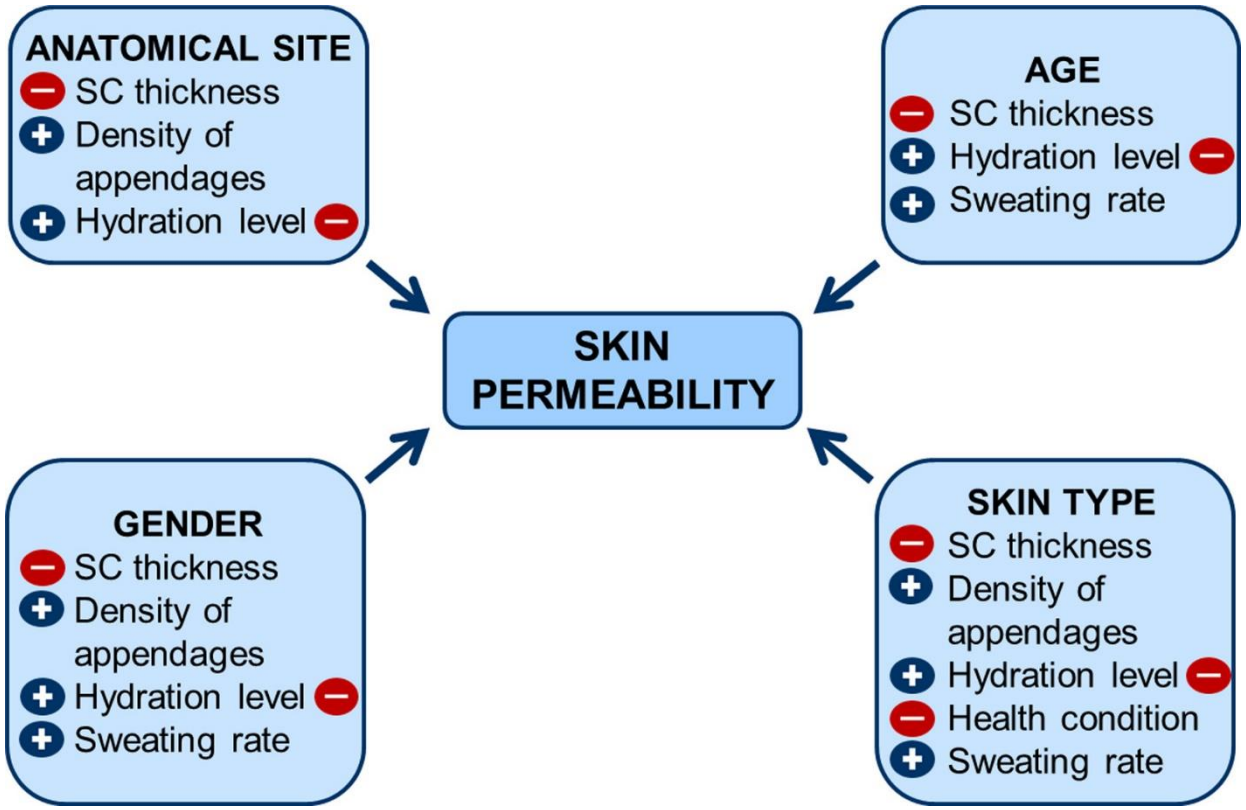
- involves the transport of substances between the cells of the SC layer. This mechanism plays a major role in skin permeability and requires the presence of component lipids, such as ceramides, that allow free lateral water diffusion by forming nanometric spaces via short range repulsive forces. The 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.



Faktory ovlivňující permeabilitu kůže. "+" a "-" symbolizují pozitivní a negativní korelace mezi jednotlivými faktory a kožní permeabilitou.

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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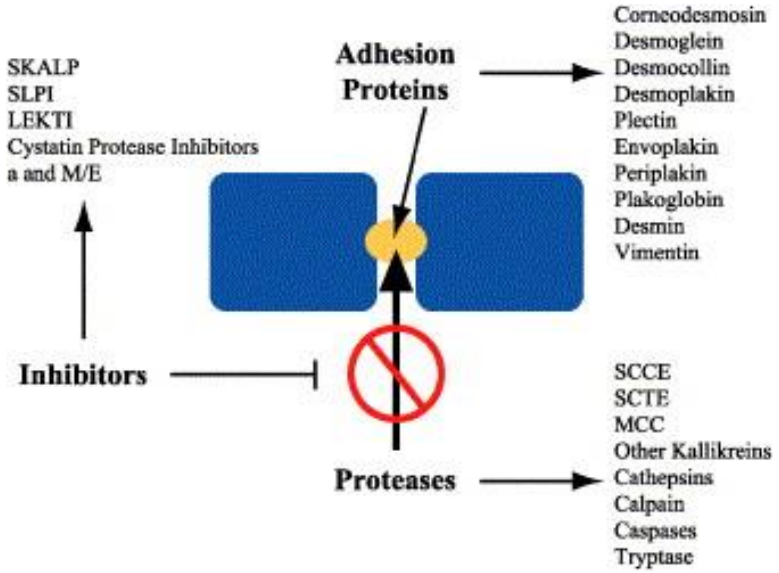
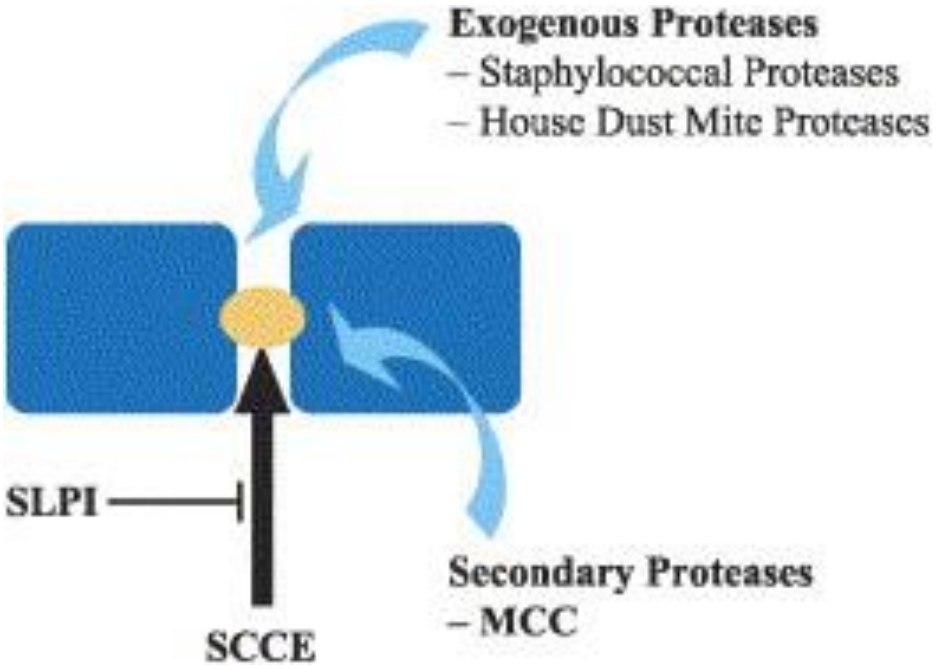
Protektivní funkce savčího stratum corneum

Funkce	Lokalizace
epidermální vodní bariéra/permeabilita	extracelulární
spuštění zánětu (aktivace cytokinů)	korneocyt
soudržnost (integrita) a deskvamace	extracelulární
antimikrobiální bariéra (vrozená imunita)	extracelulární
mechanická bariéra (proti úderu a tření)	korneocyt
proti toxickým vlivům/alergenům	extracelulární
selektivní absorpce	extracelulární
hydratace	korneocyt
proti UV	korneocyt
další	

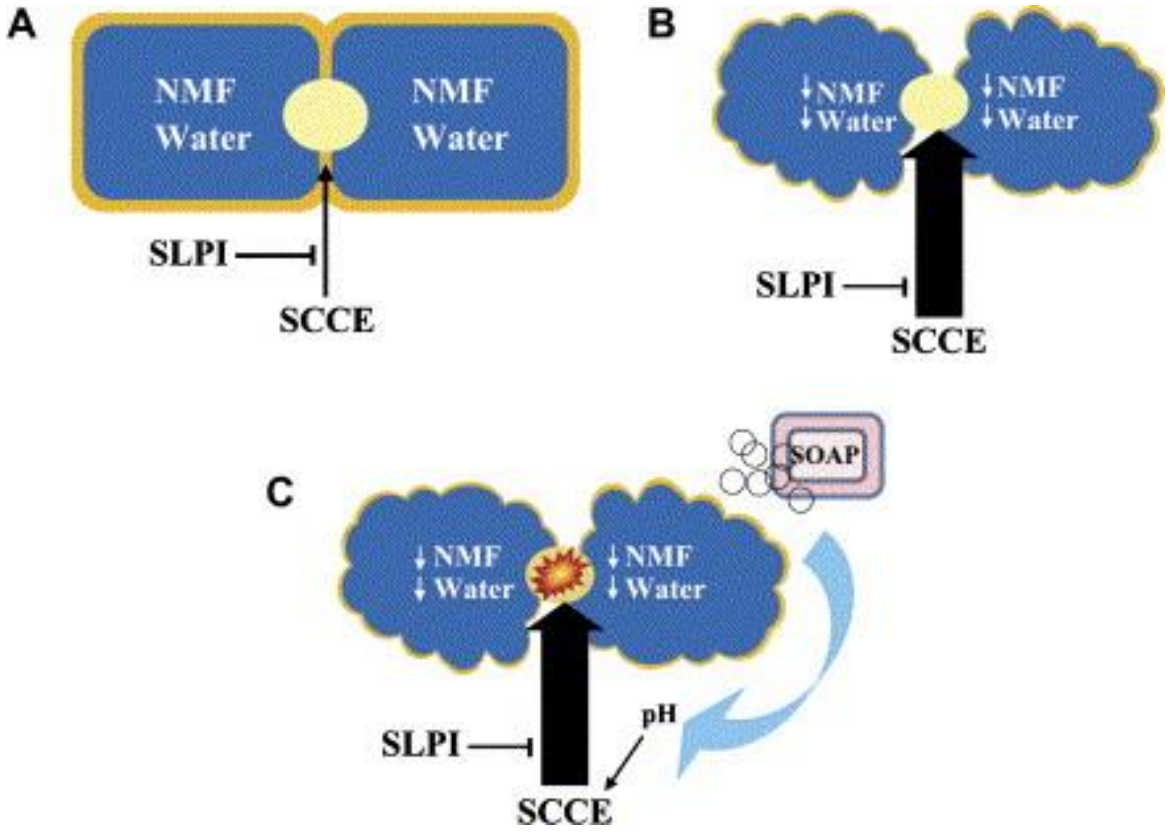


Korneocyty kožní bariéry jsou spojeny kornoedesmosomy pomocí několika adhezivních protenů. Deskvamace korneocytů se může uskutečnit pouze pod vlivem specifických kožních proteáz, jako je SCCE. Tyto proteázy jsou pod kontrolou specifických inhibitorů proteáz, jako je „skin-derived antileukoprotease“ *(SKALP)*.

SLPI, serine leukoprotease inhibitor; *LEKTI*, lymphoepithelial Kazal-type 5 serine protease inhibitor.

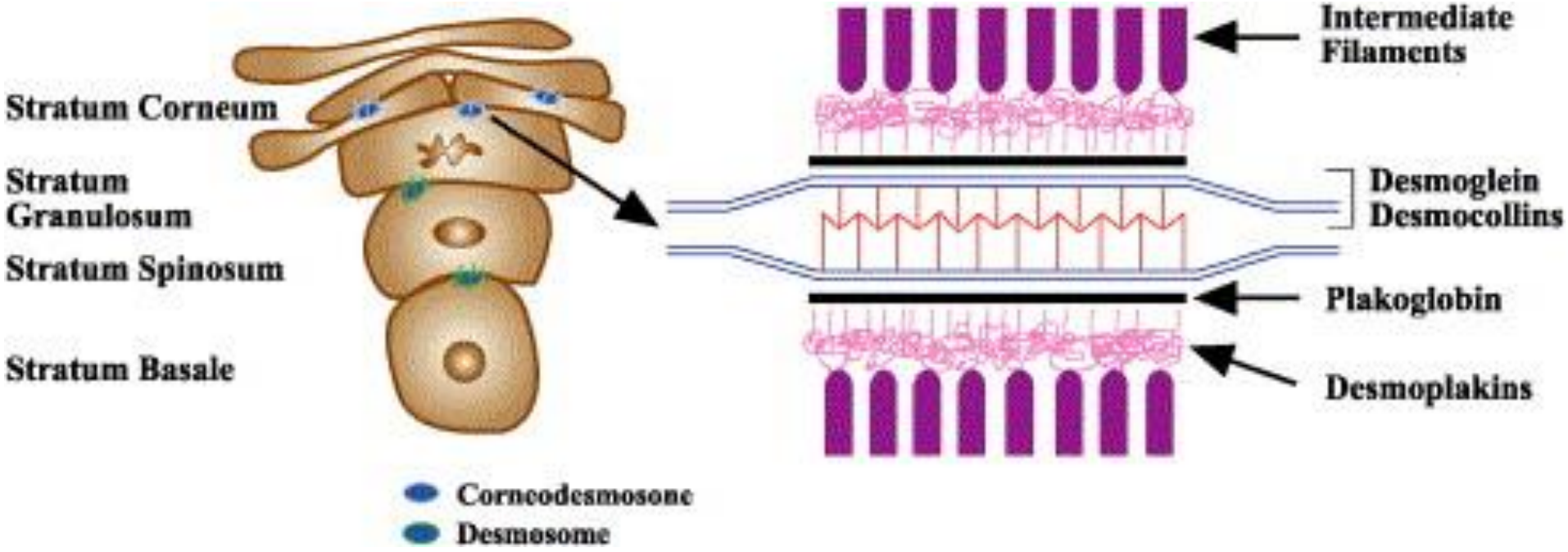


Avšak korneodesmozomy mohou být štěpeny také jinými typy proteáz. Jakýkoliv zánětlivý infiltrát (např. u klinicky manifestní AD) produkuje sekundární proteinázy (MCC). Stratum corneum je také vystaveno mnoha exogenním proteázám, jejichž zdrojem je např. *Staphylococcus aureus* nebo roztoči v domácím prachu.
SLPI, serine leukoprotease inhibitor.



