Co-Ordination of Mucosal B Cell and CD8 T Cell Memory by Tissue-Resident CD4 Helper T Cells

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Abstract: Adaptive cellular immunity plays a major role in clearing microbial invasion of mucosal tissues in mammals. Following the clearance of primary pathogens, memory lymphocytes are established both systemically and locally at pathogen entry sites. Recently, resident memory CD8 T and B cells (T_{RM} and B_{RM} respectively), which are parked mainly in non-lymphoid mucosal tissues, were characterized and demonstrated to be essential for protection against secondary microbial invasion. Here we reviewed the current understanding of the cellular and molecular cues regulating CD8 T_{RM} and B_{RM} development, maintenance and function. We focused particularly on elucidating the role of a novel tissue-resident helper T (T_{RH}) cell population in assisting T_{RM} and B_{RM} responses in the respiratory mucosa following viral infection. Finally, we argue that the promotion of T_{RH} responses by future mucosal vaccines would be key to the development of successful universal influenza or coronavirus vaccines, providing long-lasting immunity against a broad spectrum of viral strains.

Keywords: tissue resident memory T; tissue resident memory B; mucosal immunity; non-lymphoid tissues

1. Introduction

A cardinal feature of the adaptive immune system is the ability to develop immunological memory following primary antigenic encounter. Upon microbial invasion, naïve T cells, primed by antigen-presenting cells (APCs), rapidly undergo massive expansion and effector T cell differentiation to generate a large pool of antigen-specific effector T cells for the clearance of invading pathogens. Following pathogen clearance, effector T cells go through a contraction phase, in which majority of the effector T cells undergo apoptosis. The surviving effector cells or memory precursor cells convert into long-term memory T cells (including both CD4 and CD8 memory) after the contraction phase. Based on their trafficking properties, CD8 memory T cells can be further categorized into different subsets including central memory T (T_{CM}), effector memory T (T_{EM}), peripheral memory T (T_{PM}) and tissue resident memory T (T_{RM}) cells [1–5]. T_{CM} cells re-circulate through secondary lymphoid organs, T_{EM} cells have more broad capacity of mobility between blood and non-lymphoid tissues, while T_{PM} cells mainly patrol the blood vessels [4]. In contrast, T_{RM} cells are parked in non-lymphoid mucosal tissues and have an impaired capacity to enter re-circulation [6–10]. Following secondary infection with the same virus or viruses bearing conserved T cell epitopes, memory T cells are rapidly activated, undergo secondary effector T cell expansion and differentiation, and mediate prompt pathogen clearance before their systemic dissemination.

Similarly, naïve B cells can be activated and differentiated into extrafollicular plasmablasts (PBs) or germinal center (GC) B cells in secondary lymphoid organs. The primary extrafollicular PBs have been identified as short-lived antibody secreting cells and may provide a significant source of protective antibodies during microbial infections [11]. GCs are anatomically distinguished into two regions, the dark zone and the light zone [12]. Proliferation and somatic hypermutation of antigen-specific GC B cells occur in the dark zone, following which mutated B cell clones move into the light zone to terminate their differentiation. Within the light zone, B cells internalize antigens which are presented by follicular DCs (FDCs) and interact with follicular helper T (T_{FH}) cells, a major CD4 T helper subset facilitating B cell-help [13,14]. GC B cells can further differentiate into long-lived plasma cells (LLPCs) or memory B cells (MBCs). LLPCs mediate long-term antibody secretion following primary infection, while MBCs can respond to secondary infection to either differentiate into PBs or re-enter GCs to undergo further affinity maturation [15–17]. Like memory T cells, MBCs can be divided into circulating and tissue-resident (B_{RM}) populations, which reside in mucosal tissues [18].

Despite intensive studies on the cellular and molecular programming of memory lymphocyte generation over the past two decades, our understanding of the mechanisms of memory T and B cell maintenance and function, particularly in the mucosal tissues remains limited. Furthermore, little is known regarding the cellular and molecular pathways that may be targeted to simultaneously promote both B_{RM} and T_{RM} cell responses in the mucosal tissues. Here we will review the current understanding of mechanisms maintaining long-term immunological memory in mucosal tissues, with a focus on the roles of a subset of CD4 T helper cells, tissue-resident T helper cells (T_{RH}), in coordinating respiratory mucosal CD8 and B cell memory responses following viral infection.

2. Tissue-Resident Memory T (T_{RM}) and B (B_{RM}) Cells

2.1. Generation of CD8 T_{RM} Cells

CD8 T_{RM} cell development is initiated when dendritic cells (DCs), either resident within lymph nodes or following migration from peripheral tissues, prime naïve T cells into effector CD8 T cells in draining lymph nodes. Antigen-experienced effector CD8 T cells subsequently infiltrate infected tissue to mediate pathogen clearance, after which a subset of CD8 T cells persists to become T_{RM} cells. Interestingly, migrating DCs can also precondition naïve T cells towards a resident memory T cell fate via the activation and presentation of transforming growth factor (TGF)-β [19]. Furthermore, distinct DC subsets appear to differentially program lymph node homing T_{CM}, mucosal tissue-homing effector and resident memory T cells following influenza infection [20]. Therefore, T_{RM} cell development may start before the entry of effector T cells into peripheral organs. Such a notion is supported by recent genetic tracing (using retroviral barcoding) and single cell RNA-seq experiments demonstrating the existence of T_{RM} precursors in the circulating effector T cell pool [21].

