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Review Article

Lung-resident lymphocytes and their roles in respiratory infections and chronic respiratory diseases

Arka Sen Chaudhuri [a,b], Jie Sun [a,b,*]

[a] Beirne B. Carter Center for Immunology Research, University of Virginia, Charlottesville, VA 22908, USA
[b] Division of Infectious Disease and International Health, Department of Medicine, University of Virginia, Charlottesville, VA 22908, USA

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ABSTRACT

Recent scientific breakthroughs have blurred traditional boundaries between innate and adaptive immunity, revealing a sophisticated network of tissue-resident cells that deliver immediate, localized immune responses. These lymphocytes not only provide rapid frontline defense but also present a paradoxical role in the pathogenesis of respiratory diseases such as asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and the long-term tissue consequences of viral infections including severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This review traverses the intricate landscape of lung-resident lymphocytes, delving into their origins, diverse functions, and their dualistic impact on pulmonary health. We dissect their interactions with the microenvironment and the regulatory mechanisms guiding their activity, with an emphasis on their contribution to both immune protection and immunopathology. This review aims to elucidate the complex narrative of these cells, enhancing our understanding of the development of precise therapeutic strategies to combat acute and chronic pulmonary diseases. Through this exploration, the review aspires to shed light on the potential of harnessing lung-resident lymphocytes for the treatment of respiratory conditions.

Introduction

Tasked with filtering thousands of liters of air each day, the lung must navigate an intricate balance between repelling microbial invaders and tolerating inhaled particles.[1,2] At the heart of this balance lies an ensemble of specialized lung-resident lymphocytes, comprising adaptive immune cells including resident B lymphocytes, resident T lymphocytes, resident $\gamma\delta$ T lymphocyte, mucosal-associated invariant T (MAIT), and natural killer T (NKT) cells, as well as innate lymphocytes including natural killer (NK) cells, innate lymphoid cells (ILCs).[3-5] Recent advances have redefined our understanding of tissue-resident immunity, eroding the once-clear demarcations separating innate and adaptive immune responses.[6] These lung-resident lymphocytes serve as rapid first responders, poised for immediate action and eliminating the need for external recruitment, thereby fortifying a tissue-specific layer of immunological protection.[7-9] However, emerging research has also unveiled their capacity to act as a double-edged sword, contributing to respiratory conditions such as asthma, chronic obstructive pulmonary disease (COPD), and post-acute sequelae of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (PASC).

This review aims to discuss the complex roles of lung-resident lymphocytes. We will explore their origins, differential functions, and their impact on lung health and disease conditions. We will also examine how these cells interact with their surroundings and what regulates their behavior. Therefore, this review aims to present a nuanced narrative, capturing the multifaceted roles of lung-resident lymphocytes in both immune protection and immunopathology (Fig. 1). We hope to provide insights on targeted therapeutic approaches that can leverage or modulate the capabilities of these cells for the treatment of acute or chronic lung diseases.

Types of lung resident lymphocytes

T lymphocytes

Tissue-resident memory T cells (T_{RM})

Following infections or antigen exposure, naive T cells first differentiate into effector T cells, which subsequently give rise to circulating memory T cells that patrol the body or T_{RM} cells that reside in the peripheral organs. T_{RM} cells, distinct from central memory T cells (T_{CM}) and effector memory T cells (T_{EM}), exhibit specialized phenotypic markers including CD103, CD69, and CD49a.[4,10,11] Transcriptional programming of T_{RM} cells involves B-lymphocyte-induced maturation protein-1 (Blimp1), Hobit, RUNX family transcription factor 3 (Runx3), basic

* Corresponding author at: Beirne B. Carter Center for Immunology Research, University of Virginia, Charlottesville, VA 22908, USA.
E-mail address: js6re@virginia.edu (J. Sun)

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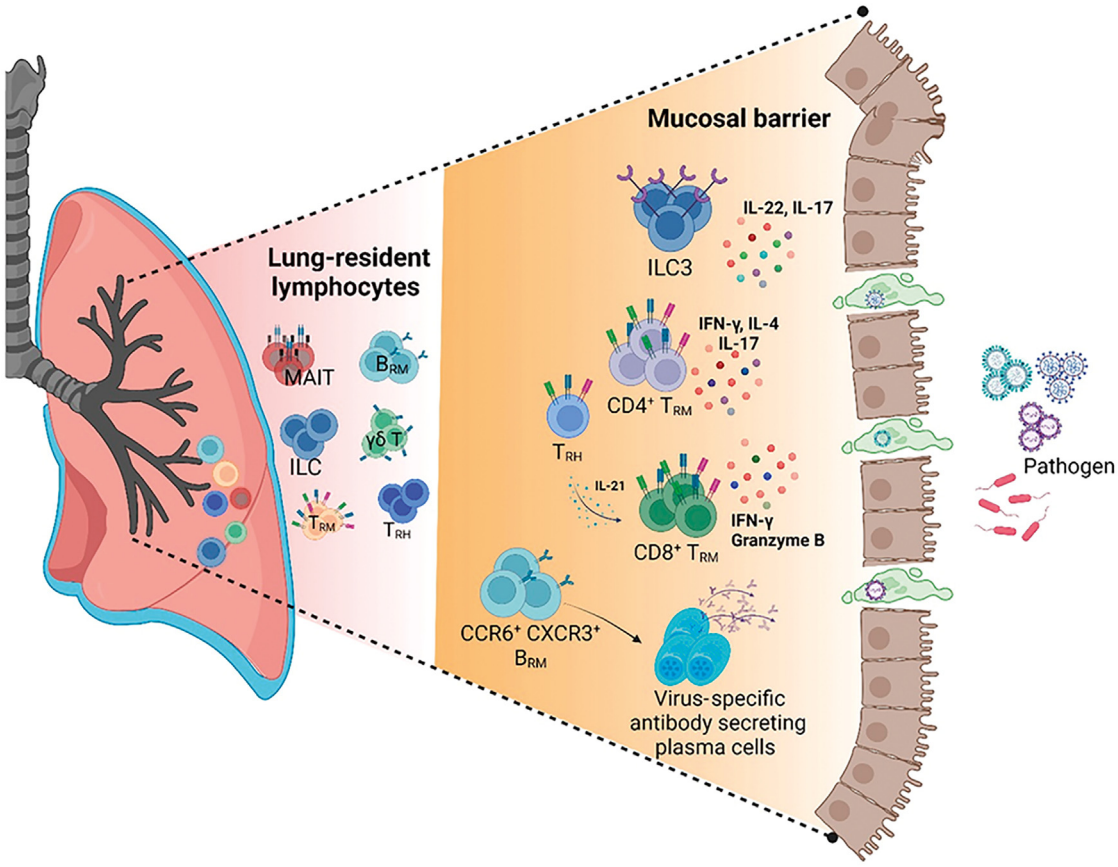

Fig. 1. Lung-resident lymphocytes as protectors in pulmonary immunity. It showcases how T_{RM} cells launch a comprehensive defense, releasing a suite of cytokines, effector molecules, and cytotoxic agents to combat and eliminate diverse pathogens, targeting cells compromised by infection. The diagram also accentuates B_{RM} cells' ability to rapidly transform into antibody-secreting plasma cells upon reencountering viruses, thus fortifying swift immunological defense. Additionally, it portrays the role of activated ILC3s in immune protection, detailing their secretion of IL-22 and IL-17, which are instrumental in tissue restoration and attracting neutrophils to infection sites. B_{RM}: Resident memory B cell; CCR6: C-C chemokine receptor 6; CXCR3: C-X-C chemokine receptor 3; IFN-γ: Interferon-γ; IL: Interleukin; ILC: Innate lymphoid cell; MAIT: Mucosal-associated invariant T; T_{RM}: Tissue-resident memory T cell; T_{RH}: Tissue-resident helper T cell.

helix-loop-helix family, member e 40 (Bhlhe40), and Notch1, whereas Krüppel-like factor 2 (KLF2), T cell factor 1 (TCF-1), and eomesodermin (EOMES) repress T_{RM} formation.[12-14] T_{RMs} develop from circulating effector T cells in the secondary lymphoid organs,[15,16] supported by common clonal origins of T_{CM} and T_{RM} cells.[17] In addition, local factors such as antigen restimulation and respiratory cytokine milieu are further required for T_{RM} maintenance.[18,19] Transforming growth factor-β (TGF-β) notably guides the maturation of $CD103^+$ $CD8^+$ T_{RM} cells, with its levels increasing with age.[4,20] Compared to $CD8^+$ T_{RM} cells, $CD4^+$ T_{RMs} are diverse, evolving into Th1, Th2, and Th17 T_{RM} subtypes depending on the pathogen involved.[21] $T_{RM}1$ cells are particularly efficient in mounting quick responses to influenza reinfections.[4,22] Additionally, a unique $CD4^+$ T-cell subset, termed "tissue-resident helper T (T_{RH}) cells", has been identified. These cells exhibit features of both follicular helper T cells (T_{FH}) and T_{RMs} and are involved in enhancing $CD8^+$ T_{RM} and lung-resident B-cell responses.[21,23-25] In humans, T_{RM} research is limited but growing. In human lungs, T_{RM} cells express low Ki67 compared to other counterparts.[26] Transcriptomic analysis reveals that human lung $CD69^+$ T_{RMs}, both $CD4^+$ and $CD8^+$, exhibit a unique gene signature, distinct from $CD69^-$ counterparts, characterized by upregulated integrins and chemokine receptors (CD103, CD49a, C-X-C motif chemokine receptor [CXCR] 6), downregulated tissue egress markers (C-C motif chemokine receptor [CCR] 7, KLF2, sphingosine-1-phosphate receptor 1 [c], and selectin L [SELL]), and elevated cytokines and immunoregulatory molecules (interleukin [IL] 2, interferon-γ [IFN-γ], IL17, IL10, CD101, programmed death-1 [PD-1], T cell immune receptor with immunoglobulin (Ig) and ITIM domains [TIGIT], and cytotoxic T-lymphocyte associated protein 4 [CTLA4]).[27] $CD103^+CD8^+$ T_{RM} cells predominantly accumulate in the epithelium, whereas $CD103^-CD4^+$ T_{RM} cells are frequently found in the lamina propria.[28] Unlike in murine models where $CD103^+$ conventional type 1 dendritic cells (cDC1) cells are instrumental, human respiratory $CD8^+$ T cells are more reliant on $CD1c^+$ dendritic cells for their development.[29] Human T_{RMs} have also been proven to be potentially derived from circulating memory T cells. Single-cell transcriptome profiling of airway T cells from human leukocyte antigen (HLA)-disparate lung transplant recipients reveals that recipient T cells comprised non-T_{RM} and similar T_{RM}-like subpopulations, suggesting lung-infiltrating recipient T cells gradually acquire T_{RM} phenotypes over months.[30]

Resident $\gamma\delta$ T cells

Gamma/delta (γ/δ) T cells are a minor yet crucial subset of T lymphocytes with a T-cell receptor (TCR) comprising γ and δ chains, serving as a link between innate and adaptive immunity.[31] Originating from common thymocyte precursors, these cells differentiate into two primary lineages: $\gamma\delta$T1, reliant on $\gamma\delta$ TCR and CD27 signaling, and $\gamma\delta$T17, which requires a complex signaling cascade involving factors such as lymphotoxin-β receptor and TGF-β.[32,33] Post-thymic, $\gamma\delta$T17 cells can self-renew in peripheral tissues. In the lung, these cells exhibit varying Vγ and Vδ chains, displaying temporal shifts and spatial distributions in different organ systems.[34] In adult C57BL/6 mice, lung $\gamma\delta$ T cells mainly express Vγ4 and Vγ6, primarily situated in the parenchyma.[35,36] These

populations show dynamic changes over time, supporting the idea of *in situ* differentiation and selection.[37,38] In human lungs, distinct $\gamma\delta$T cell subtypes, identifiable by Vδ1, Vγ9Vδ2, and Vδ2 expression, vary notably in the context of different lung conditions, pointing toward their importance in lung immunity.[39,40]

