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REVIEW

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How the Innate Lymphoid Cells Improved Our Understanding of the Mechanisms of Allergic Diseases and Influenced the Standpoint?

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ABSTRACT

Innate lymphoid cells (ILCs) are immune effector cells involved in host defence against pathogens and have changed our perception of allergic dysregulation. Unlike T and B lymphocytes, the receptors of ILCs do not undergo somatic recombination during their development and do not have an antigen specific receptor. ILCs are similar to T cells in both their transcription and cytokine expression profiles and are classified into 3 subsets. They are thus considered to be the functional counterpart of T cells in innate immunity, and they are mainly localized in mucosal tissues rather than secondary lymphoid organs such as lymph nodes and spleen. It is known that ILCs play a role in the induction and regulation of inflammation through the various effector cytokines they secrete, and also in the pathogenesis of allergic diseases by accumulating in areas of allergic inflammation. In this review, the role of ILCs in allergic diseases and the effect of an allergic microenvironment on ILC plasticity will be discussed.

Keywords: Innate lymphoid cells, ILCs, allergic diseases, ILC1, ILC2, ILC3

INTRODUCTION

The prevalence of common allergic conditions such as asthma, allergic rhinitis, atopic dermatitis, and food allergies has significantly increased in recent decades reaching up to 20% of the global population. These diseases can have fatal consequences or a serious impact on the quality of life of patients, direct and indirect costs of health economics (1). Until recently, allergic diseases were considered as manifestations of a purely adaptive immune response. We are still accepting that T helper (Th) 2-type and allergen-specific IgE responses play a primary role in allergic diseases.

In atopic individuals, a Th2-type response occurs towards allergen peptides recognized by $CD4^+$ T cells, and subsequently cytokines such as interleukin (IL)-4, IL-5, IL-9, and IL-13 are released. Allergens bind allergen-specific immunoglobulin (Ig)E via FcεRI that is expressed on the surface of eosinophil, basophil, and mast cells, which play a role in allergic inflammation. In the second encounter with the same allergen, mediators such as histamine, tryptase, and proteoglycans are rapidly released from these cells, resulting in allergic inflammation (2). These events are accompanied by impaired immune tolerance in allergic responses. Regulatory T (Treg) cells play a part in ensuring immune tolerance with the cytokines they secrete such as IL-10, IL-35, and transforming growth factor-β (TGF-β), as well as surface molecules such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (3).

Recently, various independent research groups have defined a new lymphocyte subgroup different from T and B lymphocytes. These newly discovered cells of the innate immune system are named innate lymphoid cells-ILCs (4). ILCs are effector cells of mucosal tissues, and play an active role in the response to pathogens and tissue home-

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ostasis, as well as in the pathogenesis of various allergic diseases. Although studies focusing on the role of ILCs in allergic diseases have revealed the relationship between allergic diseases and ILC2s (Figure 1), which are especially involved in the type 2 response, current studies also show the role of other ILC subgroups in allergic inflammation (4).

In this review, we will provide a general overview of the characteristics of ILCs, including their subgroups and functions, as well as the cytokines and transcription factors involved in their differentiation. The role of ILCs in various allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, and food allergies will be discussed based on the latest literature. Furthermore, we will evaluate the effects of allergen immunotherapy on ILCs.

INNATE LYMPHOID CELLS

Data on ILCs are mostly derived from human and mouse studies. Unlike T and B lymphocytes, the receptors of ILCs do not undergo somatic recombination during their development. They are germline coded cells with no antigen specific receptor (4). They display important effector and regulatory functions in the innate immune response, inflammation, and tissue regeneration. While lymphoid-derived natural killer (NK) cells of the innate immune system are predominantly involved in the cytotoxic response, ILCs are involved in cytokine release and stimulation of other cells (5).

ILCs do not express most of lineage markers such as CD3, CD4, CD19, CD14, and T cell receptor (TCR)-αβ and TCR-γδ, but do express CD45, IL-7Ra (CD127), and CD161 (6). They are divided into 3 groups according to cytokine secretion and transcription factors. Group 1 ILCs (ILC1) produce interferon-gamma (IFN-γ) and their development is dependent on the transcription factor T-bet. Group 2 ILCs (ILC2) produce IL-5 and IL-13 and require transcription factor GATA-binding 3 (GATA3). Group 3 ILCs (ILC3) produce IL-17 and IL-22 and their growth is dependent on the retinoid-related orphan receptor γt (RORγt). Recently, lymphoid tissue inducer (LTi) cells and NK cells have also been categorized as ILCs. NK cells placed within group 1 ILCs are also called cytotoxic ILCs (Figure 2) (7).