After their activation in lymphoid organs, effector CD8 T cells enter the circulation and migrate into nonlymphoid tissues to combat invading pathogens. While CD8 T_{RM} fate determination can be trained in lymphoid organs, local environment and antigenic re-encounter in the tissue further promote T_{RM} development and/or maturation. The differentiation of T_{RM} cells can occur independently of local antigen recognition in the peripheral tissue [22–24]; however, local antigenic re-stimulation of effector CD8 T cells in nonlymphoid tissue greatly enhances T_{RM} formation [25–27]. Following the formation of T_{RM} cells, it is believed that T_{RM} maintenance is largely antigen or TCR signaling independent [28]. However, chronic low levels of TCR stimulation due to persistence of antigen following influenza virus infection or following immunization with an adenoviral vector facilitates the accumulation of a protective population of CD69+ CD8 T_{RM} cells [29,30].

CD69 is a key tissue retention signal of T_{RM} cells functioning via the interference of sphingosine-1-phosphate receptor (S1pr1) activity [31,32], thereby restricting cell egress out of the tissue [31,33]. Local antigen-restimulation enhances the expression of CD69,

and concomitantly suppresses S1pr1 and Krüppel-like Factor 2 (KLF2) expression [31,34]. T_{RM} cells located within the epithelium further express CD103 (Integrin, alpha E), which binds to E-cadherin expressed on epithelial cells, supporting the accumulation and retention of T_{RM} cells in tissues [22,35,36]. In the absence of TGF-β signaling, the migrated tissue effector CD8 T cells fail to develop into CD103$^+$ T_{RM} cells due to lack of CD103 expression [35,37,38]. Interleukin (IL)-15 has been reported to provide a survival signal to memory T cells [39]. Soluble IL-15/IL-15Rα complexes in local tissue do not directly induce CXCR3 production in effector cells, but promote the recruitment of CXCR3$^+$ antigen-specific effector T cells to the mucosal area through the downregulation of KLF2 [40]. IL-7 is another important cytokine able to maintain memory T cell homeostasis through Stat5 signaling [41,42]. Interestingly, while IL-7 and IL-15 can both promote CD8 T_{RM} cell maintenance, the homeostatic persistence of skin CD4 T_{RM} cells seems mainly dependent on IL-7 produced from hair follicle of skin [43]. TGF-β has also been reported to facilitate CD8 T_{RM} cell development via down-regulation of T-box transcription factor Eomes and T-bet expression, but residual T-bet activity is critical to maintain responsiveness to IL-15 for CD8 T_{RM} cell survival [44]. In the lymphocytic choriomeningitis virus (LCMV) infection model, combination of cytokines including TGF-β, IL-33 and tumor necrosis factor (TNF) enhances the establishment of CD8 T_{RM} cells via the downregulation of S1pr1 [45]. Additionally, proinflammatory cytokines including type I interferons and IL-12 can facilitate the differentiation and accumulation of CD103$^-$ T_{RM} cells in the intestine following bacterial infection [46]. Taken together, CD8 T_{RM} generation is constantly modulated by a variety of antigenic and environmental factors at various steps of the T cell life cycle following infection.

2.2. Transcriptional Regulation of CD8 T_{RM} Development and Persistence

T_{RM} cells exhibit distinct transcriptional profiles when compared to circulating memory T cells. Several transcription factors have been demonstrated to play important roles in T_{RM} cell generation and/or maintenance in peripheral tissues. The two related transcription factors, Blimp-1 and Hobit, cooperatively instruct a tissue-residency transcriptional program in T_{RM} cells [10]. Hobit and Blimp-1 directly bind to Klf2 and Tcf7 loci, and then downregulate the expression of Ccr7 and S1pr1. Therefore, they prevent the egress of T_{RM} cells from tissues to blood circulation [10,45]. Runx3 promotes the expression of CD103 and tissue residency-associated gene programs in T_{RM} cells, while simultaneously repressing signature genes associated with circulating memory [47]. Runx3 has been reported to enhance the accessibility of the Blimp1 binding region and may facilitate the accessibility of the Hobit binding motif as well [48]. Notch signaling through RBP-jκ is also important for the formation of lung T_{RM} cells following influenza virus infection [49]. Of note, TGF-β and Notch signaling can be integrated by direct protein–protein interactions of Smad3 and the intracellular domain of Notch (NICD), potentially providing a mechanism underlying the dual requirement of TGF-β and Notch in T_{RM} formation [50,51]. Compared to circulating memory T cells, T_{RM} cells highly express the transcription factor Bhlhe40 and its-associated molecules. Bhlhe40 deficiency caused diminished expression of T_{RM} tissue residency-associated genes and molecules involved with T_{RM} effector function, largely due to impaired mitochondria fitness and function in Bhlhe40-deficient T_{RM} cells [52]. Additionally, the expression of Ahr and NR4A1 is upregulated in T_{RM} cells compared to circulating memory CD8 T cells, and their function is required for the maintenance of CD8 T_{RM} cells [37,53,54].