MAIT cells

MAIT cells constitute a specialized T cell subset vital for mucosal immunity, notably in the lungs, particularly in humans. Originating in the thymus through unique TCR–major histocompatibility complex (MHC) class I-related protein 1 (MR1) interactions with $CD4^+CD8^+$ thymocytes,[41,42] they undergo a three-stage maturation process, displaying hallmark markers like CD218, CD44, and promyelocytic leukemia zinc finger (PLZF).[43] Species-specific differences of MAIT cells do exist; mouse MAIT cells diverge into IFN-γ-producing (MAIT-1) and IL-17A-producing (MAIT-17) subtypes, but such a bifurcation is not observed in humans.[43] Post-thymic maturation and expansion of MAIT cells are influenced by microbial exposure, impacting their longevity and functionality.[43,44] Upon activation, typically TCR-mediated, MAIT cells initiate a cascade of processes including cytokine release, cytotoxicity, and proliferation.[45-48] Recent findings highlight a unique lung-resident human MAIT cell subtype that includes poly-cytotoxic properties, IL-26 secretion, and selective expression of IFN-γ and IL-12 receptors, emphasizing their rapid pro-inflammatory responsiveness.[49]

NKT cells

Mouse NKT cells, classified into invariant (iNKT) and diverse (dNKT) types, vary in phenotypes and functions. iNKT cells perform both pro- and anti-inflammatory roles, while dNKT cells mainly exhibit anti-inflammatory activity.[50-52] These cells differentiate through four stages, resulting in three functional subsets: NKT1 (IFN-γ-producing), NKT2 (IL-4-producing), and NKT17 (IL-17A-producing).[53-55] Human lung NKT cells also show diversity, with Vα24 $CD4^-CD8^-$ cells mainly producing IFN-γ and Vα24 $CD4^+$ cells known for high IL-4 and IL-13 production.[56]

B lymphocytes

Resident memory B cells (B_{RM} cells)

Compared to memory B cells in the lymphoid organs, lung-resident memory B cells (B_{RMs}) exhibit unique markers like CD69, CXCR3, and are metabolically reprogrammed for minimal cytokine reliance.[7,57,58] Originating from germinal centers, they possess distinct transcriptional profiles in humans and mice.[57,59,60] Upon reinfection, $CXCR3^+$ B_{RMs} differentiate into antibody-producing plasma cells (Fig. 1).[61] In mice, B_{RM} cells localize in the inducible bronchus-associated lymphoid tissue (iBALT) via CXCR5 expression,[61-63] and are regulated by transcription factors like BTB domain and CNC homolog 2 (Bach2), KLF2, and signal transducer and activator of transcription 5 (STAT5).[64,65] B_{RM} cells can persist for up to 6 months post-influenza infection.[7] Interestingly, "bystander" B_{RM} cells exhibit a $CXCR3^{low}$ phenotype.[59,62] Lung B_{RMs} are phenotypically and transcriptionally unique, with higher CD69 and Ig A levels and more somatic hypermutations than their counterparts in secondary lymphoid organs.[66] Currently, human B_{RM} studies are limited, but recent findings show that while CD69 is upregulated, CCR6 and CXCR3 do not delineate tissue residency in humans.[63]

Age-associated B cells (ABCs)

Age-associated B cells (ABCs), characterized by the presence of CD11c and CD11b expression, are implicated in aging and autoimmunity.[67,68] ABCs are increased in frequency with age, and express T-bet, but are low with CD21 levels.[69] ABC_S play a vital role in managing viral infections like hepatitis C virus (HCV), human immunodeficiency virus (HIV), and SARS-CoV-2, and in post-vaccination responses.[70-75] ABC differentiation is influenced by cytokine and antigenic receptors, including IFN-γ and Toll-like receptors 7 and 9 ligands.[76-78] The transition from activated follicular B cells to ABCs is complex and influenced by cytokines such as IFN-γ, IL-21, and IL-4.[78,79] In infections and vaccinations, they form a significant fraction of viral-specific B cells.[72,73,80] ABC_S are long-lived, possess memory traits, and readily become antibody-secreting cells (ASC_S) upon challenge.[81] In humans, high IgA^+ memory B-cell frequencies are linked to impaired lung function and mild-moderate asthma exacerbations.[82]

Other innate lymphocytes in the lung

ILCs

ILCs primarily inhabit mucosal regions like the respiratory and digestive tracts. Emerging evidence has suggested that ILCs play pivotal roles in lung homeostasis, pathogen defense, tissue repair, and potentially the development of chronic lung conditions.[5,83] ILCs consist of five major subsets: NK cells, ILC1, ILC2, ILC3, and lymphoid tissue inducers (LTi) cells.[5,84,85] ILC1s, regulated by T-bet, focus on intracellular infections and have varied cytokine responses.[82,83] ILC2s, guided by GATA binding protein 3 (GATA-3), counter extracellular parasites and cause allergies, and are modulated by IL-33, IL-25, and TGF-β.[86-88] In mice, natural ILC2s are responsive to IL-33, while inflammatory ILC2s, are not present under steady-state but are responsive to IL-25.[89] ILC3s, dependent on retinoid-associated orphan receptor γt (RORγt), are involved in lymphoid development and release cytokines like granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-17, and IL-22.[90,91] In humans, $CD127^+$ ILC1 cells can differentiate into ILC3-like cells when exposed to $CD103^+$ dendritic cells secreting IL-2, IL-23, and IL-1β.[92] Similarly, during severe COPD, ILC2s can transition into ILC1s in the presence of IL-1β and IL-12, raising questions about the prominence of ILC1s in inflammatory conditions and whether they originate predominantly from ILC3s influenced by IL-12 or ILC2s exposed to IL-1β.[93] A unique chemoattractant receptor-homologous molecule expressed on Th2 cells $(CRTH2)^+$ and $CRTH2^-$ ILC2 subtype was also identified, traceable to naive ILCs, and inducible by alarmin signals.[94] Elevated levels of $IL\text{-}17^+$ ILC3s were observed in the bronchoalveolar lavage fluid (BALF) of patients with severe asthma,[95] while an increased frequency of natural cytotoxicity receptor $(NCR)^+$ILC3s has been reported in non-small lung cancer patients and is associated with lung fibrosis.[96]

NK cells

Lung NK cells originate mostly from bone marrow and constitute 10–20% of lung lymphocytes in humans and about 10% in mice.[97,98] Human NK cells are $CD3^-CD56^+$ and further categorized by CD16 expression.[94-96] Phenotypic variations include $CD56^{dim}$ $CD16^+$ and $CD57^+$ $NKG2A^-$ in humans and $CD27^-$ $CD11b^+$ in mice. Both human and mouse lung NK cells exhibit a differentiated but hypofunctional state, with specific surface markers such as higher levels of CD49b, CD122, CD43, Ly49s, and CD11b, and lower levels of CD51 compared to other tissues.[99] Killer-cell immunoglobulin-like receptor (KIR) expression is crucial for NK cell cytolytic activity and is higher in lung NK cells than in other organs.[100,101] Tissue-residing NK (trNK) cells make up 10–25% of human lung NK cells, primarily $CD16^-$, while circulating $CD16^+$ NK cells are more prevalent.[102,103] trNK cells are identified by positive CD69, CD49a, and/or CD103 expression along with CD56 in humans, and by positive CD49a, CD69, and CD11b in mice.[102-107] Human lung trNK cells produce cytokines like IFN-γ and tumor necrosis fctor-α (TNF-α), but have lower lytic granule expression.[108,109] Their frequency is elevated in lung cancer tissues, higher than in healthy controls.[104,106,107]

Lung resident lymphocytes in the protection against respiratory infection and chronic respiratory diseases

Lung resident lymphocytes in respiratory viral infection

Lung resident lymphocytes in acute respiratory viral infection

T_{RM} and B_{RM}. T_{RMs} play a central role in defense against respiratory viruses including respiratory syncytial virus (RSV), influenza, and SARS-CoV-2. For instance, both $CD4^+$ and $CD8^+$ T_{RMs} in the lung are in-

duced upon primary RSV infection and persist over 100 days.[110,111] In murine and African green monkey models, airway $CD8^+$ T_{RMs} displaying effector/tissue-resident memory phenotypes ($CD95^+$ $CD28^-$/$CD69^+$ $CD103^+$) significantly reduce viral loads.[112,113] Human RSV challenge studies confirm $CD103^-$-expressing $CD8^+$ T_{RMs} peak on day 10 postinfection, correlating with diminished disease severity, and offering protection against secondary infections.[114] In managing influenza A virus (IAV), lung-residing $CD4^+$ and $CD8^+$ T_{RMs} are key frontline defenders, distinguished by their pro-inflammatory cytokine secretion, such as IFN-γ, TNF, and IL-2.[115] $CD8^+$ T_{RMs} in the lung specialize in rapid antiviral actions and express high levels of interferon-induced transmembrane protein 3 (IFITM3) and other antiviral molecules. However, these cells have reduced efficacy against secondary infections and decline in function with age, constituting a risk for the elderly.[116-118] In the setting of severe respiratory coronaviruses like SARS-CoV-2, bronchoalveolar lavage (BAL) from acute COVID-19 patients reveals a complex array of $CD8^+$ T_{RMs} with distinct functionalities.[119-121] Subtypes include $CD103^{-/low}$ T_{RMs} enriched with cytotoxic and inflammatory molecules and $CXCR6^{hi}$ effector-like tissue-resident cells, implicating them in both acute and chronic lung pathology.[122]

The B-cell response to RSV involves distinct profiles in adenoid tissue and peripheral blood, with adenoids being the primary site for inducing high-affinity RSV-specific memory B cells.[123] Unlike conventional $CD27^+$ memory B cells, these cells mainly exhibit atypical IgM^+ and/or IgD^+ profiles and migrate to the lung upon subsequent RSV exposure, enhancing local immunity.[124] The roles of B_{RMs} and ABC_S in this context remain underexplored, indicating a research gap for vaccine development. B_{RMs} add complexity to the immune response. In mice, these cells exhibit uniform CCR6 and CXCR3 expression, intermediate CD69 levels, and downregulated S1pr1, Klf2, and S1pr5.[7,125] In humans, B_{RMs} similarly upregulate CD69 but show variations in CCR6 and CXCR3.[63] Their potential for rapid conversion to ASC_s is indicated by specific marker expressions, such as CD80, 5′-nucleotidase ecto (Nt5e), zinc finger and BTB domain containing 32 (Zbtb32), and programmed cell death 1 ligand 2 (Pdcd1lg2).[126-128] T-bet expression in B cells is vital for generating haemagglutinin (HA) stalk-specific IgG2c antibodies and sustaining neutralizing responses against influenza, thereby differentiating into memory B cell (MBC) subsets and influencing humoral memory.[129] Poon et al[120] found that lung-specific IgG^+ memory B cells, expressing CD69, were closely associated with specific $CD4^+$ T cells and $CD8^+$ T_{RMs}, signifying a potential coordinated immune response with lung resident lymphocytes.

