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REVIEW ARTICLE

Topographical variations in the skin barrier and their role in disease pathogenesis

Z. Dajnoki[1,2] | **A. Kapitány**[1,2] | **K. Eyerich**[3] | **S. Eyerich**[4] | **D. Törőcsik**[1,2] | **A. Szegedi**[1,2]

[1]Department of Dermatology, MTA Centre of Excellence, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

[2]HUN-REN-UD Allergology Research Group, Debrecen, Hungary

[3]Department of Dermatology and Venerology, Medical Center, University of Freiburg, Freiburg, Germany

[4]Center for Allergy and Environment (ZAUM), Technical University and Helmholtz Center Munich, Munich, Germany

Correspondence
A. Szegedi, Department of Dermatology, MTA Centre of Excellence, Faculty of Medicine, University of Debrecen, Debrecen, Hungary.
Email: aszegedi@med.unideb.hu

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Abstract

The skin barrier can be divided into at least four functional units: chemical, microbial, physical and immunological barriers. The chemical and microbial barriers have previously been shown to exhibit different characteristics in topographically distinct skin regions. There is increasing evidence that the physical and immunological barriers also show marked variability in different areas of the skin. Here, we review recent data on the topographical variations of skin barrier components, the contribution of these variations to the homeostatic function of the skin and their impact on the pathogenesis of specific immune-mediated skin diseases (such as atopic dermatitis and papulopustular rosacea). Recognition of these topographical barrier differences will improve our understanding of skin homeostasis and disease pathogenesis and provide a basis for body site-specific targeted therapies.

SKIN BARRIER ELEMENTS AND THEIR INTERACTIONS

Barrier organs, such as the gastrointestinal, respiratory and urinary tracts and the skin, maintain the integrity of the body, connect us to the environment and protect us from harmful physical, chemical and microbial influences. Barrier organs have extremely large, specially developed, and structured surfaces that enable them to perform complex barrier functions. According to recent literature, this complex barrier function can be more easily understood if it is divided into four elements: chemical, microbiota, physical (permeability) and immunological barriers.[1–3] In this review, the same approach will be used when discussing the complex barrier function of the skin. All four elements of the barrier exhibit high variability, express extensive interrelationships and the healthy function of each is necessary for the maintenance of skin homeostasis (Figure 1).

The close interaction between the skin barrier units can be demonstrated by several examples. The acidic pH (pH 4–6), as part of the chemical barrier, plays a critical role in lipid formation and protease function, which maintains the integrity of structural proteins and the physical barrier, but also the composition of the skin-colonizing microbiota.[2,4–8] The acidic environment influences the efficacy of certain antimicrobial peptides (AMPs), directly affecting immune barrier responses.[9] Lipids from keratinocytes and sebocytes

Z. Dajnoki and A. Kapitány contributed equally to this article.

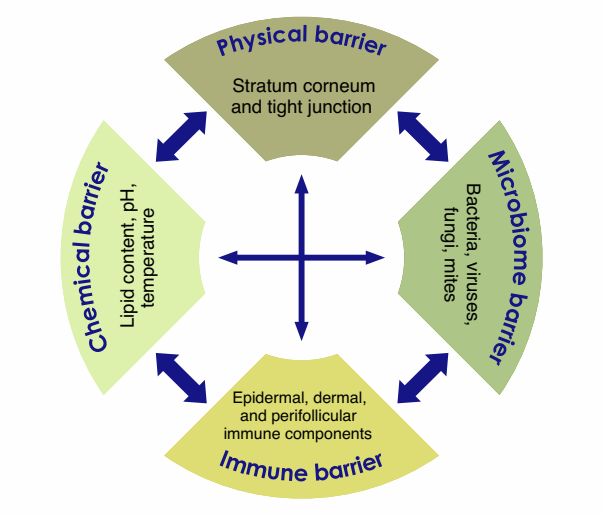

FIGURE 1 The main barrier function layers of the skin. The chemical, microbiota, physical and immune barriers, which are strictly regulated and interrelated, comprise the complex healthy skin barrier.

affect immune responses by influencing the microbiome and immune barrier coordination.[10–15] Certain free fatty acids trigger the expression of human β-defensin 2 and directly hinder bacterial growth.[16]