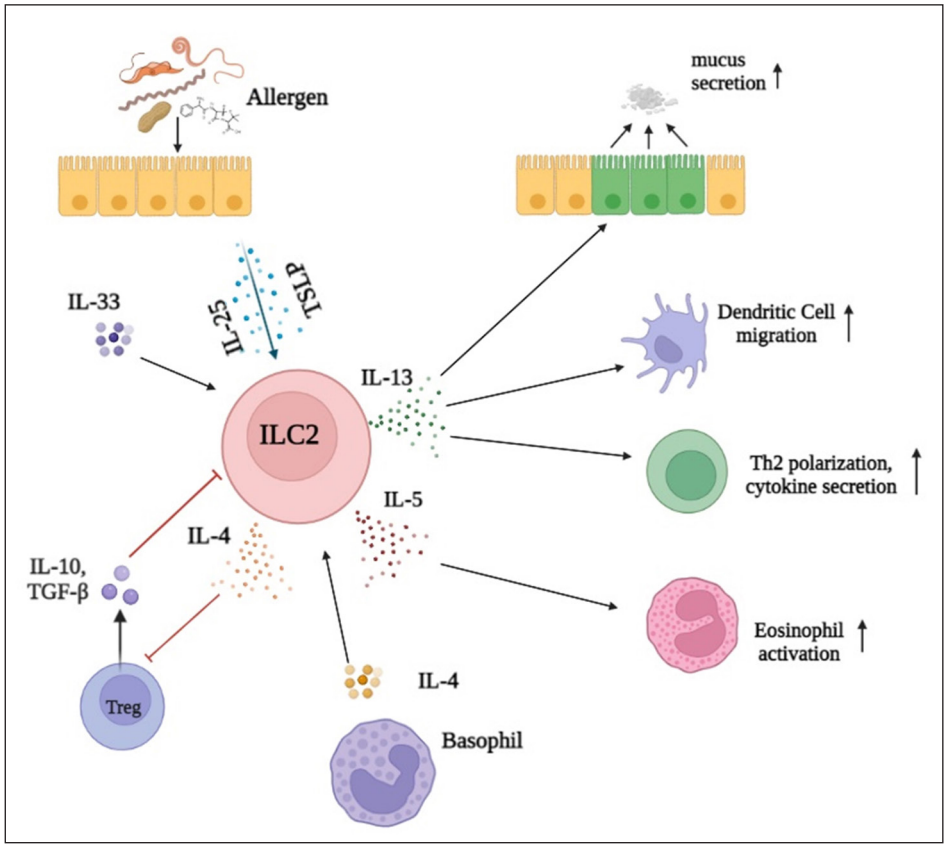

Figure 1. Activated ILC2 responses in allergic diseases. TSLP, IL-33, and IL-25 are induced by epithelial damage after exposure to allergens. IL-13 induces mucus production, dendritic cell migration and Th2 type cytokine secretion, and IL-5 promotes eosinophil activation. Secretion of IL-4 by basophils activates the ILC2 subset. Treg cells secrete IL-10 and TGF-β which suppresses ILC2 activation. Similarly, IL-4 secreted by ILC2 inhibits the Treg cell function.

TSLP: *Thymic stromal lymphopoietin,* ***IL:*** *Interleukin;* ***TGF:*** *Transforming growth factor.*

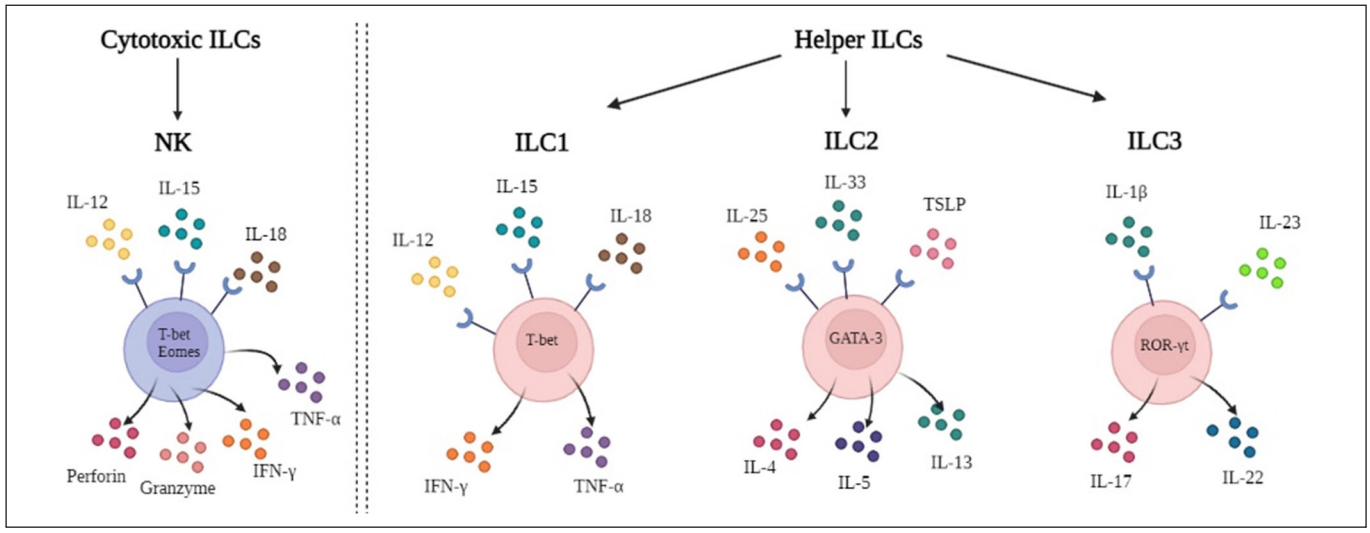

Figure 2. The human ILC subsets (cytotoxic and helper ILCs). The classification of human innate lymphoid cells into group 1-3. ILC is based on their cytokine production profiles.

NK: *Natural killer cells;* ***ILC:*** *Innate lymphoid cells;* ***IFN:*** *Interferon;* ***TNF:*** *Tumor necrosis factor;* ***TSLP:*** *Thymic stromal lymphopoietin,* ***IL:*** *Interleukin.*

When reviewed both in terms of transcription factors and secreted cytokines, ILC1, ILC2, and ILC3 cells are similar to the $CD4^+$ Th cell subgroup, which are the cells of the adaptive immune response (Th1, Th2, and Th17, respectively) and are also called helper ILCs (8). NK cells are functionally like $CD8^+$ T cells. In terms of these resemblances, NK and ILCs are functionally considered as the innate immune system counterparts of $CD8^+$ and $CD4^+$ T cells, respectively. Although this qualification is based on basic similarities, differences are found between chemokine receptor and cytokine genes when the transcriptome profiles of human ILC subgroups and $CD4^+$ T cell subsets are analysed (9).