Ve stratum cornemu zdravé kůže existuje rovnováha mezi strukturální integritou korneodesmosomů a hladinou proteáz a jejich inhibitorů **(A)**. U geneticky predisponovaných osob může zvýšená aktivita proteáz vést k předčasnému štěpení korneodesmosomů a ztenčení stratum corneum (**B** a **C**). Použití mýdla alkalizuje povrch kůže pH z 5,5 na ≥7,5), což optimalizuje podmínky pro aktivitu proteáz a podporuje štěpení korneodesmosomů a deskvamaci (**C**). ,

SLPI- skin leukoprotease inhibitor

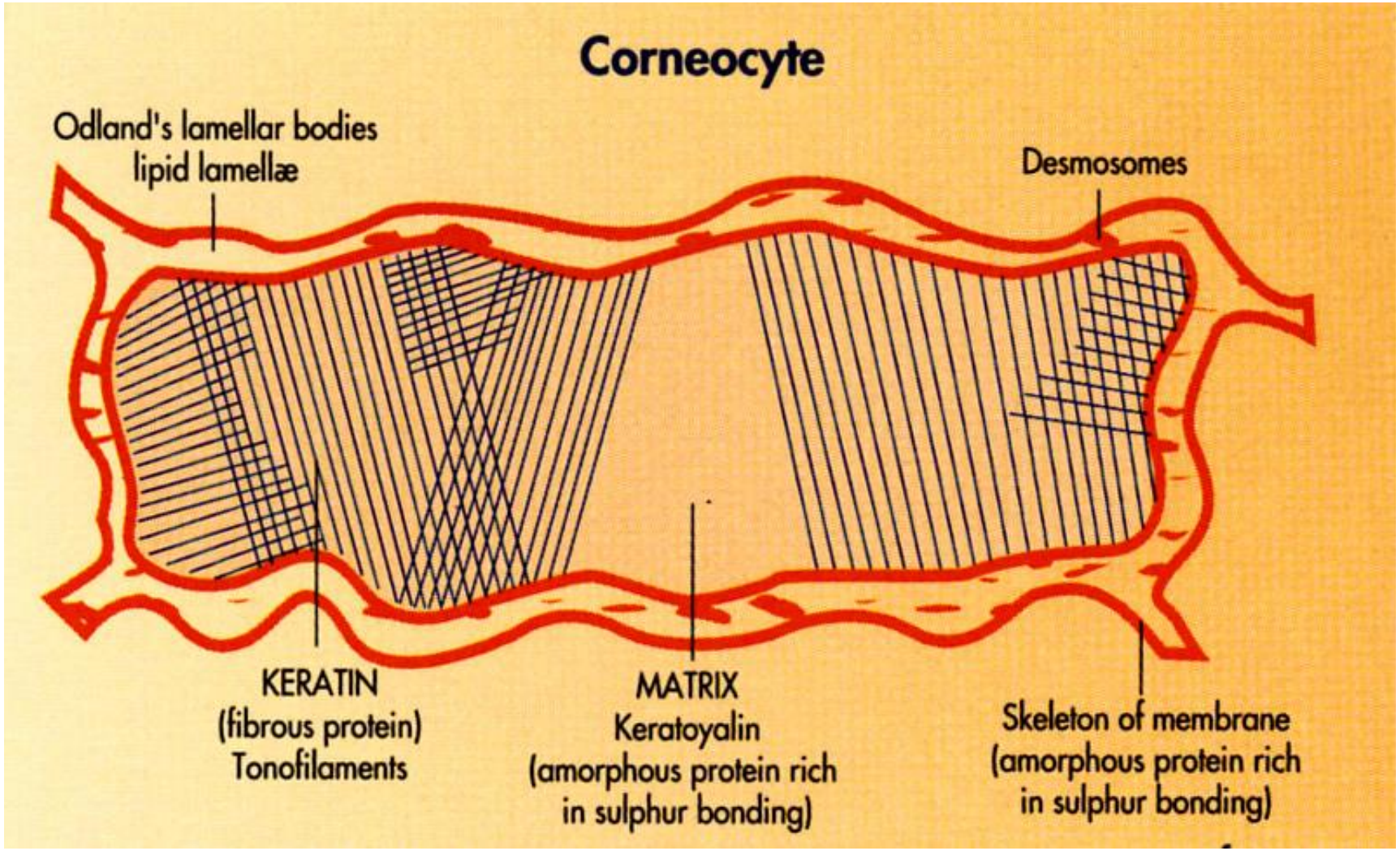


Bariéra proti průniku iritujících látek, alergenů a léků je v nižší části stratum corneum.
Strukturální integrita stratum corneum je udržována pomocí modifikovaných desmosomů (korneodesmosomů), které spojují korneocyty. Jak se korneocyty pohybují přes stratum corneum, korneodesmosomy jsou postupně štěpeny specificky kožními proteázami. Korneocyty, které už nejsou propojeny pomocí korneodesmosomů, se tak mohou odloučit od povrchu kůže (deskvamace).

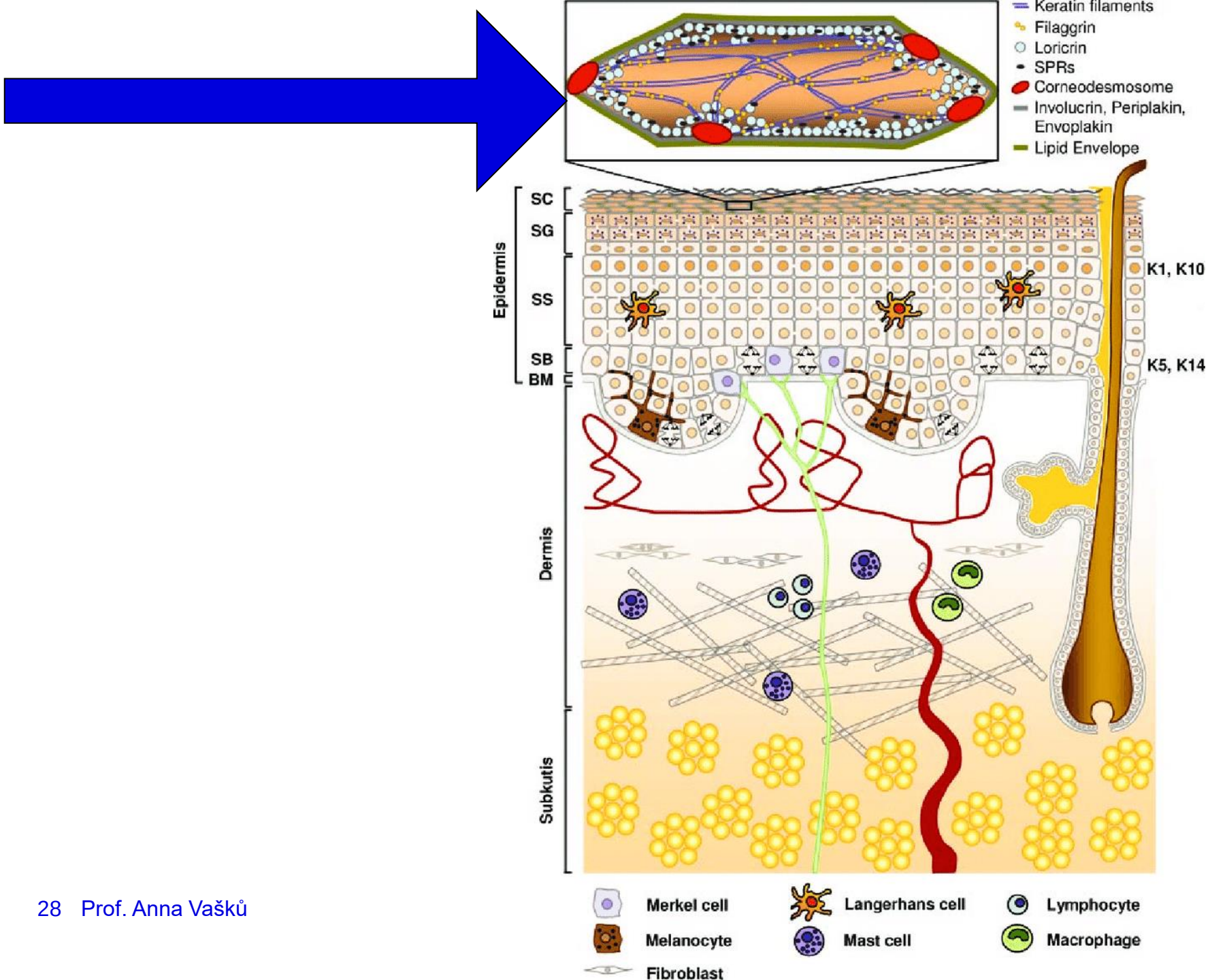
Korneocyt

- Strukturální základ str. corneum a rezervoár vody - zajištění enzymatických procesů ve stratum corneum

Korneocyt obklopuje zrohovatělý obal, 15-20 nm silná struktura a nad ní leží 5 nm vrstva specializovaných lipidů – jedna vrstva představující hydrofobní rozhraní mezi hydrofilním povrchem CE a vysoce hydrofobními dvojvrstvými lipidy.


Corneocyte
Odland's lamellar bodies
lipid lamellæ
Desmosomes
KERATIN
(fibrous protein)
Tonofilaments
MATRIX
Keratoyalin
(amorphous protein rich
in sulphur bonding)
Skeleton of membrane
(amorphous protein rich
in sulphur bonding)

Podle RoC s.a.


Keratin filaments
Filaggrin
Loricrin
SPRs
Corneodesmosome
Involucrin, Periplakin, Envoplakin
Lipid Envelope
SC
SG
SS
SB
BM
Epidermis
K1, K10
K5, K14
Dermis
Subkutis
Merkel cell
Melanocyte
Fibroblast
Langerhans cell
Mast cell
Lymphocyte
Macrophage

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Základní děje v korneocytu

Cytoplasma korneocytů

- Katabolismus filagrinu na aminokyseliny a produkty jejich deaminace

Funkce zrohovatělého obalu korneocytů

- Úplná degradace plasmatické membrány
- Příčné vazby ve zrohovatělém obalu zprostředkované transglutaminázou
- Kovalentní zachycení vnějšího obalu bohatého na hydroxyceramidy (tukový obal korneocytu)

Homeostáza epidermální vodní bariéry

- Lamelární dvouvrstevné uspořádání lipidové matrix korneocytu
- Při narušení – neodkladná sekrece lamelárních tělísek do oblasti mezi str. granulosum a str. corneum
- rovněž regulace diferenciace keratinocytů, úloha PPAR (peroxysome proliferator activated receptor) a LXR (liver X receptor)(nukleární receptory)
- aktivace PPAR a LXR endogenními lipidy, tyto naopak regulují lipidový metabolismus – „liposenzory keratinocytů“

Epidermální vodní bariéra a její antimikrobiální funkce

Antimikrobiální peptidy

- malé kationické peptidy
- součást nespecifické imunity
- aktivita proti bakteriím, virům i houbám
- aktivují další součásti vrozené i získané imunity

Hlavní součástí katelicidiny a defenziny

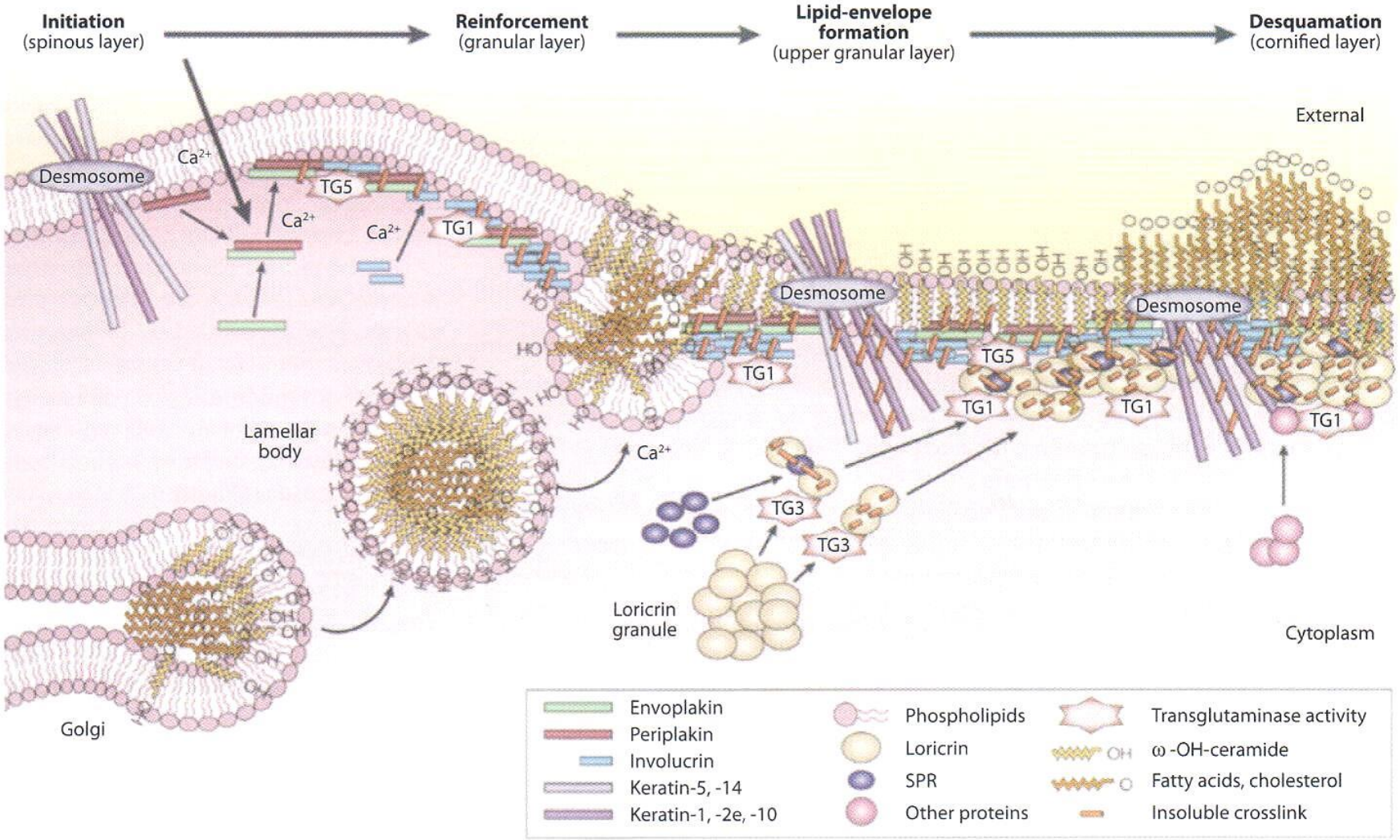


FIGURE 1 Formation of the cornified envelope. The sequence of the formation of the cornified cell envelope is the initiation stage (spinous layer), the reinforcement phase (granular layer), the formation of the lipid-envelope phase (upper granular layer), and the desquamation phase (cornified layer). SPR = small proline-rich protein; OH = hydroxide; Ca^{2+} = calcium ion; TG = transglutaminase. Reproduced, with permission, from Candi et al.[2]