At the same time, commensal microbiota shapes and mediates multiple levels of skin barrier functions. The commensal microbiota itself can prevent pathogen colonization by several mechanisms (e.g. antibiotic production, and interference with quorum sensing pathways).[17–20] Certain commensals (e.g. *Cutibacterium* acnes and *Corynebacterium* species) release lipases that produce free fatty acids by breaking down triglycerides derived from sebum.[21,22] Microbiota barrier dysbiosis can lead to tight junction alterations thereby compromising the integrity of the physical barrier.[23–26]

Both innate and adaptive immune cells sense barrier breaches and altered lipid composition, and these signals initiate immune responses and tissue repair.[2,15,27] Immune responses also regulate the microbiome by controlling pathogenic overgrowth, thereby maintaining the integrity of the microbiota barrier (Figure 1).[28,29]

Due to the strong interactions between the barrier units, alterations in any one component can lead to complex barrier dysfunction, resulting in an increased risk of infection, tumour formation or specific pathogenic responses leading to the development of immune-mediated skin diseases (barrier damage-driven skin inflammation). This close cooperation between the barrier units may also explain why regional differences in any of the barrier units can lead to regional variations in other barrier components and consequently in the complex barrier function. Such topographical differences were first identified in the context of chemical and microbiota barrier elements.

Key points

Why was the study undertaken?

- The study aims to summarize current knowledge on the topographical variations in the skin's chemical, microbial, physical and immunological barriers and their influence on skin homeostasis and contribution to immune-mediated skin diseases.

What does this study add?

- This study confirms the non-uniformity of the healthy skin, as all four elements of the barrier exhibit high topographical variability. The healthy function of each is necessary for the maintenance of skin homeostasis, damage to any of these barriers can lead to immune-mediated disease.

What are the implications of this study for disease understanding and/or clinical care?

- Regional barrier differences may explain the characteristic localization of barrier damage-initiated skin diseases and have important implications in developing local dermatological therapies or identifying tissue-derived biomarkers.

REGIONAL VARIATIONS OF THE CHEMICAL AND MICROBIOTA BARRIERS

The chemical barrier includes the secretions from various glands (e.g. sebum) and the natural moisturizing factors (NMFs) such as amino acids and derivatives, lactate, urea and electrolytes. The elements of the chemical barrier contribute to the establishment of the moisture and acid mantle of the skin and provide UV protection. Delicate anatomical differences are observed among skin regions due to the variable density and size of hair follicles and sebaceous, eccrine and apocrine glands. Consecutive variations in lipid content and glandular secretions lead to regional variations in skin pH, ranging from pH 4.2 to pH 7.9.[30,31] Within this wide range, the forehead is highly acidic (pH 4.75–5.04), the forearm has a less acidic pH (pH 5.06–5.13) while the highest pH is measured in the axillary area (pH 5.84–7.9). Skin surface temperature, which affects the chemical barrier, also varies from 29.5°C to 36.6°C in different skin regions, with the highest temperature in the axillary region (Table 1, Figure 2).[30,31]

TABLE 1 Comprehensive overview of skin barrier function differences across various skin regions.

