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REVIEW ARTICLE

The pathogenic role of innate lymphoid cells in autoimmune-related and inflammatory skin diseases

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Innate lymphoid cells (ILCs), as an important component of the innate immune system, arise from a common lymphoid progenitor and are located in mucosal barriers and various tissues, including the intestine, skin, lung, and adipose tissue. ILCs are heterogeneous subsets of lymphocytes that have emerging roles in orchestrating immune response and contribute to maintain metabolic homeostasis and regulate tissue inflammation. Currently, more details about the pathways for the development and differentiation of ILCs have largely been elucidated, and cytokine secretion and downstream immune cell responses in disease pathogenesis have been reported. Recent research has identified that several distinct subsets of ILCs at skin barriers are involved in the complex regulatory network in local immunity, potentiating adaptive immunity and the inflammatory response. Of note, additional studies that assess the effects of ILCs are required to better define how ILCs regulate their development and functions and how they interact with other immune cells in autoimmune-related and inflammatory skin disorders. In this review, we will distill recent research progress in ILC biology, abnormal functions and potential pathogenic mechanisms in autoimmune-related skin diseases, including systemic lupus erythematosus (SLE), scleroderma and inflammatory diseases, as well as psoriasis and atopic dermatitis (AD), thereby giving a comprehensive review of the diversity and plasticity of ILCs and their unique functions in disease conditions with the aim to provide new insights into molecular diagnosis and suggest potential value in immunotherapy.

Keywords: ILC; SLE; scleroderma; psoriasis; atopic dermatitis; autoimmunity

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INTRODUCTION

It has long been recognized that the human immune system is composed of two parts: the innate immune system and the adaptive immune system. The innate immunity is the first-line defender against pathogenic microbial infection before the adaptive immune system is activated, which quickly responds to pathogens without specificity. Innate lymphoid cells (ILCs), as newly described lymphoid cells, have greatly enhanced our knowledge about the immune system in the past 10 years. ILCs, as an important component of the innate immune system, promote host defense against pathogens and microorganisms,[1] maintain tissue and organ homeostasis,[2] and promote tissue remodeling, healing and repair,[3] as well as tumor development.[4] On the other hand, transcription abnormalities and functional dysregulation of ILCs play an important role in the pathogenesis of autoimmune diseases, which are related to immune tolerance and autoimmunity.

ILCs have been found in the mucosal system and visceral organs in humans and mice and are strategically enriched at mucosal sites. They are particularly abundant in the skin, lung, and intestinal mucosa and rich in adipose tissue and lymph nodes. ILCs are innate cells devoid of recombination activating gene (RAG)-dependent rearrangements; therefore, ILCs cannot express diversified antigen-specific recognition receptors, thus differing from T cells and B cells.[5] Recently, three heterogeneous subsets of ILCs, termed ILC1s, ILC2s and ILC3s, have been identified on the basis of transcription factors and the expression of effector cytokines. ILC1s are similar to T helper (Th) 1 cells, which secrete type 1 cytokines such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α. ILC1s require the Th1 cell-associated transcription factor T-bet[6] for their development. They contribute an essential role in early host protection and viral immunosurveillance at sites of initial infection.[7] ILC2s are defined by the capacity to secrete interleukin-5 (IL-5),[8] IL-9,[9] IL-13,[8] and amphiregulin[10] and are important in host resistance against nematodes[11] and mediating type 2 immunity.[12] They are composed of natural helper cells,[13] nuocytes[12] and innate helper 2 cells,[14] utilizing GATA-binding protein 3 (GATA3)[15] and retinoic acid-related orphan receptor α (RORα)[16] for their differentiation. ILC3s can be divided into natural cytotoxicity receptor (NCR)$^+$ ILC3s and NCR$^-$ ILC3s[17] and produce IL-17 and/or IL-22[18] and require retinoic acid-related orphan receptor γt (RORγt).[19] These different ILC populations have distinct patterns of cytokine production that are similar to the cytokine secretion profiles of Th cell subsets. In summary, ILCs are a heterogeneous population of non-B and non-T lymphocytes, but they are innate immune cells that have adaptive immune functions and are activated before T cells.[20]

The epithelial immune system has been shown to involved in immune surveillance of pathogens and other external factors, maintaining a dynamic balance of commensal bacteria and tissue

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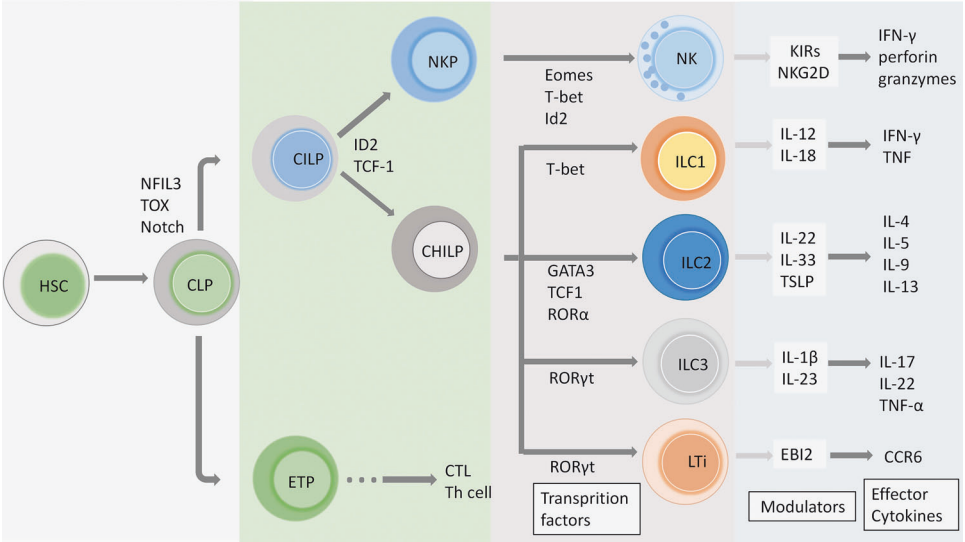

Fig. 1 The development of ILCs. ILCs differentiate from hematopoietic stem cells (HSCs) and then generate CLPs in the bone marrow at the early stage. CLPs are a cellular source of early T cell progenitors (ETPs) and CILPs, and ILCs and NK cells share some notable parallels with T cell lineage commitment. The transcriptional factor Id2 and T cell factor 1 (TCF-1) are involved in CILP regulation and differentiation into NKPs and CHILPs. These transcription factors, such as T-bet, GATA3, and RORγt, described above, drive the generation of different ILC subsets. Downstream cytokines of the ILC group participate in orchestrating the immune network, and several modulators have been proven to regulate ILC functions in disease conditions

homeostasis.[21] It is easily exposed to antigens and leads to active responses of ILCs at barrier surfaces. Studies indicate that ILCs have a high frequency in some autoimmune-related and inflammatory skin diseases and exert regulatory functions on other dermal immune cell populations.[22,23] Nevertheless, deeper mechanism remains incompletely understood, and further work remains to direct ILC development in human diseases.

