Review / Derleme

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Friend or Foe? The Potential Roles of Innate Lymphoid Cells in Lung Transplantation

Dost ya da Düşman? Akciğer Naklinde Doğal Lenfoid Hücrelerin Potansiyel Rolleri

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Abstract

Respiratory diseases are one of the major causes of death worldwide. With the developing technique and immunosuppressive treatment approaches, the number of lung transplant operations has increased. Unfortunately, despite improvements in lung transplantation, the life expectancy of lung transplant recipients has not improved as much as with other solid organ transplants. Rejection of transplanted lung is generally caused by immune responses. Thence, researchers focus on transplantation immunology for improving the results of lung transplantations. The innate lymphoid cells (ILCs) are recently identified immune cells and investigators have focused heavily on these cells over the last years. ILCs are playing various roles in immune responses by expressing inflammatory cytokines or producing ligands. The properties of ILCs are being investigated in the pathogenesis of different diseases such as cancer, autoimmune diseases, and transplantation rejections. This review discusses the roles and potential roles of ILCs in lung transplantation tolerance or in transplantation failures such as primary graft dysfunction, chronic lung rejection, and acute lung rejection.

Keywords: Innate lymphoid cells, lung transplantation, transplantation immunology, transplantation tolerance, graft rejection

Öz

Solunum yolu hastalıkları dünya çapında önde gelen ölüm nedenlerinden biridir. Gelişen teknik ve immünosüpresif tedavi yaklaşımları ile akciğer nakli operasyonlarının sayısı artmıştır. Ne yazık ki, akciğer transplantasyonundaki gelişmelere rağmen hastalardaki yaşam beklentisi, diğer katı organ nakillerinde olduğu kadar iyileşmemiştir. Akciğer nakli başarısızlıkları genellikle bağışıklık tepkilerinden kaynaklanır. Bu sebeple araştırmacılar, akciğer nakli operasyonlarının başarısını artırmak için transplantasyon immünolojisine odaklanmaktadır. Doğal lenfoid hücreler (DLH'ler) yakın zamanda tanımlanmış bağışıklık hücreleridir ve araştırmacılar son yıllarda bu hücrelere yoğun bir şekilde odaklanmışlardır. DLH'ler, enflamatuvar sitokinleri eksprese ederek veya ligandlar üreterek bağışıklık tepkilerinde çeşitli ve etkin roller oynamaktadır. DLH'lerin özellikleri kanser, otoimmün hastalıklar ve transplantasyon redleri gibi farklı hastalıkların patogenezinde araştırılmaktadır. Bu derlemede, DLH'lerin akciğer transplantasyonu toleransında veya primer greft disfonksiyonu, kronik akciğer reddi ve akut akciğer reddi gibi transplantasyon başarısızlıklarında rolleri ve potansiyel rolleri tartışılmaktadır.

Anahtar Kelimeler: Doğal lenfoid hücreler, akciğer transplantasyonu, transplantasyon immünolojisi, transplantasyon toleransı, greft reddi

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Introduction

Respiratory diseases are the fourth leading cause of death after cardiovascular disease, cancer, and accidents.[1] The number of lung transplants, that is seen as the last option in the treatment of these respiratory diseases, has increased with the developments in transplant techniques and new immunosuppressive techniques.[2] Nevertheless, developments in immunosuppressive strategies like using alemtuzumab and improvements of donor selection criteria, median survival after lung transplantation has been reported to be around 5.8 years.[3,4]

After lung transplantation, median survival has been reported to be shorter than those of other solid organ transplantations due to lung immunogenicity and anatomical position.[5] Most of rejections is caused by like T-cell-mediated immune responses.[3] The anti-graft immune response should be suppressed by appropriate treatment. Calcineurin inhibitors such as tacrolimus and cyclosporine have been used for inhibition of anti-graft immunity.[6] Immune response and tissue repair mechanisms are gaining importance in transplantation research.

