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REVIEW

Immune Memory Focus

Local memory CD4 T cell niches in respiratory viral infection

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Respiratory viral infections present a major threat to global health and prosperity. Over the past century, several have developed into crippling pandemics, including the SARS-CoV-2 virus. Although the generation of neutralizing serum antibodies in response to natural immunity and vaccination are considered to be hallmarks of viral immune protection, antibodies from long-lived plasma cells are subject to immune escape from heterologous clades of zoonotic, recombined, or mutated viruses. Local immunity in the lung can be generated through resident memory immune subsets that rapidly respond to secondary infection and protect from heterologous infection. Although many immune cells are required to achieve the phenomenon of resident memory, herein we highlight the pleiotropic functions of CD4 tissue resident memory T cells in the lung and discuss the implications of resident memory for vaccine design.

Introduction

Respiratory virus outbreaks have deleteriously impacted global health and prosperity throughout human history. A lack of immunity to emergent respiratory viral infections is the underlying cause of several global pandemics that have occurred over the past century, including influenza A pandemics (Monto and Fukuda, 2020) and novel coronavirus pandemics, such as the current SARS-CoV-2 pandemic responsible for ~2.5 million deaths (World Health Organization, 2021a). Although neutralizing antibodies produced by B cells in the bone marrow, called long-lived plasma cells (LLPCs), offer excellent protection to previously circulated strains of respiratory viruses (Lam and Baumgarth, 2019), the occasional zoonotic emergence or recombination event results in viral clades with novel surface proteins that are not well-recognized by circulating antibodies or memory lymphocytes, introducing the potential for unrestrained infection or pandemic (Gostic et al., 2016; Horimoto and Kawaoka, 2005). Even when partial immunity in many communities exists, as seen in the seasonal influenza epidemics, significant mortality and loss of productivity remains (World Health Organization, 2021b). Understanding how to elicit immunity to respiratory viruses through vaccination in order to prevent the emergence of disease is therefore a significant focus of ongoing research.

The immune system is rapidly called into action if a respiratory virus is able to productively infect a host. While it takes days to mount a primary adaptive immune response to a previously unperceived virus, memory lymphocytes can become activated in response to a prior or closely related viral infection within hours. Layers of adaptive immune memory have evolved to respond to homologous or heterologous viral antigens through a variety of mechanisms. LLPCs provide the first line of defense by constitutively secreting antibodies. While these antibodies may provide sterilizing immunity to homologous infection, they also exert immune pressure on viral surface antigens, evolutionarily driving the outgrowth of mutated virions. Cross-reactive memory T and B lymphocytes are therefore an important next layer of protection from viruses that may express closely related surface proteins but have mutated to evade the circulating LLPC-derived antibody repertoire. While some memory B cells can rapidly respond to heterologous reinfection by making antibody-secreting cells (Wong et al., 2020), others can reenter a germinal center response for further diversification (Pape et al., 2011; Shlomchik, 2018; Dogan et al., 2009). Memory T cells retain the ability to respond to homologous or heterologous viral antigens both through their ability to bind peptide:MHCs (pMHCs) with a broad range of receptor affinities and through their capacity to respond to intracellular proteins that may have avoided antibody-mediated immune pressure. This is important because many of the intracellular antigens are critical, highly conserved housekeeping proteins

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necessary for viral replication and function. For example, memory CD4 and CD8 T cells elicited by seasonal influenza A infection can be rapidly activated ex vivo in response to elements of pandemic strains of influenza, including H5N1, H3N2, and H1N1 (Chen et al., 2014; Richards et al., 2010), and their presence correlates inversely with disease severity, even in the absence of neutralizing antibodies (Sridhar et al., 2013; Wilkinson et al., 2012). When analyzed in more detail, T cell cross-reactivity to pandemic strains was heavily enriched for clones specific to the internal proteins nucleoprotein (NP) and M1 (Lee et al., 2008), supporting the notion that internal proteins are more highly conserved between seasonal and pandemic strains of virus (Sant et al., 2018).

Virus-specific memory T cells can behave as sentinels against reinfection due to their localization. Memory T cells persist in various anatomical compartments following respiratory viral infection, including the blood, lymphatic organs, and lungs (Szabo et al., 2019; Jameson and Masopust, 2018). Multiple studies have focused on the ability of resident memory T cells (T_{RM} cells) to facilitate an optimally efficient response to viral reinfection, and they have therefore become an important focus of investigation. Using parabiosis experiments in mice, virus-specific CD4 and CD8 T_{RM} cells have been observed to be retained in tissues across the body following systemic and mucosal viral infections (Steinert et al., 2015; Beura et al., 2019). Following in vivo antigen restimulation, both CD4 and CD8 T_{RM} cells can rapidly secrete cytokines, including IFN-γ, which facilitates the recruitment of circulating immune cells and the activation of other resident cells critical for protection against disease (Schenkel et al., 2014; Beura et al., 2019). For example, in two separate animal models, the activation of viral-specific CD8 and CD4 T_{RM} cells was required to control viral burden during reinfection in the skin and female reproductive tract through the production of IFN-γ (Iijima and Iwasaki, 2014; Schenkel et al., 2014). In studies focused on respiratory infection, the transfer of CD4 lung T_{RM} cells from mice that had previously cleared influenza virus protected unexposed mice from infection, while the transfer of spleen-derived memory T cells provided no better protection than naive T cells (Teijaro et al., 2011). This inability of circulating T cell memory to recapitulate the protection afforded by aspects of resident memory has been reported frequently (Wu et al., 2014; Slütter et al., 2013; Teijaro et al., 2010) and highlights the importance of understanding T_{RM} cell biology for protection against viral infections.

Herein, we will specifically focus on virus-specific CD4 T_{RM} cells and the important niches they occupy within the lung to prevent disease. We highlight the multifaceted roles that these key sentinels play in the lung tissue upon reinfection, including direct modes of pathogen control and indirect coordination of immune functions in the tissues. The ability to localize long-lived T_{RM} cells to a given mucosal tissue while simultaneously imparting the characteristics needed to coordinate the elimination of a target pathogen is the holy grail of vaccine development. We therefore also discuss key aspects of CD4 T_{RM} cell differentiation and maintenance, which can be modulated by specific vaccine strategies to harness a coordinated immune response in the lung and prevent future pandemics.

CD4 T_{RM} cells in natural infection

CD4 T_{RM} cells in the lung are critical mediators of protection against respiratory viral infections. Experiments using cell transfers in an animal model have demonstrated that unexposed recipients of influenza-specific CD4 T_{RM} cells are better protected than recipients of splenic-derived memory cells (Teijaro et al., 2010). While in these studies lung CD4 T_{RM} cells were protective in the absence of both CD8 T cells and B cells, recent studies have also demonstrated important roles for CD4 T_{RM} cells in recruiting and maintaining CD8 T cells (Son et al., 2021; Laidlaw et al., 2014) as well as in activating lung resident B cells (Swarnalekha et al., 2021). Here, we discuss these unique attributes of CD4 T_{RM} cells, including the niches they occupy in lung tissue, and the specific effector functions that have been associated with antiviral protection (Fig. 1).

Sentinel responses at sites of reinfection

T_{RM} cells act as sentinels that prevent respiratory disease through their ability to localize to tissues, reactivate in response to reinfection, and rapidly express effector molecules to limit viral replication. Although naive and resting memory T cells share the expression of ~95% of their transcriptome, memory T cells selectively possess an epigenetic landscape that retains open accessibility to genes that were expressed during their effector phase (Akondy et al., 2017; Araki et al., 2009). Demethylated chromatin at sites of effector genes, such as CXCR3, CXCR5, CCR5, IL-2Rα, IL-18Rα, IFN-γ, granzyme B, and perforin, have been detected in memory T cells, allowing for rapid transcription and accelerated effector protein production in response to TCR stimulation (Akondy et al., 2017; Weng et al., 2012). Using in vitro ovalbumin peptide simulations, ovalbumin-specific CD4 memory T cells have been shown to display an open chromatin landscape at the IFNG locus, allowing for rapid production of IFN-γ within 2 h (Lai et al., 2011). In stark contrast, a naive ovalbumin-specific CD4 T cell migrating through lymphoid organs must find an APC expressing its pMHCII in the context of costimulation and cytokines, which would lead to the upregulation of T-bet, bearing a delay of up to 24 h before it gained the ability to open the IFNG locus (Lai et al., 2011). Additionally, in response to ex vivo restimulation, CD4 T_{RM} cells isolated from human airways produced the effector cytokines IFN-γ and TNF-α faster and in larger quantities compared with circulating CD4 memory cells from the blood, suggesting that T_{RM} cells represent the memory T cell compartment that is the most epigenetically poised to respond rapidly to viral reinfection (Oja et al., 2018).

Cytokines produced rapidly by memory CD4 T_{RM} cells are essential for the accelerated recruitment, localization, and activation of innate immune cells only hours after reinfection, a process that takes up to 1 d in mice without CD4 T_{RM} cells (Soudja et al., 2014). In a model of secondary influenza infection, upregulation of the secondary effector molecules IL-1α, IL-1β, TNF-α, IL-6, and the chemokines CXCL9, CXCL10, and CCL2 by tissue-residing innate cells depended on the presence of CD4 T_{RM} cells and their interactions with $CD11c^+$ cells presenting viral antigen on pMHCII (Strutt et al., 2010; Soudja et al., 2014). In these settings, innate cells also facilitated the recruitment of

