Unraveling Immune-Epithelial Interactions in Skin Homeostasis and Injury

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The skin serves as a front line of defense against harmful environmental elements and thus is vital for organismal survival. This barrier is comprised of a water-tight epithelial structure reinforced by an arsenal of immune cells. The epithelial and immune components of the skin are interdependent and actively dialogue to maintain health and combat infectious, injurious, and noxious stimuli. Here, we discuss the molecular mediators of this crosstalk that establish tissue homeostasis and their dynamic adaptations to various stress conditions. In particular, we focus on immune-epithelial interactions in homeostatic tissue regeneration, during natural cycling of the hair follicle, and following skin injury. We also highlight the epithelial derived factors that orchestrate immunity. A comprehensive and mechanistic understanding of dynamic interactions between cutaneous immune cells and the epithelium can be leveraged to develop novel therapies to treat range of skin diseases and boost skin health.

INTRODUCTION

Skin, one of the largest organs of the body, provides a water-tight barrier that protects us from an array of environmental insults. Proper development, homeostatic maintenance, and rapid restoration following injury of this structural barrier is therefore vital for life. Hair follicle and epidermal stem and progenitor cells give rise to differentiated keratinocytes and maintain the skin’s physical barrier throughout our lifetime. This physical barrier is also reinforced by an immunological arsenal of resident and re-circulating immune cells. Communication between cutaneous immune cells and epithelial cells is emerging as a key regulator of the fitness and function of the skin epithelial barrier. In this review, we cover this essential crosstalk between the epithelial and immune cell populations that orchestrates skin homeostasis, injury responses, and inflammation.

THE SKIN IS A STRUCTURAL AND IMMUNOLOGICAL BARRIER

Structural Layers of the Skin

The skin is composed of two main compartments that are separated by a basement membrane, the epidermis and the dermis (Figure 1). The epidermis is the outermost layer of the skin which interfaces with the environment, while the dermis lies beneath providing tensile strength though its rich collagen matrix. The epidermis is cell dense and comprised of stratified epithelial layers...
that provide physical, mechanical, and chemical protection while the dermis is largely comprised of extracellular matrix and sparsely dispersed dermal fibroblasts. Both the epidermis and dermis contain resident immune cell populations that engage in an active dialogue with structural cells of the tissue (e.g. epithelia) under steady state and stress conditions [1].

The major cell type of the epidermis is the keratinocyte. Keratinocytes are stratified into four distinct layers (Figure 1). The innermost layer is the stratum basale that is comprised of stem and progenitors attached to a basement membrane. These proliferative cells differentiate upwards into the stratum spinosum. In this layer, epithelial cells lose their mitotic potential and adopt a polygonal morphology, allowing them to more effectively form a structural barrier [2]. Spinous cells move up into the stratum granulosum where they produce granules and lamellar bodies generating a lipid filled barrier [3]. These cells begin to anucleate as they differentiate upwards into the outermost epidermal layer, the stratum corneum. This layer is comprised of flat-dead cells, corneocytes, void of all organelles, though rich in proteolytic resistant proteases, hydrophobic lipids, corneodesmosomes, and tight-junctions; all of which maintain the mechanical stability and form a plastic cling wrap like water-tight seal [4-9]. While the stratum corneum is primarily responsible for the biomechanical and hydrophobic properties of the barrier, the underlying layers of the epidermis also contribute to barrier function by maintaining tight junctions, adherens junctions, desmosomes, and gap junctions [10]. Synergistic functioning of these epidermal layers is paramount to limit the penetration of harmful, inflammation-inducing, infectious, and noxious agents.