Based on many speculative models and studies on human diseases, we suggest that different subsets and transcriptional regulation networks of ILCs could be critical to autoimmune-related skin diseases and inflammatory diseases; hence, we aim to give a comprehensive review of recent research progress on the pathogenic role of ILCs in these diseases. In this review, we will discuss the current knowledge about the contribution of ILCs to the impaired immune response and epithelial dysfunction in autoimmune-related skin diseases and inflammatory diseases. In each section, we will summarize the available mechanistic evidence for ILC dysregulation and how cytokines and cellular molecules work in the cutaneous immune network. Finally, we will discuss the potential of ILCs as therapeutic targets in the context of immune-mediated diseases.

ILC DEVELOPMENT

Critically, the nomenclature and classification of three major groups of ILCs were proposed according to their phenotypical and functional characteristics in 2013.[24] Later, single-cell RNA-sequencing confirmed 15 transcriptionally homogeneous clusters of ILCs on the basis of three classical subsets, with distinct marker gene expression and indexed protein markers.[25] Collectively, the updated categorization of ILC groups includes five main subsets, natural killer (NK) cells, ILC1s, ILC2s, ILC3s, and lymphoid tissue inducer (LTi) cells, and this categorization was recently approved by the International Union of Immunological Societies.[20] NK cells and LTi cells were identified before the conception of ILCs. NK cells are now known as the prototypical ILC subset, were found in the spleen of adult mice in 1975[26] and are involved in immune responses against cancer cells and viral infection. LTi cells are instrumental in the initiation of lymph nodes, accumulating during late fetal and early neonatal life, and were identified as a novel subset of the hematopoietic lineage in 1997.[27] Although several lymphocytes that lack RAG and differ from B cells and T cells have already been discovered, the ILCs were only discovered in the laboratory setting in the last 10 years and have been extensively studied since. The following detail the development (Fig. 1) and major content of each ILC subset and the extended biological role of ILCs in homeostatic or pathological conditions.

ILCs originate from the common lymphoid progenitor (CLPs), which reside in fetal liver and adult bone marrow and can give rise to common innate lymphoid progenitors (CILPs), as well as B and T cells lineages.[28,29] Through lineage tracing and transfer studies in mice, CILPs have been found that located in the downstream of CLP and have restricted potential to generate ILCs and NK cells.[29] CILPs differentiate into different progenitors, including NK cell precursors (NKPs) cells and common helper innate lymphoid progenitors (CHILPs).[30] CHILPs give rise to LTi progenitors and ILC precursors, developing to LTi cell and ILC1, ILC2, and ILC3, respectively.[31] Inhibitor of DNA binding 2 (Id2) has a high expression in all ILC lineages but not T or B cells, and contribute to immune cell fate decisions.[32] Id2 expression is pivotal in transcriptional network establishing ILC fate.[33] ILC lineages have been defined by distinct transcription factors. T-bet is necessary for development of ILC1 and NK cells, while Eomes is uniquely required for NK differentiation.[34] GATA3, potently regulated by thymic stromal lymphopoietin (TSLP), are essential for ILC2 development[35] and present similar fate decision of Th2 cells.[15] On the other hand, ILC3s are dependent on RORγt for their development and function.[36]

ILC SUBSETS

NK cells and ILC1s

NK cells originate from bone marrow and secondary lymphoid tissues, are present in many peripheral tissues, with a high frequency in the lung, uterus and liver, and include a large diversity of cell types.[37–39] There are few major subsets of NK cells: $CD56^{bright}$, $CD56^{dim}$ NK cells and other diverse subsets that are driven by killer cell immunoglobulin-like receptors,[40] NK group 2, member A[41] and epigenetic reprogramming.[42] In recent studies, NK cells have been regarded as an important part of orchestrating

early viral immunity and human cancer, and currently, more mechanisms of NK cell-mediated immunosurveillance and immunotherapy have been revealed.[43,44] Moreover, their functions are broader than originally appreciated, being involved in transplantation and degeneration of injured axons. NK cells help clear damaged axons to reduce postinjury hypersensitivity, suggesting their therapeutic potential to resolve painful neuropathy.[45] Viral immune-evasion restrains NK cell effector function via NK cell receptors, suggesting their instrumental role in innate immunity and the host-pathogen interplay.[46] NK cells contribute to the recruitment of conventional dendritic cells into the tumor microenvironment via the NK cell-derived chemokines CC-type chemokine ligand 5 and lymphotactin and may be useful in therapeutic strategies for cancer immunology.[47] Recent studies have found that trifunctional NK cell engagers, connecting NK cells with cancer cells by targeting NKp46, CD16 and tumor antigen, promote antibody-dependent cell-mediated cytotoxicity and enhance the antitumor efficacy of NK cells. Remarkably, trifunctional NK cell engagers have been proven to have efficacy superior to that of therapeutic antibodies in vitro and in vivo.[48] Moreover, the cytotoxic activity of NK cells regulate their detachment from target cells, thus leading to sustained calcium signaling and hypersecretion of pro-inflammatory cytokines, such as TNF-α and IFN-γ, suggesting a role in inflammatory pathologies in several diseases.[49]

ILC1s were first named by Bernink in 2013 to delineate a subset of lineage negative (Lin^-) $CD127^+$c-Kit^-NKp44^- ILCs in tonsils and inflamed intestinal mucosa that expressed T-bet and produced the pro-inflammatory cytokine IFN-γ,[50] which was similar but distinct from NK cells that T-bet and Eomes drive NK cell differentiation;[51] in fact, the substantial functional and phenotypic overlap between ILC1s and NK cells delayed studies on ILC1s. Recent research has shown that promyelocytic leukaemia zinc finger (PLZF) contribute to map the lineage divergence between ILC1s and classical NK cells, which is located, as expected, at the initial branching of the two subsets.[52] ILC1s are important components of the first line of immune defense against viral infection along with NK cells and even initiate the immune response prior to NK cells. Orr-El Weizman found that ILC1s were the first and main source of IFN-γ in the early stages of viral infection driven by conventional dendritic cells in a signal transducer and activator of transcription (STAT4)-dependent manner.[7] In addition to host protection, ILC1s also play a nonredundant role in hapten-specific memory responses. Interestingly, haptens can induce the migration of IL-$7Rα^+$ ILC1s to skin-draining lymph nodes in a CXC chemokine receptor (CXCR) type 3-dependent fashion. The microenvironment of the liver, which is rich in CXCR6 and IL-7, supports ILC1 residency and longevity.[53] Although we usually define ILC1s as members of the innate immune system, evidence, as mentioned above, has emerged that ILC1s possess adaptive immune features.

ILC2s

ILC2s were first reported in splenocytes from immune-deficient (RAG KO) mice. These cells were IL-25-responsive and produced IL-13. They were detected as non-T/non-B cells[54] and could initiate worm expulsion and protect against helminth parasite infection.[55] Later, in 2010, natural helper cells,[13] nuocytes[12] and innate helper 2 cells[14] were combined into a group: ILC2s or 'group 2 innate lymphoid cells'.[24] ILC2s are regarded as a unique subset and produce the Th2 cell-associated cytokines with large amounts of IL-5, IL-9, and IL-13 but very little IL-4.[35,56,57] In some cases, IL-33, usually work as an ILC activator, did not induce high level of IL-4 production.[58] We suppose the potential mechanisms were certain trigger alone may be not sufficient to induce IL-4 production and it requires additional signals for exerting a strong synergistic effect. Quantification of human ILC2s are significant elevated by the co-stimulation of IL-2 plus IL-1β or IL-33. Moreover, cytokines produced by ILC2s including IL-4, IL-5, and IL-13 are remarkable increased.[59] Evidence also demonstrates that both freshly isolated ILC2s and presented ILC2s are triggered by TSLP and are responded with the increasing of IL-4, IL-5 and IL-13.[55] In addition, ILC2-derived IL-4 has the capacity to antagonize oral tolerance to food allergy and impair the suppressive function of allergen-specific Treg cells.[60] It also has been proved that IL-4 plays an important role in activating ILC2s and promoting type 2 cytokine production.[61] Thus, IL-4 may work as a vital regulator in an autocrine manner.