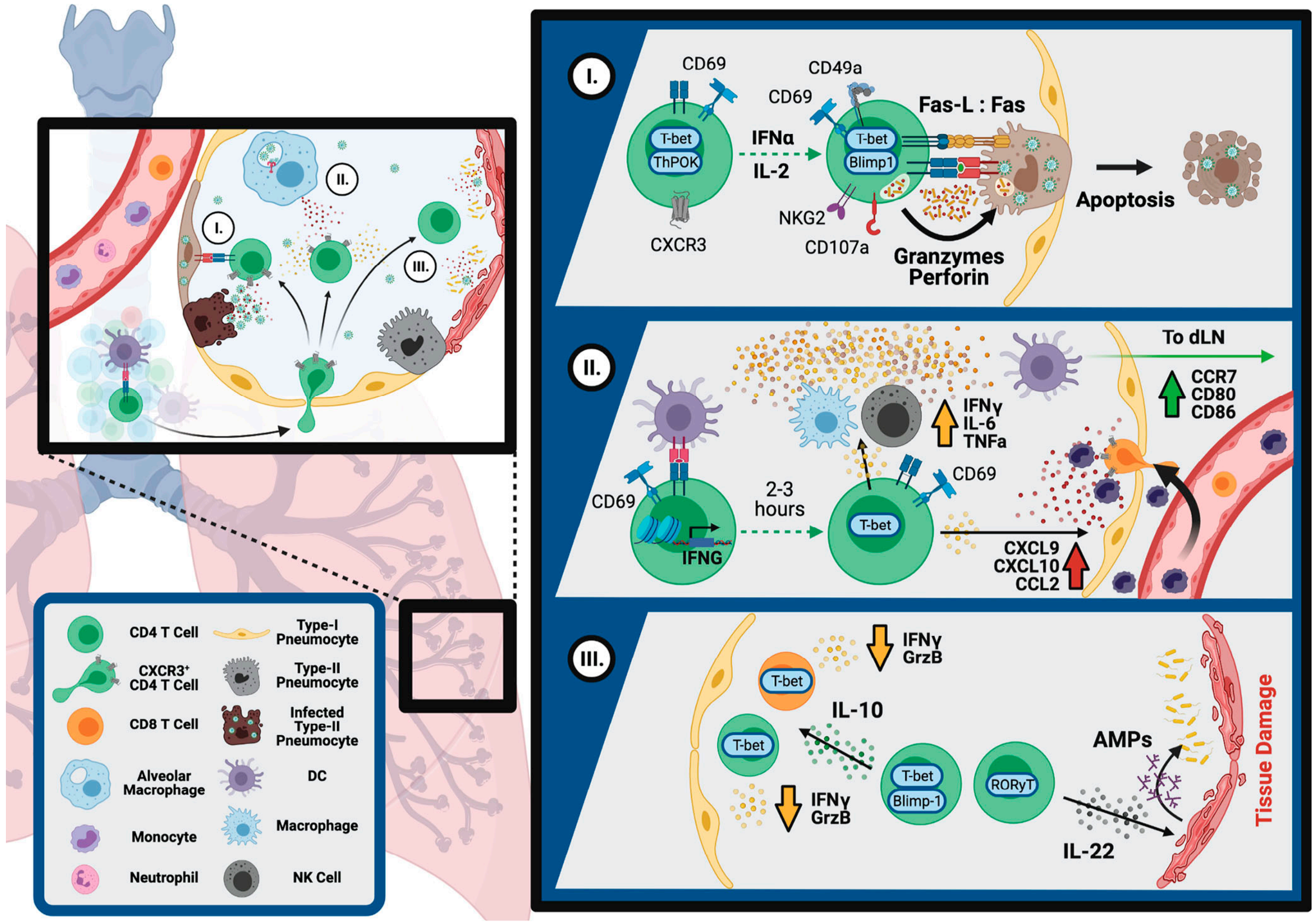

Figure 1. **Polyfunctional CD4 T_{RM} cells mediate control of secondary viral infections.** Upon recognition of cognate peptide in perivascular niches, CD4 T_{RM} cells use CXCR3 to migrate into infected airways and home to sites of viral infection. (I) CD4 T_{RM} cells develop into CTLs through perception of type I IFN and IL-2 and engage in MHCII-restricted cell lysis through the release of granzymes and perforin of infected type I pneumocytes, leading to anti-inflammatory modes of cell death, such as apoptosis. (II) Virus-specific CD4 T_{RM} cells upregulate effector molecules, such as IFN-γ, within hours of TCR stimulation because of an open chromatin landscape. CD4 T_{RM} cell–derived effector molecules facilitate the activation of (a) resident innate immune cells, such as parenchymal macrophages and natural killer (NK) cells, to amplify the alarmin response through the production of secondary effector molecules; (b) resident DCs to migrate to the draining LN (dLN) and present viral antigen to virus-specific central memory and naive T cells; and (c) the epithelium to upregulate selectins and chemokines essential for the recruitment of peripherally circulating effector memory virus-specific T cells and inflammatory innate cells, such as monocytes and neutrophils. (III) Upon resolution of viral infection, activated CD4 T_{RM} cells (a) upregulate their production of IL-10 to restrain tissue damage and facilitate transition to immune senescence and (b) produce the cytokine IL-22 to facilitate the recovery of damaged epithelium and clearance of secondary bacterial superinfections.

Ly6C$^+$ monocytes from the bloodstream to further amplify rapid antiviral activity (Soudja et al., 2014).

Importantly, through their immediate production of IFN-γ, CD4 T_{RM} cells can modulate the localization of key effector cells to sites of active viral replication in the respiratory tract. Since most respiratory viruses propagate by infecting cells within the airways and not the parenchyma, many viral-specific CD4 T_{RM} cells constitutively express the chemokine receptor CXCR3 and integrin CD49a (VLA-1) and can rapidly migrate to subepithelial or bronchoalveolar spaces in response to the CXCR3 ligands CXCL9 and CXCL10 produced by infected airway epithelial cells (Guvenel et al., 2020; Chapman et al., 2011; Chapman and Topham, 2010). Unlike what is seen in certain bacterial infections like *Mycobacterium tuberculosis* (Moguche et al., 2015), viral-specific CD4 T cells localized to the airways produce the largest amount of cytokines, including IFN-γ, IL-10, and IL-2. In a model of SARS-CoV vaccination, the blockade of IFN-γ either by administration of IFN-γ–blocking antibody or depletion of CD4 T_{RM} cells in the airway led to a loss in protection from viral challenge (Zhao et al., 2016). In this study, it was determined that IFN-γ from CD4 T_{RM} cells was needed to activate resident dendritic cells (DCs) and recruit CXCR3$^+$ memory CD8 T_{RM} cells to the airway through the IFN-γ–dependent upregulation of CXCL9 and CXCL10. Notably, only the blockade of IFN-γ during a secondary, but not a primary, infection with influenza restricted viral clearance (Teijaro et al., 2010), underscoring its select role in secondary responses.

In addition to IFN-γ, CD4 T_{RM} cells can also rapidly produce the cytokines TNF-α and IL-10, although these cytokines have been shown to be either beneficial or detrimental to the host depending on the model of infection studied. In a model of respiratory syncytial virus (RSV) infection, mice that received TNF-α–blocking antibodies developed reduced tissue pathology and clinical disease. In this study, mice treated with anti–TNF-α also produced lower levels of IFN-γ from their CD4 T cell compartment, suggesting that TNF-α production may cause T cell–dependent pathology in the lung (Hussell et al., 2001). Conversely, TNF-α KO mice during primary influenza infection displayed reduced viral burden and weight loss and heightened levels of both IFN-γ–producing virus-specific CD8 T cells in the lungs and hemagglutinin (HA)-specific antibody in the serum, suggesting that TNF-α production was actually suppressing a productive adaptive immune response (Damjanovic et al., 2011). Additionally, in coronavirus infection, the i.n. administration of recombinant TNF-α to naive mice 12 h before challenge with SARS-CoV led to decreased survival (Zhao et al., 2016). These conflicting reports and the relatively small body of detailed research on the mechanism of TNF-α during viral infection highlights the need to study this important cytokine, especially as it is often used as a proxy of productive antiviral immunity, and its blockade is a common therapy for diseases such as rheumatoid arthritis and inflammatory bowel disease.

IL-10, a key regulatory cytokine in the lung, has been shown to be produced by T-bet$^+$ FOXP3$^-$ effector (Sun et al., 2009) and memory (Zhao et al., 2016) CD4 T cells in the lung. To prevent lethal immunopathology during the late stages of influenza infection, CD4 T cells are required to orchestrate a contraction of the inflammatory immune response through the upregulation of IL-10 in activated effector T cells (Sun et al., 2011; O'Garra and Vieira, 2007). Although necessary for restraining lethal inflammation, IL-10 has also been shown to diminish the antibody response to influenza virus (Sun et al., 2010), and its deletion led to survival in a model of lethal influenza infection (McKinstry et al., 2009). Therefore, as is likely the case for TNF-α, the role of IL-10 and the relative production of IL-10 by CD4 T$_{RM}$ cells may vary depending on the timing, nature, and severity of the infection. For example, compared with a primary response, lower levels of IL-10 are produced during the secondary response to influenza infection (Strutt et al., 2012). This phenomenon is likely explained by the accelerated antiviral response to secondary infection when local T cell memory is present. Since viral burden is kept in check, the immune system does not employ a highly inflammatory response to clear infection and perhaps does not need large quantities of anti-inflammatory mediators, such as IL-10, to dampen inflammation.

In addition to cytokine production, some CD4 T cells have been shown to engage in pMHCII-restricted lysis of virus-infected cells, a mechanism of viral control previously thought to be restricted to CD8 CTLs (Brown et al., 2012). CD4 CTLs have been described clustered around infected cells in the airways and produce the effector molecules granzyme B and perforin (Marshall et al., 2017). CD4 CTLs depend on IL-2, Blimp-1, and Eomes for their generation (Qui et al., 2011) as well as type I IFN (Hua et al., 2013), which is produced by infected airway epithelial cells (Ioannidis et al., 2013). Intriguingly, CD4 T cell differentiation to a CD8 CTL-like fate is mediated by repression of the transcription factor ThPOK (Mucida et al., 2013), which alternatively is needed to repress CD8-associated molecules in thymic and peripheral differentiation of CD4 T cells (He et al., 2005; Wang et al., 2008). More research is needed to determine the fate of these cells following viral clearance as T$_{RM}$ cells are not detected in the airways at memory time points (Turner et al., 2014), and ThPOK is necessary for the generation of functional central memory CD4 T cells and their production of IL-2 (Ciucci et al., 2019).

FOXP3$^+$ regulatory T$_{RM}$ cells

Regulatory T cells (T reg cells) expressing the transcription factor FOXP3 are essential to constrain the damaging effects of the immune response in many instances of inflammation, including respiratory viral infection (Josefowicz et al., 2012). During influenza, virus-specific T reg cells have been shown to expand in response to antigen presented on pMHCII in conjunction with a costimulatory signal from CD86 (Betts et al., 2012; Bedoya et al., 2013; Moser et al., 2014). T reg cells restrain inflammation by limiting effector T cell cytokine release, natural killer cell accumulation, and neutrophil activity at stages where viral burden has started to decrease (Lee et al., 2010; Fulton et al., 2010). It is thought that early release of type I IFNs leads to activation of CD11c$^+$ DCs, which then produce IL-6 and suppress T reg cells, allowing for useful inflammation to ensue (Srivastava et al., 2014; Hashimoto et al., 2014). Once the virus is cleared and because of their expression of the high-affinity IL-2 receptor CD25, T reg cells act as a sink for IL-2, restricting further effector T cell propagation and restraining inflammatory tissue damage (Chinen et al., 2016). Through their production of amphiregulin and independent from their suppressive mechanisms, T reg cells have also been reported to have an essential role in tissue repair directly at the site of influenza infection in the lung (Arpaia et al., 2015). The role for virus-specific T reg cells in secondary infection is unknown, although IL-10 is not needed for protection from lung injury, which suggests that the efficiency of the immune response to secondary infection may supersede the necessity for T reg cell–mediated suppression and repair.