2.3. Development and Maintenance of B_{RM} Cells

Long-term humoral immunity is generally maintained by LLPCs in the bone marrow (BM) [55], while resting MBCs provide rapid and augmented antibody (Ab) responses upon recognition of same/conserved antigens following secondary infections [56]. The development of both cell types is initiated within the GC structure following help from CD4 T cells [57,58]. Analogous to memory T cells, MBCs can be divided into circulat-

ing and tissue-resident (B_{RM}) populations. B_{RM} cells, mainly residing in non-lymphoid peripheral tissues, express similar tissue-homing and retention molecules as T_{RM} cells. For instance, influenza hemagglutinin-specific lung-residing memory B cells [59] highly express CXCR3 and CD69, which are believed to mediate their tissue-homing and residency respectively [59]. In humans, a large number of $CD19^+CD27^+CD45RB^+CD69^+$ B_{RM} cells have been identified in the gut and tonsil but not in blood and BM [60].

Compared to circulating memory B cells, B_{RM} cells facilitate rapid recall responses in the tissue and may exhibit unique phenotypical and functional markers. For instance, mouse lung B_{RM} expresses lower CD73 than those MBCs in the blood or spleen [18]. Furthermore, respiratory B_{RM} cells reside in specific niches; in the upper respiratory tract, these are located in the nasal-associated lymphoid tissue (NALT) whereas they are found in the inducible bronchus associated lymphoid tissue (iBALT) in the lower respiratory tract [61–63]. Like T_{RM} cell development, B_{RM} cells are thought to be initiated following CD4 T cell help in secondary lymphoid organs, but the full establishment of B_{RM} cells in peripheral tissue requires local antigenic re-encounter [18]. Additionally, GC B cells of the lung, particularly those developed early post infection, may also supply B_{RM} precursors following influenza virus infection [64,65]. Thus, optimal B_{RM} development is subject to both distal regulation in the lymphoid organs and local regulation inside the peripheral tissue.

The functions of B_{RM} cells have not been fully elucidated yet. However, B_{RM} cells are thought to provide immediate and rapid responses against pathogen entry at mucosal tissues [66]. MBCs re-activated by pathogens have been reported to either differentiate into antibody secreting cells (ASCs) or undergo expansion and affinity maturation through re-entry of GC [67–69]. Lung influenza-specific B_{RM} cells are reported to directly differentiate into ASCs upon recognition of the same viral antigen during influenza reinfection, but do not re-enter the GC structure, thereby facilitating viral clearance in the respiratory mucosa [18]. Interestingly, influenza-specific lung B_{RM} cells developed from local GC responses possess high cross-reactivity to viral escape mutants [64,65], and thus they may exert broadly protective function against distinct viral strains. Furthermore, B_{RM} cells located in tertiary lymphoid structures are also considered potential APCs and may facilitate T cell responses in the respiratory mucosa [66,70]. In addition to influenza infection, antigen-specific B_{RM} cells are also developed following *pneumococcal* infection, although tertiary lymphoid organ (i.e., iBALT) formation was not observed. Importantly, depletion of $PD-L2^+$ lung B_{RM} cells caused diminished bacterial clearance and reduction of *pneumococcus*-reactive antibodies in the lung upon pneumococcal reinfection, suggesting that lung B_{RM} cells are vital for pulmonary antibacterial immunity [71].

3. Characteristic Tissue-Resident CD4 T Cells

3.1. Heterogeneity of Tissue-Resident CD4 T Cells

The mechanisms underlying CD4 T_{RM} cell formation and maintenance are relatively less well-studied compared to those of CD8 T_{RM} cells. Similar to CD8 T_{RM} cells, activated CD4 T cells migrate into peripheral tissues and survive long term to form CD4 T_{RM} cells. CD4 T_{RM} cells share tissue-residency markers like CD69 and CXCR6 with CD8 T_{RM} cells [72,73]. Like mouse T_{RM} cells, human CD4 T_{RM} cells also express high level of CD69 while circulating CD4 memory T cells do not [73,74]. Unlike effector CD8 T cells, which mainly produce type 1 cytokines such as IFN-γ and TNF, effector CD4 T cells can be subdivided into distinct subtypes based on their cytokine production including IFN-γ producing T helper type 1 (T_H1), IL-4/5/13-producing T helper type 2 (T_H2), IL-17 producing T helper type 17 (T_H17) and IL-21 producing follicular helper T (T_{FH}) cells [75,76]. In the murine model, tissue-resident T_H1 (T_H1 T_{RM}) cells have been reported following respiratory infection. Lung T_H1 T_{RM} cells developed following influenza virus infection rapidly produce IFN-γ and contribute to host protection upon secondary infection [77,78]. T_H1 T_{RM} cells have also been identified in the skin and gut following *Leishmania* and *Listeria* infections, respectively [79–81]. T_H1 T_{RM} cells generated by *tuberculosis* are characterized by high

expression of CXCR3 and low expression of KLRG1 [82,83]. For long-term maintenance in tissues, T_H1 T_{RM} cells express high levels of CD11a and VLA-1 to promote their retention and survival in the tissue niche [84]. T_H2 T_{RM} are usually generated during allergic responses or parasitic infections. In a house dust mite (HDM)-induced allergic asthma model, it was shown that lung T_{RM} cells and circulating T_H2 memory cells cooperatively induce allergic inflammation in the lung [85]. During *Heligmosomoides polygyrus* infection, T_H2 T_{RM} cells are formed and persist in the lamina propria and peritoneal cavity (PC). Interestingly, T_H2 T_{RM} cells in both sites produce general T_H2 cytokines like IL-4, IL-5 and IL-13 following TCR restimulation, but only T_H2 T_{RM} in PC can respond with IL-33 and IL-7 upon TCR-independent restimulation [86]. T_H17 T_{RM} can be generated following *Candida albicans* (*C. albicans*) infection in both mouse and human subjects. Both circulating T_H17 memory cells and T_H17 T_{RM} cells are important to clear the *C. albicans* upon rechallenge, but T_H17 T_{RM} cells are more effective in rapidly clearing the pathogens [87]. In *Mycobacterium tuberculosis* (*M. tuberculosis*)-infected patients, lung CD4 T_{RM} cells produce IL-17 following antigenic stimulation, which along with IL-17 and IL-2 produced by T_H17 T_{RM} cells suppress the growth of *M. tuberculosis* in 3D culture system [88].

