Trends in Immunology

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REVIEWS

Review

Skin-Resident Innate Lymphoid Cells – Cutaneous Innate Guardians and Regulators

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Skin is the largest barrier organ and an important interface between the body and the outside environment. Immune surveillance and homeostatic regulation of skin function are governed by complex interactions between resident lymphoid and myeloid cells and their communications with the surrounding parenchyma. Recent studies have provided exciting insights about the unique characteristics of skin-resident innate lymphoid cells (ILCs). Here, we discuss advances demonstrating how skin ILCs contribute to tissue homeostasis by regulating microbiome balance in steady-state and how their dysregulation can trigger and promote inflammatory skin diseases such as atopic dermatitis and psoriasis. We review the phenotypic and functional similarities and differences of ILCs between the skin and other organs and highlight future areas of investigation for this field.

Highlights

Based on phenotypical, transcriptomic, and functional analysis, skin ILCs display distinct characteristics compared with ILCs in other tissues. Skin ILCs have a distinct dependency on cytokines and chemokines for their residency and activation.

Skin-resident ILCs play critical roles in the maintenance of barrier immunity, the regulation of microbial balance, and tissue repair.

Natural killer (NK) cells and ILC1s may be associated with the immunological memory response in contact hypersensitivity.

ILC2s are enriched in lesional skin of patients with atopic dermatitis and promote MC903-induced atopic inflammation in mice, likely via the production of type 2 cytokines such as interleukin (IL)-5 and IL-13. Skin ILC2s are activated by a variety of tissue-derived cytokines including thymic stromal lymphopoietin (TSLP), IL-33, IL-25, and IL-18.

ILC3s accumulate in lesional skin of patients with psoriasis and contribute to imiquimod-induced psoriatic inflammation in mice.

Immune Ecosystem in Skin

The skin is a complex immune organ that provides a protective barrier for the host. Immune cells are well represented throughout the skin layers and form an interactive immune network with nonhematopoietic parenchymal cells, including epithelial cells, fibroblasts, adipocytes, and neurons, to ensure barrier homeostasis. The skin parenchymal cells help to regulate the tissue residency, recruitment, and activation of immune cells, while immune cells produce effector cytokines as well as growth and regulatory factors to maintain and promote barrier functions. The skin also harbors a community of resident microbes that have symbiotic relationships with host immune cells. Mammalian skin comprises three anatomically different layers: the **epidermis** (see Glossary), **dermis**, and **subcutis** (Figure 1). Each compartment carefully orchestrates a mechanical and immunological barrier, the latter comprising a wide variety of tissue-resident immune cells, including αβ and γδ T cells, dendritic cells (DCs), and macrophages [1–3]. Accumulated evidence has now demonstrated that a new innate immune subset of lymphoid lineage, referred to as ILCs, plays a fundamental role in barrier immunity, and ILCs are also well represented in the skin. Despite extensive characterization of ILCs in the lung and intestine, our understanding of skin ILCs is still developing. In this review, we summarize recent insights on the unique features, plasticity, and functions of mammalian skin-resident ILCs and highlight discoveries on their pathological roles in skin diseases such as contact dermatitis, atopic dermatitis, and psoriasis, which could have implications for new therapeutic interventions.

Classification of the ILC Family

ILCs (described in humans and mice) produce effector cytokines similar to helper T (Th) cells and have been considered as the innate counterpart of adaptive T lymphocytes [4,5]. In contrast to T cell activation, which requires T cell receptor–MHC class II interactions, ILCs are activated by sensing epithelial-cell-, stromal-cell- or myeloid-cell-derived signals such as **alarmins**, cytokines, and other inflammatory mediators, which enable rapid responses to environmental cues. ILCs have been classified into three groups based on their developmental trajectories, strictly determined by the expression of key transcription factors [4,5]: group 1 ILCs comprise natural killer

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https://doi.org/10.1016/j.it.2019.12.004

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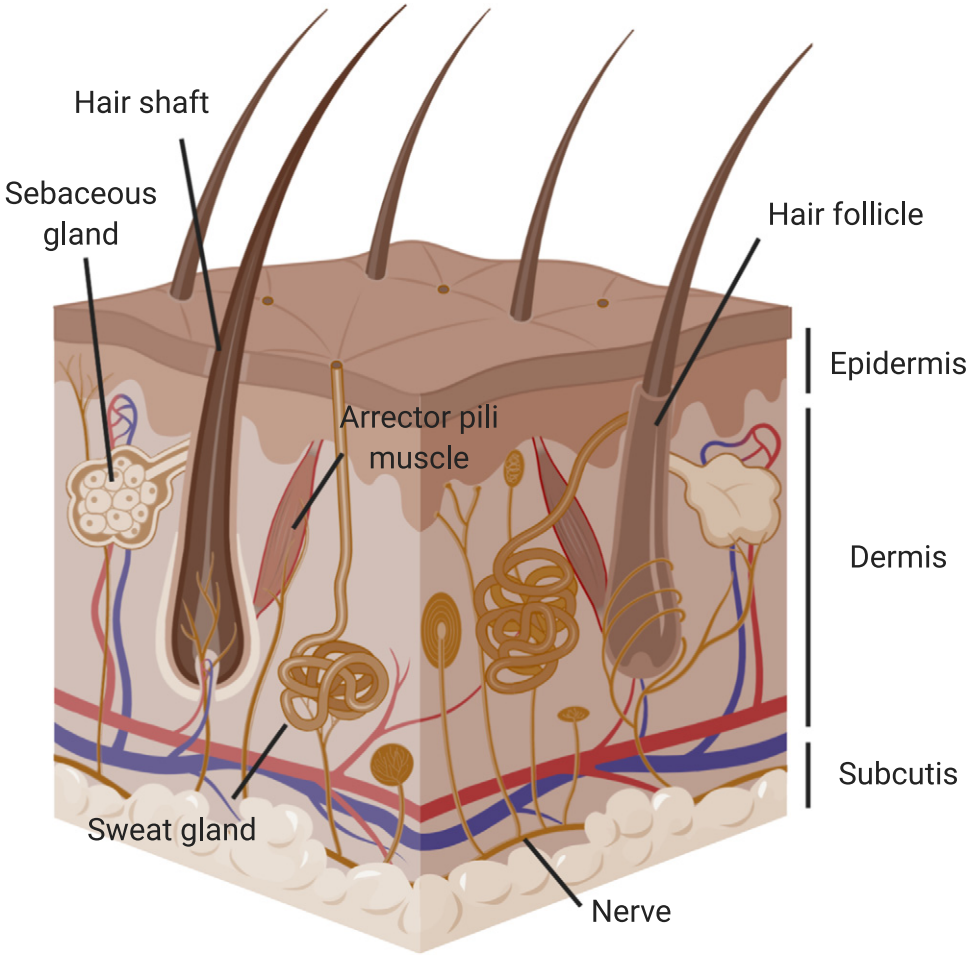