Innate lymphocytes. Lung NK cells exhibit a stage-dependent role in RSV infection, participating in both innate and adaptive immunity. Initially, NK cells are recruited before T cells and can exacerbate lung injury via IFN-γ secretion, but also facilitate T-cell activation for viral clearance.[130-132] As the infection progresses, they shift to a harmful role, inhibiting antibody responses and promoting lung pathology.[131,132] NK cells also modulate Th2 responses, exacerbating severe RSV outcomes.[131,133,134] NK cells act as immediate antiviral responders during influenza virus infection. These cells accumulate in the lungs within 2–3 days postinfection.[135] Direct interaction between NK cells and influenza HA occurs via NKp46 and can facilitate NK cell lysis of virus-infected cells.[136] NK cells also contribute to viral clearance through death-receptor pathways, such as influenza-induced TNF-related apoptosis-inducing ligand (TRAIL) expression, and blocking this pathway impairs viral clearance.[137] Similarly, ILC1s have also been shown to contribute to the control of viral infection and dissemination.[138] ILC2s can facilitate the resolution of inflammation and tissue repair following respiratory viral injury largely through their production of amphiregulin (AREG).[9,139,140] Additionally, ILCs and NK cells can also produce IL-22, a known tissue-protective cytokine that promotes inflammation resolution and tissue repair in the respiratory tract, facilitating host recovery after influenza virus infection.[141]

Lung resident lymphocytes in post-acute sequelae of viral infection

More and more evidence has suggested that respiratory viral infections can lead to enduring complications in both pulmonary and extrapulmonary systems. Particularly, viruses like severe influenza and various coronaviruses can cause persistent lung inflammation and fibrosis stemming from acute diffuse alveolar damage (DAD), emphasizing the long-term impact of these acute infections on overall health.[142,143]

$CD8^+$ T cells, essential for virus-infected cell clearance, can induce persistent tissue damage and fibrotic sequelae if unchecked.[144,145] Aging amplifies post-viral risks, possibly due to the aged lung environment, which promotes non-resolving chronic immunopathology that leads to persistent pathology and impaired lung function. Virus-specific $CD8^+$ T_{RM} cells accumulate more in aged lung tissues after severe influenza infection, but become dysfunctional in providing secondary immunity against heterologous influenza challenge.[20,146] Consistently, persistent $CD8^+$ T_{RM} cells in COVID-19 survivors have been associated with diminished lung function, emphasizing their potential roles in long-term pulmonary complications.[20,122,147] Current research has not definitively established a connection between $CD4^+$ T_{RM} cells and the progression of disease following viral infections. However, the identification of a pathological $CD69^+CD103^{lo}$ T_{RM} cell population, which arises from chronic *Aspergillus fumigatus* exposure and shows proinflammatory and profibrotic tendencies, hints at a possible influence of $CD4^+$ T_{RM} cells in chronic lung diseases postinfection. This hypothesis gains support from the observed prevalence of $CD4^+$ T_{RM} cells in patients experiencing PASC infection, where they appear alongside the associated CXCR3 ligands, suggesting a contributory role in post-viral lung complications.[148–150] Additionally, T_{RH} cells have been identified to boost $CD8^+$ T_{RM} and B cell responses, raising queries about their possible dysfunctional role in postinfection sequelae.[21,23,24] Our recent study compared BAL single-cell RNA sequencing (scRNAseq) data from clinical PASC samples and mouse models, revealing abnormal macrophage–resident T cell interactions in respiratory PASC, and identified IFN-γ as a pivotal mediator; neutralizing IFN-γ postinfection improved lung function in respiratory PASC mouse models.[147,151]

Lung resident lymphocytes in bacterial and fungal infection

Building on the understanding of T_{RM} cells in viral infections, it is important to note that bacteria targeting the respiratory tract can similarly induce T_{RM}-cell responses, with distinct roles for $CD4^+$ T_{RM} cells in local protection. Unlike viral infections, respiratory $CD4^+$ T_{RM} cells serve a key role in protecting against respiratory tract bacterial infections compared to $CD8^+$ T_{RM} cells.[152-154] Severe *Streptococcus pneumoniae* (Spn) infection can often cause pneumonia, and in mouse models, repeated Spn challenge elicited a robust $CD4^+$ $T_{RM}17$ response, providing lobe-specific protection against reinfection through IL-17-mediated neutrophil recruitment.[153,155] Additionally, these $CD4^+$ T_{RM} cells can prevent pneumococcal colonization on the respiratory mucosa and contribute to the control of *Mycobacterium Tuberculosis* (*M. tuberculosis*) infections.[156,157] Vaccine strategies inducing lung T_{RM} cells, particularly $T_{RM}17$ cells, have shown superior protection against bacterial and fungal infections, including *Klebsiella pneumoniae* and *Cryptococcus gattii*.[158,159] B_{RM} cells are also crucial for pulmonary immunity in mice and humans after pneumococcal infections. These cells, marked by CD69, programmed death ligand 2 (PD-L2), CD80, and CD73, enhance bacterial clearance and antibody production, highlighting their role in antibacterial defense.[160] ILCs regulate tissue inflammation and homeostasis in response to various pathogens. When intracellular bacterial pathogens enter the mucosal tissue, ILC1s secrete cytokines, such as IFN-γ, to limit pathogen spread. During fungal infections, ILC2s can be activated by epithelial cell-derived alarmins to secrete cytokines like IL-13, aiding in the defense against these pathogens. Additionally, ILC3s play a crucial role in bacterial infections by producing IL-22, which is essential for bacterial clearance through the regulation of antimicrobial gene expression in epithelial cells.[161] Thus, ILCs are

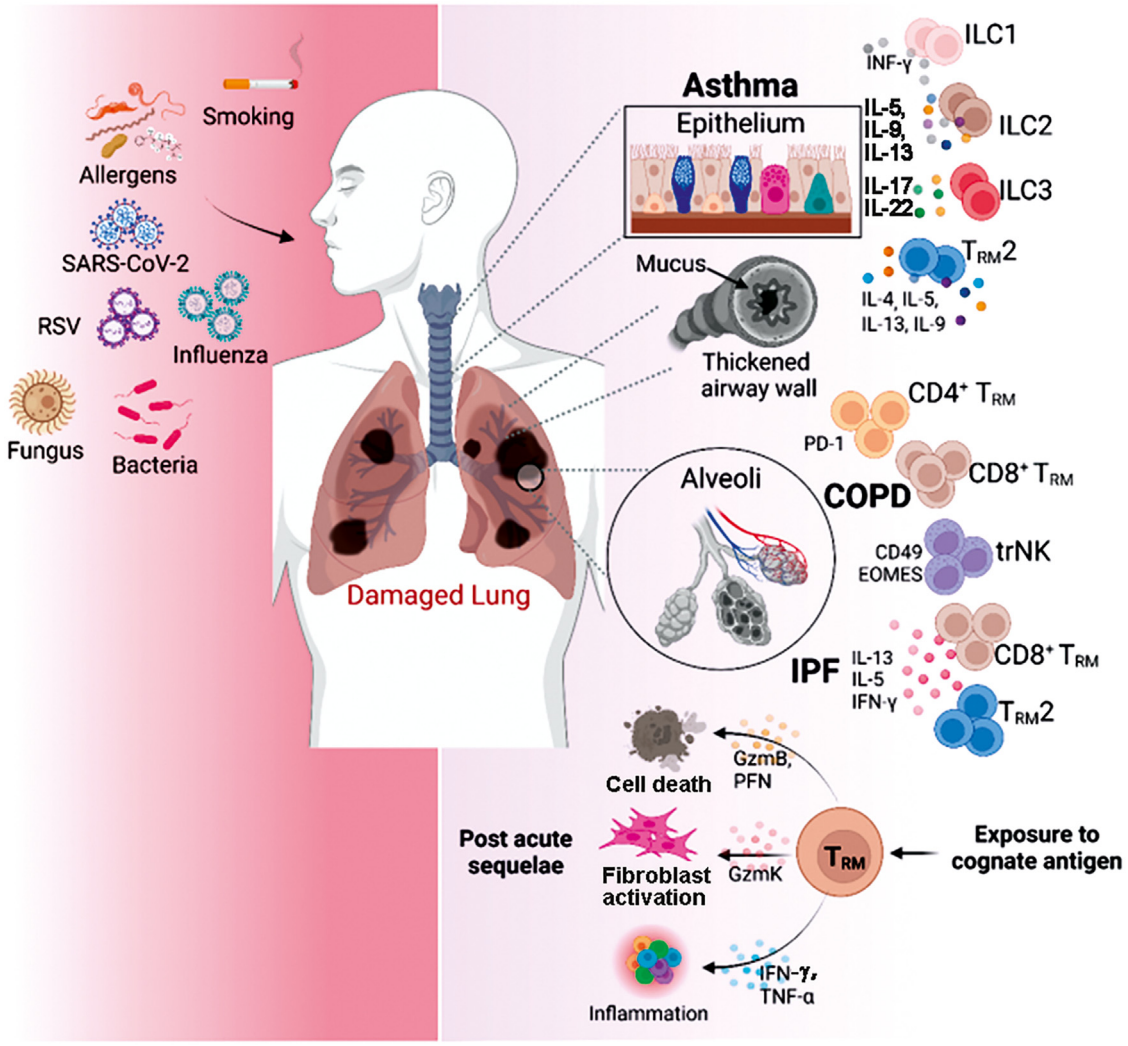

Fig. 2. Overview of the roles of lung-resident lymphocytes in immunodynamics across various pulmonary conditions. This schematic provides a comprehensive view of how these lymphocytes function within the immune landscape of different lung diseases such as asthma, pulmonary fibrosis, COPD, and post-acute sequelae. These conditions may be induced by various factors, including allergens and pathogens like influenza, SARS-CoV-2, and RSV. The figure also highlights the specific cytokine responses associated with each pulmonary condition, emphasizing the intricate immunological interactions in lung pathophysiology. COPD: Chronic obstructive pulmonary disease; EOMES: Eomesodermin; GzmB: Granzyme B; GzmK: Granzyme K; IL: Interleukin; ILC: Innate lymphoid cell; IFN-γ: Interferon-γ; IPF: Idiopathic pulmonary fibrosis; PD-1: Programmed cell death 1; PFN: Perforin; RSV: Respiratory syncytial virus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; TNF-α: Tumor necrosis factor-α; T_{RM}: Tissue-resident memory T cell; trNK: Tissue-residing natural killer.

important in controlling bacterial and fungal infections through the secretion of inflammatory mediators and interactions with other immune cells.

Lung resident lymphocytes in chronic respiratory diseases

Chronic respiratory diseases, such as COPD, asthma, and complications following viral infections, significantly affect global health. Recent studies highlight the crucial roles lung-resident lymphocytes may play in managing, evolving, or exacerbating these illnesses. These immune cells are key in various scenarios, exacerbating pulmonary damage post-acute viral infections and influencing the disease course in chronic pulmonary conditions, emphasizing the need for a deeper understanding of their functions and behaviors in diverse chronic lung diseases (Fig. 2).

Pulmonary fibrosis and COPD

Pulmonary fibrosis is associated with increased presence of $CD4^+$ and $CD8^+$ T_{RM} cells.[4] In mice, *Aspergillus fumigatus* exposed chronic pulmonary fibrosis model, lung-resident $CD4^+$ T_{RMs}, specifically the IL-5 and IL-13-producing $CD69^{hi}$ $CD103^{lo}$ $CD4^+$ $T_{RM}2$ subset, were identified as mediators of fibrotic processes.[150] In patients with interstitial lung diseases, an upregulation of $CD103^+$ $CD4^+$ T cells exhibiting a T-helper 1-like effector phenotype was noted in the airway, corroborated by elevated IFN-γ and IL-13-double producing $CD4^+$ T cells in BAL fluid.[28,162-164] We have also reported increased $CD8^+$ T_{RM} cells in the parenchymal tissue adjacent to fibrotic areas in idiopathic pulmonary fibrosis (IPF) patients.[144] These observations necessitate further investigation to ascertain the specific protective or pathological functions of $CD4^+$ and $CD8^+$ T_{RM} cells in the pathogenesis and progression of pulmonary fibrosis. ILC2s in IPF are implicated in the disease's progression through their increased production of IL-13, which is stimulated by elevated levels of IL-25 in lung tissues.[165,166] This IL-13 release, in turn, triggers collagen deposition, thereby contributing to lung fibrosis.