ILC2s are usually located throughout mucosal and barrier surfaces in the intestines and airways and also reside in the lymph nodes and liver. Evidence shows that liver-resident ILC2s are significantly upregulated by IL-33 and play a potentially synergistic role in the pathogenesis of liver fibrosis.[62] Small intestinal tuft cell and ILC2s were activated by natural intestinal parasites and promoted small intestinal remodeling.[63,64] In addition, ILC2s also contribute to pathological inflammation in allergic asthma, and the mechanism is intriguing; recently, the neuropeptide neuromedin U was found to increase ILC2-induced inflammation as a modulator after allergic sensitization.[65] The β2-adrenergic receptor is regarded as a negative regulator in molecular pathways.[66] Interestingly, both the neuropeptide neuromedin U and β2-adrenergic receptor provide evidence of a neuronal-derived regulatory circuit in type 2 inflammatory regulation.[65–67] Dysregulated ILC2 responses were found to be critical to obesity, and IL-33 plays a role in limiting adiposity in mice by eliciting beiging of white adipose tissue, indicating that ILC2s can regulate adipose function and metabolic homeostasis.[68]

ILC3s

RORγt is a ligand-dependent nuclear hormone receptor[69] and is regarded as a central molecule for distinguishing ILC3s from other subpopulations.[70] Group 3 ILCs were initially found to express NK cell receptors, such as NKp44, in human tonsils and to produce the Th17-associated cytokines IL-17 and/or IL-22.[70,71] The subset of ILC3s can be classified by the cell surface expression of NKp46[72] (in mice) and NKp44[73] (in humans) and can be further divided into NCR^+ ILC3s or NCR^- ILC3s or termed IL-17- or IL-22-producing cells on the basis of cytokine secretion.[73] They are predominantly located in the intestinal lamina propria. In addition to RORγt, another transcription factor that is essential for LTi-like cells and NCR^+ ILC3s is the ligand-activated arylhydrocarbon receptor (AHR), which activated by environmental clues, endogenous factors as well as microbial metabolites.[74,75] Genetic or pharmacological activation of AHR have been reported to regulate ILC2-ILC3 balance and host immunity.[76]

Recent studies indicate that ILC3s are relevant to human cancer and involved in intestinal homeostasis. Carrega P found that NCR^+ ILC3s were recruited in human non-small-cell lung cancer tissue and that their presence was linked with intratumoral lymphoid structures.[77] Additionally, more detailed mechanisms of ILC3 regulation in intestinal inflammation and homeostasis have been revealed recently. A study discovered that ILC3s regulate epithelial cell glycosylation in the intestinal microenvironment.[78] $NKp46^-$ and $NKp46^+$ ILC3 cells constitute most NKR-$P1B^+$ lymphocytes in human intestine. While, the deletion of NKR-P1B results in a higher frequency and number of ILC3 and γδ T cells in the gut lamina propria and may contribute to innate immunity.[79] Neuroimmune regulation plays an important role in intestinal homeostasis through the glial-ILC3 regulatory arm in a myeloid differentiation primary response gene 88-dependent manner.[80,81] Interestingly, dissection of the vagus nerve is correlated with a decreased number of ILC3s, and acetylcholine upregulates the protecting conjugate in tissue regeneration biosynthetic pathway in mouse and human ILC3s. Moreover, the protecting conjugate in tissue regeneration can control macrophage responses and infections.[82] Mechanistically, complex class II^+ ILC3s regulate host-microbe symbiosis via repressing pathologic $CD4^+$ T cell responses in

inflammatory conditions, indicating a novel role in maintenance intestinal homeostasis and potential target for chronic intestinal inflammation treatment.[83]

ILCS IN AUTOIMMUNE-RELATED AND INFLAMMATORY SKIN DISEASES

As discussed above, abnormal populations and dysregulation of ILCs are instrumental factors in the development of many diseases, such as autoimmune diseases, inflammatory diseases and asthma. ILCs are mainly tissue-resident lymphocytes located in the mucosal barriers of the intestine, skin and lung and play a role in immunity, inflammation and tissue homeostasis. The skin, as the primary interface between the host and the environment, provides an early and prompt defensive immune response to protect epithelial integrity by serving as a physical and immunological barrier containing cells from both the innate and the adaptive immune systems. The local interplay between keratinocytes and immune cells, such as naive T cell by cell contact and costimulatory signaling, contribute to the disease pathogenesis under pro-inflammatory conditions.[84] A much more heterogeneous population of immunological cells resides in the dermis, including dermal subsets of dendritic cells, mast cells, $CD4^+$ and $CD8^+$ T cells, B cells, macrophages, NK cells and the newly identified ILCs.[85,86]

Skin-resident ILCs locate at surface barrier and perform an important role in regulating microbial commensalism and cutaneous inflammation. As a large epithelial surface for interaction with microbes, mammalian skin protects body health against pathogenic microorganisms, but also facilitate host-microbe symbiosis.[87] Furthermore, follicular and the interfollicular epithelial surface support a vast interface for microbes habitat, as well as host immunity.[88] Kobayashi et al. have found that a population of skin-resident $ROR\gamma t^+$ ILCs located around hair follicles in close proximity to sebaceous glands. More detailed researches have been reported that sebaceous function, especially free fatty acid production, were regulated by TNF-producing ILC via Notch signaling and were altered to significantly antimicrobial activity against skin-associated Gram-positive cocci. ILCs deficiency results in alteration of the microbial landscape by regulating sebocyte growth and antimicrobial lipids production, highlighting the significant role of ILC in skin commensals and barrier immunity.[89] In addition, it is recently reported that atopic dermatitis (AD)-like murine model with filaggrin mutation do not develop skin inflammation under germ-free compared to SPF conditions. This model develops spontaneous AD-like skin inflammation with a significant elevation in dermal ILC2 numbers, indicting a crucial role for the microbiome in promoting type 2 innate immune responses.[90]

Furthermore, there may exit genetic association between ILC and autoimmune diseases and inflammatory diseases. ILC super-enhancers, demarcating cohorts of cell identity genes, are enriched for autoimmune-associated single nucleotide polymorphisms (SNPs). ILC3-specific super-enhancers had the most autoimmune SNPs, including IL23R and STAT3, perhaps revealing critical regulatory elements for differential gene expression in autoimmune diseases.[91] Several susceptibility loci have been uniquely associated with psoriasis are involved in innate immune responses, with roles in IFN-mediated antiviral responses (DDX58), macrophage activation (ZC3H12C), and NF-κB signaling (CARD14 and CARM1).[92] In addition, RUXN3, identified as psoriasis susceptibility loci that regulate T cell function, is also essential for ILC development and orchestrate RORγt expression in ILC3 cells.[93] Consistent with dysregulation of ILC3s in psoriasis patients, RUXN3 may be a potential genetic regulator of ILC3s in psoriasis, still, more direct evidences are needed. ADAM17 deficiency leads dampened Notch signaling and results in increasing production of TSLP in atopic barrier immunity.[94] Most importantly, Notch deficiency induces keratinocyte-mediated release of TSLP.[95] As a fact of TSLP receptor expressed on ILC2s, TSLP is involved in inflammatory skin of AD associated with enhanced production of IL-5 and IL-13 from ILC2s.[96] Notch have been recognized as a common regulator in ILC lineage differentiation.[97] In addition, evidence links Notch signaling to ILC2 plasticity that Notch could change the cytokine responsiveness of ILC2.[98] In line with these researches, ILCs are now a focus of skin homeostasis research as a critical factor in the innate immunity that protects against invading pathogens and in the regulatory functions in cutaneous inflammation and the pathogenesis of autoimmune diseases.