Figure 1. The Anatomical Structure of Mammalian Skin. The skin comprises three anatomically distinct layers: epidermis, dermis, and subcutis (hypodermis). Hair follicles begin at the surface of the epidermis and extend into the dermis. A hair follicle unit is attached to sebaceous glands and the arrector pili muscle. The dermis comprises fibroblasts and connective tissue such as collagen and elastin and is enriched with a variety of immune cells. The subcutis is the deepest layer of skin and is enriched with adipocytes. This figure was created using BioRender (https://biorender.com/).

(NK) cells and ILC1s (Box 1); group 2 ILCs are ILC2s (Box 2); and group 3 ILCs comprise lymphoid tissue-inducer (LTi) cells and ILC3s (Box 3 and Figure 2).

It is noteworthy that new findings on the developmental pathways and functions of ILCs have considerably changed the classification of ILC subsets since the first proposal of a standard

Box 1. NK Cells and ILC1s

While conventional NK cells and ILC1s are developmentally distinct, they have several characteristics in common [83]. Both express the transcription factor T-bet and promote type 1 immunity, critical for controlling intracellular microbial infections and restraining tumor development. However, NK cells and ILC1s in mice seem to have differential dependency on T-bet and Eomes [84,85]. While NK cells require Eomes but are present in the absence of T-bet, ILC1s are strictly dependent on T-bet but can develop in the absence of Eomes. Functionally, NK cells have strong cytotoxic potential, expressing granzymes and perforins, whereas ILC1s produce much higher concentrations of IFN-γ than NK cells. For this reason, NK cells and ILC1s are considered the innate counterparts of $CD8^+$ cytotoxic T cells and Th1 cells, respectively. Unlike other ILCs that require IL-7R signaling, NK cells and ILC1s are more reliant on IL-15 for their development [86].

Box 2. ILC2s

Reports of innate non-T cell lymphoid populations that contribute to helminth expulsion in mice [87–89] led to a series of seminal discoveries involving ILC2s, which are dependent on the transcription factors GATA3 and RORα and produce the type 2 cytokines IL-4, IL-5, IL-9, and IL-13 in response to tissue-derived cytokines such as IL-33, IL-25, and TSLP [90–92]. Specifically, ILC2s play protective roles in the expulsion of intestinal parasites and tissue repair in mice [78,79] and could contribute to the homeostatic maintenance of metabolism by altering the type 2 immune microenvironment of adipose tissue in mice [93,94]. By contrast, ILC2s can promote allergic inflammation at multiple barrier organs. ILC2s provoke asthma-like lung inflammation in various experimental models [95,96].

nomenclature [4,5]. Single-cell RNA-seq of ILCs from the small intestine in mice identified 15 ILC clusters with distinct transcriptional profiles [6]. Moreover, the plasticity of ILCs can increase their diversity and heterogeneity [7]. Human ILC2-to-ILC1 and ILC3-to-ILC1 conversions have been demonstrated *in vitro* and *in vivo* in humanized mice, which may be important for their functional fitness as a way to preserve optimal tissue health [8,9]. Furthermore, recent reports have identified the conversion of murine as well as human skin ILC2s into interleukin (IL)-17-producing ILC3-like cells, which might have physiological relevance in the pathology of psoriasis [10,11]. Accordingly, unsupervised transcriptional profiling of ILC2s from different tissues in mice has uncovered tissue-imprinting signatures that are established early in development [12,13]. In particular, skin ILC subsets in mice appear to have distinct characteristics that set them apart, including their differential expression of chemokine and cytokine receptors as well as their dependency on tissue-derived cytokines for residency and activation in the skin, indicating functional adaptation to the environment [14] (Figure 3, Key Figure).

Tissue Residency and Regulation of ILCs in the Skin

It has become clear over recent years that immune cells are strategically positioned in tissues to be efficient at creating protective immunity and maintaining tissue homeostasis. Experiments in **parabiotic mice** have demonstrated that ILCs in gut, lung, and skin are maintained and expanded locally both under physiological conditions and during inflammation, with only a minor contribution of circulating progenitors [14–16]. *In vivo* assessment of the migration of ILCs by using **Kaede photoconvertible mice** elegantly revealed the differential migratory nature of skin ILC subsets. ILC1s continuously traffic between the circulation and peripheral lymph nodes (LNs) in a CD62L- and CCR7-dependent manner, which promotes Th1 cell generation via interferon (IFN)-γ production after immunization; by contrast, ILC2s and ILC3s are tissue resident [17]. ILC2s and ILC3s are highly compartmentalized in different anatomical layers in murine skin: transcriptome analysis by bulk and single-cell RNA-seq revealed that ILCs expressing ILC2-signature genes (*Gata3*, *Il5*, *Areg*, and *Klrg1*) were enriched in the subcutis, whereas ILCs in the epidermis predominantly expressed ILC3/LTi-related genes (*Rorc*, *Tcf7*, and *Lta*) but also expressed genes that have been associated with ILC2s, such as *Il13* and *Il2*. The dermis contained ILCs that shared features with epidermal and subcutaneous ILCs [14]. It will be interesting to use reporter mice or other approaches to characterize the localization of various ILC subsets in the skin and across species. Using imaging techniques in combination with mouse models of inflammatory skin disease might also allow an assessment of the local proliferation, mobility, or recruitment of these cells from different zones of the skin (or from distant sites) and