ILCs form a heterogeneous population that exhibits diversity and can be classified into different subsets. However, the boundaries and definitions between these subsets are still unclear. This can pose challenges in the identification and classification of ILCs. Additionally, ILCs can exhibit phenotypic and functional variability depending on the tissue microenvironment (10,11). This can further complicate the study of ILCSs.

Using specific markers to accurately identify distinct subsets of ILCS is crucial. However, some markers may also be present in other cell types (12,13). This makes it difficult to clearly separate specific subsets of ILCs during research. There are technical limitations in the analysis and characterization of ILCs. Factors such as the rarity of these cells, low expression of specific markers, or suboptimal methods for isolating certain subsets contribute to these limitations.

Group 1 ILCs

Group 1 ILCs include both cytotoxic NK cells and non-cytotoxic ILC1. NK cells, one of the important elements of innate immunity, reacts to tumour cells, viruses, and bacterial agents with cytokine release and cytotoxic activity, and play a role in the regulation of the adaptive immune response (14). In a study examining the gene expression profiles of ILC subgroups in the mouse intestine, spleen, and liver tissues, it was shown that the cytotoxic properties of tissue-resident NK cells were reduced, and their cytokine expression profiles were more similar to the ILC1 subset (15). The significance of NK cells are often ignored since the main focus is generally the helper ILC subsets.

ILC1 cells differ from other subsets of ILCs by showing the immune phenotype of $Lineage^-CD45^+CD127^+CD161^+$ as well as not expressing prostaglandin (PDG2) receptor (CRTH2) and c-kit (CD117) (16). T-bet transcription factor expression occurs in ILC1 and is activated by inflammatory cytokines such as IL-12, IL-15, and IL-18 (17). ILC1s secrete high amounts of IFN-γ and tumor necrosis factor (TNF)-α (14). However, they can also express low amounts of perforin and granzyme (18).

Table I: The cytokines and subgroups of ILCs in allergic diseases.

Disease	ILCs Subgroup	Affected Molecules/Cells	Developmental Novel Drugs	Associated Gene Loci	References
Asthma	ILC2	↑ IL-4 IL-5 IL-13 IL-33 TSLP PGD2	CRTH2 antagonists (Setipiprant, AZD1981, QAW039)	*IL-33* *IL-1RL1 (ST2)*	(80-90)
	ILC3	↑ IL-17 Neutrophil M1 macrophage			
Allergic Rhinitis	ILC2	↑ IL-5 IL-13 IL-25 IL-33 TSLP ↓ IL-35 HDL		*IL-4* *IL-6* *IL-13* *IL-27* *IL-33* *TLR-2* *TLR-4*	(100-108)
Atopic Dermatitis	ILC2	↑ IL-25 IL-33 TSLP	Dupilumab, anti-IL-5 antibody treatment in mice	*IL-2* *IL-5* *IL-5R* *IL-23R*	(111-121)
	ILC3	↑ IL-17 IL-22 Neutrophil			
Food Allergy	ILC2	↑ IL-4 IL-5 IL-9 IL-13 IL-25 IL-33 TSLP		*IL-4* *IL-33*	(54, 124-127)

ILC1s are mostly localized in tissues such as the liver and skin and in tissue-related mucous membranes of the intestinal system (8). They play a critical role in the initial response and tissue inflammation against infections caused by intracellular pathogens such as viruses and bacteria. The role of ILC1 has been demonstrated in the pathogenesis of many diseases such as inflammatory bowel disease (IBD), Crohn's disease, infectious colitis, and diabetes (19-22).

Group 2 ILCs

ILC2 differ from other subsets of ILCs by expressing the immune phenotype of Lineage$^-$CD45$^+$CD127$^+$CD161$^+$ as well as expressing CRTH2 and c-kit (5,16). ILC2, which expresses the main transcription factor GATA-3, is activated by various soluble factors such as IL-25, IL-33, thymic stromal lymphopoietin (TSLP), lipid mediators, and neurotransmitters. With this activation, ILC2s secrete cytokines such as IL-4, IL-5, IL-6, IL-9 and IL-13 (23). It has been shown that ILC2s stimulated with IL-2 and IL-7 increase their proliferation and cytokine content when IL-33 or IL-25 is added to the medium (24).

Although ILC2 was first detected in various tissues in mice, it was later revealed that they also are tissue-resident cells in many tissues such as the intestinal system, adipose tissue, heart, liver, salivary glands, etc. in humans. It has been suggested that ILC2s have different phenotypic and functional properties according to their localization in tissues (11). In mice, the subgroup called natural (n) ILC2 is mostly located in lung and adipose tissue and is mainly activated by IL-33 (5). On the other hand, the group called inflammatory ILC2 is mainly activated by IL-25 and plays a role in inflammation (5,11). Despite their functional similarities, the localizations of ILC2s in mice and humans

differ. While ILC2s constitute the majority of ILCs in the mouse intestinal tract, the ILC2 percentage in the adult human intestinal tract is quite low (11). In addition, in a study in rats, ILC2s were dominant in the rat intestinal lamina propria, unlike humans (25).

