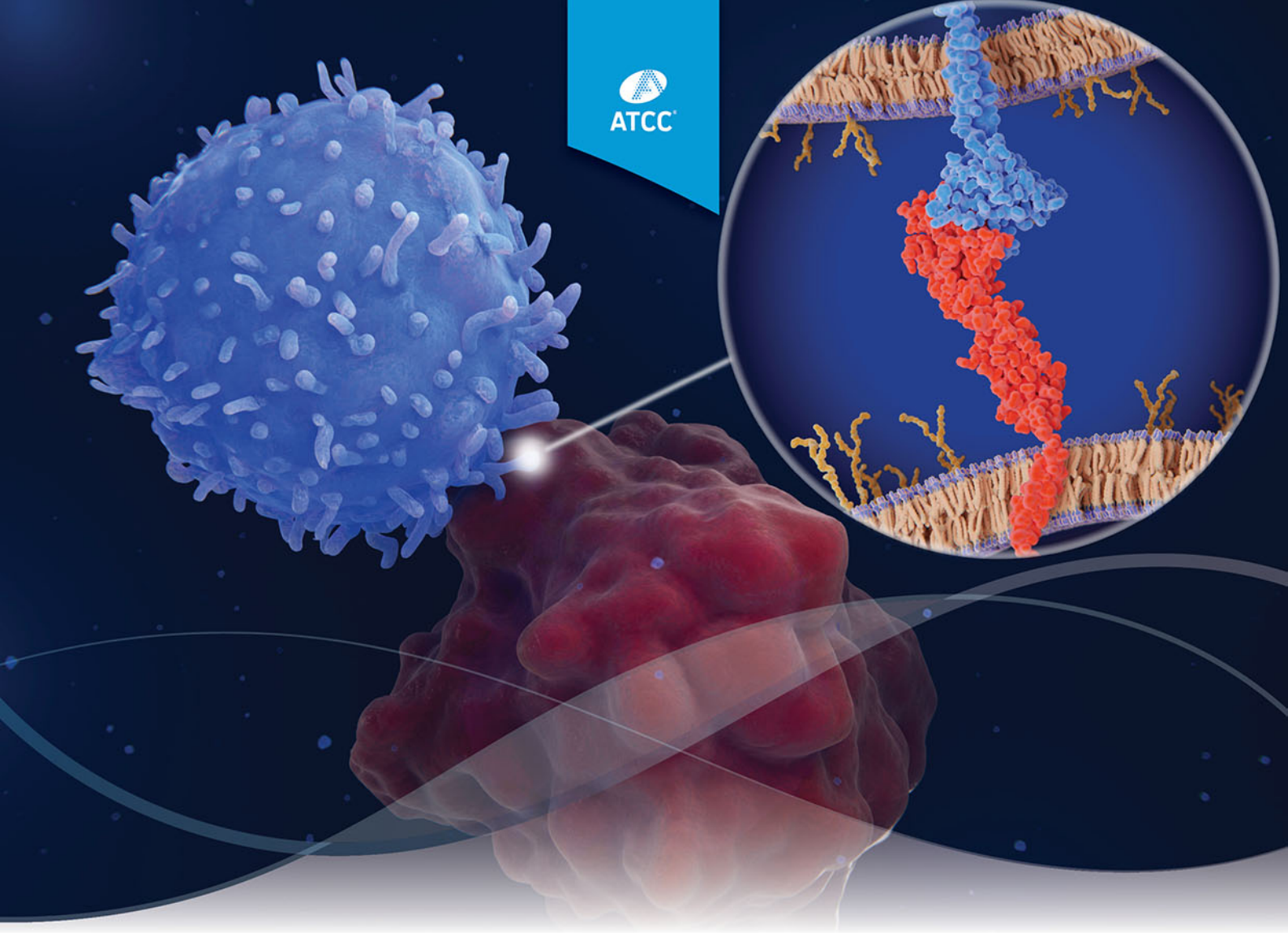

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INVITED REVIEW

Tissue-resident memory T cells and lung immunopathology

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Summary

Rapid reaction to microbes invading mucosal tissues is key to protect the host against disease. Respiratory tissue-resident memory T (T_{RM}) cells provide superior immunity against pathogen infection and/or re-infection, due to their presence at the site of pathogen entry. However, there has been emerging evidence that exuberant T_{RM}-cell responses contribute to the development of various chronic respiratory conditions including pulmonary sequelae post-acute viral infections. In this review, we have described the characteristics of respiratory T_{RM} cells and processes underlying their development and maintenance. We have reviewed T_{RM}-cell protective functions against various respiratory pathogens as well as their pathological activities in chronic lung conditions including post-viral pulmonary sequelae. Furthermore, we have discussed potential mechanisms regulating the pathological activity of T_{RM} cells and proposed therapeutic strategies to alleviate T_{RM}-cell-mediated lung immunopathology. We hope that this review provides insights toward the development of future vaccines or interventions that can harness the superior protective abilities of T_{RM} cells, while minimizing the potential for immunopathology, a particularly important topic in the era of coronavirus disease 2019 (COVID-19) pandemic.

KEYWORDS
immunopathology, lung, protection, T_{RM} cells, viral sequelae

1 | INTRODUCTION

Naïve T cells, including $CD8^+$ and $CD4^+$ T cells, become activated upon recognizing specific peptide–MHC complexes presented by antigen-presenting cells (APCs). Subsequently, the cells proliferate and differentiate into effector T cells, eliminating the pathogen and infected cells via different mechanisms.[1,2] During acute infection by respiratory viruses such as the respiratory syncytial virus (RSV) and influenza A virus (IAV), antigen-specific $CD8^+$ effector T-cell responses in the lungs generally peak at Day 8–10 post-infection.[3-6] Then, effector T cells undergo contraction during which most cells undergo apoptosis, whereas a group of effector T cells remain and further differentiate into memory cells—providing long-term protection against reinfection by the same or related pathogens.[1,2] Memory T cells have remarkable heterogeneity vis-à-vis their circulating patterns, functions, and expression of specific markers. Memory T cells can generally be classified as central memory T cells (T_{CMs}), effector memory T cells (T_{EMs}), and tissue-resident memory T cells (T_{RMs}). In both humans and mice, T_{CM} cells express L-selectin (CD62L) and CC-chemokine receptor 7 (CCR7) and migrate within lymphoid organs.[7-9] T_{EM} cells exhibited higher basal expression of effector molecules compared to T_{CM} cells[10,11] and can

In Su Cheon and Young Min Son authors contributed equally to this work.

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circulate throughout the blood, secondary lymphoid organs, and non-lymphoid tissues. T_{RM} cells mainly reside in non-lymphoid tissues and remain primarily parked inside the tissue without entering the circulation.[12-14] T_{RM} cells have been observed in almost all non-lymphoid tissues including skin,[12,15-17] lung,[18-22] gut,[23-25] brain,[26,27] and the reproductive tract[28,29] of humans and animal models. T_{RM} cells typically express tissue residency-related molecules including CD69 and CD103. CD69 expression on T_{RM} cells prevents tissue exit by suppressing the activity of sphingosine 1-phosphate receptor-1 (S1P1),[30,31] while CD103 facilitates T_{RM} tissue retention by binding to E-cadherin—which is usually expressed on epithelial cells.[16,32] Pulmonary T_{RM} cells can reside in two different sites, the airway and the lung interstitium.[33] Airway T_{RM} cells and interstitial T_{RM} cells differ in phenotypic markers, turn-over rates, and cytotoxic potentials, but both confer protection against lethal viral rechallenge via the rapid production of antiviral cytokines.[33-35]

Owing to their presence at the site of viral entry and high levels of expression of effector molecules, respiratory T_{RM} cells provide superior protection against secondary infections compared to T_{CM} and T_{EM} cells. In particular, it has been shown that T_{RM} cells can confer nearly sterilizing immunity if present in sufficient numbers.[20,36] T_{RM} cells can be rapidly reactivated to kill pathogen-infected cells directly, produce effector cytokines to establish a local antiviral state and/or activate a series of downstream signaling cascades to impede viral replication and dissemination. Therefore, the induction of robust T_{RM} responses may hold promise for development of the next generation of vaccines capable of providing superior and broad protection against different pathogen variants in the mucosal tissue.[37] However, on the opposite side of the same coin, exuberant or dysregulated T_{RM} responses have also been shown to contribute significantly to lung immunopathology. Emerging evidence has found that T_{RM} cells may drive and/or contribute to the development of several chronic lung diseases including asthma, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis. Furthermore, exuberant T_{RM} responses may also result in the development of chronic lung sequelae post-acute viral infections including influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In this review, we first describe the general characteristics and protective functions of pulmonary T_{RM} cells in the context of respiratory infections. Then, we detail the pathological roles of T_{RM} cells in the development of chronic respiratory disease and persistent sequelae after acute infection, as well as likely underlying mechanisms. Finally, we discuss the potential of targeting pathological T_{RM} cells to resolve or attenuate lung immunopathology in respiratory diseases.

2 | RESPIRATORY T_{RM} CELL DEVELOPMENT AND CHARACTERISTICS

Naive T cells generally undergo priming, proliferation and differentiation into effector T cells at the lung-draining mediastinal lymph node (mLN) after respiratory viral infection. Activated effector T cells then migrate to the site of infection in the lungs. After pathogen clearance, a group of effector T cells or T_{RM} precursors survive the contraction phase and further differentiate into mature T_{RM} cells. T_{RM} cells are phenotypically and functionally distinct from circulating T_{CM} and T_{EM} cells. For instance, in order to maintain their residence in tissues, respiratory T_{RM} cells downregulate surface molecules such as CD62L, CCR7, and S1P1, which are required for the entry of lymphocytes into circulation.[38-40] Furthermore, T_{RM} cells gain the expression of tissue residency molecules including CD69, CD103, and CD49a. CD69 antagonizes the function of S1P1 and CD103 is required for binding to epithelial integrin. CD49a, the α1 integrin, binds to collagen IV and facilitates the survival of lung T_{RM} cells.[41] T_{RM} development and maintenance are also dependent on a number of transcription factors (TFs). Particularly, the PR domain zinc finger protein 1 Blimp-1, and the Blimp-1 homolog, Hobit, have been shown to instruct a transcriptional program required for T-cell tissue residency in the respiratory tract.[15] Runx3, Notch1, the orphan nuclear receptor Nur77, the aryl hydrocarbon receptor (Ahr), and the basic helix–loop–helix family member Bhlhe40 have also been shown to be required for optimal respiratory T_{RM} responses.[22] Conversely, transcription factors such as the Kruppel-like factor KLF2, the T-cell factor TCF-1 and Eomesodermin (Eomes) can inhibit the expression of the tissue residency gene program, instead promoting genes associated with T-cell circulation.[39,42,43] Specific pathways and molecules that are important for respiratory $CD8^+$ or $CD4^+$ T_{RM} responses are listed below.