Like effector T_{RM} subsets, Foxp-3 expressing regulatory T cells (T_{REG}) cells in the tissue can express CD69 and possess tissue-residency features. Importantly, tissue-resident T_{REG} cells may provide an essential check point for the pathogenic activities of T_{RM} cells. Chronic exposure of *Aspergillus fumigatus* induces the formation of CD69^{hi}CD103^{lo}CD4 T_{RM} cells, which contribute to pulmonary fibrosis. At the same time, CD69^{hi}CD103^{hi}Foxp3$^+$ T_{REG} cells constrain the effects of pathogenic CD103^{lo} CD4 T_{RM} cells and limit their fibrogenic potential [89]. Furthermore, lung tissue T_{REG} cells produce amphiregulin (Areg), an epidermal growth factor receptor ligand, to repair tissue damage following influenza virus infection [90].

Common gamma-chain cytokines such as IL-2, IL-15 and IL-7 are essential to develop or maintain memory CD4 T cells. The cytokines have recently been reported to be essential in the formation of CD4 T_{RM} cells. Autocrine IL-2 signaling in infiltrating tissue CD4 T cells is critical for the generation of T_H1 T_{RM} cells in the lung [91]. In the absence of IL-2R signaling, T_H1 T_{RM} cells induced by intranasal LCMV infection or allergic T_H2 T_{RM} cells generated following HDM administration fail to be maintained over the long-term within the lung [92,93]. High levels of IL-7 receptor are expressed by lung T_{RM} cells compared to circulating memory T cells, and IL-7 treatment in vivo induces the infiltration of circulating CD4 T cells into the lung to form T_{RM} cells [94]. Similarly, IL-15 supports the development of lung CD4 T_{RM} post influenza virus infection [95].

3.2. Niches of Local CD4 T Cells

Tissue-resident CD4 T cells are typically located under epithelial layers and inside the ectopic lymphoid structures with stromal cells or APCs [96]. In the skin, particularly the dermis, lymphoid structures are generated around hair follicles with CD4 T cells and CD11b$^+$DCs [97,98]. CCL5, IL-7 and IL-15 which are produced in the local environment, promote the maintenance of CD4 T_{RM} clusters in skin [43,97]. The female reproductive tract (FRT) is a mucosal tissue that consists of two different areas, including the upper FRT and the lower FRT. Mucosa-associated lymphoid tissues (MALT) composed of B cells and CD4 T_{RM} cells are typically developed in the lamina propria (LP) of the upper FRT. Furthermore, CD4 T cells can migrate to upper FRT following skin infection with *Chlamydia* to form a cluster with B and CD8 T_{RM} cells [99,100]. In the lower FRT, there are no MALT at steady state, but CD4 T_{RM} cells along with B cells, DC and macrophages form clusters during the clearance of an intravaginal HSV-2 infection. APCs including B cells and DCs facilitate CD4 T_{RM} maintenance in the lower FRT area [101,102].

The respiratory tract is an entry site for many viruses including influenza, respiratory syncytial virus (RSV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The respiratory tract can also be divided into two compartments, the upper respiratory tract (URT) and the lower respiratory tract (LRT). Nasal-associated lymphoid tissues (NALT)

localized in URT contain CD4 T$_{RM}$ cells [96]. iBALTs within the LRT are the primary niches for lung CD4 T$_{RM}$ cells [64,103,104] following influenza infection, which is in contrast to those influenza-specific CD8 T$_{RM}$ cells that are primarily localized to the site of regeneration in the lung parenchyma following tissue injury [33,105].

4. CD4 Help and Memory B and CD8 T Cell Responses

4.1. CD4 Help and Memory B Cell Generation

CXCR5 and PD-1 expressing CD4 helper T cells that localize in the GC are termed T$_{FH}$ cells [106]. T$_{FH}$ cells express the transcription factor BCL6, the cytokine IL-21 and provide CD4 T cell help to B cells in the GC. Therefore, T$_{FH}$ cells are important in the development of long-term humoral immunity mediated by MBCs and plasma cells (PCs), which are mainly derived from GC B cells. T$_{FH}$ cell formation goes through two sequential steps [58], including T cell priming first at the T cell zone by DCs followed by subsequent maturation in the B cell zone through interactions with B cells via ICOS-ICOS-L and MHC II-TCR. Cytokines including IL-6, IL-12 and IL-21 can promote T$_{FH}$ formation, while IL-2 and type I IFNs potently suppress T$_{FH}$ cell generation [58,107–110].

