Skin Innate Lymphoid Cells: Physiological and Pathological Roles

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Abstract

Innate lymphoid cells (ILCs) are tissue-resident lymphocytes that lack rearranged antigen receptors. Cutaneous ILCs, mainly ILC2s, are essential for sustaining tissue equilibrium, contributing to physiological and pathological roles. Here, this review explores the characteristics of cutaneous ILCs in different conditions. This review highlights the role of skin ILCs in maintaining tissue homeostasis by regulating microbiome balance. It examines how their dysfunction can lead to inflammatory skin diseases like atopic dermatitis, psoriasis, and melanoma. ILC-related factors contribute to physiological functions and their implications in various pathological conditions, potentially highlighting key areas for future research. We now explore how these studies have enhanced our understanding of ILC regulation and the potential therapeutic applications of targeting these cells in skin inflammation based on microbiota and metabolism.

Key Words Innate Lymphoid Cell; Skin Homeostasis; Tissue Repair; Hair Follicle; Cutaneous Inflammatory Disease; Melanoma

Introduction

The skin is the body's largest organ and serves as a protective barrier. It employs diverse non-immune and immune mechanisms across its epidermis, dermis, and subcutis layers[1]. The diversity of immune cells in the skin regulates homeostasis and includes Langerhans cells, dendritic cells (DCs), mast cells, macrophages, T cells, natural killer cells (NK), and ILCs[2].

The immune function of the skin is associated with T cells that can react to stimuli within this organ[3]. T cells serve as a central orchestrator in maintaining immune balance and responding to aberrant conditions in both health and disease.[4-5]. In addition to the pivotal role of T cells, the functional contribution of ILCs provides supplementary insights into cutaneous immunity. They reveal a crucial connection in unraveling the complex immune mechanisms that regulate skin homeostasis.

Skin-resident ILCs, situated at the forefront of the body's surface barrier, shape the functional dynamics of the skin and uniquely contribute to cutaneous immunity. In healthy individuals, the predominant subset of effector skin ILCs comprises ILC2s. ILC3s are typically found in both human and murine psoriatic skin[8-10]. The characterization of ILC1s is less defined, but conventional NK cells and various ILC1-like cell populations have been reported in the skin[11].

This review offers an in-depth analysis of the diverse characteristics of ILCs and their intricate tissue-specific features. It investigates the variations observed in the developmental and functional processes of ILCs, which are regulated by distinct transcriptional profiles metabolic characteristics, and epigenetic features. Through a systematic exploration of ILC characteristics in both physiological and pathological conditions, this review provides valuable insights, pinpointing key areas for future research.

Development and Classification of ILCs

ILCs are closely associated with T cells and arise from common lymphoid precursors (CLPs). Through the influence of crucial transcription factors, CLPs

undergo stepwise differentiation into common innate lymphoid progenitors (CILPs), common helper innate lymphoid progenitors (CHILPs), and other lymphoid progenitors[12-13]. Ultimately, these progenitors differentiate into various types of ILCs[14-16]. The details of the common development of ILCs and T cells are shown in **Figure 1**.

Different subtypes of ILCs have special features and functions. ILCs can be meticulously divided into five categories: NK cells, ILC1s, ILC2s, ILC3s, and lymphoid tissue inducer cells (LTi)[6]. ILC1s and NK cells promote type 1 immune responses against intracellular pathogens by producing IFN-γ, granzymes, and perforin[17-18]. ILC2s secrete cytokines such as IL-4, IL-5, IL-9, IL-13, and amphiregulin to regulate type 2 immunity[19]. Upon stimulation with IL-1β, IL-23, and the aryl hydrocarbon receptor (AhR) ligand, distinct subsets of ILC3s release specific cytokines, including IL-17, IL-22, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF)[20]. In a balanced state, the predominant subset of ILCs found in the skin of mice, namely $GATA3^+$ ILC2s, are accompanied by a small proportion of $ROR\gamma t^+$ ILC3s[8,21]. In the human skin, ILC2s are also the primary subset within the ILC population[22].

Skin ILCs are derived from the bone marrow. The early to mid-pregnancy period is a critical turning point for the development of innate lymphoid cells in the fetal skin, where skin ILCs and NK cells originate from a common precursor pool[67]. Also, ILCs were differentiated in the skin-draining lymph nodes with specialized homing and functional characteristics that enable their localization and role in the skin. [24-25]. In adult mice, dermal and subcutaneous ILCs demonstrated notable expression of *Gata3* and *Rora*, crucial transcription factors associated with ILC2s, and specific to their respective tissue environments. Conversely, within epidermal ILC clusters, there was an enrichment of cells expressing *Rorc*. However, *Tbx21*, a transcription factor typically linked with ILC1s, remained undetected[26].

Cutaneous ILCs in the Physiological States

ILCs are vital for maintaining the physiological functions of the skin by regulating interactions among skin microbiota, hair follicles, and tissue repair processes. The diversity of skin microbiota significantly affects ILC function, ILC deficiencies can lead to dysbiosis, disrupting skin physiology. This dysbiosis compromises hair follicle integrity, as ILC2s are essential for skin health and controlling microbial populations like *Demodex mites*. After tissue injury, ILCs release cytokines that promote repair, linking their activity to restoring microbiota balance and hair follicle function. Thus, ILCs are essential mediators in the interplay of skin microbiota, hair follicles, and tissue repair, underscoring their fundamental physiological role.

Skin Microbiota

The skin hosts a varied array of microorganisms, including bacteria, fungi, viruses, and mites. These microorganisms, collectively known as the skin microbiota, play a fundamental role in skin physiology and immunity[27]. The changes in the diversity and abundance of skin microbiota composition, termed dysbiosis, can induce alterations in both physiological and pathological states by disrupting the balance of T cell and ILC subpopulations[28].