2.1 | $CD8^+$ T_{RM} cells

Naïve $CD8^+$ T cells are activated by APCs, particularly the migratory $CD103^+$ conventional dendritic cells (cDC1) in the mLN. The effector T cells then migrate to infected tissues, including the lung parenchyma or airways.[44,45] The development of T_{RM} cells from infiltrating effector T cells relies on instructional signals from the pulmonary microenvironment. These essential local factors include cognate antigen re-stimulation, proper cytokine milieu and engagement with neighboring cells.

The necessity of local antigen restimulation for establishing lung T_{RM} cells has been demonstrated over multiple studies.[36,46,47] For instance, it has been shown that intraperitoneal primary influenza virus immunization induces circulating effector T cells, which can be pulled to the respiratory tract with subsequent CpG single intranasal administration. However, intranasal CpG treatment failed to generate robust $CD8^+$ T_{RM} responses unless cognate antigen was combined with CpG in the administration.[46] These data suggest that antigen re-encounter is essential for the optimal generation of respiratory T_{RM} cells. Besides the requirement of antigen re-encounter in the effector phase, low levels of persistent TCR/MHC-I signaling also facilitates the maintenance of a group of "exhausted-like" lung T_{RM} cells that are specific to the influenza nucleoprotein (NP)[36] (further discussion below). Unlike lung parenchymal $CD8^+$ T_{RM} cells, nasal and upper respiratory tract T_{RM} cells seem to develop independent of local antigen re-engagement and are regulated by TGF-β signaling.[48]

TGF-β is well-established to be an essential cytokine for the development of CD103$^+$ T_{RM} cells in mucosal tissues such as the skin, gut, and lung via the induction of CD103 expression.[16,23,49,50] The deficiency of TGFβRII appeared to also diminish CD69$^+$ CD103$^-$ T_{RM} cell numbers in lungs,[36] indicating TGF-β signaling is essential for both CD103$^+$ and CD103$^-$ T_{RM} cell development in the respiratory tract. Interestingly, CD103-expressing cDC1s may preferentially promote lung CD8$^+$ T_{RM} cells after viral infection and selectively targeting antigens to CD103$^+$ DCs markedly augmented CD8$^+$ T_{RM} cell development post vaccination—a process dependent on TGF-β signaling.[49] Moreover, lungs of aged mice express elevated levels of TGF-β compared to young mice, resulting in increased CD8$^+$ T_{RM} cell levels after influenza infection.[51] Thus, modulating TGF-β signaling in vivo may serve as an effective strategy to boost CD8$^+$ T_{RM} responses. Notably, human lung CD1c$^+$ DCs, but not CD141$^+$ DCs, produce the membrane-bound form of TGF-β1 which can induce CD103 expression in respiratory CD8$^+$ T cells.[52]

The release of another anti-inflammatory cytokine, IL-10, also enhanced TGF-β expression, thus promoting early commitment of effector T cells to the T_{RM} cell lineage.[53] IL-10 was shown to suppress early effector T-cell expansion and acute inflammation, while promoting CD8$^+$ T_{RM} formation during SARS-CoV-2 infection in rhesus macaques.[54] Interestingly, a major source of IL-10 during respiratory viral infections is effector CD8$^+$ T cell themselves,[6,55] indicating autocrine CD8$^+$ T cell IL-10 signaling may also contribute to CD8$^+$ T_{RM} responses. IL-15 is considered a central regulator of memory CD8$^+$ T cells, but T_{RM} cells were believed to be less dependent on IL-15 for maintenance in vivo.[56] However, activation of IL-15 signaling by IL-15 complexes (IL-15c) treatment stimulated rapid proliferation and expansion of both CD8$^+$ circulating memory and T_{RM} cells.[57] Interestingly, IL-15 influenced the migratory ability of activated CD8$^+$ T cells into the airway following influenza virus infection.[58] IL-21 is an important cytokine that has been implicated in facilitating CD8$^+$ effector and memory T-cell responses. IL-21 blockade at the memory phase selectively reduced a population of CD8$^+$ T_{RM} cells that are specific to the influenza NP protein. IL-21 functioned to promote BATF expression and NP-specific CD8$^+$ T_{RM} survival, suggesting that IL-21 regulates protective CD8$^+$ T_{RM} responses in an epitope-specific manner within the respiratory tract[21] .

2.2 | CD4$^+$ T_{RM} cells

In contrast to the extensive characterization of CD8$^+$ T_{RM} cell development and maintenance, relatively fewer studies have elucidated CD4$^+$ T_{RM} responses. CD4$^+$ T_{RM} cells also uniformly express CD69, but less CD103 compared to CD8$^+$ T_{RM} cells. The general mechanism underlying respiratory CD4$^+$ T_{RM} cell development resembles that of CD8$^+$ T_{RM} cells. Naïve CD4$^+$ T cells are stimulated by antigen-presenting DCs, mainly the IRF4-expressing CD11b$^+$ CD103$^-$ cDC2s,[59] in the draining mLN. Activated and differentiated CD4$^+$ effector T cells then migrate to the lung, where they further upregulate tissue-resident markers such as CD69, CXCR6, and/or CD103. One distinct characteristic of CD4$^+$ T_{RM} cells compared to CD8$^+$ T_{RM} cells is their ability to differentiate into several T_{RM}-cell subtypes expressing distinct cytokine profiles, including T-helper (Th)1 T_{RM} (T_{RM}1), Th2 T_{RM} (T_{RM}2), and Th17 T_{RM} (T_{RM}17) cells, depending on the nature of the pathogen.[60] Pulmonary T_{RM}1 cells rapidly respond to influenza virus reinfection to produce interferon gamma (IFN-γ).[61,62] T-bet$^+$ T_{RM}1 cells are mainly located on the border of the inducible bronchus-associated lymphoid tissue (iBALT) structure,[63] and express high levels of CD11a and VLA-1 for their retention and survival.[64] T_{RM}2 cells are generated in response to allergens or parasitic infections, and usually produce Th2 cytokines such as IL-4, IL-5, and IL-13.[65,66] Following extracellular bacterial or fungal infection of the respiratory tract, IL-17A-expressing CD4$^+$ T_{RM} cells can be detected in the lungs.[67] High levels of IL-17- and IL-2-expressing T_{RM}17 cells have also been observed in human lungs after *Mycobacterium tuberculosis* (*M. tuberculosis*) infection.[68]

We recently observed a hybrid CD4$^+$ T-cell population expressing features of both follicular helper T cells (T_{FH}) and tissue-resident cells in the lung, which mainly localize within iBALT structures following influenza virus infection.[60,63] These cells express high levels of IL-21, and their development is dependent both on the T_{FH} transcription factor BCL-6 and the T_{RM} transcriptional factor Bhlhe40. Functionally, this cell population assists lung-resident B cell responses and lung CD8$^+$ T_{RM} formation and maintenance. Based on their gene expression and function, we termed this population "tissue-resident helper T (T_{RH}) cells".[21,60,63] Similar to lung T_{RH} cells, IL-21-expressing CD4$^+$ T cells have been observed in the brain and found to influence brain-resident CD8$^+$ T cell development following mouse polyomavirus infection.[69]

3 | PROTECTIVE ROLE OF T_{RM} CELLS IN RESPIRATORY TRACT

Sterilizing protective immunity against pathogen reinfection is usually mediated by pre-existing antibody (Ab) responses, particularly the mucosal Ab response. Insufficient mucosal antibody levels and/or frequent mutations of pathogen surface proteins often facilitate re-infection by the same or related pathogens. In these cases, memory T cell responses are vital for the protection against pathogen dissemination and severe host disease. Indeed, pre-existing memory T-cell levels can predict disease severity following influenza exposure in humans.[70,71] Furthermore, memory T cells induced by vaccination and/or previous infection are believed to be essential for the protection against severe coronavirus disease 2019 (COVID-19).[72,73] To this end, both local (T_{RM}) and systemic (T_{CM} and T_{EM}) T-cell memory are likely required to provide optimal protection. In the following section, we summarize the protective roles of T_{RM} cells against respiratory pathogen infection (Figure 1).

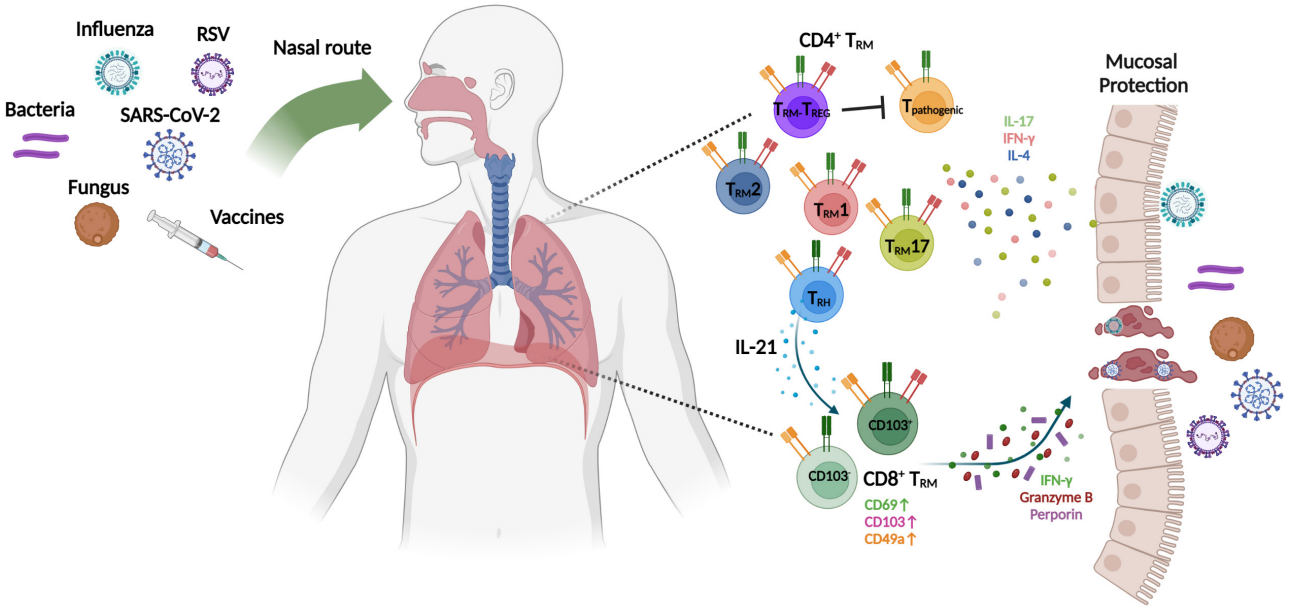

FIGURE 1 Mucosal immune protection mediated by respiratory T_{RM} cells. Respiratory infections or intranasal vaccination elicits $CD4^+$ or $CD8^+$ T_{RM} cell responses in the respiratory tract. Based on their cytokine expression, $CD4^+$ T_{RM} cells can be categorized into specific subtypes including $T_{RM}1$, $T_{RM}2$, $T_{RM}17$, T_{RM}-T_{REG}, or T_{RH} cells, which confer protection against different categories of pathogens. $CD8^+$ T_{RM} cells can be divided into $CD103^+$ and $CD103^-$ sub-populations and produce a variety of effector and cytotoxic molecules to directly kill pathogen-infected cells and/or induce a tissue anti-pathogen state.

