Cutaneous barriers and skin immunity – differentiating a connected network

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Abstract

The skin is the outermost barrier of the organism that ensures protection from external harm. Lately our view of the skin evolved from an inert mechanical barrier to an active organ that can sense danger signals and to mount perfectly adapted defense measures in response to invading pathogens. This review highlights the different levels of the cutaneous barrier – the microbiome-, the chemical-, the physical-, and the ***immune barrier*** - their characteristics, and their functional, highly interconnected network of cells and mediators that allow balanced defense measures to protect the body and to maintain barrier integrity.

The skin, with roughly two square meters, is our largest organ, and gives our organism integrity and identity. It further allows exchange with our environment, but at the same time mediates protection from it. The skin balances body temperature, protects from UV light, transmits sensations and represents a tight barrier against myriads of microbes, toxins, and other dangers. Historically, the skin was seen as an organ consisting of an outermost layer, the epidermis, and an subjacent connective tissue, the dermis. Whereas the epidermis consists of different stages of differentiated keratinocytes building up a layer of cornified cells, the stratum corneum (SC), that creates a mechanical barrier against potentially harmful invaders, the dermis is rich of collagen fibres, fibroblasts and nerve endings. Today, we know four functional levels of the cutaneous barrier that are carefully orchestrated: the ***microbiome barrier***, the ***chemical barrier***, the ***physical barrier***, and the ***immune barrier***. These developed during evolution and are functional to both stabilize or restore cutaneous homeostasis and to mount measures of defense when needed. Alterations in each component of the skin barrier can cause pathogenic conditions, such as skin infections, sterile skin inflammation, allergic sensitization, or cutaneous tumor development. Consequently, the best possible understanding of the functioning of the different parts of the cutaneous barrier is a prerequisite to develop strategies to conserve the integrity of the skin and to support the recovery of disturbed barriers. This review will highlight the peculiarities of each barrier compartment, their interconnection and summarizes recent insights into dysregulation and disease development based on skin barrier dysfunction.

The cutaneous barrier: its levels and basic functions

The ***microbiome barrier*** is the outermost layer of the cutaneous barriers (Figure 1). It consists of diverse microbial communities, which cover all surface areas of the skin. The composition of these microbial communities includes bacteria, fungi and viruses and is fairly stable. Culture independent genomic approaches have shown that, in contrast to the gut microbiome, the skin microbiota is dominated by Actinobacteriae with an abundance of Gram-positive bacteria such as the Staphylococcus family, Propionibacterium – and Corynebacterium species. Stability is preserved through a multitude of communication pathways and several checks and balances that exist between the microbes, their communities and skin cells [1]. Several studies addressed how commensal bacteria within

these communities control potentially pathogenic bacteria. For example, the serine protease Esp secreted by *Staphylococcus (S.) epidermidis* inhibits colonization with *S. aureus* and blocks the formation of *S. aureus* biofilms [2]. Some *S. epidermidis or S. lugdunensis* strains furthermore produce antibiotics to specifically control *S. aureus* survival [3, 4]. In human keratinocytes, *S. epidermidis* induces expression of antimicrobial peptides/proteins (AMPs) and activates pathways distinct from *S. aureus* resulting in *S. epidermidis* orchestrated innate immune alertness [5].

The microbial communities on the skin also constitute a living and ideal first response barrier to environmental factors. They act as a border post and transmit external signals to the skin´s functional, immune network. The outcome of this threefold crosstalk between skin cells, skin immune system and skin microbiota determines functionality of the ***microbiome barrier*** [6].

The definition of the ***chemical barrier*** of the skin is less sharp compared to other parts of the cutaneous barrier and is tightly connected to the ***physical barrier*** (see next paragraph). Commonly, `***chemical barrier***´ comprises factors that contribute to the acidic surface pH and compounds that together make up the `natural moisturizing factor` (NMF) (Figure 1). Schade and Marchionini coined the term “Säuremantel” of the skin explaining the safety belt of acidity covering the skin [7]. The NMF collectively refers to these hygroscopic compounds and represents about 20-30% of the corneocytes’ dry weight [8]. Much of the NMF is composed by amino acids and their derivatives (pyrrolidone carboxylic acid and urocanic acid), derived from the proteolysis of epidermal filaggrin (FLG) [9, 10]. Changes in the NMF are thought to also alter the SC pH and the SC lipids, indicating an interdependence between the ***chemical*** and the ***physical barrier*** functions [11]. Other components of the NMF found within but also external to the corneocytes include lactates, urea, and electrolytes. Lactate and potassium also play an important role in maintaining the state of hydration and physical properties of the SC such as the pH [8, 12].