$CD8^+$ T_{RM} have been identified as key contributors in in COPD pathogenesis and progression, and their levels positively correlate with smoking intensity.[167,168] IFN-γ derived from tissue-resident lymphocytes including T_{RM}s can hinder alveolar stem cell growth and worsen emphysema.[169] The involvement of T_{RM} cells, specifically $CD8^+$ T_{RMs}, offers

a potential avenue for targeted therapeutic strategies aimed at ameliorating the symptoms and progression of COPD. Elevated B cell counts in COPD lungs are associated with disease severity and impaired IgA-mediated mucosal immunity, implicating a role in COPD progression.[170] B cell-rich lymphoid follicles are predominantly linked with the emphysema phenotype, and their signaling functions appear to be protective during acute exacerbations, although further studies are needed for confirmation.[171]

Mouse and human COPD models also reveal marked changes in CD49a$^+$ trNK cells, more so than circulating NK cells, correlating with disease severity. Upon re-exposure to influenza A, specialized trNK cell populations, notably CD49a$^+$CD49b$^+$EOMES$^+$ and CD49a$^+$CD49b$^-$EOMES^{lo}, exhibit increased activation and markers of tissue residency such as NKG2D, CD103, and CD69.[172] Human COPD samples display greater *ex vivo* influenza responsiveness, potentially worsening inflammation.[172] In contrast, IPF lung explants show fewer total and circulating NK cells but more pro-inflammatory trNK cells with altered gene expression. Blood samples indicate skewed cytokine-induced NK (ciNK) to trNK ratios, indicating impaired recruitment and systemic accumulation, consistent with previous findings on trNK dysfunction in IPF.[173]

Asthma

In mouse models of asthma, CD4$^+$ T_{RMs} are found to persist in the lungs for an extended period and are critical for promoting asthma symptoms upon allergen re-exposure, dependent on IL-2 and IL-7 signaling.[174,175] Research using a house dust mite allergen-based murine model reveals that although inhibiting circulatory T cell migration reduces the initial expansion of T_{RM} cells, subsequent allergen challenges still lead to robust lung inflammation and T_{RM} cell accumulation, emphasizing the role of T_{RM} cells in the exacerbation of asthma symptoms independently once established.[176] Human studies corroborate this, showing that patients with moderate to severe asthma have elevated levels of airway CD4$^+$ T_{RM} cells expressing pathogenic cytokines such as IL-9, as well as the IL-33 receptor, suppression of tumorigenicity 2 (ST2).[177-179] Additionally, these T_{RM} cells display a tissue-adaptation signature distinct from T_{CM} cells, contributing to different aspects of airway inflammation, including mucus metaplasia and eosinophil activation, which are key components in the exacerbation and maintenance of asthma symptoms.[174,175,180] Therefore, strategies targeting both the development and effector functions of lung-resident T cells are essential for managing and potentially preventing the exacerbation of asthma. This is particularly crucial in severe cases, where CD103-expressing CD4$^+$ T_{RM} cells contribute to a pro-inflammatory state associated with persistent airway inflammation and remodeling.[181]

ILCs, particularly ILC2s, are critical modulators of allergic asthma, orchestrating eosinophilic recruitment via IL-5 and epithelial barrier disruption through IL-13 secretion.[182,183] The regulatory role of ILC2s in allergic asthma is complex, involving not only the neuropeptide neuromedin U, which potently activates ILC2s and an inducer of asthma, but also a diverse set of molecular modulators such as IL-1β, arginase 1, and transcription factors like interferon regulatory factor 7 (IRF7).[184-186]

Therapeutic implications

The involvement of different lung resident lymphocyte populations in the pathophysiology of various lung disease conditions suggests that it might be promising to target these cells for developing new therapeutics. Emerging research accentuates that CD8$^+$ T_{RM} cells are fundamentally implicated in the pathogenesis of COPD, underscored by their pronounced accumulation in the lung tissues of affected individuals and their critical role in mediating pulmonary damage consequent to prolonged smoking exposure, thereby spotlighting these cells as pivotal targets for the innovation of effective therapeutic strategies aimed at mitigating COPD's progression and its associated exacerbations. Notch signaling, which is essential for lung T_{RM} cell maintenance,[187,188] could be targeted with AL101, an Food and Drug Administration (FDA)-designated drug for adenoid cystic carcinoma (NCT03691207), to dampen chronic exuberant T_{RM}-mediated lung diseases such as COPD, asthma, etc.

Similarly, TGF-β signaling, crucial for T_{RM} cell development and implicated in pulmonary fibrosis,[189,190] could be moderated to alleviate T_{RM}-induced lung damage, although its blockade poses toxicity risks due to its diverse tissue roles. IL-21, which augments CD8$^+$ T cell responses after influenza infection,[4,191] is another target. IL-21 blockers, like avizakimab (NCT03371251) in trials for systemic lupus erythematosus (SLE), can be potentially beneficial for preventing inflammation and lung fibrosis after viral pneumonia.[192] As dupilumab targets the IL-4Rα, inhibiting the IL-4 and IL-13 pathways crucial in type 2 inflammation,[193] its speculated interaction with lung-resident lymphocytes could herald a new era in managing chronic respiratory conditions like COPD. Its established efficacy, highlighted in the phase 3 clinical trial (NCT03930732), not only provides immediate therapeutic benefits but also sets the stage for future investigations into its long-term impact on pulmonary immune modulation and disease progression.[194]

In this context, the SECOVID study (NCT04948203), another phase 3 clinical trial, investigating the use of sirolimus in COVID-19 pneumonia patients presents a significant therapeutic implication. Given mammalian target of rapamycin (mTOR)'s critical role in lung resident lymphocyte regulation and its influence on T_{RM} and memory B cell functions, sirolimus, an mTOR inhibitor may offer a strategic approach to mitigating pulmonary fibrosis. By modulating mTOR pathways,[195] sirolimus could potentially stabilize or even reverse the pathological immune responses and fibrotic processes exacerbated by severe COVID-19, providing a hopeful avenue for preventing long-term pulmonary complications. Considering the crucial role of T_{RM} cells in sustaining inflammation and tissue damage post-viral infection, Paxlovid's role, particularly its component nirmatrelvir (NCT05595369), was studied in a phase 2 clinical trial, which extends beyond antiviral action, offering a potential therapeutic strategy to modulate T_{RM} cell activity. Curtailing viral replication promptly might impede the persistent stimulation of T_{RM} cells, thereby preventing their excessive responses that contribute to prolonged lung pathology and the progression of conditions like PASC.

Emerging strategies, such as intranasal boosters with adenovirus-expressing spike protein[196] and novel adjuvants like S100A4, AS03, or MF59, show promise in enhancing lung-specific immunity and broadening the B-cell repertoire, potentially offering an innovative approach to fortify the respiratory system against pathogens.[197-199] While prior vaccination is shown to be effective in reducing the risk of PASC development to subsequent infection, whether vaccination after the occurrence of infection is still effective in reducing PASC risk remains debatable.[200] The complex etiology of PASC, involving dysregulated CD8$^+$ T cell–macrophage interactions and abnormal immune–epithelial dynamics, highlights potential interventions targeting cytokines like IFN-γ, TNF, and IL-1β for improved pulmonary recovery.[147,201] A better understanding of the pathophysiology of PASC aligns with existing strategies to mitigate chronic lung diseases through targeted therapies such as Notch and TGF-β signaling and IL-21 modulation, etc, emphasizing a comprehensive approach to managing long-term respiratory immune challenges.

Conclusions

In summary, the intricate delicacy of the respiratory tract is under the vigilant watch of a dynamic immune system that walks a fine line between immune protection and immune pathology. While resident lung immune cells serve as the first responders to airborne threats, they also can overreact, leading to undesirable outcomes like inflammation and fibrosis. Just as a two-faced coin, the role of these cells can either be lifesaving or detrimental, contingent upon the context in which they operate. Unlocking the secrets of tissue-resident immune populations in the lung could, therefore, provide transformative avenues for therapeutic interventions. Although animal studies offer valuable insights, the

focus is now shifting toward immune regulation research in human tissues to demystify how these cells function *in situ*, paving the way for future therapeutic strategies and prevention measures.

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Conflicts of interest

J.S. receives a research contract from Isovax that is unrelated to this work. The authors declare no other conflicts of interest.