3.1 | The protective effect of T_{RM} cells against respiratory viral infection

3.1.1 | Respiratory syncytial virus

RSV primarily targets children and the elderly, typically causing mild common cold-like symptoms in most individuals. However, it may also result in severe bronchitis, bronchiolitis, and even pneumonia in a fraction of individuals.[74] Several studies have demonstrated a strong protective function of T_{RM} cells against RSV infection.[75-77] Over 20 years ago, primary RSV infection was shown to induce the development of lung T_{RM} responses.[78] Subsequent studies have found that RSV-specific $CD4^+$ and $CD8^+$ T_{RM} cells can persist for more than 100 days after infection.[79] Furthermore, RSV-specific $CD8^+$ T_{RM} cells provided protection against secondary infection in the absence of circulating memory cells.[79] Similarly, in a study with RSV challenge in healthy volunteers, it was found that the abundance of pre-existing RSV-specific $CD8^+$ T_{RM} cells prior to infection negatively correlated with disease severity and viral load.[80] Interestingly, RSV-specific T_{RM} recall responses during the secondary viral exposure also relied on the instructional signals from the innate immune responses, specifically the Mitochondrial antiviral-signaling *protein* (MAVS) signaling-mediated type I interferon responses.[77] Together these data suggest that T_{RM} cells contribute significantly to protection against secondary RSV infection. Future RSV vaccine candidates focusing on the generation of robust T_{RM} populations within the lung are likely to be effective in protection against symptomatic RSV re-infection. Indeed, in an immunization model with murine cytomegalovirus vector (MCMV-M) encoding the RSV matrix (M) gene, it was found that intranasal vaccination generated robust and durable $CD8^+$ T_{RM} responses which protected against secondary RSV challenge in an IFN-γ dependent manner.[75]

3.1.2 | Influenza virus

Influenza infection causes up to 35.6 million illnesses and 140,000 to 710,000 hospitalizations in the United States alone annually.[81,82] Influenza virus infection can result in a range of clinical manifestations, ranging from asymptomatic infection to severe lower airway infection, pneumonia, and death. In addition to seasonal outbreaks, the emergence of pandemic influenza strains can cause catastrophic illness and death. More than twenty years ago, it was found that influenza infection can elicit robust antigen-specific memory $CD8^+$ T cell responses, which persist for several months after primary infection.[83] Similarly, influenza-specific T_{RM} cells capable of proliferating and producing functional molecules were also observed in human lungs.[84,85] Numerous studies have demonstrated remarkable protective capabilities of lung $CD4^+$ and $CD8^+$ T_{RM} cells against influenza virus infection, particularly in the context of heterotypic influenza viruses that escape pre-existing antibodies.[20,22,33,86] Using parabiosis and/or FTY720 treatment to block circulating memory T-cell infiltration, studies have found that both $CD4^+$ and $CD8^+$ T_{RM} cells are sufficient to protect against lethal influenza virus rechallenge.[21,62,87] Moreover, when present in sufficient numbers, T_{RM} cells can provide nearly sterilizing protective immunity against influenza infection.[88]

Upon viral entry, $CD8^+$ T_{RM} cells that can recognize infected cells are activated to become secondary effector cells, producing

functional effector molecules including IFN-γ, tumor necrosis factor alpha (TNF-α), perforin, and granzyme B.[89] Both $CD4^+$ and $CD8^+$ T_{RM} cells have been shown to rely on IFN-γ for their protective activities against secondary influenza infection, partially due to its function in activating an antiviral state in the lungs.[34,90,91]

The reactivation of influenza T_{RM} cells is mainly mediated by the recognition of cognate antigens. Interestingly, lung $CD8^+$ T_{RM} cells are reactivated more quickly, yet less efficiently, than their counterparts in the draining LNs (mLN) during secondary infection.[92] Reactivated lung T_{RM} cells upregulate antiviral and cytotoxic molecules, while reactivated mLN memory T cells more robustly upregulated genes involved in proliferation. Thus, lung T_{RM} cells are more specialized in executing rapid antiviral functions, whereas lymphoid memory T cells may provide sustained responses to counter viral dissemination if lung T_{RM} cells are unable to constrain the virus. Notably, respiratory T_{RM} cells can also be activated by bystander inflammation, particularly type I IFNs, inducing the expression of antiviral interferon-stimulated genes (ISGs) and granzymes which may contribute to secondary antiviral responses.[92,93] Furthermore, lung $CD8^+$ T_{RM} cells expressed high interferon-induced transmembrane protein 3 (IFITM3) levels compared to spleen memory $CD8^+$ cells following influenza infection. IFITM3 functions to protect $CD8^+$ T_{RM} cells against direct viral infection and IFITM3-deficient lung $CD8^+$ T_{RM} cells are lost during secondary viral infection.[94]

Respiratory tract $CD4^+$ T_{RM} cells have been reported to exert direct protective functions during secondary viral encounter. When influenza virus antigen-specific memory $CD4^+$ T cells were transferred into a lymphocyte-deficient mouse model, donor $CD69^+CD11a^+$ lung $CD4^+$ T_{RM} cells provided greater lung protection compared to splenic memory $CD4^+$ T cells after secondary influenza infection in an IFN-γ dependent manner.[90] Recently, we found that T_{RH} cells can protect mice from secondary lethal viral infection, likely due to their ability to assist optimal resident memory B cell and $CD8^+$ T_{RM} responses.[21] Taken together, these results suggest that $CD4^+$ T_{RM} cells are involved in direct and indirect protection against influenza viral infection.

Frequent mutations in the surface hemagglutinin and neuraminidase of influenza virus have endowed the virus with great capacity to evade protective antibody responses elicited by prior infection and/or the current influenza vaccines. Since T cells can recognize more conserved influenza epitopes, the induction of robust memory T cell including T_{RM} responses holds promise for the development of a "universal vaccine," which can provide strain-independent protection against a broad spectrum of influenza viruses.[37] Various immunization strategies have been explored for the induction of strong T_{RM} responses in the respiratory tract.[95] In particular, an adenoviral vector-based influenza vaccination strategy has been shown to generate robust $CD8^+$ T_{RM} responses in the lungs that can be maintained for at least 1 year post vaccination.[95]

3.1.3 | SARS-CoV-2

The current COVID-19 pandemic, caused by the SARS-CoV-2 infection, is estimated to have claimed more than 18 million lives worldwide by 2022.[96] The global scientific community rapidly responded to the crisis and has gained tremendous insight into the mechanisms underlying viral pathogenesis and host responses, including effector and memory T-cell responses post SARS-CoV-2 infection and/or vaccination. However, most studies have focused on the immune responses in circulation, and we have comparatively limited information regarding responses in the respiratory tract, the primary site of infection. Using single cell RNA sequencing (scRNAseq), respiratory immune responses in the bronchoalveolar lavage (BAL) fluid of acute COVID-19 patients was examined.[97] A number of effector $CD8^+$ T cells and potential $CD8^+$ T_{RM} precursors were observed in the BAL. During the acute phase, $CD8^+$ T_{RM} precursors were more prominent in patients with mild COVID-19, whereas cells from severe patients tended to exhibit naïve T cell-like action.[98] Later, Poon et al.[99] found that SARS-CoV-2-specifc memory T cells were present in multiple tissues of COVID-19 convalescents, including the bone marrow, spleen, lungs, lymph nodes, and blood. Notably, lung tissue harbored the highest number of SARS-CoV-2-specific $CD69^+$ $CD103^+$ $CD4^+$, or $CD8^+$ T_{RM} cells in COVID-19 convalescents. Moreover, lung memory cells exhibited greater functional profiles with distinct cytokine production, indicating that SARS-CoV-2-specific lung T_{RM} cells may be protective against potential SARS-CoV-2 re-infection. Consistent with this data, we also found the presence of $CD69^+$ $CD103^{+/-}CD4^+$, or $CD8^+$ T_{RM} cells in BAL samples from COVID-19 convalescent patients. BAL $CD4^+$ and $CD8^+$ T_{RM} cells demonstrated significantly greater levels of cytokine production following in vitro SARS-CoV-2-peptide re-stimulation compared to blood memory T cells,[100] suggesting that SARS-CoV-2-specific T cells are more enriched at the site of infection.

The generation of T_{RM} cells after SARS-CoV-2 infection has also been captured in animal studies.[101,102] Currently, the function of T_{RM} cells in protection against SARS-CoV-2 reinfection remains controversial in animal studies, depending on the model chosen for the study.[37] Intranasal vaccination strongly induced lung $CD8^+$ T_{RM} cells with superior polyfunctional phenotypes and conferred partial protection against SARS-CoV-2 challenge with a lethal dose.[101] On the other hand, another study demonstrated that lung $CD8^+$ T_{RM} induced after severe SARS-CoV-2 infection provided insufficient protection against SARS-CoV-2 reinfection in the K18-hACE2 transgenic mouse infection model.[103]

Unfortunately, the current mRNA vaccination strategy induces negligible $CD4^+$ or $CD8^+$ T_{RM} cells in the respiratory tract.[37,104] To this end, intranasal booster immunization with adenovirus expressing spike protein (Ad5-S) or spike protein alone could promote robust lung $CD4^+$ and $CD8^+$ T_{RM} cells in mRNA-immunized animals.[37,104,105] These studies indicate that vaccination strategies with systemic prime plus a respiratory booster may be effective in generating respiratory T_{RM} responses required for optimal protection against future SARS-CoV-2 variants.

