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Type 2 Innate Lymphoid Cells in Allergic Airway Inflammation: Mechanisms, Roles, and Therapeutic

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Abstract

Innate lymphoid cells (ILCs) are innate immune cells crucial for immune defense against various threats in humans. They play key roles in tissue homeostasis, organogenesis, infection resistance, allergic inflammation, microbiota control, and mucosal pathology. Specifically, Type 2 ILCs (ILC2s) respond to specific cytokines and are essential for anti-helminth immunity, airway repair, and allergic inflammation.Recent studies suggest that blockage of ILC2 activators, activation of inhibitory pathways of ILC2s, and suppression of ILC2-mediated pathways including type 2 cytokines (IL-5, IL-13, IL-4Ra) may become therapeutic strategies for airway type 2 inflammatory diseases.This review highlights recent insights into information on the pathogenesis of ILC2s in allergic airway inflammation and potential immunotherapy, which could be beneficial in the treatment of airway inflammation, allergy, and asthma.

Keywords: Innate Lymphoid Cells (Ilcs); Type 2 Innate Lymphoid Cells (ILC2); IL-25; IL-33; TSLP; IL-4; IL-5; IL-13; Allergic Rhinitis; Asthma

Introduction

Innate lymphoid cells (ILCs) are a identified group of innate immune cells, According to the amount and variety of cytokines produced by ILCs and their potential importance in immune regulation, ILCs are devided into group 1 ILCs (comprising ILC1s and NK cells), group 2 ILCs (comprising ILC2s) and group 3 ILCs (comprising ILC3s and LTi cells)[1]. Numerous studies in both mice and humans have shown that ILC2s induce airway inflammation through inflammatory signals, including cytokines and other mediators derived from immune or non-immune cells [2-3]. ILC2s promotes features of allergic airway diseases including asthma, allergic rhinitis and chronic rhinosinusitis (CRS) through secretion of the type 2 cytokines IL-4, IL-5 and IL-13 [1-5].

ILC2s lack T cell receptors and lack surface receptors expressed by the major hematopoietic lymphocyte lineages including B, T, natural killer T (NKT), and natural killer (NK) cells, so ILC2s are a non-B, non-T cell population that responded to IL-25, IL-33, thymic stromal lymphopoietin (TSLP)and provided a crucial innate source of type-2 cytokines. The critical and diverse roles of ILCs subsets appear increasingly apparent in controlling intestinal immunity and inflammation.

Recent years, ILC2s were a crucial role in type 2 inflammation, being highly elevated in allergic rhinitis, chronic rhinosinusitis with nasal polyps, and asthma [5]. However, information on the pathogenesis of ILC2s in allergic airway inflammation and potential immunotherapy is limited, this review highlight our current understanding of the functional role of ILC2s in allergic airway inflammation, especially in allergic rhinitis.

Innate Lymphoid Cells（Ilcs）

Innate lymphoid cells (ILCs) have been identified group of non-T, non-B effector cells that have conserved powerful effector cell functions [1]. Positioned at the forefront of the immune system, ILCs are pivotal in mounting defense against allergens, antigens, pathogens, and microorganisms in humans. These cells are strategically distributed throughout the mucosal surfaces of mucosa-associated lymphoid tissue, encompassing the oral cavity, gastrointestinal tract, lungs, and other tissues constantly exposed to external stimuli [3]. Functionally, ILCs play critical roles in orchestrating immune responses, maintaining tissue homeostasis, facilitating tissue remodeling, and regulating inflammation [6,7]. Notably, ILCs lack specific antigen recognition receptors and are lineage marker-negative (LIN-), relying on recombination-activating genes for their development. Consequently, ILCs exhibit antigen nonspecificity but exhibit rapid and versatile responsiveness to a diverse array of innate signals, primarily mediated through various cell surface receptors including pattern recognition receptors (PRRs) and pathogen-associated molecular patterns (PAMPs). Upon activation, ILCs recognize molecular patterns on pathogen surfaces, swiftly generating effector molecules and eliciting immune responses through distinct signal transduction pathways without undergoing clonal expansion. The emerging paradigm underscores the significant contribution of ILCs as sources of cytokines, complementing the traditional understanding of adaptive lymphoid cells in immune regulation.While the exact defining features and characteristics of innate lymphoid cells (ILCs) remain incompletely elucidated, a preliminary classification system has been established [8]. This classification is based on the diverse array of cytokines produced by ILCs and their significant role in immune regulation.