	Sebaceous region	Dry region	Moist region	References
Chemical barrier				
Lipid content	High lipid content, including sebum	Lower lipid content	Moderate lipid content	30,31
ph	4.2–5.9	5.06–5.55	5.84–7.9	31
Temperature	31.8–33-4	32.2–33.3	32.9–36.6	31
NMFs	n.d.			–
Microbiota barrier				
Bacteria	Dominated by lipophilic species, especially Propionibacteria	High diversity of bacteria from different phyla (Actinobacteria, Proteobacteria, Firmicutes, Bacteroidetes)	Dominated by Staphylococcus and Corynebacteria species	31–38,40
Most abundant bacteria	*Cutib.* acnes, *Staph.* epidermidis, *Coryneb.* tuberculostearicum, *Staph.* capitis, *Coryneb.* simulans, *Strept.* mitis, *Staph.* hominis, *Coryneb.* aurimucosum, *Coryneb.* kroppenstedtii, *Coryneb.* Amycolatum	*Cutib.* acnes, *Coryneb.* tuberculostearicum, *Strept.* mitis, *Strept.* oralis, *Strept.* pseudopneumoniae, *Strept.* sanguinis, *Micrococcus* luteus, *Staph.* epidermidis, *Staph.* capitis, *Veillonella* parvula	*Coryneb.* tuberculostearicum, *Staph.* hominis, *Cutib.* acnes, *Staph.* epidermidis, *Staph.* capitis, *Coryneb.* fastidiosum, *Coryneb.* afermentans, *Micrococcus* luteus, *Enhydrobacter* aerosaccus, *Coryneb.* simulans	31–38,40
Most abundant Eukarya	M. restricta, M. globosa, M. sympodialis, Aureoumbra lagunensis, Tilletia walkeri, Pycnococcus provasolii, Gracilaria tenuistipitata, Pyramimonas parkeae, Parachlorella kessleri, Leucocytozoon majoris, Demodex	M. restricta, M. globosa, Aspergillus tubingensis, Candida parapsilosis, Zymoseptoria tritici, M. sympodialis, Epidermophyton floccosum, Pyramimonas parkeae, Nannizzia nana, Parachlorella kessleri	M. globosa, M. restricta, Tilletia walkeri, Malassezia sympodialis, Pyramimonas, parkeae, Parachlorella kessleri, Aspergillus tubingensis, Zymoseptoria tritici, Nephroselmis olivacea, Cyanophora paradoxa	31–33,36–38,40,41
Most abundant viruses	Cutib. phage, Molluscum contagiosum virus, Merkel cell polyomavirus, Polyomavirus HPyV6, HPV(γ), HPV(β), Acheta domestica densovirus, Staph. phage, Gammapapillomavirus HPV127, Enterobacteria phage	Molluscum contagiosum virus, Cutib. phage, Merkel cell polyomavirus, Polyomavirus HPyV7, Acheta domestica densovirus, HPV(β), Actinomyces phage, Simian virus, Strept. phage, Stenotrophomonas phage	Molluscum contagiosum virus, Cutib. phage, Polyomavirus HPyV6, Merkel cell polyomavirus, Polyomavirus HPyV7, HPV(β), Acheta domestica densovirus, HPV(γ), Staph. phage, Actinomyces phage	32,36–38
Physical barrier				
Barrier function (TEWL)	Significantly higher (vs. dry area)	Significantly lower (vs. sebaceous and moist areas)	Significantly higher (vs. dry area)	45,46
Stratum corneum thickness	Lower thickness (vs. dry area)	Higher thickness (vs. sebaceous area)	n.d.	59
Cornified envelop formation	No significant difference in FLG, LOR, KRT1, KRT10, LCE1D, LCE1F, SPRR1A, SPRR2A, TGM1 and TGM5 levels			46
(Corneo)-desmosome organization	Significantly lower CDSN and DSG1 protein levels (vs. dry areas)	Significantly higher CDSN (vs. sebaceous area) and DSG1 protein levels (vs. sebaceous and moist areas)	Significantly lower DSG1 protein levels (vs. dry area)	46
Corneocyte desquamation	Higher KLK5 and KLK7 presence and activity (vs. dry areas)	Lower KLK5 and KLK7 presence and activity (vs. sebaceous and moist areas)	Higher KLK5 and KLK7 presence (vs. dry area)	46,47

(Continues)

TABLE 1 (Continued)

	Sebaceous region	Dry region	Moist region	References
Tight junction formation	Significantly lower OCLN protein levels (vs. dry areas)	Significantly higher OCLN (vs. sebaceous and moist areas) and CLDN1 protein levels (vs. moist area)	Significantly lower OCLN and CLDN1 protein levels (vs. dry area)	46
Lipid lamellae formation	No significant difference (vs. dry area)	Significantly lower ABCA12 protein levels (vs. moist area)	Significantly higher ABCA12 lipid transporter protein levels (vs. dry area)	46
Immune barrier				
Epidermis				
KC cytokines	IL-23, IL-17C, IL-18	IL-25, IL-33, IL-36RA, IL-38, IL-18	IL-25, IL-33, IL-23, IL-18	61
KC chemokines	Significantly higher CCL2, CCL3, CCL19, CCL20, CCL23 and CCL24 expression (vs. dry areas)	Low chemokine and AMP levels	Significantly higher expression of CCL2 and CCL20 (vs. dry area)	57–59
KC AMPs	Significantly higher levels of hBD2, lacritin, lysozyme, cathelicidin, lipocalin-2 and S100A family members (vs. dry area)	Significantly lower levels of hBD2, lacritin, lysozyme, cathelicidin, S100A members (vs. sebaceous area) and lipocalin-2 (vs. sebaceous and moist areas)	Significantly higher lipocalin-2 levels (vs. dry area)	57–60
Langerhans cells	No significant difference			58,62
	Elevated Langerin+ and CD1a + LCs (vs. dry areas)	Lower Langerin+ and CD1a + LCs (vs. sebaceous areas)	n.d.	59
Dermis				
CD3+ T cells	Significantly higher numbers (vs. dry areas)	Significantly lower cell counts (vs. sebaceous and moist areas)	Significantly higher counts (vs. dry areas)	58,59,62
CD4+ T cells				58,62
Treg				58,59,62,63
Noninfl. Th17				58,62
CD11c + DCs				58,59,62
Macrophages, neutrophils, eosinophils, mast cells	No significant difference in cell counts			62
Follicle	Regional differences need to be explored			–