The skin possesses appendages such as the pilosebaceous unit comprised of hair follicle, sebaceous gland, and arrector pili muscle, as well as eccrine and apocrine sweat glands (Figure 1). These “mini-organs” are essential for thermoregulation and organismal responses to stress via the secretion of surface lipids, regulation of water loss, and generation of protective hair. Keratinocytes of the hair follicle, like those of the interfollicular epidermis, are also organized into stratified layers differentiating perpendicular from the basement membrane with unique characteristics going down the hair follicle to the...
The dermal compartment lies beneath the epidermis, and is structured into the papillary, reticular, and hypodermin (Figure 1). The papillary dermis is the region directly below the basement membrane and houses epidermal appendages (sweat glands and hair follicles), while the reticular dermis lies between the papillary dermis and the hypodermis (white adipose tissue) [20,21]. Papillary fibroblasts provide a supportive niche for the development and maintenance of the hair follicle while the reticular fibroblasts provide structural support by producing fibrillar extracellular matrix, and during wound repair, express smooth muscle actin [22,23]. In addition to papillary and reticular fibroblasts, sweat glands, and hair follicles, the dermis also contains structural cells of lymphatic vessels, blood vessels, periphery nerve cells, and immune cells. These cell types work in unison to ensure proper functioning of the skin barrier and immunological protection. However, an in-depth discussion of the constellation of interactions between these cellular populations is beyond the present scope and discussed in detail by Hsu and colleagues [24]. Here we focus on the essential dialogue between epithelial cells of the epidermis and hair follicle with cutaneous immune cells.

Stratification of the Skin Immunological Barrier

Healthy human and murine skin is populated by a diverse array of immune cells including dendritic cells, innate lymphoid cells, T lymphocytes, and macrophages [25]. Their recruitment, retention, and survival are tightly regulated and spatially restricted. This allows for precise targeting of cells to microenvironments within the skin where they exert their effects, and whose milieu meets the survival signals of each immune cell type (Figure 1).

Immune cells residing above the basement membrane, in the epidermis, include Langerhans cells (LCs), CD8⁻ resident memory T cells (T_{REM}), innate lymphoid cells (ILCs), and in mouse Skin Dendritic Epidermal γδ T cells (DETCs) [17,25] (Figure 1). As prototypic antigen presenting cells (APCs), LCs continually surveil the epidermis, take up, and process antigens for presentation to T cells [26,27]. Of the epidermal resident cells derived from the lymphoid lineage, ILCs are highly responsive to local cytokine cues whereas the T cells rely on antigen presentation and cytokine signals from adjacent epithelia and/or innate immune cells for activation [17,28]. Even in the epidermis, there is regional segregation of ILCs that relates to their tissue modulatory function. For instance, the interfollicular epidermis is enriched for Type 3 ILCs (ILC3) while Type 2 ILCs (ILC2) localize to the sebaceous gland epithelium to limit sebocyte hyperplasia [17]. Phenotypically heterogeneous populations of CD8⁺ T_{RM} reside in the interfollicular epidermis and rapidly respond to injury and infections [29,30]. T_{RM} can persist and re-activate even in the absence of cognate antigen by heterogenous inflammatory cues [30]. In addition, mouse epidermis uniquely contains DETCs that take up residence in the neonatal epidermis and provide key signals for tissue repair [31].

Dermal T cells include effector and regulatory CD4⁺ T cells (Th1, Th2, Th17, and T_{reg}) and interleukin (IL)-17A producing γδ T cells [32,33] (Figure 1). Dermal T cell populations, both effector and regulatory, are localized in close proximity of hair follicle [16]. The papillary dermis is also enriched for MHCII expressing dendritic cells [2,27] and under both steady state and inflammatory conditions, CD4⁺ T effector populations are intimately associated with dendritic cell populations [34,35].

Innate immune cells are also stratified to provide a tiered sentinel system with dendritic cells residing in the papillary dermis and macrophages in the lower dermal layers [36] (Figure 1). Both epidermal and dermal dendritic cells continually collect exogenous antigens through the epidermal barrier and engage T cells [35,37]. By contrast, resident macrophages are thought to localize to and survey post-capillary venules for systemic threats in the blood [38,39]. The proper development and maintenance of this organized network of immune cells is essential for optimal immune surveillance in the skin barrier. Below we discuss the key epithelial factors that direct the location and activity of immune cells.