BCL6^{lo}CD69^{hi} GC-B cells that express high levels of IRF4 favor the differentiation into PCs [111], while CCR6 has been reported as a marker for memory B cell precursors [112]. Recently, IL-9 producing T$_{FH}$ cells have been reported to support the development of GC-derived memory precursor B cells and subsequent optimal formation of memory B cells [113]. Interestingly, the strength of the interaction between GC B and T$_{FH}$ cells affects the formation of memory B cells. Cells prone to enter the memory B cell pool typically exhibit lower B cell receptor affinity and express high levels of Bach2, which has been found to be inversely correlated with the strength of help provided by T$_{FH}$ cells [114].

4.2. CD4 T Cell Help and CD8 Memory T Cell Responses

CD4 T cell help plays an indispensable role in the primary CD8 T cell response in certain infection and/or immunization models [115–117]. CD4 help is critical for licensing APCs to support optimal CD8 T cell activation and differentiation [118]. In this case, interaction of CD4 T cells with APCs promotes the expression of key co-stimulatory molecules and pro-inflammatory cytokines required for maximal CD8 T cell activation [119,120]. Additionally, cytokines produced by CD4 T cells such as IL-2 can facilitate CD8 T cell expansion and effector generation [121]. However, in infectious models that generate strong inflammatory responses such as influenza infection, the primary CD8 T cell responses are largely independent of CD4 T cell help, potentially due to the direct activation of DCs by robust TLR signaling [122].

In contrast to the context-dependent roles of CD4 T cells in helping primary CD8 T cell responses, CD4 T cell help is uniformly required for the generation, maintenance and/or recall responses of memory CD8 T cell responses. To this end, CD4 T cell-derived IL-2 has been linked to promote secondary CD8 T cell responses [123,124]. Furthermore, CD4 T cells could license APCs to produce IL-15, a key cytokine involved in memory CD8 T cell formation and/or maintenance [120]. Additionally, T$_{REG}$ cell-derived IL-10 has been shown to promote memory CD8 T cell maturation during the contraction phase via the suppression of pro-inflammatory cytokine production by DCs [125]. Lastly, activated CD4 T cells may directly interact with effector CD8 T cells via CD40-CD40L to facilitate memory CD8 T cell differentiation [126]. Regardless of the molecular cues provided by CD4 T cells for CD8 memory T cell generation, un-helped CD8 T cells are prone to apoptosis and could undergo activation-induced cell death, possibly through the induction of TRAIL expression [116,127].

Besides the role of CD4 help in the generation of circulating effector and memory T cells, recent advances have suggested that CD4 T cell help is important in mucosal T cell responses and the induction of CD8 T$_{RM}$ responses. During HSV-2 infection, CD4 T cells control the migration of CTL through the secretion of IFN-γ and induction of local chemokine secretion in the infected tissue [128]. During influenza infection, CD4 T cell

help occurs at the priming phase of T cell responses, which is critical for the development of CD8 T_{RM} cells in the lung. In the absence of CD4 T cell help, CD8 T cells failed to properly localize to the lung niches supporting optimal T_{RM} development. Furthermore, un-helped CD8 T cells exhibited high levels of T-bet expression, which interferes with CD103 expression through the modulation of TGF-β responsiveness [129]. These results demonstrate the importance of CD4 helper T cells in the formation of CD8 T_{RM} cell precursors, while the role of CD4 T cell help in CD8 T_{RM} cell maintenance has not been elucidated.

5. CD4 Tissue-Resident Helper Cells Coordinate T_{RM} and B_{RM} Responses in the Respiratory Mucosa

5.1. T_{FH}-Like Cells in Non-Lymphoid Tissues

Although T_{FH} cells are generally localized in secondary lymphoid organs, T_{FH}-like cells can be found in circulation or in non-lymphoid tissues [130,131]. In human joint tissue from patients with rheumatoid arthritis, a subset of T_{FH}-like peripheral helper CD4 T cells (T_{PH}) that exhibits potent B cell help activities was recently identified [132]. Phenotypically, T_{PH} cells share key signatures with T_{FH} cells including high levels of PD-1 expression, production of IL-21, expression of BCL6 and the lack of expression of other T helper lineage cytokines and/or transcription factors. However, T_{PH} cells have distinct features from T_{FH} cells, including the lack or low expression of CXCR5 expression and the high expression of Blimp1. T_{PH} or T_{PH}-like cells have been observed in tertiary lymphoid structures developed in various inflammatory conditions such as rheumatoid arthritis (RA), Crohn's disease and malignancy [133–136].

Tissue-infiltrating T_{FH}-like cells have also been reported in animal models, particularly in inflammatory lung conditions [130,137,138]. In an HDM-induced allergic model, IL-21 producing T_{FH}-like cells, which lack expression of CXCR5, were found in the inflamed lung [137]. Furthermore, IL-21 produced by those T_{FH}-like cells promotes lung T_H2 responses, eosinophil recruitment and HDM-specific IgG1 production [137]. Like human T_{PH} cells, antigen-specific T_{FH}-like cells expressed high levels of IL-21, PD-1 and ICOS, but lower BCL6, CXCR5 than lymph node T_{FH} cells. In a model of LPS-adjuvanted airway immunization model, lung-infiltrating T cells were identified to exhibit follicular helper-like properties including the potential to provide help to naive B cells. These T_{FH}-like cells did not express classical T_{FH} markers, CXCR5 and PD-1, but expressed molecules involved in B cell help including CD40L and IL-21. As such, these T_{FH}-like cells supported the generation of GC B cells in situ within the lung [138]. Together, these data demonstrate the presence of a T_{FH}-like CD4 helper population in non-lymphoid tissues, but the roles of these cells in regulating local B and CD8 memory T cells have not been examined. Furthermore, the cellular and molecular cues regulating the development of T_{FH}-like cells in peripheral tissue are still unknown.