Abbreviations: ABCA, ATP-binding cassette sub-family A member; AMP, Antimicrobial peptide; CCL, Chemokine (C-C motif) ligand; CDSN, Corneodesmosin; CLDN, Claudin; Coryneb., Corynebacteria; Cutib., Cutibacteria; DC, Dendritic cell; DSG, Desmoglein; FLG, Filaggrin; hBD, Human beta-defensin; HPV, Human papillomavirus; IL, Interleukin; KC, Keratinocyte; KLK, Kallikrein-related peptidase; KRT, Keratin; LC, Langerhans cell; LCE, Late cornified envelope; M., Malassezia; n.d., not determined; NMF, Natural Moisturizing Factor; Noninfl., Non-inflammatory; OCLN, Occludin; S100A, S100 calcium-binding protein A; SPRR, Small Proline Rich Protein; Staph., Staphylococcus; Strept., Streptococcus; TEWL, Transepidermal water loss; TGM, Transglutaminase; Th, T helper; Treg, Regulatory T cell.

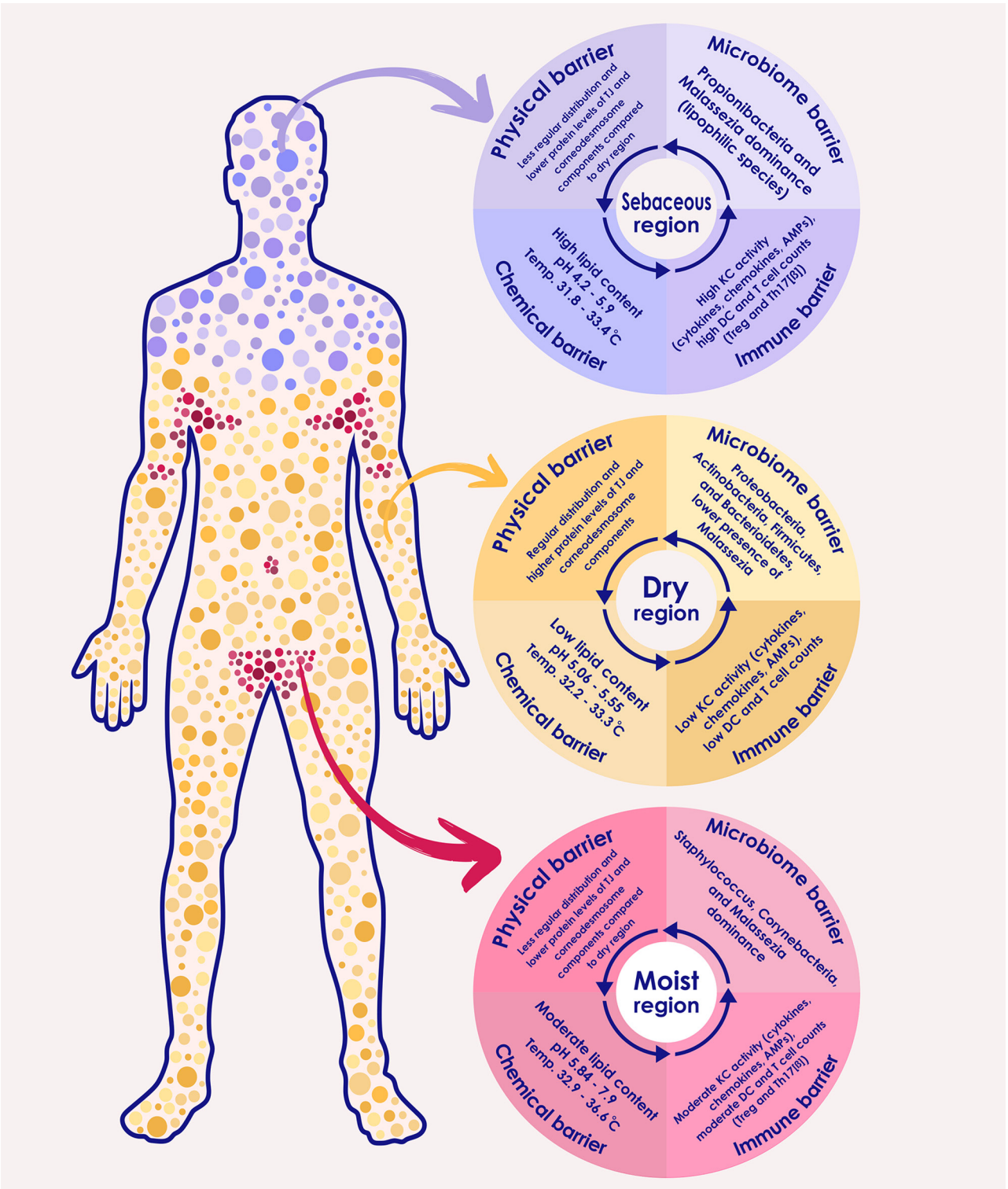

FIGURE 2 Regionally distinct characteristics of the main barrier function layers. All four elements and, consequently, the complex barrier exhibit regional differences across the skin surface. These regional differences should be considered during investigations into homeostatic skin functioning or disease development. AMP, Antimicrobial peptide; CDSN, Corneodesmosin; CLDN, Claudin; DC, Dendritic cell; DSG, Desmoglein; KC, Keratinocyte; OCLN, Occludin; Th17(β), Non-inflammatory T helper 17; TJ, Tight junction; Treg, Regulatory T cell.

Chemical barrier variations lead to the colonization of different regions of human skin by distinct microbiota (bacterial, viral and fungal) communities. Skin microbiota composition has been subjected to intensive research.[1,32–39] According to the microbiota composition revealed by these studies, healthy human skin in adulthood can be divided into three main regions, namely sebaceous (rich in sebaceous glands), moist (with higher moisture levels including