Recent studies have shown that human ILC2s are divided into 2 subgroups according to c-kit expression (26). While the ILC2 subgroup with low c-kit expression expressed more Th2-like cytokines, it was shown that the subgroup with high c-kit expression expressed the ILC3 markers and CCR6 chemokine receptor in response to IL-1β and IL-23 stimulation and was able to produce IL-17A. It is also reported that the ILC2 subgroup with high c-kit expression expresses more IFN-γ (26). TGF-β increases the expression of genes such as c-kit, CCR6, and IL-23R in ILCs, and it has been shown to be involved in the differentiation of these cells into ILC3-like cells expressing ROR-γt (26).

ILC2s are involved in the response to helminth infections, tissue repair, allergic diseases, and in the formation of inflammation in the lungs and airways after viral and allergen exposure. ILC2 deposition has been demonstrated in nasal polyps of patients with chronic rhinosinusitis, as well as in the bronchoalveolar lavage fluids of asthma patients (27). Eosinophils in visceral adipose tissue contribute to the maintenance of M2-type macrophages and insulin sensitivity. Adipose tissue ILC2s have also been shown to play a role in metabolic homeostasis by controlling the development of M2-type macrophages and by providing eosinophil accumulation and activation in visceral adipose tissue. In addition, it has been reported that saturated fatty acids suppress M2-type macrophages and differentiate macrophages towards M1. ILC2s also play a role in the prevention of obesity and chronic inflammation by regulating saturated fatty acid absorption (28).

Group 3 ILCs

Group 3 ILCs have the phenotype of Lineage$^-$ CD45$^+$CD127$^+$CD161$^+$ and do not express CRTH2. C-kit expression differentiates them from other subgroups of ILCs (5, 16). Group 3 ILC3, the main transcription factor of which is ROR-γt, consists of two subgroups, LTi cells and ILC3s, which are involved in the organogenesis of secondary lymphoid tissues in the foetal period. ILC3s are activated by IL-1β and IL-23. They secrete Th17-related cytokines such as IL-17A, IL-17F and IL-22 and granulocyte macrophage colony stimulating factor (GM-CSF) (5,29). Human ILC3s are divided into two subgroups according to their NK cell receptor (NCR) expression: NCR$^+$ ILC3 that secretes IL-22 and the NCR$^-$ ILC3 subset that secretes IL-17A and IL-17F. In general, it is possible to define these subgroups according to the expression of NKp44 in human ILC3 and NKp46 in the mouse ILC3 subset (14).

Recent studies have identified a new subset of CD40L-expressing ILC3. It has been reported that B cell-activating factor (BAFF) secreted from ILC3s triggers IL-15 expression in B cells, and IL-15 stimulates CD40L expression in circulating and tonsillar ILC3s (30). CD40L$^+$ ILC3s have been shown to contribute to B-cell survival, proliferation, and differentiation into IL-10-producing cells (30). Although it is known that ILC3s regulate immune responses mainly by cytokine secretion, studies performed on cells isolated from tumor-infiltrating lymph nodes of breast cancer patients show that the CD56-expressing ILC3 subgroup in the ILC3 subset is cytotoxic and produces IFN-γ (31).

ILC3s are especially located in the intestinal tissue, are involved in intestinal homeostasis, and are also localized in many other tissues such as skin and tonsils (5). It is known that they play a role in the response to extracellular pathogens, repair of skin tissue, and the pathogenesis of autoimmune diseases by promoting neutrophil infiltration through the cytokines they secrete. ILC3s contribute to intestinal homeostasis by interacting with macrophages, especially in the intestinal system. IL-1β, released by both microbial products and macrophages, provides GM-CSF secretion from ILC3s, GM-CSF stimulates the production of retinoic acid and IL-10 from both macrophages and dendritic cells, providing regulator T (Treg) cell proliferation (29). Deactivation of GM-CSF may alter the function of phagocytes, resulting in decreased Treg numbers and impaired oral tolerance (29).

In addition to these protective roles in the intestinal system, ILC3s are also known to play a role in the pathogenesis of various diseases such as inflammatory bowel disease (IBD) and Crohn's disease (29). It has been reported that functional dysregulation of ILC3 subgroups, differentiation of NCR$^+$ ILC3 into an ILC1-like phenotype, and dysfunction of regulatory ILCs are associated with the progression and severity of the inflammatory diseases. NKp44$^+$ ILC3 ratios are decreased in inflammatory tissues of IBD patients, and this situation is associated with disease

severity (32). In our experience, increased total ILCs and ILC3 were found in active Behcet's disease (BD) patients compared to inactive BD patients and healthy subjects. Additionally, high amounts of IL-17 expressing NK and NKp44^{-} ILC3 were found in BD. We speculated that ILCs might be differentiated to ILC3 because of the inflammatory status of BD patients and that IL-17 released by NK cells might have a role in neutrophilic infiltration (33). Additionally, our recent study focused on the immune response in COVID-19 patients, NKp44^{+} ILC3s were higher in patients with mild COVID-19 than in healthy subjects and those with severe COVID-19 (34).