5.2. Identification of Tissue-Resident Helper T Cells in the Lung

As stated above, many questions remain unanswered regarding the nature and function of T_{FH}-like cells in non-lymphoid tissues. First, are the T_{FH}-like cells tissue-resident in non-lymphoid tissues? Second, what are the mechanisms underlying the phenotypic similarity and difference between conventional T_{FH} cells in secondary lymphoid organs and T_{FH}-like cells in the non-lymphoid tissues? Third, what are the physiological functions of T_{FH}-like cells in regulating local tissue immunity?

Using single-cell RNA sequencing, our group and the group of Carolyn King recently found that lung parenchyma CD4 T cells exhibit marked heterogeneity following primary influenza virus infection. In addition to traditional T_H1-like T_{RM}, T_H17-like T_{RM} cells and tissue T_{REG} cells, lung parenchyma CD4 T cell compartment contains a T_{FH}-like CD4 T cell population [64,104]. This T_{FH}-like cell population appeared around two weeks after infection, following clearance of infectious virus and persisted through the memory phase, i.e., more than two months after infection. The T_{FH}-like cells expressed modest BCL6

and CXCR5, and high levels of PD-1, IL-21 and FR4, thus exhibiting key T_{FH} phenotypic markers. Compared to splenic T_{FH} cells, these T_{FH}-like cells had higher levels of the tissue residency gene program, the transcription factor Bhlhe40 and peripheral homing marker CXCR6, thus exhibiting T_{RM} features. Indeed, using parabiosis, we demonstrated that these tissue T_{FH}-like cells were tissue-resident. Furthermore, the optimal responses of these lung T_{FH}-like cells required the presence of both BCL6 and Bhlhe40, demonstrating the dual requirement of T_{FH} and T_{RM} gene programs for its development [52]. Thus, these tissue T_{FH}-like cells appear to be a "hybrid" population of T_{FH} and T_{RM} cells. Based on the transcriptional, phenotypic and non-migratory characteristics, we termed these cells tissue-resident helper T cells (T_{RH}).

5.3. Promotion of Local B Cell Immunity by T_{RH} Cells

Like T_{FH} cells, T_{RH} cells express key B cell helping molecules including ICOS, CD40L and/or IL-21. As such, T_{RH} ablation severely impaired lung GC B cell responses and iBALT formation (Figure 1).
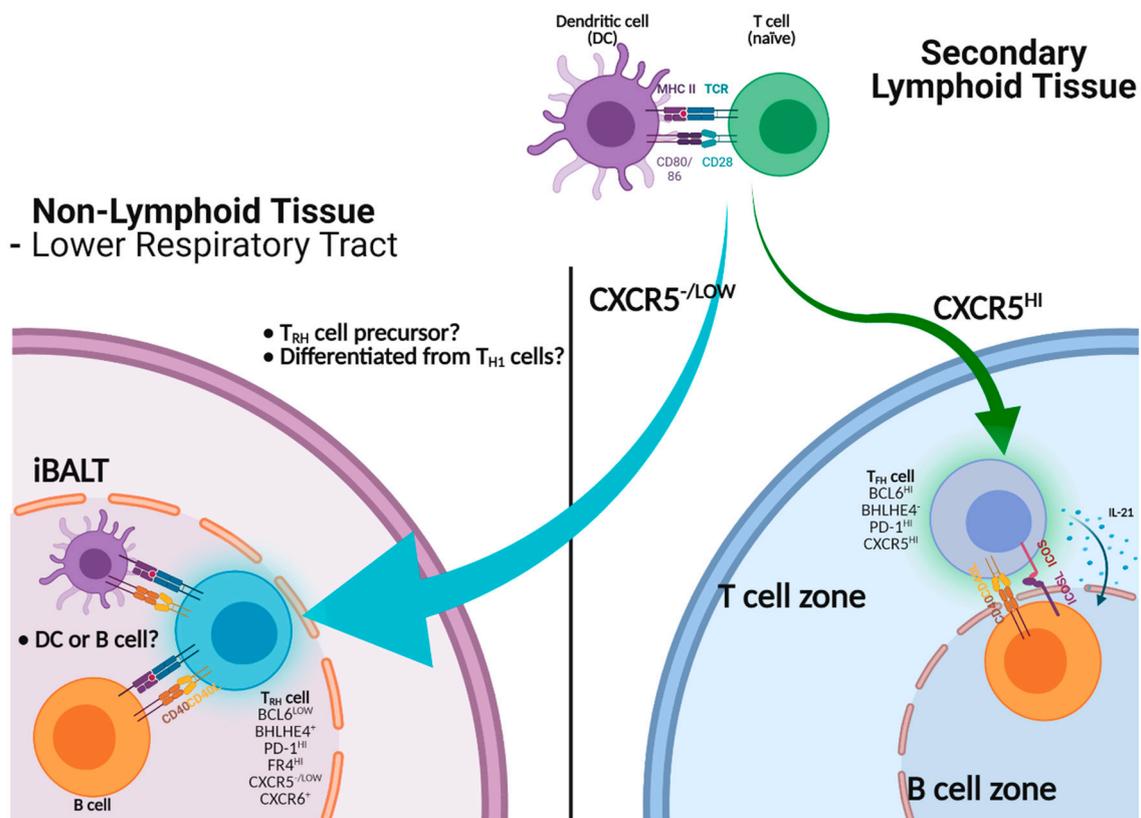