Základní děje ve stratum corneum

Extracelulární „processing“

- Proteolýza desmozomů
- Katabolismus lamelárními tělísky dodaných polárních lipidů enzymy:
  - Sekreční fosfolipáza
  - Beta-glukocerebrosidáza
  - Steroidní sulfatáza
  - Kyselá sfingomyelináza

Podle Eliase, 2006

Korneodesmozom

- Odpovídá desmozomům v hlubší epidermis
- Primární faktor v soudržnosti stratum corneum
- Vazba na proces deskvamace
- Desmokolin, desmoglein

Lamelární tělísko

- Zásadní a ústřední role v tvorbě, zachování a reparaci epidermální vodní bariéry

- Heterogenní obsah, hlavní složka **glukosylceramid**

- **Kaveoliny** – bílkoviny s vazbou na cholesterol

Tvorba lamelárních tělísek

Zvýšena	Snížena
Psoriasis	
Ozáření UVB, X	
Retinoidy	Glukokortikoidy
Porušení bariéry	Stárnutí kůže
Nethertonův syndrom	

Enzymy obsažené v lamelárním tělísku

Enzymy	*Funkce*
Lipidové hydrolázy	
Beta-glukocerebrosidáza	Konvertuje glukosylceramidy na ceramidy
Kyselá sfingomyelináza	Konvertuje sfingomyelin na ceramidy
Sekreční fosfolipáza A2	Konvertuje fosfolipidy na volné mastné kyseliny
Kyselá lipáza	Deacyluje omega-esterifikované ceramidy

Enzymy obsažené v lamelárním tělísku

Enzymy	***Funkce***
Proteázy	
Chemotryptický enzym SC	Degraduje korneodesmozomy Aktivuje IL-1beta
Aspartátové proteázy (např. katepsin L)	Deskvamace
Glykosidázy	Deskvamace?
Kyselá fosfatáza	Neznámá funkce
Inhibitory proteáz	
Inhibitory serin proteáz	Deskvamace, aktivace cytokinů?
Inhibitory cystein proteáz	Deskvamace

Podle Eliase, 2006

Gradient epidermálního kalcia

- Nejnižší hladiny ve str. basale, nejvyšší ve str. granulosum

- Změny koncentrace iontů vápníku ve str. granulosum mohou přímo indukovat reparaci bariéry, dokonce beze změn epidermální vodní bariéry

Patofyziologie sekrečního sytému lamelárního tělíska

Sekrece

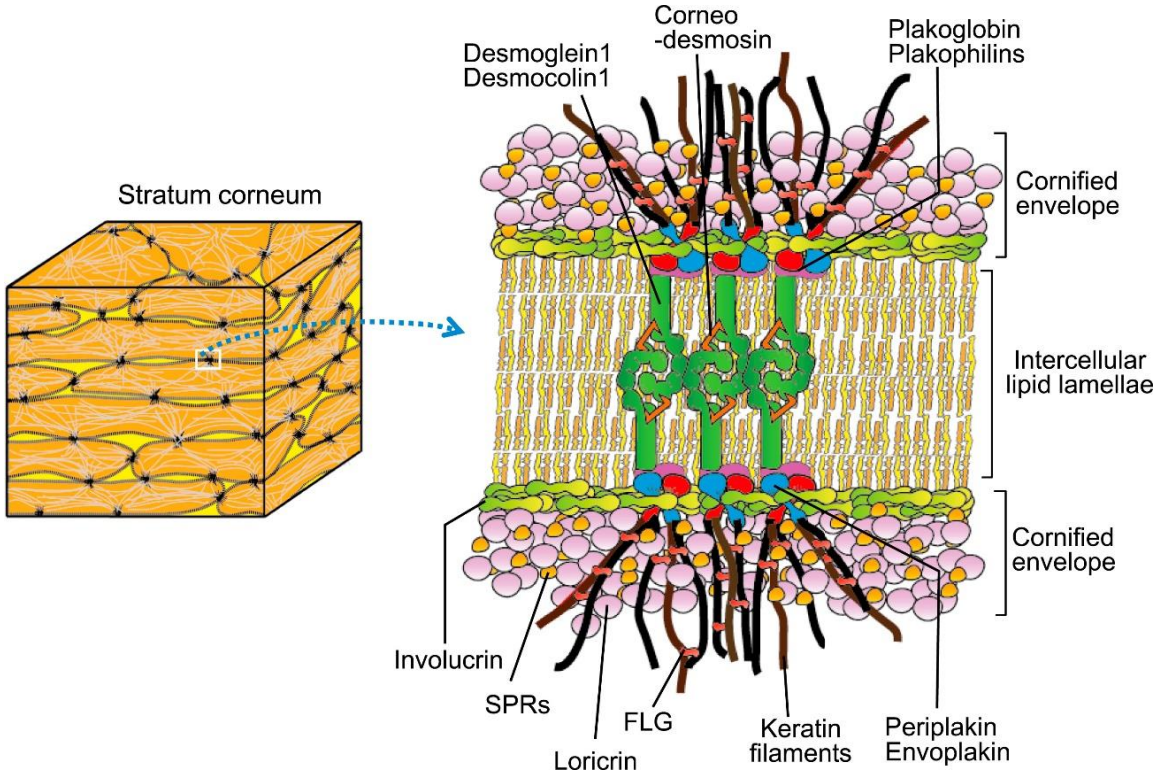
Zvýšena

Psoriasis

Porušení bariéry

Snížena

Atopická dermatitida



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

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 SPRs.
Envoplakin-periplakin heterodimers conjugate keratin filaments.

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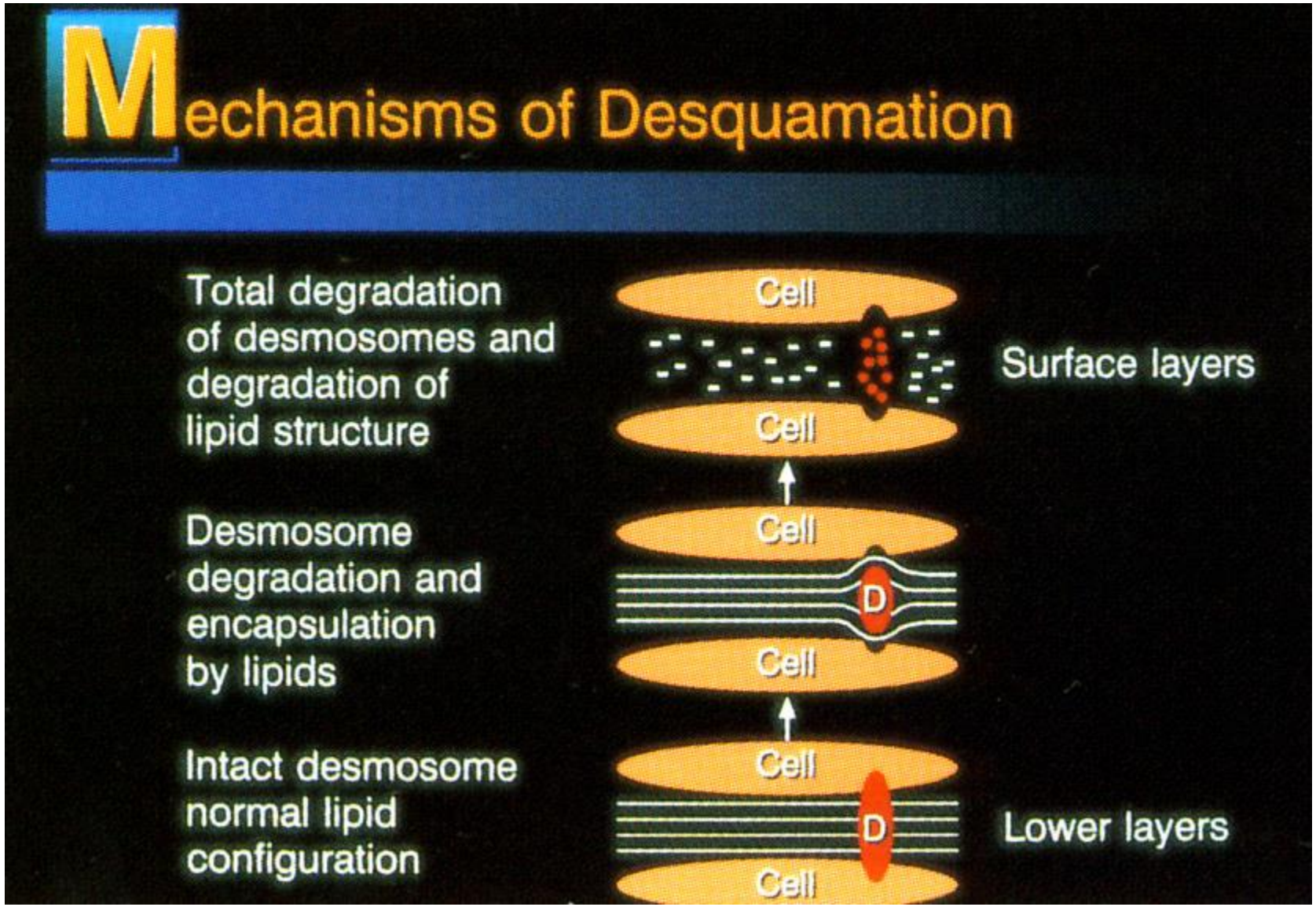


Podle Rawlingse, 1993

Složky antimikrobiální obrany v bariérovém systému lidské kůže

Bariéra	Složky
Kyselé pH	Na+/H+ výměník typu 1 Kyselina urokanová Kyselina mléčná Volné mastné kyseliny
Lipidy	Volné mastné kyseliny Glykosfingolipidy Fosfolipidy Sfingosiny
Antimikrobiální peptidy	Defenziny Katelicidiny Dermcidiny Chemokiny Enzymy Neuropeptidy

Kateliciciny a defenziny

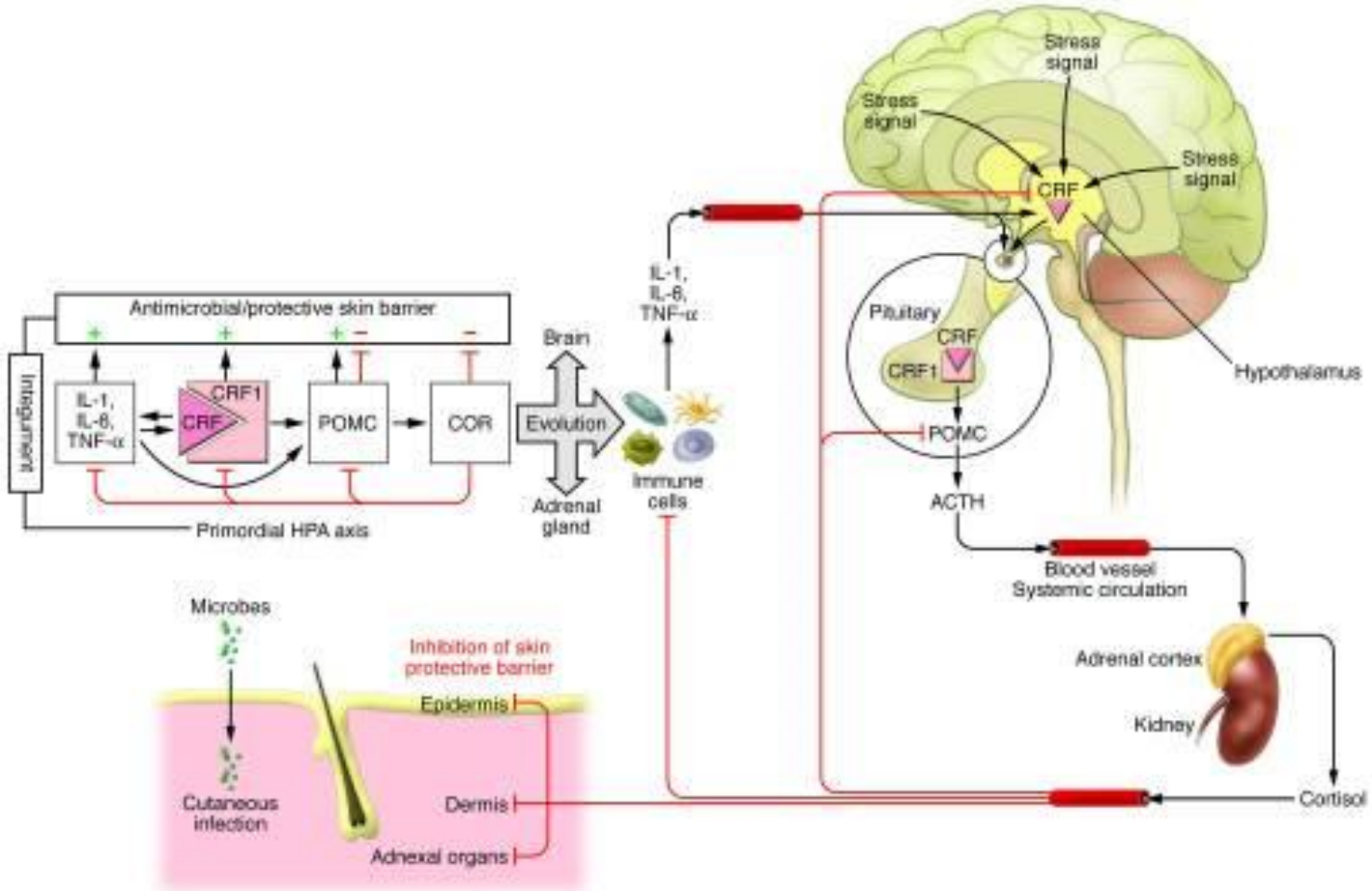
- Aktivní ve stratum corneum, jejich syntéza především na úrovni str. spinosum a granulosum
- Lidský beta-defenzin 2 (human beta- defensin 2, HBD-2) – lokalizován v lamelárních tělíscích, základních mikroorganelách v rámci epidermální bariéry
- Propojení funkcí v rámci regulace permeability a antimikrobiální obrany
- HBD- 2 a HBD- 3 – vyšší hladiny v projevech psoriázy, nižší u atopické dermatitidy