ILCs in systemic lupus erythematosus (SLE)

SLE is a chronic, multifactorial autoimmune disease and complicated immune disorder that has not been characterized extensively. Autoreactive T and B cell clones, increased autoantibodies and cytokines, and abnormal signal transduction constitute essential elements of the pathogenesis of lupus.[99,100] High levels of IFN-α in peripheral blood have been noted in SLE for many years.[101] Recently, study has found that IFN-α is able to promote transitional B cells survival and enhance pro-inflammatory activities and could contribute to the breach of B cell tolerance in this condition.[102,103] As a result, research interests in recent decades have focused mainly on studying autoantibody-mediated tissue damage and identifying the role of adaptive immunity in SLE, often neglecting the involvement of cells central to innate immunity.

Currently, ILCs, especially ILC1s, are regarded as emerging modulators of immunity in SLE, and evidence suggests that ILC2s are potential protective factors. Hou recently found that ILC1s and ILC3s were significantly increased in the peripheral blood, whereas circulating ILC2s were decreased.[22] Recently, evidence has shown that kidney-residing ILC2s are decreased in the MRL/MpJ-Fas^{lpr} lupus mouse model and are inhibited by the T cell- and myeloid cell-derived pro-inflammatory cytokines IFN-γ and IL-27. Furthermore, these ILC2s could be effectively expanded by IL-33 treatment and later had moderate beneficial effects on renal outcome and improve survival.[104] Interestingly, another study found that ILC1s were markedly altered in the peripheral blood of SLE patients and then became the dominant ILC subset but were reduced after steroid and cyclophosphamide treatment. Moreover, after treatment with SLE plasma or IL-2/IL-12/IL-18, increased IFN-γ was secreted by ILC1s, which has been implicated in the pathogenesis of SLE.[105] In addition, SLE patients with moderate and severe disease activities had a decreased frequency of ILC2s and ILC3s in one study.[105] Blokland et al. also found that ILC1 frequencies were increased in blood circulation of SLE patients. Conversely, ILC2s or ILC3s did not differ between patients with SLE and healthy controls in peripheral blood; however the IFN signature was associated with elevated Fas expression on ILC2 and ILC3 subsets in circulation.[106] In the present study, the divergent results in different ILC populations may be associated with the heterogeneity of and different treatments used for SLE patients, as SLE is not only the prototypical systemic autoimmune disease but also one of the most heterogeneous illnesses.

In addition, NK cells stand at the crossroads of innate and adaptive immunity as the third main lymphocyte lineage after T and B cells and work as an important element in the pathogenesis of SLE. A previous study found that NK activity could be inhibited by serum from SLE patients and was correlated with the presence of clinically active disease.[106] Schepis D et al. showed that the $CD56^{bright}$ NK cell count was decreased in patients with active SLE, but the specific mechanism behind this finding remains unclear.[107] Alterations in several cytokines, such as a reduction in IL-2, increased TNF-α and IFN-γ and may modulate NK cell phenotype and function in SLE by enhancing local autoimmune injury.[108] A recent study reported that two clusters of NK cells were found in the kidneys of patients with lupus nephritis,

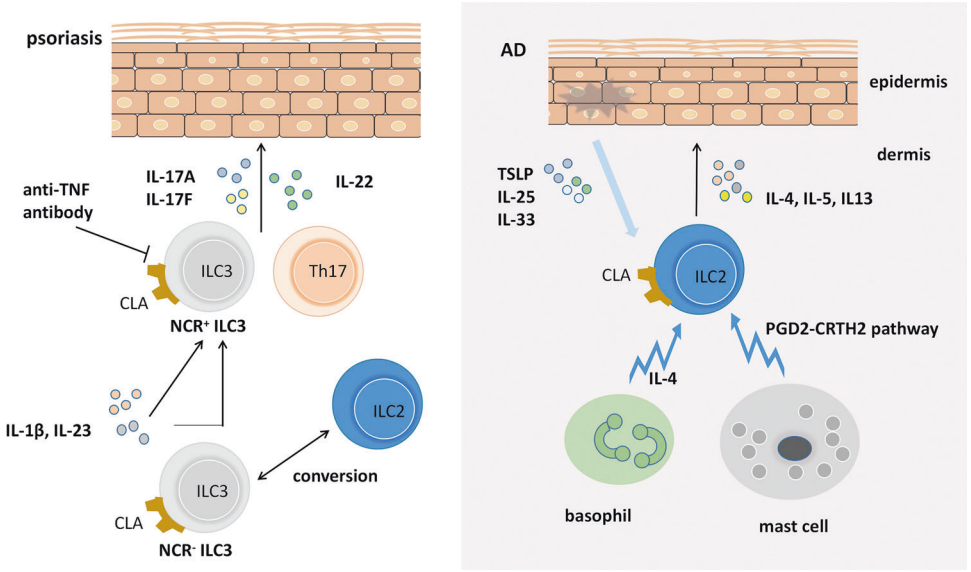

Fig. 2 The pathogenic role of ILCs in psoriasis and AD. ILC3s are elevated in the skin of psoriasis patients. RORγt$^+$ ILC3s secret IL-17A, IL-17F, and IL-22 and become a critical factor in promoting psoriasiform lesions. However, anti-TNF treatment can decrease the elevated level of circulating NCR+ ILC3s. Notably, ILCs can change phenotype. NCR$^-$ ILC3s in healthy skin can be converted to NCR$^+$ ILC3s when cultured with IL-1β plus IL23. In addition, ILC2s play a central role in the skin in AD in both mouse models and humans through the secretion of IL-4, IL-5, and IL-13. Emerging evidence shows that IL-25, IL-33, and TSLP are all involved in the modulation of ILC2s in inflamed skin. In addition, ILC2s interact with mast cells and basophils and participate in driving pathology in atopic dermatitis through cell interactions

including tissue-resident CD56^{bright}CD16$^-$ NK cells and CD56^{dim}CD16$^+$ NK cells. These dividing cytotoxic T lymphocytes and NK cells were increased in patient kidneys, indicating a role of cytotoxic activity in lupus nephritis.[109] Although circulating cytokines and antibodies could affect local skin immunity, ILC frequency and functions are poorly understood in lesional and nonlesional skin in SLE patients. Nevertheless, more powerful evidence is required to explore the mechanism of ILCs in SLE.