Regulator ILCs as a Novel Subgroup of ILCs

Recent studies have shown that inflammatory responses can also be regulated independently of adaptive immunity (35,36), and ILCs might contribute to regulate the immune response via secreting IL-10 (37,38). Kim et al. have indicated that Lineage^{-}CD45^{+}CD127^{+}Sca-1^{+} cells secrete IL-10 in the oxazolone-induced contact hypersensitivity (CHS) mice and these cells have been described as ILC10. They have shown that ILC10 cells are increased in the ear tissue and the inguinal and axillary lymph nodes of CHS mice (37). However, it has been shown that KLRG1^{+} ILC2 cells secrete IL-10 upon activation with retinoic acid and IL-33, and that these cells can regulate the response of Th and promote epithelial cell integrity. Compared to healthy subjects, IL-10^{+}KLRG1^{+} ILC2s were decreased in patients with grass allergy. The IL-10 secreting capacity of ILC2 in these patients was restored after sublingual immunotherapy with grass-pollen (39). In addition, a subgroup that expresses IL-10 within ILC2s has been identified in lung tissue and it has been shown that these cells play a role in suppressing inflammatory immune responses (40). On the other hand, Wang et al., have identified for the first time a different cell group from other ILC subgroups and Treg cells in human and mouse intestinal tissue (41). These cells, defined as regulatory ILC (ILCreg), are Lineage^{-}CD45^{+}CD127^{+}IL-10^{+} cells (41,42). At the same time, these cells express IL-2Rα (CD25), Sca-1 and CD90 on their surface. They do not express T-bet, GATA-2, RORγt, and FOXP3, which are specific to other ILC and Treg cells (43). It has been speculated that ILCreg are different from other ILC subsets since they originate from the common helper-like innate lymphoid precursor (CHILP)-α4β7^{+}Id2^{high}. It has been reported that ILCreg cells differ from other IL-10 secreting ILC cells like ILC2 by expressing Id3 (38). Also, ILCregs contribute to the termination of intestinal inflammation by suppressing ILC1 and ILC3 subsets through IL-10 secretion. It has been stated that ILCregs might be target cells in the development of new and potential treatments for restoration of immune tolerance in chronic inflammatory and autoimmune diseases (40).

ILCs in Asthma

Asthma is a chronic inflammatory respiratory disease characterized by variable airway obstruction and airway hyperresponsiveness. This is a condition that affects approximately 300 million people, and its prevalence is still increasing. Asthma was previously seen as an allergic type Th2 disease, but the term is widely acknowledged as an umbrella for several asthma phenotypes today, due to the heterogeneous nature and immunological complexity (44). Understanding the immunologic mechanism underlying different asthma phenotypes is even more important today for the selection of an accurate biological agent and for the treatment of the severe forms of this condition. The Th2 endotype includes early onset allergic asthma, late onset eosinophilic asthma, and aspirin-exacerbated respiratory disease, whereas the T2-low endotype involves obesity- or smoking-associated asthma (45). In addition to T lymphocytes, mast cells, eosinophils, and macrophages, the further knowledge of Treg-like cells, NK cells and finally ILCs have helped us to learn more about asthma pathogenesis (44).

Genome-wide association studies (GWASs) show that IL-33 and its receptor IL-1RL1 (ST2) loci are strongly associated with asthma. In support of this, another GWAS has identified a new 5 kb region that binds to the promoter region of IL-33 and regulates its expression. This was found to be associated with the IL-33 protein expression in the human plasma via differential binding (46). During inflammation and tissue homeostasis, IL-33 secreted from epithelial and endothelial cells strongly stimulates ST2 receptor-carrying cells such as ILC2s and mast cells (47). When the innate airway allergic reaction was evaluated after intranasal administration of alternaria extract (Alt-Ext) to BALB/c (wild type /WT), TSLP receptor-deficient (TSLPR$^{-/-}$) and IL-33 receptor-deficient (ST2$^{-/-}$) mice, (TSLPR^{-}/$^{-}$) mice showed a significant decrease in the number of lung ILC2 expressing IL-5 and IL-13 compared to wild type (WT), and it also alleviated eosinophilic inflammation, IL-4, IL-5 and IL-13 levels in lung tissue and the lung inflammation was observed to decrease. In (ST2$^{-/-}$)

mice, Alt-Ext-induced TSLP expression was decreased, while exogenous or endogenous TSLP administration was shown to increase IL-33 release (48). In this study, it was shown that both IL-33 and TSLP activate ILC2s by inducing the expression of each other (48).

Apart from the IL-33/ST2 pathway, the prostaglandin D2 (PGD2)/CRTH2 pathway is also known to cause the accumulation of ILC2 cells in the tissue during inflammation. Recombinant IL-33 administration in WT- and CRTH2-deficient ($Gpr^{-/-}$) mice induced PDG2 expression in both WT and $Gpr^{-/-}$ mice, whereas ILC2 accumulation was decreased in $Gpr^{-/-}$ mice compared to WT mice. CRTH2 was shown to partake in this accumulation (49). In a study conducted in asthma patients, it was reported that PGD2 induced IL-13 release in ILC2s, both alone and synergistically with IL-25 and IL-33 (50). Therefore, it is thought that the IL-33/ST2 pathway and PGD2/CRTH2 pathways affect each other and induce the contribution of ILC2s to inflammation. It has been proposed that recently developed CRTH2 antagonists (Setipiprant, AZD1981, QAW039) may constitute an important treatment option for asthma control and preservation of lung functions in the coming years (51-53).

In current studies, it has been reported that serum IL-33 levels of asthma patients are higher than in healthy individuals (54). Studies in primary human airway epithelial cells (AECs) and mouse models show that the use of IL-33 antagonists protects against the onset and exacerbation of experimental asthma (55). In addition, it has been shown that the glucocorticoid therapy in asthmatic patients might play a role in reducing the frequency of ILC2 subset and the levels of IL-5, IL-9 and IL-13 of ILC2s by acting on the STAT3, STAT5, STAT6, JAK3, and MEK signal pathways (56).

In summary, activated ILC2s secrete IL-5 and IL-13 and trigger the activation of eosinophils, airway hyperresponsiveness, mucus overproduction, and disruption of tight junction formation. In addition, IL-13 mediates dendritic cell migration and Th2 induction. IL-4 released from ILC2s inhibits Treg functions (57).