Deficiency in ILCs results in sebaceous hyperplasia, thereby influencing the skin microbial environment[26]. In neonatal mice, $NK1.1^+$ ILC1s in the skin play a crucial role in controlling the opportunistic pathogen *Pseudomonas aeruginosa* and regulating proper microbiota colonization. These results indicate that skin $NK1.1^+$ ILCs are responsive to the initial establishment of commensal bacterial colonization in neonatal mice[24]. HIF-1α is essential for the skin's antimicrobial defense by modulating NK cell activity against *Staphylococcus aureus* and group A *Streptococcus*. The interaction between HIF-1α and NK cells is crucial for balancing antimicrobial defense and tissue repair processes in the skin[29].

The absence of hair follicle-associated ILC2s was associated with increased *Demodex mite* colonization, and decreased type 2 cytokine expression in patients diagnosed with rhinophyma. This study reveals a pivotal function of skin ILC2s and

IL-13, acting as an immune checkpoint that sustains skin integrity and limits excessive colonization by *Demodex mites*[30]. Additionally, impairment of the ADAM10-Notch signaling axis gives rise to a dominant follicular dysbiosis, characterized by excessive growth of *Corynebacterium mastitidiss*. This dysbiosis, in turn, triggers inflammation, predominantly mediated by ILC2s[31].

These findings indicate distinct roles for lymphocytes and ILCs in regulating the skin microbiota. The absence of ILCs led to sebaceous hyperplasia, characterized by increased production of antimicrobial lipids and a limitation on the coexistence of Gram-positive bacterial communities[26]. The skin microbiota fosters the development of RORγt$^+$ IL-17A-producing ILCs, thereby exacerbating cutaneous leishmaniasis-induced skin inflammation. Colonization by *S. epidermidis* and *S. xylosus* before *L. major* infection enhances inflammatory reactions and promotes the expansion of IL-17A$^+$ ILCs[32].

Hair Follicle

Hair follicles (HFs) are essential for hair growth, as their structure and function are closely linked to skin microbiota and immune responses. Furthermore, the immune system can influence the structure of HFs and skin microbiota[33]. HFs chemotactically attract T cells and ILCs to regulate epithelial cell quiescence, proliferation, and differentiation during both physiological and injured states[34]. During the process of HF recycling, Jagged-1-expressing regulatory T cells gather around the bulge region of HF, enhancing the activation of HF stem cells and triggering the anagen phase efficiently[34].

Skin ILCs are also related to HF, sebaceous glands, skin microbiota, and hair growth. IL-13 originating from ILC2s is intricately linked to the hair cycle and can suppress stem cell proliferation. The absence of HF-associated ILC2s results in heightened epithelial proliferation and increased *Demodex* mite colonization. This phenomenon leads to a shift away from repair-related gene programs towards aberrant inflammation, consequently compromising barrier function and leading to HF exhaustion[30].

Skin ILCs can influence the function of sebaceous glands to regulate the microbial homeostasis of the skin. ILCs can limit the growth of sebocytes and exert their effect through the Notch signaling pathway by producing TNF and lymphotoxins. Moreover, the absence of ILCs can lead to abnormal sebaceous gland function and sebaceous gland hyperplasia, further affecting the microbial homeostasis of the skin and potentially influencing hair growth in the body. This study also revealed a pronounced compartmentalization of ILCs, each exhibiting distinct characteristics across various anatomical layers of the skin[26].

Similarly, the Notch signaling pathway is intricately linked to the regulation of HFs and skin ILCs. The disruption of the ADAM10-Notch signaling axis compromises the intrinsic epithelial barrier, facilitating the dominance of *Corynebacterium* in the microbiome. This dysbiosis instigates inflammation mediated by ILC2s, dependent on IL-7R, CCR6, and S1P receptor 1. Consequently, it results in pyroptotic cell death of HFs, culminating in irreversible alopecia. This also highlights the functional role of ILCs in hair growth and the maintenance of skin microbial homeostasis[31].

The production of IL-17, typically associated with ILC3s, was observed in cutaneous GATA3^{high} ILC2s[31]. The diminished expression of GATA3 fostered the amplification of RORγt fate-mapped (RORγt^{fm+}) skin ILC2s during the postnatal period. Throughout HF regeneration, these RORγt^{fm+} skin ILC2s gathered around the dermal papilla region to facilitate hair regrowth. This study illuminates the unique regulatory function of GATA3 in skin ILC2s, particularly in promoting RORγt^{fm+} skin ILC2s to facilitate HF recycling[35]. The study has also investigated the increase of ILC1-like innate lymphoid cells in both lesional and non-lesional sites among patients with alopecia areata[36]. The diagram illustrating the relationship between ILCs and HF function is shown in **Figure 2.**

Skin Tissue Repair

Tissue repair is a physiological and biochemical process involving multiple tissues, microorganisms in wounds can also affect the skin repair process, potentially resulting in or preventing pathological infection[37]. Many immune cells, including mast cells,

Mφ, neutrophils, T cells, and ILCs usually function in the regulation of the tissue repair process[38]. Particularly, ILCs exert the tissue repair functions in various organs such as the small intestine, thymus, and skin[39].

The cytokines and chemokines derived from NK cells contribute to the inflammatory response and may adversely affect skin tissue repair. The absence of NK cells in the skin results in increased wound re-epithelization and collagen deposition, revealing the potential negative role of NK cells in skin tissue repair[40]. NK cell depletion results in a notably accelerated wound closure, evident as early as two days post-injury. HIF-1α-deficient NK cells, due to their compromised capacity to release IFN-γ and GM-CSF, play a pivotal role in facilitating tissue repair[29]. In contrast to the skin, NK cells in the cornea promote tissue repair by attenuating the innate acute inflammatory response to injury, which is related to the excessive accumulation and tissue damage caused by neutrophil activity[41].