Box 3. ILC3s and LTi Cells

ILC3s and LTi cells commonly depend on RORγt, but their distribution and functions are distinct [4]. Specifically, LTi cells mediate the development of lymphoid tissues during embryogenesis via the production of lymphotoxin [97]. ILC3-produced IL-22 has been reported to directly act on intestinal epithelial cells and mediate resistance to intestinal infections such as *Citrobacter rodentium* and *Salmonella typhimurium* [98,99]. IL-22 production from ILC3s is dependent on AhR and is essential for postnatal intestinal lymphoid tissues and protection against intestinal bacterial infection in mice [100]. In addition, ILC3s appear to play a more nuanced role in the regulation of the symbiotic relationship with intestinal microbiota [101,102].

Glossary

Alarmins: danger signals released from damaged tissues. They include IL-33, IL-25, TSLP, IL-1α, and HMGB1 and recruit and activate innate immune cells.
Atopic march: natural history of the sequential emergence of atopic diseases such as atopic dermatitis, allergic rhinitis, asthma, and food allergy.
Dermis: comprises fibers and extracellular matrix produced by fibroblasts. In addition to T cells and ILCs, dermal immune components include DCs, macrophages, mast cells, eosinophils, and basophils.
Epidermis: outermost layer of the skin; primarily comprises keratinocytes. Multiple immune cells reside in the epidermis, including αβ and γδ T cells, ILCs, and Langerhans cells.
Hair follicle: anatomical structure that generates hair, a defining feature of mammals. Hair follicles are a continuous layer of epidermal keratinocytes and equipped with sebaceous glands, which produce sebum to the skin surface. Hair follicles harbor several types of immune cells and act as an immunological epicenter in the skin.
Hapten-induced contact hypersensitivity (CHS): mouse model of contact dermatitis. Haptens are small-molecule irritants that bind to proteins and elicit an immune response. Antigen-specific memory T cells have been shown to drive classical type 1 adaptive immunity.
Kaede photoconvertible mice: transgenic mice expressing the Kaede protein, a photoconvertible fluorescent protein that changes from green to red on exposure to violet light.
Langerhans cells: skin-resident macrophages in the epidermis with dendritic functions such as antigen uptake, migration to LNs, and antigen presentation to T cells.
Parabiotic mice: surgically joined mice sharing their bloodstreams. Parabiotic mice are often used to investigate the tissue residency of immune cells.
Regulatory T cells (Tregs): T cells with a role in regulating or suppressing other immune cells.
Regulome: the whole set of regulatory elements in a cell; for example, chromatin regions accessible to transcription factors, which serve as *cis*-acting enhancers, repressors, or silencers of gene expression.
Subcutis: also called subcutaneous adipose tissue or hypodermis;

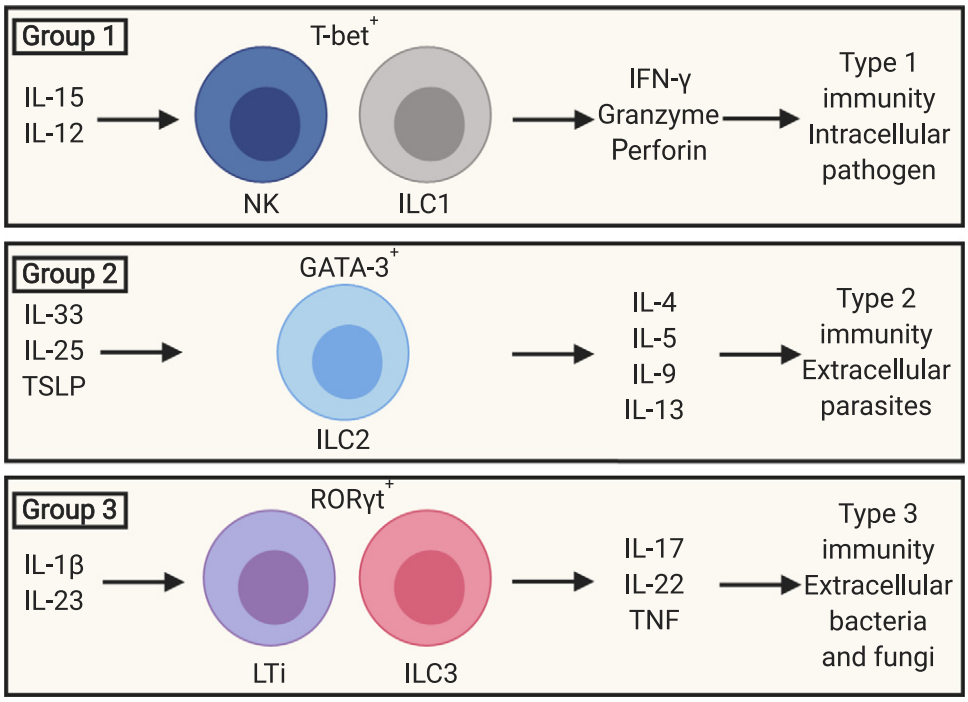


Figure 2. Classification of the Innate Lymphoid Cell (ILC) Family in Mice and Humans. Members of the ILC family are classified based on their developmental trajectory and their functional characteristics. Natural killer (NK) cells and ILC1s are T-bet dependent and produce interferon (IFN)-γ, granzymes, and perforins (group 1). They react to intracellular microorganisms such as viruses and bacteria and mediate type 1 immunity. ILC2s require GATA-3 for development and produce interleukin (IL)-4, IL-5, IL-9, and IL-13. They respond to parasites and allergens and initiate type 2 immunity (group 2). RORγt^{+} lymphoid tissue-inducer (LTi) cells mediate the development of lymphoid organs and RORγt^{+} ILC3s produce IL-17, IL-22, and tumor necrosis factor (TNF) and promote type 3 immunity to combat extracellular microbes (group 3). This figure was created using BioRender (https://biorender.com/). Abbreviation: TSLP, thymic stromal lymphopoietin.

thus enable a better understanding of their role in the skin and in the pathophysiology of inflammatory skin diseases.