ILCs are categorized into three main groups: group 1 ILCs, which encompass ILC1s and natural killer (NK) cells; group 2 ILCs, consisting of ILC2s; and group 3 ILCs, comprising ILC3s and lymphoid tissue inducer (LTi) cells [9]. Notably, this classification scheme mirrors the differentiation of CD4 adaptive T cell subsets, specifically Th1, Th2, h17, and Th22 cells, all arising from a common precursor cell. Th1 cells are characterized by the production of interferon-γ (IFN-γ), interleukin-2 (IL-2), and lymphotoxin-α (LTα), driving type-1 immune responses that combat intracellular pathogens. In contrast, Th2 cells typically secrete IL-4, IL-5, IL-9, and IL-13, contributing to type-2 immune responses essential for combating extracellular parasite infections but also implicated in the immunopathology observed in patients with allergies and asthma [6, 7]. These ILC groups can

be likened to the previously described CD4+ T helper cell subsets TH1, TH2, and TH17. However, while ILCs exhibit functions similar to adaptive CD4+ T cells, they are distinct in their response to innate signals without the need for antigen-specificity, and they possess unique phenotypic and functional characteristics [8].While the lineage relationships among ILC subtypes remain somewhat ambiguous, recent advancements have led to the identification of key transcription factors crucial for the development of each specific ILC subtype [9-10].

While known for their crucial role in protective immunity against helminth parasites in the intestinal and respiratory tracts, as well as in promoting lung epithelial repair during influenza infections, ILC2s have also been implicated in driving pathological allergic inflammation at various barrier surfaces [11]. Significantly, these cells have been associated with the development of several allergic diseases in humans, including asthma, allergic rhinitis, and atopic dermatitis (AD)[12].

Initially believed to belong to the ILC2-like cell population, multipotent progenitor type 2 (MPPtype2) cells have emerged as distinct entities critical for supporting type 2 cytokine-mediated immune responses to helminth infections. Unlike ILC2s, MPPtype2 cells are primarily induced by IL-25 rather than IL-33, showcasing a progenitor phenotype capable of differentiating into various granulocyte populations. Moreover, MPPtype2 cells exhibit unique developmental requirements, possess a distinct genome-wide transcriptional profile compared to ILC2s, and undergo extramedullary hematopoiesis [13-15], the function of ILCs is similar to Th2 cells in the immune system. In 2001, ILCs2 were first reported by Hort et , the researchers discovered a non-B, non-T cell population that responded to IL-25 and provided a crucial innate source of type-2 cytokines (IL-4, IL-5, IL-13) was identified in Rag2-/ - mice lung [16], and subsequently ILC2s were found that they play a key role in the antiparasite immunity through secreting IL-13 [17]. Now variously termed by different laboratories nuocytes [18], natural helper cells (NHCs) [19], innate helper (Ih2) cells [20], multipotent progenitortype 2 cells (MPPtype2) [21] and type 2 innate lymphoid cells (ILC2s) [22-24]. Currently they are unifiedly named ILC2s. ILC2s mainly produce IL-5, IL-9 and IL-13, also produce a small amount of IL-4, IL-6 and IL-10 cytokines. ILC2s do not express conventional lineage markers of T lymphocytes, B lymphocytes and other granulocyte - monocyte cell (CD3, TCRαβ, CD19, CD11c, CD16, CD56, FcεRIα), but express the chemoattractant receptor homologous molecule express on Th2 cells receptors (CRTH2) and CD161, and also express receptors of damage-associated molecular patterns (DAMPs) , such as IL-25 (IL17BR) and IL -33 (T1/ST2) [22-24]. ILC2s distribute variously in different species, tissues or organs, and mainly in the lungs, mesenteric lymph nodes, peripheral blood and nasal tissues of human and mouse [22-24]. ILC2s do not require RORγt for their development but instead require the transcription factor retinoic acid receptor–related orphan receptor (ROR)α [25,26] and the GATA transcription factor Gata3 [27]. ILC2s could mediate eosinophilia and goblet cell hyperplasia, both of which are critical for antihelminth responses and for allergic diseases.

Mechanisms of Action of ILC2s in Allergic Airway Inflammation

Asthma and ILC2s

Asthma is a complex lower airway inflammatory condition characterized by its heterogeneity, often classified into two main phenotypes: type 2 high (eosinophilic) asthma and type 2 low (neutrophilic) asthma. Numerous studies have consistently demonstrated elevated levels of innate lymphoid cells type 2 (ILC2s) in the peripheral blood and sputum of individuals suffering from asthma, particularly in those with severe eosinophilic asthma of the type 2 high variety. This increase in ILC2s in asthma patients suggests a potential role for these cells in the pathogenesis of the disease, particularly in the context of eosinophilic inflammation. Further research is warranted to elucidate the precise contribution of ILC2s in asthma subtypes and to explore their therapeutic potential as a target for intervention in asthma management [22, 27-29].