IL-33-dependent ILC2s are associated with cutaneous tissue repair following the injury of the full-thickness dermis. These ILC2s exhibit higher CD25 and GATA3 expression in response to skin injury. The absence of IL-33 results in diminished ILC2 response and reduced skin tissue repair. This study highlights the beneficial role of IL-33 and ILC2s in skin tissue repair[42].

In uninjured skin, resident ILC3s are typically scarce in the dermis. However, upon injury, the epidermal Notch1 signaling pathway can be activated, leading to the recruitment of ILC3s through TNFα-related mechanisms. This recruitment results in the production of CCL3 and IL-17F, which play pivotal roles in regulating both epidermal proliferation and the recruitment of Mφ, both of which are essential for tissue repair[43]. The study also shows that *Gpr34*$^{-/-}$ and *Il22*$^{-/-}$ mice demonstrate reduced skin and intestine tissue repair ability. Specifically, ILC3s regulate the G protein-coupled receptor 34 (GPR34), which can sense lysophosphatidylserine (LysoPS) released by apoptotic neutrophils, and they subsequently secrete the effector cytokine IL-22 to promote tissue repair and homeostasis. This highlights the significance of ILC3 activation in tissue repair and tissue homeostasis in the skin[44].

Drawing upon the distinctive subsets of ILCs and the various cytokines they produce, it has been observed that ILCs play a crucial role in maintaining skin homeostasis and facilitating the process of skin tissue repair. The diagram illustrating the relationship between ILCs and tissue repair is shown in **Figure 3.** Under physiological circumstances, the skin governs hair growth, modulates the skin microbiome, and facilitates tissue repair following injury. Conversely, under pathological conditions such as atopic dermatitis, psoriasis, and melanoma, ILC subpopulations undergo various alterations, resulting in discernible functional consequences.

Skin ILCs in Pathological States

In the investigation of the immunological mechanisms underlying specific cutaneous disorders, ILCs are recognized as crucial mediators, particularly in atopic dermatitis, psoriasis, cutaneous melanoma and other inflammatory skin conditions. These cells exhibit diverse functions and intricate interactions across different pathological contexts, thereby elucidating their potential roles in disease progression and therapeutic interventions. This discourse will systematically examine the contributions of ILCs to the pathophysiology of AD and psoriasis, alongside their dynamic influence within the skin immune microenvironment.

Atopic Dermatitis

Atopic dermatitis (AD) is typically characterized by chronic skin inflammation resulting from immune system abnormalities. There is a significant correlation between AD and autoimmunity, with particular emphasis on innate host immunity and T-cell function. This underscores the importance of both autoimmune regulation and innate immunity in AD. The pathogenesis of AD involves interactions among type 2 immune cells, including mast cells, ILCs, and Th2 cells[45-46].

Type 2 immunity is indispensable in the inflammatory pathology of AD. Among the various subsets of ILCs, ILC2s are the primary functional subgroup in the skin of

healthy individuals and AD patients. Single-cell transcriptomic analysis has revealed that the majority of ILCs in AD patients belong to the CRTH2$^+$ ILC2s subset, displaying significant phenotypic plasticity[47]. Additionally, E-cadherin suppresses the secretion of IL-5 and IL-13 from ILC2s, and its downregulation is an important pathological mechanism in AD. Furthermore, reduced skin swelling and inflammation were observed for the MC903-dependent skin model in *Il17br*$^{-/-}$, *Il1rl1*$^{-/-}$, and *Tslpr*$^{-/-}$ mice[48].

AD-like skin lesions spontaneously developed in hK14mIL33tg mice, exhibiting epidermal thickening, infiltration of eosinophils, and increased expression of eosinophil peroxidase and major basic protein genes[49]. Moreover, in the absence of eosinophils, there is a reduction in the populations of ILC2s and related cytokines, such as IL-5 and IL-13, in hK14mIL33tg mice. This observation suggests that IL-33-induced inflammation resembling AD relies on the collaboration between ILC2s and eosinophils[50].

The studies also found that the number of blood NK cells in AD patients is reduced, which is associated with the enhanced effect of type 2 inflammation in the skin. By investigating the amelioration of AD symptoms after the augmentation of NK cells through the IL-15 superagonist, the study observed enhanced activity of blood and skin NK cells, correlating with improvements in AD-like symptoms in mice based on histological scores and ear thickness[51-53]. The diagram for the relationship between ILCs and AD is depicted in **Figure 4.**

Psoriasis

Psoriasis and AD have overlapping but distinct populations, clinical manifestations, and pathogenesis. Psoriasis is a common chronic inflammatory skin disease, characterized by the appearance of red plaques with white scales on the skin and other areas. T cells and ILCs are critical components in the occurrence, development, and homeostasis of psoriasis[54].

ILC2s are the primary ILCs that exert biological functions in healthy skin, while ILC3s tend to aggregate at the lesional sites of psoriasis. Elevated levels of Nkp44$^+$

ILC3s were observed in the peripheral blood and lesional and non-lesional skin regions of psoriasis patients. Research suggests that Rorγt-dependent ILCs and γδ T cells make a substantial contribution to the formation of psoriatic plaques in mice, with the production of factors such as IL-17A, IL-17F, and IL-22 performing essential functional roles in plaque development[11, 23, 55, 56].