Important parts of the ***physical barrier*** are the SC and the system of tight junctions (TJ) and their regulation (Figure 1). Forming the SC is the consequence of keratinocytes maturing, moving up the epidermal layers to finally become corneocytes by terminal differentiation. These corneocytes are flattened and denucleated keratinocytes and their membranes are replaced by the `cornified envelope´ [13]. Keratinocytes of one layer

below the SC, the stratum granulosum, contain i) granules with important proteins such as FLG, loricrin and keratin filaments and ii) laminar bodies (LB) with lipids, corneodesmosins and kallikreins [10, 14]. The contents of those fill the intercellular space of the SC, which is often referred to as `mortar between bricks´ [15]. Many of the proteins that contribute to the `mortar´ were understood once monogenetic diseases such as peeling skin syndrome, skin fragility syndromes or ichthyosis were unraveled [14]. Adjacent keratinocytes of the stratum granulosum are further connected by so-called tight junction (TJ) proteins to form a barrier especially against water and solutes [14]. TJ proteins are mostly transmembraneous and examples are the claudins, occludin, and the zona occludens (ZO) proteins. TJ protein claudin-1 null mutations lead to neonatal ichthyosis sclerosing cholangitis (NISCH) syndrome demonstrating its crucial role for the ***physical barrier*** of the skin [16] and the suppression of claudin-1 expression is also involved in inflammatory skin diseases [17]. Claudin-1, claudin-4, occluding, and ZO-1 are highly effective in regulating the transport of intermediate sized and large molecules as well as ions from inside to outside as these are stopped at the TJ level of the stratum granulosum following dermal injection [18, 19]. It is believed that this holds also true for the outside-to-inside transport, but evidence is less firm in this respect.

Cells of the physical barrier further contribute to chemical barrier function by production of epidermal lipids. Here, keratinocytes deliver mainly triglycerides and cholesterols, whereas sebaceous glands secrete triglycerides, wax esters and squalene containing sebum into the upper part of the hair follicle and thereby deliver it directly onto the SC. Bacteria and yeasts then hydrolyze triglycerides into free fatty acids and thereby contribute to acidification (see also prior paragraph) of the skin [20]. These intercellular lipids provide a tight and effective barrier also regulating the trans-epidermal water loss (TEWL). However, most of the water in the SC is inside the corneocytes and there is no free water between the lamellae.

The **immune barrier** represents the final part of the cutaneous barrier and is composed of a variety of resident immune cells populating the epidermis and dermis (Figure 1). The cellular composition of the ***immune barrier*** consists of innate sentinels such as several types of resident antigen presenting cells, innate lymphoid cells, innate-like cells, keratinocytes and adaptive derived tissue resident memory cells that all work hand in

hand to maintain barrier integrity. This immune armada efficiently senses microbial danger signals via PAMPs and DAMPs and initiates an adequate immune response, subsequent tissue inflammation by recruitment of circulating counterparts and further barrier disruption to clear the invasion. Besides this necessary but harmful action, resident immune cells further contribute to barrier repair and homeostasis. As cells of the ***immune barrier*** are distributed over all parts of the skin, it is highly interconnected with the other levels of the cutaneous barrier, e.g. responds to signals derived of epithelial cells and secrets signals that orchestrate epithelial behavior. Components of the ***immune barrier*** sense microbial signals of the ***microbiome barrier***, are shaped by the condition of the ***physical barrier***, directly respond to parts of the ***chemical barrier*** and can orchestrate these by disturbing, but also by supporting the regeneration and recovery of the previous levels of the cutaneous barrier (Figure 2).

Crosstalk of the microbiome barrier and other barrier elements

The cutaneous microbial communities evolved together with the skin and their composition and functional interdependence is essential to the overall function of the skin and its barriers. Breakdown of the cutaneous microbial communities is associated with skin diseases as shown for atopic dermatitis dominated by *S. aureus* [21] and contributes to disease persistence [22]. On the other hand, recovery of the cutaneous microbiome indicates resolution of disease [21]. The breakdown of these well balanced microbial communities is often referred to as dysbiosis. Dysbiosis may either be a consequence of the dysfunction of other parts of the cutaneous barrier or even its cause. While the `hen and egg´ problem in atopic dermatitis is not solved regarding dysbiosis and cutaneous inflammation, recent studies identified that *S. aureus* expansion precedes detectable skin inflammation [23] and that *S. epidermidis* strain diversity associates with less severe disease whereas clonal *S. aureus* strains are found in more severely affected patients [24], suggesting that dysbiosis is one of the initiating event in this case. Experimental models showed that missing skin microbiome in full germ free mice results in impaired anti-infectious IL-17 responses. These anti-infectious immune responses are mediated by $CD8^+$ T cells (Tc17) and were shown to be effective against *Candida albicans* or