Figure 1. Help of B cell immunity by T_{RH} or T_{FH} cells. Activated CD4 T cells migrate into the B cell zone to become mature CXCR5^{hi} T_{FH} cells to help B cells via CD40-CD40L, ICOS-ICOS-L interactions and cytokines including IL-21. T_{RH} precursors, which express low levels of CXCR5, can infiltrate into non-lymphoid tissues such as the lung. T_{RH} precursors adapt to the lung environment to become mature T_{RH} cells, thereby assisting B cell immunity in situ through the expression of CD40L.

As discussed above, lung GC contributes to respiratory B_{RM} development and iBALT is likely a niche for lung B_{RM} cells. Consequently, we found that T_{RH} ablation impaired influenza-specific lung B_{RM} responses but not systemic B cell memory. Those B_{RM} cells that are cross-reactive to viral escape mutants were also diminished following T_{RH} depletion, suggesting that T_{RH} cells may be key for the development of broadly reactive memory B cells against heterologous influenza strains [64]. In a subsequent study, Swarnalekha et al. further showed that lung antigen-specific ASCs were significantly decreased in T_{RH} cell-

ablated mice following influenza virus rechallenge [104], demonstrating the importance of T_{RH} cells in mediating memory B cell recall responses.

These studies have established the critical roles of T_{RH} in assisting the development local effector and memory B cell responses during both primary and recall responses following influenza virus infection. Swarnalekha et al. also showed that T_{RH} cells are localized within the iBALT structure, while T_{H1} T_{RM} cells are more concentrated outside or at the border of the iBALT, suggesting that T_{RH} cells may lend their help to B cells within the tertiary lymphoid organ. Similar to T_{FH} cells, T_{RH} development requires B cells and is facilitated by prolonged antigen presentation [104]. Interestingly, we found that the B cell helper function of T_{RH} cells was dependent on the CD40-CD40L interaction, but not IL-21, which is required for T_{FH}-mediated B cell help. Thus, T_{RH} and T_{FH} cells may have both common and distinct B cell help mechanisms.

5.4. T_{RH} Cells and the Maintenance of CD8 T_{RM} Cells

During experiments dissecting the physiologic function of T_{RH} cells, perhaps the biggest surprise came from the observation that T_{RH} depletion selectively diminished a population of CD8 T_{RM} cells specific to the influenza Nucleoprotein peptide 366–374 ($NP_{366–374}$) [64]. Previously, we found that $NP_{366–374}$ specific CD8 T_{RM} cells receive persistent low-levels of antigenic stimulation at the memory stage, due to the delayed clearance of the NP antigen [29]. These $NP_{366–374}$ T_{RM} cells expressed high levels of PD-1 but low levels of CD103 and possessed features of both memory and exhausted-like T cells, compared to those of conventional $CD69^+CD103^+$ T_{RM} cells [29]. Importantly, the $NP_{366–374}$ T_{RM} cells offered critical protective function against secondary heterologous viral infection. Conversely, the blockade of PD-1 activity at the memory stage selectively expanded these T_{RM} cells and promoted the lung pathological responses [29]. Thus, those PD-1^{Hi} exhausted-like T_{RM} cells are important in maintaining the balance between T_{RM}-mediated protection and pathology. When T_{RH} cells were ablated, we found that the quantity of $NP_{366–374}$ T_{RM} cells were significantly decreased, but not those of conventional T_{RM} cells restricted to other peptides such as the influenza polymerase peptide 224–233 ($PA_{224–233}$). Consequently, T_{RM}-mediated protective immunity against heterologous viral reinfection was diminished following T_{RH} ablation. These data suggest that T_{RH} cells are vital for maintaining protective T_{RM} responses following influenza infection.

As discussed above, BCL6-expressing T_{RH} cells are located inside the iBALT [104]. Previous results have shown that CD8 T_{RM} cells are found outside the iBLAT (nearby border area), most of which are particularly localized near repair associated memory depots (RAMD) [105]. It is thus intriguing that T_{RH} cells facilitate $NP_{366–374}$ T_{RM} maintenance in a contact-independent way, as T_{RH} and T_{RM} are likely localized in different lung niches. IL-21 has been showed to be a critical molecule mediating CD4 T cell help for optimal CD8 T cell responses during chronic viral infection [64]. Since $NP_{366–374}$ T_{RM} cells exhibit features of exhausted CD8 T cells from chronic viral infection, we hypothesized that IL-21 produced by T_{RH} cells is critical to sustain $NP_{366–374}$ T_{RM} responses (Figure 2).