Helper mechanisms within ectopic lymphocyte clusters

Although many virus-specific CD4 T$_{RM}$ cells migrate to the airways in order to combat active viral replication (Zhao et al., 2016), there is also a functionally distinct population of CD4 T$_{RM}$ cells that remains in the parenchymal lung tissue and provides important helper functions to other virus-specific immune cells. Following contraction of a primary immune response, two distinct populations of CD4 T$_{RM}$ cells form in the lung that can be detected by their reciprocal expression of folate receptor 4 (FR4) and P-selectin glycoprotein ligand 1 (PSGL1; Swarnalekha et al., 2021; Son et al., 2021). PSGL1$^+$FR4$^-$ CD4 T$_{RM}$ cells express higher levels of T-bet and CXCR6, resembling a sentinel CD4 T$_{RM}$ cell subset that rapidly migrates to areas of infection and engages in direct viral clearance. In contrast, FR4$^+$PSGL1$^-$ CD4 T$_{RM}$ cells selectively express PD-1, CXCR5, CXCR4, and ICOS; depend on BCL-6, MHCII, and B cells for their development; and colocalize with B cells within the parenchymal lung tissue (Swarnalekha et al., 2021; Son et al., 2021). During influenza reinfection, mice that did not develop CD4 T$_{RM}$ cells with the capability to cluster with B cells had an inability to produce large amounts of HA- or NP-specific B cells or antibodies and displayed reduced survival (Son et al., 2021).

The clustering of CD4 T$_{RM}$ cells with other immune cells, including B cells, CD21$^+$ follicular DCs, and CD8 T cells, in peribronchial areas of the lung was previously described and is sometimes referred to as inducible bronchus-associated lymphoid tissue (iBALT; Moyron-Quiroz et al., 2004). iBALT has been shown to have direct access to inhaled antigen through specialized M cells (Kim et al., 2011) and provides a niche for adaptive immune cells to interact and proliferate in response to infection, suggesting an advantageous role as a local lymphatic compartment that can provide the functions of a traditional lymphoid organ while being located at the site of infection. Although iBALT can form independently of the lymphoid tissue inducer cells necessary for development of lymphoid organs, iBALT formation does require the upregulation of CXCL13 and CCL19, which are important mediators of lymphoid architecture, by stromal cells and DCs (Rangel-Moreno et al., 2011). The regulation of ectopic sources of CXCL13/CCL19 is complex and likely requires multiple factors, although in one model of influenza infection, the release of type I IFN drove the production of CXCL13 by lung fibroblasts and facilitated recruitment of CXCR5$^+$ B cells to the lung parenchyma, which were necessary for iBALT formation (Denton et al., 2019). Indeed, B cells are active mediators of iBALT functionality, as the depletion of B cells led to a decrease in BCL-6, CXCR5, and ICOS-expressing CD4 T_{RM} cells and a concomitant decrease in CD8 T_{RM} cell maintenance and the production of antibody from lung residing B cells (B_{RM} cells) during reinfection events (Swarnalekha et al., 2021; Son et al., 2021). Further, respiratory viral infection in µMT mice, which lack B cells, drove more virus-specific T cells to the lung parenchyma during effector phases of the infection but led to reduced numbers of long-lived memory CD4 T_{RM} cells compared with WT mice, suggesting that B cells are essential for the survival and maintenance of CD4 T_{RM} cells in the lung in the memory phase (Hondowicz et al., 2018). Therefore, iBALT represents an important niche for the maintenance of these virus-specific CD4 T_{RM} cell populations in the lung, as has been shown in ectopic memory lymphocyte clusters in other tissues (Iijima and Iwasaki, 2014) and in an allergic airway model of pulmonary inflammation (Shinoda et al., 2016). Upon reactivation in iBALT, CD4 T_{RM} cells have been shown to colocalize with B_{RM} cells, providing a rapid burst of virus-specific antibodies from local plasmablasts (Allie et al., 2019; Swarnalekha et al., 2021) while also leading to further affinity maturation of lung B_{RM} cells toward broadly neutralizing, cross-reactive epitopes that are highly protective in heterologous infections (Adachi et al., 2015; Onodera et al., 2012; Son et al., 2021). Indeed, CD4 T_{RM} cells aid in local production of antibodies by B_{RM} cells in other models of inflammation (Rao et al., 2017).

In addition to B cells, CD4 T_{RM} cells have been shown to colocalize with CD8 T cells and conventional DCs in perifollicular areas of iBALT (Moyron-Quiroz et al., 2004) and to augment CD8 T cell homing and fitness through their production of IFN-γ and/or IL-21 during late stages of influenza infection (Nakanishi et al., 2009; Son et al., 2021; Laidlaw et al., 2014; Laidlaw et al., 2016). Further, in a model of CD8 T_{RM} cell reactivation by latent herpes simplex virus infection, signals from CD4 T cells in the tissue were shown to be essential for the expansion of virus-specific CD8 T_{RM} cells through a tripartite interaction involving recruited monocyte-derived DCs (Wakim et al., 2008). These data further support seminal work that showed impaired virus-specific CD8 T cell recall responses in the lymphoid tissue in the absence of CD4 T cells (Belz et al., 2002). Interestingly, CD4 T cells are not required for the resurgence of CD8 effector mechanisms, such as specific lysis or IFN-γ production on a per-cell basis, suggesting that signals from CD4 T cells may selectively modulate the expansion of CD8 T cells, perhaps representing a mechanism to amplify the CD8 secondary effector response depending on viral load or inflammatory cues during reinfection.

As a note, iBALT with organized follicles containing germinal center B cells, CXCR5$^+$ T follicular helper cells, and CD21$^+$ follicular DCs are not detected in all instances of respiratory viral infection (Rangel-Moreno et al., 2011). However, even when iBALT is not present, loose clusters of PD-1$^+$ CD4 T cells and B cells are still detected in the lung parenchymal tissue, and these T cells are able to provide help to B_{RM} cells to induce activation and class switching to IgA (Vu Van et al., 2016). Further, CD4 T_{RM} cells in the female reproductive tract, which does not feature densely organized iBALT-like structures, have been shown to induce an expansion of CD8 CTLs, B cells, and activated CCR2$^+$ and CCR7$^+$CD86$^+$ DCs in response to secondary stimulation with sterile antigen in vivo (Beura et al., 2019). Therefore, even in the absence of distinct iBALT structures, helper functions of CD4 T cells still persist, although more research is needed to determine the importance of these structures in secondary viral infection.

Type 17 and type 2 immune responses to respiratory viral infection

During the first days of a primary response to respiratory viral infection, APCs present a combination of viral antigen and cytokines to naive T cells to prime their proliferation and maturation into virus-specific effector cells. Depending on the milieu of cytokines produced by innate cells during priming, naive CD4 T cells divert into distinct effector modes, which have been canonically defined by the effector cytokines they produce (Ruterbusch et al., 2020). Viral infections of the respiratory tract, such as influenza virus, coronavirus, and rhinovirus, primarily induce the production of type I IFN and IL-12 from APCs, priming virus-specific naive T cells to become T helper 1 (Th1) cells that express the transcription factor T-bet. Indeed, the sentinel functions discussed above are performed by Th1 cells, although Th17 and Th2 effector modes are elicited in some viral infections and are therefore discussed below.

Th17 cells are defined by their expression of the transcription factor RORγT and their ability to produce the effector cytokines IL-17, IL-22, and IL-26 (Mangan et al., 2006; Ivanov et al., 2006). Although their presence during the early stages of viral infection induces severe lung pathology, Th17 cells paradoxically provide important functions in the resolution phase of primary viral respiratory infections. In a mouse model of RSV infection, the blockade of IL-17A reduced mucus production and granulocyte accumulation in the airways, and this correlated with improved recruitment of RSV-specific CD4 and CD8 T cells and a reduced viral load (Mukherjee et al., 2011). In mouse models of lethal H1N1 influenza infection, IL-17 KO mice have been shown not only to survive but also to lose minimal weight during infection (Li et al., 2012), suggesting that Th17 cells may be the drivers of mortality. When analyzed in more detail, it was shown that IL-17 was predominantly produced by γδ-T cells, and the blockade of

IL-17A led to improved survival; a concomitant decrease in the inflammatory cytokines IL-6, IL-8, and G-CSF; and a reduction of neutrophil recruitment into the airways (Crowe et al., 2009). Indeed, neutrophil recruitment to the airways is a hallmark of pathology in severe viral infection and has been known to be directly mediated by IL-17 (Laan et al., 1999; Ye et al., 2001).

Paradoxically, Th17 cells also have multiple beneficial roles during the resolution phase of respiratory viral infection. Histological analysis of tissue samples from the 1918 and 2009 influenza A pandemics have revealed that bacterial superinfection causing bacterial pneumonia, in conjunction with viral infection, was the overwhelming cause of death (Morens et al., 2008; Bautista et al., 2010). Interestingly, IL-22, a cytokine almost exclusively produced by Th17 cells, mediates barrier tissue repair and potent mucosal host defense against many forms of bacterial infections (Liang et al., 2006). Indeed, in the late stages of influenza infection, the IL-22R is expressed on lung epithelial cells, and the infection of IL-22 KO mice led to decreased lung tissue function and reduced survival (Pociask et al., 2013). IL-22 has pleiotropic effects on the lung epithelium, inducing proliferation and repair mechanisms while also stimulating the production of antimicrobial peptides. Both these mechanisms are important in resolving potential instances of secondary bacterial superinfection (Aujla et al., 2008). Strikingly, in multiple models of influenza infection, it has been shown that the production of type I IFN directly inhibits the ability to develop a Th17 response and limits the ability to clear a subsequent superinfection with *Staphylococcus aureus*, suggesting that susceptibility to bacterial superinfection may have a direct immunological link and is not exclusively due to damage to the epithelium (Shahangian et al., 2009; Kudva et al., 2011). Finally, IL-17 production from CD4$^+$ cells during resolution of infection is necessary for iBALT formation, specifically highlighting the importance of IL-17 for the generation of immune memory (Rangel-Moreno et al., 2011). Th17 cells in respiratory viral infection are therefore somewhat dichotomous in nature: While they can induce IL-17–dependent hyperresponsiveness in acute viral infection, they can also provide reparative signals to epithelial cells, control occurrence of secondary bacterial superinfections, and induce iBALT (Stockinger and Omenetti, 2017). Additionally, whether Th17 cells persist to the memory phase and what their role is during secondary infection are active topics of discussion, as they have been shown to display plasticity and, therefore, varying longevity in different contexts (Pepper et al., 2010; Lee et al., 2009; Amezcua Vesely et al., 2019).

Th2 cells, defined by their expression of the transcription factor GATA-3 and the production of the cytokines IL-4, IL-5, and IL-13, are very poor at clearing viral infections and are associated with adverse responses to RSV (Dakhama et al., 2005). Seminal work in the field has shown that Th2 cells are generally not associated with protection from type 1–inducing viral infections, as demonstrated by the lack of protection engendered by the transfer of large numbers of influenza-specific Th2 clones into naive mice (Graham et al., 1994). RSV infection in mice and humans can induce symptomatic airway hyperresponsiveness that depends on the Th2 cytokines IL-4 and IL-13 (Dakhama et al., 2005; You et al., 2013). Studies have suggested that some RSV strains more efficiently polarize a type 2 immune response in the lung (Moore et al., 2009; Lukacs et al., 2006), and this response is dramatically heightened in neonates due to an inability of neonatal plasmacytoid DCs to produce type I IFN before 3 wk of age, leading to an absence in Th1 cells in the lung that produce IFN-γ (Marr et al., 2014; Cormier et al., 2014). In the case of neonatal infection, the administration of type I IFN or the transfer of adult plasmacytoid DCs into neonatal mice rescued them from airway hyperresponsiveness in primary and secondary responses and eliminated the production of Th2 cytokines (Cormier et al., 2014). Recent work has defined type 2 immune niches in the lung that are generated following pulmonary hyperresponsiveness and harbor stromal cells that express the Th2 cytokines IL-33 and thymic stromal lymphopoietin (Dahlgren et al., 2019). The danger of a permanent type 2 environment is apparent in neonatal RSV infection, where even when mice are reinfected in a context capable of driving a Th1 response, Th2 cytokines dominate and induce airway hyperresponsiveness (Culley et al., 2002).