3.2 | Protective roles of T_{RM} cells against bacterial and fungal infection

Similar to respiratory viral infection, bacteria that target the respiratory tract have been known to induce T_{RM}-cell responses. Unlike viral infections, respiratory $CD4^+$ T_{RM} cells appear to serve a key

role in providing local protection against bacterial infections of the respiratory tract compared to CD8$^+$ T_{RM} cells.[67,106-108] Severe *Streptococcus pneumonia* (Spn) infection can often cause pneumonia. In mouse models, repeated Spn challenge elicited a robust CD4$^+$ T_{RM}17 response. Interestingly, these CD4$^+$ T_{RM} cells can provide lung region-specific protection against Spn re-infection.[106] When lung was infected by Spn in a lobe-specific manner, it was found that IL-17-producing CD4$^+$ T_{RM}17 cells were mainly confined to the previously infected lobe, but not throughout the entire lower respiratory tract. Importantly, pneumonia protection was also restricted to the immunologically experienced lobe, indicating that CD4$^+$ T_{RM} cells provide localized but superior tissue protection compared to circulating memory cells.[106] Mechanistically, CD4$^+$ T_{RM} cells prevented the colonization of pneumococcal bacteria on the mucosa of the respiratory tract via IL-17-mediated neutrophil recruitment.[107] Furthermore, IL-17 produced by lung CD4$^+$ T_{RM} cells contributed to the control of *M. tuberculosis* infection in humans.[68] In the animal model, *M. tuberculosis* specific CD4$^+$ T_{RM} cells showed enhanced protective effects compared to intravascular counterparts.[109] Vaccines that can induce lung robust T_{RM} cells provide superior protection against bacteria re-infection. Combination with outer membrane protein from *Klebsiella pneumoniae* and an adjuvant that strongly induces lung T_{RM}1 and T_{RM}17 cells was shown to confer critical protection against lethal Klebsiella infection.[110]

Similar to bacterial infections, T_{RM} cells have been identified in tissues after exposure to fungi. *Aspergillus fumigatus* infection generated two distinct T_{RM} subsets based on their surface marker expression. CD69^{hi} CD103^{low} CD4$^+$ T_{RM} exhibited pathological features, whereas CD69^{hi} CD103^{hi} Foxp3$^+$ resident CD4$^+$ regulatory T cells suppressed the detrimental activities of the CD103^{low} CD4$^+$ T_{RM} cells.[111] Of note, a DC-based vaccine strategy was found to promote lung T_{RM}17 cell generation, which provided significant protection against highly virulent fungus *Cryptococcus gattii*.[112] These results suggest that lung T_{RM} cells can be generated after vaccination for the protection against fungal infections.

4 | T_{RM} AND CHRONIC RESPIRATORY DISEASE

Chronic respiratory diseases such as asthma and COPD affect hundreds of millions of individuals globally and are a leading cause of mortality and morbidity worldwide. In the past decade, increasing evidence has suggested that respiratory CD4$^+$ and/or CD8$^+$ T_{RM} cells are a major contributor, if not a driver, of the development and/or progression of many chronic respiratory diseases. Below we have summarized our current understanding of the roles of T_{RM} cells in multiple respiratory disease conditions (Figure 2).

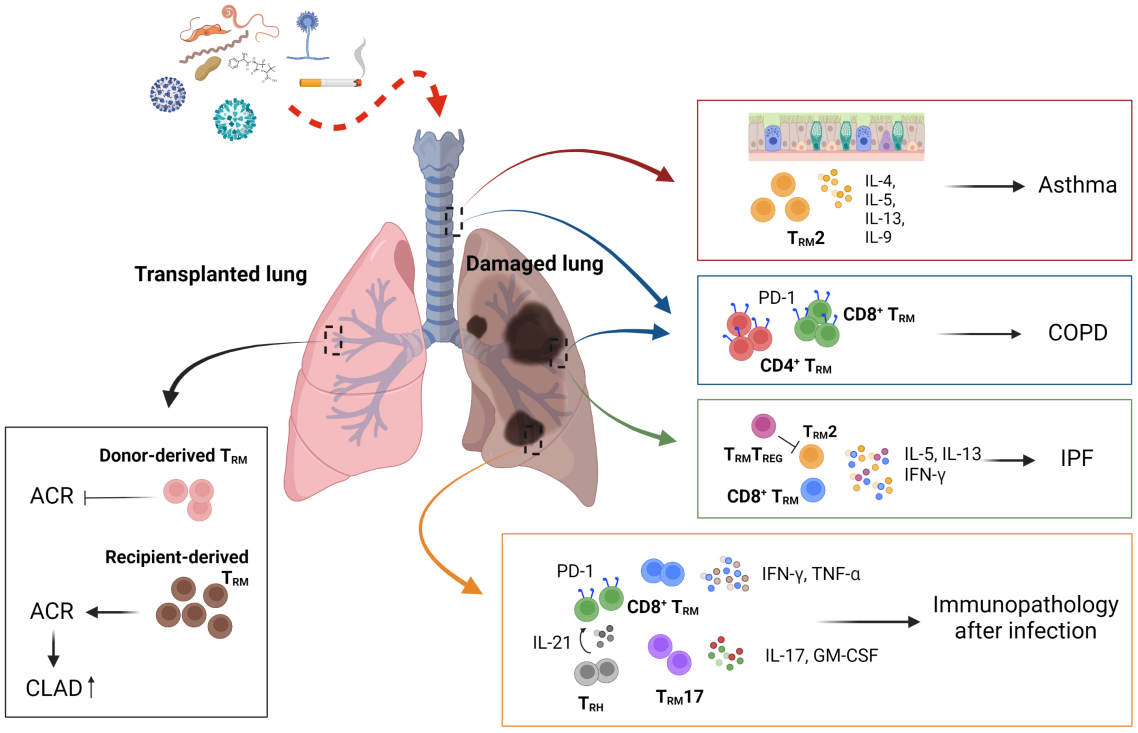

FIGURE 2 Contribution of T_{RM} cells to respiratory diseases. Dysregulated CD4$^+$ or CD8$^+$ T_{RM} cells in the respiratory tract are associated with the development of various respiratory diseases. Reactivation of T_{RM}2 cells that express type 2 cytokines appear to be a driver of asthma symptoms. Elevated CD4$^+$ or CD8$^+$ T_{RM} cell levels likely promote disease progression in COPD. Furthermore, T_{RM}2, T_{RM}17, and/or CD8$^+$ T_{RM} cells are involved in the development of pulmonary fibrosis. In the aftermath of respiratory infection, exuberant CD4$^+$ and/or CD8$^+$ T_{RM} cell responses result in chronic lung immunopathology. In the transplanted lung, T_{RM} cell origin may have distinct functions. Donor-derived T_{RM} cells are likely protective, but recipient-derived T_{RM} cells may promote ACR and CLAD. COPD: chronic obstructive pulmonary disease; ACR: acute cellular rejection; CLAD: chronic lung allograft dysfunction.

4.1 | T_{RM} in allergies and asthma

Allergy and asthma are chronic inflammatory disorders in the airway that affect hundreds of millions of people globally.[113] $CD4^+$ T cells, particularly Th2 cells, are well-known to orchestrate the development of asthma.[114,115] In response to seasonal exposures to allergens, memory T cells, particularly memory Th2 cells, are believed to mediate intermittent flares of asthma. The role of $CD4^+$ T_{RM} cells in regulating allergic asthma has been the focus of several recent studies. In a mouse model of house dust mite (HDM) induced allergic inflammation, HDM-specific T_{RM} cells were formed after allergen sensitization and persisted in the lung for more than 100 days after initial sensitization.[116] The development and/or maintenance of these $CD4^+$ T_{RM} cells in the lung was found to be dependent on IL-2 and IL-7 signaling.[116,117] Importantly, these lung T_{RM} cells were sufficient to promote asthma symptoms, independent of memory cells in secondary lymphoid organs, highlighting the importance of lung $CD4^+$ T_{RM} cells in driving pathology after allergen re-exposure.[116,118] Comparison of the gene profiles of T_{CM} cells in the lymphoid organs and T_{RM} cells in the lung, Rahimi et al.[65] found that T_{CM} and T_{RM} cells shared a core Th2 gene signature, while T_{RM} cells uniquely expressed a tissue-adaptation signature including genes involved in regulating and interacting with the extracellular matrix. Both T_{CM} and T_{RM} cells contributed to the recall response after allergen re-exposure, but they appeared to have different functions. Recall of circulating T_{CM} cells promoted perivascular inflammation and eosinophil recruitment, while T_{RM} cells augmented peri-bronchial inflammation including mucus metaplasia, airway hyperresponsiveness, and airway eosinophil activation.[65,116,117]

In a chronic intranasal HDM exposure model, both $CD4^+$ and $CD8^+$ T cells infiltrated into the lungs during the acute phase of challenge, but only $CD4^+T_{RM}$ cells persisted in the lungs following cessation of allergen exposure.[118] Lung $CD4^+$ T_{RM} cells were localized around airways and responded rapidly upon allergen re-exposure, leading to airway hyperresponsiveness, recruitment and activation of other immune cells, and production of IL-4, IL-5, and IL-17.[118] Additionally, a subset of multi cytokine-producing $CD4^+$ T_{RM} cells also expressed high levels of IL-9, which was critical to mediate rapid allergen recall responses and promoted the infiltration of multiple immune cells into the allergic lung.[119]

Consistent with mouse data, patients with moderate to severe asthma had increased levels of airway $CD4^+$ T cells expressing T_{RM} markers, compared to subjects with mild asthma and healthy controls—indicating a role of $CD4^+$ T_{RM} cells in asthma pathophysiology.[120] Furthermore, allergic patients also harbored pathogenic IL-9-expressing T_{RM} cells that co-expressed the IL-33 receptor, ST2, and multiple other cytokines.[121,122] Together, pathological $CD4^+$ T_{RM} cells may represent a major driver for the development of airway inflammation and asthmatic symptoms following allergen exposure and re-exposure. Thus, interventions targeting $CD4^+$ T_{RM} development, maintenance and/or their effector activities will be crucial for the development of effective therapies against asthma.

4.2 | T_{RM} in COPD and IPF

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease with progressive fibrotic tissue remodeling and lung scarring.[123,124] IPF is an irreversible disease and the median survival rate after diagnosis is only 2–4 years.[125] There are two FDA-approved medications for IPF, but unfortunately, neither of them has been shown to extend the median survival time following diagnosis.[126] Thus, it is an urgent need to better understand the cellular and molecular mechanisms modulating IPF development and progression in order to develop more effective therapeutic interventions. T cells, particularly Th2 and Th17 cells, have been found to promote lung fibrosis in animal models.[123,127] In a mouse model of fibrosis induced by chronic exposure to *Aspergillus fumigatus*, lung resident $CD4^+$ T_{RM} cells, but not circulating $CD4^+$ T cells, caused lung inflammation and fibrosis. In particular, IL-5 and IL-13 producing $CD69^{hi}$ $CD103^{lo}$ $CD4^+$ $T_{RM}2$ cells mediated fibrotic processes, whereas $CD69^{hi}$ $CD103^{hi}$ lung-resident $CD4^+$ regulatory T cells suppressed the pathological $T_{RM}2$ responses. These data suggest that $CD4^+$ T_{RM} cells are heterogenous in the lung and their pathological or immunosuppressive effects could be delineated by CD103 expression level.[111]

In human, the population of $CD103^+$ $CD4^+$ T cells were significantly increased in the airway of patients with fibrotic lung disease.[128] Both airway $CD103^+$ and $CD103^-$ $CD4^+$ T cells highly expressed CD69, but $CD103^+$ $CD4^+$ T cells expressed higher other T_{RM}-associated markers such as CD101, CD49a and VLA-2. Interestingly, the $CD103^+$ $CD4^+$ T cells in the human lungs expressed IFN-γ and exhibited a T-helper 1-like effector phenotype.[128,129] Consistent with these earlier findings, patients with progressive fibrosing interstitial lung disease (PF-ILD) harbored higher levels of IFN-γ and IL-13-double producing $CD4^+$ T cells in BAL compared to controls. Notably, these BAL $IL\text{-}13^+/IFN\text{-}\gamma^+$ $CD4^+$ T cells from PF-ILD patients exhibited characteristics of conventional T_{RM} cells.[130] In addition to $CD4^+$ T_{RM} cells, lungs from IPF patients also had increased levels of $CD103^+CD8^+$ T_{RM} cells. Using scRNAseq, it was recently found that both $CD4^+$ and $CD8^+$ $T_{RM,}$ as well as $CD8^+$ T_{EM} cells, were increased in the lungs of IPF patients. Furthermore, the response to the IFN-γ pathway was enriched in $CD4^+$ T_{RM} and $CD8^+$ T_{RM} cells in IPF, along with other T-cell activation and signaling pathways.[131] These data highlight the potential involvement of both $CD4^+$ and $CD8^+$ T_{RM} cells in pulmonary fibrosis, but their exact protective or pathological functions in the development and/or progression of fibrosis remain to be determined in further studies.