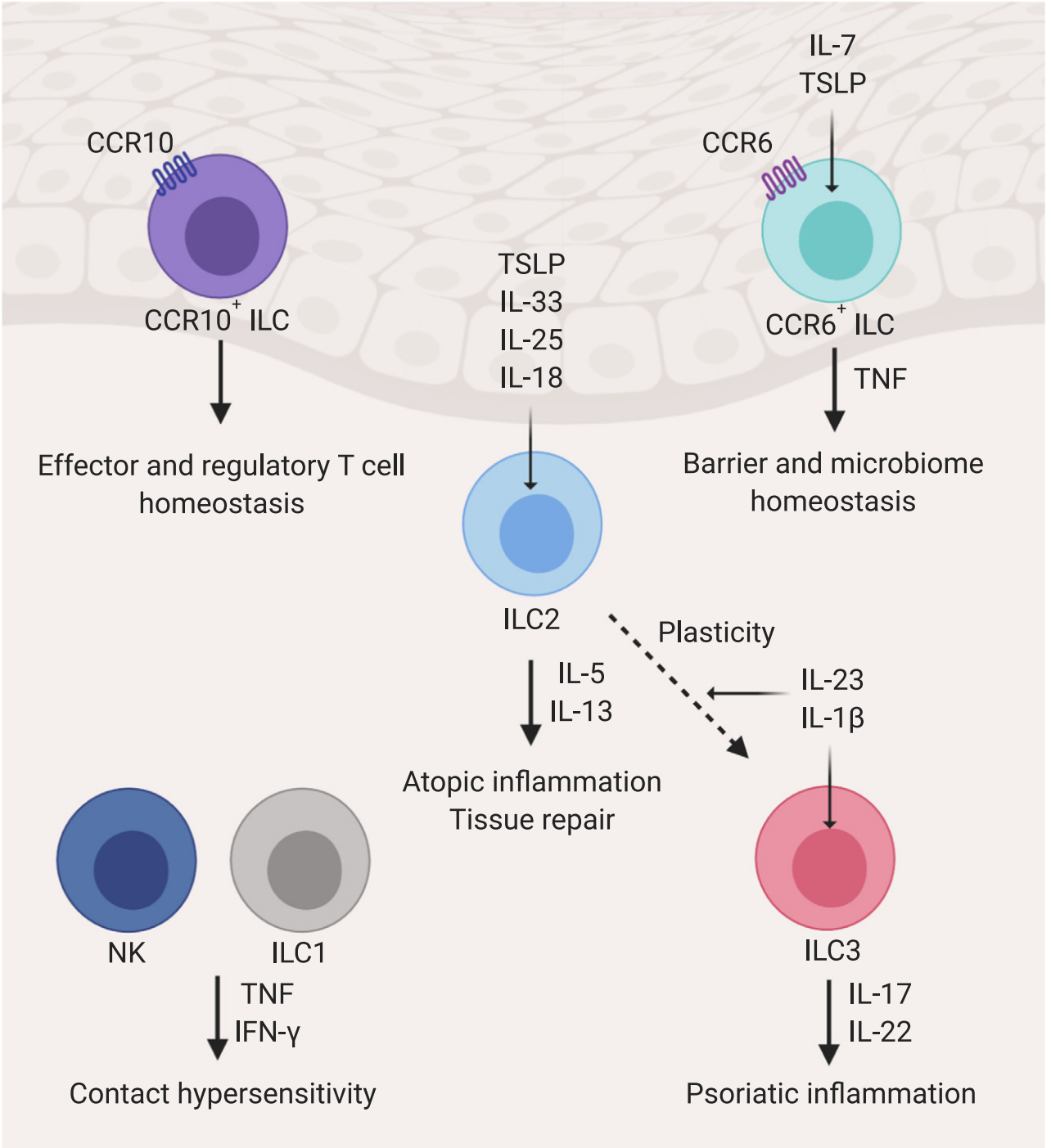
The residency and localization of immune cells are governed by the crosstalk between parenchymal and immune cells. **Hair follicles**, which primarily produce hair shafts to physically protect the mammalian body, act as a control tower guiding **Langerhans cells** into the epidermis and maintaining memory T cell residency by producing IL-7 and IL-15 [18,19]. Skin ILCs seem to have a unique dependency on tissue-derived cytokines for residency. Specifically, while ILC2s in the subcutis were absent in *Il7*$^{-/-}$ mice, lack of IL-7 led to only modest reduction of epidermal and dermal ILCs relative to wild-type (WT) control mice. Simultaneous deletion of IL-7 and thymic stromal lymphopoietin (TSLP) in *Il7*$^{-/-}$*Tslp*$^{-/-}$ mice resulted in complete loss of ILCs in skin, suggesting cooperative regulation of skin ILC residency by IL-7 and TSLP [14].

The positioning of ILCs is also dictated by their patterns of chemokine receptor expression. ILCs that reside in the murine epidermis express CCR6 and are enriched in the upper hair follicles where CCL20, a ligand of CCR6, is highly expressed [18,20]. CCR6-deficient mice (*Ccr6*$^{GFP/GFP}$) have been reported to exhibit a lack of ILCs in the epidermis relative to WT control mice, suggesting that the CCL20–CCR6 axis is important for hair follicle positioning of ILCs [14]. The CCL20–CCR6 axis is also operative in the neonatal migration of murine **regulatory T cells (Tregs)** into the skin,

comprises adipocytes and other stroma, which interact with immune cells.
Trained immunity: for instance, the ability of innate immune cells to mount resistance to reinfection in an antigen-independent manner.
Type 2 cytokines: cytokines released from Th2 cells, ILC2s, mast cells, and basophils, including IL-4, IL-5, IL-9, and IL-13.
Type 2 immunity: immunity mediated by type 2 cytokines; provides protection against helminths and toxins and is involved in tissue repair.