In summary, much is still to be learned concerning the dynamics and diverse functions of CD4 T_{RM} cells during natural viral infection of the respiratory tract. For example, it is currently unknown whether the reactivation dynamics of memory CD4 T_{RM} cells mirrors the bifurcation events that occur in primary and secondary responses that have been described in lymphoid organs (Pepper et al., 2011; Pepper and Jenkins, 2011; DiToro et al., 2018). Additionally, it will be important to understand the particular effector mechanisms that are required of CD4 T_{RM} cells during secondary infections, as most research has focused on primary infection and provides conflicting conclusions on the role of certain cytokines, such as IL-10, TNF-α, and IL-17.

Harnessing virus-specific T_{RM} cells by vaccination

Although virus-specific resident memory cells provide numerous benefits during a reinfection event, current vaccination strategies instead often target the development of circulating neutralizing antibodies. Studies are beginning to address the added benefits of T_{RM} cells in vaccination. In a mouse model of influenza vaccination, Zens et al. (2016) compared the ability of dead inactivated virus or live, attenuated influenza virus (LAIV) administered either i.m. or as an aerosol i.n. to elicit T_{RM} cells. They found that only LAIV administered i.n. drove the development of CD69$^+$ CD8 and CD4 T_{RM} cells that resembled canonical resident memory cells in the lung, suggesting that yearly human tri- or quadrivalent influenza vaccinations, which are administered i.m., do not drive T_{RM} cell formation. Further, although i.m. inactivated virus drove a more potent anti-HA antibody response in the serum, only i.n. LAIV vaccination protected mice from disease after infection with a heterologous influenza strain. Studies such as these highlight the urgency for approved vaccination strategies that can drive tissue-resident memory. From studies in natural infections, we know that the generation of potent T_{RM} cells in vivo requires numerous cellular signals occurring in both the lymphatic organs and the tissues. Although the developmental pathway driving CD4 and CD8 T_{RM} cells are not likely identical, studies have revealed overarching tissue residency modules in lymphocytes (Mackay et al., 2016), and CD4 and CD8 T cells share many similar molecular axes that can be harnessed through creative vaccination strategies to develop universal vaccines and prevent future pandemics.

Priming of antiviral T_{RM} cells in the LN

As described above, the differentiation cascade of a memory T cell begins in the LN. Cues from cellular sources of costimulation and cytokines not only have the potency to drive T cells to distinct effector modes (Th1/Th2/Th17) but also act on virus-specific T cells to modulate their transcriptional and epigenetic landscape, affording them the potential to leave the lymphatics, enter the tissue, and become T_{RM} cells. Within 6 h of antigen recognition, and before proliferation, it has been shown that virus-specific T cells that receive heightened TCR signals rapidly upregulate IL-2 and B cell lymphoma 6 (BCL-6) transcripts (DiToro et al., 2018). This increase in BCL-6 represses the ability of these IL-2–producing cells to perceive IL-2 signals through the repression of the IL-2Rα. Conversely, BCL-6^{-} virus-specific T cells retain the ability to perceive IL-2 signals. Signaling through STAT5 leads to the upregulation of transcripts encoding Blimp-1, KLF2, and S1pr1, all associated with exit from the lymphoid tissue (DiToro et al., 2018; He et al., 2020). Indeed, in models of respiratory virus and lung hypersensitivity, the depletion of IL-2Rα on CD4 T cells ablates their ability to migrate to the lung tissue and establish tissue residence (Hondowicz et al., 2016; Hondowicz et al., 2018). Although the administration of recombinant IL-2 in the context of a vaccine would expand T reg cells, which express the high-affinity receptor IL-2Rα, cytokine mimetics have been produced that only bind the low-affinity receptors and indeed drive more T cells out of the lymphoid organs and into tissues (Silva et al., 2019). Intriguingly, in models of cutaneous and respiratory viral infections, the depletion of CD103^{+} DCs expressing IL-12, IL-15, and CD24 during early priming events selectively ablated the ability to produce CD8 T_{RM} cells, but not effector or circulating memory CD8 T cells, suggesting that a specific DC subset may impart the cues necessary to drive T_{RM} cell potential (Iborra et al., 2016). The coupling of viral antigen to specific rare DC subsets to promote uptake and presentation has been used successfully in other models of vaccination and could be a promising avenue to maximize T_{RM} cell generation in the lung (Lahoud et al., 2011; Fernandez-Ruiz et al., 2016). Further, vaccine strategies that depend on adjuvants for successful immune activation must take into account the inflammatory milieu that is induced by that adjuvant design. For example, in a study that tested adjuvant in formulations with influenza HA, the adjuvants Alum or MF59 were observed to drive IL-5 production by HA-specific T cells, whereas GLA-SE or IC31, which include TLR4 and TLR9 agonists, respectively, drove IFN-γ production to the same antigen (Knudsen et al., 2016). Additionally, the use of adjuvants that generate T_{RM} cells that produce Th2/Th17 cytokines immediately upon respiratory viral infection will likely be detrimental. Additionally, in the case of Th1-driven CD8 T_{RM} cells, heightened perception of the type 1 cytokine IL-12 or type I IFN drives cells progressively to a fate of terminal differentiation and inhibited memory formation. This highlights the need for further investigation into the titering of the inflammatory milieu to produce large numbers of Th1 memory cells that persist for long periods of time (Duckworth et al., 2021; Joshi et al., 2007).

Accumulation and maintenance of antiviral T_{RM} cells in the tissue

Even if T cells obtain all the necessary signals in the lymphoid organs, they cannot become T_{RM} cells without local signals in the tissue to elicit their infiltration and mediate their retention. As mentioned above, the administration of LAIV i.n., where the antigen and inflammation were localized to the lung tissue, resulted in both CD4 and CD8 T_{RM} cells in the tissue (Zens et al., 2016). The necessity for local antigen was also apparent in a study that used an adenovirus vaccine platform to prolong antigen presentation in the lung for up to 80 d. As opposed to natural infection, where CD8 T_{RM} cells seem to wane after prolonged periods of senescence (Slütter et al., 2017), this platform elicited high numbers of CD8 T_{RM} cells that were detected out to 1 year, the farthest time point analyzed (Uddbäck et al., 2020). In addition to antigen, T cells require help from other resident lymphocytes to facilitate their survival. In models of respiratory viral infection, CD4 T_{RM} cells required B cells and MHCII for their long-term persistence in the lung tissue (Hondowicz et al., 2018; Swarnalekha et al., 2021). Similarly, during influenza infection, CD8 T_{RM} cells require help from the CD4-derived cytokines IFN-γ and IL-21 in order to localize to the airways and develop into T_{RM} cells (Laidlaw et al., 2014; Son et al., 2021). Further, multiple studies have reported attrition of T cells in the lung (Slütter et al., 2017; Wu et al., 2014; Liang et al., 1994) and further research into whether this attrition results in reduced protection over time or, alternatively, is the result of continuous retrograde migration of T_{RM} cells to the lung draining LN (Stolley et al., 2020). Therefore, understanding how to induce parenchymal lymphatic niches through vaccination is a promising strategy to promote immune memory niches more efficiently in the tissues.

Concluding remarks and SARS-COV-2–specific T_{RM} cells

Establishment of T_{RM} cells is a dominant and potent mechanism of immune protection from pathogen reinfection at mucosal barrier tissues, but investigation into SARS-CoV-2–specific T_{RM} cell generation following COVID-19 infection or SARS-CoV-2 vaccination has been limited. Even so, important studies that sampled the bronchoalveolar fluid of severely and moderately infected patients found similar correlates in SARS-CoV-2 to those previously seen in severe influenza, notably the expansion of pathogenic Th17-like T_{RM} cells expressing IL-17A and GM-CSF (Zhao et al., 2021). Further, a rigorous longitudinal analysis of T cells in the airway of COVID-19 patients revealed an enrichment in markers of resident memory, including *CXCR6*, *ITGA1*, and *PDCD1*, while also expressing higher levels of the effector molecule transcripts *IFNG*, *CCL2*, and *CCL4* (Szabo et al., 2021), recapitulating data in mice that suggest that T_{RM} cells are more potent mediators of viral clearance than blood-derived T cells (Zhao et al., 2016). Current SARS-CoV-2 vaccination strategies aim to drive circulating neutralizing antibodies that bind the receptor-binding domain of SARS-CoV-2 Spike protein. Although circulating IgG antibody is thought to be capable of restricting breakthrough SARS-CoV-2 infection in the lungs of vaccinated individuals, instances of active infection in the nasal tissue have been detected in previously vaccinated individuals, suggesting that sterilizing immunity is not always achieved (Hacisuleyman et al., 2021). Induction of local immunity at the portal of virus entry may complement vaccine strategies that elicit circulating immune memory, and more research is needed to determine the advantages of inducing local mucosal immunity that may be more protective in the face of already worrisome instances of receptor-binding domain variance and mutation (Starr et al., 2021). Future research into facets of T_{RM} cell–mediated protection in natural respiratory infection and the mechanisms in which T_{RM} cells are generated will provide invaluable information for vaccines designed to elicit local immunity in tissue niches and provide protection from future pandemics.