COPD is a chronic lung inflammatory disease affecting the lung parenchyma and small airways, leading to irreversible and progressive airflow limitation. COPD is usually caused by chronic cigarette smoking or long-term inhalation exposure to harmful substances. Both $CD8^+$ and $CD4^+$ T cells have been implicated in the inflammatory response of COPD.[132] Particularly, the percentage of BAL $CD8^+$ T cells positively correlated with the number of cigarettes smoked per day in male smokers with COPD—indicating a potential causative correlation between smoking and T_{RM} levels. More recently, using mass spectrometry, it was found that both $CD103^+$

$CD4^+$ and $CD103^+$ $CD8^+$ T_{RM} cells were increased in the lungs of COPD patients compared to healthy controls. Also, T_{RM} cells expressing high levels of PD-1 were found within the walls of small airways.[133,134] Consistent with the human data, cigarette smoking in mice caused elevated accumulation of $CD8^+$ T cells in lungs. Notably, CD8-deficient, but not CD4-deficient, mice had reduced inflammation and airspace enlargement,[135] suggesting lung tissue $CD8^+$ T cells promote tissue destruction during chronic smoking. Moreover, CD69-deficient mice exhibited reduced inflammation after smoking.[136] Additionally, in a viral model of COPD exacerbation, it was shown that IFN-γ derived from tissue-resident lymphocytes including T_{RM} cells suppressed alveolar stem cell growth, promoting emphysema exacerbation.[137] Together, these data suggest a potential role of T_{RM} cells, particularly $CD8^+$ T_{RM} cells, in the development or exacerbation of COPD. Since there are currently no effective therapeutics for COPD, targeting the pathological functions of $CD8^+$ T_{RM} cells may pave the way for the development of potent treatment strategies against COPD in the future.

4.3 | T_{RM} in the rejection of lung transplantation

Lung transplantation is performed in individuals with various end-stage lung diseases. However, the long-term survival rate after lung transplant is still relatively low compared to other solid organs due to increased frequency of acute and chronic rejection of the transplants.[138,139] The lower threshold for activation, along with faster response compared to naïve T cells implicates memory T cells in acute cellular rejection (ACR) of lung transplants.[140-143] ACR also increases the risk of chronic lung allograft dysfunction (CLAD), which is the major limiting factor to long-term survival after lung transplantation.[142] Since T_{RM} cells have the potential to mediate rapid immune responses in situ, T_{RM} cells are likely important in orchestrating the allogeneic rejection process after transplantation.[142,144] Indeed, there are several reports indicating that T_{RM} cells are associated with allograft rejection. For instance, T_{RM} cells mediate allograft rejection after kidney transplantation in mouse models[145] and CD103 expression from patients of renal allograft predicted the acute rejection response.[146]

During lung transplantation, donor T cells expressing T_{RM} markers such as CD69 and CD103 persisted in lung allografts for over 1 year after transplantation.[147] Furthermore, recipient T cells infiltrating the lungs gradually acquired T_{RM} phenotypes months after transplantation. Interestingly, the long-term persistence of mature donor T_{RM} cells ($CD69^+$ $CD103^+$) was associated with lower incidence of primary graft dysfunction (PGD) and ACR.[147] In contrast, ACR was characterized by the perivascular infiltration of recipient T cells in the lung. Recipient T cells underwent clonal expansion and expressed high levels of genes related to cytotoxicity, inflammation and tissue residency in the lung allografts—consistent with the notion that recipient T cells mediate lung ACR.[148,149] Of note, after the administration of systemic glucocorticoids, T_{RM} cells continued to persist for months but gene expression profiles were reprogrammed toward diminished cytotoxic functions.[148,150] These data suggest that maintaining donor derived T_{RM} and/or preventing the replacement of donor T_{RM} cells with recipient-derived T_{RM} cells may be the key to improve clinical outcomes following transplantation.[144] Also, drugs capable of inducing T_{RM} cell reprogramming toward less inflammatory phenotypes and/or capable of depleting alloreactive T_{RM} cells could be promising to prevent lung allograft rejection and increase long-term survival rates after lung transplantation.[150]

5 | T_{RM} AND VIRUS-INDUCED LUNG IMMUNOPATHOLOGY

Respiratory viral infections are a leading cause of mortality, accounting for more than 2 million deaths globally per year.[151] Occasionally, viral pandemics, such as influenza pandemics and the current COVID-19 pandemic, could result in even greater burden of disease. Besides the acute diseases caused by viral infections, there is growing evidence indicating the prevalence of chronic pulmonary sequelae after the resolution of primary infection. Exuberant T_{RM} cell, particularly $CD8^+$ T_{RM}-cell responses have been recently shown to play a prominent role in driving persistent lung immunopathology after acute viral infection in the respiratory tract.

5.1 | Influenza

Influenza infection may cause persistent pulmonary and extrapulmonary sequelae after the resolution of acute diseases in both humans and animal models.[152-156] As mentioned above, $CD8^+$ T_{RM} cells express high levels of effector and cytolytic molecular, which potentiate their rapid responses to re-infection. However, enhanced effector molecule expression not only augments their anti-microbial activity but can also potentially cause bystander inflammation and tissue injury if dysregulated.[157] In a model of influenza infection in aged mice, we found that aged hosts exhibited persistent inflammatory and fibrotic responses after the resolution of infection. Similar delays in recovery of the lung during aging has been recognized after human pneumonia as well.[51] RNA-seq analysis found that aged lungs exhibited increased signatures of T cell-associated genes and pro-inflammatory mediators, indicating the induction of excessive T_{RM} cell responses. Indeed, using flow cytometry and parabiosis, we confirmed that aged lungs had both increased antigen-specific and bystander $CD8^+$ T_{RM} cells (both $CD69^+$ $CD103^+$ and $CD69^+$ $CD103^-$) compared to young mice. Interestingly, aged lungs mounted increased T_{RM} responses despite diminished circulating memory counterparts, suggesting that the local tissue environment preferentially supports the development of exuberant T_{RM} responses. The transfer of T cells from young mice into aged lungs resulted in increased T_{RM} responses compared with those of T cells administered into the young lungs, confirming that the aged environment was responsible for this phenomenon.[51] To this end, elevated TGF-β expression was observed in aged lungs and the transfer of TGFβRII-deficient T cells abrogated the

elevated T_{RM} response, indicating that the excessive age-associated $CD8^+$ T_{RM} response was dependent on TGF-β signaling.

Of note, the increased accumulation of $CD8^+$ T_{RM} cells in aged lungs did not provide better protection against heterologous influenza reinfection compared to young counterparts.[51,158] Using scRNAseq, we found that $CD8^+$ T_{RM} cells in aged lungs exhibited altered phenotypes and lacked a T_{RM} sub-population that expressed high levels of protective molecules. Furthermore, T_{RM} cells from aged lungs expressed lower levels of downstream TCR signaling genes and appeared to be more senescent in producing effector cytokines in response to peptide mediated TCR, but not phorbol myristate acetate (PMA)/ionomycin, stimulation. Collectively, these data suggest that altered functional capacity, particularly after antigenic restimulation, underlies the impaired protection provided by $CD8^+$ T_{RM} cells during aging. Strikingly, the depletion of $CD8^+$ T_{RM} cells with a high dose of anti-CD8 Ab administration, but not the depletion of circulating $CD8^+$ T cells with a low dose of CD8 Ab administration, alleviated lung inflammation and fibrosis.[51] In addition, the lungs from aged mice with $CD8^+$ T_{RM} cell depletion showed diminished expression of multiple inflammatory cytokines and chemokines compared with the lungs of mice that received control antibody. Furthermore, $CD8^+$ T_{RM} cell depletion resulted in reduced recruitment of inflammatory monocytes and neutrophils to the tissue. These results together indicate that $CD8^+$ T_{RM} cells in aged lungs are a driver for the development of chronic lung sequelae following primary influenza pneumonia.

After influenza infection, young mice also developed persistent lesions in the lung characterized by patches of inflammatory, mucus hypersecretion and fibrotic regions, resulting in dysplastic epithelial repair.[159,160] However, the persistence of pathological sequelae in young mice was less frequent and milder compared to aged mice. Interestingly, the depletion of $CD8^+$ T cells at the memory stage did not alter the pathological responses in young mice, suggesting that $CD8^+$ T_{RM} cells may not contribute to chronic lung sequelae in young hosts. Rather, dysregulated myeloid responses appeared to play an important role in the development of chronic lung sequelae after viral pneumonia.[152,161] However, excessive T_{RM} responses and activity could also cause chronic lung pathology and fibrosis when the brake on T_{RM} cells was released.[36,51]

To this end, $CD8^+$ T_{RM} cells expressed multiple inhibitory receptors including PD-1.[162,163] Particularly, $CD8^+$ T_{RM} cells specific to the $H2D^b$-restricted $NP_{366\text{-}374}$ peptide highly expressed PD-1 and other inhibitory receptors including T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) and lymphocyte-activation gene 3 (LAG-3) compared to T_{RM} cells specific to other influenza epitopes and circulating memory cells. Despite viral clearance for over 4 weeks, T_{RM} cells upregulated gene programs similar to "exhausted" or effector-like $CD8^+$ T cells, thus termed as "exhausted-like" T_{RM} cells.[36,164] $NP_{366\text{-}374}$-specific "exhausted-like" T_{RM} cells showed persistent activation of TCR signaling at the memory phase. Indeed, these "exhausted-like" T_{RM} cells exhibited persistent low levels of TCR signaling, and the ablation of MHC-I after viral clearance led to diminished PD-1 expression and decreased levels of "exhausted-like" T_{RM} cells. These data suggest that chronic TCR signaling after the clearance of infectious viruses due to persistent NP antigen (given their abundance during primary viral replication), induced the generation of $PD\text{-}1^{hi}$ $CD8^+$ "exhausted-like" T_{RM} cells following primary viral infection.