Immune responses are compound biostructures that are composed of heterogeneous pathways and various cells.[7] The innate immunity also plays distinct roles in tissue repairing and inflammation.[8] Those responses are associated with allograft tolerance and allograft rejection.[9] The innate immune system consists of different cells such as innate lymphoid cells (ILCs) and eosinophils.[10] ILCs are the most recently identified members of the innate immune system. These cells have been extensively studied in the last five years.[11] ILCs consist of 3 main groups: ILC1 resembling TH1 cells, ILC2 resembling TH2 cells, and ILC3 resembling TH17 cells.[11] ILCs are generally resident in epithelial and mucosal barriers, especially in the intestinal and respiratory systems.[11] ILCs express different ligands such as Amphiregulin (AREG) and various cytokines such as IL-10 and Il-17. ILC-derived cytokines and ligands play an important role in tissue regulation, chronic inflammation, and regulation of leukocyte migration.[11] Further, ILCs have been demonstrated to play a role in the inflammatory pathogenesis of many diseases such as cancer, allergy, and transplantation.[12,13] In addition, the plasticity of ILCs in various conditions such as chronic inflammation makes them a potential prognostic factor. In chronic obstructive pulmonary disease (COPD), the ILC1:ILC2 ratio is a factor indicating the level of inflammation and lung destruction.[14]

ILC1

Group-1 innate lymphoid cells (ILC1s) is a TH1-like a member of the ILC family.[15] ILC1s are found in different tissues however they are found extensively in tissues such as the liver, thymus, and gut.[16] ILCs have different subtypes such as Thymic ILC1 or Hepatic ILC1, having different expression profiles.[16] ILC1s play an important role in innate immunity.[17]

In the lungs, ILC1s express pro-inflammatory cytokines such as interferon gamma (IFN-γ) and tumor necrosis factor-α (TNF-α), and express surfaces markers such as CD49.[18] IFN-γ also is named as type II interferon which is a member of the class of interferons.[19] IFN-γ is essential for adaptive and innate immune responses.[19] TNF-α is a member of the TNF superfamily.[20] TNF-α is an effective cytokine mediator of pro-inflammatory and immune functions.[20] CD49a is also named integrin alpha-1 and it is combined with CD29 to form a receptor for collagen and laminin.[21] This receptor plays a role in cell-to-cell adhesion during inflammation and fibrosis.[21]

ILC1 in Primary Graft Dysfunction

Primary graft dysfunction (PGD) is the most important complication after lung transplantation, generally occurring 72 hours after transplantation.[22] PGD has been a major adverse event for early mortality after lung transplantation.[22] Cytokines such as TNF-α and IFN-γ are defined as significant for the pathogenesis of PGD.[23,24] ILC1s that are important sources of IFN-γ,[25] lead to PGD by different mechanisms.[24] IFN-γ mediates T-cell response by promoting dendritic cell maturation and stimulating MHC-II expression.[26-28] IFN-γ also induces immune response by activating macrophages and inducing macrophages to express pro-inflammatory cytokines.[19] In parallel to IFN-γ functions, it has been demonstrated that elevated IFN-γ levels are associated with PGD.[29] TNF-α, another cytokine produced by ILC1, plays a key role in pro-inflammatory pathways.[19] TNF-α has been found to stimulate MHC expression in antigen-presenting cells (APC) enhancing T-cell-APC interactions.[30] Furthermore, TNF-α has been shown to be a substantial recruiting factor for neutrophils.[31] According to this paper, elevated serum TNF-α levels were associated with PGD.[32] Eventually, ILC1-derived cytokines were found to be key promotors of PGD hence ILC1 might be a potential therapeutic target in the prevention and treatment of PGD (Figure 1).

ILC1 in Acute Rejection

Acute lung rejection (ALR) is characterized by perivascular leukocyte infiltration into lung allograft tissue.[33] ALR develops in approximately one-third of lung transplant recipients within 1 year of transplantation.[34] IFN-γ as one of the ILC1-derived cytokines has been defined as a key mediator for ALR via inducing macrophages and promoting APC maturation.[35] A study demonstrated that IFN-γ levels markedly elevated in the bronchoalveolar

lavage (BAL) of lung transplant recipients with early acute rejection.[36] TNF-α, another ILC1-derived cytokine, was found to be associated with ALR that was concluded by a study by Hodge and colleagues.[37] They also showed that TNF-α levels were elevated in BAL in patients with acute lung rejection.[37]