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References

Adachi, Y., T. Onodera, Y. Yamada, R. Daio, M. Tsuiji, T. Inoue, K. Kobayashi, T. Kurosaki, M. Ato, and Y. Takahashi. 2015. Distinct germinal center selection at local sites shapes memory B cell response to viral escape. *J. Exp. Med.* 212:1709–1723. https://doi.org/10.1084/jem.20142284

Akondy, R.S., M. Fitch, S. Edupuganti, S. Yang, H.T. Kissick, K.W. Li, B.A. Youngblood, H.A. Abdelsamed, D.J. McGuire, K.W. Cohen, et al. 2017. Origin and differentiation of human memory CD8 T cells after vaccination. *Nature.* 552:362–367. https://doi.org/10.1038/nature24633

Allie, S.R., J.E. Bradley, U. Mudunuru, M.D. Schultz, B.A. Graf, F.E. Lund, and T.D. Randall. 2019. The establishment of resident memory B cells in the lung requires local antigen encounter. *Nat. Immunol.* 20:97–108. https://doi.org/10.1038/s41590-018-0260-6

Amezcua Vesely, M.C., P. Pallis, P. Bielecki, J.S. Low, J. Zhao, C.C.D. Harman, L. Kroehling, R. Jackson, W. Bailis, P. Licona-Limón, et al. 2019. Effector T_H17 cells give rise to long-lived T_{RM} cells that are essential for an immediate response against bacterial infection. *Cell.* 178:1176–1188.e15. https://doi.org/10.1016/j.cell.2019.07.032

Araki, Y., Z. Wang, C. Zang, W.H. Wood III, D. Schones, K. Cui, T.-Y. Roh, B. Lhotsky, R.P. Wersto, W. Peng, et al. 2009. Genome-wide analysis of histone methylation reveals chromatin state-based regulation of gene transcription and function of memory CD8+ T cells. *Immunity.* 30: 912–925. https://doi.org/10.1016/j.immuni.2009.05.006

Arpaia, N., J.A. Green, B. Moltedo, A. Arvey, S. Hemmers, S. Yuan, P.M. Treuting, and A.Y. Rudensky. 2015. A distinct function of regulatory T cells in tissue protection. *Cell.* 162:1078–1089. https://doi.org/10.1016/j.cell.2015.08.021

Aujla, S.J., Y.R. Chan, M. Zheng, M. Fei, D.J. Askew, D.A. Pociask, T.A. Reinhart, F. McAllister, J. Edeal, K. Gaus, et al. 2008. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. *Nat. Med.* 14:275–281. https://doi.org/10.1038/nm1710

Bautista, E., T. Chotpitayasunondh, Z. Gao, S.A. Harper, M. Shaw, T.M. Uyeki, S.R. Zaki, F.G. Hayden, D.S. Hui, J.D. Kettner, et al. Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. 2010. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N. Engl. J. Med.* 362:1708–1719. https://doi.org/10.1056/NEJMra1000449

Bedoya, F., G.-S. Cheng, A. Leibow, N. Zakhary, K. Weissler, V. Garcia, M. Aitken, E. Kropf, D.S. Garlick, E.J. Wherry, et al. 2013. Viral antigen induces differentiation of Foxp3+ natural regulatory T cells in influenza virus-infected mice. *J. Immunol.* 190:6115–6125. https://doi.org/10.4049/jimmunol.1203302

Belz, G.T., D. Wodarz, G. Diaz, M.A. Nowak, and P.C. Doherty. 2002. Compromised influenza virus-specific CD8(+)-T-cell memory in CD4(+)-T-cell-deficient mice. *J. Virol.* 76:12388–12393. https://doi.org/10.1128/JVI.76.23.12388-12393.2002

Betts, R.J., N. Prabhu, A.W.S. Ho, F.C. Lew, P.E. Hutchinson, O. Rotzschke, P.A. Macary, and D.M. Kemeny. 2012. Influenza A virus infection results in a robust, antigen-responsive, and widely disseminated Foxp3+ regulatory T cell response. *J. Virol.* 86:2817–2825. https://doi.org/10.1128/JVI.05685-11

Beura, L.K., N.J. Fares-Frederickson, E.M. Steinert, M.C. Scott, E.A. Thompson, K.A. Fraser, J.M. Schenkel, V. Vezys, and D. Masopust. 2019. $CD4^+$ resident memory T cells dominate immunosurveillance and orchestrate local recall responses. *J. Exp. Med.* 216:1214–1229. https://doi.org/10.1084/jem.20181365

Brown, D.M., S. Lee, M.L. Garcia-Hernandez, and S.L. Swain. 2012. Multifunctional CD4 cells expressing gamma interferon and perforin mediate protection against lethal influenza virus infection. *J. Virol.* 86:6792–6803. https://doi.org/10.1128/JVI.07172-11

Chapman, T.J., and D.J. Topham. 2010. Identification of a unique population of tissue-memory CD4+ T cells in the airways after influenza infection that is dependent on the integrin VLA-1. *J. Immunol.* 184:3841–3849. https://doi.org/10.4049/jimmunol.0902281

Chapman, T.J., K. Lambert, and D.J. Topham. 2011. Rapid reactivation of extralymphoid CD4 T cells during secondary infection. *PLoS One.* 6: e20493. https://doi.org/10.1371/journal.pone.0020493

Chen, L., D. Zanker, K. Xiao, C. Wu, Q. Zou, and W. Chen. 2014. Immunodominant CD4+ T-cell responses to influenza A virus in healthy individuals focus on matrix 1 and nucleoprotein. *J. Virol.* 88:11760–11773. https://doi.org/10.1128/JVI.01631-14

Chinen, T., A.K. Kannan, A.G. Levine, X. Fan, U. Klein, Y. Zheng, G. Gasteiger, Y. Feng, J.D. Fontenot, and A.Y. Rudensky. 2016. An essential role for the IL-2 receptor in T_{reg} cell function. *Nat. Immunol.* 17:1322–1333. https://doi.org/10.1038/ni.3540

Ciucci, T., M.S. Vacchio, Y. Gao, F. Tomassoni Ardori, J. Candia, M. Mehta, Y. Zhao, B. Tran, M. Pepper, L. Tessarollo, et al. 2019. The emergence and functional fitness of memory $CD4^+$ T cells require the transcription factor Thpok. *Immunity.* 50:91–105.e4. https://doi.org/10.1016/j.immuni.2018.12.019

Cormier, S.A., B. Shrestha, J. Saravia, G.I. Lee, L. Shen, J.P. DeVincenzo, Y.I. Kim, and D. You. 2014. Limited type I interferons and plasmacytoid dendritic cells during neonatal respiratory syncytial virus infection permit immunopathogenesis upon reinfection. *J. Virol.* 88:9350–9360. https://doi.org/10.1128/JVI.00818-14

Crowe, C.R., K. Chen, D.A. Pociask, J.F. Alcorn, C. Krivich, R.I. Enelow, T.M. Ross, J.L. Witztum, and J.K. Kolls. 2009. Critical role of IL-17RA in immunopathology of influenza infection. *J. Immunol.* 183:5301–5310. https://doi.org/10.4049/jimmunol.0900995

Culley, F.J., J. Pollott, and P.J.M. Openshaw. 2002. Age at first viral infection determines the pattern of T cell-mediated disease during reinfection in adulthood. *J. Exp. Med.* 196:1381–1386. https://doi.org/10.1084/jem.20020943

Dahlgren, M.W., S.W. Jones, K.M. Cautivo, A. Dubinin, J.F. Ortiz-Carpena, S. Farhat, K.S. Yu, K. Lee, C. Wang, A.V. Molofsky, et al. 2019. Adventitial stromal cells define group 2 innate lymphoid cell tissue niches. *Immunity.* 50:707–722.e6. https://doi.org/10.1016/j.immuni.2019.02.002

Dakhama, A., J.-W. Park, C. Taube, A. Joetham, A. Balhorn, N. Miyahara, K. Takeda, and E.W. Gelfand. 2005. The enhancement or prevention of airway hyperresponsiveness during reinfection with respiratory syncytial virus is critically dependent on the age at first infection and IL-13 production. *J. Immunol.* 175:1876–1883. https://doi.org/10.4049/jimmunol.175.3.1876

Damjanovic, D., M. Divangahi, K. Kugathasan, C.-L. Small, A. Zganiacz, E.G. Brown, C.M. Hogaboam, J. Gauldie, and Z. Xing. 2011. Negative regulation of lung inflammation and immunopathology by TNF-α during acute influenza infection. *Am. J. Pathol.* 179:2963–2976. https://doi.org/10.1016/j.ajpath.2011.09.003

Denton, A.E., S. Innocentin, E.J. Carr, B.M. Bradford, F. Lafouresse, N.A. Mabbott, U. Mörbe, B. Ludewig, J.R. Groom, K.L. Good-Jacobson, and M.A. Linterman. 2019. Type I interferon induces CXCL13 to support ectopic germinal center formation. *J. Exp. Med.* 216:621–637. https://doi.org/10.1084/jem.20181216

DiToro, D., C.J. Winstead, D. Pham, S. Witte, R. Andargachew, J.R. Singer, C.G. Wilson, C.L. Zindl, R.J. Luther, D.J. Silberger, et al. 2018. Differential

IL-2 expression defines developmental fates of follicular versus nonfollicular helper T cells. *Science*. 361:eaao2933. https://doi.org/10.1126/science.aao2933

Dogan, I., B. Bertocci, V. Vilmont, F. Delbos, J. Mégret, S. Storck, C.-A. Reynaud, and J.-C. Weill. 2009. Multiple layers of B cell memory with different effector functions. *Nat. Immunol.* 10:1292–1299. https://doi.org/10.1038/ni.1814

Duckworth, B.C., F. Lafouresse, V.C. Wimmer, B.J. Broomfield, L. Dalit, Y.O. Alexandre, A.A. Sheikh, R.Z. Qin, C. Alvarado, L.A. Mielke, et al. 2021. Effector and stem-like memory cell fates are imprinted in distinct lymph node niches directed by CXCR3 ligands. *Nat. Immunol.* 22:434–448. https://doi.org/10.1038/s41590-021-00878-5

Fernandez-Ruiz, D., W.Y. Ng, L.E. Holz, J.Z. Ma, A. Zaid, Y.C. Wong, L.S. Lau, V. Mollard, A. Cozijnsen, N. Collins, et al. 2016. Liver-resident memory CD8$^+$ T cells form a front-line defense against malaria liver-stage infection. *Immunity*. 45:889–902. https://doi.org/10.1016/j.immuni.2016.08.011

Fulton, R.B., D.K. Meyerholz, and S.M. Varga. 2010. Foxp3+ CD4 regulatory T cells limit pulmonary immunopathology by modulating the CD8 T cell response during respiratory syncytial virus infection. *J. Immunol.* 185:2382–2392. https://doi.org/10.4049/jimmunol.1000423

Gostic, K.M., M. Ambrose, M. Worobey, and J.O. Lloyd-Smith. 2016. Potent protection against H5N1 and H7N9 influenza via childhood hemagglutinin imprinting. *Science*. 354:722–726. https://doi.org/10.1126/science.aag1322

Graham, M.B., V.L. Braciale, and T.J. Braciale. 1994. Influenza virus-specific CD4+ T helper type 2 T lymphocytes do not promote recovery from experimental virus infection. *J. Exp. Med.* 180:1273–1282. https://doi.org/10.1084/jem.180.4.1273

Guvenel, A., A. Jozwik, S. Ascough, S.K. Ung, S. Paterson, M. Kalyan, Z. Gardener, E. Bergstrom, S. Kar, M.S. Habibi, et al. 2020. Epitope-specific airway-resident CD4+ T cell dynamics during experimental human RSV infection. *J. Clin. Invest.* 130:523–538. https://doi.org/10.1172/JCI131696

Hacisuleyman, E., C. Hale, Y. Saito, N.E. Blachere, M. Bergh, E.G. Conlon, D.J. Schaefer-Babajew, J. DaSilva, F. Muecksch, C. Gaebler, et al. 2021. Vaccine breakthrough infections with SARS-CoV-2 variants. *N. Engl. J. Med.* 384:2212–2218. https://doi.org/10.1056/NEJMoa2105000

Hashimoto, H., R. Ueda, K. Narumi, Y. Heike, T. Yoshida, and K. Aoki. 2014. Type I IFN gene delivery suppresses regulatory T cells within tumors. *Cancer Gene Ther.* 21:532–541. https://doi.org/10.1038/cgt.2014.60