In contrast to healthy skin, psoriatic skin has been noted to have an augmentation of $NKp44^{-}$ ILC3s and a reduction in $CRTH2^{+}$ ILC2s within the dermal layer. The transition of human c-Kit^{+} ILC2s into IL-17 producers and their accumulation within cutaneous lesions of psoriasis patients underscores the potential pathogenic role of ILC2 to ILC3 plasticity in psoriasis[57].

Likewise, the proportion and changes of ILCs under psoriasis conditions are crucial parts of the disease's development. In response to IL-23, tissue-resident ILCs, which include quiescent-like cells and ILC2s, undergo activation, adopting a convergent program reminiscent of ILC3-like pathology. The simultaneous production of IL-13 and IL-22, or IL-13 and IL-17A characterized this program. This provides new strategies for potential psoriasis treatments by inhibiting the transformation of skin-resident ILCs into skin-pathogenic ILC3s and demonstrates the transformation potential of resident ILCs in the skin[10]. The diagram for the relationship between ILCs and psoriasis/AD is shown in **Figure 4.**

Cutaneous Melanoma

In addition to the aforementioned chronic inflammation, melanoma is a malignant tumor that commonly occurs in the skin and mucous membranes. The communication between immune cells significantly affects the immune response to melanoma[58-59]. NK cells and ILCs are key subsets involved in the immune response to melanoma, coordinating the reactions of other immune cells and improving the prognosis of clinical immunotherapy.

An expansion of $CD56^{dim}$ $CD57^{+}$ NK cells infiltrating the lymph nodes in melanoma, where these NK cells demonstrate tumor-killing cytotoxicity against autologous melanoma cells[60]. Studies have shown that the loss of NK cell-associated

gene features in patients with metastatic melanoma is correlated with low overall survival. Tumors can induce the remodeling of the immune microenvironment and immune escape to promote tumor reshaping[61]. Additionally, fibroblasts can restrict the cytotoxicity of NK cells. This suppressive function is mainly dependent on the production of prostaglandin E2, indicating the mutual interaction between other cells and NK cells in the tumor immunoregulation microenvironment. Other immune escape mechanisms involve melanoma cells inhibiting the expression of NK-relevant receptors such as NKp30 and NKp44. This inhibitory effect ultimately results in the suppression of NK cell cytolytic activity against tumor cells[62]. Interventions targeting these factors may restore NK cell immune surveillance, thereby achieving NK cell anti-tumor function and anti-metastasis capabilities.

Besides the role of NK cells in melanoma, research has also identified an aggregation of ILC1s in peripheral blood monocytes and tumor-infiltrated lymph nodes of patients. However, their secretion capacity of cytokines is impaired. This impairment is attributed to the dysregulation and reshaping of the immune microenvironment caused by the presence of kynurenine and adenosine. These findings indicate a preliminary mechanism of ILC1s' involvement in the melanoma immune microenvironment and the immune microenvironment imbalance[63-64].

Melanoma patients with high infiltration of ILC2s have a favorable clinical prognosis. ILC2s can produce GM-CSF, driving eosinophil accumulation in melanoma cells and enhancing tumor immunity. However, it has been observed that infiltrating ILC2s in melanoma exhibit high expression of PD-1, which limits their anti-tumor capability. Enhancing anti-tumor ability through IL-33 induction and anti-PD-1 combination improves the restricting effect of the high PD-1 expression and anti-melanoma immunity[65]. The IL-33-mediated ILC2s-eosinophil axis can inhibit tumor growth. However, tumor-derived lactate weakens the function and survival of ILC2s; tumors with reduced lactate show increased infiltration of ILC2s. Studies reveal the role of ILC2s and eosinophils in melanoma, highlighting lactate as a novel strategy for regulating ILC2s subsets and melanoma treatment intervention[66].

Regulation Network

Skin ILCs possess unique epigenetic characteristics, transcriptional profiles, and interaction regulations under different physiological and pathological conditions. Various transcriptional factors drive ILCs and other lymphoid cell differentiation and maturation. cutaneous ILCs display dynamic expression profiles of transcription factors that orchestrate cell differentiation and facilitate distinct cellular functions throughout fetal skin development[25]. Transcription factors participate in the development of various cell populations, and when comparing precursor and relatively mature ILCs, a discernible panel of transcription factors exhibits distinct expression profiles[67]. Skin-resident ILCs lack the expression of transcription factors T-bet and Eomes, which are typically associated with ILC1s. Instead, the principal regulatory network of transcription factors relies on the expression of *Gata3* and *Rorc*. Reduced levels of GATA3 alter the fate of mouse cutaneous ILCs, promoting hair follicle recycling. RORγt and GATA3 collaboratively drive the terminal differentiation of RORγt^{fm+} cutaneous ILC2s[26, 35].

Under the stimulation of classical cytokines such as IL-1β, IL-23, IL-25, IL-33, and TSLP in the skin, both ILC2s and ILC3s secrete classical effector molecules to exert their functions[10]. In particular, skin ILC2s have a high level of IL-18R expression compared with other tissues, and IL-18 can independently mediate the activation of the ILC2 subset. IL-18 not only regulates the basal activation of ILC2s under normal conditions but also plays a role in their function in AD[68].

The regulation network is also related to the sex hormone and metabolites, skin ILC2s can secrete GM-CSF to maintain DC homeostasis under the activation of androgens, and this axis responds to the balance of commensal bacterial infection[69]. Based on mass spectrometry metabolomics analysis, LysoPS from apoptotic neutrophils in the intestine can activate ILC3s in vitro. This mechanism is on the GPR34 pathway, which is also shown in skin ILC3s[44].

Under physiological conditions, these networks can promote immune homeostasis, influencing interactions with skin microbiota, hair follicles, and skin tissue repair.