Recent studies reveal a strong association between obesity and asthma (58). It has been reported that NK cells and ILC3s are involved in obesity-induced airway hyperactivity in obese asthmatics with nonatopic asthma (59,60). In addition, recent studies have shown that eosinophils are dominant in the lung tissue of these patients and there is an increase in ILC2s (61). The ILC3 subset, which also expresses IL-17 in humans, has been observed to accumulate in the bronchoalveolar lavage fluids of asthmatic patients (62,63). It was found that pro-inflammatory cytokines and ILC3 cell ratios were increased in the sputum and blood samples of obese individuals who smoked, and this positively correlated with circulating neutrophil counts and frequency of M1 type macrophages (64). However, MHC class II-expressing ILC3 groups with antigen-presenting features have been identified in some studies, and it has been reported that these cells restrict eosinophilia, Th2 and Th17 responses, and airway neutrophilia. These cells have also been shown to play a role in the regulation of immune tolerance of the airway by limiting pro-inflammatory T cell responses to allergens and microbes (65).

It is thought that ILCs may have a role in the inflammation and airway hyperreactivity (AHR) in non-allergic asthma. Jonckheere et al. have developed a murine neutrophilic asthma model that mimics certain features of non-allergic neutrophilic asthma by endonasal administration of 2 μg of lipopolysaccharides (LPS) four times a day. In this study, ILC2 subset did not change in murine lung tissue after LPS exposure, but the total ILC, ILC1 and NCR^{+} ILC3 and NCR^{-} ILC3 subsets, as well as IL-1β, IL-17A, TNF-α, IL-22, IL-6, IL-13, and IFN-γ secretion have also been shown to be increased. It was observed that IL-1β and IL-17, in addition to neutrophil-attracting chemokines and keratinocyte-derived chemokines increased after LPS stimulation in severe combined immunodeficiency mice. These findings indicated that adaptive immune responses had no role in LPS-induced airway inflammation, and it was shown that ILCs play a role in the induction of AHR, whereas IL-17 and neutrophils do not (66).

ILCs in Allergic Rhinitis

Allergic rhinitis (AR), the clinical result of IgE-mediated inflammation that occurs with allergen contact in the nasal mucosa, is a worldwide growing public health-related, medical, and economic problem with its increased incidence in recent years. It is known that environmental factors such as climate change, pollution, and some genetic factors play a role in the epidemiology of this condition (67).

Although AR is supposed to have an IgE dominant mechanism, this is not the only mechanism responsible for the occurrence of symptoms (67). Recent studies have

shown that besides the T and B lymphocytes, ILCs, and especially ILC2, also play a role in AR immunopathogenesis (68). While IL-25, IL-33, and TSLP were detected in the nasal lavage of house dust mite-susceptible individuals, it was shown that IL-33 and TSLP mRNA expression levels increased in the nasal epithelial tissue (44). In addition, increased ILC2 ratios were observed in house dust mite-sensitive AR patients and these were correlated with the total 5 symptoms score (T5SS). In this study, it was also found that ILC2 rates were increased in peripheral blood mononuclear cells (PBMC) of patients with pediatric AR, regardless of the allergen (69).

It has been reported that the Th2-type responses observed in AR are suppressed by IL-35 secreted from Treg cells. Liu et al., found that the rates of IL-35 producing Treg (iTreg) cells, and IL-35 expression decreased in patients with AR. They also found that IL-35 were negatively correlated with the ILC2, IL5$^+$ ILC2, IL-13$^+$ ILC2 cell ratios (70). In addition, they showed that IL-35 suppressed the expression of GATA-3 and ROR-α and the proliferation of ILC2s under in vitro conditions and decreased the expression of IL-5 and IL-13 in these cells. Whereas in iTreg-ILC2 co-culture studies, Treg cells had both IL-35 and surface molecules such as ICOS-ICOSL to inhibit ILC2 cells (70). IL-35 administration has been shown to reduce house dust mite (Der p1)-specific IgE levels and allergic responses in the AR mouse model (70).

High density lipoprotein (HDL), which has anti-inflammatory and antioxidant properties, is known to suppress the activation of immune system cells (71). It has been reported that increased ILC2, IL-5$^+$ ILC2, and IL-13$^+$ ILC2 cell ratios and low serum HDL levels are negatively correlated in AR patients (72). When PBMCs were cultured with HDL, proliferation of ILC2 cells and expression of GATA-3 and ROR-α mRNA, and IL-5 and IL-13 protein levels in culture supernatants were found to decrease as HDL concentration increased (72).

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a condition characterized by chronic inflammation in the nose and sinuses. The inflammatory process suggests a role for IILCs, particularly the ILC2 subset. It is believed that ILC2s are increased in patients with CRSwNP and can trigger inflammation and mucus production through the release of various cytokines. They are also thought to enhance eosinophil infiltration in CRSwNP, which contributes to disease progression. Furthermore, ILC2s are associated with elevated tissue and blood eosinophilia and are considered to potentially play a role in the activation and survival of eosinophils during Th2 immune responses (73). Additionally, a recent study has shown that a high blood eosinophil count was associated with a poor outcome in CRSwNP patients (74). Th2 and ILC2 are the main cells secreting IL-5, which is a key mediator of tissue eosinophilia in CRSwNP patients (75).

ILCs in Atopic Dermatitis

Atopic dermatitis (AD) is a recurrent, chronic, inflammatory, eczematous skin disease that usually starts in childhood. Although the etiology is not exactly known, complex multifactorial pathways are thought to play a role with the participation of genetic, environmental and infectious factors (76).