He, X., X. He, V.P. Dave, Y. Zhang, X. Hua, E. Nicolas, W. Xu, B.A. Roe, and D.J. Kappes. 2005. The zinc finger transcription factor Th-POK regulates CD4 versus CD8 T-cell lineage commitment. *Nature*. 433:826–833. https://doi.org/10.1038/nature03338

He, K., A. Hettinga, S.L. Kale, S. Hu, M.M. Xie, A.L. Dent, A. Ray, and A.C. Poholek. 2020. Blimp-1 is essential for allergen-induced asthma and Th2 cell development in the lung. *J. Exp. Med.* 217:e20190742. https://doi.org/10.1084/jem.20190742

Hondowicz, B.D., D. An, J.M. Schenkel, K.S. Kim, H.R. Steach, A.T. Krishnamurty, G.J. Keitany, E.N. Garza, K.A. Fraser, J.J. Moon, et al. 2016. Interleukin-2-dependent allergen-specific tissue-resident memory cells drive asthma. *Immunity*. 44:155–166. https://doi.org/10.1016/j.immuni.2015.11.004

Hondowicz, B.D., K.S. Kim, M.J. Ruterbusch, G.J. Keitany, and M. Pepper. 2018. IL-2 is required for the generation of viral-specific CD4$^+$ Th1 tissue-resident memory cells and B cells are essential for maintenance in the lung. *Eur. J. Immunol.* 48:80–86. https://doi.org/10.1002/eji.201746928

Horimoto, T., and Y. Kawaoka. 2005. Influenza: lessons from past pandemics, warnings from current incidents. *Nat. Rev. Microbiol.* 3:591–600. https://doi.org/10.1038/nrmicro1208

Hua, L., S. Yao, D. Pham, L. Jiang, J. Wright, D. Sawant, A.L. Dent, T.J. Braciale, M.H. Kaplan, and J. Sun. 2013. Cytokine-dependent induction of CD4+ T cells with cytotoxic potential during influenza virus infection. *J. Virol.* 87:11884–11893. https://doi.org/10.1128/JVI.01461-13

Hussell, T., A. Pennycook, and P.J.M. Openshaw. 2001. Inhibition of tumor necrosis factor reduces the severity of virus-specific lung immunopathology. *Eur. J. Immunol.* 31(9):2566–2573. https://doi.org/10.1002/1521-4141(200109)31:9<2566::aid-immu2566>3.0.co;2-l

Iborra, S., M. Martínez-López, S.C. Khouili, M. Enamorado, F.J. Cueto, R. Conde-Garrosa, C. Del Fresno, and D. Sancho. 2016. Optimal Generation of Tissue-Resident but Not Circulating Memory T Cells during Viral Infection Requires Crosspriming by DNGR-1$^+$ Dendritic Cells. *Immunity*. 45:847–860. https://doi.org/10.1016/j.immuni.2016.08.019

Iijima, N., and A. Iwasaki. 2014. T cell memory. A local macrophage chemokine network sustains protective tissue-resident memory CD4 T cells. *Science*. 346:93–98. https://doi.org/10.1126/science.1257530

Ioannidis, I., F. Ye, B. McNally, M. Willette, and E. Flaño. 2013. Toll-like receptor expression and induction of type I and type III interferons in primary airway epithelial cells. *J. Virol.* 87:3261–3270. https://doi.org/10.1128/JVI.01956-12

Ivanov, I.I., B.S. McKenzie, L. Zhou, C.E. Tadokoro, A. Lepelley, J.J. Lafaille, D.J. Cua, and D.R. Littman. 2006. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell*. 126:1121–1133. https://doi.org/10.1016/j.cell.2006.07.035

Jameson, S.C., and D. Masopust. 2018. Understanding subset diversity in T cell memory. *Immunity*. 48:214–226. https://doi.org/10.1016/j.immuni.2018.02.010

Josefowicz, S.Z., L.-F. Lu, and A.Y. Rudensky. 2012. Regulatory T cells: mechanisms of differentiation and function. *Annu. Rev. Immunol.* 30:531–564. https://doi.org/10.1146/annurev.immunol.25.022106.141623

Joshi, N.S., W. Cui, A. Chandele, H.K. Lee, D.R. Urso, J. Hagman, L. Gapin, and S.M. Kaech. 2007. Inflammation directs memory precursor and short-lived effector CD8(+) T cell fates via the graded expression of T-bet transcription factor. *Immunity*. 27:281–295. https://doi.org/10.1016/j.immuni.2007.07.010

Kim, D.-Y., A. Sato, S. Fukuyama, H. Sagara, T. Nagatake, I.G. Kong, K. Goda, T. Nochi, J. Kunisawa, S. Sato, et al. 2011. The airway antigen sampling system: respiratory M cells as an alternative gateway for inhaled antigens. *J. Immunol.* 186:4253–4262. https://doi.org/10.4049/jimmunol.0903794

Knudsen, N.P.H., A. Olsen, C. Buonsanti, F. Follmann, Y. Zhang, R.N. Coler, C.B. Fox, A. Meinke, U. D'Oro, D. Casini, et al. 2016. Different human vaccine adjuvants promote distinct antigen-independent immunological signatures tailored to different pathogens. *Sci. Rep.* 6:19570. https://doi.org/10.1038/srep19570

Kudva, A., E.V. Scheller, K.M. Robinson, C.R. Crowe, S.M. Choi, S.R. Slight, S.A. Khader, P.J. Dubin, R.I. Enelow, J.K. Kolls, and J.F. Alcorn. 2011. Influenza A inhibits Th17-mediated host defense against bacterial pneumonia in mice. *J. Immunol.* 186:1666–1674. https://doi.org/10.4049/jimmunol.1002194

Laan, M., Z.-H. Cui, H. Hoshino, J. Lötvall, M. Sjöstrand, D.C. Gruenert, B.-E. Skoogh, and A. Lindén. 1999. Neutrophil recruitment by human IL-17 via C-X-C chemokine release in the airways. *J. Immunol.* 162:2347–2352.

Lahoud, M.H., F. Ahmet, S. Kitsoulis, S.S. Wan, D. Vremec, C.-N. Lee, B. Phipson, W. Shi, G.K. Smyth, A.M. Lew, et al. 2011. Targeting antigen to mouse dendritic cells via Clec9A induces potent CD4 T cell responses biased toward a follicular helper phenotype. *J. Immunol.* 187:842–850. https://doi.org/10.4049/jimmunol.1101176

Lai, W., M. Yu, M.-N. Huang, F. Okoye, A.D. Keegan, and D.L. Farber. 2011. Transcriptional control of rapid recall by memory CD4 T cells. *J. Immunol.* 187:133–140. https://doi.org/10.4049/jimmunol.1002742

Laidlaw, B.J., N. Zhang, H.D. Marshall, M.M. Staron, T. Guan, Y. Hu, L.S. Cauley, J. Craft, and S.M. Kaech. 2014. CD4+ T cell help guides formation of CD103+ lung-resident memory CD8+ T cells during influenza viral infection. *Immunity*. 41:633–645. https://doi.org/10.1016/j.immuni.2014.09.007

Laidlaw, B.J., J.E. Craft, and S.M. Kaech. 2016. The multifaceted role of CD4(+) T cells in CD8(+) T cell memory. *Nat. Rev. Immunol.* 16:102–111. https://doi.org/10.1038/nri.2015.10

Lam, J.H., and N. Baumgarth. 2019. The multifaceted B cell response to influenza virus. *J. Immunol.* 202:351–359. https://doi.org/10.4049/jimmunol.1801208

Lee, L.Y.-H., L.A. Ha, C. Simmons, M.D. de Jong, N.V.V. Chau, R. Schumacher, Y.C. Peng, A.J. McMichael, J.J. Farrar, G.L. Smith, et al. 2008. Memory T cells established by seasonal human influenza A infection cross-react with avian influenza A (H5N1) in healthy individuals. *J. Clin. Invest.* 118:3478–3490. https://doi.org/10.1172/JCI32460

Lee, Y.K., H. Turner, C.L. Maynard, J.R. Oliver, D. Chen, C.O. Elson, and C.T. Weaver. 2009. Late developmental plasticity in the T helper 17 lineage. *Immunity*. 30:92–107. https://doi.org/10.1016/j.immuni.2008.11.005

Lee, D.C.P., J.A.E. Harker, J.S. Tregoning, S.F. Atabani, C. Johansson, J. Schwarze, and P.J.M. Openshaw. 2010. CD25+ natural regulatory T cells are critical in limiting innate and adaptive immunity and resolving disease following respiratory syncytial virus infection. *J. Virol.* 84:8790–8798. https://doi.org/10.1128/JVI.00796-10

Li, C., P. Yang, Y. Sun, T. Li, C. Wang, Z. Wang, Z. Zou, Y. Yan, W. Wang, C. Wang, et al. 2012. IL-17 response mediates acute lung injury induced by the 2009 pandemic influenza A (H1N1) virus. *Cell Res.* 22:528–538. https://doi.org/10.1038/cr.2011.165

Liang, S., K. Mozdzanowska, G. Palladino, and W. Gerhard. 1994. Heterosubtypic immunity to influenza type A virus in mice. Effector mechanisms and their longevity. *J. Immunol.* 152:1653–1661.

Liang, S.C., X.-Y. Tan, D.P. Luxenberg, R. Karim, K. Dunussi-Joannopoulos, M. Collins, and L.A. Fouser. 2006. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *J. Exp. Med.* 203:2271–2279. https://doi.org/10.1084/jem.20061308

Lukacs, N.W., M.L. Moore, B.D. Rudd, A.A. Berlin, R.D. Collins, S.J. Olson, S.B. Ho, and R.S. Peebles Jr. 2006. Differential immune responses and pulmonary pathophysiology are induced by two different strains of respiratory syncytial virus. *Am. J. Pathol.* 169:977–986. https://doi.org/10.2353/ajpath.2006.051055

Mackay, L.K., M. Minnich, N.A. Kragten, Y. Liao, B. Nota, C. Seillet, A. Zaid, K. Man, S. Preston, D. Freestone, et al. 2016. Hobit and Blimp1 instruct a universal transcriptional program of tissue residency in lymphocytes. *Science.* 352:459–463. https://doi.org/10.1126/science.aad2035

Mangan, P.R., L.E. Harrington, D.B. O'Quinn, W.S. Helms, D.C. Bullard, C.O. Elson, R.D. Hatton, S.M. Wahl, T.R. Schoeb, and C.T. Weaver. 2006. Transforming growth factor-β induces development of the T(H)17 lineage. *Nature.* 441:231–234. https://doi.org/10.1038/nature04754

Marr, N., T.-I. Wang, S.H.Y. Kam, Y.S. Hu, A.A. Sharma, A. Lam, J. Markowski, A. Solimano, P.M. Lavoie, and S.E. Turvey. 2014. Attenuation of respiratory syncytial virus-induced and RIG-I-dependent type I IFN responses in human neonates and very young children. *J. Immunol.* 192: 948–957. https://doi.org/10.4049/jimmunol.1302007