Conversely, in pathological states such as atopic dermatitis, psoriasis, and cutaneous melanoma, these networks may lead to the abnormal activation or functional dysregulation of innate lymphoid cells, exacerbating the condition. Therefore, a deeper understanding of the mechanisms underlying this regulatory network is crucial for comprehending the occurrence and progression of immune-related diseases.

Crosstalk

The interaction between ILCs and other cell types yields regulatory functions within the skin. This complex interplay among ILCs, DCs, T cells, and additional cell populations constitutes a regulatory network crucial for maintaining skin homeostasis[69-70]. Skin ILC2s express many functional receptors to react to many cytokines and other molecules, including IL-18, IL-25, IL-33, prostaglandin D2, and B7-H6. Subsequently, ILC2s produce type 2 cytokines to maintain or damage skin homeostasis[48, 68, 71, 72].

The androgen-ILC2-DC axis orchestrates skin homeostasis during both commensal colonization and infection phases. Skin ILC2s play a pivotal role by secreting GM-CSF to preserve the homeostasis of the immune cell network, which encompasses dendritic cells and T cells[69]. ILC2s can also control eosinophil and basophil homeostasis, as basophils can promote immune responses of skin ILCs in inflamed skin. In vivo, the elicitation of cutaneous ILC2 responses relies on IL-4 derived from basophils, while ex vivo, it directly governs the proliferation of ILC2s[73-74]. And IL-5^+ ILC2s are needed to maintain M2-like dermal tissue-resident macrophages in non-healing *L. major* infection[75]. Under this *L. major* infection, $CD103^+$ DCs are essential for the dependence of *S. epidermidis* on IL-17-producing ILCs[32].

The interplay between ILCs and other immune and non-immune cells is crucial for physiological functions, including regulating skin microbiota, maintaining hair follicle health, and facilitating skin tissue repair. By interacting with these components, ILCs help maintain immune balance in the skin. Conversely, this interaction can also affect the occurrence and progression of diseases such as atopic dermatitis, psoriasis, and

cutaneous melanoma. In these conditions, dysregulation of ILC functions can lead to abnormal immune responses that worsen symptoms. Thus, understanding the crosstalk between ILCs and other cells is vital for developing new therapies for immune-related diseases.

Insights

Recent research has begun to unveil the roles of ILCs in the skin and elucidate the mechanisms governing the development and function of these ILC populations. However, due to the relatively limited research time, many unresolved issues remain in the field of cutaneous ILCs.

The classical transcription factors of ILCs include T-bet, GATA3, and RORγt. As typical tissue-resident cells, ILCs exhibit differential transcriptional characteristics across various tissues. This is particularly evident in the skin, where the interactions among key transcription factors and the fate decisions of ILCs at different time points vary significantly under different disease conditions. Therefore, it is essential to understand the unique transcriptional regulatory features of skin-resident ILCs[10, 35]. Additionally, other transcription factors such as c-Maf, RUNX2, and RUNX3 also play crucial roles in skin ILCs and other immune cells. Hence, a deeper understanding of the transcriptional regulation and epigenetic characteristics of ILCs under various conditions is vital for alleviating skin inflammation[76].

The skin is innervated by sensory nerves from the dorsal root ganglia (DRG) and trigeminal ganglia (TG). Skin-innervating sensory neurons recognize different stimuli, such as pathogens and immune-related cytokines. The transient receptor potential cation channel, subfamily V member 1 (TRPV1) is activated by many inflammatory mediators to trigger a neurogenic inflammatory response[77]. $TRPV1^+$ neuron activation can induce the expansion of IL-17-producing γδ T cells and $CD4^+$ T cells. The neuro-cytokine-immunity axis functions in cutaneous diseases such as psoriasis and AD[78-80]. Current research on neuro-cytokine-immunity interactions in the skin mainly focuses on T cells, DCs, and Langerhans cells, with most studies on neuro-ILC relationships

conducted in the lungs and intestines[81-84]. However, studies investigating the interactions between neurons and ILCs are still lacking. Single-cell RNA-seq reveals decreased or increased percentages of cutaneous ILC populations in different pain models such as the Zymosan, UV burn, and incision models. Detailed studies on the interactions between the nervous system and ILCs in the skin are still lacking. Whether ILCs can integrate these cells' functions and receive signals from the epithelium and the nervous system in the skin remains to be further explored. Future research based on disease models and sequencing results is needed to investigate the role of ILCs in this neuro-cytokine-ILC axis[85-86].

Skin homeostasis is highly associated with metabolites, cytokine targets, and hormones about ILCs within this microenvironment. However, recent studies mainly focus on controlling ILCs in the intestine for inflammatory bowel diseases or managing Th cells in skin homeostasis. In the intestine, the administration of cytokines influences the functions of ILCs as strategies for inflammatory bowel diseases. And using ketogenic diets as the approach to regulate intestinal barrier and ILCs function in interventing inflammatory diseases[87-88]. In the skin, diet intervention and cytokines or metabolites treatment can also influence skin barrier homeostasis and mediate skin inflammation. Increases in oxysterols driven by diet exacerbate γδT17-cell-mediated psoriatic inflammation, highlighting diet as a key factor in controlling cutaneous inflammatory diseases. Other studies also show the intervention by metabolic and cytokines to maintain skin homeostasis by various approaches[89-93]. Similarly, androgens negatively regulate cutaneous ILC2s, altering the DC network and resulting in a stronger adaptive immune response in female mice compared to male mice during commensal colonization and infection. This suggests that targeting local sex hormone control could be a potential strategy for regulating skin immunity[69]. Further research is needed on the metabolic, hormonal, and cytokine targets to modulate cutaneous ILCs and thereby regulate skin homeostasis. Studies on T cells in the skin for metabolism intervention can be referenced, while specific interventional mechanisms for ILCs need to be addressed.