**EPITHELIUM INSTRUCT HOMEOSTATIC IMMUNITY AND INITIATION IMMUNE RESPONSES**
Epithelial Signals Govern Immune Cell Localization and Survival in the Skin

Complex stratified immune networks in the skin are established via homing of the immune cells to distinct cutaneous microenvironments through tightly regulated and spatially restricted epithelial expression of chemokines and survival factors. Different fractions of the hair follicle have unique chemokine signatures [11] (Figure 2A). For instance, infundibular epithelia express CCL20, those of the isthmus CCL2, and of the bulge CCL8 [11]. Infundibular keratinocyte derived CCL20 binds to CCR6 as a skin homing signal for both effector and regulatory T cells, and ILCs to be recruited to their vicinity [17,40]. CCR10 expressing DETCs and TRM are recruited to the epidermis by CCL27 expressing interfollicular basal cells. Under inflammatory conditions, epithelia express a number of inflammation specific chemokines, but also amplify their expression of CCL20 and CCL27 to future recruit T cells to their vicinity [41-43]. Thus, this axis may be valuable to target for limiting inflammatory diseases or augmenting anti-pathogen responses.

Bone marrow derived precursors replenish inflammation-depleted LCs in the epidermis through tightly regulated chemokine signals that involve both positive and negative spatial regulation. Expression of CCL20 and CCL2 by infundibular and isthmus epithelia directs recruitment of LC precursors to this region giving them access to the epidermis in inflammation. In this setting, hair follicle bulge epithelia express CCL8 to repel LC precursors from perifollicular regions [11]. While epithelial derived chemokines direct the localization of cells to distinct compartments within the skin, cellular retention and long-term tissue residency relies on expression of integrins that can interact with epithelial surface integrins and cadherins. ILCs and T cells express integrin αE that can bind to E-cadherin which enables interactions with adjacent epithelial cells and controls their residency in the epidermis [17,44].

Additionally, epithelial cells also supply essential survival signals to ensure the persistence of immune cells in their vicinity (Figure 2B). Epidermal resident ILCs utilize keratinocyte derived IL-7 and thymic stromal lymphopoietin (TSLP) in order to populate the epidermis where they are localize to sebaceous gland epithelia [17]. CD8+ TRMs require infundibular and isthmus derived IL-7 and IL-15 for survival in the epidermal niche [16], while CD4+ T cells only required IL-7 but not IL-15 [16]. These epithelial derived immune survival factors are also co-opted in pathological settings, for instance epithelial derived IL-7/IL-15 was shown to be central for the pathology of Cutaneous T-Cell Lymphoma [16].

Epithelial production of IL-34 is essential for signaling through the colony-stimulating factor 1 receptor (CSF1R) for maintenance of LCs [45] (Figure 2B). These cells enter the skin at embryonic day (E)14.5 as monocyte derived precursors marked by their expression of CX3CR1 where their development and entry into the
epidermis is observed at (E)18.5 coinciding with expression levels of IL-34 greatly increasing as the embryo develops from (E)17.5, driving LC expansion [45,46]. The epidermal developmental programs responsible and teleological reasons for this embryonic expansion of LCs remains elusive. One possibility is that expansion of these immune sentinels at the epidermal interface, just prior to birth, may be necessary for sensing and responding to the plethora of terrestrial antigens that the new born is exposed to at birth.

Keratinocytes as Instigators of Inflammation

As a key interface with the terrestrial environment, the skin epithelium is constantly faced with injurious and inflammatory stimuli. Far from inert structural components, epithelial cells express a number of pattern recognition receptors (PRRS) and can directly sense and respond to stressors by producing antimicrobial peptides, cytokines, and chemokines, to actively engage immune cell function and facilitate inflammation.