Key Figure

Skin Innate Lymphoid Cell (ILCs) in Homeostasis and Inflammation



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which is augmented by commensal bacterial colonization [20]. CCR10$^+$ ILCs in skin-draining LNs migrate into the skin in a CCR10-dependent manner and regulate the homeostasis of Th cells and Tregs [21]. CCR10 has been reported to be involved in the localization of resident effector memory T cells and Tregs [22,23]. In addition, the majority of ILCs in human skin were shown to express CCR10 [24]. How distinct ILCs subsets may have differential utilization of chemokine–chemokine receptor pairs for their positioning in murine and human skin remains to be determined.

From another angle, it is well established that commensal bacteria also play an important role in the proper development of functional immune cells and in skin-specific protective immunity in mice [25,26]. However, whether distinct ILCs require bacterial signals for their development remains controversial. For instance, significant differences have not been observed in either the number or the activation state of ILC2s in the lung, skin, and gut of germ-free mice compared with mice under specific-pathogen-free (SPF) conditions [12,27]. It is important to note that, compared with mice from an SPF facility, mice caught in the wild or purchased from a pet store have been documented to present more differentiated T cells in peripheral blood [28]. Co-housing of SPF mice with pet-store mice resulted in a profound increase in the number of innate and adaptive immune cells, including ILCs, in the lung and skin; this suggested that environmental factors could alter the basal numbers of ILCs. Moreover, disrupting the intestinal microbiota by germ-free condition or antibiotic treatment altered the transcriptional and **regulome** profiles of ILCs, suggesting a potential contribution of commensal microbiota in the proper maturation of ILCs [6]. Identification of specific microbes or microbial factors that train ILCs may lead to a better understanding of the regulation of ILC activation as well as the pathology of ILC2-related inflammatory diseases.

NK Cells and ILC1s in Contact Hypersensitivity

NK cells represent the prototypical members of the ILC family and their role has been investigated in cancer immune surveillance [29]. Although most NK cells and ILC1s are not skin resident [17], several reports now provide new insights into their contribution to allergic skin diseases. Allergic contact dermatitis is an inflammatory skin disease triggered by the penetration of low-molecular-weight chemicals or metals. In **hapten-induced contact hypersensitivity (CHS)** in mice [30], recent evidence supports the concept that antigen-specific or nonspecific innate immune memory may contribute to hapten-induced responses. Liver-resident NK cells, which are now referred to as ILC1s, induce hapten-specific memory responses in CHS models independent of adaptive T and B lymphocytes, suggesting that there are memory-like properties in NK cells or ILC1s [31,32]. In contrast to the tissue residency of ILC2s and ILC3s, IL-7 receptor (IL-7R)$^+$ ILC1s are primed and acquire hapten-specific memory potential in skin-draining LNs and are recruited to the liver via CXCR6, and maintained through IL-7R signaling in mice [33]. However, the mechanisms by which IL-7R$^+$ memory-like ILC1s migrate from liver to skin where they mediate CHS remain unclear. Although hapten-specific memory responses have not been shown in human ILC1s or NK cells, NK cells accumulate in the skin of patients with allergic contact dermatitis and release IFN-γ in the presence of hapten-driven IL-2-producing T lymphocytes *in vitro* [34]. These studies highlight the existence of the innate memory response (or **trained immunity**), which is now a rapidly developing area of immunology research [35]. In addition to NK cells and ILC1s, ILC2s have been demonstrated to acquire antigen nonspecific memory-like

Figure 3. Heterogeneous populations of ILCs with distinct functions reside in the skin (as identified in mice and humans). Skin-resident CCR6$^+$ ILCs can maintain the microbiota by regulating sebaceous gland function. CCR10$^+$ ILCs maintain adaptive lymphocyte homeostasis. Natural killer (NK) cells and ILC1s play a role in contact hypersensitivity. ILC2s, which are activated by thymic stromal lymphopoietin (TSLP), interleukin (IL)-33, IL-25, and/or IL-18, contribute to atopic inflammation by the production of type 2 cytokines. ILC2s also promote tissue repair. ILC3s produce IL-17 and IL-22, which mediate psoriatic inflammation. Plasticity between skin ILC subsets might be also involved in disease pathology. This figure was created using BioRender (https://biorender.com/). Abbreviation: TNF, tumor necrosis factor.

properties in allergen-induced lung inflammation [36]. Also, while several studies now have linked 'innate memory' to epigenetic reprogramming, the underlying mechanisms responsible for the long-term persistence of the ILC-mediated immune response remain to be investigated.

ILC2s in Atopic Inflammation

Expansion of the research on ILCs has been largely driven by enthusiasm for investigating ILCs as a therapeutic target. In this regard, the research on ILC2s in the context of allergic diseases has led to a great advance in our knowledge of ILC biology. Since the identification of ILC2s in both murine and human skin [24,37,38], many studies have now provided compelling evidence that ILC2s might be indispensable players in the pathophysiology of atopic dermatitis. Atopic dermatitis is a chronic inflammatory skin disease that manifests with dry skin and relentless itch. Barrier disruption and a prolonged **type 2 cytokine**-mediated immune response (**type 2 immunity**) in patients with atopic dermatitis often lead to the progressive development of asthma and food allergy, a process referred to as the **atopic march** [39,40]. Notably, the susceptibility loci for atopic dermatitis identified by genome-wide association studies include genes encoding IL-33R, IL-18R, IL-7R, IL-2R, TSLP, IL-4, and IL-13 [41,42], all of which have been associated with the activation or effector functions of ILC2s [4,5]. ILC2s have been reported to be highly enriched in the lesional skin of patients with atopic dermatitis, with an increase in circulating ILC2s in these patients relative to healthy individuals [24,37].