Marshall, N.B., A.M. Vong, P. Devarajan, M.D. Brauner, Y. Kuang, R. Nayar, E.A. Schutten, C.H. Castonguay, L.J. Berg, S.L. Nutt, and S.L. Swain. 2017. NKG2C/E marks the unique cytotoxic CD4 T cell subset, ThCTL, generated by influenza infection. *J. Immunol.* 198:1142–1155. https://doi.org/10.4049/jimmunol.1601297

McKinstry, K.K., T.M. Strutt, A. Buck, J.D. Curtis, J.P. Dibble, G. Huston, M. Tighe, H. Hamada, S. Sell, R.W. Dutton, and S.L. Swain. 2009. IL-10 deficiency unleashes an influenza-specific Th17 response and enhances survival against high-dose challenge. *J. Immunol.* 182:7353–7363. https://doi.org/10.4049/jimmunol.0900657

Moguche, A.O., S. Shafiani, C. Clemons, R.P. Larson, C. Dinh, L.E. Higdon, C.J. Cambier, J.R. Sissons, A.M. Gallegos, P.J. Fink, and K.B. Urdahl. 2015. ICOS and Bcl6-dependent pathways maintain a CD4 T cell population with memory-like properties during tuberculosis. *J. Exp. Med.* 212: 715–728. https://doi.org/10.1084/jem.20141518

Monto, A.S., and K. Fukuda. 2020. Lessons From Influenza Pandemics of the Last 100 Years. *Clin. Infect. Dis.* 70:951–957. https://doi.org/10.1093/cid/ciz803

Moore, M.L., M.H. Chi, C. Luongo, N.W. Lukacs, V.V. Polosukhin, M.M. Huckabee, D.C. Newcomb, U.J. Buchholz, J.E. Crowe Jr., K. Goleniewska, et al. 2009. A chimeric A2 strain of respiratory syncytial virus (RSV) with the fusion protein of RSV strain line 19 exhibits enhanced viral load, mucus, and airway dysfunction. *J. Virol.* 83:4185–4194. https://doi.org/10.1128/JVI.01853-08

Morens, D.M., J.K. Taubenberger, and A.S. Fauci. 2008. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. *J. Infect. Dis.* 198: 962–970. https://doi.org/10.1086/591708

Moser, E.K., M.M. Hufford, and T.J. Braciale. 2014. Late engagement of CD86 after influenza virus clearance promotes recovery in a FoxP3+ regulatory T cell dependent manner. *PLoS Pathog.* 10:e1004315. https://doi.org/10.1371/journal.ppat.1004315

Moyron-Quiroz, J.E., J. Rangel-Moreno, K. Kusser, L. Hartson, F. Sprague, S. Goodrich, D.L. Woodland, F.E. Lund, and T.D. Randall. 2004. Role of inducible bronchus associated lymphoid tissue (iBALT) in respiratory immunity. *Nat. Med.* 10:927–934. https://doi.org/10.1038/nm1091

Mucida, D., M.M. Husain, S. Muroi, F. van Wijk, R. Shinnakasu, Y. Naoe, B.S. Reis, Y. Huang, F. Lambolez, M. Docherty, et al. 2013. Transcriptional reprogramming of mature CD4^{+} helper T cells generates distinct MHC class II-restricted cytotoxic T lymphocytes. *Nat. Immunol.* 14:281–289. https://doi.org/10.1038/ni.2523

Mukherjee, S., D.M. Lindell, A.A. Berlin, S.B. Morris, T.P. Shanley, M.B. Hershenson, and N.W. Lukacs. 2011. IL-17-induced pulmonary pathogenesis during respiratory viral infection and exacerbation of allergic disease. *Am. J. Pathol.* 179:248–258. https://doi.org/10.1016/j.ajpath.2011.03.003

Nakanishi, Y., B. Lu, C. Gerard, and A. Iwasaki. 2009. CD8(+) T lymphocyte mobilization to virus-infected tissue requires CD4(+) T-cell help. *Nature.* 462:510–513. https://doi.org/10.1038/nature08511

O'Garra, A., and P. Vieira. 2007. T(H)1 cells control themselves by producing interleukin-10. *Nat. Rev. Immunol.* 7:425–428. https://doi.org/10.1038/nri2097

Oja, A.E., B. Piet, C. Helbig, R. Stark, D. van der Zwan, H. Blaauwgeers, E.B.M. Remmerswaal, D. Amsen, R.E. Jonkers, P.D. Moerland, et al. 2018. Trigger-happy resident memory CD4^{+} T cells inhabit the human lungs. *Mucosal Immunol.* 11:654–667. https://doi.org/10.1038/mi.2017.94

Onodera, T., Y. Takahashi, Y. Yokoi, M. Ato, Y. Kodama, S. Hachimura, T. Kurosaki, and K. Kobayashi. 2012. Memory B cells in the lung participate in protective humoral immune responses to pulmonary influenza virus reinfection. *Proc. Natl. Acad. Sci. USA.* 109:2485–2490. https://doi.org/10.1073/pnas.1115369109

Pape, K.A., J.J. Taylor, R.W. Maul, P.J. Gearhart, and M.K. Jenkins. 2011. Different B cell populations mediate early and late memory during an endogenous immune response. *Science.* 331:1203–1207. https://doi.org/10.1126/science.1201730

Pepper, M., and M.K. Jenkins. 2011. Origins of CD4(+) effector and central memory T cells. *Nat. Immunol.* 12:467–471. https://doi.org/10.1038/ni.2038

Pepper, M., J.L. Linehan, A.J. Pagán, T. Zell, T. Dileepan, P.P. Cleary, and M.K. Jenkins. 2010. Different routes of bacterial infection induce long-lived TH1 memory cells and short-lived TH17 cells. *Nat. Immunol.* 11:83–89. https://doi.org/10.1038/ni.1826

Pepper, M., A.J. Pagán, B.Z. Igyártó, J.J. Taylor, and M.K. Jenkins. 2011. Opposing signals from the Bcl6 transcription factor and the interleukin-2 receptor generate T helper 1 central and effector memory cells. *Immunity.* 35:583–595. https://doi.org/10.1016/j.immuni.2011.09.009

Pociask, D.A., E.V. Scheller, S. Mandalapu, K.J. McHugh, R.I. Enelow, C.L. Fattman, J.K. Kolls, and J.F. Alcorn. 2013. IL-22 is essential for lung epithelial repair following influenza infection. *Am. J. Pathol.* 182: 1286–1296. https://doi.org/10.1016/j.ajpath.2012.12.007

Qui, H.Z., A.T. Hagymasi, S. Bandyopadhyay, M.C. St Rose, R. Ramanarasimhaiah, A. Ménoret, R.S. Mittler, S.M. Gordon, S.L. Reiner, A.T. Vella, and A.J. Adler. 2011. CD134 plus CD137 dual costimulation induces Eomesodermin in CD4 T cells to program cytotoxic Th1 differentiation. *J. Immunol.* 187:3555–3564. https://doi.org/10.4049/jimmunol.1101244

Rangel-Moreno, J., D.M. Carragher, M. de la Luz Garcia-Hernandez, J.Y. Hwang, K. Kusser, L. Hartson, J.K. Kolls, S.A. Khader, and T.D. Randall. 2011. The development of inducible bronchus-associated lymphoid tissue depends on IL-17. *Nat. Immunol.* 12:639–646. https://doi.org/10.1038/ni.2053

Rao, D.A., M.F. Gurish, J.L. Marshall, K. Slowikowski, C.Y. Fonseka, Y. Liu, L.T. Donlin, L.A. Henderson, K. Wei, F. Mizoguchi, et al. 2017. Pathologically expanded peripheral T helper cell subset drives B cells in rheumatoid arthritis. *Nature.* 542:110–114. https://doi.org/10.1038/nature20810

Richards, K.A., D. Topham, F.A. Chaves, and A.J. Sant. 2010. Cutting edge: CD4 T cells generated from encounter with seasonal influenza viruses and vaccines have broad protein specificity and can directly recognize naturally generated epitopes derived from the live pandemic H1N1 virus. *J. Immunol.* 185:4998–5002. https://doi.org/10.4049/jimmunol.1001395

Ruterbusch, M., K.B. Pruner, L. Shehata, and M. Pepper. 2020. In vivo CD4^{+} T cell differentiation and function: revisiting the Th1/Th2 paradigm. *Annu. Rev. Immunol.* 38:705–725. https://doi.org/10.1146/annurev-immunol-103019-085803

Sant, A.J., A.T. DiPiazza, J.L. Nayak, A. Rattan, and K.A. Richards. 2018. CD4 T cells in protection from influenza virus: Viral antigen specificity and functional potential. *Immunol. Rev.* 284:91–105. https://doi.org/10.1111/imr.12662

Schenkel, J.M., K.A. Fraser, L.K. Beura, K.E. Pauken, V. Vezys, and D. Masopust. 2014. T cell memory. Resident memory CD8 T cells trigger protective innate and adaptive immune responses. *Science.* 346:98–101. https://doi.org/10.1126/science.1254536

Shahangian, A., E.K. Chow, X. Tian, J.R. Kang, A. Ghaffari, S.Y. Liu, J.A. Belperio, G. Cheng, and J.C. Deng. 2009. Type I IFNs mediate development of postinfluenza bacterial pneumonia in mice. *J. Clin. Invest.* 119: 1910–1920. https://doi.org/10.1172/JCI35412

Shinoda, K., K. Hirahara, T. Iinuma, T. Ichikawa, A.S. Suzuki, K. Sugaya, D.J. Tumes, H. Yamamoto, T. Hara, S. Tani-Ichi, et al. 2016. Thy1+IL-7+ lymphatic endothelial cells in iBALT provide a survival niche for memory T-helper cells in allergic airway inflammation. *Proc. Natl. Acad. Sci. USA.* 113:E2842–E2851. https://doi.org/10.1073/pnas.1512600113

Shlomchik, M.J. 2018. Do memory B cells form secondary germinal centers? Yes and no. *Cold Spring Harb. Perspect. Biol.* 10:a029405. https://doi.org/10.1101/cshperspect.a029405

Silva, D.A., S. Yu, U.Y. Ulge, J.B. Spangler, K.M. Jude, C. Labão-Almeida, L.R. Ali, A. Quijano-Rubio, M. Ruterbusch, I. Leung, et al. 2019. De novo design of potent and selective mimics of IL-2 and IL-15. *Nature.* 565: 186–191. https://doi.org/10.1038/s41586-018-0830-7

Slütter, B., L.L. Pewe, S.M. Kaech, and J.T. Harty. 2013. Lung airway-surveilling CXCR3(hi) memory CD8(+) T cells are critical for protection against influenza A virus. *Immunity.* 39:939–948. https://doi.org/10.1016/j.immuni.2013.09.013

Slütter, B., N. Van Braeckel-Budimir, G. Abboud, S.M. Varga, S. Salek-Ardakani, and J.T. Harty. 2017. Dynamics of influenza-induced lung-resident memory T cells underlie waning heterosubtypic immunity. *Sci. Immunol.* 2:eaag2031. https://doi.org/10.1126/sciimmunol.aag2031