Leishmaniasis [25]. In addition, a defect in or complete loss of the cutaneous barrier integrity also allows invasion of bacteria into deeper layers of the skin [26]. On the other hand, components of the cutaneous microbiome also shape pathways and players of regulatory immune responses and immune tolerance as shown for early in life exposure to skin commensals and the marked expansion and influx of Tregs into the skin (Figure 3) [27].

The “control” of the microbial composition on the skin is also maintained by the upper most cellular layer of the skin, the keratinocytes and their products. Following the encounter of danger signals or immune triggers, keratinocytes produce antimicrobial peptides such as human β-defensins, cathelicidins, and RNAses to co-regulate the composition of the microbial communities (Figure 1). In addition, these signals upregulate pattern recognition receptors like Toll-like receptors to allow keratinocytes to mount adequate responses to microbial signals [28-30]. Conversely, *S. aureus* was shown *in vitro* and in porcine models to decrease density and expression of tight junction (TJ) proteins such as claudin-1, Zona occludens (ZO) ZO-1 (TJP-1), ZO-2 (TJP-2), occludin and adherens junction (AJ) protein E-cadherin, demonstrating that the composition of the microbial communities or its dysbiosis co-determine the setup of the ***physical barrier*** [31, 32].

Barrier disruption at different levels results in microbial dysbiosis with expanding pathogenic bacteria causing inflammation and inflammation derived signals from the skin causing further barrier disruption, which sustains the growth of pathogenic bacteria – especially *S. aureus* [33]. This is also mirrored by monogenic diseases such as the Netherton syndrome evolving from mutations in SPINK5 that encodes for a serine peptidase inhibitor and whose loss of function results in defects of the physical and ***chemical barriers***. Netherton syndrome and hyper IgE syndrome can also cause skin barrier disruption at the level of the ***immune barrier***, with STAT1/STAT3 mutations resulting in defects of the type 17 immune response and leading to chronic skin inflammation that includes eczema and shift in the microbiota towards *S. aureus* and *Acinetobacter* species [34-36]. This shift further enhances impaired immune response as *Acinetobacter* actively represses the cytokine production (TNF-α, IFN-γ, IL-22) upon *C. albicans* or *S. aureus* stimulation in T cells and thereby further reduces the antimicrobial tissue defense [36]. Commensal bacteria seem to furthermore directly shape adaptive

immune responses. Here, *S. epidermidis* has been shown in mouse models to secrete peptides that are presented on non-classical MHCI molecules to induce *S. epidermidis* specific Tc1 and Tc17 cells [37]. These Tc17 cells express markers of tissue residency and a specific signature that allows induction of tissue repair after wounding. Thereby, commensal bacteria do not only prevent colonization with pathogenic bacteria by secretion of antibiotics, but also regulate adaptive immune surveillance. (Further recent publications and reviews focusing on the interaction between microbiome and immune system can be found in Table 1)

ADAM17 (A disintegrin and metalloproteinase 17)-deficiency also leads to eczematous dermatitis and pustular lesions with *S. aureus* infections [38]. ADAM17 is a transmembrane protease that cleaves a variety of membrane-bound proteins to release their soluble forms and plays a major role in the shedding of TNFα and epidermal growth factor receptor (EGFR) that is involved in these signaling pathways [39]. In concordance with this, a mouse model with ADAM17 deficiency manifested a phenotype similar to the human monogenic disease, with the development of atopic dermatitis associated with barrier impairment and chronic inflammatory skin disease. Importantly, microbiome analysis of eczematous dermatitis of these ADAM17 deficient mice showed *S. aureus* dominated dysbiosis [33]. Of note, a common side effect of the treatment of cancer patients with EGFR inhibitors is the development of skin rashes with pustules [40], from which *S. aureus* can be isolated [41, 42].

The ***microbiome barrier*** is therefore to be interpreted as an integrated part of the cutaneous barriers (Figure 2). The diversity of the components of the cutaneous barriers, their plasticity and flexibility, together with their enormous potential to regenerate, partly relies on a well-functioning ***microbiome barrier*****.** Precise orchestration of cutaneous barrier functioning through regulation of the microbial composition is a promising mission to also intervene with disease development.