ILCs in psoriasis

Psoriasis is an immune-mediated, inflammatory and predominantly skin-tropic disease with multifactorial symptoms and is mediated by cells and molecules of both the innate and adaptive immune systems.[110] Both genetic and environmental factors have been linked with the onset of psoriasis. HLA-Cw6, as a major disease allele of PSORS1, confers the strongest genetic linkage to susceptibility to psoriasis.[111] Infections,[112] trauma,[113] some drugs such as β-adrenergic-blocking agents[114] and a wealth of external elements contribute to psoriasis lesions and disease aggravation. Currently, it is widely held that divergent factors trigger plasmacytoid dendritic cells and then activate autoaggressive Th cells through IL-23, IL-12, IL-6, and TNF-α, leading to T lymphocyte subset dysfunction and immune responses in psoriatic plaques.[114] ILCs are also an important source of the Th17 representative cytokines TNF-α, IL-17, and IL-22, suggesting a synergistic role between ILCs and Th17 cells in psoriasis via the innate immune response.[13,57] The latest research has begun to discuss this possible relationship (Fig. 2).

ILCs are proposed to contribute to the pathogenesis of psoriasis plaque formation and are a source of psoriasis-related cytokine in a murine model. The use of ILCs in inducing murine psoriasis was first uncovered in a murine model induced by topical application of the Toll-like receptor 7 agonist imiquimod (IMQ). There is mounting evidence that the Th17 signature cytokines IL-17A, IL-17F, and IL-22 play a predominant role in psoriasis, and Th17 cells act as a primary source of these pathogenic cytokines.[110,115] However, skin-invading γδ T cells and RORγt$^+$ ILCs secrete IL-17A, IL-17F, and IL-22 and then become an essential predisposing factor in the formation of acute psoriasiform lesions in mice, indicating that dysregulated innate immunity participates in psoriatic plaque formation.[116] This research demonstrates that mice topically administered IMQ develop psoriasiform skin inflammation to the same extent as Rag1$^{-/-}$ mice lacking T and NK T cells. However, Rag2$^{-/-}$Il2rg$^{-/-}$ mice, which additionally lack NK cells and ILCs, do not develop IMQ-driven plaques, indicating a unique function of ILCs in this pathogenic condition. Previously, evidence confirmed that RORγt, now also regarded as a transcription factor of group 3 ILCs,[19] is a key regulator in Th17 differentiation and IL-17 secretion,[117] and more in-depth research and relevant evidence are required in human diseases.

To interrogate whether ILC3s are present in human skin and altered in psoriasis, Villanova et al. performed flow cytometric analysis and found that NKp44$^+$ ILC3s were increased in the skin and blood of psoriasis patients, with a significant enrichment of the ILC population in the skin compared with the blood.[118] Almost at the same time, similar results showed that a significantly elevated proportion of NKp44$^+$ ILC3s was located both in human skin lesions and in peripheral blood from psoriasis patients compared with healthy individuals, and skin NKp44$^+$ ILC3s were correlated with psoriasis severity.[17] Moreover, recent research has confirmed the role of ILC3s in the pathogenesis of psoriasis. Intradermal injection of human CD3$^-$RORγt$^+$NKp44$^+$ ILC3s leads to the development of lesions with psoriatic histological features in humanized severe combined immunodeficient mice using healthy human skin grafts.[17] These results highlight that ILC3s not only are increased in psoriasis but also drive the development of the human psoriatic phenotype independent of Th17 cells.

In addition, mature ILC subtypes have the capacity to modify their phenotype and function in response to local environmental cues, sharing a similar feature of plasticity with Th cells. A study revealed that ILC2s and NCR$^-$ ILC3s constitute the major ILC groups in healthy skin. Interestingly, NCR$^-$ ILC3s in healthy skin can be converted to NCR$^+$ ILC3s through culture with IL-1β plus IL-23, which have already been found to be elevated in psoriatic lesions and implicated in the pathogenesis of psoriasis.[17] A similar phenotype switching of ILCs has also been described in the intestinal lamina propria, and such a switch is reversible in specific microenvironments.[119] A type of ILC2, inflammatory ILC2s, also

expresses RORγt and is able to secrete IL-17 and respond to IL-25, and they have been referred to as transient ILC progenitors that could develop into IL-33-responsive natural ILC2s and ILC3-like cells.[120] Studies have discovered that NKp44$^-$ ILC3s may be derived from ILC2s and are elevated in psoriasis lesions, corresponding with a decrease in the frequency of CRTH2$^+$ ILC2s. Moreover, data show that these IL-17-producing ILC3s can switch back to ILC2-like cells when cultured with IL-1β and IL-4, suggesting a potential target for therapeutic intervention.[73]

Several studies have demonstrated the possible mechanism for the role of ILCs in the development of inflammation in psoriasis patients. Bruggen et al. performed ILC in situ mapping in human skin and revealed that psoriasis lesions contained a prominent population of TBET$^+$ ILC1s and RORC$^+$ ILC3s with nearly absent GATA3$^+$ ILC2s, identified on the basis of different transcription factors between different ILC subpopulations. Using immunofluorescence in situ staining, these ILCs were found to reside beneath the dermoepidermal junction and in close proximity to T lymphocytes. The intimate contact between ILCs and T cells suggests a potential functional relationship between these cells and provides new insight into the shared mechanisms between psoriasis mechanism and innate immunity.[121] A numerical increase in ILC3s was later found in both nonlesional and lesional psoriatic skin, whereas altered cytokine levels were not observed before cutaneous changes. Additionally, the cytokine IL-23 and the NK group 2 member D ligand MICA, which are both remarkably upregulated in lesions, were shown to have the potential to activate group 3 ILCs in lesional psoriatic skin.[122] Thus, we hypothesize that the ILC imbalance acts before the IL-23/IL-17 axis and IL-22 production changes and that ILCs have emerging roles in the early stage of psoriasis. Previous studies both noticed that peripheral blood ILC subsets express skin-homing markers cutaneous lymphocyte antigen (CLA) at a high frequency,[17,118] which indicates a potential source of skin ILCs. However, the deeper mechanism remains unclear. A Lin$^-$CD123$^+$CD127^{low} population with characteristics of ILCs transmigrated through endothelial cells in response to CXCR4-stromal cell-derived factor-1 under inflammatory conditions in psoriasis.[73,121] Taken together, these results suggest that ILCs, especially ILC3s, play a predominate role in the early part of psoriasis pathogenesis. Deeper insights into how ILCs make a substantial contribution may reveal potential immunopathological hallmarks of psoriasis and therapeutic approaches in the future.

ILCs in AD

AD, also known as atopic eczema, is a chronic, relapsing inflammatory skin disease that was originally regarded as a childhood disorder and includes a familial propensity to become IgE-sensitized against environmental allergens.[73,121] It is now recognized as a lifelong disposition with persistent pruritus and recurrent eczematous lesions, and both epidermal barrier dysfunction and immune system dysregulation, especially Th2 cell adaptive immune responses, contribute to AD pathogenesis based on strong heritability.[123] The gene encoding filaggrin (FLG), an epidermal structural protein, is strongly associated with AD as an important player in deficient barrier function.[124,125] A genome-wide association analysis revealed new candidate genes related to innate immune signals and the T cell response.[123] Notably, ILCs, especially ILC2s, were found to act as a critical predisposing factor in the pathogenesis of AD skin lesions and work as members of the signaling pathways involved (Fig. 2).