areas rich in apocrine glands) and dry (gland-poor) skin areas (Table 1, Figure 2).[31–38] Notably, these skin regions are not sharply separated, but rather form a continuum into each other. The sebaceous region includes the face, scalp, areas behind the ears, upper back and chest. The moist areas are represented by the axilla, antecubital fossa, popliteal fossa and inguinal folds. The dry region includes the trunk and extremities.[34,35] Lipophilic species dominate the sebaceous areas and include *Cutibacteria*. Moist areas are primarily characterized by *Staphylococcus* and *Corynebacteria* species, while dry regions exhibit a high diversity of bacteria from different phyla, including *Actinobacteria*, *Proteobacteria*, *Firmicutes and Bacteroidetes*.[32–35] Various fungal species favour regions rich in sebaceous and apocrine glands. The dominant fungal species on human skin is *Malassezia*, with high prevalence in sebaceous and moist regions.[32,33,40]

Similar to fungi, eukaryotic mites such as *Demodex folliculorum* are highest in number in the sebaceous region, although they can be found on all skin sites.[41] Regarding eukaryotic DNA viruses on the skin, prominent variability was detected, however, variance occurs individually rather than by anatomical site (Table 1, Figure 2).[32]

Regional variations in the microbiota barrier mentioned above are a characteristic feature of adult skin. In childhood, the microbiota composition is less stable with only minor regional differences.[37] This is probably due to the fact that the above-mentioned regional differences in the chemical milieu have not yet developed in childhood, as the levels of sebum and other glandular secretions are similarly low in all topographically different skin areas. This is supported by investigations showing that an extreme physiological shift in skin microbiota composition occurs during puberty (between Tanner 3 and 4 groups) when the sebaceous and apocrine glands mature under the influence of sex hormones.[42] The glandular secretions lead to an alteration in the local chemical and consequently in the microbiota milieu. This change affects all skin regions; however, it is less pronounced in the gland-poor region whereas prominent in gland-rich regions. In conclusion, regional variations of the chemical and microbiota barriers seem to develop during adolescence and characterize the adult skin.