Although the role of T cells in the skin has been extensively discussed, the distinctive functions of ILCs as counterparts to Th cells should be given further attention. ILCs have the advantage of a rapid response, which is particularly significant in the skin, frequently exposed to external environments and microbiota. They function through cytokine signaling rather than TCR signals, playing a crucial role in defending against pathogens and regulating the skin microbiome. Existing research has investigated the interactions between skin microbiota and ILCs. Sequencing methods can analyze the composition and proportions of ILC-associated microbiota, while isolation and culture techniques can explore the detailed effects of microbiota on ILCs[26, 94, 95]. However, such detailed studies are currently lacking. Differences at various microbiota levels can influence skin disease pathogenesis and cutaneous ILCs. Therefore, understanding the interactions between skin microbiota and ILCs, as well as the rapid response for ILCs, is crucial for the prevention and treatment of skin diseases.

Conclusion

This review focuses on the characteristics of ILCs in skin homeostasis and explores the phenotypic characteristics, transcriptional profiles, and epigenetic features of ILCs that contribute to the skin microenvironment. In this review, the diversity, subpopulation characterization, and plasticity of cutaneous ILCs are extensively investigated. ILCs, especially ILC2s, exert a pivotal influence over tissue repair and skin microbiota by interacting with epithelial cells and immune responses. Cutaneous ILC2s and ILC3s regulate hair follicle function and are significantly important in dermatopathology, including the pathological development of psoriasis. For psoriasis, skin-resident ILCs can transform into pathogenic ILC-like cells, thereby promoting disease progression. In addition, patients with AD have increased numbers of ILCs and NK cells in the skin, exhibiting phenotypic plasticity and being strongly associated with disease progression. Besides, ILCs have a close relationship with malignancy, functioning in the tumor microenvironment, tumor immune surveillance, immunotherapy, and tumor invasion and metastasis.

In conclusion, this review provides a comprehensive overview of the relationship between ILCs and the skin, discussing the characterization and function of ILCs in skin homeostasis. The review highlights the tissue specificity and diversity of cutaneous ILCs and emphasizes the importance of maintaining skin physiological functions and pathological roles.

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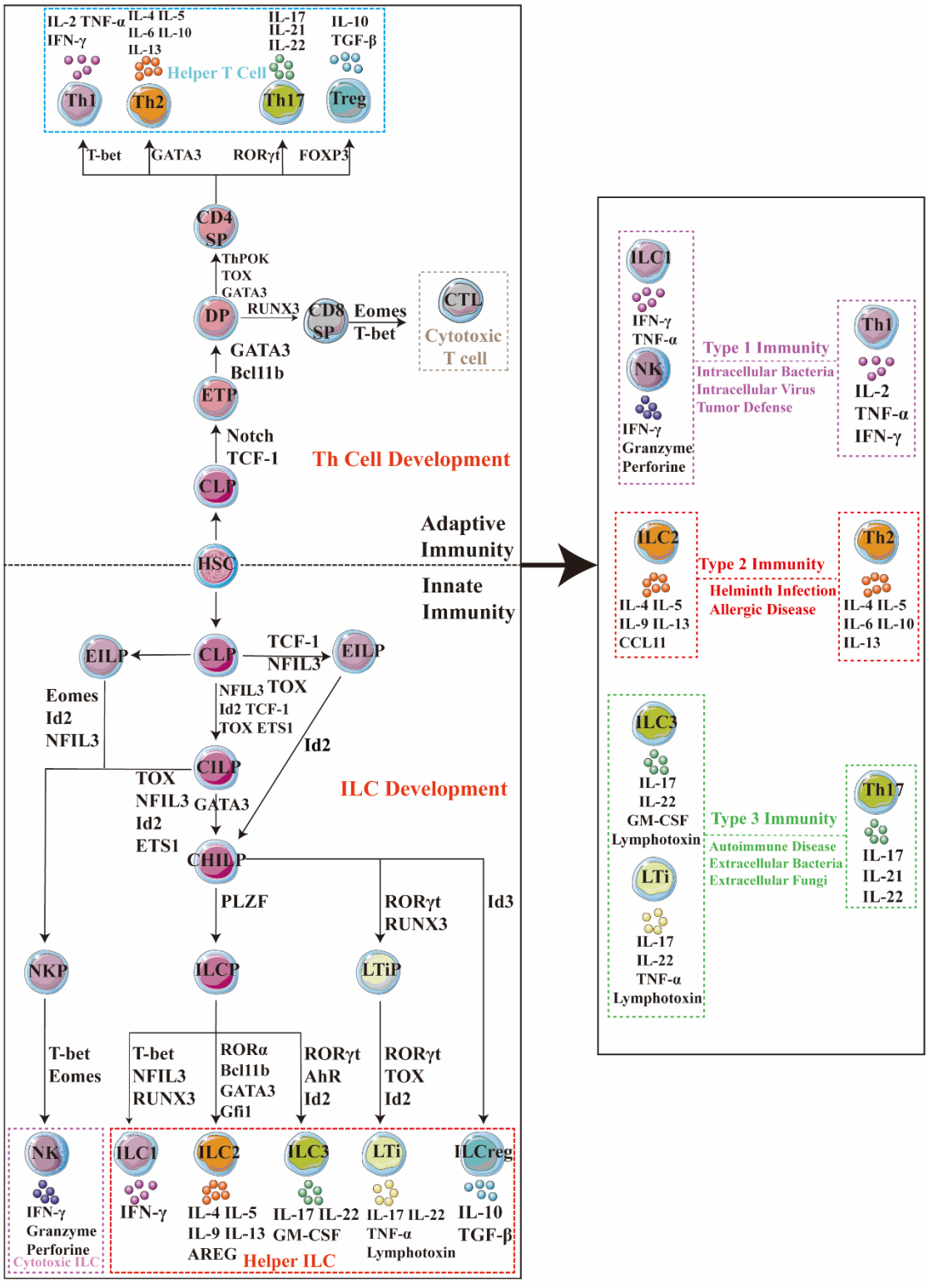

Figure 1 The Comparisons between ILCs and T Cells for the Development and Differentiation. The figure outlines the developmental trajectories of T cells and ILCs, emphasizing essential factors influencing their maturation. The illustrations include components sourced from **Servier Medical Art**.