The detrimental roles of ILC2s in promoting atopic inflammation are supported by experimental data from mouse models of atopic dermatitis. Topical application of the vitamin D3 analog calcipotriol (MC903) induces atopic dermatitis-like skin inflammation [43,44] and has gained increased attention as a model of atopic dermatitis in mice. The critical involvement of ILC2s in MC903-induced dermatitis has been demonstrated by experiments in which lymphocyte-deficient *Rag1*$^{-/-}$ mice exhibited inflammation but deletion of ILCs via intraperitoneal administration of anti-CD25 antibody or anti-CD90.2 antibody attenuated dermatitis [37]. Whereas genetic disruption of IL-33–IL-33R signaling (*Il33*$^{-/-}$) or IL-25–IL-25R signaling (*Il17rb*$^{-/-}$) did not affect ILC2 responses, disruption of TSLP–TSLPR signaling (*Tslpr*$^{-/-}$) significantly impaired ILC2 responses and ameliorated skin inflammation relative to WT control mice [37]. In another study, intravital multiphoton microscopy showed that IL-7-dependent IL-13-producing ILC2s interacted with mast cells in the dermis of murine skin [38]. Dermal ILC2s expressed CD25 and expanded in response to *in vivo* IL-2 treatment, leading to cutaneous inflammation characterized by dermal eosinophil infiltrates and activated mast cells relative to nontreated mice.

Cytokines required for ILC2 activation in the skin appear to be much more complex than previously thought. Transgenic mice overexpressing the IL-33 gene (*Il33*) driven by a human keratin 14 promoter (hK14mIL33tg) exhibited spontaneous development of atopic-like dermatitis and an increase in IL-33R^{+} ILC2s in the skin relative to WT control mice [45]. Intraperitoneal administration of an anti-IL-5 antibody reduced eosinophil infiltration and improved dermatitis relative to nontreated control mice [45]. In such mice, basophils and IL-33R^{+} ILC2s were also required for inflammation [46]. In the above mentioned study in which patients with atopic dermatitis exhibited enriched IL-33R^{+} ILC2s in skin lesions, IL-33 *in vitro* treatment stimulated type 2 cytokine production from human skin-derived ILC2s [24]. These studies collectively suggest a role of IL-33 in ILC2 activation in the skin. Moreover, in a model of MC903-induced inflammation, dermatitis was significantly ameliorated in RORα-deficient mice (*Rora*$^{sg/sg}$) relative to WT control mice. RORα-deficient mice had a profound deficit in ILC2 development [47]. Furthermore, mice lacking IL-25R (*Il17rb*$^{-/-}$) exhibited the greatest reduction in MC903-induced inflammation and ILC2 numbers relative to WT control mice. In addition, the absence of IL-33R (*Il1rl1*$^{-/-}$) also resulted in a significant reduction in dermatitis and ILC2 numbers [47].

Of note, TSLP was required for MC903-induced skin inflammation in mice bearing a C57BL/6 strain background [37], whereas the absence of IL-25 and IL-33 markedly reduced skin inflammation and ILC2 numbers relative to WT mice in a BALB/c strain [24]; this suggests that different genetic backgrounds might affect ILC2 responsiveness – an issue that merits further consideration in future research. In addition, the treatment dose and duration of MC903 application vary among studies. The tools that specifically target ILC2s but not other ILCs or T lymphocytes also remain limited. Thus, the case for differential versus redundant contributions of IL-33, IL-25, and TSLP in ILC2 activation and ILC2-mediated skin inflammation, as well as how the expression of these tissue-derived cytokines are regulated under different contexts, remains to be determined.

A recent study undertook an unbiased approach to the transcriptomic analysis of mouse tissue ILC2s from the skin and other organs: bulk and single-cell RNA-seq analysis was performed on sorted ILC2s from the bone marrow, lung, fat, gut, and skin of IL-5 reporter mice (*Red5*) [48]. Clustering analysis revealed marked segregation of ILC2s in various tissues as well as tissue-specific patterns of activating receptor expression [12]. In particular, under homeostatic conditions, skin ILC2s preferentially expressed the gene encoding the IL-18 receptor 1 (*Il18r1*) and responded to IL-18 treatment *in vitro* in the presence of TSLP. In addition, the accumulation of ILC2s and eosinophils was reduced in the skin of IL-18 deficient mice ($Il18^{-/-}$) that were treated with MC903 relative to WT control mice [12]. Consistent with this, transgenic mice overexpressing murine IL-18 under the control of the human keratin 14 promoter (KIL-18Tg) exhibited dermatitis and a type 2 immune response independent of IgE/IgG1 [49]. Although the involvement of ILC2s was not assessed in these transgenic mice, IL-18-activated ILC2s might contribute to the atopic inflammation observed in these mice, and further experiments are warranted.

The promising clinical efficacy of monoclonal antibodies blocking IL-4 and IL-13 signaling in patients with atopic dermatitis has definitively demonstrated a predominant role for type 2 cytokines in the pathogenesis of atopic dermatitis [50,51]. Type 2 effector cytokines can alter and shape the cutaneous immune environment in a variety of ways. Studies using *in vivo* transgenic mice as well as *in vitro* human cell cultures have shown that IL-4 and IL-13 mediate epidermal thickening and decreased the expression of epidermal barrier proteins and antimicrobial peptides, as well as IgE production [52,53]. Studies utilizing a diphtheria toxin (DT)-based conditional basophil deletion system (BasTRECK) revealed that basophils could regulate ILC2 activation via IL-4 production in protease-induced airway inflammation and MC903-induced atopic skin inflammation mouse models [54,55]. Selective depletion of $ICOS^{+}$ ILC2s through DT administration in iCOS-T mice [56] demonstrated that ILC2-derived IL-13 was critical for the production of chemokine CCL17 by DCs, thus potentiating memory Th2 cell responses to allergens [57]. These results suggest that the ILC2–DC–Th2 axis may be important in allergic inflammation. In addition, targets of type 2 cytokines are not limited to immune cells but also include nonimmune components. IL-4 and IL-13 can directly activate human sensory neurons *in vitro*, and scratching is significantly reduced by sensory neuron-specific genetic deletion of IL-4Ra in mice (NaV1.8-Cre^{+} IL-$4Ra^{fl/fl}$) relative to WT control mice, suggesting the development of chronic itch via neuronal IL-4Ra signaling [58]. The neuroimmune crosstalk in which ILC2s can interact with sensory nerves via neuropeptides has been an exciting area of research [59]. Thus, it will be intriguing to investigate whether skin ILC2s have any interactions with neurons in the context of atopic itch or whether they play any other role in homeostasis in the cutaneous neuroimmune axis. Further understanding of the regulatory mechanisms of ILC2s and their interaction with other cells provides a potential basis for therapeutic intervention in atopic diseases.