The demonstration of molecules such as IL-17, IL-19, IL-33, and TSLP as important role players in the pathogenesis of AD has increased the number of studies focusing on the role of ILCs in this process (77). Expressions of IL-25, IL-33, and TSLP have been shown to be elevated in AD patients. It has been reported that ILC2 ratios are increased in skin lesions, peripheral blood, and regional lymph nodes of animals with AD. Just as in other allergic diseases, these cells are an important source of IL-5 in AD. Anti-IL-5 antibody treatment was reported to improve the eosinophilia observed in these mice (78).

It has been shown that ILC2 is the dominant ILC subset in healthy and AD skin punch biopsies. Single cell analyses of samples obtained from skin lesions showed that ILC2 response dominance and ILC3-related cytokines such as IL-17, IL-22, and IL-26 were remarkably co-expressed in these cells (79). In the immunohistochemistry study performed on tissue samples from AD and psoriasis patients and healthy individuals, the number of ILCs was low in healthy tissues and they were mostly in the ILC1 and AHR$^+$ ILC3 subgroups. By contrast, there was a predominant ILC2 presence in the skin lesions of AD patients as well as AHR$^+$ ILC3 cells. It has been shown that ILC are located close to the epidermis, adjacent to T lymphocytes (80). However, the role of IL-17 in AD has not yet been clearly demonstrated. In a study in mice, it was shown that IL-17-producing ILC3 increased in an AD mouse model and suppression of IL-17 delayed the development of AD, and adoptive transfer of ILC3 increased the severity of AD (81).

It is known that elevated IL-4 and IL-13 observed in AD patients stimulate Th2 and ILC2 responses, and induce inflammation and barrier disruption. IL-4Rα is a common subunit involved in the binding of both IL-4 and IL-13 to its receptor. Therefore, IL-4Ra appears to be an important therapeutic target in AD (82). Dupilumab, a monoclonal antibody developed specifically for IL-4Rα, has been started to be used in patients with moderate and severe AD. Blocking IL-4Rα signalling has been shown to restore skin barrier function and lipid metabolism (83). When the circulating Th2 and ILC2 responses in AD patients were examined before and after dupilumab treatment, it was observed that Th2 and ILC2 and ILC2/ILC3 ratios decreased at the 4th month after treatment. Between 0 and 4 months after dupilumab administration, the Th2 and ILC2 cluster gene signatures were downregulated when single-cell RNA sequencing analyses were performed after Th2 and ILC cells were isolated from the peripheral blood of the patients (84).

ILCs in Food Allergy

Food allergy occurs as a result of abnormal reactions developed by the immune system against some food proteins. Food allergens can trigger IgE-mediated and non-IgE-mediated reactions (44). While the immune system is supposed to tolerate foods, this tolerance is impaired in allergic individuals. Under normal conditions, CX3CR1^{+} cells take antigens from the intestinal lumen through their extensions and transfer them to CD103^{+} dendritic cells. During antigen presentation to naive T cells, these cells direct the T cells to Tregs with concomitant secretion of TGF-β and retinoic acid and contribute to the maintenance of tolerance (85).

Mast cells, basophils, and Th2 and Treg cells play an important role in the development of food allergy (86). However, studies show that especially Th2 type cytokines such as IL-4, IL-5, IL-9, IL-13 secreted by ILC2 contribute to the immunopathogenesis of food allergy (86). In another study conducted in a mouse model of food allergy, it was shown that ILC2 ratios increased, and IL-4 secreted from these cells suppressed Tregs, while activating the mast cells and contributing to the allergic response. In this study, it was found that ILC2 responses were reduced and protective against anaphylaxis in IL-33R deficient mice (87). Similarly, Burton et al. showed that ILC2 ratios decreased in Igh7$^{-/-}$ mice where the gene locus encoding IgE was deficient and in Il4raF709 Kit$^{W\text{-}sh}$ mice with mast cell deficiency. They also showed that mast cells activate ILC2 to secrete IL-13 over IL-4Ra, and active ILC2s exacerbate anaphylaxis (88). In another study, it was found that the expression of IL-25, IL-33 and C-C motif chemokine 11 (Ccl1, eotaxin 1) increased in mice sensitized by intragastric ovalbumin (OVA) administration. It has been shown that IL-25 overexpressed in IL-25 transgenic mice induces IL-5 and IL-13 secretion, and the main source of these two cytokines is ILC2. In addition, in this study, it was shown that IL-25 and Th2 cells induced by ingested antigens contribute to the formation of IgE-mediated experimental food allergy by increasing the production of ILC2-derived IL-13 (89).

Eosinophilic esophagitis (EoE) is characterized by chronic inflammation in the esophagus due to infiltration. It has been demonstrated that ILC2 also plays an important role in this condition. In affected individuals, an increase in both eosinophilic infiltration and ILC2 cells, along with elevated release of IL-5 and IL-13, has been observed. It is believed that ILC2s are effective in triggering the inflammatory response and promoting eosinophil infiltration in the esophagus (90). In a study conducted using esophageal biopsies, it was found that ILCs could be overlooked in immunostaining due to their lack of expression of other lymphocyte markers on their surface. However, it was also reported that ILC2 cells could contribute to the lymphocytic infiltration of EoE, suggesting that ILC infiltration may be more prevalent in affected cases than previously recognized (91). In another study, it was observed that IL-33 mRNA levels were increased in biopsy samples from pediatric EoE cases. When mice were treated with IL-33 for one week, based on these findings, it was observed that ILC2 cells, along with marker genes for M2 macrophages and Th2 cytokines including IL-13, were increased. Furthermore, IL-33 treatment inhibited the expression of genes involved in Treg cell function, while promoting transmural eosinophilia, mucosal hyperproliferation, and increased expression of eosinophilic genes and chemokines (92).