Účinky stresu na mnohočetné obranné funkce

Stresor funkce	Společně regulované
Porušení bariéry/vnější inzult	Epidermální vodní bariéra Zánět
Psychologický stres	Epidermální vodní bariéra Integrita a soudržnost stratum corneum
Zvýšení pH	Epidermální vodní bariéra Integrita a soudržnost stratum corneum Aktivace cytokinů/zánět Antimikrobiální bariéra

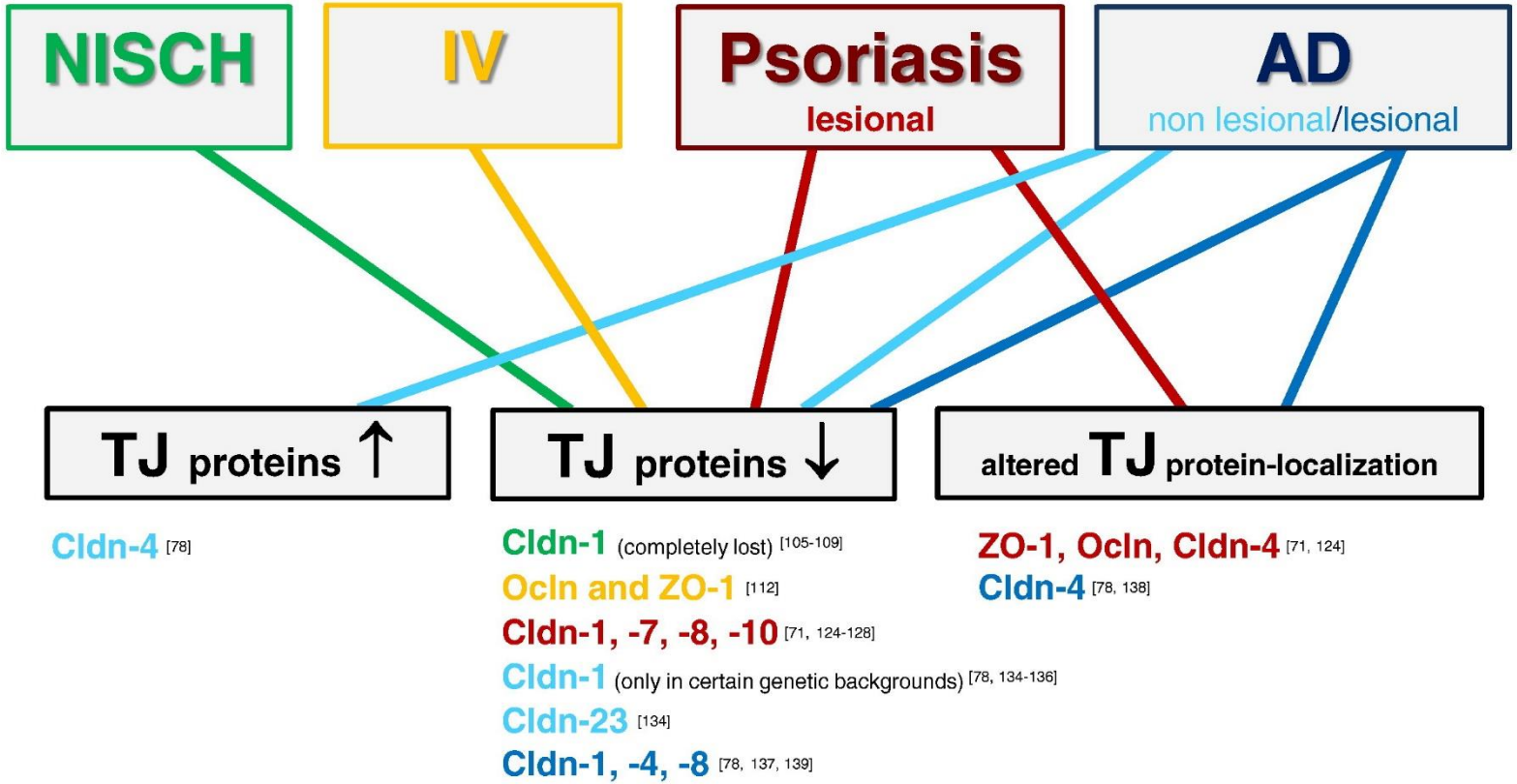
Podle Eliase, 2006

Hypothalamicko-hypofyzární osa a kůže



Poškozená kožní bariéra

- Podporuje průnik externích alergenů a rychle vyvolává zánět kůže. To dále podporuje interakci těchto alergenů as lokálními imunocyty, což může vést až k systémovým imunitním odpovědím. To se nazývá hypotéza „z vnějšku dovnitř“ a vysvětluje asociaci mezi dysfunkcí kožní bariéry a zvýšeným rizikem rozvoje alergických nemocí, včetně atopické dermatitidy, astmatu, potravinových alergií a alergické rinitidy.
- Chronický zánět kůže dále oslabuje kožní bariéru, což dále podporuje exacerbaci patologické smyčky mezi kožní bariérou a kožní imunitou (“outside-to-inside-and-back-to-outside” hypothesis).

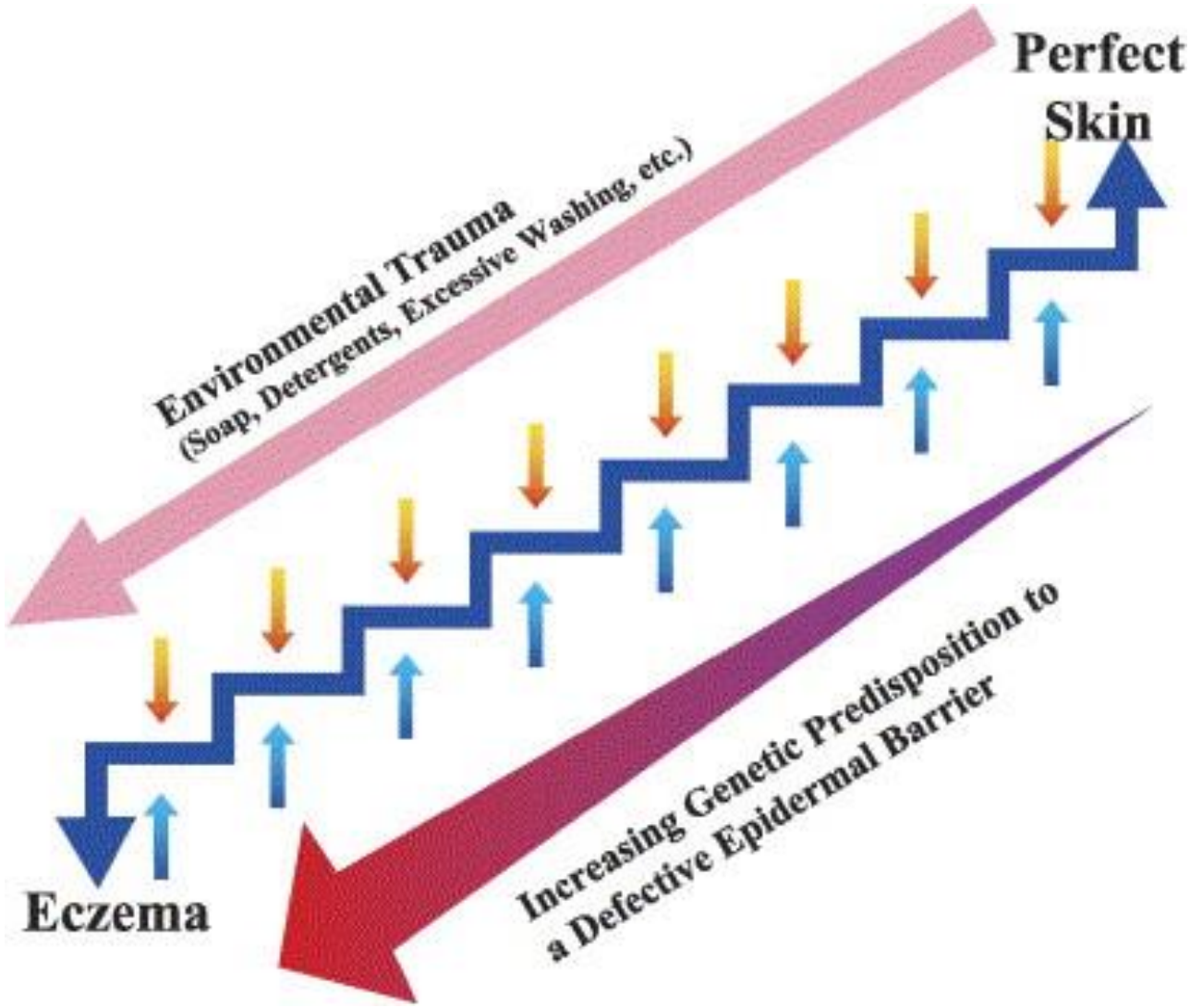


Alteration of tight junction proteins in skin diseases. The different colors denote the different diseases and the corresponding TJ protein alterations. AD: atopic dermatitis Cldn: claudin; IV: ichthyosis vulgaris; NISCH: neonatal ichthyosis sclerosing cholangitis; Ocln: occludin, ZO-1: zonula occludens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

Different combinations of genetic and environmental factors

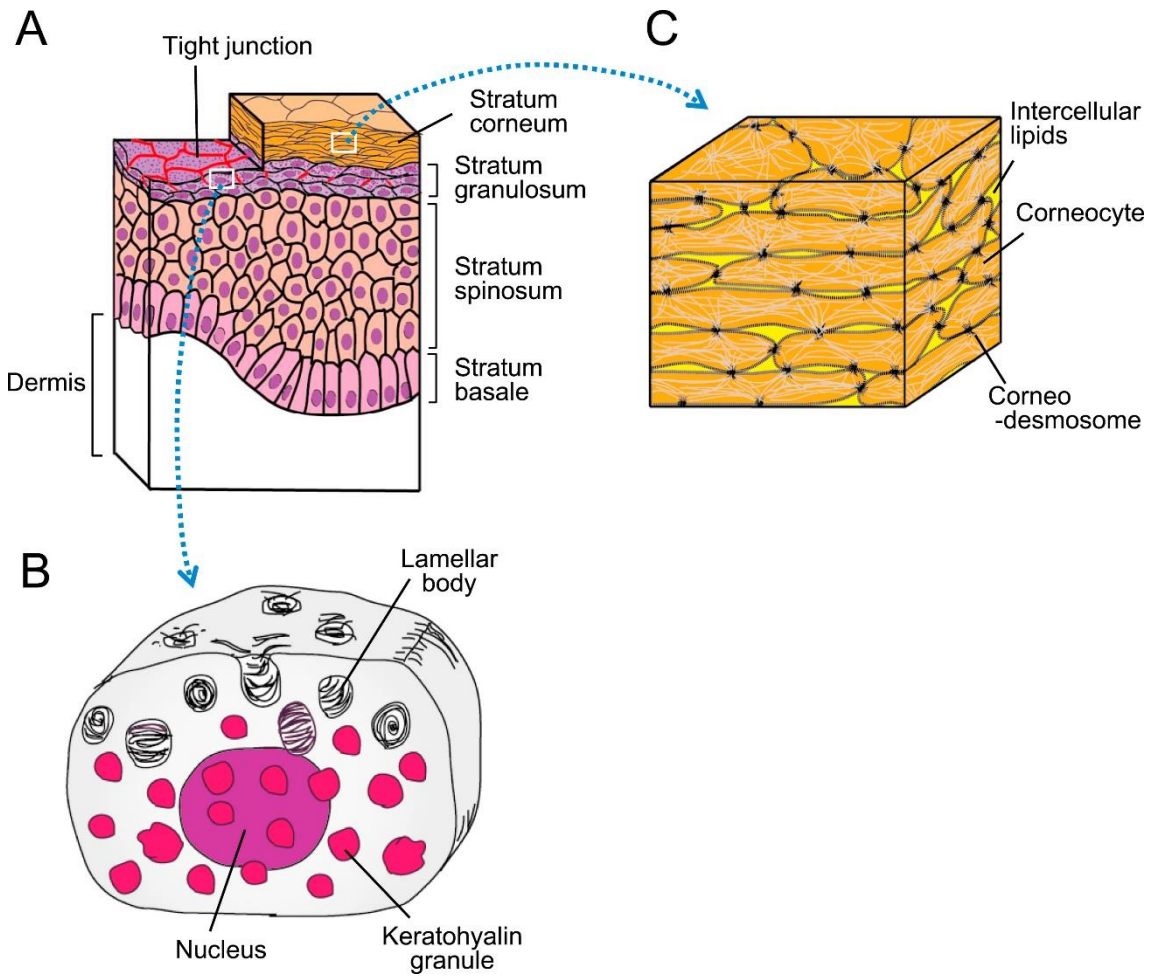
contribute to the development of multifactorial diseases, such as AD. Focusing on the skin barrier, severe barrier breakdown could be caused by a combination of functional variants in adhesion protein, protease, and protease inhibitor genes **(A)** or by a single major environmental insult. Alternatively, 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**).