ILC3s in Psoriatic Inflammation

The proinflammatory function of ILC3s in the skin has been best characterized by their involvement in the pathogenesis of psoriasis. Psoriasis is a chronic inflammatory skin disease characterized by well-demarcated red, scaly plaques. While different types of immune cells and effector cytokines have been implicated in the disease process, the high efficacy of monoclonal antibodies against IL-23 and IL-17 in its treatment has demonstrated a pivotal contribution of the IL-23–IL-17 axis in psoriatic inflammation [60]. In response to IL-23, Th17 cells produce IL-17, which has broad inflammatory effects on keratinocytes and immune cells [61,62]. Although Th17 cells were thought to be the predominant source of IL-17, since the identification of ILCs IL-17-producing ILC3s have also attracted attention as potential players in the pathogenesis of psoriasis. Natural cytotoxicity receptor (NCR)$^+$ ILC3s have been documented to accumulate in the skin lesions and peripheral blood of patients with psoriasis relative to healthy individuals, and these cells potently produce IL-22 [63]. Moreover, the numbers of RORγt$^+$CD56$^+$ ILC3s, known to produce IL-22, have also been increased in both nonlesional and lesional skin in patients with psoriasis compared with healthy controls [64]. Another study demonstrated that NKp44$^+$ ILC3s, which produce both IL-17 and IL-22, were increased in the blood and skin of psoriasis patients relative to normal individuals [65]. In this study, a positive correlation between therapeutic response to anti-TNF (tumor necrosis factor) treatment and the decreased number of circulating ILC3s was observed in a patient [65]. The abovementioned studies provide compelling evidence for a pathogenic role of ILC3s in psoriasis in human patients.

In murine studies, a role for ILC3s has been examined in the psoriasiform skin inflammation that is induced by topical application of the Toll-like receptor (TLR)7 agonist imiquimod [66]. Imiquimod treatment can induce marked production of IL-17 and IL-22 from RORγt$^+$ γδT cells and ILCs in the skin of mice [67]. Given observations of an increased representation of RORγt$^+$ ILCs in the murine epidermis at steady state [14], we are not surprised that dysregulation of the number and activity of these cells in this layer might readily contribute to the pathogenesis of psoriasis in these animal models. Of note, imiquimod-induced psoriasiform skin inflammation has been nonetheless observed in *Rag1*$^{-/-}$ and *Rag2*$^{-/-}$ mice lacking T cells compared with WT control mice, albeit reduced in *Tcrd*$^{-/-}$ mice lacking γδT cells; by contrast, *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice, which are devoid of all lymphoid cells, are completely resistant to imiquimod treatment; this suggests a contribution of nonadaptive lymphoid cells in murine models of psoriasis [67,68]. Of note, no skin inflammation has been observed in *Rorc*$^{-/-}$ mice treated with imiquimod [67]. Therefore, imiquimod-induced psoriasiform plaque formation seems to be dependent on RORγt in ILCs and γδT cells [67]. However, further studies are needed to fully demonstrate this possibility. Recently, the functional involvement of human ILC3s was tested in a humanized mouse model of psoriasis, in which normal human skin xenografts on the mice were injected with autologous activated peripheral blood mononuclear cells (PBMCs) [69]. Human NKp44$^+$ ILC3s, purified from IL-2- and aryl hydrocarbon receptor (AhR) agonist-activated PBMCs were injected into the mice and sufficed to induce psoriatic lesions with increased numbers of IL-17-, IL-22-, and TNF-producing cells relative to control mice [69]. This study is relevant in that it provides the first evidence that human ILC3s can drive the development of a psoriatic phenotype, albeit in a humanized mouse model. Although imiquimod-induced psoriatic inflammation occurred independent from T lymphocytes as observed in *Rag2*$^{-/-}$ mice [67], more research is needed to reveal the extent and validity of the relative contributions of Th17 cells and ILC3s in human psoriasis.

Nevertheless, ILC3s appear to be a promising target for psoriasis treatment. For instance, CCR6 and CCR10 are highly expressed by murine skin ILCs and regulate their recruitment and localization [14,21] and a recent study demonstrated CCR6-dependent recruitment of ILCs into MC903-induced inflamed skin of mice [17]. In addition, the lesional skin of patients with psoriasis has been

reported to harbor abundant expression of CCL20 and aggregation of $CCR6^+$ DCs and T cells [70,71]. Other studies have also documented an essential role of CCR6 in IL-23-induced psoriatic dermatitis in mice [68,72,73]. Upregulation of CCL27, a ligand of CCR10, has been reported in lesional skin of patients with psoriasis relative to healthy control subjects [74]. A recent in-depth transcriptomic and phenotypic analysis of human ILCs provided evidence that dermal ILC2s could convert into IL-17-producing ILC3-like cells and that $ROR\gamma t^+$ peripheral blood ILC2s could express CCR6 and CCR10 and produce IL-17 [10]. Furthermore, skin biopsies from patients with psoriasis revealed a marked increase in ILC3s and a decrease in ILC2s compared with healthy donor skin, suggesting an involvement of ILC2-derived ILC3s in psoriatic inflammation [10]. Collectively, these findings suggest that inhibition of migration of ILCs into the psoriatic skin by targeting CCR6 and/or CCR10 might represent a putative therapeutic option in psoriasis, although robust testing is evidently warranted. Of note, a combination of single-cell transcriptomics and fate-mapping analyses of ILCs in an IL-23-injected murine psoriasis model have revealed a trajectory of quiescent-like ILCs in healthy skin into activated ILC2s, which are further converted into IL-17- and IL-22-expressing ILC3-like cells in IL-23-injected skin [11]. We posit that the dynamic and plastic activation of skin ILCs in response to IL-23 may add new insights into the immunological landscape of psoriatic inflammation on further testing. Targeting ILC3s as well as their activation and recruitment might therefore represent a potential strategy for therapeutic interventions in psoriasis.