Similar to chronic viral infections where blocking the interaction between PD-1 and PD-L1 increased the expansion of exhausted $CD8^+$ T cells,[165] inhibition of PD-1 and PD-L1 interaction at the memory stage elevated the abundance of $NP_{366\text{-}374}$-specific "exhausted-like" $CD8^+$ T_{RM} cells, but not other $CD8^+$ T_{RM} cells following influenza infection. PD-L1 blockade also increased the production of effector cytokines, particularly TNF, by $NP_{366\text{-}374}$-specific $CD8^+$ T_{RM} cells and further enhanced their protective function against influenza re-infection. Thus, persistent PD-L1 signaling in $CD8^+$ T_{RM} cells restricted their effector activities and protective functions against secondary infection.

However, the enhanced protection against secondary influenza infection comes at a cost. Anti-PD-L1 treated lungs exhibited enhanced inflammatory and fibrotic sequelae after primary influenza virus infection. Notably, the depletion of $CD8^+$ T cells alleviated tissue pathology, suggesting that enhanced $CD8^+$ T_{RM} cell responses directly caused the chronic sequelae. The selective expansion and increased effector activity of "exhausted-like" NP-specific T_{RM} cells after PD-L1 blockade suggested that the exaggerated responses of T_{RM} cells specific to the $NP_{366\text{-}374}$ epitope are likely the cause of the observed lung sequelae. Thus, high levels of PD-1 expression on certain T_{RM} cells functions to balance the protective versus pathological functions of T_{RM} cells. Notably, $PD\text{-}1^{hi}$ $CD8^+$ T_{RM} cells were observed in the pancreas, and reduced PD-1 expression in pancreatic T_{RM} cells was observed in chronic pancreatitis, indicating important roles for PD-1 in constraining T_{RM} cell activity and maintaining tissue homeostasis in humans.[163] Increased PD-1 expressing T_{RM} cells were also observed in IPF patients.[36] Whether dysregulated or diminished PD-1 or PD-L1 signaling also has a role in pulmonary fibrosis development requires future investigation. Additionally, a small percentage of cancer patients receiving immune checkpoint blockade (ICB) develop pneumonitis and fibrosis.[166,167] It is possible that the activation of pre-existing influenza or viral-specific T_{RM} cells, which are abundant in human lungs, may contribute to disease development after receiving ICB. Altogether, these data suggest that the primary function of the expression of inhibitory receptors on T_{RM} cells is to restrain their cytotoxic and pathological activities to promote recovery and maintenance of immune homeostasis. Additionally, lung T_{RM} cells express the cytokine IL-10,[168] which may endow T_{RM}-cell anti-inflammatory or regulatory properties to resolve tissue inflammation after primary viral infection or during the T_{RM} recall responses after secondary viral exposure.

5.2 | SARS-CoV-2

The symptoms of acute COVID-19 vary from mild to severe, potentially resulting in death due to respiratory failure. Of note, COVID-19

symptoms may persist, or new symptoms may arise months after recovery from acute diseases, which are generally referred as post-acute sequelae of COVID-19 (PASC) or long COVID-19. Both acute and long COVID are particularly a concern among older people or people with pre-existing comorbidities.[156,169,170] Rapid clearance of the SARS-CoV-2 virus and complete recovery of the host requires timely and robust T-cell responses, whereas improper T-cell responses have been reported to contribute to disease after infection. Dysregulated T_{RM}-cell responses have also been reported to promote pulmonary pathology in both acute and chronic stages after SARS-CoV-2 infection.

For instance, immune profiling in the BAL of COVID-19 patients identified that clonally expanded $CD4^+$ $T_{RM}17$ cells were associated with severe lung damage in COVID-19 patients.[171] These $T_{RM}17$ populations exhibited high levels of expression of pro-inflammatory cytokines such as *IL-17A* and *CSF2* (GM-CSF). These cells also expressed the transcription factor, RBPJ, which is known to regulate Th17 cell pathogenicity.[172,173] Furthermore, bioinformatics analysis found that $T_{RM}17$ cells had potential interactions with other tissue-specific immune cells, including macrophages and $CD8^+$ T cells, collectively promoting severe COVID-19. In addition to $CD4^+$ T_{RM} cells, $CD8^+$ T_{RM}-like cells have also been identified in the BAL of acute COVID-19 patients. Hobbit (ZNF683)-expressing $CD8^+$ T_{RM}-like cells likely represented SARS-CoV-2-specific $CD8^+$ T cells and were more enriched in patients with moderate infection compared to patients with severe disease, suggesting that the presence of these cells may be beneficial to the host.[97]

Bona fide SARS-CoV-2 antigen-specific T_{RM} cells have been detected in the lungs of COVID-19 convalescents after primary infection.[174] Poon et al showed that SARS-CoV-2–specific memory T cells are maintained across diverse tissue sites.[99] In a cohort of aged control and COVID-19 convalescents, we found that $CD8^+$ T cells were highly increased in the BAL of COVID-19 convalescents. Most of these BAL $CD8^+$ T cells express CD69 and a portion of those cells co-express CD103, indicating their tissue residency phenotype. Significant BAL $CD8^+$ T_{RM} cell populations in COVID-19 convalescents produced IFN-γ and TNF-α upon antigenic stimulation in vitro, indicating their polyfunctional features. Compared with the $CD69^+$ $CD103^+$ double positive "conventional" T_{RM} cells, the higher frequency of $CD69^+$ $CD103^-$ T_{RM} cell population was observed in the respiratory tract, although quantities of both populations were increased after SARS-CoV-2 infection—consistent with the overall increase in $CD8^+$ T cells within the BAL of COVID-19 convalescents. Of note, majority of this aged COVID-19 convalescents cohort exhibited moderate to severe chronic lung pathology and impaired lung gas exchange function as measured by quantitative computed tomography (CT) and pulmonary function tests. Interestingly, total BAL $CD8^+$ T cells positively correlated with radiographic abnormalities such as ground glass opacification (GGO) or reticular densities and consolidation. BAL $CD8^+$ T_{RM} cells and the $CD69^+$ $CD103^-$ sub-population in particular, showed significantly negative correlation with lung function parameters including forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO) – indicating a detrimental role of T_{RM} cells in recovery after primary SARS-CoV-2 infection.

Using scRNAseq technique, we further analyzed the characteristics of BAL $CD8^+$ T cells. We identified three BAL $CD8^+$ T-cell populations expressing tissue residency gene programs compared with circulating $CD8^+$ T cells in blood, including Hobbit and CD103-expressing conventional T_{RM} cells, $CD69^+$ $CD103^{-/low}$ T_{RM} cells, and a population of $CXCR6^{hi}$ effector-like tissue-resident cells. Compared to the $CD103^+$ conventional T_{RM} cells, $CD103^{-/low}$ T_{RM} cells expressed higher levels of cytotoxic and/or inflammatory molecules that can promote inflammation and fibroblast activation after infection. $CD103^{-/low}$ T_{RM} cells also were enriched with TCR signaling downstream genes, indicating that they may receive chronic antigen stimulation from persistent viral antigens and/or auto-antigens. These data suggest that the $CD103^{-/low}$ T_{RM} cells may have higher pathogenic potential than those of conventional T_{RM} cells. The BAL $CXCR6^{hi}$ $CD8^+$ T cells exhibited fewer T-cell memory features, but higher effector T-cell features compared to other subsets of BAL $CD8^+$ T cells.[100] Consistent with another study in the context of the liver where $CXCR6^{hi}$ $CD8^+$ T-cell population exhibited pathological activity and promoted liver tissue damage,[175] this subset of BAL $CD8^+$ T cells was enriched in gene signatures associated with inflammation and tissue destruction. Alternatively, these $CXCR6^{hi}$ $CD8^+$ T cells may represent effector $CD8^+$ T cells that provide protective function after a severe SARS-CoV-2 infection since transcriptome-wide association studies (TWAS) studies suggested that lower expression of CXCR6 in $CD8^+$ T_{RM} cells was associated with severe disease development following acute COVID-19.[176] Nevertheless, our study has demonstrated that exuberant responses of respiratory $CD8^+$ T_{RM} cells likely contributes to impaired lung function and the development of chronic pulmonary sequelae after the resolution of acute COVID-19 in aged individuals.[100] In a more recent study using proteome profiling of convalescent airway and blood, various inflammatory chemokines and proteins associated with tissue damage were observed to be dysregulated in the airways of COVID-19 convalescents compared to controls. Notably, albumin and lactate dehydrogenase (LDH), which serve as indicators of ongoing cell death and damage, were increased in the BAL of COVID-19 convalescents with persistent symptoms. Interestingly, different BAL immune cells including $CD8^+$ T cells positively correlated with lung pathophysiology in COVID-19 convalescents with chronic pulmonary symptoms. Similar to our findings, pulmonary T_{RM} cells were found to be elevated in the COVID-19 convalescents with persistent conditions and negatively correlated with certain lung function parameters.[177] These findings indicate that persistent elevated $CD8^+$ T_{RM} cells in the airway may cause constant damage to the respiratory epithelium, leading to pathology long after recovery from acute disease.

6 | MECHANISMS REGULATING T_{RM} PATHOGENICITY IN VIRUS-INDUCED LUNG SEQUELAE

As discussed above, dysregulated T_{RM} cell responses are linked to the development of chronic lung sequelae following the recovery

from acute viral infection, particularly during aging. At present, the underlying mechanisms by which lung T_{RM} cells cause the development of chronic disease are largely unknown and require further mechanistical studies in animal models (Figure 3).

Although transcriptional analyses have suggested that circulating $CD8^+$ terminally differentiated effector cells (TEMRA) may exhibit greater cytolytic activity than T_{RM} cells in human,[178,179] mouse T_{RM} cells exhibited higher expression of cytotoxic molecules including Granzyme B and perforin compared to circulating memory cells.[40] It is possible that the activity of exuberant T_{RM} cells in the lung can result in tissue microinjury, inducing increased cell death due to constant release of cytotoxic molecules. To this end, it is worth noting that persistent non-healing epithelial microinjuries may further induce a cascade of inflammatory and fibrotic responses,[123,180] which is believed to be a major driver of pulmonary fibrosis. Furthermore, T_{RM} cells produce high levels of pro-inflammatory cytokines such as TNF, CCL3, and IFN-γ, which may be needed to not only optimally mediate their protective functions but also potentially lead to chronic tissue inflammation and lung damage under certain conditions.[34,51] Of note, T cells, particularly memory T cells, usually do not constitutively release cytotoxic molecules and/or produce cytokines without antigenic or inflammatory stimuli despite gene expression.[181,182] Thus, antigenic or environmental cues in the tissue are needed to perpetuate the inflammatory cascade.