ILC Plasticity

Plasticity can be defined as the ability of a cell to take on the characteristics of different subgroups of that cell at the same time or at different times during its life cycle under the influence of environmental conditions (93). This feature provides, for example, the ability to a CD4^{+} T cell to differentiate into different CD4^{+} T cell subsets, both

phenotypically and functionally. The signal transduction pathways and (epi)genetic control mechanisms play an important role in the control of plasticity (94).

Recent reviews state that cellular metabolism plays a role in ILC plasticity. Decreased oxidative phosphorylation (OXPHOS) inside the cell and TGF-β stimulation from the outside cause NK cells to differentiate towards ILC1, while increased glycolysis and OXPHOS in ILC1 differentiate these cells towards ILC3. The increase in fatty acid oxidation transforms ILC3 in the direction of ILC2, while the decrease in fatty acid oxidation and increase in vitamin A causes ILC2 to transform in the direction of ILC3 (95).

Ohne et al. have shown that when ILC2 cells isolated from human peripheral blood were stimulated with various cytokines, co-stimulation of IL-1β and IL-2 increased ILC2 cell proliferation similar to IL-33+IL-22 stimulation and they expressed IL-1R1 on the surface of ILC2 cells. Again, when ILC2 cells were stimulated with IL-1β and IL-12 for 7 days, IL-5 and IL-13 production in ILC2 cells decreased, while IFN-γ production increased (96). These results show that IL-1β and IL-12 have an important role in ILC2-ILC1 plasticity.

Effect of Allergen Immunotherapy on ILC

The clinic effect of pollen immunotherapy is well known and changes that occur on adaptive immune responses, mostly T- and B-cell responses, have been well studied. However, the data about the effect of aeroallergen immunotherapy on ILC is scarce. Researchers have found a suppression of peripheral ILC2s during the pollen season in pollen-allergic patients treated with subcutaneous immunotherapy (97). Another study has demonstrated a downregulation in ILC2s and ILC3s together with an upregulated ILC1s during the course of allergen immunotherapy (AIT). The AIT-induced systemic decrease of ILC2s and increase of ILC1s remains stable up to the third year of AIT (98).

While the rates of KLRG1$^+$ ILC2 producing IL-10 before immunotherapy are quite low in patients with grass-pollen allergy compared to healthy individuals, it has been reported that there is an increase in these cell rates and IL-10 levels after treatment, and that these increases are negatively correlated with clinical scores (39). When ILC subgroups were analysed in AR patients receiving house dust mite (HDM)-specific subcutaneous immunotherapy, it was found that ILC2 and ILC3 ratios were decreased in patients who responded to AIT compared to non-responder AIT and AR patients who did not receive AIT, while ILC1 ratios increased. It has been stated that this ratio could be an indicator of successful AIT implementation (99). Similarly, another study investigating the changes within ILC2 among patients receiving sublingual HDM AIT, also showed a decrease in the frequency of ILC2, levels of their transcription factors, and ILC2-related cytokines in the SLIT group.

CONCLUSION

However, further research aimed at clearly elucidating the underlying molecular mechanisms of these interactions is needed to provide a more comprehensive understanding of how ILCs regulate immune responses in both allergic and non-allergic human diseases. This will contribute to an improved comprehension of the underlying mechanisms and aid in the development of targeted therapeutic strategies. While alterations in the numbers and activity of ILCs have been observed in various diseases, it is crucial to establish whether these changes correlate with symptoms and disease severity. Various studies have indicated that an increase in the number of ILCs, changes in the expression of various markers such as chemokine receptors, activation of the ILC2 pathway, and infiltration of ILCs into tissues could potentially serve as biomarkers in various diseases such as asthma and allergic rhinitis (100-102). However, further research is needed in this direction to validate these parameters as biomarkers."

In conclusion, ILCs are a unique family of effector immune cells that functionally resemble T cells but lack clonal distributed antigen receptors. Demanding work has been performed to reveal the function and regulation of ILCs and specifically ILC2 in allergic diseases in recent years. It is known that regulator cells like Treg play an important role in the tolerance to allergens and this tolerance is impaired in allergic diseases. On the other hand, IL-10-producing Treg cells are increased in peripheral blood and local tissues after AIT protocols. Although it is generally stated that IL-10 production in ILCs is due to the functional plasticity of ILC2, recent studies indicated that there is a separate group of ILCreg that produce IL-10. However, there is an ongoing fascinating debate on how to classify these cells. Further studies focusing on IL-10-secreting ILC subset will contribute to the classification of these cells and to elucidate their role in the pathogenesis of

allergic diseases. Both murine and human studies suggest that ILCs play an important role in the immunopathology of allergic diseases, and the role of ILC2s toward allergy development or suppression is crucial to utilize ILC2s as therapeutic approaches to prevent allergic disorders.

Conflict of Interest

The authors report no conflicts of interest.

Authorship Contributions

Concept: **Metin Yusuf Gelmez, Leyla Pur Ozyigit, Gunnur Deniz,** Design: **Metin Yusuf Gelmez, Leyla Pur Ozyigit, Gunnur Deniz,** Data collection or processing: **Metin Yusuf Gelmez, Leyla Pur Ozyigit,** Analysis or Interpretation: **Metin Yusuf Gelmez, Leyla Pur Ozyigit,** Literature search: **Metin Yusuf Gelmez, Leyla Pur Ozyigit,** Writing: **Metin Yusuf Gelmez, Leyla Pur Ozyigit, Gunnur Deniz,** Approval: **Metin Yusuf Gelmez, Leyla Pur Ozyigit, Gunnur Deniz.**

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