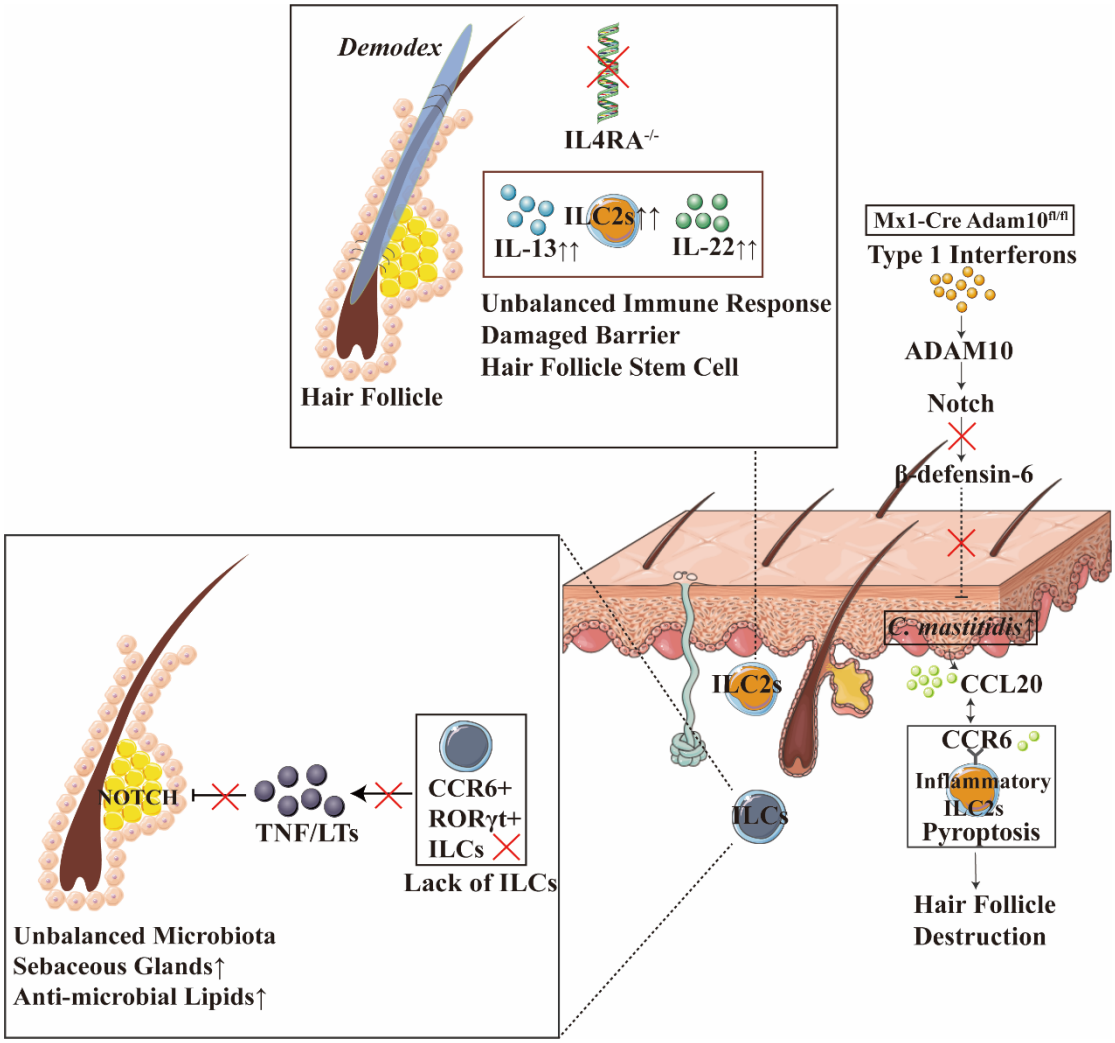

Figure 2 The Schematic Diagram of ILCs Regulating Hair Growth and Skin Microbiota.

Inflammatory ILC2s contribute significantly to the function of hair follicles through Notch, CCL20, CCR6, ADAM10, and other factors. $CCR6^{+}ROR\gamma t^{+}$ ILCs are related to the microbiota, sebaceous glands, and anti-microbial lipids for the immune-epithelia homeostatic in the skin. ILC2s interact with cytokines such as IL-13 and IL-22 to produce relevant biological effects.