Numerous studies have demonstrated that ILC2s are involved in skin inflammation and are significantly increased in lesional AD skin compared to healthy human skin, as well as being increased in an AD-like dermatitis mouse model. Elevated ILC2s have been reported in the skin of AD patients and are identified by the specific markers CD25 (IL-2Ra) and IL-33R (ST2) expressed by lineage negative cells.[126] Similar results are observed in the AD murine model: vitamin D analog calcipotriol (MC903)-treated naïve C57BL/6 wild-type mice develop AD-like dermatitis associated with Th2 cell-associated cytokine production and elevated serum IgE. Histopathologic changes exist similar to those observed in human atopic lesions, including epidermal hyperplasia and mononuclear leukocyte and granulocyte infiltration. Cutaneous CD25$^+$IL-33R$^+$ group 2 ILCs were increased on flow cytometric analysis, as was the expression of the effector cytokines IL-5 and IL-13, which are typical type 2 cytokines produced by Th2 cells and are now also regarded as innate sources. The data resemble those in the skin-draining lymph nodes. More strikingly, after intradermal injection of purified ILC2s sorted from MC903-treated C57BL/6 wild-type mice into naïve C57BL/6 wild-type mice, the recipients develop AD-like inflammatory response and histological features in the skin.[126] On the other hand, the number of CRTH2$^+$IL-7Rα$^+$ ILC2s are elevated in skin suction blisters from nonlesional skin of patients with FLG mutations compared with the number in those of patients without FLG mutations.[127] Furthermore, a filaggrin-mutant mouse model, also called "flaky tail" mice, shows spontaneous AD-like inflammation and pro-inflammatory cytokine production, eliciting ILC2 alterations and Th2 cell responses.[127] Therefore, these results demonstrate ILC2 dysregulation in AD patients and murine models; thus, ILC2s have become a promising means to study the pathogenesis of AD, and the deeper mechanism remains to be discussed.

Notably, ILC2s have been found to play a central role in AD independent of adaptive immunity. Increasing numbers of ILC2s and cytokine secretion have been observed in lymphocyte-deficient Rag1$^{-/-}$ mice. The effective depletion of CD25$^+$IL-33R$^+$ ILCs by anti-CD25 or anti-CD90.2 monoclonal antibodies reduced skin lesions in a Rag1$^{-/-}$ mouse model of AD-like skin inflammation, indicating that the ILC2-mediated immune response plays a major role in AD independent of adaptive immunity.[126] Moreover, RORα-deficient bone marrow chimaera mice that lack ILC2s have ameliorated cellular infiltration in the skin and markedly reduced ear swelling. In addition, the increased susceptibility of Rag1$^{-/-}$Flg$^{ft/ft}$ mice to contact hypersensitivity inflammation reveals that innate immunity mediates spontaneous inflammatory lesions. Furthermore, in this model, an adaptive immune response is required for the progression from dermatitis to pulmonary inflammation.[127] In a recently described Zn^{2+}-finger DHHC-domain-containing protein 13 (ZDHHC)-deficient mouse model, which features mutations of DHHC-domain-containing palmitoyl acyltransferases, animals develop an impaired skin barrier and abnormal filaggrin due to the deficiency of ZDHHC. Moreover, the Rag1$^{-/-}$;Zdhhc13$^{k/k}$ double-mutant mice generated to further explore adaptive immune functions in AD still develop inflamed skin with substantial mast cell accumulation and abundant ILC2s, highlighting ILC2s as a main pro-inflammatory cell, and the initiation of dermatitis may activate the innate immune response independent of adaptive immunity.[128] Therefore, ILC2s are linked with the pathogenesis of AD, and moreover, it is interesting that ILC2s can be self-governed without adaptive immunity in murine models.

To investigate the modulators that promote ILC2 activation in the context of AD-like inflammation, studies have focused on whether and to what extent ILC2s respond to IL-25, IL-33, and TSLP, given their expression of the membrane-bound IL-33 receptor ST2, IL-25R, and TSLP receptor. Studies have demonstrated that epithelium derived IL-25 and IL-33 can induce the accumulation of ILC2s in the lung tissue and local lymph nodes.[129,130] Moreover, Kim et al. found that ILC2s and the cytokines IL-5 and IL-13 were increased in AD lesion and draining lymph nodes.[96] This finding was critically dependent on TSLP, rather than IL-25 and IL-33, which have been proven to be associated with ILC2 activation in intestinal lymphoid tissue and the lung parenchyma.[2] Skin-specific expression of IL-33 was also proved to be a critical activator of ILC2s to induce AD-like dermatitis with eosinophil infiltrates with

the establishment of a transgenic mouse model that overexpresses IL-33 in keratinocytes.[126] Another relevant study confirmed the role of $Lin^{-}CD45^{hi}IL\text{-}7R\alpha^{+}CRTH2^{+}$ ILC2s in allergic skin inflammation and further indicated that the initiating cytokines IL-25 and IL-33 played a predominate role over TSLP in a BALB/c mouse model of dermatitis.[128] Discrepancies seem to exist in mice with different genetic backgrounds, and the role of IL-33 remains a matter of debate. However, what does make sense is the extent that ILC2s are dependent on IL-33 or TSLP in humans. Collectively, IL-25, IL-33 and TSLP are all involved in the modulation of ILC2s in inflammatory skin from patients with AD. Additionally, ILC2s express the skin-homing receptors CLA, complete cytogenetic response 10 and complete cytogenetic response 4 and infiltrate AD skin.[131] Further studies need to focus on more detailed mechanisms and their therapeutic implications.

ILC2s also interact with multiple cell populations to drive pathology in AD, especially mast cells and basophils. A unique population of skin-resident $CD103^{+}$ ILC2s, called dermal ILC2s, promote eosinophil influx and cutaneous inflammation. In assessing the skin by multiphoton microscopy, a novel interaction was uncovered between these dermal ILC2s and mast cells. Human mast cell-derived prostaglandin D2 triggers ILC2 migration and cross-regulation through a prostaglandin D2-CRTH2-dependent pathway in the skin.[132] Interactions may also exist between ILC2s and basophils,[96] while the upstream innate cellular mechanism remains unclear. Later, a close proximity of ILC2s and basophils was reported in the dermis of human AD lesions. Kim et al. found that basophil-derived IL-4 was necessary for skin inflammation and ILC2 proliferation in murine AD-like skin lesions.[133] In addition, basophils were positively correlated with the frequency of skin ILC2s but not ILC3s in the lesions of AD patients.[134] Basophils have been report to be accumulated in the skin biopsies of patients with AD and are responsive for AD-related chemokine expression.[135,136] Skin basophils significantly expressed IL-4 following ex vivo stimulation, indicating a potential therapeutic target in AD.[134] On the other hand, dermal ILC2s could act as immune-regulatory factors in steady-state conditions, producing IL-13, which is capable of promoting homeostatic function.[23] There is indeed a need to focus on the regulation and functional interactions of ILC2s in cutaneous inflammation, aiming to inhibit the switch to a pro-inflammatory phenotype for potential therapies in the future.