Crosstalk of the chemical barrier and other barrier elements

The acidic skin pH (4-6) plays a central role in the functioning of the SC and the cutaneous barrier, because proteases and enzymes involved in the generation of SC lipids function in a pH dependent manner and e.g. the formation of the lamellae requires an acidic pH

[43-45]. Neutralization of the SC pH alone results in aberrant permeability of the barrier and decreased ***physical barrier*** integrity [46]. Acidity of the SC and the sweat is also important for anti-microbial activity. The diverse composition of the cutaneous microbiome is maintained by an acidic pH, because pathogens like *S. aureus* are inhibited, which favors coagulase-negative staphylococci and corynebacteria [47, 48]. Furthermore, efficacy of anti-microbial peptides depends on the acidic pH of the skin. This is shown e.g. for Dermcidin, an anti-microbial peptide derived from sweat. It functions optimally at pH 5.5 while activity is down to 60% already at pH 6.5 [49]. This highlights the strong dependence of a healthy ***microbiome barrier*** on the maintenance of the ***chemical barrier*** (Figure 2).

Crosstalk of the physical barrier and other barrier elements

Proteins of the TJ undergo regulations upon contact to microbes both during homeostatic colonization and infection. While low microbial loads strengthens TJ function partly by triggering pathogen recognition receptors (PRR), e.g. TLR2 on keratinocytes [50], more intense contact with microbes, such as during infection or in highly colonized and inflamed skin, results in downregulation of TJ proteins as shown in atopic dermatitis for claudin 1 [51]. Importantly, infection and inflammation regulate TJ proteins, but TJ proteins also determine inflammation as shown for dose-dependent regulation of claudin 1 featuring atopic dermatitis in animal models [17]. Furthermore, keratinocyte and sebocyte derived lipids do not only have moisturizing function, but actively influence immune reactions as they drive the differentiation of alternatively activated macrophages [52] and contribute to the survival of memory T cells in the skin [53]. Furthermore, proteases and protease inhibitors contribute to the shaping of the ideal lipid composition and functioning forming the unique organization of lipid lamellae [54].

These interactions with the microbiome and the ***immune barrier*** furthermore highlight the role of keratinocytes derived constituents and corneocytes for the functioning of the skin barrier and demonstrate how sensing and appropriately reacting to alterations in the local microenvironment contribute to its proper composition (Figure 2).

Cutaneous innate immune sensing: handing over information outside in and inside out.

Innate immune pathways such as the NFκB pathway, the inflammasome, or other cytokine activated signal transduction can be operative in keratinocytes, epidermal immune cells such as Langerhans Cells or γδ T cells as well as in dermal resident innate immune cells (different dendritic cells (DC) subtypes, mast cells, macrophages, ILCs), resident adaptive immune cells (resident T cells) or recruited innate and adaptive immune cells. Keratinocytes have recently been appreciated to participate in immune responses and to represent an innate immune cell capable of initiating cascades of immune events relevant for e.g. inflammatory disease development such as in atopic dermatitis, microbial defense, and wound healing [55-60]. Innate immune receptors constantly encountering signals from the outside are among others the pathogen recognition receptors (PRR) such as the toll like receptor (TLR) family, the NOD-like receptors (NLR) or the C-type lectin receptors (CLR). Importantly, the expression of these receptors is tightly regulated, especially in the cells of the outermost layer of the skin [61-64]. In addition, the engagement of more than one innate immune receptor may be necessary for activation, thus ensuring proper regulation of responses [64, 65]. For example in keratinocytes, a pro-inflammatory conditioning such as through TNF or IL-6 may be necessary to establish responsiveness to TLR ligands [66]. Consequently, this safety lock stays closed in response to commensal bacteria or mechanical stress, but once it opens, relevant mediators are produced, among them inflammation-amplifying cytokines such as TNF or IL-6 and anti-microbial peptides regulating bacterial colonization (and more). Recruited immune cells downstream of innate induced keratinocyte activation and TNF, IL-6 and IL-17C production further amplify inflammation, as seen in psoriasiform and atopic dermatitis-like cutaneous inflammation [67, 68]. In the latter situation, we have shown that innate signals active through TLR2-6 upregulate cutaneous IL-6 by about 400-fold leading to systemic recognition of inflammation and accumulation of Gr1+CD11b+ myeloid derived suppressor cells (MDSC) that suppress T-cell mediated immune responses in the skin [68]. The recruitment of MDSC into the skin may contribute to the resolution of inflammation, but in case of exacerbated skin inflammation relevant cutaneous immune suppression is established [68]. Another important immune function of keratinocytes is their production of immune mediators such as TSLP, IL-25 or IL-33, that are critical orchestrators of type 2 cutaneous