ILC1 in Chronic Rejection

Chronic lung allograft dysfunction (CLAD) leads to diminished function of transplanted lung.[38] CLAD presents with airway constriction and obstruction and it is predominantly caused by chronic rejection.[38] Neutrophil infiltration and accumulation in BAL were found to be pivotal in CLAD development.[39] ILC1-derived cytokine TNF-α was found to mediate neutrophil recruitment and infiltration.[33] Suwara et al.[39] measured TNF-α levels in BAL and they found that TNF-α levels were elevated in patients with primary airway neutrophilia.High expression of inflammatory cytokines contributed to the development of CLAD.[37] IFN-γ was found to activate macrophages to increasing the expression of inflammatory cytokines, in turn it led to IFN-γ mediating the development of CLAD.[37]

In conclusion, ILC1-derived cytokines are found to be significant mediators of rejection of transplanted lung (Figure 1). Evidence with regards to cytokine profile of ILC1 indicates that ILC1 may be a prognostic factor or therapeutic promise in lung transplantation.

ILC2

Group-2 innate lymphoid cells (ILC2s) as a subset of ILCs are morphologically similar to Th2 cells.[40] ILC-2s are

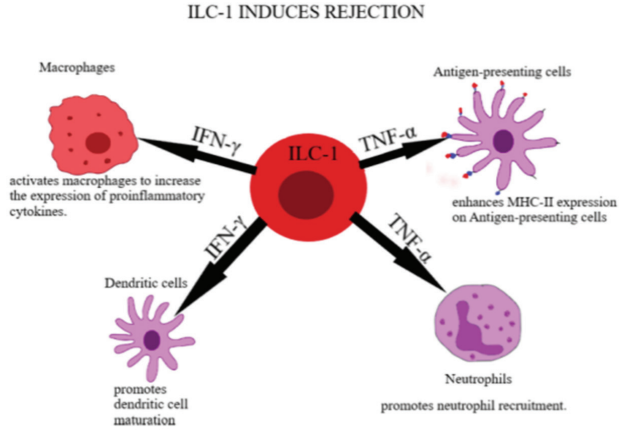


Figure 1. Role of cytokines derived from ILC1 in transplantation rejection: ILC1-derived IFN-γ activates macrophages and increases proinflammatory cytokine secretion. In addition, IFN-γ promotes dendritic cell maturation. Another ILC1-derived cytokine is TNF-α that promotes neutrophil recruitment and enhances the antigen-presenting ability of antigen-presenting cells (APCs) through enhancing MHC-II expression on APCs.
ILC: Innate lymphoid cells, IFN: Interferon gamma, TNF: Tumor necrosis factor

a heterogeneous group consisting of native ILC2 (nILC 2) induced by IL-33 and inflammatory ILC2 (iILC2) induced by IL-25.[41] Mostly, ILC2s are resident in mucosal and epithelial barrier tissues. Moreover, ILC2s play disparate roles in mucosal and epithelial barrier tissues.[42] They were shown to be originated from $CD34^+$ progenitor cells and they had various surface markers such as st2, CD127, CD161, and CRTH2.[43] Furthermore, the ILC2s produce type-2 cytokines such as IL-4, IL-5, IL-9, and IL-13,[44,45] and ILC2s are activated by IL-25, IL-33, and thymic stromal lymphopoietin.[46] In addition, ILC2s were found to express distinct ligands like AREG which was a type of epidermal growth factor receptor (EGFR) ligand, and Met-enkephalin, called opioid growth factor.[8] Because of those properties, ILC2s were thought to be one of the keystones of innate immunity.

Innate immunity pathways play significant roles in immune responses.[5] Those pathways are divided into pro-inflammatory and anti-inflammatory pathways.[11] Those pathways were found to be regulated by cytokines such as IL-5, IL-10.[47,48] ILC2s were shown to produce both pro-inflammatory and anti-inflammatory cytokines. For this reason, ILC2s have distinct immunologic effects.[49,50]

ILC-2 Derived Cytokines in Allograft Tolerance

ILC2s are primarily resident in the epithelium and exert different protective immune functions.[51] ILC2s were found to have a protective role by regulating innate immune pathways against infection and tissue damage. ILC2s were likely to play a crucial role in transplant tolerance.[52]