Excess sun exposure leads to sun burns with significant inflammation. Ultraviolet (UV) B radiation (wavelength 280-315nm) is thought to be responsible for the inflammatory and carcinogenic effects of sun exposure [47] (Figure 3A). UVB exposure can induce keratinocyte production of immune mediators by influencing epidermal calcium levels and consequently the release of IL-1β and neutrophil infiltration [48]. Furthermore, UVB damaged keratinocytes upregulate the expression of a noncoding RNA, U1 RNA, and during necrosis, release double stranded RNAs (dsRNAs) [49,50]. These dsRNAs are sensed by Toll like receptor 3 (TLR3) in adjacent keratinocytes, inducing the production of inflammatory cytokines, ATP transporters, and proteins for lipid biosynthesis and metabolism. This pathway is co-opted during injury insult where release of dsRNA in damaged keratinocytes facilitates wound induced hair follicle neogenesis [51]. Paradoxically, UVB exposure is also known to cause immune suppression by dampening antigen presentation and augmenting anti-inflammatory factors such as IL-10 [52]. Whether immunosuppression results from direct UVB sensing by immune cells versus epithelial mediated responses to UVB remains an open question.

Apart from sun exposure, a number of topical irritants have been used to highlight the central role of keratinocytes in skin inflammation. In mice, topical application of a vitamin D analog, calcipotriol, engages Vitamin D receptor (VDR) driving keratinocyte expression of TSLP able to be presented by dendritic cells leading to Type 2 immune response and atopic inflammation, similar to atopic dermatitis [53] (Figure 3B). Keratinocytes subjected to 2-4,dinitrofluorobenzene (DNFB), a topical
irritant, produce and activate IL-1β and IL-18 via NLRP3 in a caspase-1/ASC dependent manner [54]. IL-18 signals to LCs to activate their migratory programs to potentiate contact hypersensitivity [55]. Another hapten, 12-O-tetradecanoylphorbol-13-acetate (TPA), induces MAPK and PI3K/Akt-dependent NF-κB signaling in keratinocytes resulting in the overexpression of inflammatory cytokines inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) [56] (Figure 3B).

The skin is home to a myriad of commensal microbes and is also a major portal of pathogen entry. The epithelium is thus tasked with maintaining tolerance to commensals while limiting the penetration of microbes [57] (Figure 3C). In vitro studies have revealed that keratinocytes can directly sense and respond to microbial ligands such as *Escherichia coli* derived Lipopolysaccharide (LPS) and *Staphylococcus aureus* derived peptidoglycan (PGN) and lipoteichoic acid (LTA), to induce production of proinflammatory cytokines and chemokines [58,59] (Figure 3C). However, microbial stimuli can also dampen inflammation in a context specific manner. For instance, LTA from certain commensal *Staphylococcus epidermidis* strains was able to suppress the expression of inflammatory cytokines following skin injury [60]. Commensals also influence the epithelial barrier circuitously by augmenting homeostatic effector T cells, which secrete cytokines such as IL-17A. This baseline T cell activity is essential to upregulate expression of anti-microbial peptides in healthy epithelium and ultimately serves to limit the establishment infections by barrier penetration of cutaneous pathogens [35].

In addition to exogenous signals, keratinocyte specific deletion of cell-cell interaction molecules and transcriptional regulatory machinery have highlighted that epithelial perturbations are sufficient to drive cutaneous inflammation. This notion was first demonstrated in a landmark study by Wagner and colleagues. Deletion, specifically in epidermal cells, of the AP-1 family transcriptional regulators c-Jun/JUNB led to the rapid onset of skin inflammation in adult mice [61]. Indeed, cJun/JUNB are expressed at lower levels in psoriatic epithelium and cJun/JUNB loci were identified by genome wide association studies with increases in psoriasis susceptibility [61]. Deletion, in distinct keratinocyte subsets, of the cell-cell interaction proteins E-cadherin or p120 is sufficient to activate the inflammatory transcription factor Nuclear-Factor Kappa B (NF-κB) and a cascade of downstream inflammatory responses [62,63]. Altogether, keratinocytes have proven themselves as key instigators of inflammation through intrinsic stress sensing and direction of immune activity.