REGIONAL VARIATIONS IN THE SKIN PHYSICAL BARRIER

The physical (permeability) barrier consists of two main components: the lower layers of the stratum corneum and the tight junction network.[43,44] Regional differences in the physical barrier were first demonstrated using functional analyses that showed higher transepidermal water loss (TEWL) in gland-rich areas compared to TEWL in dry regions; the highest TEWL was detected in moist skin (Table 1, Figure 2).[45,46]

Studies focusing on regional differences of molecules involved in the formation and function of each physical barrier component are limited. In one of these studies, Komatsu et al. performed a detailed mass spectrometry analysis on Kallikrein-related peptidases (KLKs) in the sweat collected from distinct skin sites. These enzymes have a prominent role in desquamation (especially KLK5 and KLK7) since they cleave corneodesmosome components (DSG1, DSC1 and CDSN), allowing the physiological shedding of the skin. Higher levels of KLKs are present in the sweat derived from gland-rich areas (face and armpit) compared to dry skin region.[47] However, it has not been raised that topographical variations in the amount and activity of KLKs may contribute to regional differences in other physical barrier components.

Another detailed molecular investigation found extracellular tight junction and desmosome components in significantly lower amounts at the protein level (but similar mRNA levels) in the gland-rich areas compared to the dry region while no regional differences were detected in intracellular structure molecules of the cornified envelope (Table 1, Figure 2).[46] The gland-rich regions were also characterized by substantially disorganized TJ and corneodesmosome structures (Table 1, Figure 2). These results, indicating differences only in the protein expression of extracellular binding elements, suggest that probably their proteolytic degradation by KLKs (as was detected by Komatsu), rather than reduced protein production, is responsible for the less intact junction components in gland-rich skin areas.

These limited literature data indicate that gland-rich areas exhibit slightly weaker physical barrier features than dry regions under steady-state. Nevertheless, further studies are needed to determine whether the differences found are also present in childhood or whether they develop later, after undergoing a major change during puberty, similar to the chemical and microbiota barrier. In the future, it is also important to study this barrier unit in the elderly, as some cornified envelope components have been shown to change substantially with advancing age.[48]

REGIONAL VARIATIONS IN THE IMMUNOLOGICAL BARRIER OF THE SKIN

The chemical, microbiota and physical barriers are anatomically and functionally related to the uppermost layer of the skin. However, the anatomic and functional elements of the immunological barrier encompass the entire skin. The immunological barrier includes three main niches that may be worth discussing separately: the interfollicular epidermis and dermis, and the follicular-perifollicular areas.[49–51]

In the epidermis, not only professional immune cells but also keratinocytes have essential immune functions. They act as immune sensors through their pattern recognition receptors and as immune effectors by producing immune mediators.[50,52–56] The immune function of KCs exhibits topographical variance with significantly different AMP, chemokine and cytokine production in distinct healthy skin regions (Table 1, Figure 2).[57–61] Production of AMPs and

chemokines by KCs is substantially enhanced in the sebaceous area, somewhat elevated in the moist area and low in the dry skin area.[57–60] In terms of KC-derived cytokines, the sebaceous and dry areas show distinct patterns (IL-23 and IL-17C in sebaceous and IL-25, IL-33, IL-36RA and IL-38 in dry), while the moist area has a mixed cytokine pattern.[61] Data related to Langerhans cells (LCs) are inconsistent; in one study, no significant difference was detected in distinct skin regions, whereas in another study, elevated Langerin+ LC counts were found in the sebaceous area compared to the dry region (Table 1, Figure 2).[58,59,62]

To date, three studies investigated the dermal immune cells in distinct skin areas. Although similar macrophage and mast cell counts were observed between the three skin regions, significantly more DCs and T cells are present in the sebaceous and moist versus dry skin region.[58,59,62,63] Although higher densities of certain immune cells characterize the gland-rich skin areas, DCs exhibit no substantial activity and T cells are mainly Tregs and non-inflammatory Th17 cells, indicating a non-inflammatory, homeostatic IL-10/IL-17 milieu in gland-rich dermal regions (Table 1, Figure 2).[58,59,62,63] The dermal immune components are qualitatively very similar in the sebaceous and moist regions, differences occur in terms of quantity with higher activity in the sebaceous area.