ILCs in other autoimmune-related and inflammatory diseases

Systemic sclerosis (SSc), also known as scleroderma, is an immune-mediated disease featuring fibroblast activation, progressive tissue fibrosis of the skin and internal organs and vasculopathy.[137] Skin tightness and itching are early features, and later, vasculature and musculoskeletal damage and fibrosis are involved.[138] Genetic clues as well as chemical exposure and several chemotherapy drugs might be important drivers of molecular and clinical diversity within SSc.[139,140] Notably, ANAs and anti-RNA polymerase III antibodies[141] are specific hallmarks of SSc; moreover, reactive CD4 T cells are observed,[142] and autoimmunity might be central to the initiation or progression of the disease. Increased proportions of ILC1s and $NKp44^{+}$ ILC3s have been reported in the peripheral blood of individuals with SSc compared with healthy controls, while $NKp44^{-}$ ILC3 frequencies are decreased. Interestingly, the elevated ILC1s were predominantly attributable to changes in $CD4^{+}$ ILC1s, which have lower expression of T-bet than $CD4^{-}$ ILC1s and alteration of IL-6Rα.[143] Moreover, deficiency of the transcription factor T-bet has been proven to increase sensitivity to bleomycin-induced dermal sclerosis in a mouse model, and this also occurs in mouse models lacking T and B cells.[144] Expansion of ILC2 numbers has also been revealed in the skin and blood of SSc patients; in addition, skin ILC2s have fibrotic manifestations, and circulating ILC2s correlate with the extent of skin fibrosis and interstitial lung disease.[145] The expression of the skin-homing marker CLA on resident ILCs provides potential insights into the source of cutaneous ILC2s, which are activated locally in the skin.[17,131]

Anti-neutrophil cytoplasmic autoantibody-associated vasculitis (AAV) is a group of autoimmune diseases characterized by necrotizing small-vessel vasculitis that largely affects the kidneys, respiratory tract and skin and circulating autoantibodies to myeloperoxidase or proteinase 3, which are helpful for the classification of AAV.[146,147] The major subgroups of AAV are microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic GPA.[148] A study has demonstrated that the total ILCs in peripheral blood are markedly decreased in patients with GPA and MPA during the acute phase but are restored in the remission phase. Notably, ILC1s have a higher frequency in acute-phase GPA patients than in GPA patients in the remission phase. Decreased frequencies of ILC2s and $NKp44^{-}$ ILC3s can be seen during the acute phase in both GPA and MPA compared with the respective frequencies in healthy controls and matched patients the remission phase.[149] However, more details need to be understood, and the function of ILCs in the pathogenesis of AAV, especially MPA and GPA, needs to be assessed.

Allergic contact dermatitis is a series of inflammatory reactions in the skin with contact with low-molecular-weight organic chemicals or metal ions, ultimately resulting in the development of intensely pruritic erythema, edema and even vesicles.[150] The hapten-mediated activation of the innate immune system and cutaneous antigen-presenting cells play a critical role in skin inflammation.[151] Increasing numbers of ILCs and their respective marker cytokines have been reported, with the number of NK cells and the expression of IFN-γ and TNF being highest 24 h after allergen challenge and paralleling the strongest skin inflammatory response. Moreover, depletion of ILCs, especially ILC2s, leads to increased contact hypersensitivity responses, providing compelling evidence for the role of ILCs in inflammation associated with contact dermatitis.[152] A recent study revealed that ILC2 deficiency elicited an obvious decrease in cutaneous infiltrating Th2 cell numbers following allergen rechallenge in sensitized animals, demonstrating that ILC2s are important for orchestrating efficient localized memory Th2 cell responses to allergens.[152]

APPLICATIONS OF ILCS IN MOUSE MODELS AND EMERGING THERAPEUTIC TARGETS

Previous studies have shown that ILCs play critical, nonredundant roles in the activation of the immune response and pro-inflammatory cytokine secretion. Research and early stage trials have been performed on murine models based on their similar physiological and pathological states to those seen in human diseases. With more in-depth investigations, ILCs have been observed to induce an inflammatory response in vivo, suggesting their role in disease pathogenesis and their increased potential for establishing animal disease models. On the other hand, ongoing studies continue to reveal emerging therapies for immune regulation and the inflammatory response in the skin targeting the ILC group. Several questions and specific mechanism of ILC in the pathogenesis of SLE, scleroderma and allergic contact dermatitis are still remain addressed, limiting the therapeutic applications. However, abundant evidences suggest that ILC contribute to skin inflammation in psoriasis and AD patients. These findings establish fundamental therapeutic ideas as target interventions, and actually evidence has already shown ILC could serve as promising therapeutic targets in disease models.

It is intriguing to find ILC prompt the devolopment of psoriasis and targeting the corresponding cytokines has potential treatment effect. Intradermal injection of specific ILC subsets has been used to precisely define the function of ILCs in skin immunity, and evidence has demonstrated that human ILC3s have the capacity to induce psoriatic lesions on healthy human skin grafts in

Table 1. ILC subtypes in different autoimmune-related and inflammatory diseases

Disease	ILC subset	Cell surface markers	Tissue samples	Function	Model	Reference
Psoriasis	ILC1s(-)	Lin^- $CD127^+$ CRTH2 $CD117^-CD161^+$ ILCs	Human lesional skin	- (no significant difference)	Psoriasis patients	17
	ILC2s(-)	Lin^- $CD127^+$ $CRTH2^+$ ILCs	Human lesional skin	- (no significant difference)	Psoriasis patients	17
	ILC3s(↑)	$ROR\gamma t^+$ ILCs	Mouse lesional skin	Psoriatic plaque formation	IMQ-induced $Rag1^{-/-}$ and $Rag2^{-/-}Il2rg^{-/-}$ mice	19
		$NKp44^+$ ILC3s	Human lesional skin and blood	Correlate with psoriasis severity	Psoriasis patients	17
		$CD3^-$ $ROR\gamma t^+$ $NKp44^+$ ILC3s	Human blood	Induce psoriatic lesions	Intradermal injection into healthy human skin grafts on severe combined immunodeficient mice	153
		c-kit^+ $CRTH2^-$ ILCs	Human lesional skin	Resident c-kit^+ $CRTH2^-$ ILCs are derived from ILC2s and could switch back to ILC2-like cells	Cutaneous ILCs cultured in vitro	72
		NCR^+ ILC3s	Human skin	NCR^+ ILC3s elevated both in lesional and nonlesional skin	Psoriasis patient	122
AD	ILC1s(-)	Lin^- IL-$7R\alpha^+$ T-bet^+ ILCs	Mouse skin	- (no significant difference)	$Flg^{ft/ft}$ mice	127
	ILC2s(↑)	Lin^- $CD25^+$ IL-$33R^+$ ILC2s	Human lesional skin	Higher frequency of ILC2s in the skin of patients	AD patients	126
		Lin^- $CD25^+$ IL-$33R^+$ ILC2s	Mouse lesional skin	Promoting AD-like disease	MC903-treated naïve C57BL/6 mice	
		$CRTH2^+$ IL-$7R\alpha^+$ ILC2s	Human nonlesional skin	FLG mutations in AD patients are associated with ILC2s frequency in nonlesional skin	AD patients	126
		Lin^- $CD127^+$ $CD25^+$ $CD90^+$ ILC2s	Mouse lesional skin	Increasing ILC2s serve as pro-inflammatory factors	Filaggrin-mutant mouse model	127
		Lin^- $CD25^+$ IL-$33R^+$ ILCs	Mouse lesional skin	ILC2s develop AD-like dermatitis independent of adaptive immunity	$Rag1^{-/-}$mouse model, $Rag1^{-/-}Flg^{ft/ft}$ mice, $Rag1^{-/-}$; $Zdhhc13^{k/k}$ double-mutant mice	127,128,131
	ILC3s(-)	Lin^- IL-$7R\alpha^+$ $ST2^-$ $ROR\gamma T^+$ ILCs	Mouse skin	- (no significant difference)	$Flg^{ft/ft}$ mice	127
SLE	ILC1s(↑)	Lin^- $CD127^+$ $CRTH2^-$ $CD117^-$ ILCs	Human blood	Increasing in patients and decreasing after treatment	SLE patients	104
	ILC2s(↓)	Lin^- $CD127^+$ $CD25^{hi}$ $GATA3^+$ ILCs	Human blood	Benefit renal outcome and improve survival	SLE patients	22
	ILC3s(?)	Lin^- $CD127^+$ $CD117^+$ $CRTH2^-$ ILCs	Human blood	Remains unclear	SLE patients	22,106
	NK cells(↓)	$CD56^{bright}$NK cell	Human blood	Local autoimmune injury	SLE patients	106
	NK cells(↑)	$CD56^{bright}$ CD16- NK cells and $CD56^{dim}$ $CD16^+$ NK cells	Human kidney	Cytotoxic activity	Lupus nephritis patients	107