### IMMUNE CELL REGULATION OF EPITHELIAL TURNOVER AND INJURY RESPONSE

**Immune Cells Direct Hair Follicle Homeostasis and Injury**

The epidermis is maintained by distinct subsets of stem or progenitor cells each with their unique “micro-niche.” Immune cells have surfaced as prominent effectors of epidermal stem cell niches, dynamically regulating their activation and differentiation. While the interfollicular epidermis is continually regenerating, the hair follicle undergoes cyclical bouts of rest (telogen), growth (anagen), and regression (catagen), all mediated by the Hair Follicle stem cell (HFSCs) [3] (Figure 4A). The immune derived signals that may regulate the homeostatic turnover of the interfollicular epidermis remain unexplored. However, cross-talk between HFSCs and immune cells has been an area of active investigation as perifollicular immune cells have been shown to potentially influence the follicle cycle [64]. Two cell types in particular, macrophages and T<sub>reg</sub> have emerged as key instructors of hair follicle behavior.

Macrophages influence the hair cycle in a number of distinct ways (Figure 4A). During anagen, the HFSCs proliferate and differentiate to drive follicular growth. The metabolic requirements of this tremendous undertaking are beginning to unfold and macrophage-supplied iron has recently been implicated in follicle maintenance [65]. Iron metabolism is important for multiple cellular functions and absence of cellular iron is linked to G1/S phase mitotic arrest [66]. Macrophage specific deletion of an iron exporter, ferreportin, results in a profound disruption of the hair follicle cycle and hair loss [65]. Loss of the macrophage supplied tissue iron results in reduced epithelial proliferation. Apart from nutrient support, macrophage derived signals dictate the balance of epithelial quiescence and activation through soluble factors [67,68]. During telogen, a subset of perifollicular TREM2<sup>+</sup> macrophages secrete Oncostatin M (OSM) which binds to its receptors OSMRβ and gp160 on HFSCs, inducing a JAK-STAT5 signaling cascade to maintain quiescence [67] (Figure 4A). The downstream targets of STAT5 in HFSCs that maintain cell quiescence remain opaque and future studies examining how STAT5 synergizes with other known quiescence factors such as NFATc1 are necessary to decode the complex molecular regulation of this cellular state [69]. During homeostatic shift from telogen to anagen, follicle-associated macrophages undergo apoptosis and release the HFSC-activating Wnt ligands Wnt7b and Wnt10a [68] (Figure 4A). Taken together, these data indicate that macrophages provide temporal signals to promote quiescence and activation. However, tissue macrophages are known to have distinct develop-
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Sebaceous gland, ILC2s produce TNF and lymphotoxins LTα3 and LTα1β2 resulting in the downregulating of a Notch ligand JAG-2 and Notch-regulated transcription factor PBX1 in sebocytes [17] (Figure 3). In the absence of ILCs, unregulated sebocytes hyperproliferate and augment lipids production, which in turn alters the composition of surface commensal bacteria [17]. How expression the Notch ligand Jagged is regulated in skin lymphocyte populations remains unclear. Both ILC2 and skin Tregs express high levels of the transcription factor GATA3 [71] and have been demonstrated as important niche factors to drive epithelial differentiation. Notch ligands, robustly expressed by the epithelia, are known to directly regulate GATA3 expression in Th2 cells [72]. Thus, it is tempting to speculate that epidermal Notch ligands may signal into ILCs and Tregs to induce or reinforce GATA3 expression, and adaptation to the epidermal microenvironment.

Hair plucking represents a micro-injury scenario, that results in injury or wound-induced activation of anagen (WIH-A). Perifollicular Treg facilitate HFSC proliferation by localizing to the follicle and producing a Notch ligand Jagged 1 (Jag-1) [70]. However, in experiments where Treg populations are depleted, Notch response gene Hey1, indicative of HFSC proliferation, was increased rather than decreased [63]. Thus, it is tempting to speculate that Treg support of homeostatic hair follicle cycling may be through other known Treg factors such as amphiregulin signaling to Epidermal Growth Factor Receptor (EGFR) [63]. Notch signaling in the epidermis is also regulated by ILCs [17]. In the sebaceous gland, ILC2s produce TNF and lymphotoxins LTα3 and LTα1β2 resulting in the downregulating of a Notch ligand JAG-2 and a downstream inflammatory cascade. Lymphoplasaccharide (LPS), Peptidoglycan (PNG), Lipoteichoic Acid (LTA).