The ILC2 derived IL-4 was shown to be an immune suppressor cytokine involving with anti-inflammatory pathways such as inducing M2 type macrophage differentiation.[53] ILC2 derived IL-9 was found to show different roles in immune pathways such as stimulating mast cells thereby dendritic cells might differentiate to tolerogenic direction and induce tolerance in T-cell regulators (Tregs).[54-56] Furthermore, ILC2s produce IL-13, and ILC2 derived IL-13 plays a major role in immune suppression and prolongs allograft survival.[57] As a result, ILC2s produce tolerogenic cytokines (Figure 2), whereby they may be promising to improve allograft survival, however, the mechanisms have not been fully elucidated.

ILC2 in Graft Rejection

ILC2 Induces Fibrosis in Pulmonary Tissues

ILC2s prevalently were localized in mucosal tissues such as bronchial tract. They also protect epithelial and mucosal barrier tissues from tissue damage and effect of allergens.[58] ILC-2s were shown produce IL-4 which stimulates eosinophils to exert their functions in the airway inflammation.[59] IL-4 plays a significant role in

airway remodeling.[60] Furthermore, high IL-4 levels were detected in BAL of patients with cystic fibrosis.[60] ILC-2-derived IL-13 was shown to activate fibroblasts to produce collagen. In addition, IL-13 was found to induce mucus hypersecretion in the respiratory epithelium.[61] The ILC2s were not only found to contribute to cytokine secretion leading to fibrosis. ILC2s were shown to produce ligands like AREG.[62] AREG is an EGFR ligand that plays a critical role in fibrosis and induces bronchial epithelial cells to produces hyaluronan.[62,63] Moreover, AREG was found in BAL of patients with CLAD.[64] According to those data, ILC2s were found to induce fibrosis in airways and that in turn serves a potential therapeutic target for prevention of transplantation rejection.

Role of ILC2s in Immune Responses During Allograft Rejection

Acute transplant rejections are mediated by immune responses. ILC2s are members of innate immunity, and they can carry out those immune responses.[65] ILC2s produce IL-4 that activates T-cells via increase in MHC-II expression in antigen-presenting cells.[66] IL-4 has been found to induce leukocyte infiltration.[67] ILC2 derived IL-4 can contribute to acute rejection of the lung transplant.[67] ILC2s can also activate eosinophils via the secretion of IL-5.[51] IL-5 activates eosinophils and contributes to inflammation.[68] Consequently, ILC2 derived cytokines are associated with immune responses (Figure 3) thus strategies for regulating ILC2 may serve as a therapeutic promise to prevent allograft rejection.

ILC3

Group-3 innate lymphoid cell (ILC3s) is a component of the innate immune system, defined by expression of the transcription factor retinoid-related orphan receptor.[69] Two subsets of ILC3 cells are identified:[70] Lymphoid tissue-inducing cell (LTi) type that mediates the development of secondary lymphoid organs and natural cytotoxicity receptor-expressing (NCR) type cells which express NCR receptors of NK cells capable of recognizing pathogenic molecules.[71] ILC3s play a crucial role in tissue homeostasis, regulating inflammation through ILC3-derived cytokines such as IL-17 and surface proteins such as MHC-II.[72]

ILC3s were shown to express IL-17A, IL-17F, IL-22, and GM-CSF.[73] It was shown that ILC3 cells expressed distinct surface proteins such as programmed cell death-1(PD-1), T-cell immunoglobulin, and mucin domain-containing protein 3 (TIM-3).[74]

ILC3s that are found in mucosal and epithelial tissues contribute tissue-barrier homeostasis through IL-22 that stimulates stem cell regeneration.[75] Moreover, ILC3 stimulates Bronchus-associated lymphoid tissue (BALT). BALT is a tertiary lymphatic organ (TLO) that is located in the lung which is a lymphatic tissue in a non-lymphoid tissue.[76] ILC3s have been found to proliferate in response to chronic inflammation and contribute to immune-tolerance.[77] BALT has been reported to be associated with lymphangiogenesis.[74] According to this paper, pro-lymphangiogenesis therapies prevent acute allograft rejection after lung transplantation.[78] According to a study, RORγt-cre AHRfl/fl mice had fewer follicles per section than those of wild-type mice. For this reason, BALT development seemed to be dependent on IL-22 derived from ILC3.[79] Moreover, ILC3-derived IL-22 prevents the activation of T-cells.[80] ILC3s produce GM-CSF inducing IL-10 which is anti-inflammatory cytokine secreted from mononuclear phagocytic cells.[81] IL-1β induces IL-2 that