Perfect
Skin
Environmental Trauma
(Soap, Detergents, Excessive Washing, etc.)
Increasing Genetic Predisposition to
a Defective Epidermal Barrier
Eczema

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.

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



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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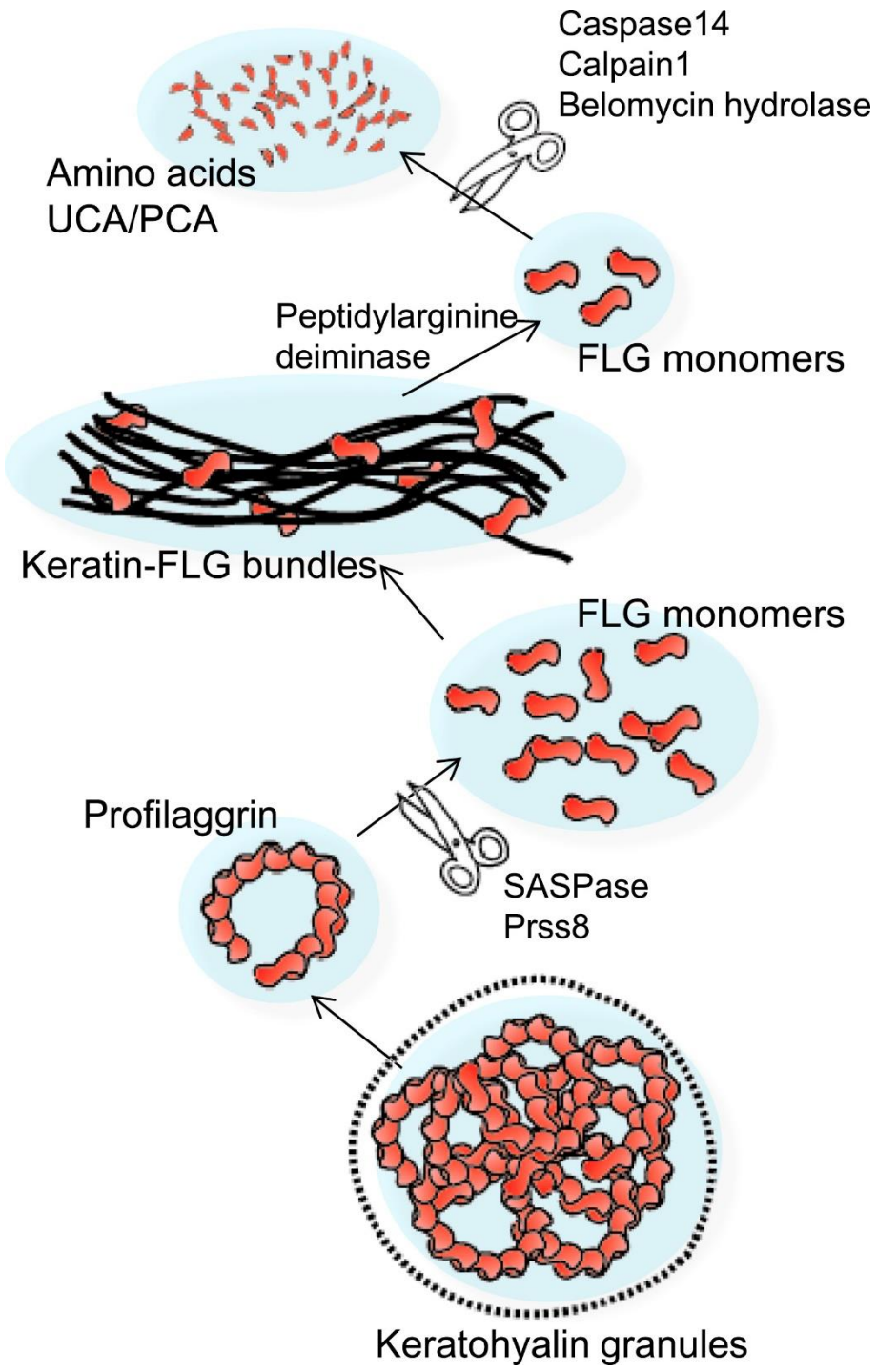

Egawa G, Kabashima K. Barrier dysfunction in the skin allergy. *Allergol Int*. 2018;67(1):3-11. doi:10.1016/j.alit.2017.10.002

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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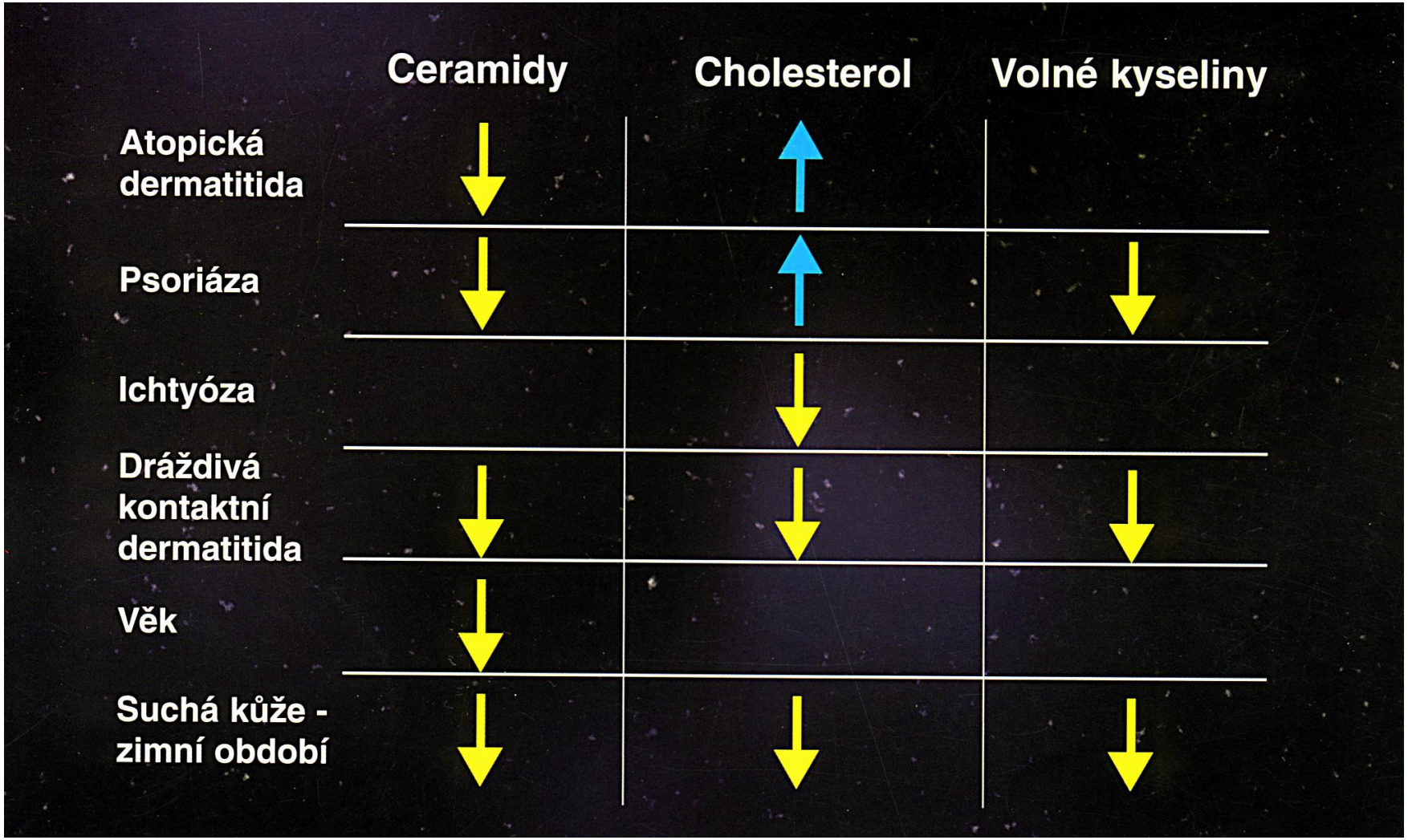
Stavy a choroby, které ovlivňují kožní bariéru a snižují hydrataci epidermis

Zánětlivé stavy ovlivňující epidermis

- Atopická dermatitida
- Psoriáza
- Kontaktní dermatitida
- Jiné ekzémy
- Prurigo
- Dermatofytózy a jiné povrchové kožní mykózy
- Fyzikální nebo chemické postižení
- Bulózní autoagrese
- Benigní a maligní tumory epidermis
- Ichtyózyformní dermatózy

Stavy snižující pouze hydrataci kůže

- ***Senilní xeróza***
- ***Fotostárnoucí kůže***
- ***Diabetes mellitus***


Ceramidy
Cholesterol
Volné kyseliny
Atopická dermatitida
Psoriáza
Ichtyóza
Dráždivá kontaktní dermatitida
Věk
Suchá kůže - zimní období

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.

Patogeneze psoriázy

- Je komplexní a ne plně osvětlená. V patogenezi psoriázy je zřejmě nejdůležitější excesivní aktivace některých složek adaptivního imunitního systému.
- V počátečních fázích sekretují některé typy buněk (dendritické, keratinocyty, NK buňky, makrofágy) cytokiny, které aktivují myeloidní dendritické buňky. Tyto aktivované buňky sekretují IL-12 a IL-23.
- IL-12 indukuje diferenciaci naivních T buněk do Th1 buněk.
- IL-23 má klíčovou roli v podpoře přežití a proliferace T_H17 a T_H22 buněk.
- Buňky T_H1 produkují interferon gama (IFN-γ) a TNF-α;
- Buňky T_H22 sekretují IL-22;
- Buňky T_H17 sekretují IL-17, IL-22 a TNF-α.
- Mezi těmito cestami je zřejmě dominantní T_H17 aktivovaná IL-23.
- Signalizace IL-23 je intracelulárně řízena cestami Tyk2-Jak2 a STAT3, což vede k transkripci klíčových mediátorů zánětu. Tyto cytokiny podporují proliferaci keratinocytů, zvyšují expresi angiogenních mediátorů a endoteliálních adhezivních molekul a způsobují infiltraci postižené kůže buňkami imunitního systému.

Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. JAMA. 2020 May 19;323(19):1945-1960

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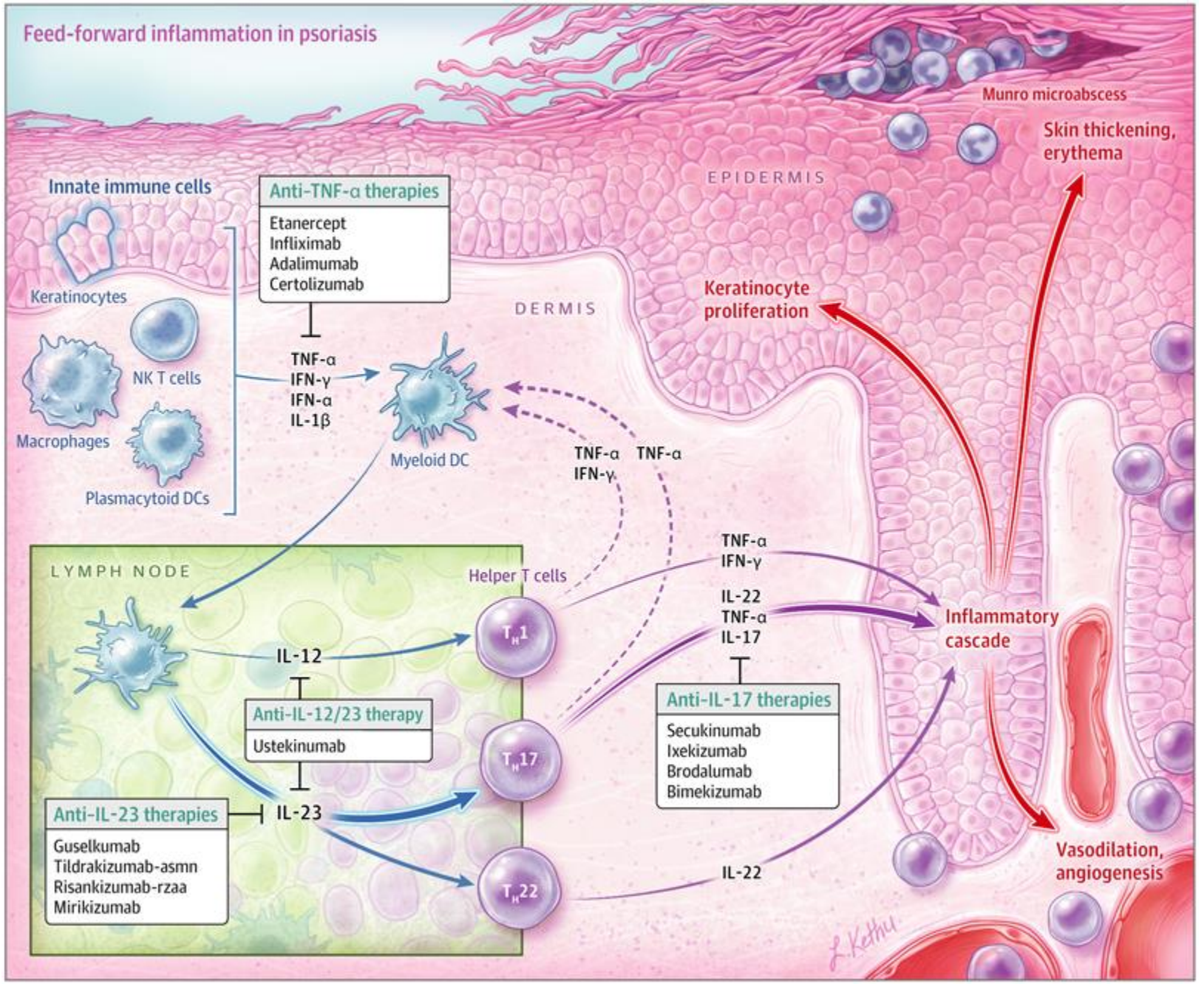


Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. JAMA. 2020 May 19;323(19):1945-1960

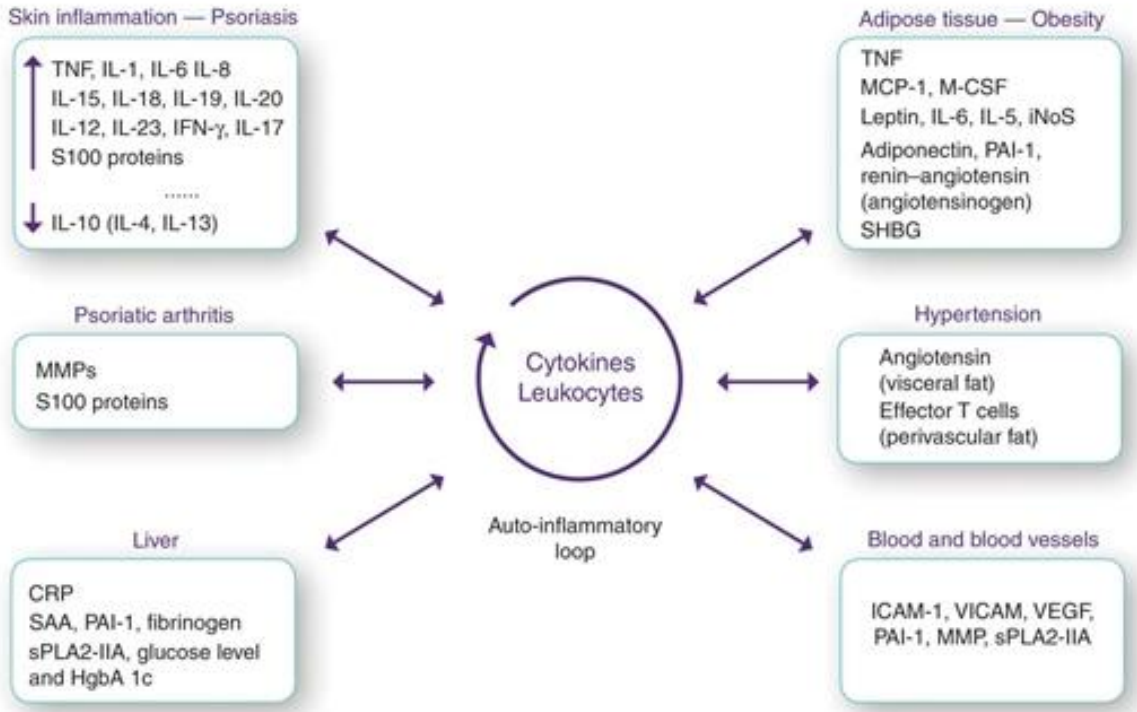


Figure 2. "Vicious circle of inflammation": mediators of inflammation produced in different organs or tissues are released into the systemic circulation and thus may contribute to the increased risk of inflammation in additional organs or tissues. CRP, C-reactive protein; HgbA 1c, hemoglobin A 1c; iNOS, inducible nitric oxide synthase; MCP-1, monocyte-chemoattractant protein 1; M-CSF, macrophage colony-stimulating factor; MMP, matrix metalloproteinase; PAI-1, plasminogen activator inhibitor-1; SAA, serum amyloid A; sPLA2-IIA, secretory phospholipase A2 group IIA; TNF-α, tumor necrosis factor α; VEGF,vascular endothelial growth factor; VICAM, vascular intercellular adhesion molecule.

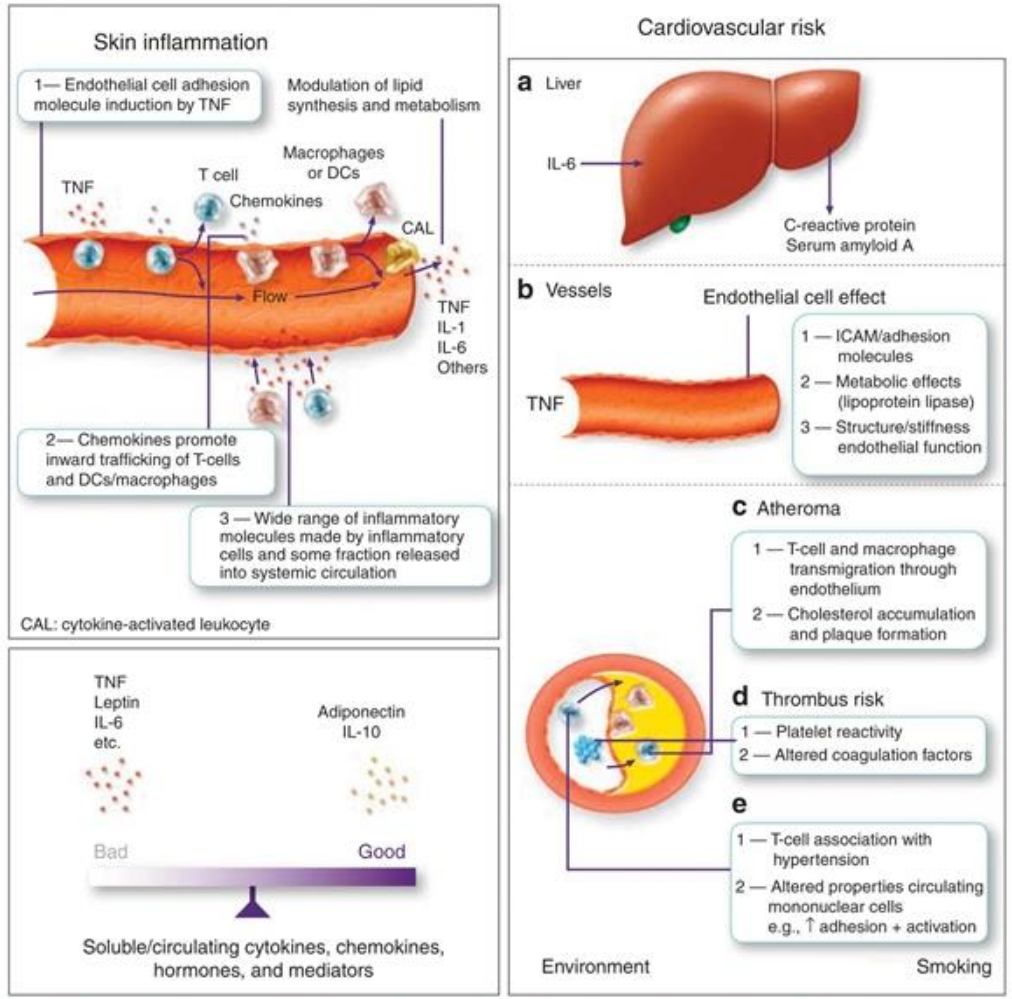


Figure 4. "Cardiovascular risk factors": some potential cellular and molecular inflammatory pathways that could be triggered in the skin (left) and that would then reach target tissues for cardiovascular risk (right). Cytokine (chemokine)-activated leukocytes (CAL) in cutaneous sites could either enter the skin tissue or circulate after rolling on inflamed endothelial cells in psoriasis lesions. These cells and cytokines released into the systemic circulation, e.g., tumor necrosis factor (TNF), IL-1, or IL-6, may alter the function of hepatocytes (**a**), vascular cells (**b**), atheroma (**c**), thrombus risk (**d**), or leukocyte physiology (**e**) to increase cardiovascular risk factors or overt pathological pathways, as detailed in the right side of this figure. DCs, dendritic cells.

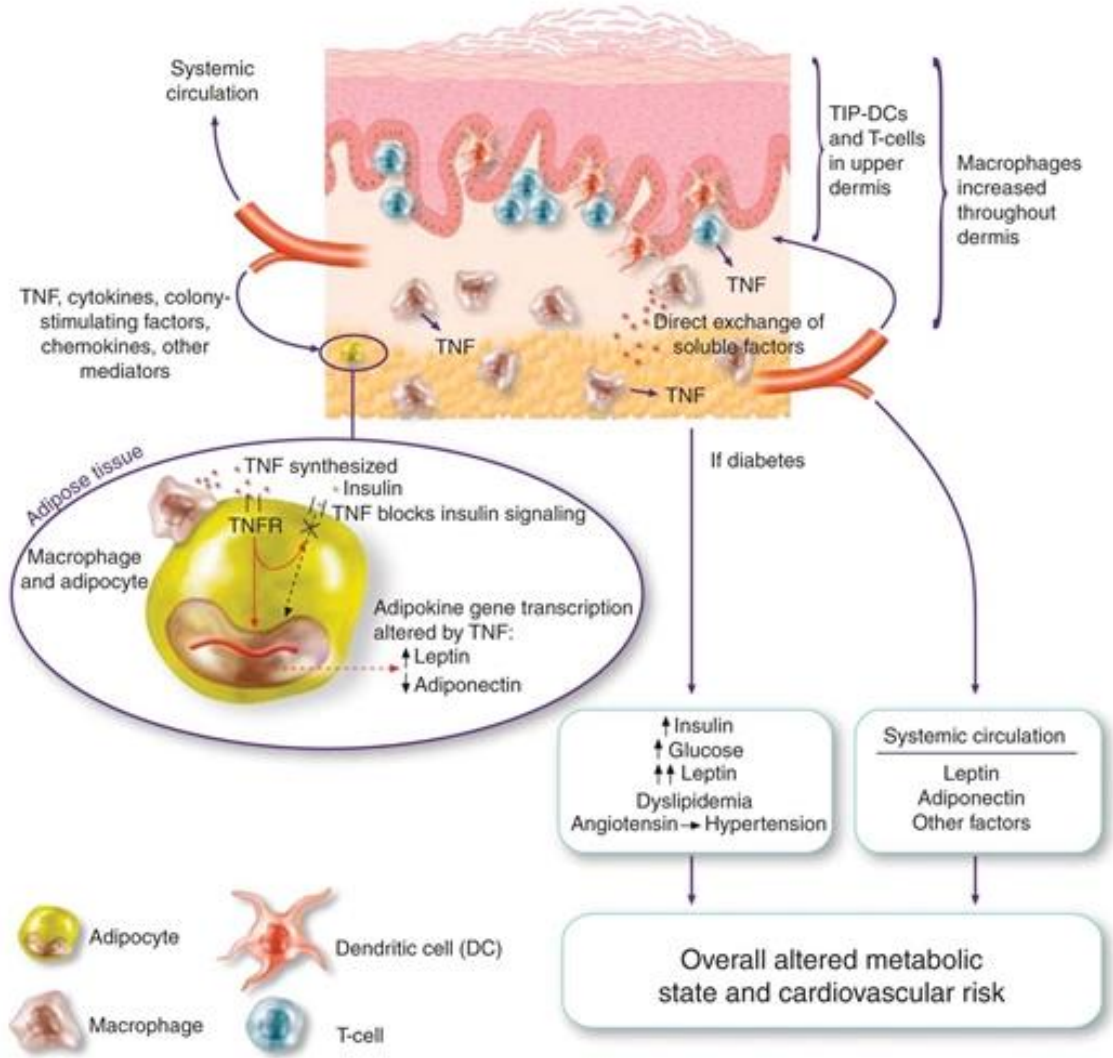
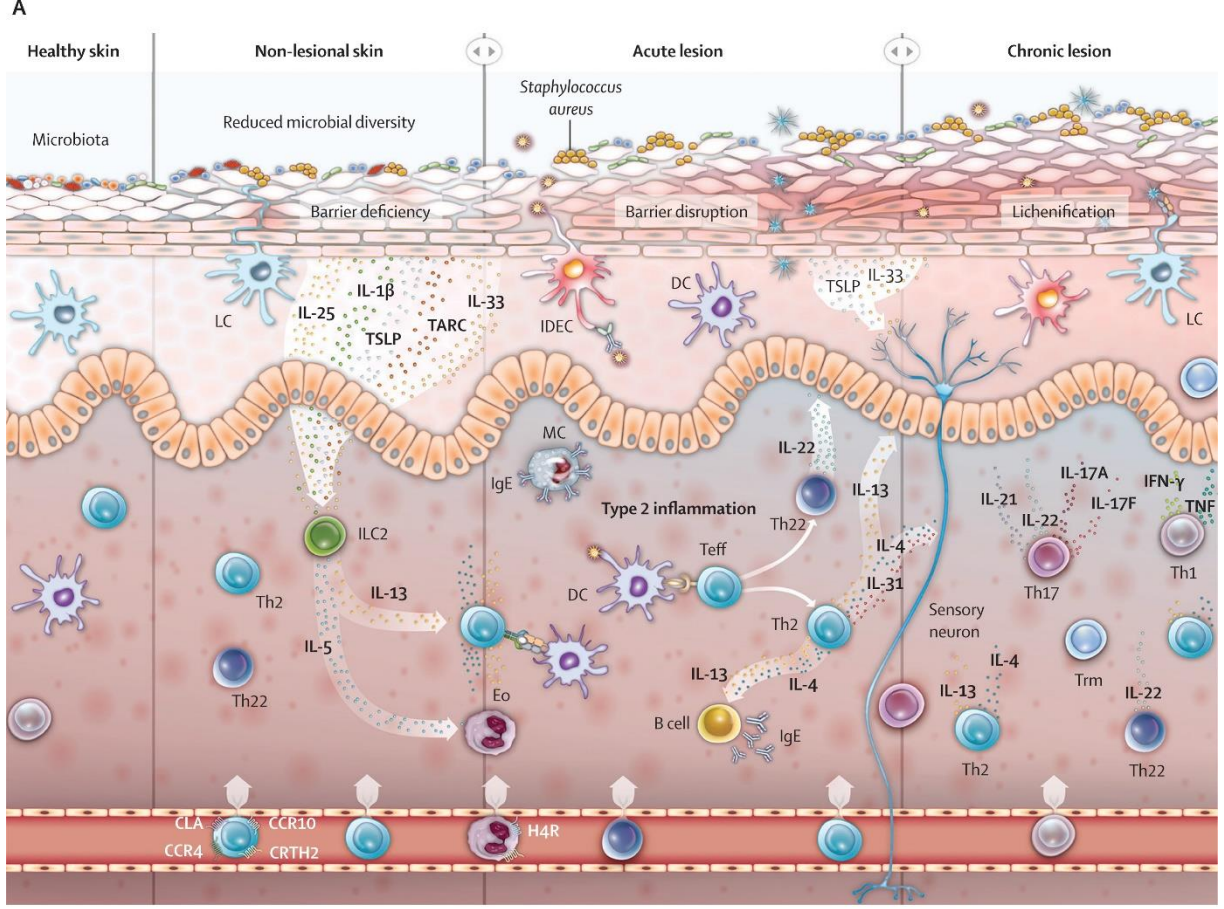
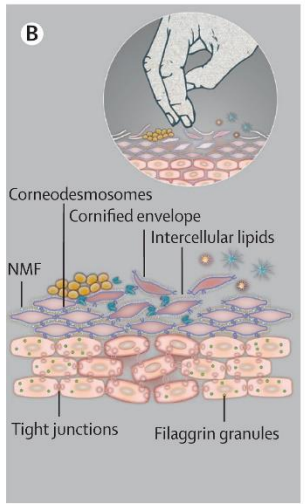