To this end, it is increasingly recognized that acute respiratory viral infection may result in chronic deposition of viral antigens, remnants and/or establish a persistent virus reservoir. For instance, the persistence of viral RNA and/or antigen in the lung was observed months after influenza virus infection.[183] Indeed, persistent inflammatory and fibrotic foci were shown to be enriched with influenza viral RNAs months after viral clearance, suggesting an association between viral genes/antigens and tissue damage.[152] Influenza viral antigens, particularly the NP protein, was shown to be deposited in an irradiation-resistant lung structural cell type after infectious viral clearance.[183] Using Nur77-GFP transgenic mice, we further showed that lung T_{RM} cells specific to the $NP_{366\text{-}374}$ peptide had persistent low levels of TCR signaling as evidenced by the GFP expression for more than one month after influenza infection. Furthermore, the ablation of MHC I signaling resulted in diminished $NP_{366\text{-}374}$-specific T_{RM} cells, indicating chronic TCR signaling at the memory phase is critical for their maintenance in the lung.[36] Notably, the potential of persistent TCR stimulation in driving chronic disease is balanced by high expression of inhibitory molecules such as PD-1 on T_{RM} cells in young hosts.[36,184] However, the activity of these checkpoints is likely insufficient to completely curb the pathological activities of exuberant T_{RM} cell responses upon chronic stimulation by persistent antigens in aged hosts. Additionally, aging may further delay the clearance of viral antigens and/or viral remnants, resulting in elevated or extended antigenic stimulation to T_{RM} cells. All these mechanisms may contribute to the age-associated pathological roles of T_{RM} cells after viral pneumonia.

Emerging evidence has also suggested that SARS-CoV-2 infection may lead to persistent deposition of viral antigens, remnants and even reservoirs. A recent study using a large number of autopsy samples demonstrated that SARS-CoV-2 virus could potentially replicate in multiple respiratory and non-respiratory tissues as late as 230 days following symptom onset.[185] Furthermore, SARS-CoV-2 viral RNAs and/or antigens have been detected in the gastrointestinal

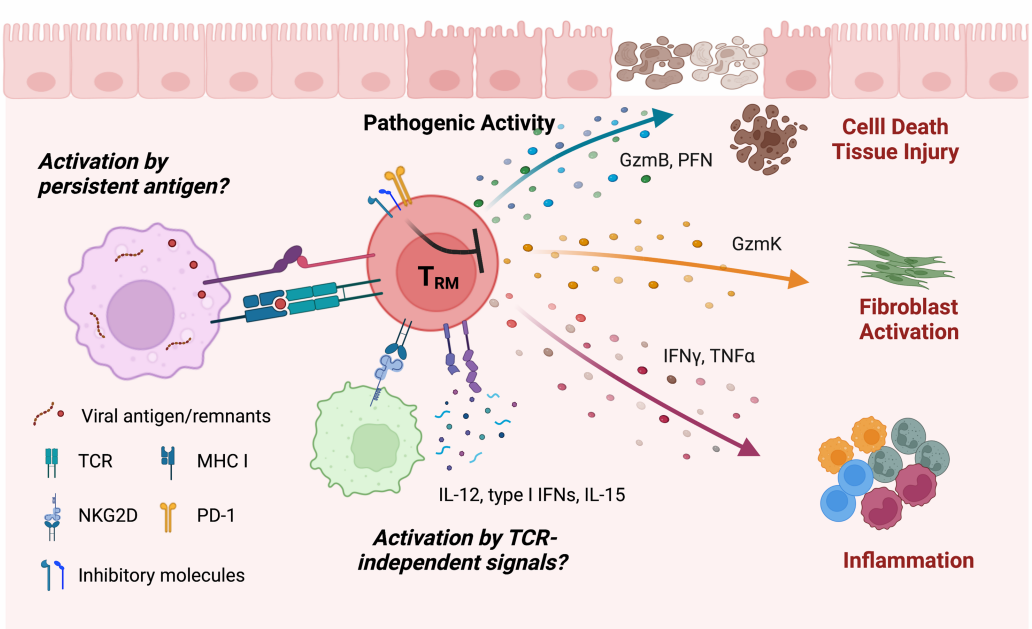

FIGURE 3 Potential mechanisms regulating T_{RM} cell-mediated pathogenesis in lung sequelae after infection. Persistent antigen presence or environmental cues such as inflammatory cytokines stimulate T_{RM} cells to produce a variety of pathogenic molecules, leading to development chronic inflammatory and/or fibrotic lung pathology.

(GI) tract, liver, and olfactory epithelium in COVID-19 convalescents, although the persistence of viral remnants or antigens in the respiratory tract remain unknown. The CD69$^+$ CD103$^-$ T_{RM} subset found in the BAL of aged COVID-19 convalescents was highly enriched with TCR signaling pathway genes, indicating antigen-mediated stimulation of T_{RM} cells after resolution of primary SARS-CoV-2 infection.[100] Therefore, it is possible that persistent antigen deposited in the lung may drive chronic activation of this T_{RM} subset, thereby promoting the development of post COVID-19 lung sequelae.

Alternatively, viral antigen-independent signals may play a role in regulating chronic lung sequelae after primary respiratory viral infection. It is possible that the antigenic signal to T_{RM} cells may be derived from an autoantigen. Such a possibility is particularly relevant given the fact that antibodies against autoantigen have been frequently reported after SARS-CoV-2 infection.[186,187] Furthermore, memory T cells can be activated or stimulated by inflammatory cytokines such as IL-12, type I IFNs and/or IL-15, independent of TCR signaling.[188] Certain co-stimulatory molecules such as NKG2D can also activate memory T cells independent of TCR. Thus, it is possible that persistent tissue inflammation following viral infection stimulates T_{RM} cell activation even after viral clearance, resulting in tissue destruction and chronic lung sequelae. Notably, IL-15 has been shown to be a survival and activation signal for a CXCR6^{hi} T_{RM}-like subset that was enriched with gene programs involved in tissue inflammation in the liver.[189,190] Persistent IL-15 levels may promote the development and/or function of these T cells in the respiratory tract, contributing to the development of chronic lung sequelae after primary viral pneumonia including SARS-CoV-2 infection.

While T_{RM} cells in other tissue such as skin, liver or intestinal mucosal are stable and long-lasting, pulmonary antigen-specific T_{RM} cells are relatively short-lived and steadily decline over time after the primary infection.[22,191,-194] However, it is important to note that this phenomenon was documented using animal models, and whether this is true in humans after respiratory viral infections remains to be fully established. Nevertheless, given the potential danger of persistent and over-reactive T_{RM} cells in chronic lung conditions, lung T_{RM} cell decrease may be beneficial to facilitate the complete recovery and return to tissue homeostasis after acute infection. Particularly, higher order mammals such as primates and humans are likely to encounter many episodes of pulmonary infection throughout their lifetime. Then, a steady decline of potentially dangerous T_{RM} cells in the lung is likely an evolutionarily benefit to avoid chronic accumulation of tissue pathology in a critical organ following multiple pathogen exposures. Therefore, even though T_{RM} cells are very powerful in protecting against viral infection and should be harnessed by future vaccine strategies, it is crucial to carefully calibrate their activities to avoid potential collateral damage.

As discussed, T_{RM} cells in the lung have both protective and pathological functions. Currently, little is known on whether these activities are coupled or not, that is, mediated by the same molecular pathways and/or the same cells. To this end, T_{RM}-cell heterogeneity is being increasingly appreciated[195-197] with several studies revealing various subsets of respiratory T_{RM} cells in mice and humans.[18,22,162] For instance, we found at least three T_{RM} or T_{RM}-like subsets in the BAL of COVID-19 convalescents.[100] Although CD69$^+$ CD103$^-$ and CXCR6^{hi} T_{RM}-like cells exhibited higher levels of autoinflammatory features, the conventional CD69$^+$ CD103$^+$ T_{RM} cells appeared to be less inflammatory based on gene expression. Therefore, we speculate that the pathological and protective functions of T_{RM} cells could potentially be, at least in part, mediated by different T_{RM} cell subsets. Furthermore, different molecules may also separate the protective and detrimental activities of T_{RM} cells in the lungs. TNF can cause epithelial apoptosis and is considered to be a major factor contributing to fibroblast activation.[198,199] Furthermore, Granzyme K is highly expressed by age-associated T cells and can also activate fibroblasts.[200,201] However, it is less cytotoxic against virus-infected cells compared to other granzymes.[200,201] Thus, it is possible that constitutive TNF and Granzyme K expression by T_{RM} cells preferentially leads to chronic tissue pathology rather than protection against secondary infection. In contrast, IFN-γ production by T_{RM} cells mediates their protective function against secondary viral infection, although its effects in tissue injury or fibrosis have not been tested. Thus far, there is no solid experimental evidence supporting the uncoupling of protection and pathogenicity of T_{RM} cells, but this would be an extremely important to study in the future. If this is true, it would be imperative to promote protective T_{RM} subset function and/or effector molecule expression, while selective dampening the activity of pathological T_{RM} subsets after primary viral infection or following vaccination. Alternatively, the determinant of T_{RM} protective function versus pathogenic activity may be simply the time. T_{RM} may exert their antiviral functions to provide beneficial effects at the early times after infection, whereas prolonged engagement of the same T_{RM} cells or the "protective" molecules in T_{RM} cells causes deleterious outcome to the host after the clearance of infectious virus. Further studies are required to examine all these potential possibilities.

7 | TARGETING T_{RM} TO RESOLVE OR ATTENUATE IMMUNOPATHOLOGY IN RESPIRATORY TRACT

As discussed, exuberant T_{RM} responses contribute significantly to various lung conditions. Thus, means targeting dysregulated T_{RM} responses may be a promising strategy to mitigate the burden of lung diseases. In this section, we discuss potential approaches that may be employed to diminish exuberant respiratory T_{RM}-cell responses and/or their pathogenic activities, which can likely lead to the development of new immunomodulatory treatments for various lung conditions in the future.

7.1 | Targeting chronic antigenic signaling in T_{RM} cells

As discussed above, viral antigen persistence is likely a reason for the persistence and stimulation of exuberant T_{RM} cell responses

after viral pneumonia. Evidence for this notion comes from both animal models as well as recent studies in the COVID-19 pandemic. Thus, interventions that can target and eliminate viral reservoirs and/or antigen persistence may be a useful strategy in ameliorating pathology due to uncontrolled T_{RM} responses. To this end, treatment with antiviral drugs that can block viral replication may be efficacious in preventing chronic sequelae. Paxlovid is an FDA-approved antiviral drug capable of reducing SARS-CoV-2 burden during primary infection. Treatment with nirmatrelvir, the antiviral component of Paxlovid, within 5 days post symptoms onset has been shown to reduce the overall risk of the development of PASC including respiratory symptoms such as shortness of breath.[202,203] Currently, Paxlovid is still under active investigation with regard to its function in dampening PASC in a large cohort of COVID-19 patients[202,203] (NCT05595369). Similarly, oseltamivir (Tamiflu), an antiviral drug for influenza infection, may be employed to decrease the incidence of post influenza lung sequelae.[204,205] Of note, most of antiviral drugs function to inhibit active viral replication. Thus, they are likely most effective in eliminating antigen reservoirs and mitigating chronic sequelae upon administration during early disease, when the host harbors substantial levels of replicating virus. It is still unknown whether they may be used to reduce antigen deposition, T_{RM} cell activation, and lung pathology after the clearance of infectious virus.