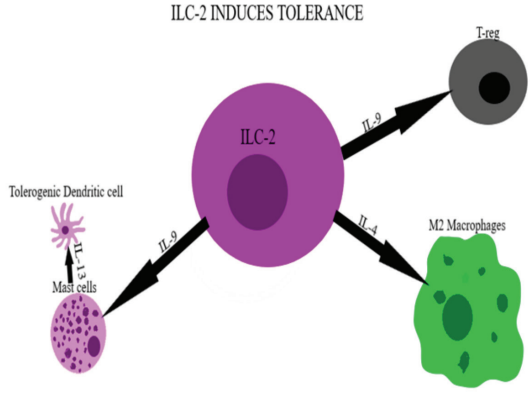


Figure 2. Potential roles of ILC2-expressed cytokines in transplantation tolerance; IL-4 mediates the tolerogenic differentiation of macrophages. IL-9 stimulates mast cells to secrete IL-13 and thus induces dendritic cells to differentiate in a tolerogenic direction. Additionally, it induces tolerance in Tregs.
ILC: Innate lymphoid cells

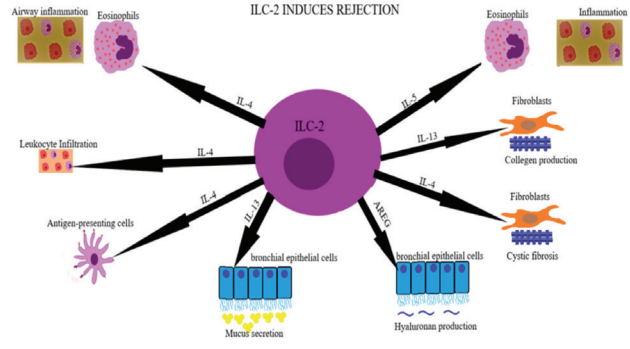


Figure 3. ILC2s potential roles in allograft rejection mechanisms by expressing various cytokines and ligands; IL-4 and IL-13 expressed by ILC2 induce collagen production and fibrosis by stimulating fibroblasts. Moreover, the AREG ligand expressed by ILC2 supports the production of hyaluronan from the bronchial epithelium. ILC2 expressed in the mechanisms of airway inflammation plays a role in expression of IL5 (that plays role in eosinophil activation) and IL-4 (that plays role in lymphocyte infiltration). Moreover, IL-4 stimulates MHC-II expression and enhances T-cell activation in this way. IL-13 induces mucus secretion from bronchial epithelial cells.
ILC: Innate lymphoid cells, AREG: Amphiregulin

is secreted from ILC3. IL-2 induces allograft tolerance in lung transplantation. Furthermore, ILC3-derived IL-2 stimulates LAG3 which is immune-checkpoint protein expression in Tregs.[81-83] One more immunosuppressive feature of ILC3 was reported to be PD-1 expression which was an immune checkpoint protein.[74] PD1:PDL1 pathway plays a crucial role in protecting chronic allograft rejection.[84] Consequently, ILC3 may be a therapeutic potential in inducing allograft lung transplant tolerance (Figure 4). However, many features and interactions of ILC3 have not been fully elucidated.