Activated ILC2 produces a significant amount of type 2 cytokines (IL-4, IL-5, IL-9, and IL-13), altogether contributing to type 2 inflammation in the airways. ILC2s are mediators of type 2 immunity for many type 2 inflammatory diseases such as asthma, since ILC2s were reported to play an important role in asthma pathogenesis [12]. In humans, Lin– CD127+ CRTH2+ and Lin–

CD127+ CD25+ CD90+ IL-33R+ lung ILC2s were initially identified in healthy fetal and adult lung tissue using flow cytometry [27]. Subsequently, these cells were visualized through immunofluorescence as Lin− c-Kit+ CD161+ cells [28]. While ILC2s have not yet been shown to be enriched in disease states, increased expression of IL-25, IL-33, and TSLP has been observed in the lung tissue of individuals with asthma [30-32]. Moreover, human peripheral blood ILC2s have been found to respond to the asthma-associated prostaglandin D2 (PGD2) by producing IL-13, with this response being inhibited by lipoxin A4 (LX-A4)[33-34] .

Recent studies have demonstrated that in murine models, the pathogenic responses of lung ILC2s initiated by LTD4 were effectively suppressed by montelukast treatment, suggesting that ILC2s could serve as a viable therapeutic target for asthma patients [35-37]. However, further investigations involving human subjects are warranted to elucidate the potential pathogenic role of ILC2s in human asthma and to explore the feasibility of targeting these cells for therapeutic interventions

Moreover, it is widely recognized that lipid mediators such as LTC4, LTD4, and PGD2 play a significant role in the pathogenesis of asthma. Leukotriene receptor antagonists are commonly utilized in the management of asthma to target these specific mediators. The findings indicating the marked elevation and activation of ILC2s in individuals with asthma imply that epithelial-derived cytokines and lipid mediators may indeed serve as crucial factors in driving ILC2-mediated type 2 inflammation in this patient population [38-40].

Allergic Rhinitis and ILC2s

Currently, the pathogenesis of allergic rhinitis has not been completely clear. The traditional view consider that allergic rhinitis is mainly as an immunologic disease mediated by TH2 cells and adaptive immunity including sneezing, itchiness, difficulty breathing, and discharge [41,42]. When the nasal mucosa is exposure to allergen, allergen is captured and processed by antigen-presenting cells (APC) in the mucosa, antigen peptide is presented to naive T lymphocytes which differentiate into Th2 cells, large amounts of IL-4, IL-5, IL-13 and other Th2 -type cytokines are secreted. Interleukin-4 (IL-4) as an inducer of Th2 differentiation can promote B-cell producing immunoglobulin E (IgE), Interleukin-5 (IL-5) mainly act as an eosinophil growth and differentiation factor , it can also enhance the activities of basophils by priming them to release mediators such as histamine and leukotrienes in response to allergen, IL-13 can directly cause upper- airway hyperreactivity. Therefore, the classical view think that the downstream biological effects of Th1/Th2 imbalance is the main causes of allergic rhinitis. Recently, more and more studies indicate that the newly identified type 2 innate immune cells (ILC2s) involved in allergic inflammation through the secretion of Th2 cytokines, particularly IL-5 and IL-13, so ILC2s may be the main source of Th2-type cytokines in the AR patient [43,44]. The first work to vertify the relationship between ILC2s and AR indicate that nasal cat allergen challenge in cat-sensitized AR patients led to significantly increased percentage of ILC2s in peripheral blood compared to control challenge [45]. After that, Lao-Araya Ma et al consistently report found that ILC2s were increased in grass pollen-sensitized AR patients during the pollen season compared with the control group, and the ILC2 levels were reduced after subcutaneous immunotherapy [46]. Fan D et al found the percentage of ILC2s was significantly elevated in patients of monosensitized to house dust mite compared to mugwort-AR patients and healthy controls, AR patients sensitized to HDM or mugwort allergen have distinct phenotypic and functional profiles in ILC2s frequencies [47].Therefore, in this article, we chiefly review the close relationships between Type 2 innate lymphoid cells and allergic airway inflammation, and summarize its pathological roles in allergic airway inflammation. Taken together, these aboving findings demonstrate that ILC2s may participate in the process of AR. So more studies are needed to discover the whole role of ILC2s in nasal disorder.

Other Allergic Inflammation and ILC2s

ILC2s are characterized by the secretion of type-2 cytokines, notably IL-5, IL-13 and IL-6. In response to cytokines IL-25, IL-33, thymic stromal lympho-poietin, and leukotriene D4, ILC2s as an non-B, non-T cell population which provides an early

source of type-2 cytokines during helminthic infection, ILC2s may be involved in allergic inflammation, In addition, ILCs2 also interact with other immune cells through their cell surface markers.

Recently, more evidence suggests that the initial phase of type-2 immune response occurs independently of adaptive immunity, since IL-33 or IL-25 can initiate type-2 cytokines production in Rag2-/-mice, accompanied by eosinophilic inflammation and AHR(48,49). So ILC2s show its important role in the pathophysiology of asthma and allergic inflammation [50,51].