The pilosebaceous unit, consisting of a hair follicle and sebaceous gland, is a third major niche of the immunological barrier. Several studies demonstrated prominent immune cell infiltrates near the immune-privileged pilosebaceous units under homeostatic conditions.[2,49,64–67] Characterization of T cells next to pilosebaceous units revealed prominent numbers of CD4+IL-17+ T cells and potential homeostatic cross-talk between Th17 cells and sebocytes was proposed.[10–13,68] Follicles and glands are more abundant in gland-rich areas; however, whether the perifollicular immune infiltrate per se is responsible for the dermal immune cell differences, or whether the interfollicular dermis alone carries distinct immune cell counts is not known. Within the sebaceous region, follicle-rich (scalp) and follicle-sparse (face) areas are characterized by similarly high T-cell and DC counts, suggesting that perifollicular infiltrate is not the only source of dermal differences.[62] In line with this observation, in another study, the authors could not detect a strong correlation between the number of hair follicles and the CD3+ T-cell count.[59] However, more research is needed.

These findings confirm the non-uniformity of the healthy skin immunological barrier in adulthood, similar to the chemical, microbiota and permeability barriers (Table 1, Figure 2). However, whether immune-related topographical differences exist in childhood and how these regional variations change in later life remain unanswered.

TOPOGRAPHICAL BARRIER DISTINCTIONS IN DISEASES

Direct data on regional barrier differences in the skin are recent and limited, particularly regarding the permeability and the immune barrier. On the other hand, indirect evidence also supports topographical barrier differences. Microbiological differences between skin areas are well accepted and proven, and the close association of the skin microbiome with other barrier elements indicates the existence of regional differences in other barrier functions.[1] Overall, further studies are needed to confirm and extend the data on the topographical differences of our skin and its barrier properties, as well as the implications of this knowledge for our clinical practice.

The main known pathological mechanisms involved in immune-mediated skin diseases are allergic-immune, autoimmune and autoinflammatory reactions. In the last two decades, it has been discovered that barrier damage through alarmin-type cytokine production, DC and T-cell activation, closely related to the previous pathomechanisms, can also drive immune-mediated inflammatory skin diseases. Although the main characteristics of these barrier damage-induced skin diseases are not yet defined, the following features can be considered: (a) because of the close relationship between the four barrier units, all four barrier elements are probably disturbed; (b) alteration of probably any barrier element can initiate the disease, as breakdown of one barrier unit leads to alteration of others, ultimately leading to a vicious circle; (c) their regional localization is probably quite characteristic, linked to the regionally somewhat different barrier characteristics.

There is strong evidence to suggest that atopic dermatitis (AD) may be a barrier damage-driven inflammatory skin disease in which genetic and/or acquired chemical, microbial, permeability and immune barrier alterations may initiate and develop the characteristic skin inflammation. Alterations in chemical (altered pH, lipid and ceramide content),[69,70] microbial (Staphylococci overgrowth)[71] and physical (permeability) barrier functions (damaged TJs and terminal differentiation, increased transepidermal water loss [TEWL])[69,72,73] have long been recognized in AD and a genetic predisposition of patients to Th2 inflammatory responses has also emerged as a possible initiating factor.[74] However, there is no consensus as to which particular barrier element is compromised as a driver of the disease. It is also possible that the initial barrier damage varies from patient to patient and as the disease progresses, each barrier element will become altered. The localization of the disease is characteristic and in adults occurs mainly on very dry areas of the skin.

There is data to suggest that rosacea may also be considered as another barrier disorder, although the evidence is not as strong as for AD. Severe skin dryness, increased pH and TEWL,[75] altered lipid content,[76,77] activation of serine proteases,[78] decreased levels of physical barrier and junctional molecules,[79,80] microbial alterations[81,82] and overreactive innate and adaptive immune mechanisms[62,83] are all characteristic features of rosacea. Localization to central facial areas is very characteristic (it is interesting to note that when AD affects the face, it is not in the central facial area, but rather around the eyes and mouth).

On the other hand, the question may arise as to why two skin diseases initiated by barrier damage, such as AD and rosacea, have such different clinical and histological appearances. The answer is currently unknown but may be related to the topographical differences in the skin barrier as described in this review. Regions of the skin that have different barrier properties under healthy conditions may develop different disease patterns following barrier damage. In AD, which is mainly confined to dry areas, Staphylococcal overgrowth, physical barrier damage and Th2-type inflammation are characteristic, as dry areas are already characterized during homeostasis by Staphylococcal dominance and pro-Th2-type KC cytokine production (IL-25, IL-33, IL-36RA and IL-38).[32,35,61] Of note, some degree of Th1/17 type inflammation can also be seen in AD, which may be related to the fact that this disease does not always respect regional boundaries and can also occur in sebaceous and moist regions. In rosacea, which is a disease of the mid-facial sebaceous region (which is usually spared in AD), the main inflammatory pathway is Th1/17-type inflammation, the physical barrier damage is similar to that of AD, and the main microbiological factor is the presence of Demodex folliculorum,[41,62,79,83] all of which can be linked to the homeostatic characteristics of the sebaceous area, with pro-Th17 type epithelial cytokines (IL-23 and IL-17C), the presence of dermal non-inflammatory Th17 T cells, a weaker physical barrier and the presence of Demodex. Taken together, it can be suggested that, in skin diseases initiated by barrier damage, the homeostatic barrier properties of the regions may influence the characteristics of the disease that develops after barrier damage.[61]