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References

1. Saluzzo S, Gorki AD, Rana BMJ, et al. First-breath-induced type 2 pathways shape the lung immune environment. *Cell Rep*. 2017;18:1893–1905. doi:10.1016/j.celrep.2017.01.071.
2. Hewitt RJ, Lloyd CM. Regulation of immune responses by the airway epithelial cell landscape. *Nat Rev Immunol*. 2021;21:347–362. doi:10.1038/s41577-020-00477-9.
3. Allie SR, Randall TD. Resident memory B cells. *Viral Immunol*. 2020;33:282–293. doi:10.1089/vim.2019.0141.
4. Cheon IS, Son YM, Sun J. Tissue-resident memory T cells and lung immunopathology. *Immunol Rev*. 2023;316:63–83. doi:10.1111/imr.13201.
5. Barlow JL, McKenzie ANJ. Innate lymphoid cells of the lung. *Annu Rev Physiol*. 2019;81:429–452. doi:10.1146/annurev-physiol-020518-114630.
6. Sun H, Sun C, Xiao W, Sun R. Tissue-resident lymphocytes: From adaptive to innate immunity. *Cell Mol Immunol*. 2019;16:205–215. doi:10.1038/s41423-018-0192-y.
7. Allie SR, Bradley JE, Mudunuru U, et al. The establishment of resident memory B cells in the lung requires local antigen encounter. *Nat Immunol*. 2019;20:97–108. doi:10.1038/s41590-018-0260-6.
8. Schenkel JM, Fraser KA, Beura LK, Pauken KE, Vezys V, Masopust D. T cell memory. Resident memory CD8 T cells trigger protective innate and adaptive immune responses. *Science*. 2014;346:98–101. doi:10.1126/science.1254536.
9. Monticelli LA, Sonnenberg GF, Abt MC, et al. Innate lymphoid cells promote lung-tissue homeostasis after infection with influenza virus. *Nat Immunol*. 2011;12:1045–1054. doi:10.1031/ni.2131.
10. Zheng MZM, Wakim LM. Tissue resident memory T cells in the respiratory tract. *Mucosal Immunol*. 2022;15:379–388. doi:10.1038/s41385-021-00461-z.
11. Tang J, Sun J. Lung tissue-resident memory T cells: The gatekeeper to respiratory viral (re)-infection. *Curr Opin Immunol*. 2023;80:102278. doi:10.1016/j.coi.2022.102278.
12. Skon CN, Lee JY, Anderson KG, Masopust D, Hogquist KA, Jameson SC. Transcriptional downregulation of S1pr1 is required for the establishment of resident memory CD8+ T cells. *Nat Immunol*. 2013;14:1285–1293. doi:10.1038/ni.2745.
13. Zhang J, Lyu T, Cao Y, Feng H. Role of TCF-1 in differentiation, exhaustion, and memory of CD8+ T cells: A review. *FASEB J*. 2021;35:e21549. doi:10.1096/fj.202002566R.
14. Parga-Vidal L, Behr FM, Kragten NAM, et al. Hobit identifies tissue-resident memory t cell precursors that are regulated by Eomes. *Sci Immunol*. 2021;6:eabg3533. doi:10.1126/sciimmunol.abg3533.
15. Mueller SN, Gebhardt T, Carbone FR, Heath WR. Memory T cell subsets, migration patterns, and tissue residence. *Annu Rev Immunol*. 2013;31:137–161. doi:10.1146/annurev-immunol-032712-095954.
16. Iborra S, Martínez-López M, Khouili SC, et al. Optimal generation of tissue-resident but not circulating memory T cells during viral infection requires crosspriming by DNGR-1+ dendritic cells. *Immunity*. 2016;45:847–860. doi:10.1016/j.immuni.2016.08.019.
17. Rotrosen E, Kupper TS. Assessing the generation of tissue resident memory T cells by vaccines. *Nat Rev Immunol*. 2023;23:655–665. doi:10.1038/s41577-023-00853-1.
18. McMaster SR, Wein AN, Dunbar PR, et al. Pulmonary antigen encounter regulates the establishment of tissue-resident CD8 memory T cells in the lung airways and parenchyma. *Mucosal Immunol*. 2018;11:1071–1078. doi:10.1038/s41385-018-0003-x.
19. Takamura S, Yagi H, Hakata Y, et al. Specific niches for lung-resident memory CD8+ T cells at the site of tissue regeneration enable CD69-independent maintenance. *J Exp Med*. 2016;213:3057–3073. doi:10.1084/jem.20160938.
20. Goplen NP, Wu Y, Son YM, et al. Tissue-resident CD8+ T cells drive age-associated chronic lung sequelae after viral pneumonia. *Sci Immunol*. 2020;5:eabc4557. doi:10.1126/sciimmunol.abc4557.
21. Son YM, Sun J. Co-ordination of mucosal B cell and CD8 T cell memory by tissue-resident CD4 helper T cells. *Cells*. 2021;10:2355. doi:10.3390/cells10092355.
22. Teijaro JR, Turner D, Pham Q, Wherry EJ, Lefrançois L, Farber DL. Cutting edge: Tissue-retentive lung memory CD4 T cells mediate optimal protection to respiratory virus infection. *J Immunol*. 2011;187:5510–5514. doi:10.4049/jimmunol.1102243.
23. Son YM, Cheon IS, Wu Y, et al. Tissue-resident CD4+ T helper cells assist the development of protective respiratory B and CD8+ T cell memory responses. *Sci Immunol*. 2021;6:eabb6852. doi:10.1126/sciimmunol.abb6852.
24. Swarnalekha N, Schreiner D, Litzler LC, et al. T resident helper cells promote humoral responses in the lung. *Sci Immunol*. 2021;6:eabb6808. doi:10.1126/sciimmunol.abb6808.
25. Ren HM, Kolawole EM, Ren M, et al. IL-21 from high-affinity CD4 T cells drives differentiation of brain-resident CD8 T cells during persistent viral infection. *Sci Immunol*. 2020;5:eabb5590. doi:10.1126/sciimmunol.abb5590.
26. Thome JJ, Yudanin N, Ohmura Y, et al. Spatial map of human T cell compartmentalization and maintenance over decades of life. *Cell*. 2014;159:814–828. doi:10.1016/j.cell.2014.10.026.
27. Kumar BV, Ma W, Miron M, et al. Human tissue-resident memory T cells are defined by core transcriptional and functional signatures in lymphoid and mucosal sites. *Cell Rep*. 2017;20:2921–2934. doi:10.1016/j.celrep.2017.08.078.
28. Szabo PA, Miron M, Farber DL. Location, location, location: Tissue resident memory T cells in mice and humans. *Sci Immunol*. 2019;4:eaas9673. doi:10.1126/sciimmunol.aas9673.
29. Yu CI, Becker C, Wang Y, et al. Human CD1c+ dendritic cells drive the differentiation of CD103+ CD8+ mucosal effector T cells via the cytokine TGF-β. *Immunity*. 2013;38:818–830. doi:10.1016/j.immuni.2013.03.004.
30. Snyder ME, Finlayson MO, Connors TJ, et al. Generation and persistence of human tissue-resident memory T cells in lung transplantation. *Sci Immunol*. 2019;4:eaav5581. doi:10.1126/sciimmunol.aav5581.
31. Hayday A, Tigelaar R. Immunoregulation in the tissues by gammadelta T cells. *Nat Rev Immunol*. 2003;3:233–242. doi:10.1038/nri1030.
32. Michel ML, Pang DJ, Haque SFY, Potocnik AJ, Pennington DJ, Hayday AC. Interleukin 7 (IL-7) selectively promotes mouse and human IL-17-producing $\gamma\delta$ cells. *Proc Natl Acad Sci U S A*. 2012;109:17549–17554. doi:10.1073/pnas.1204327109.
33. Chien YH, Zeng X, Prinz I. The natural and the inducible: interleukin (IL)-17-producing $\gamma\delta$ T cells. *Trends Immunol*. 2013;34:151–154. doi:10.1016/j.it.2012.11.004.
34. Itohara S, Farr AG, Lafaille JJ, et al. Homing of a gamma delta thymocyte subset with homogeneous T-cell receptors to mucosal epithelia. *Nature*. 1990;343:754–757. doi:10.1038/343754a0.
35. Wands JM, Roark CL, Aydintug MK, et al. Distribution and leukocyte contacts of gammadelta T cells in the lung. *J Leukoc Biol*. 2005;78:1086–1096. doi:10.1189/jlb.0505244.
36. Paget C, Chow MT, Gherardin NA, et al. CD3bright signals on $\gamma\delta$ T cells identify IL-17A-producing Vγ6Vδ1+ T cells. *Immunol Cell Biol*. 2015;93:198–212. doi:10.1038/icb.2014.94.
37. Haas JD, González FH, Schmitz S, et al. CCR6 and NK1.1 distinguish between IL-17A and IFN-gamma-producing gammadelta effector T cells. *Eur J Immunol*. 2009;39:3488–3497. doi:10.1002/eji.200939922.
38. Ribot JC, deBarros A, Pang DJ, et al. CD27 is a thymic determinant of the balance between interferon-gamma- and interleukin 17-producing gammadelta T cell subsets. *Nat Immunol*. 2009;10:427–436. doi:10.1038/ni.1717.
39. Cheng M, Hu S. Lung-resident $\gamma\delta$ T cells and their roles in lung diseases. *Immunology*. 2017;151:375–384. doi:10.1111/imm.12764.
40. Arish M, Qian W, Narasimhan H, Sun J. COVID-19 immunopathology: From acute diseases to chronic sequelae. *J Med Virol*. 2023;95:e28122. doi:10.1002/jmv.28122.
41. Martin E, Treiner E, Duban L, et al. Stepwise development of MAIT cells in mouse and human. *PLoS Biol*. 2009;7:e54. doi:10.1371/journal.pbio.1000054.
42. Tilloy F, Treiner E, Park SH, et al. An invariant T cell receptor alpha chain defines a novel TAP-independent major histocompatibility complex class Ib-restricted alpha/beta T cell subpopulation in mammals. *J Exp Med*. 1999;189:1907–1921. doi:10.1084/jem.189.12.1907.
43. Koay HF, Gherardin NA, Enders A, et al. A three-stage intrathymic development pathway for the mucosal-associated invariant T cell lineage. *Nat Immunol*. 2016;17:1300–1311. doi:10.1038/ni.3565.
44. Leeansyah E, Loh L, Nixon DF, Sandberg JK. Acquisition of innate-like microbial reactivity in mucosal tissues during human fetal MAIT-cell development. *Nat Commun*. 2014;5:3143. doi:10.1038/ncomms4143.
45. Godfrey DI, Koay HF, McCluskey J, Gherardin NA. The biology and functional importance of MAIT cells. *Nat Immunol*. 2019;20:1110–1128. doi:10.1038/s41590-019-0444-8.
46. Le Bourhis L, Martin E, Péguillet I, et al. Antimicrobial activity of mucosal-associated invariant T cells. *Nat Immunol*. 2010;11:701–708. doi:10.1038/ni.1890.
47. Gold MC, Cerri S, Smyk-Pearson S, et al. Human mucosal associated invariant T cells detect bacterially infected cells. *PLoS Biol*. 2010;8:e1000407. doi:10.1371/journal.pbio.1000407.
48. Kjer-Nielsen L, Patel O, Corbett AJ, et al. MR1 presents microbial vitamin B metabolites to MAIT cells. *Nature*. 2012;491:717–723. doi:10.1038/nature11605.
49. Meermeier EW, Zheng CL, Tran JG, et al. Human lung-resident mucosal-associated invariant T cells are abundant, express antimicrobial proteins, and are cytokine responsive. *Commun Biol*. 2022;5:942. doi:10.1038/s42003-022-03823-w.
50. Carreño LJ, Saavedra-Ávila NA, Porcelli SA. Synthetic glycolipid activators of natural killer T cells as immunotherapeutic agents. *Clin Transl Immunology*. 2016;5:e69. doi:10.1038/cti.2016.14.
51. Wu L, Van Kaer L. Natural killer T cells and autoimmune disease. *Curr Mol Med*. 2009;9:4–14. doi:10.2174/156652409787314534.