ILC3s in Chronic Allograft Rejection

Bronchiolitis obliterans (BO) which is also named as constrictive bronchiolitis and popcorn lung is the most major pathological sequelae of chronic lung transplantation rejection.[85] It is characterized by inflammation of the bronchioles which are the smallest airways of the lung.[85] Furthermore, BO develops in more than 50% of recipients after a lung transplant within five years.[86] Although the pathogenesis of this disease is yet to be elucidated, some studies have shown that certain cytokines play a role in the pathogenesis.[87] IL-17A which played a crucial role in BO pathogenesis, was shown to be produced by ILC3.[73] The IL-17 family, which consisted of six members (IL-17 A to F), were disclosed to have different effects.[88] IL-17A was reported to be produced by ILC3 and to play a significant role in transplantation immunology.[73,89] IL-17A induces fibrosis by inducing macrophages to stimulate collagen production from fibroblasts.[90] According to a study, IL-17A levels elevated after lung transplantation recipient mice which had BO. In addition, neutralizing anti-IL-17A prevents bronchiolitis obliterans syndrome (BOS).[91] According to another study about BOS, diverse drugs like macrolide and azithromycin had significant therapeutic effects in patients with BOS that was previously found to suppress IL-17-induced IL-8 production from smooth muscle cells.[92] As a result, ILC3s seem to produce important cytokines in chronic rejection. Thereby, ILC3 may be a therapeutic target in chronic lung transplantation rejection (Figure 5).

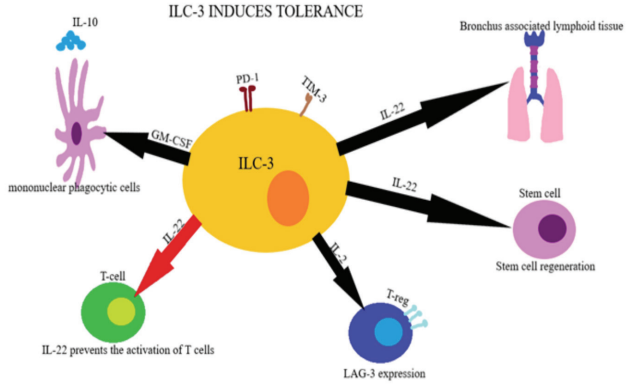


Figure 4. Potential roles of ILC3 in transplantation tolerance. ILC3 participates in immunosuppression by expressing immune checkpoint proteins such as PD-1 and TIM-3 on its surface. ILC3 produces Gm-CSF that induces mononuclear phagocytic cells to express IL10. Moreover, ILC3 expresses IL-22. The IL-22 induces the development of bronchus-associated lymphatic tissue, which is involved in lung transplantation tolerance, and also prevents T-cell activation. Moreover, IL-22 promotes tissue healing. In addition, IL-2 Tregs expressed by ILC3 stimulate the production of immune checkpoints.
ILC: Innate lymphoid cells

ILC3 in Acute Allograft Lung Rejection

It was reported that IL-17 was produced by ILC3, and it played a substantial role in ALR.[71] It was also shown that, IL-17 contributed to ALR via promoting chemotaxis of neutrophils by inducing IL-8 production.[93] Another pro-inflammatory role of IL-17 is that it seems to induce various chemotactic ligands like CXCL1, CXCL2, and CCL20. Those molecules have been found to promote immune infiltration.[94] Moreover, IL-17 has different effects on immune cells such as inducing dendritic cell maturation, inducing neutrophil accumulation in the lungs besides contributing to other features of T-cell-mediated immunity.[95] IL-17 blockade was demonstrated to increase graft survival in a mouse cardiac allograft model.[96] All these data suggested that ILC3 might play an important role in acute rejection.[97]

In conclusion, all these features of ILC3 make it an important immune factor in transplantation immunology.

Conclusion

Graft failure in patients with lung transplantation such as acute lung rejection, chronic lung rejection, and PGD,

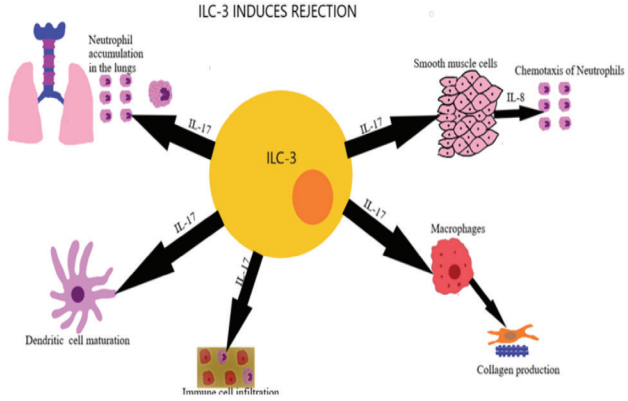


Figure 5. Potential roles of ILC3 in allograft rejection. ILC3 is an important source of IL-17. IL-17 is involved in several proinflammatory mechanisms, specifically in the infiltration of neutrophils into the lungs and in the infiltration of immune cells into the allograft in general. In addition, IL-17 stimulates macrophages to increase collagen production by fibroblasts, which can lead to the development of bronchiolitis obliterans syndrome. In addition, this may play a role in adaptive immune responses by promoting maturation of dendritic cells.
ILC: Innate lymphoid cells