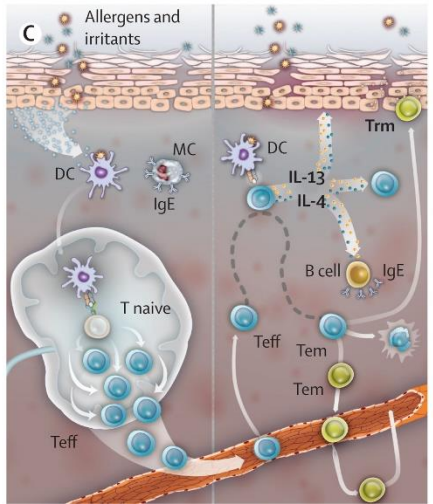
Figure 3. "Psoriasis and obesity": a two-compartment model of inflammation. This diagram depicts inflammation in the epidermis and dermis associated with psoriasis vulgaris and likely inflammatory molecules that would be produced in adipose tissue of obese individuals. The model proposes that soluble factors could enter the systemic circulation from either dermal or adipose tissue beds and, in addition, there could be direct exchange (diffusion) of factors between dermal and adipose sites. The steps involved in blockade of insulin signaling and alteration of the production of adipokines by tumor necrosis factor (TNF) are shown. DC, dendritic cell; TNFR, tumor necrosis factor receptor.

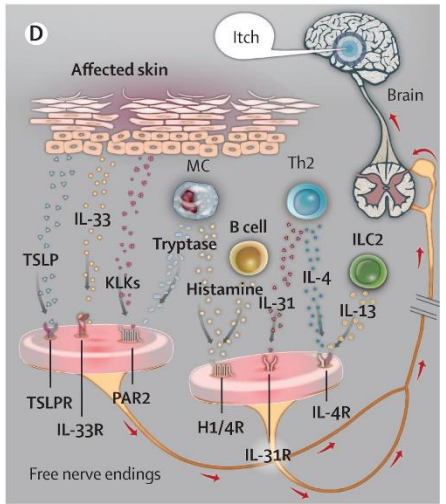
Atopic dermatitis

- 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.
- 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.









Patofyziologiue atopické dermatitidy

(A) Klinicky nepostižená kůže vykazuje známky bariérové dysfunkce epidermis s redukovanou diverzitou kožního mikrobiomu. V postižené kůži jsou Langerhansovy buňky (prozánětlivé epidermální dendritické buňky nesoucí specifické IgE vázané na vysoce afinitní receptor pro IgE) a dermální dendritické buňky, které vážou alergeny a antigeny. Th2 cytokiny IL-4, IL-13, and IL-31 přímo aktivují senzorické nervy a způsobují svědění (pruritus). U chronického průběhu dochází k progresivnímu nárůstu cytokinů produkovaných keratinocyty a Th lymfocyty.

(B–D). Rozvoj pruritu

Zkratky:

CCR=CC chemokine receptor. CLA=cutaneous lymphocyte-associated antigen. CRTH2=chemoattractant receptor-homologous molecule expressed on Th2 cell. DC=dendritic cell. Eo=eosinophil. H1/4=histamine 1/4. IDEC=inflammatory dendritic epidermal cell. IFN=interferon. IL=interleukin. ILC=innate lymphoid cell. KLK=kallikrein-related peptidase. LC=lymphoid cell. MC=mast cell. NMF=natural moisturising factor. PAR2=protease-activated receptor 2. TARC=thymus and activation-regulated chemokine. Teff=effector T cell. Tem=effector memory T cell. Th= T-helper cell. Tnaive=naive T cell. TNF=tumour necrosis factor. Trm=tissue-resident memory T cell. TSLP=thymic stromal lymphopoietin.

Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet. 2020 Aug 1;396(10247):345-360.

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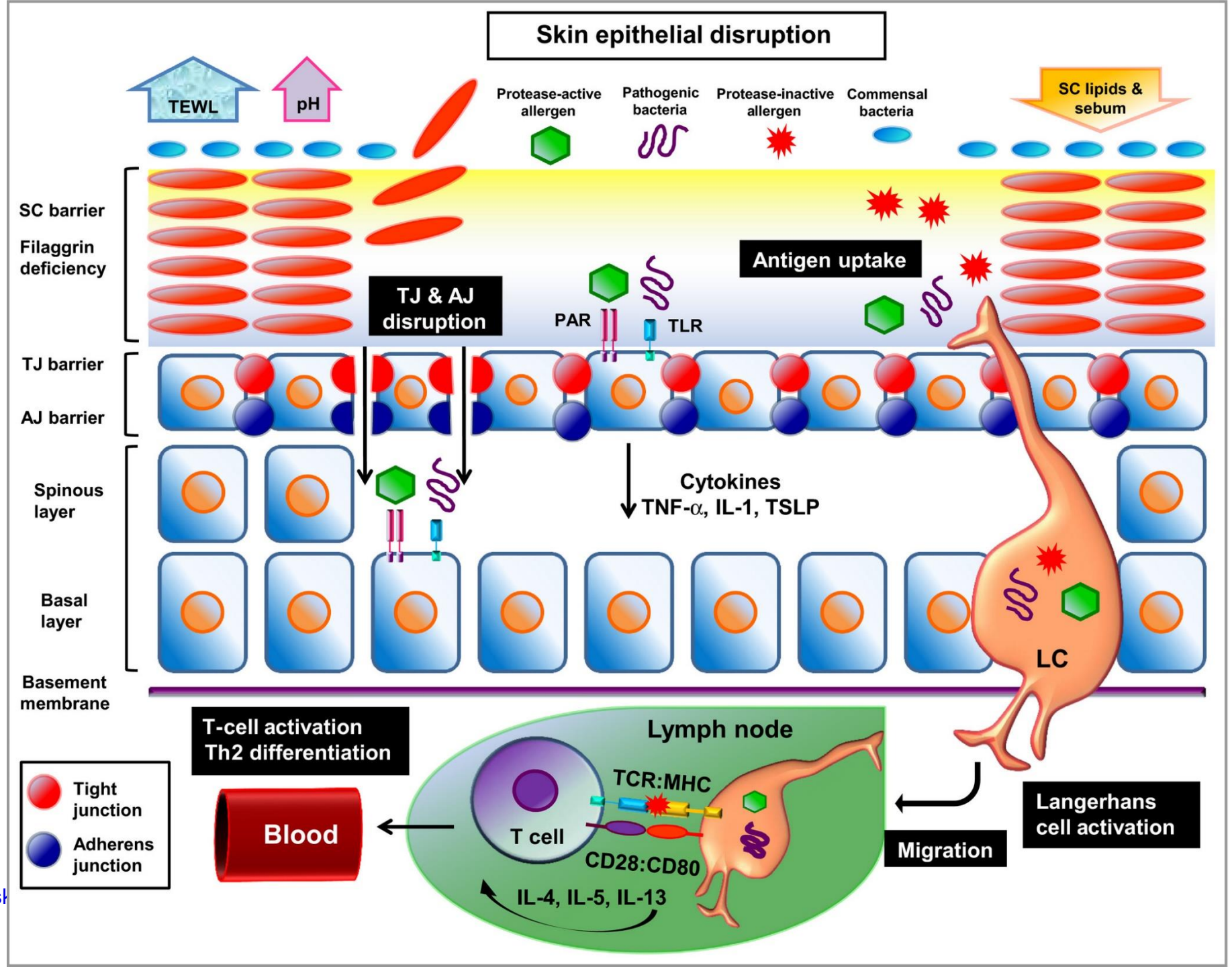
Table 1 **Epithelial skin dysfunction in atopic dermatitis**

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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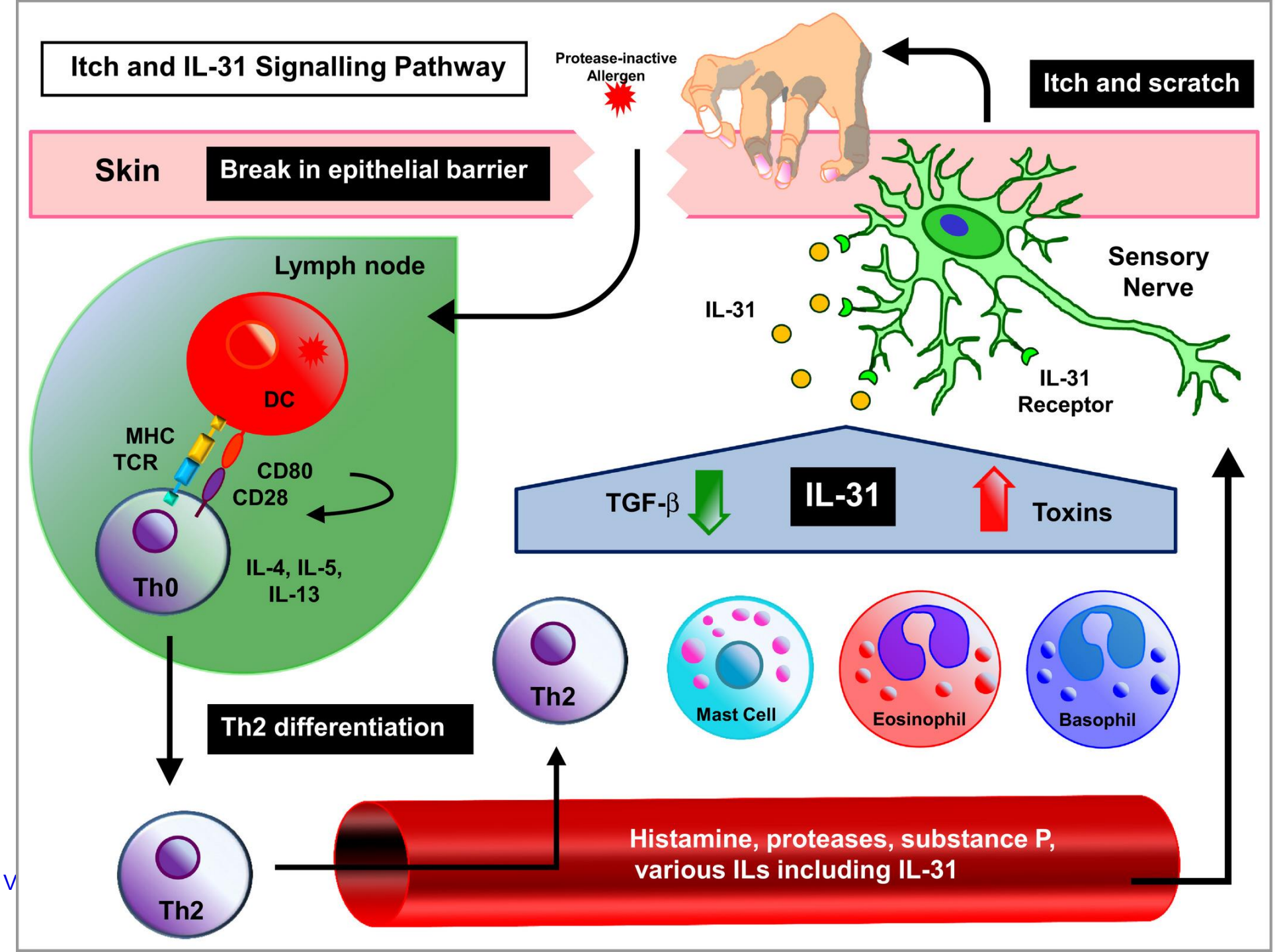
Skin barrier disruption