Table 2. Emerging targets of ILCs in disease therapy

ILC subsets	Transcription factor	Effector cytokines	Therapeutic targets	Treatment efficacy	Reference
ILC1s	T-bet	IFN-γ	–	–	–
ILC2s	RORα, GATA3	IL-4,IL-5, IL-13	RORα/γ inverse agonist (SR1001)	Reversing impaired keratinocyte differentiation and epidermal barrier disruption	107
			Anti-IL-5 antibody	Reducing thickened epidermis changes and eosinophils infiltrates	159
ILC3s	RORγt, AHR, T-bet	IL-17, IL-22	RORγt inhibitor	Suppressing the IL-17 production	155
			IL-22 neutralizing antibody and neutrophil infiltration	Improving keratinocyte dysregulation	154
			Anti-TNF antibody	Elevated circulating NCR+ILC3s are decreased	118

recipient mice.[153] As suggested by studies of ILC activity in human psoriasis, ILC3 alterations and production of downstream cytokines production, such as IL-22, TNF-α and IL-17, are important in disease conditions. Using an IMQ-induced psoriasis mouse model, an IL-22 neutralizing antibody was shown to have the capacity to improve keratinocyte dysregulation and neutrophil infiltration in skin inflammation.[154] The elevated level of circulating NCR^+ ILC3s decreased following treatment with an anti-TNF antibody, suggesting a potential role of these cells as a therapeutic target or biomarker in psoriasis.[118] Recently, a novel RORγt inhibitor significantly blocked the development of psoriatic skin inflammation in mice by suppressing all subsets of IL-17-producing cells, including Th17 cells, dermal γδ T cells and ILC3s, and followed with dose-dependently decreasing of IL-17 production,[155] suggesting its promise in therapeutic interventions for psoriasis. Actually, clinical trials of several anti-IL-17 antibodies in psoriasis patients are ongoing. Furthermore, drugs like Secukinumab,[156] Ixekizumab,[157] and Brodalumab[158] that target IL-17A or IL-17F provide new biologic therapies with high effectiveness for psoriasis patients.

Nevertheless, some efforts have focused on ILC-relevant therapy in AD. After injecting ILC2s into the dermis, AD-like inflammatory responses and histological changes similar to dermatitis in AD patients can be seen in mice.[126] Moreover, models with ILC-related gene mutations, such as RORα-deficient bone marrow chimaera mice,[126] which have a deficiency of one type of ILC, also broaden the scope of new potential animal models that can be used to explore the complex immune network. A synthetic RORα/γ inverse agonist (SR1001) treatment suppressed MC903-induced TSLP expression and reversed impaired keratinocyte differentiation and epidermal barrier disruption, thus alleviating skin inflammatory responses in the MC903-induced AD mouse model and acting as a potential therapeutic compound in AD patients.[159] Moreover, IL-5 and IL-13 are type 2 cytokines that are markedly elevated in lesions, regional lymph nodes and peripheral blood, corresponding with an increase in ILC2s. Anti-IL-5 antibody, as a neutralizing monoclonal antibody used to treat a spontaneous itchy dermatitis mouse model, reduces epidermis thickening and reduces eosinophil infiltrates in inflamed skin.[160] However, a clinical trial in patients with AD did not show a promising improvement after the use of an anti-human IL-5 antibody (mepolizumab).[161] Perhaps the low dose of mepolizumab administered was responsible for the limited decreases in eosinophil levels. However, evidence has shown that mepolizumab is an available strategy and a well-tolerated targeted therapy that can reduce asthma exacerbations and blood eosinophil counts and benefit quality of life; the lowest dose of mepolizumab (75 mg) has been identified to be close to the plateau of the dose-response curve.[162,163] However, previous studies have revived interest in the biological targeting of IL-5 and other potential molecules.

CONCLUDING REMARKS

In summary, emerging evidence suggests that ILCs play an important, nonredundant role in the abnormal immune response and epithelial dysfunction seen in conditions of autoimmunity and chronic inflammatory disorders (Table 1). The study of ILCs has been rapidly increasing recently, but is still in its infancy, and most available evidence has been obtained from murine models or from small numbers of human patients. Abundant studies have revealed the key role of ILCs in lung and intestine inflammation, while the locations and functional potential of ILCs in the skin remain poorly understood. The identification of different ILC subsets that reside at the skin barrier indicates that productive immune responses against invading microbes and regulatory functions are initiated in the dermis. Currently, ILC populations are known to be altered in many autoimmune-related and

inflammatory skin diseases, and dysregulation of ILCs can result in complex immune responses via cytokine secretion and cell interactions.

Alterations in the ILC population and different subset percentages have been reported in both peripheral blood and skin in SLE patients.[22,104,106] However, studies have been limited to identifying whether ILCs play a predominate role in disease pathogenesis or the specific factors that lead ILCs to become imbalanced. NK cells, ILC1s and ILC2s may be potential regulatory factors in lupus, but more powerful evidence is required. Notably, ILC function seems more relevant in inflamed skin. In psoriasis patients, NCR^{+} ILC3s are elevated and associated with disease severity.[17] Evidence shows that ILC3s may be regulated by CXCR4-stromal cell-derived factor-1[164] under inflammatory conditions and act before IL-23 and IL-17A changes, indicating emerging roles for ILC3s in the initial stage of psoriasis.[122] Although ILC3s are the predominant ILC type in psoriasis, ILC2s play a predominant role in the pathogenesis of AD. IL-25,[131] IL-33,[131,160] and TSLP[126] are all involved in the modulation of ILC2s in an adaptive immune response-independent manner.[126,128] Moreover, abundant evidence has revealed that in other pathological conditions in human skin, ILCs also play an provital role in orchestrating the immune response. Taken together, the findings so far suggest that ILCs can serve as promising therapeutic targets in autoimmunity and inflammatory skin diseases by modulating transcription factors and effector cytokines (Table 2). Deciphering ILC biology and function in epithelial immune barriers will be important in the future, and additional studies are required to explore specific ILC-directed treatment strategies.

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AUTHOR CONTRIBUTIONS

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ADDITIONAL INFORMATION

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