immune responses through the conditioning of DCs [55, 56]. Accordingly, NFκB and inflammasome activation in the skin tend to drive type 17 immune responses, as regularly found in psoriasis. Direct PAMP sensing in innate immune cells such as DC may lead to pro- and anti-inflammatory immune responses depending on the co-stimulation [64, 69]. TLR2 sensing amplifies modulatory IL-10 active in sensing non-pathogenic bacteria, however, in the presence of type 2 immune cytokines such as IL-4, this IL-10 is shut off leading to persistent inflammation. As the cutaneous cytokine profile may translate into T cell profiles, the cascade of immune events may produce also stable immune phenotypes [22, 70]. Many examples demonstrate that innate immune cells such as mast cells [71, 72], macrophages [73] and ILCs [74, 75] in the cutaneous microenvironment can govern the decisions between resistance to or amplification of inflammation. These influences are critical to balance local homeostasis and health with immune defense or inflammatory disease, the latter possibly with systemic consequences.

Physical barrier disruption as activator of skin immune sentinels

Epithelial barrier integrity is a prerequisite to prevent penetration of potential harmful substances from the surrounding environment. Skin resident immune cells are fine-tuned sensors of barrier breaches as they are either activated or induced to migrate by barrier disruption and altered lipid composition, potentially leading to the initiation of immune responses also in the draining lymph nodes. One essential molecule in this scenario is E-Cadherin expressed on epithelial cells, as it inhibits the activation of ILC2 cells [76]. Upon barrier disruption, E-Cadherin is downregulated and cytokines such as TSLP, IL-33 and IL-25 are released. These mediators consecutively activate ILC2 cells to secrete IL-4, IL-5, IL-13 and amphiregulin, in turn leading to a plethora of downstream functions involved in defense and allergic responses. Another important but less well understood indicator of tissue disruption is the local composition of lipids. Invariant natural killer cells (iNKT) that express an invariant TCRα chain (Vα24-Jα18) combined with a TCRβ chain with limited specificity are activated by glycolipids presented by CD1d molecules [77]. iNKT cells not only recognize lipids of bacterial origin, but also can also be activated in response to changes in the lipid composition of the skin upon barrier disruption. Like Th cells and ILCs, iNKT cells come in different flavors [78] and ensure efficient and relevant cytokine responses to defend against the infecting pathogen or restore barrier integrity.

The skin is not only populated by cells of the innate branch of immunity, but also by cells belonging to adaptive immunity. Indeed, the skin contains $1x10^6$ resident memory T cells (Trm)/m^2 – representing $2x10^{10}$ cells in total reside in human skin, twice as much as circulate in blood [79, 80]. Trm persist in the skin for long periods of time, probably throughout life, and are present in both the dermis and epidermis. Whereas CD69 expression and its interaction with E-Selectin blocks the egress of Trm cells from the dermis and epidermis by sequestering the sphingosine-1-phosphate-receptor (S1PR) [81], epidermal Trm co-express CD103 that binds to E-Cadherin on keratinocytes and further keeps them in place at the outermost barrier. Trm cells however, do not only sense ***physical barrier*** disruption, but also recognize changes in the ***microbiome barrier***. Various studies using infection models could prove that the residency of T cells establishes after an initial infection and remains highest at the site of first encounter of the pathogen. In skin, Trm cells specific for herpes simplex [82], varizella zoster [83] and vaccinia virus [84] as wells as *Leishmania* [85] were identified, highlighting that Trm cells in skin protect the barrier from pathogens that are commonly encountered in this organ. Interestingly, the newly developed memory is not only skin specific, but spreads to other barrier organs to provide an overall surface protection (Figure 3). The potential of Trm cells to provide lifelong protection is addressed for example in vaccines´ development, but the mechanisms behind this longevity are not well understood. Pan Y et al. recently showed that also the ***chemical barrier*** impacts on the immune memory in skin. Here, free fatty acids (FFA) have been shown to not only support the functionality of Trm, but also to prolong their survival and therefore provide tissue-specific signals that are critical for maintaining protection [53]. How the lipid composition during barrier disruption is altered and how this could potentially influence vaccination strategies aiming at efficient induction of long-term memory should be investigated further.