Figure 4. Keratinocytes can directly sense and respond to inflammatory and microbial stressors. A) Ultraviolet B Waves (UVB) leads to neutrophil recruitment and inflammatory signaling. B) Keratinocyte responses to chemical hapten insult and the consequent inflammatory signaling. 2,4-dinitrofluorobenzene (DNFB), 12-O-tetradecanoylphorbol-13-acetate (TPA), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) C) Bacterial sensing through expression of pattern recognition receptors such as TLR4 results in activation of the inflammatory transcription factor NF-κB and a downstream inflammatory cascade. Lipopolysaccharide (LPS), Peptidoglycan (PNG), Lipoteichoic Acid (LTA).
Immune Cells Activate Keratinocytes to Facilitate Wound Healing

Rapid repair of the skin epithelium following injury or inflammation is paramount for organismal survival. Stress-stimulated regeneration engages a distinct repertoire of immune-epithelial interactions and homeostatic epithelial turnover.

While hair follicles themselves must recover after injury, they also provide a source of stem cells for repair of the interfollicular epidermis [18]. Crosstalk between epithelia and both effector and regulatory T cells comes into play to ensure rapid re-epithelialization of the barrier (Figure 5). During wounding, T_{reg} stimulate HFSC proliferation and upward mobility to the interfollicular epidermis [74]. In mice depleted of T_{reg}, Th17 cells accumulate and signal to keratinocytes through IL-17A to produce CXCL5 for the recruitment of neutrophils. The IL-17A-CXCL5-neutrophil axis results in a delay in repair of the interfollicular epidermis [74]. TNF-α-producing macrophages promote HFSC function and wound induced hair follicle neogenesis by activating β-catenin in an AKT dependent manner. Precisely how TNF-α activates β-catenin, and if this activation is mediated by direct TNF-α signaling or through secondary mediators, remains to be determined [75]. Additionally, after wounding, dermal γδ T cells also signal to promote hair follicle neogenesis (WIHN), the generation of new follicles [76] (Figure 5). γδ T cell derived Fgf9 signals to dermal fibroblast inducing the production of Wnt2a that in turn signals into keratinocytes to generate new hair.

During healthy repair epidermal αβ and γδ T cells produce epithelial growth factors such as production of insulin growth factor 1, however T cells isolated from chronic nonhealing wounds failed to produce these ligands [78]. Thus, impaired immunity may be a key underlying feature of non-healing wounds. Indeed, in aged animals, DETCs fail to accumulate around the wound’s edge and promote efficient repair. This impairment results from a loss of Stat3 dependent keratinocyte expression of the DETC activating ligands Skint3/9 at the wound’s edge, inducible via recombinant IL-6 stimulation [31]. After

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Figure 5. Epithelial-immune interactions underlie injury responses. The schematic illustrates immune-epithelial interactions in full thickness wound healing in which damage is caused to the intrafollicular epidermis and hair follicle resulting in induced Hair follicle Neogenesis (WIHN).
wounding, damaged keratinocytes release dsRNA, which signal through TLR3 in adjacent undamaged keratinocytes and induce production IL-6 [51]. Whether the dsRNA-TLR3-IL-6 axis is operative in activation of DETCs at the edge of the wound, or other DAMPS/PAMPS play a role, remains to be examined. Thus, the immune-epithelial crosstalk may be used as a lever to kickstart healing. Further studies defining the immune basis of healthy and impaired healing will open doors to immune-based therapies for wound repair.

CONCLUSION

The skin epithelium is tasked with shielding our internal organs from environmental assaults and relies on a dynamic crosstalk with immune cells for optimal barrier function. In addition to classical anti-pathogen functions, the immune-epithelial crosstalk has also emerged as an essential regulator of epithelial regeneration in homeostasis and following injury. The epithelium recruits and maintains resident immune cells, which in turn supply key regenerative signals to maintain the skin’s integrity. As our understanding of the molecular mediators of the immune-epithelial crosstalk improves, including relevant microbial and damage sensors and effectors, it may lead to the generation of novel therapeutics that boost skin health and mitigate disease.

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