To this end, vaccination may be employed to target viral reservoirs, remnants and/or antigen persistence. Indeed, emerging evidence has suggested that COVID-19 convalescents with ongoing PASC may benefit from vaccination.[206,207] In this case, it is possible that vaccination-induced humoral and/or cellular immunity may accelerate the clearance of viral remnants and/or antigen in the tissue, thereby diminishing T_{RM} cell activation and lung sequelae.

Other modalities that can dampen TCR signaling can also be potentially employed to curb T_{RM} cell pathogenicity and lung sequelae. For instance, teplizumab, an FDA-approved anti-CD3 antibody that can induce T-cell anergy,[208] or abatacept (CTLA-4 Ig) may be potentially employed to inhibit TCR signaling in T_{RM} cells to mitigate lung pathology.[209,210] Small molecule inhibitors targeting downstream TCR signaling may also be useful in diminishing exuberant T_{RM}-cell activity.

7.2 | Potential strategies to target pathological T_{RM}-cell persistence and maintenance

Notch signaling has been shown to promote the maintenance of lung T_{RM} cells after viral infection.[32,211] To this end, exuberant Notch signaling has been associated with chronic inflammatory diseases including lung cancer, asthma, and pulmonary fibrosis.[212,213] Thus, interventions targeting Notch signaling may attenuate immunopathology caused by lung T_{RM} cells. AL101 is a potent and selective inhibitor of gamma secretase required for Notch signaling and has been granted by FDA as an orphan drug designation for the treatment of patients with adenoid cystic carcinoma (NCT03691207). Antibodies against Notch ligands may also be effective in diminishing exuberant T_{RM} cell responses and associated lung disease.

As mentioned before, TGF-β signaling is required for the development and maintenance of lung T_{RM} cell responses. We found that increased TGF-β expression in aged lung is responsible for the increased levels of T_{RM} cells during aging. Additionally, TGF-β signaling is considered as the most important driver for pulmonary fibrosis.[214,215] Therefore, it is reasonable to assume that the blockade of TGF-β signaling may help to dampen pathogenic T_{RM} responses and diminish lung pathology and fibrosis after viral infection. However, neutralization of TGF-β and/or inhibition of TGF-β downstream signaling has been shown to be extremely toxic to hosts due to the diverse roles of TGF-β in tissue homeostasis. To this end, therapies targeting specific TGF-β activation pathways, including the blockade of β6 or β8 integrin function may be less toxic but functional to diminish pathological T_{RM} responses in lung viral sequelae or pulmonary fibrosis.

IL-21 is an important cytokine that can potently augment $CD8^+$ T cell responses. IL-21 is usually derived from activated $CD4^+$ T cells, especially T_{FH} cells, and can mediate $CD4^+$ T cell help for $CD8^+$ T cell activation and/or maintenance, particularly in with the context of chronic antigen deposition.[216] Influenza infection induced the development of IL-21 producing T_{RH} cells in the lungs, and IL-21 blockade selectively decreased the number of $CD8^+$ T_{RM} cells that received persistent antigenic signals in the lung after influenza infection.[21] Therefore, the blocking IL-21 activity in the respiratory tract may serve to selectively dampen pathological T_{RM} cell responses, thereby diminishing chronic lung sequelae. Conversely, IL-21 has been shown to promote pathogenic $CD8^+$ T cells after bleomycin administration. Furthermore, the blockade of IL-21 function ameliorated $CD8^+$ T cell-mediated lung fibrosis after bleomycin administration in mice.[217] A human monoclonal antibody, avizakimab, that can inhibit IL-21 bioactivity, is currently in phase 2 clinical trials for systemic lupus erythematosus (SLE)[218] (NCT03371251). It would be worth exploring the utility of IL-21 mAb to prevent chronic lung pathology including lung fibrosis following viral infection.

7.3 | Targeting $CD8^+$ T_{RM} effector activities

$CD8^+$ T_{RM} cells highly express multiple effector molecules, which upon dysregulation could cause chronic inflammatory and/or fibrotic responses. Thus, interventions neutralizing the effector molecules released by $CD8^+$ T_{RM} cells and/or their downstream signaling may potentially mitigate $CD8^+$ T_{RM}-mediated lung pathology. TNF has been recognized as an important driver of tissue immunopathology during acute influenza and SARS-CoV-2 infection.[219-221] TNF is also considered to be an important contributor to pulmonary fibrosis and anti-TNF treatment has been investigated in several pulmonary disease models.[219] However, its role in T_{RM}-mediated immunopathology has not been firmly established. Nevertheless, we found that a main function of PD-1

on T_{RM} cells was to counter-balance TNF production, suggesting that excess production of TNF by $CD8^+$ T_{RM} cells may be detrimental after viral pneumonia. Furthermore, the $CXCR6^{hi}$ T_{RM}-like cells identified in the BAL of COVID-19 convalescents, not only correlated with impaired lung function but also produced high levels of TNF,[100] indicating TNF may contribute to adverse outcomes after acute COVID-19. To this end, TNF neutralizing monoclonal Ab such as adalimumab or infliximab may be used for the treatment of T_{RM}-mediated lung pathology. Notably, TNF blockade may also exacerbate certain lung diseases and so further studies are required to definitively address the beneficial versus adverse effects of TNF in regulating T_{RM}-mediated immunopathology.[222-224]

Even though IFN-γ per se exhibits little fibrogenic activities as discussed above, excessive production of IFN-γ has been associated with the development of lung injury in the late phase of SARS-CoV-1 infection.[225] T cell-derived IFN-γ and macrophage interactions have been implicated in driving the immunopathology after influenza and SARS-CoV-2 infection.[226,227] Moreover, IFN-γ was found to be persistently elevated in COVID-19 convalescents exhibiting PASC symptoms,[228,229] suggesting that IFN-γ neutralizing Abs, that is, emapalumab-lzsg (Gamifant), which is a FDA-approved monoclonal antibody, or its receptor blocking Abs maybe employed to block T_{RM}-induced immunopathology. Alternatively, inhibitors blocking the IFN-γ downstream signaling such as JAK inhibitors including tofacitinib and baricitinib, may also be utilized. Granzyme K (GzmK) is a pro-inflammatory granzyme capable of stimulating inflammatory activities of other cell types.[230] In particular, GzmK has been shown to induce inflammatory cytokine secretion and proliferation of human lung fibroblasts.[231] Further, GzmK-derived from age-associated $CD8^+$ T cells can promote the senescent phenotype of aged stromal cells.[232] We observed that GzmK is highly produced in the BAL $CD69^+$ $CD103^-$ T_{RM} cell subset of COVID-19 convalescents.[100,201] Thus, inhibitors or Abs that can neutralize GzmK activity may be promising to dampen T_{RM}-mediated lung immunopathology. Additionally, inhibitors targeting other cytotoxic granzymes such as Granzyme B may also be utilized if studies implicate the cytotoxic activities of T_{RM} cells in lung immunopathology.

7.4 | Targeting $CD4^+$ T_{RM} pathogenic activities

As discussed above, $CD4^+$ T_{RM} cells could also potentially contribute to lung pathology in various chronic lung diseases as well as the post-viral sequelae. Currently, the cues required for the development and/or maintenance of respiratory $CD4^+$ T_{RM} cells are relatively less understood compared to $CD8^+$ T_{RM} cells. We expect that some of the interventions inhibiting $CD8^+$ T_{RM} activation and maintenance in the lungs, including the suppression of persistent antigenic signaling, may also be effective in mitigating persistent $CD4^+$ T_{RM} responses. Below we mainly focus on the potential countermeasures that can inhibit the effector activities of $CD4^+$ T_{RM} cells.

As stated, $CD4^+$ T_{RM} cells can be categorized based on their cytokine production. $T_{RM}17$ cells, which produce IL-17, can potentially activate lung inflammatory and fibrogenic responses, largely dependent on the recruitment of neutrophils, as evidenced by several studies.[171,233-235] Furthermore, IL-17, $T_{RM}17$, and neutrophils have been implicated in acute COVID-19 as well as PASC.[236-238] Additionally, GM-CSF production by $T_{RM}17$ cells may contribute to the development of lung pathology in COVID-19.[171,239] Therefore, Abs such as tildrakizumab that can block IL-23, which is required for Th17 maintenance and activity, may be used to diminish $T_{RM}17$-mediated lung pathology. Alternatively, IL-17 neutralizing Ab (such as secukinumab and ixekizumab), IL-17 receptor blocking Ab (such as brodalumab) and/or GM-CSF blocking Ab (such as Lenzilumab and mavrilimumab) could be potentially employed to mitigate $T_{RM}17$-mediated immunopathology.

Besides $T_{RM}17$ cells, $T_{RM}2$ cells have been implicated in driving asthma related pathologies and lung fibrosis. Additionally, type 2 cytokines have been implicated in the development of pulmonary sequelae of viral pneumonia including COVID-19.[152,240-242] Thus, the blockade of $T_{RM}2$ effector activities, that is, inhibiting the function of $T_{RM}2$-released cytokines, would likely be effective in dampening $T_{RM}2$-mediated tissue pathology. To this end, IL-5 Ab, IL-13 Ab, or IL-13 receptor Abs have been approved for treating moderate to severe asthma and may be further repurposed to treat other lung conditions including fibrosis and post viral sequelae. IL-9 is increasingly being appreciated as an important mediator of $T_{RM}2$-mediated lung inflammation during chronic asthma.[119] Abs targeting IL-9 or IL-9 receptor may also be utilized for treating $T_{RM}2$-associated pathology, particularly during acute exacerbation of chronic asthma. IL-9 is also upregulated in PASC patients and whether the inhibition of IL-9 activity can be employed to treat pulmonary sequelae warrants further investigation. Other means that can potentially mitigate $T_{RM}2$ activity such as the blockade of IL-33 or ST-2 may also be employed to selectively dampen immunopathology caused by $T_{RM}2$ cells.

8 | CONCLUSION

Without a doubt, T_{RM} cells are extremely powerful in terms of their ability to protect against respiratory viral infections and re-infections. However, there is increasing evidence indicating that detrimental role of uncontrolled T_{RM} cell responses, either quantitatively or qualitatively, in the development of immunopathology and/or chronic lung diseases. Exuberant T_{RM} cell activity has been reported in several human inflammatory and fibrotic diseases of the respiratory tract. The phenotype and functions of these cells are highly influenced by several parameters including age, antigen persistence, tissue milieu, and disease conditions. Emerging data also suggest that respiratory T_{RM} cells exhibit remarkable phenotypic and functional heterogeneity, which may dictate their beneficial versus pathological functions. The burgeoning burden of chronic lung sequelae in COVID-19 convalescents over the course of the pandemic necessitates the rapid understanding of

the mechanisms underlying T_{RM} cell-mediated protection and immunopathology. With these insights, we will be able to develop new therapeutic avenues or vaccines, that harnessing the potent protective functions of T_{RM} cells, while minimizing their pathological activity in the lungs.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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