and induction of lung tolerance are dependent on immune responses and tissue repair mechanisms. A wide variety of cells such as macrophages, T-cells, neutrophils, dendritic cells, and ILCs seem to play roles in these immune responses. ILCs are recently identified immune cells that are involved in various immune pathways such as tissue repair mechanisms, immune responses, and regulation of inflammation. Their important roles make themselves the focal point of many diseases such as cancer, autoimmune diseases, and inflammatory diseases, in which immunity plays a role.

ILCs play critical roles in tissue repair, inflammation, and immune regulation, making them effective in various lung pathologies (Table 1). The roles of ILCs in asthma and allergy, pulmonary fibrosis, COPD, and lung inflammation make it a potential target for elucidating rejection mechanisms in lung transplants, preventing allograft rejection, and prolonging allograft survival. Due to the plastic nature of ILCs in various conditions, they can be used as a prognostic factor in various pathologies such as the use of ILC1:ILC2 ratio in COPD. Owing to that feature of ILCs, ILC1:ILC2 or ILC3:ILC2 ratios in blood samples may be prognostic factors for CLAD. Although there are several studies on the role of ILCs in lung pathologies, the role of innate immune cells in lung transplantation is still not fully elucidated. Further studies are required.

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Authorship Contributions

Concept: H.İ.B., Design: H.İ.B., Data Collection or Processing: H.İ.B., Analysis or Interpretation: H.İ.B., A.T., Literature Search: H.İ.B., Writing: H.İ.B., A.T.

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Table 1. ILC subgroups mechanism of action in various lung pathologies such as allergic asthma, COPD, airway and lung inflammation, and airway fibrosis.

Innate lymphoid cell (ILC) subgroups	Mechanism of action of ILC in pathogenesis	Lung pathology	References
ILC1	The genes expressed by ILC1s in patients with emphysema were found to be enriched in inflammatory cell infiltrate. ILC1 counts increased in patients with COPD compared to healthy controls. In addition, it has been demonstrated that the ILC1:ILC2 ratio may be a prognostic factor in patients with COPD and emphysema.	COPD	13,17,24
ILC1	ILC1 is involved in airway and lung inflammation by expressing IFN-γ and TNF-α.	Airway and Lung Inflammation	17,24
ILC2	ILC2 promotes allergic inflammation through the expression of IL-5 and IL-13, which are proinflammatory cytokines.	Allergic Asthma	12,24,49,56,63
ILC2	The frequency of ILC2s, which play a role in tissue healing, is decreased in patients with COPD. It has been suggested that ILC2s convert to ILC1s in patients with COPD.	COPD	17,24
ILC2	ILC2 mediates airway inflammation by expressing IL5, which activates eosinophils, and IL-4, which leads to increased IgE production.	Airway and Lung Inflammation	6,47,50
ILC2	ILC2 was found to induce fibroblast activation and exacerbate pulmonary fibrosis by secreting IL-13. Further, BAL fluid was found to contain elevated ILC2 in patients with pulmonary fibrosis.	Airway Fibrosis	13,62
ILC3	It has been suggested that ILC3 may play a role in the pathogenesis of non-allergic asthma by expressing proinflammatory cytokines such as IL-17 and IL-1β.	Allergic Asthma	24
ILC3	The frequency of ILC3 is increased in patients with COPD. It has been suggested that ILC3s are involved in the pathophysiology of COPD by playing a role in ectopic lymphocyte accumulation.	COPD	17,24
ILC3	It has been stated that ILC3s can cause neutrophilia in the lung by expressing IL-17.	Airway and Lung Inflammation	13,17

COPD: Chronic obstructive pulmonary disease

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