- 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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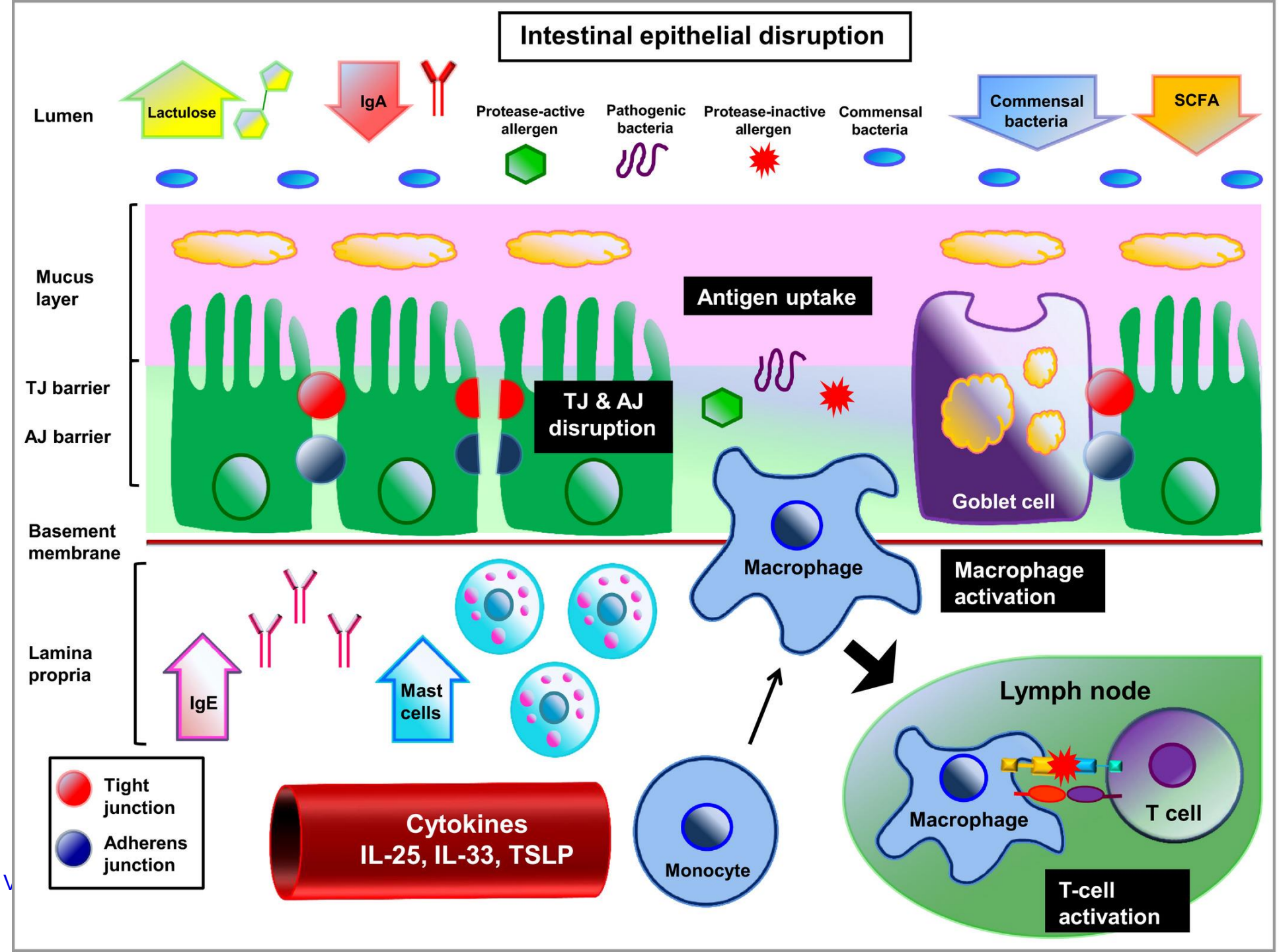
Itch and interleukin (IL)-31 signalling pathway

- 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.

Dermotest

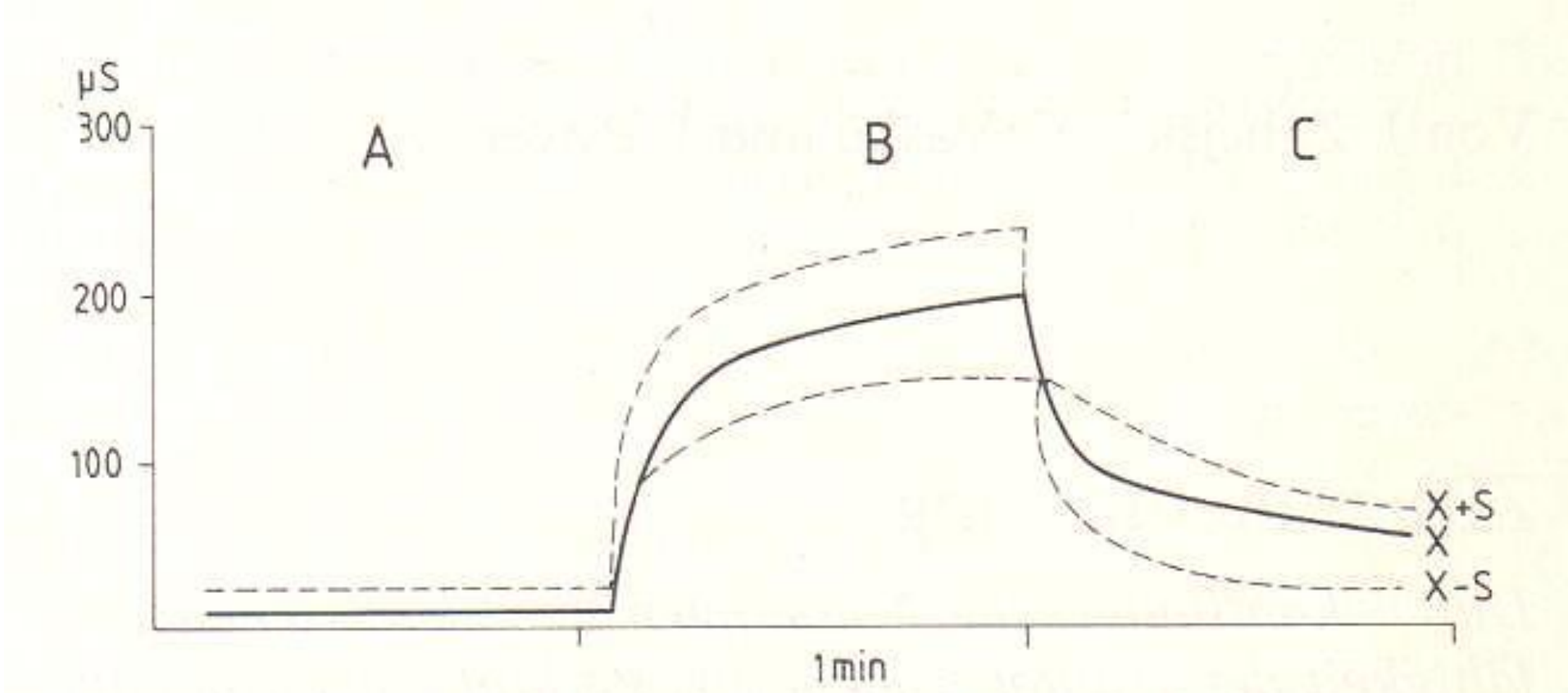

Abb. 1: Registration der elektrischen Leitfähigkeit vor (A), im Verlauf (B) und nach Beendigung der Iontophorese (C).

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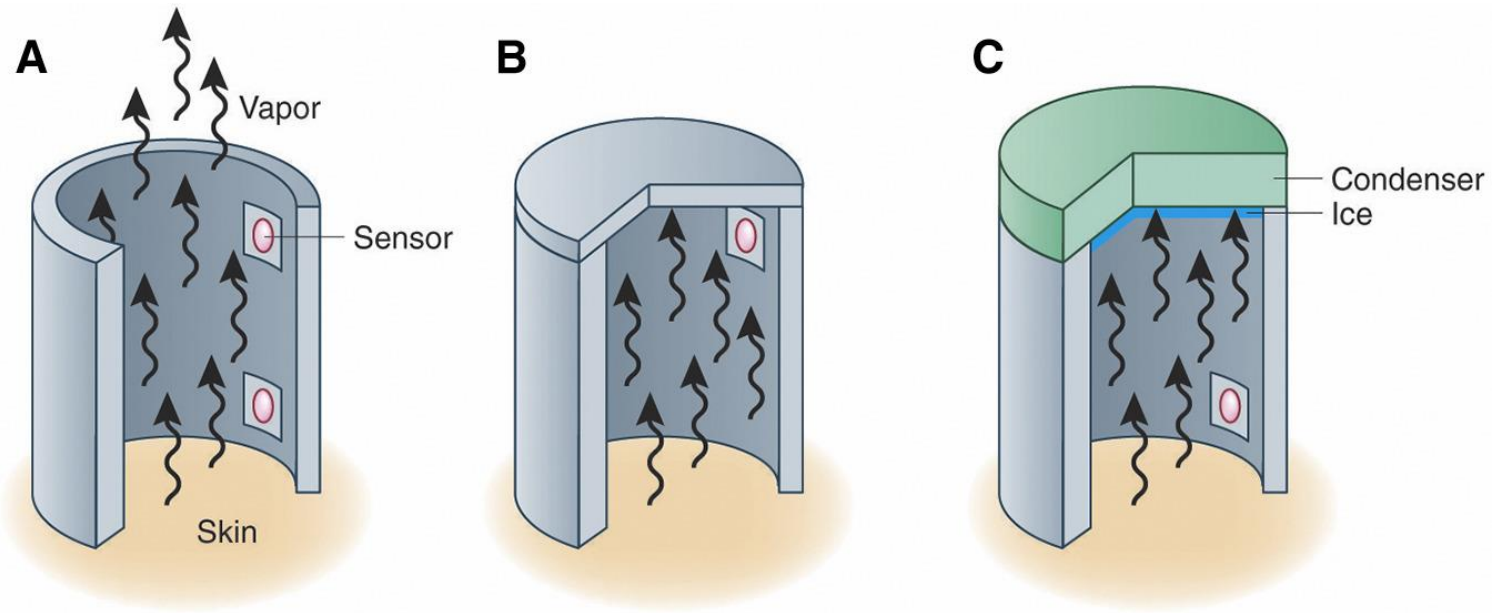
Alexander H, Brown S, Danby S, Flohr C. Research Techniques Made Simple: Transepidermal Water Loss Measurement as a Research Tool. *J Invest Dermatol*. 2018;138(11):2295-2300.e1. doi:10.1016/j.jid.2018.09.001



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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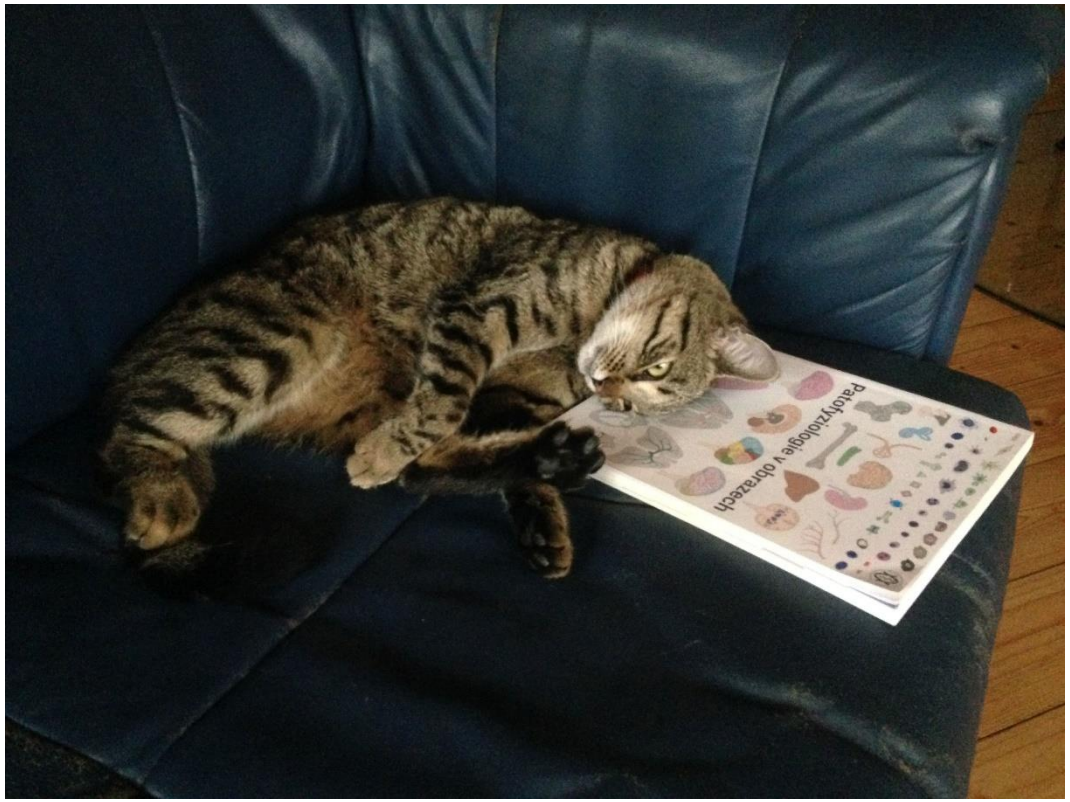
TEWL

TEWL differences in different ethnic groups have been found. For instance, TEWL is higher in black and Asian skin compared with Caucasian skin.
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. In adults, some studies suggest that TEWL decreases with age but others have found no association between TEWL and age

Děkuji za pozornost



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