In mouse asthma model created by OVA or house dust mite, many scholars found that ILC2s are the main source of IL-5 and IL-13, even in T cell-deficient mice, ILC2s still have the same function of secreting type-2 cytokines and are the primary participants in allergic airway inflammation mainly [52,53]. Salimi et al show that human ILC2s express skin homing receptors and infiltrate the skin after allergen challenge, where they produce the type 2 cytokines IL-5 and IL-13. Skin-derived ILC2s express the IL-33 receptor ST2, which is up-regulated during activation, and are enriched in lesional skin biopsies from atopic patients [54]. In 2011, Mjösberg et al found a new subgroup of ILCs2 (named ILC2s) in chronic rhinosinusitis with nasal polyps (CRSwNP), a typical type 2 inflammatory disease. There was enrichment for CRTH2+ ILCs in nasal polyps and peripheral blood of chronic rhinosinusitis, the CRTH2+ ILCs secrete IL-5 and IL-13 under the action of epithelial cells-derived DAMPs [55-59]. Recently, Nussbaum et al show that serum IL-5 levels are maintained by long-lived type 2 innate lymphoid cells (ILC2) resident in peripheral tissues. ILC2 cells secrete IL-5 constitutively and are induced to co-express IL-13 during type 2 inflammation, resulting in localized eotaxin production and eosinophil accumulation [44]. The above research proved that ILC2s contribute to human allergic diseases.

Epithelial cytokines IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) are Th2 type cytokines , also known as DAMPs, they play an important role in allergic inflammation, this view has been confirmed by numerous studies [31-33]. Hammad et al firstly discovered house dust mite could promote the secretion of IL-25, IL-33, TSLP and induce asthma by acting on Toll-like receptor 4 located in lung epithelial cell surface [34]. ILC2s cell surface express the receptors of IL-25 IL-33, by acting on the IL-25R , IL-33R , ILC2s participate in the pathological process of asthma [35,36]. In animal models of atopic dermatitis , the epithelial cell-derived IL-25, IL-33 and TSLP promote ILC2s to secrete Th2 cytokines and involve in allergic skin inflammation [37]. Mjösberg et al found that ILC2s stimulated by IL-25 , IL-33 in vitro could secrete IL-13. After that, this study group also found that nasal polyp epithelial cells express TSLP and IL-33 which promote ILC2s secrete Th2 cytokines by intracellular GATA3 pathway. Other studies have shown that the expression of IL-25, IL-33 and TSLP in nasal epithelial cells of allergic rhinitis increased [38], but the fact that DAMPs induced allergic rhinitis whether by mechanism of acting on ILCs2 or not is still not clear, further study are needed.

ILC2s can interact with other immune cells through markers expressed on the cell surface. Studies have shown that NHC can induce B1-B cells self-renewal and promotes B cells in spleen synthese IgA. ILC2s identify the corresponding ligands expressing on B cells through costimulatory molecules expressed on ILC2s cells surface, but the specific mechanism of ILC2s regulating B cell remains unclear [39]. Mirchandani et al found that ILC2s cell surface express MHC Ⅱ molecules, ILC2s can present antigen and promote naive CD4+ T lymphocytes differentiate to Th2 cells [40]. The activated Th2-cells produce IL-5, IL-6 and IL-13 cytokines which may facilitate ILCs secreting Th2 cytokines, thus promote the development of allergic inflammation.

Conclusion

Since the discovery of ILC2s in 2010, we have a paradigm shift in the understanding of allergic airway disease pathogenesis, ILC2s may contribute significantly to the primary source of type 2 cytokines . Emerging evidence indicates a significant accumulation of ILC2s and their activators in human airway type 2 inflammatory diseases, such as allergic rhinitis, chronic rhinosinusitis with nasal polyps, and asthma. These findings underscore the pivotal role of ILC2s in driving the production of type 2 cy-

tokines, notably IL-5 and IL-13, within these disease contexts. While current therapeutic approaches primarily rely on glucocorticoid treatment due to the absence of specific ILC2-targeting therapies, recent progress has shed light on the mechanisms governing the activation and inhibition of ILC2s. The elucidation of these pathways in the past decade offers promising prospects for the development of novel therapeutic strategies targeting ILC2-mediated type 2 inflammation. Future research endeavors may focus on disrupting ILC2 activators and promoting inhibitory pathways to mitigate the impact of these diseases.These findings will help us explore ILC2-specific therapies that target specific mediators upstream of ILC2s and improve the life quality of allergic airway patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors have appropriate approval upon submission of the manuscript. Rong Sun contributed to conceptualization, data management, formal analysis, funding acquisition, Tingting Wu contributed to methodology, Writing: original draft;Yang Yang and Xinye Tang contributed the writing: editing and review.

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