52. Liao CM, Zimmer MI, Shanmuganad S, Yu HT, Cardell SL, Wang CR. Dysregulation of CD1d-restricted type ii natural killer T cells leads to spontaneous development of colitis in mice. *Gastroenterology*. 2012;142:326–334.e1–2. doi:10.1053/j.gastro.2011.10.030.
53. Hogquist K, Georgiev H. Recent advances in iNKT cell development. *F1000 Res*. 2020;9:F1000 Faculty Rev–127. doi:10.12688/f1000research.21378.1.
54. Montoya CJ, Pollard D, Martinson J, et al. Characterization of human invariant natural killer T subsets in health and disease using a novel invariant natural killer T cell-clonotypic monoclonal antibody, 6B11. *Immunology*. 2007;122:1–14. doi:10.1111/j.1365-2567.2007.02647.x.
55. Lee YJ, Starrett GJ, Lee ST, et al. Lineage-specific effector signatures of invariant NKT cells are shared amongst $\gamma\delta$ T, innate lymphoid, and Th cells. *J Immunol*. 2016;197:1460–1470. doi:10.4049/jimmunol.1600643.
56. Lee PT, Benlagha K, Teyton L, Bendelac A. Distinct functional lineages of human V(alpha)24 natural killer T cells. *J Exp Med*. 2002;195:637–641. doi:10.1084/jem.20011908.
57. Kurosaki T, Kometani K, Ise W. Memory B cells. *Nat Rev Immunol*. 2015;15:149–159. doi:10.1038/nri3802.
58. Laidlaw BJ, Cyster JG. Transcriptional regulation of memory B cell differentiation. *Nat Rev Immunol*. 2021;21:209–220. doi:10.1038/s41577-020-00446-2.
59. Oh JE, Song E, Moriyama M, et al. Intranasal priming induces local lung-resident B cell populations that secrete protective mucosal antiviral IgA. *Sci Immunol*. 2021;6:eabj5129. doi:10.1126/sciimmunol.abj5129.
60. Weisel NM, Joachim SM, Smita S, et al. Surface phenotypes of naive and memory B cells in mouse and human tissues. *Nat Immunol*. 2022;23:135–145. doi:10.1038/s41590-021-01078-x.
61. MacLean AJ, Richmond N, Koneva L, et al. Secondary influenza challenge triggers resident memory B cell migration and rapid relocation to boost antibody secretion at infected sites. *Immunity*. 2022;55:718–733.e8. doi:10.1016/j.immuni.2022.03.003.
62. Gregoire C, Spinelli L, Villazala-Merino S, et al. Viral infection engenders bona fide and bystander subsets of lung-resident memory B cells through a permissive mechanism. *Immunity*. 2022;55:1216–1233.e9. doi:10.1016/j.immuni.2022.06.002.
63. Tan HX, Juno JA, Esterbauer R, et al. Lung-resident memory B cells established after pulmonary influenza infection display distinct transcriptional and phenotypic profiles. *Sci Immunol*. 2022;7:eabf5314. doi:10.1126/sciimmunol.abf5314.
64. Palm A-KE, Henry C. Remembrance of things past: Long-term B cell memory after infection and vaccination. *Front Immunol*. 2019;10:1787. doi:10.3389/fimmu.2019.01787.
65. Song S, Matthias PD. The transcriptional regulation of germinal center formation. *Front Immunol*. 2018;9:2026. doi:10.3389/fimmu.2018.02026.
66. Mathew NR, Jayanthan JK, Smirnov IV, et al. Single-cell BCR and transcriptome analysis after influenza infection reveals spatiotemporal dynamics of antigen-specific B cells. *Cell Rep*. 2022;41:111764. doi:10.1016/j.celrep.2022.111764.
67. Hao Y, O'Neill P, Naradikian MS, Scholz JL, Cancro MP. A B-cell subset uniquely responsive to innate stimuli accumulates in aged mice. *Blood*. 2011;118:1294–1304. doi:10.1182/blood-2011-01-330530.
68. Rubtsov AV, Rubtsova K, Fischer A, et al. Toll-like receptor 7 (TLR7)-driven accumulation of a novel CD11c^{+} B-cell population is important for the development of autoimmunity. *Blood*. 2011;118:1305–1315. doi:10.1182/blood-2011-01-331462.
69. Pritchard GH, Kedl RM, Hunter CA. The evolving role of T-bet in resistance to infection. *Nat Rev Immunol*. 2019;19:398–410. doi:10.1038/s41577-019-0145-4.
70. Chang L-Y, Li Y, Kaplan DE. Hepatitis C viraemia reversibly maintains subset of antigen-specific T-bet+ tissue-like memory B cells. *J Viral Hepat*. 2017;24:389–396. doi:10.1111/jvh.12659.
71. Eccles JD, Turner RB, Kirk NA, et al. T-bet+ memory B cells link to local cross-reactive IgG upon human rhinovirus infection. *Cell Rep*. 2020;30:351–366.e7. doi:10.1016/j.celrep.2019.12.027.
72. Knox JJ, Buggert M, Kardava L, et al. T-bet+ B cells are induced by human viral infections and dominate the HIV gp140 response. *JCI Insight*. 2017;2:e92943. doi:10.1172/jci.insight.92943.
73. Austin JW, Buckner CM, Kardava L, et al. Overexpression of T-bet in HIV infection is associated with accumulation of B cells outside germinal centers and poor affinity maturation. *Sci Transl Med*. 2019;11:eaax0904. doi:10.1126/scitranslmed.aax0904.
74. Woodruff MC, Ramonell RP, Nguyen DC, et al. Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19. *Nat Immunol*. 2020;21:1506–1516. doi:10.1038/s41590-020-00814-z.
75. Villadolid MC, Takano K, Hizuka N, et al. Twenty-four hour plasma GH, FSH and LH profiles in patients with Turner's syndrome. *Endocrinol Jpn*. 1988;35:71–81. doi:10.1507/endocrj1954.35.71.
76. Berland R, Fernandez L, Kari E, et al. Toll-like receptor 7-dependent loss of B cell tolerance in pathogenic autoantibody knockin mice. *Immunity*. 2006;25:429–440. doi:10.1016/j.immuni.2006.07.014.
77. Harris DP, Goodrich S, Gerth AJ, Peng SL, Lund FE. Regulation of IFN-gamma production by B effector 1 cells: Essential roles for T-bet and the IFN-gamma receptor. *J Immunol*. 2005;174:6781–6790. doi:10.4049/jimmunol.174.11.6781.
78. Naradikian MS, Myles A, Beiting DP, et al. Cutting edge: IL-4, IL-21, and IFN-γ interact to govern T-bet and CD11c EXPRESSION in TLR-activated B cells. *J Immunol*. 2016;197:1023–1028. doi:10.4049/jimmunol.1600522.
79. Mouat IC, Horwitz MS. Age-associated B cells in viral infection. *PLoS Pathog*. 2022;18:e1010297. doi:10.1371/journal.ppat.1010297.
80. Johnson JL, Rosenthal RL, Knox JJ, et al. The transcription factor T-bet resolves memory B cell subsets with distinct tissue distributions and antibody specificities in mice and humans. *Immunity*. 2020;52:842–855.e6. doi:10.1016/j.immuni.2020.03.020.
81. Lau D, Lan LY, Andrews SF, et al. Low CD21 expression defines a population of recent germinal center graduates primed for plasma cell differentiation. *Sci Immunol*. 2017;2:eaai8153. doi:10.1126/sciimmunol.aai8153.
82. Habener A, Grychtol R, Gaedcke S, et al. IgA^{+} memory B cells are significantly increased in patients with asthma and small airways dysfunction. *Eur Respir J*. 2022;60:2102130. doi:10.1183/13993003.02130-2021.
83. Gasteiger G, Fan X, Dikiy S, Lee SY, Rudensky AY. Tissue residency of innate lymphoid cells in lymphoid and nonlymphoid organs. *Science*. 2015;350:981–985. doi:10.1126/science.aac9593.
84. Spits H, Artis D, Colonna M, et al. Innate lymphoid cells–a proposal for uniform nomenclature. *Nat Rev Immunol*. 2013;13:145–149. doi:10.1038/nri3365.
85. Robinette ML, Colonna M. Immune modules shared by innate lymphoid cells and T cells. *J Allergy ClinImmunol*. 2016;138:1243–1251. doi:10.1016/j.jaci.2016.09.006.
86. Xue L, Salimi M, Panse I, et al. Prostaglandin D2 activates group 2 innate lymphoid cells through chemoattractant receptor-homologous molecule expressed on TH2 cells. *J Allergy ClinImmunol*. 2014;133:1184–1194. doi:10.1016/j.jaci.2013.10.056.
87. Chang YJ, Kim HY, Albacker LA, et al. Innate lymphoid cells mediate influenza-induced airway hyper-reactivity independently of adaptive immunity. *Nat Immunol*. 2011;12:631–638. doi:10.1038/ni.2045.
88. Petrova T, Pesic J, Pardali K, Gaestel M, Arthur JSC. p38 MAPK signalling regulates cytokine production in IL-33 stimulated type 2 innate lymphoid cells. *Sci Rep*. 2020;10:3479. doi:10.1038/s41598-020-60089-0.
89. Huang Y, Guo L, Qiu J, et al. IL-25-responsive, lineage-negative KLRG1(hi) cells are multipotential 'inflammatory' type 2 innate lymphoid cells. *Nat Immunol*. 2015;16:161–169. doi:10.1038/ni.3078.
90. Pearson C, Thornton EE, McKenzie B, et al. ILC3 GM-CSF production and mobilisation orchestrate acute intestinal inflammation. *Elife*. 2016;5:e10066. doi:10.7554/eLife.10066.
91. Constantinides MG, McDonald BD, Verhoef PA. Bendelac A. A committed precursor to innate lymphoid cells. *Nature*. 2014;508:397–401. doi:10.1038/nature13047.
92. Bernink JH, Krabbendam L, Germar K, et al. Interleukin-12 and -23 control plasticity of Cd127+ group 1 and group 3 innate lymphoid cells in the intestinal lamina propria. *Immunity*. 2015;43:146–160. doi:10.1016/j.immuni.2015.06.019.
93. Bal SM, Bernink JH, Nagasawa M, et al. IL-1β, IL-4 and IL-12 control the fate of group 2 innate lymphoid cells in human airway inflammation in the lungs. *Nat Immunol*. 2016;17:636–645. doi:10.1038/ni.3444.
94. Mazzurana L, Czarnewski P, Jonsson V, et al. Tissue-specific transcriptional imprinting and heterogeneity in human innate lymphoid cells revealed by full-length single-cell RNA-sequencing. *Cell Res*. 2021;31:554–568. doi:10.1038/s41422-020-00445-x.
95. Kim HY, Lee HJ, Chang YJ, et al. Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. *Nat Med*. 2014;20:54–61. doi:10.1038/nm.3423.
96. Carrega P, Loiacono F, Di Carlo E, et al. NCR(+)ILC3 concentrate in human lung cancer and associate with intratumoral lymphoid structures. *Nat Commun*. 2015;6:8280. doi:10.1038/ncomms9280.
97. Grégoire C, Chasson L, Luci C, et al. The trafficking of natural killer cells. *Immunol Rev*. 2007;220:169–182. doi:10.1111/j.1600-065X.2007.00563.x.
98. Marquardt N, Kekäläinen E, Chen P, et al. Human lung natural killer cells are predominantly comprised of highly differentiated hypofunctional CD69−CD56dim cells. *J Allergy Clin Immunol*. 2017;139:1321–1330.e4. doi:10.1016/j.jaci.2016.07.043.
99. Wang J, Li F, Zheng M, Sun R, Wei H, Tian Z. Lung natural killer cells in mice: Phenotype and response to respiratory infection. *Immunology*. 2012;137:37–47. doi:10.1111/j.1365-2567.2012.03607.x.
100. Cong J, Wei H. Natural killer cells in the lungs. *Front Immunol*. 2019;10:1416. doi:10.3389/fimmu.2019.01416.
101. Anfossi N, André P, Guia S, et al. Human NK cell education by inhibitory receptors for MHC class I. *Immunity*. 2006;25:331–342. doi:10.1016/j.immuni.2006.06.013.
102. Marquardt N, Kekäläinen E, Chen P, et al. Unique transcriptional and protein-expression signature in human lung tissue-resident NK cells. *Nat Commun*. 2019;10:3841. doi:10.1038/s41467-019-11632-9.
103. Franklin M, Connolly E, Hussell T. Recruited and tissue-resident natural killer cells in the lung during infection and cancer. *Front Immunol*. 2022;13:887503. doi:10.3389/fimmu.2022.887503.
104. Cooper GE, Ostridge K, Khakoo SI, Wilkinson TMA, Staples KJ. Human CD49a+ lung natural killer cell cytotoxicity in response to influenza A virus. *Front Immunol*. 2018;9:1671. doi:10.3389/fimmu.2018.01671.
105. Dogra P, Rancan C, Ma W, et al. Tissue determinants of human NK cell development, function, and residence. *Cell*. 2020;180:749–763.e13. doi:10.1016/j.cell.2020.01.022.
106. Brownlie D, Scharenberg M, Mold JE, et al. Expansions of adaptive-like NK cells with a tissue-resident phenotype in human lung and blood. *Proc Natl Acad Sci U S A*. 2021;118:e2016580118. doi:10.1073/pnas.2016580118.
107. Sojka DK, Plougastel-Douglas B, Yang L, et al. Tissue-resident natural killer (NK) cells are cell lineages distinct from thymic and conventional splenic NK cells. *Elife*. 2014;3:e01659. doi:10.7554/eLife.01659.
108. Nagler A, Lanier LL, Cwirla S, Phillips JH. Comparative studies of human FcRIII-positive and negative natural killer cells. *J Immunol*. 1989;143:3183–3191. doi:10.4049/jimmunol.143.10.3183.
109. Poli A, Michel T, Thérésine M, Andrès E, Hentges F, Zimmer J. CD56bright natural killer (NK) cells: An important NK cell subset. *Immunology*. 2009;126:458–465. doi:10.1111/j.1365-2567.2008.03027.x.
110. Ostler T, Hussell T, Surh CD, Openshaw P, Ehl S. Long-term persistence and reactivation of T cell memory in the lung of mice infected with respiratory syncytial virus. *Eur J Immunol*. 2001;31:2574–2582. doi:10.1002/1521-4141(200109)31:9(2574.
111. Luangrath MA, Schmidt ME, Hartwig SM, Varga SM. Tissue-resident memory T cells