ILCs in Tissue Homeostasis and Repair and Crosstalk with the Microbiome

The tissue-resident nature of ILCs empowers them to exert their specialized functionality for the maintenance of barrier functions under physiological conditions. Skin-resident ILCs that are enriched in the hair follicles in close proximity to sebaceous glands can help to regulate the homeostatic balance of the microbiome in the skin [14]. Epidermal ILCs, phenotypically resembling $CCR6^+$ ILC3s and LTi cells, produce TNF and lymphotoxins, which can limit the growth of sebocytes. Lack of ILCs in $Rag2^{-/-}Il2rg^{-/-}$ mice can lead to enlarged sebaceous glands and increased production of antimicrobial free fatty acids, resulting in restricted commensalism of aerobic Gram-positive cocci and the relative increase of anaerobic bacteria, detected by 16S rRNA microbiome analysis. By contrast, the absence of lymphocytes can lead to increased proportions of Gram-positive cocci [14]. The differential regulation of the microbiome by ILCs and tissue-resident lymphocytes may represent a counterbalancing mechanism that tunes microbial equilibrium on the skin surface. pSTAT3 staining by quantitative multiplex immunohistochemistry in the murine intestine suggested that ILC3s and adaptive $CD4^+$ T lymphocytes could coordinately operate the establishment of steady-state commensalism mediated by pSTAT3 activation in epithelial cells and ILCs in response to IL-23 and IL-22; this suggested sequential activity of innate and adaptive lymphocytes for microbial regulation [75]. Mostly, the functions of immune cells at barrier sites have been previously investigated in experimentally infected tissues. Therefore, our understanding of host–microbe interactions has been limited mainly to the inflammatory responses against pathogens. Thus, these two studies have provided new avenues to investigate how innate and adaptive immune systems might differentially maintain host–microbe mutualism under homeostatic conditions.

Tissue repair is a fundamental property of type 2 immunity (proposed to have evolutionarily developed in the context of tissue remodeling for helminth expulsion). In helminth infections such as *Nippostrongylus brasiliensis*, the murine intestinal epithelium produces IL-25, which can activate ILC2s triggering ILC2-secreted type 2 cytokines that further induce intestinal epithelial cell differentiation and expansion to promote helminth clearance [76–78]. In the skin, depletion of ILC2s using anti-CD90.2 antibodies in $Rag1^{-/-}$ mice resulted in delayed wound closure relative to control IgG-treated mice [79]. Delayed wound healing was also evident in IL-33-deficient mice

(*Il33*$^{-/-}$), which showed impaired activation of ILC2s compared with WT control mice, suggesting that IL-33-mediated ILC2 responses played a role in optimal wound closure in mice [79]. Furthermore, other studies have shown that ILC2s produce the EGFR ligand amphiregulin, implicated in the remodeling of respiratory tissues after influenza-virus-induced damage in mice [27], and in intestinal tissue protection from intestinal damage and inflammation in the dextran sodium sulfate (DSS)-induced mouse model [80]. Langerhans cells and IL-17-producing CD8$^+$ T cells in the skin of mice can contribute to tissue repair, likely via the production of EGFR ligands [81,82]. However, the question of whether skin ILC2s can promote wound healing and overall tissue health via the production of amphiregulin or other factors remains an open area of investigation.

Concluding Remarks

The identification of ILC family members has elicited a fundamental reassessment of the role of the innate immune system in pathogen defense and tissue homeostasis. ILCs are not merely an ancient type of adaptive lymphocyte. ILCs play critical roles in host protective immunity, the regulation of barrier and microbial homeostasis, metabolism, and tissue repair. Since the effector cytokines that ILCs produce can be detrimental factors when present in excess in allergy and chronic inflammatory diseases, understanding ILC biology could offer new avenues on how to think about novel therapeutic targets to treat skin inflammatory diseases (among others). Many challenges remain (see Outstanding Questions). Our understanding of ILC biology in the skin is still developing relative to current knowledge of ILC2s in the lung or ILC3s in the intestine. Clarification of the skin-specific roles of ILCs and the translation of those findings from mouse models to humans is needed to fully understand the role of ILCs in disease pathogenesis and potential treatments. Future studies should investigate how skin ILCs are activated and regulated under different contexts and how they communicate with microorganisms and other tissue-resident immune cells, as well as with the surrounding stroma, such as epithelial cells, fibroblasts, and neurons. ILCs could be one last piece of the puzzle to decipher sophisticated immune ecosystems in the skin.

Outstanding Questions

What are the predominant cytokines that promote the activation of skin ILC2s and ILC3s? Is there redundancy or differential contribution among TSLP, IL-33, IL-25, and IL-18?

Is there plasticity of skin-resident ILCs? Can ILC2s give rise to ILC3s and vice versa?

Do ILCs and T lymphocytes differentially contribute to the pathophysiology of inflammatory skin diseases such as atopic dermatitis or psoriasis? What are the potential interventions aiming to regulate both innate and adaptive immune responses?

What is the turnover of various ILC populations in the skin? Are ILCs replenished from local precursors, bone marrow precursors, or both?

Do ILCs contribute to the immunological memory response? Are ILCs trained through epigenetic reprogramming in the context of infections and chronic inflammation?

What are the roles of ILCs in the maintenance of skin barrier homeostasis in addition to the regulation of microbial composition and tissue repair? What are the relative contributions and interactions of skin-resident lymphoid cells, including αβ effector memory T cells and Tregs, γδ T cells, and ILCs to skin homeostasis?

Acknowledgments

T.K. was supported by the Incentive Research Projects of RIKEN. R.R.R.-G. is supported by grants from the National Institutes of Health (AR075880) and the Robert Wood Johnson Foundation Harold Amos Medical Faculty Development Program (74257).

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