Immune cells and the restoration of barrier integrity

Inflammatory processes are beneficial for the host in terms of eradicating pathogens, but almost always go along with tissue damage and temporary loss of tissue functionality. To restore barrier integrity, two prerequisites have to be fulfilled – initiation of tissue healing and restoration of the ***microbiome barrier***. Wound healing processes in skin are mediated by various cells of innate and adaptive origin that work hand in hand to repair

barrier breaches (Figure 2). For instance, Notch1 is activated in epithelial cells via its ligands, Jagged 1 and 2, leading to the induction of TNF-α and chemokines and in turn to the recruitment of IL-17F and IL-22 producing Rorγt+ ILC3 [86]. IL-22 in turn leads to wound healing by induction of proliferation and migration of keratinocytes [87, 88], myofibroblast differentiation and extracellular matrix deposition [89]. The role of IL-17F in this scenario is not well understood and it is thought that it is not involved directly in wound closure, but instead keeps the local microbiota in check via the induction of anti-microbial peptides in keratinocytes. Another important mediator of tissue repair is IL-33, that is induced upon barrier disruption in epithelial cells. IL-33 activates resident ILC2 cells by binding to the ST2 receptor to induce the secretion of IL-13, IL-5 and amphiregulin that enhance the differentiation of M2 macrophages [90] and the proliferation of epithelial cells via the interaction with the epidermal growth factor receptor (EGFR) [91], respectively.

Whereas wound healing responses are largely well understood, the restoration of the ***microbiome barrier*** is currently under intensive investigation. Interaction between the immunological barrier (IL-17 and IL-22) and the ***physical barrier*** (keratinocytes) lead to the induction of anti-microbial peptides (AMPs) and the eradication of pathogenic bacteria, viruses and fungi. However, how these AMPs can selectively affect pathogenic invaders and not the commensal flora has been not elucidated yet. It is assumed that commensal bacteria are resistant to the effects of host AMPs [92] and that they furthermore produce their own set of bacterial AMPs to defend against pathogens and to create an advantage for commensals to colonize microbial niches on the skin [3].

Concluding remarks

A well balanced cutaneous barrier is a prerequisite to maintain body integrity and health. We now know that the cutaneous barrier is a multi-faceted structure consisting of four different functional barrier compartments - the **microbiome**-, the **chemical**-, the **physical**-, and the ***immune barrier***. Despite having their own characteristics and compositions, all parts of the cutaneous barrier are highly interconnected. This complex network is instrumental in the skin's ability to fulfil its major tasks: the maintenance of the body´s integrity that includes protection from external harm, and rapid restoration of the barrier and immune homeostasis in case of disturbances. However, if one barrier

compartment is dysbalanced this might lead to a vicious circle of inflammation and consecutively the development of skin disease**.** Challenge for future treatment approaches will be to understand the interdependence of all parts of the cutaneous barrier and to apply specific regimens that re-balance the cutaneous barrier.

Figure legends

Figure 1: Levels and components of the cutaneous barrier**.**

FAA: free fatty acids; ILC: innate lymphoid cell; iNKT: invariant natural killer cell; Trm: tissue resident memory cell

Figure 2: Homeostasis and dysbiosis – a delicate balance between microbial diversity, inflammation and barrier repair

Under homeostatic condition, commensals, epithelial cells, chemical barrier components and immune cells quietly work hand in hand to maintain barrier integrity. In case of dysbiosis, inflammatory pathways are activated that lead to barrier disruption and a vicious circle of inflammation and consecutively enhanced dysbiosis. This vicious circle can be stopped, however, by immune cells themselves as they induce antimicrobial peptides in epithelial cells and activate M2 macrophages and EGFR signaling that in turn mediate barrier repair.

AMPs: antimicrobial peptides; CLR: C-type lectin receptor; EGFR: epidermal growth factor receptor; IL: interleukin; ILC: innate lymphoid cell; iNKT: invariant natural killer cell; NLR: Nod-like receptor; Th: T helper cell; TLR: Toll-like receptor; Trm: tissue resident memory cell

Figure 3: A well balanced cutaneous microbiome with its commensal bacteria has the potential to shape immune responses by setting up i) T_{reg} cells and their immigration into the skin already by `early in life´ exposure and ii) IL-17 producing CD4+ and $CD8^+$ T cells (Th/Tc17) assuring effective immune defense against pathogens.

DC: dendritic cell; Tc: cytotoxic T cell; Th: T helper cell

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