in the lungs protect against acute respiratory syncytial virus infection. *Immunohorizons*. 2021;5:59–69. doi:10.4049/immunohorizons.2000067.
112. Li H, Callahan C, Citron M, et al. Respiratory syncytial virus elicits enriched CD8+ T lymphocyte responses in lung compared with blood in African green monkeys. *PLoS One*. 2017;12:e0187642. doi:10.1371/journal.pone.0187642.
113. Kinnear E, Lambert L, McDonald JU, Cheeseman HM, Caproni LJ, Tregoning JS. Airway T cells protect against RSV infection in the absence of antibody. *Mucosal Immunol*. 2018;11:249–256. doi:10.1038/mi.2017.46.
114. Jozwik A, Habibi MS, Paras A, et al. RSV-specific airway resident memory CD8+ T cells and differential disease severity after experimental human infection. *Nat Commun*. 2015;6:10224. doi:10.1038/ncomms10224.
115. Pizzolla A, Nguyen TH, Sant S, et al. Influenza-specific lung-resident memory T cells are proliferative and polyfunctional and maintain diverse TCR profiles. *J Clin Invest*. 2018;128:721–733. doi:10.1172/JCI96957.
116. Wu T, Hu Y, Lee YT, et al. Lung-resident memory CD8 T cells (TRM) are indispensable for optimal cross-protection against pulmonary virus infection. *J Leukoc Biol*. 2014;95:215–224. doi:10.1189/jlb.0313180.
117. Wakim LM, Gupta N, Mintern JD, Villadangos JA. Enhanced survival of lung tissue-resident memory CD8 + T cells during infection with influenza virus due to selective expression of IFITM3. *Nat Immunol*. 2013;14:238–245. doi:10.1038/ni.2525.
118. Nguyen TH, McAuley JL, Kim Y, et al. Influenza, but not SARS-CoV-2, infection induces a rapid interferon response that wanes with age and diminished tissue-resident memory CD8+ T cells. *Clin Transl Immunology*. 2021;10:e1242. doi:10.1002/cti2.1242.
119. Liao M, Liu Y, Yuan J, et al. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nat Med*. 2020;26:842–844. doi:10.1038/s41591-020-0901-9.
120. Poon MML, Rybkina K, Kato Y, et al. SARS-CoV-2 infection generates tissue-localized immunological memory in humans. *Sci Immunol*. 2021;6:eabl9105. doi:10.1126/sciimmunol.abl9105.
121. Wauters E, Van Mol P, Garg AD, et al. Discriminating mild from critical COVID-19 by innate and adaptive immune single-cell profiling of bronchoalveolar lavages. *Cell Res*. 2021;31:272–290. doi:10.1038/s41422-020-00455-9.
122. Cheon IS, Li C, Son YM, et al. Immune signatures underlying post-acute COVID-19 lung sequelae. *Sci Immunol*. 2021;6:eabk1741. doi:10.1126/sciimmunol.abk1741.
123. Shehata L, Wieland-Alter WF, Maurer DP, et al. Systematic comparison of respiratory syncytial virus-induced memory B cell responses in two anatomical compartments. *Nat Commun*. 2019;10:1126. doi:10.1038/s41467-019-09085-1.
124. Weston-Bell N, Townsend M, Di Genova G, Forconi F, Sahota SS. Defining origins of malignant B cells: A new circulating normal human IgM+D+ B-cell subset lacking CD27 expression and displaying somatically mutated IGHV genes as a relevant memory population. *Leukemia*. 2009;23:2075–2080. doi:10.1038/leu.2009.178.
125. Onodera T, Takahashi Y, Yokoi Y, et al. Memory B cells in the lung participate in protective humoral immune responses to pulmonary influenza virus reinfection. *Proc Natl Acad Sci U S A*. 2012;109:2485–2490. doi:10.1073/pnas.1115369109.
126. Kim CC, Baccarella AM, Bayat A, Pepper M, Fontana MF. FCRL5 + memory B cells exhibit robust recall responses. *Cell Rep*. 2019;27:1446–1460.e4. doi:10.1016/j.celrep.2019.04.019.
127. Takatsuka S, Yamada H, Haniuda K, et al. IL-9 receptor signaling in memory B cells regulates humoral recall responses. *Nat Immunol*. 2018;19:1025–1034. doi:10.1038/s41590-018-0177-0.
128. Zuccarino-Catania GV, Sadanand S, Weisel FJ, et al. CD80 and PD-L2 define functionally distinct memory B cell subsets that are independent of antibody isotype. *Nat Immunol*. 2014;15:631–637. doi:10.1038/ni.2914.
129. Gordon SM, Chaix J, Rupp LJ, et al. The transcription factors T-bet and Eomes control key checkpoints of natural killer cell maturation. *Immunity*. 2012;36:55–67. doi:10.1016/j.immuni.2011.11.016.
130. Bhat R, Farrag MA, Almajhdi FN. Double-edged role of natural killer cells during RSV infection. *Int Rev Immunol*. 2020;39:233–244. doi:10.1080/08830185.2020.1770748.
131. Kaiko GE, Phipps S, Angkasekwinai P, Dong C, Foster PS. NK cell deficiency predisposes to viral-induced Th2-type allergic inflammation via epithelial-derived IL-25. *J Immunol*. 2010;185:4681–4690. doi:10.4049/jimmunol.1001758.
132. Van Erp EA, Van Kampen MR, Van Kasteren PB, De Wit J. Viral infection of human natural killer cells. *Viruses*. 2019;11:243. doi:10.3390/v11030243.
133. Harker JA, Yamaguchi Y, Culley FJ, Tregoning JS, Openshaw PJM. Delayed sequelae of neonatal respiratory syncytial virus infection are dependent on cells of the innate immune system. *J Virol*. 2014;88:604–611. doi:10.1128/jvi.02620-13.
134. Binns E, Tuckerman J, Licciardi PV, Wurzel D. Respiratory syncytial virus, recurrent wheeze and asthma: A narrative review of pathophysiology, prevention and future directions. *J Paediatr Child Health*. 2022;58:1741–1746. doi:10.1111/jpc.16197.
135. Zhou G, Juang SW, Kane KP. NK cells exacerbate the pathology of influenza virus infection in mice. *Eur J Immunol*. 2013;43:929–938. doi:10.1002/eji.201242620.
136. Mandelboim O, Lieberman N, Lev M, et al. Recognition of haemagglutinins on virus-infected cells by NKp46 activates lysis by human NK cells. *Nature*. 2001;409:1055–1060. doi:10.1038/35059110.
137. Ishikawa E, Nakazawa M, Yoshinari M, Minami M. Role of tumor necrosis factor-related apoptosis-inducing ligand in immune response to influenza virus infection in mice. *J Virol*. 2005;79:7658–7663. doi:10.1128/jvi.79.12.7658-7663.2005.
138. Lujan RA, Vrba SM, Hickman HD. Antiviral activities of group I innate lymphoid cells. *J Mol Biol*. 2022;434:167266. doi:10.1016/j.jmb.2021.167266.
139. Califano D, Furuya Y, Roberts S, Avram D, McKenzie ANJ, Metzger DW. IFN-γ increases susceptibility to influenza A infection through suppression of group II innate lymphoid cells. *Mucosal Immunol*. 2018;11:209–219. doi:10.1038/mi.2017.41.
140. Jamieson AM, Pasman L, Yu S, et al. Role of tissue protection in lethal respiratory viral-bacterial coinfection. *Science*. 2013;340:1230–1234. doi:10.1126/science.1233632.
141. Wei X, Narasimhan H, Zhu B, Sun J. Host recovery from respiratory viral infection. *Annu Rev Immunol*. 2023;41:277–300. doi:10.1146/annurev-immunol-101921-040450.
142. Narasimhan H, Wu Y, Goplen NP, Sun J. Immune determinants of chronic sequelae after respiratory viral infection. *Sci Immunol*. 2022;7:eabm7996. doi:10.1126/sciimmunol.abm7996.
143. Zheng Z, Peng F, Zhou Y. Pulmonary fibrosis: A short- or long-term sequelae of severe COVID-19? *Chin Med J Pulm Crit Care Med*. 2023;1:77–83. doi:10.1016/j.pccm.2022.12.002.
144. Wang Z, Wang S, Goplen NP, et al. PD-1hi CD8+ resident memory T cells balance immunity and fibrotic sequelae. *Sci Immunol*. 2019;4:eaaw1217. doi:10.1126/sciimmunol.aaw1217.
145. Keeler SP, Agapov EV, Hinojosa ME, Letvin AN, Wu K, Holtzman MJ. Influenza A virus infection causes chronic lung disease linked to sites of active viral RNA remnants. *J Immunol*. 2018;201:2354–2368. doi:10.4049/jimmunol.1800671.
146. Cookenham T, Lanzer KG, Tighe M, Ward JM, Reiley WW, Blackman MA. Visualization of resident memory CD8 T cells in the lungs of young and aged influenza memory mice and after heterosubtypic challenge. *Immunohorizons*. 2021;5:543–556. doi:10.4049/immunohorizons.2100032.
147. Narasimhan H, Cheon IS, Qian W, et al. Proximal immune-epithelial progenitor interactions drive chronic tissue sequelae post COVID-19. *bioRxiv*. 2023. doi:10.1101/2023.09.13.557622.
148. Phetsouphanh C, Darley DR, Wilson DB, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat Immunol*. 2022;23:210–216. doi:10.1038/s41590-021-01113-x.
149. Vijayakumar B, Boustani K, Ogger PP, et al. Immuno-proteomic profiling reveals aberrant immune cell regulation in the airways of individuals with ongoing post-COVID-19 respiratory disease. *Immunity*. 2022;55:542–556.e5. doi:10.1016/j.immuni.2022.01.017.
150. Ichikawa T, Hirahara K, Kokubo K, et al. CD103hi Treg cells constrain lung fibrosis induced by CD103 tissue-resident pathogenic CD4 T cells. *Nat Immunol*. 2019;20:1469–1480. doi:10.1038/s41590-019-0494-y.
151. Li C, Qian W, Wei X, et al. Comparative single-cell analysis reveals IFN-γ as a driver of respiratory sequelae post COVID-19. bioRxiv. doi: 10.1101/2023.10.03.560739.
152. Sakai S, Kauffman KD, Schenkel JM, et al. Cutting edge: Control of *Mycobacterium tuberculosis* infection by a subset of lung parenchyma–homing CD4 T cells. *J Immunol*. 2014;192:2965–2969. doi:10.4049/jimmunol.1400019.
153. Smith NM, Wasserman GA, Coleman FT, et al. Regionally compartmentalized resident memory T cells mediate naturally acquired protection against pneumococcal pneumonia. *Mucosal Immunol*. 2018;11:220–235. doi:10.1038/mi.2017.43.
154. Amezcua Vesely MC, Pallis P, Bielecki P, et al. Effector TH17 cells give rise to long-lived TRM cells that are essential for an immediate response against bacterial infection. *Cell*. 2019;178:1176–1188.e15. doi:10.1016/j.cell.2019.07.032.
155. O'Hara JM, Redhu NS, Cheung E, et al. Generation of protective pneumococcal-specific nasal resident memory CD4+ T cells via parenteral immunization. *Mucosal Immunol*. 2020;13:172–182. doi:10.1038/s41385-019-0218-5.
156. Dubois MF, Mezger V, Morange M, Ferrieux C, Lebon P, Bensaude O. Regulation of the heat-shock response by interferon in mouse L cells. *J Cell Physiol*. 1988;137:102–109. doi:10.1002/jcp.1041370112.
157. Ogongo P, Tezera LB, Ardain A, et al. Tissue-resident-like CD4+ T cells secreting IL-17 control *Mycobacterium tuberculosis* in the human lung. *J Clin Invest*. 2021;131:e142014. doi:10.1172/JCI142014.
158. Iwanaga N, Chen K, Yang H, et al. Vaccine-driven lung TRM cells provide immunity against *Klebsiella* via fibroblast IL-17R signaling. *Sci Immunol*. 2021;6:eabf1198. doi:10.1126/sciimmunol.abf1198.
159. Ueno K, Urai M, Sadamoto S, et al. A dendritic cell-based systemic vaccine induces long-lived lung-resident memory Th17 cells and ameliorates pulmonary mycosis. *Mucosal Immunol*. 2019;12:265–276. doi:10.1038/s41385-018-0094-4.
160. Barker KA, Etesami NS, Shenoy AT, et al. Lung-resident memory B cells protect against bacterial pneumonia. *J Clin Invest*. 2021;131:e141810. doi:10.1172/JCI141810.
161. Leupold T, Wirtz S. ILCs—crucial players in enteric infectious. *Int J Mol Sci*. 2022;23:14200. doi:10.3390/ijms232214200.
162. Braun RK, Foerster M, Grahmann PR, Haefner D, Workalemahu G, Kroegel C. Phenotypic and molecular characterization of CD103+ CD4 + T cells in bronchoalveolar lavage from patients with interstitial lung diseases. *Cytometry B Clin Cytom*. 2003;54:19–27. doi:10.1002/cyto.b.10021.
163. Sikkeland LIB, Qiao SW, Ueland T, et al. Lung CD4+ T-cells in patients with lung fibrosis produce pro-fibrotic interleukin-13 together with interferon-γ. *Eur Respir J*. 2021;57:2000983. doi:10.1183/13993003.00983-2020.
164. Serezani APM, Pascoalino BD, Bazzano JMR, et al. Multiplatform single-cell analysis identifies immune cell types enhanced in pulmonary fibrosis. *Am J Respir Cell Mol Biol*. 2022;67:50–60. doi:10.1165/rcmb.2021-0418OC.
165. Hams E, Armstrong ME, Barlow JL, et al. IL-25 and type 2 innate lymphoid cells induce pulmonary fibrosis. *Proc Natl Acad Sci U S A*. 2014;111:367–372. doi:10.1073/pnas.1315854111.
166. Xu X, Luo S, Li B, Dai H, Zhang J. IL-25 contributes to lung fibrosis by directly acting on alveolar epithelial cells and fibroblasts. *Exp Biol Med (Maywood)*. 2019;244:770–780. doi:10.1177/1535370219843827.
167. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. *J Allergy ClinImmunol*. 2016;138:16–27. doi:10.1016/j.jaci.2016.05.011.
168. Richmond B, Serezani A, Schaff J, Blackwell T. Tissue resident memory T cells are