Many skin diseases are not primarily initiated by barrier damage, but their characteristic occurrence on specific skin sites may be related to the regionally different barrier properties of our skin. The manifestation of pemphigus foliaceus or Darier and Hailey-Hailey disease predominantly on gland-rich areas may be related to the weak physical barrier properties of these areas, although the underlying causes of the disease (presence of autoantibodies, genetic alterations) are common to all skin areas.[84–90] In addition, cancer development may be related to topographical differences in the immune barrier of the skin, as suggested by a clinical study showing higher rates of cutaneous metastasis in the head and neck area, possibly related to the increased abundance of Tregs in the sebaceous skin region, as suggested by the authors.[63]

SUMMARY AND FUTURE PERSPECTIVES FOR CLINICIANS AND RESEARCHERS

In barrier organs such as the gastrointestinal tract, in addition to the known anatomical and physiological differences between its regions, there is increasing evidence that these regions have different chemical, microbiota and immune barrier properties.[91,92] In the skin, anatomical differences are less obvious but also exist (different follicle counts, distinct numbers and types of glands). Recently, topographical differences in microbiota, chemical, physical and immunological barrier elements have also been identified, meaning that the barrier components and function of the skin have topographical differences across the body surface (Figure 2). At present, at least three main regions (sebaceous, moist and dry) can be identified in adults. Although further studies are needed to collect data on the regional differences in the skin, this important knowledge can already be considered in both clinical practice and dermatological research.

Regional differences in pH, enzyme function and microbial communities should be considered in the development of new skincare products to preserve and maintain the homeostatic skin barrier. Clarification of the topographical variations in the immunological barriers of healthy skin is crucial when performing skin allergy testing, applying epicutaneous immunotherapy or even administering vaccinations in clinical practice.[59] Clinicians should also be aware that barrier damage-initiated skin diseases may present differently depending on the homeostatic regional characteristics of the skin area in which they occur. In disease, all four barrier functions are severely compromised, suggesting that therapeutic targeting should focus on all these barrier elements, taking into account the initial barrier characteristics of the region.

An important message for dermatological science is that to better understand healthy and diseased skin barrier function and pathology, control skin samples from the corresponding area of disease should always be used. The above findings also raise several other questions. How many regions can be distinguished in the skin? When do these regions develop (during childhood or after puberty)? Which diseases are affected by regional differences in barrier function and how?

Notably, topographical differences occur not only in the composition and function of the skin barrier but also in other skin components. Regional and anatomical differences shape dermal fibroblast diversity and C nerve fibre distribution affecting itch intensity.[93–96] A recent article also emphasizes that standardizing skin data requires considering regional characteristics.[97]

Overall, recent research has highlighted the important role of tissue organization in disease pathogenesis (tumour formation/progression, immune-mediated disease initiation/development). Following this avenue of scientific interest, current dermatological research highlights regional variations in the skin barrier and tissues, similar to previous observations made by rheumatologists and gastroenterologists regarding the musculoskeletal system and the gastrointestinal tract.[91,92] Dermatologists increasingly acknowledge that location is also important for the skin, as our skin is not uniform.

AUTHOR CONTRIBUTIONS

Conceptualization: ZD, AK and AS; supervision: AS; visualization: ZD; writing – original draft: ZD, AK and AS; writing – reviewing and editing: ZD, AK, KE, SE, DT and AS.

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CONFLICT OF INTEREST STATEMENT

The authors state no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICAL APPROVAL

Not applicable.

ETHICS STATEMENT

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ORCID

Z. Dajnoki https://orcid.org/0000-0002-7787-1002
K. Eyerich https://orcid.org/0000-0003-0094-2674

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