Son, Y.M., I.S. Cheon, Y. Wu, C. Li, Z. Wang, X. Gao, Y. Chen, Y. Takahashi, Y.-X. Fu, A.L. Dent, et al. 2021. Tissue-resident CD4$^+$ T helper cells assist the development of protective respiratory B and CD8$^+$ T cell memory responses. *Sci. Immunol.* 6:eabb6852. https://doi.org/10.1126/sciimmunol.abb6852

Soudja, S.M., C. Chandrabos, E. Yakob, M. Veenstra, D. Palliser, and G. Lauvau. 2014. Memory-T-cell-derived interferon-γ instructs potent innate cell activation for protective immunity. *Immunity.* 40:974–988. https://doi.org/10.1016/j.immuni.2014.05.005

Sridhar, S., S. Begom, A. Bermingham, K. Hoschler, W. Adamson, W. Carman, T. Bean, W. Barclay, J.J. Deeks, and A. Lalvani. 2013. Cellular immune correlates of protection against symptomatic pandemic influenza. *Nat. Med.* 19:1305–1312. https://doi.org/10.1038/nm.3350

Srivastava, S., M.A. Koch, M. Pepper, and D.J. Campbell. 2014. Type I interferons directly inhibit regulatory T cells to allow optimal antiviral T cell responses during acute LCMV infection. *J. Exp. Med.* 211:961–974. https://doi.org/10.1084/jem.20131556

Starr, T.N., A.J. Greaney, A. Addetia, W.W. Hannon, M.C. Choudhary, A.S. Dingens, J.Z. Li, and J.D. Bloom. 2021. Prospective mapping of viral mutations that escape antibodies used to treat COVID-19. *Science.* 371:850–854. https://doi.org/10.1126/science.abf9302

Steinert, E.M., J.M. Schenkel, K.A. Fraser, L.K. Beura, L.S. Manlove, B.Z. Igyártó, P.J. Southern, and D. Masopust. 2015. Quantifying memory CD8 T cells reveals regionalization of immunosurveillance. *Cell.* 161:737–749. https://doi.org/10.1016/j.cell.2015.03.031

Stockinger, B., and S. Omenetti. 2017. The dichotomous nature of T helper 17 cells. *Nat. Rev. Immunol.* 17:535–544. https://doi.org/10.1038/nri.2017.50

Stolley, J.M., T.S. Johnston, A.G. Soerens, L.K. Beura, P.C. Rosato, V. Joag, S.P. Wijeyesinghe, R.A. Langlois, K.C. Osum, J.S. Mitchell, and D. Masopust. 2020. Retrograde migration supplies resident memory T cells to lung-draining LN after influenza infection. *J. Exp. Med.* 217:e20192197. https://doi.org/10.1084/jem.20192197

Strutt, T.M., K.K. McKinstry, J.P. Dibble, C. Winchell, Y. Kuang, J.D. Curtis, G. Huston, R.W. Dutton, and S.L. Swain. 2010. Memory CD4+ T cells induce innate responses independently of pathogen. *Nat. Med.* 16:558–564: 1p: 564. https://doi.org/10.1038/nm.2142

Strutt, T.M., K.K. McKinstry, Y. Kuang, L.M. Bradley, and S.L. Swain. 2012. Memory CD4+ T-cell-mediated protection depends on secondary effectors that are distinct from and superior to primary effectors. *Proc. Natl. Acad. Sci. USA.* 109:E2551–E2560. https://doi.org/10.1073/pnas.1205894109

Sun, J., R. Madan, C.L. Karp, and T.J. Braciale. 2009. Effector T cells control lung inflammation during acute influenza virus infection by producing IL-10. *Nat. Med.* 15:277–284. https://doi.org/10.1038/nm.1929

Sun, K., L. Torres, and D.W. Metzger. 2010. A detrimental effect of interleukin-10 on protective pulmonary humoral immunity during primary influenza A virus infection. *J. Virol.* 84:5007–5014. https://doi.org/10.1128/JVI.02408-09

Sun, J., H. Dodd, E.K. Moser, R. Sharma, and T.J. Braciale. 2011. CD4+ T cell help and innate-derived IL-27 induce Blimp-1-dependent IL-10 production by antiviral CTLs. *Nat. Immunol.* 12:327–334. https://doi.org/10.1038/ni.1996

Swarnalekha, N., D. Schreiner, L.C. Litzler, S. Iftikhar, D. Kirchmeier, M. Künzli, Y.M. Son, J. Sun, E.A. Moreira, and C.G. King. 2021. T resident helper cells promote humoral responses in the lung. *Sci. Immunol.* 6:eabb6808. https://doi.org/10.1126/sciimmunol.abb6808

Szabo, P.A., M. Miron, and D.L. Farber. 2019. Location, location, location: Tissue resident memory T cells in mice and humans. *Sci. Immunol.* 4:eaas9673. https://doi.org/10.1126/sciimmunol.aas9673

Szabo, P.A., P. Dogra, J.I. Gray, S.B. Wells, T.J. Connors, S.P. Weisberg, I. Krupska, R. Matsumoto, M.M.L. Poon, E. Idzikowski, et al. 2021. Longitudinal profiling of respiratory and systemic immune responses reveals myeloid cell-driven lung inflammation in severe COVID-19. *Immunity.* 54:797–814.e6. https://doi.org/10.1016/j.immuni.2021.03.005

Teijaro, J.R., D. Verhoeven, C.A. Page, D. Turner, and D.L. Farber. 2010. Memory CD4 T cells direct protective responses to influenza virus in the lungs through helper-independent mechanisms. *J. Virol.* 84:9217–9226. https://doi.org/10.1128/JVI.01069-10

Teijaro, J.R., D. Turner, Q. Pham, E.J. Wherry, L. Lefrançois, and D.L. Farber. 2011. Cutting edge: Tissue-retentive lung memory CD4 T cells mediate optimal protection to respiratory virus infection. *J. Immunol.* 187:5510–5514. https://doi.org/10.4049/jimmunol.1102243

Turner, D.L., K.L. Bickham, J.J. Thome, C.Y. Kim, F. D'Ovidio, E.J. Wherry, and D.L. Farber. 2014. Lung niches for the generation and maintenance of tissue-resident memory T cells. *Mucosal Immunol.* 7:501–510. https://doi.org/10.1038/mi.2013.67

Uddbäck, I., E.K. Cartwright, A.S. Schøller, A.N. Wein, S.L. Hayward, J. Lobby, S. Takamura, A.R. Thomsen, J.E. Kohlmeier, and J.P. Christensen. 2020. Long-term maintenance of lung resident memory T cells is mediated by persistent antigen. *Mucosal Immunol.* 14(1):92–99. https://doi.org/10.1038/s41385-020-0309-3

Vu Van, D., K.C. Beier, L.-J. Pietzke, M.S. Al Baz, R.K. Feist, S. Gurka, E. Hamelmann, R.A. Kroczek, and A. Hutloff. 2016. Local T/B cooperation in inflamed tissues is supported by T follicular helper-like cells. *Nat. Commun.* 7:10875. https://doi.org/10.1038/ncomms10875

Wakim, L.M., J. Waithman, N. van Rooijen, W.R. Heath, and F.R. Carbone. 2008. Dendritic cell-induced memory T cell activation in nonlymphoid tissues. *Science.* 319:198–202. https://doi.org/10.1126/science.1151869

Wang, L., K.F. Wildt, E. Castro, Y. Xiong, L. Feigenbaum, L. Tessarollo, and R. Bosselut. 2008. The zinc finger transcription factor Zbtb7b represses CD8-lineage gene expression in peripheral CD4+ T cells. *Immunity.* 29:876–887. https://doi.org/10.1016/j.immuni.2008.09.019

Weng, N.P., Y. Araki, and K. Subedi. 2012. The molecular basis of the memory T cell response: differential gene expression and its epigenetic regulation. *Nat. Rev. Immunol.* 12:306–315. https://doi.org/10.1038/nri3173

Wilkinson, T.M., C.K.F. Li, C.S.C. Chui, A.K.Y. Huang, M. Perkins, J.C. Liebner, R. Lambkin-Williams, A. Gilbert, J. Oxford, B. Nicholas, et al. 2012. Preexisting influenza-specific CD4+ T cells correlate with disease protection against influenza challenge in humans. *Nat. Med.* 18:274–280. https://doi.org/10.1038/nm.2612

Wong, R., J.A. Belk, J. Govero, J.L. Uhrlaub, D. Reinartz, H. Zhao, J.M. Errico, L. D'Souza, T.J. Ripperger, J. Nikolich-Zugich, et al. 2020. Affinity-restricted memory B cells dominate recall responses to heterologous flaviviruses. *Immunity.* 53:1078–1094.e7. https://doi.org/10.1016/j.immuni.2020.09.001

World Health Organization. 2021a. WHO Coronavirus Disease (COVID-19) Dashboard. https://covid19.who.int (accessed March 2, 2021).

World Health Organization. 2021b. Seasonal Influenza Fact Sheet. https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal) (accessed February 18, 2021)

Wu, T., Y. Hu, Y.T. Lee, K.R. Bouchard, A. Benechet, K. Khanna, and L.S. Cauley. 2014. Lung-resident memory CD8 T cells (TRM) are indispensable for optimal cross-protection against pulmonary virus infection. *J. Leukoc. Biol.* 95:215–224. https://doi.org/10.1189/jlb.0313180

Ye, P., F.H. Rodriguez, S. Kanaly, K.L. Stocking, J. Schurr, P. Schwarzenberger, P. Oliver, W. Huang, P. Zhang, J. Zhang, et al. 2001. Requirement of interleukin 17 receptor signaling for lung CXC chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. *J. Exp. Med.* 194:519–527. https://doi.org/10.1084/jem.194.4.519

You, D., N. Marr, J. Saravia, B. Shrestha, G.I. Lee, S.E. Turvey, F. Brombacher, D.R. Herbert, and S.A. Cormier. 2013. IL-4Rα on CD4+ T cells plays a pathogenic role in respiratory syncytial virus reinfection in mice infected initially as neonates. *J. Leukoc. Biol.* 93:933–942. https://doi.org/10.1189/jlb.1012498

Zens, K.D., J.K. Chen, and D.L. Farber. 2016. Vaccine-generated lung tissue-resident memory T cells provide heterosubtypic protection to influenza infection. *JCI Insight.* 1:e85832. https://doi.org/10.1172/jci.insight.85832

Zhao, J., J. Zhao, A.K. Mangalam, R. Channappanavar, C. Fett, D.K. Meyerholz, S. Agnihothram, R.S. Baric, C.S. David, and S. Perlman. 2016. Airway memory CD4(+) T cells mediate protective immunity against emerging respiratory coronaviruses. *Immunity.* 44:1379–1391. https://doi.org/10.1016/j.immuni.2016.05.006

Zhao, Y., C. Kilian, J.-E. Turner, L. Bosurgi, K. Roedl, P. Bartsch, A.-C. Gnirck, F. Cortesi, C. Schultheiß, M. Hellmig, et al. 2021. Clonal expansion and activation of tissue-resident memory-like Th17 cells expressing GM-CSF in the lungs of severe COVID-19 patients. *Sci. Immunol.* 6:eabf6692. https://doi.org/10.1126/sciimmunol.abf6692