increased in the lungs of COPD patients. *ERJ Open Res*. 2022;8(Suppl 8):247. doi:10.1183/23120541.LSC-2022.247.
169. Wang C, Hyams B, Allen NC, et al. Dysregulated lung stroma drives emphysema exacerbation by potentiating resident lymphocytes to suppress an epithelial stem cell reservoir. *Immunity*. 2023;56:576–591.e10. doi:10.1016/j.immuni.2023.01.032.
170. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350:2645–2653. doi:10.1056/nejmoa032158.
171. Polverino F, Seys LJM, Bracke KR, Owen CA. B cells in chronic obstructive pulmonary disease: Moving to center stage. *Am J Physiol Lung Cell Mol Physiol.*. 2016;311:L687–L695. doi:10.1152/ajplung.00304.2016.
172. Cooper GE, Mayall J, Donovan C, et al. Antiviral responses of tissue-resident CD49a+ lung natural killer cells are dysregulated in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2023;207:553–565. doi:10.1164/rccm.202205-0848OC.
173. Cruz T, Jia M, Sembrat J, et al. Reduced proportion and activity of natural killer cells in the lung of patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2021;204:608–610. doi:10.1164/rccm.202012-4418LE.
174. Hondowicz BD, An D, Schenkel JM, et al. Interleukin-2-dependent allergen-specific tissue-resident memory cells drive asthma. *Immunity*. 2016;44:155–166. doi:10.1016/j.immuni.2015.11.004.
175. Yeon SM, Halim L, Chandele A, et al. IL-7 plays a critical role for the homeostasis of allergen-specific memory CD4 T cells in the lung and airways. *Sci Rep*. 2017;7:11155. doi:10.1038/s41598-017-11492-7.
176. Sethi GS, Gracias D, Croft M. Contribution of circulatory cells to asthma exacerbations and lung tissue-resident CD4 T cell memory. *Front Immunol*. 2022;13:951361. doi:10.3389/fimmu.2022.951361.
177. Smyth LJC, Eustace A, Kolsum U, Blaikely J, Singh D. Increased airway T regulatory cells in asthmatic subjects. *Chest*. 2010;138:905–912. doi:10.1378/chest.09-3079.
178. Seumois G, Ramírez-Suástegui C, Schmiedel BJ, et al. Single-cell transcriptomic analysis of allergen-specific T cells in allergy and asthma. *Sci Immunol*. 2020;5:eaba6087. doi:10.1126/SCIIMMUNOL.ABA6087.
179. Wambre E, Bajzik V, DeLong JH, et al. A phenotypically and functionally distinct human TH2 cell subpopulation is associated with allergic disorders. *Sci Transl Med*. 2017;9:eaam9171. doi:10.1126/scitranslmed.aam9171.
180. Rahimi RA, Nepal K, Cetinbas M, Sadreyev RI, Luster AD. Distinct functions of tissue-resident and circulating memory Th2 cells in allergic airway disease. *J Exp Med*. 2020;217:e20190865. doi:10.1084/jem.20190865.
181. Herrera-De La Mata S, Ramírez-Suástegui C, Mistry H, et al. Cytotoxic CD4+ tissue-resident memory T cells are associated with asthma severity. *Med*. 2023;4:875–897.e8. doi:10.1016/j.medj.2023.09.003.
182. Nussbaum JC, Van Dyken SJ, von Moltke J, et al. Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature*. 2013;502:245–248. doi:10.1038/nature12526.
183. Sugita K, Steer CA, Martinez-Gonzalez I, et al. Type 2 innate lymphoid cells disrupt bronchial epithelial barrier integrity by targeting tight junctions through IL-13 in asthmatic patients. *J Allergy ClinImmunol*. 2018;141:300–310.e11. doi:10.1016/j.jaci.2017.02.038.
184. He J, Yang Q, Xiao Q, et al. IRF-7 is a critical regulator of type 2 innate lymphoid cells in allergic airway inflammation. *Cell Rep*. 2019;29:2718–2730.e6. doi:10.1016/j.celrep.2019.10.077.
185. Monticelli LA, Buck MD, Flamar AL, et al. Arginase 1 is an innate lymphoid-cell-intrinsic metabolic checkpoint controlling type 2 inflammation. *Nat Immunol*. 2016;17:656–665. doi:10.1038/ni.3421.
186. Wallrapp A, Riesenfeld SJ, Burkett PR, et al. The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation. *Nature*. 2017;549:351–356. doi:10.1038/nature24029.
187. Hombrink P, Helbig C, Backer RA, et al. Erratum: Programs for the persistence, vigilance and control of human CD8+ lung-resident memory T cells (Nature Immunology (2016) 17 (1467–1478)). *Nat Immunol*. 2017;18:246. doi:10.1038/ni0217-246d.
188. Hombrink P, Helbig C, Backer RA, et al. Programs for the persistence, vigilance and control of human CD8 + lung-resident memory T cells. *Nat Immunol*. 2016;17:1467–1478. doi:10.1038/ni.3589.
189. Budi EH, Schaub JR, Decaris M, Turner S, Derynck R. TGF-β as a driver of fibrosis: Physiological roles and therapeutic opportunities. *J Pathol*. 2021;254:358–373. doi:10.1002/path.5680.
190. Sheppard D. Transforming growth factor β: A central modulator of pulmonary and airway inflammation and fibrosis. *Proc Am Thorac Soc*. 2006;3:413–417. doi:10.1513/pats.200601-008AW.
191. Zander R, Kasmani MY, Chen Y, et al. TFH-cell-derived interleukin 21 sustains effector CD8+ T cell responses during chronic viral infection. *Immunity*. 2022;55:475–493 e5. doi:10.1016/j.immuni.2022.01.018.
192. Hussaini A, Mukherjee R, Berdieva DM, Glogowski C, Mountfield R, Ho PTC. A double-blind, phase I, single ascending dose study to assess the safety, pharmacokinetics, and pharmacodynamics of BOS161721 in healthy subjects. *Clin Transl Sci*. 2020;13:337–344. doi:10.1111/cts.12715.
193. Le Floc'h A, Allinne J, Nagashima K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. *Allergy*. 2020;75:1188–1204. doi:10.1111/all.14151.
194. Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. *N Engl J Med*. 2023;389:205–214. doi:10.1056/nejmoa2303951.
195. Jones RG, Pearce EJ. MenTORing immunity: mTOR signaling in the development and function of tissue-resident immune cells. *Immunity*. 2017;46:730–742. doi:10.1016/j.immuni.2017.04.028.
196. Tang J, Zeng C, Cox TM, et al. Respiratory mucosal immunity against SARS-CoV-2 after mRNA vaccination. *Sci Immunol*. 2022;7:eadd4853. doi:10.1126/sciimmunol.add4853.
197. Sen Chaudhuri A, Yeh YW, Zewdie O, et al. S100A4 exerts robust mucosal adjuvant activity for co-administered antigens in mice. *Mucosal Immunol*. 2022;15:1028–1039. doi:10.1038/s41385-022-00535-6.
198. Jackson LA, Campbell JD, Frey SE, et al. Effect of varying doses of a monovalent H7N9 influenza vaccine with and without AS03 and MF59 adjuvants on immune response a randomized clinical trial. *JAMA*. 2015;314:237–246. doi:10.1001/jama.2015.7916.
199. Galson JD, Trück J, Kelly DF, van der Most R. Investigating the effect of AS03 adjuvant on the plasma cell repertoire following pH1N1 influenza vaccination. *Sci Rep*. 2016;6:37229. doi:10.1038/srep37229.
200. Notarte KI, Catahay JA, Velasco JV, et al. Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic review. *EClinicalMedicine*. 2022;53:101624. doi:10.1016/j.eclinm.2022.101624.
201. Arish M, Sun J. Monocyte and macrophage function in respiratory viral infections. *Animal Dis*. 2023;3:30. doi:10.1186/s44149-023-00095-7.