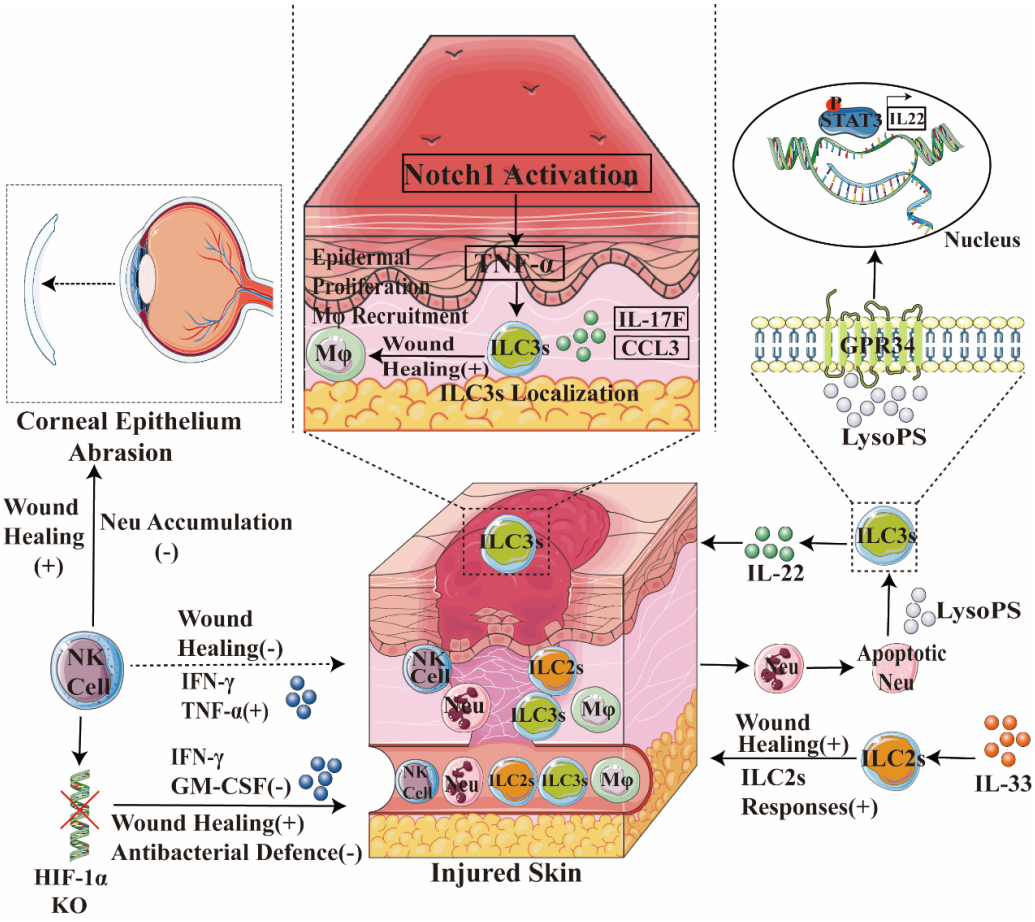

Figure 3 The Diagram of the Relationship Between ILCs and Skin Tissue Repair. NK cells, ILC2s, ILC3s, Mφ, Neu, and other immune cells participate in the regulation of skin tissue repair.

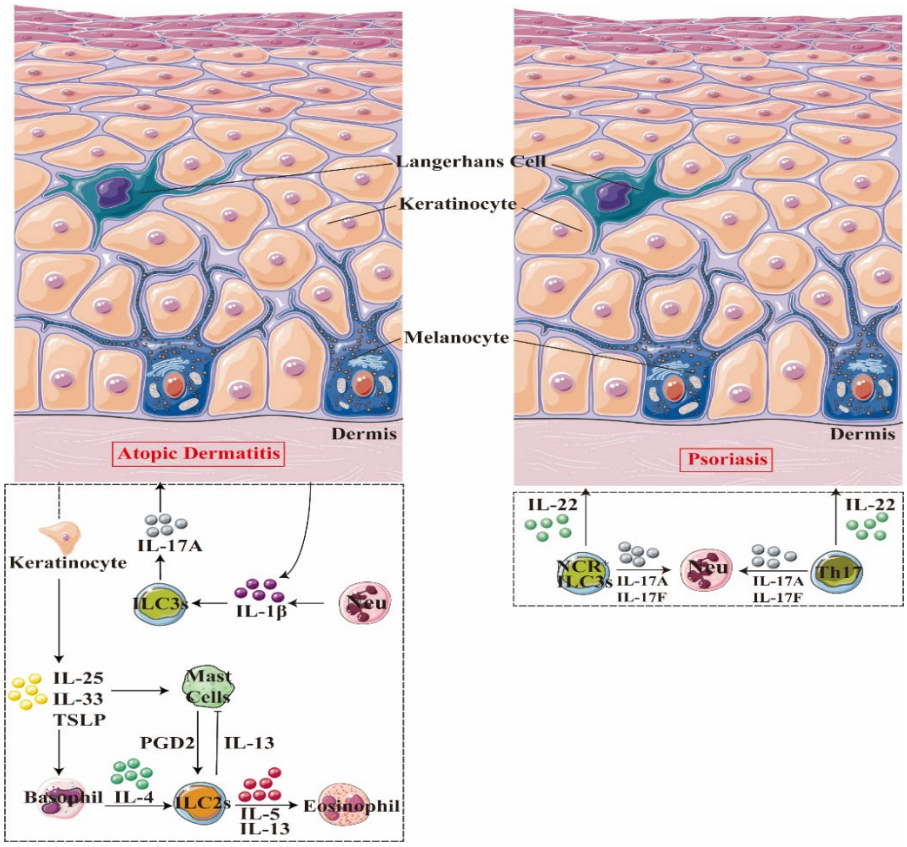

Figure 4 ILCs in the Regulation for AD and Psoriasis. For AD, ILC2s and inflammatory factors are intricately linked to an enhanced type 2 immune response, while ILC3s are associated with Neu, IL-17A, and IL-1β. In psoriasis, NCR^{+} ILC3s and Th17 cells serve as an integral component in Neu modulation through IL-17A and IL-17F.