Indeed, IL-21R blockade following influenza viral clearance led to diminished $NP_{366–374}$ T_{RM} responses. Furthermore, IL-21 is mainly produced by T_{RH} cells in the lung following influenza infection [64]. These data suggest that T_{RH} cells maintain optimal T_{RM}-mediated protective immunity through IL-21, which may act over a relatively longer range to provide help to CD8 T_{RM} cells compared to their help to B cells, which is mediated by cell surface molecule CD40L. Consistent with our observations, antigen-specific IL-21 producing CD4 T cells have also been identified in the brain of mice after polyomavirus (MuPyV) infection. The IL-21-producing CD4 T cells express high-affinity TCRs and T_{FH} cell markers like PD-1 and CXCR5. Importantly, in the absence of IL-21 signaling, brain CD8 T cells failed to differentiate into T_{RM} cells with sufficient CD103 expression [139]. Although it is not known whether these brain T_{FH}-like cells had T_{RM} features (thus being equivalent to brain T_{RH} cells), these data do suggest that tissue T_{FH}-like cells may be required for sustaining maximal CD8 T_{RM} responses in a broad spectrum of nonlymphoid tissues.
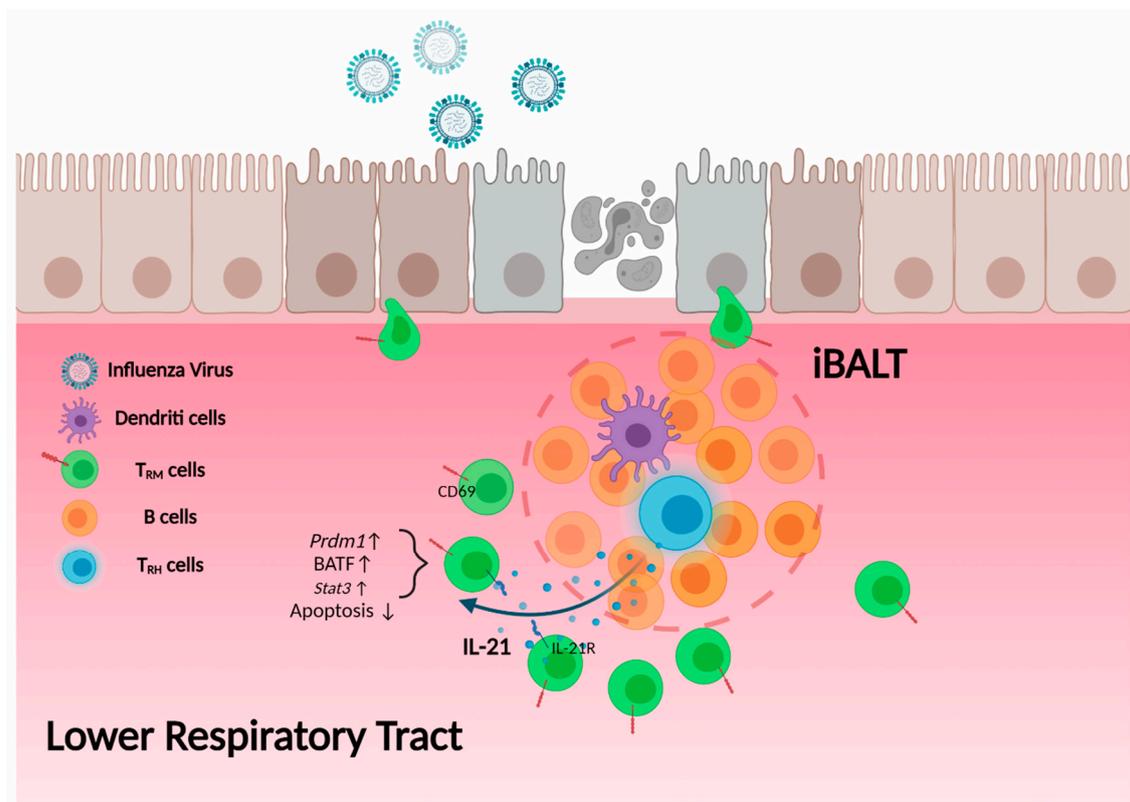
Figure 2. T_{RH} cell help to CD8 T_{RM} cells. T_{RH} cells, which localize within the iBALT, secrete IL-21. Influenza $NP_{366-374}$-specific CD8 T_{RM} cells are located outside but near the border of iBALT structure and express high levels of IL-21 receptor. IL-21 secreted from T_{RH} cells promotes the expression of Blimp-1 (Prdm1), BATF and other molecules in CD8 T_{RM} cells, thereby maintaining $NP_{366-374}$-specific T_{RM} cell retention and survival in the lung.

6. T_{RH} cells as a Potential Target for Mucosal Vaccine against Respiratory Viral Infection

Lower respiratory tract viral infections represent a major public health challenge and economic burden worldwide. In a matter of months, SARS-CoV2 infection completely altered societal norms, stagnated economies, and overwhelmed healthcare infrastructures across the globe. Annual influenza epidemics cause up to 500,000 deaths globally and there exists an ever-present threat of the emergence of a pandemic influenza strain in the future [140]. Vaccination still remains the best approach to mitigate disease burden caused by respiratory viral infection. Current vaccines against influenza and SARS-CoV2 infections are mainly administered via the systemic route, which induces strong systemic but typically weak mucosal immune responses [141–144].

The efficacy of the current influenza vaccines in providing protection against infection is still relatively limited, even in the years when the predicted vaccine strains perfectly match circulating strains. Furthermore, due to escape mutants generated by the rapid mutation of influenza virus, the current influenza vaccines require an annual update. To this end, the "holy grail" of influenza vaccine development is to create a universal influenza vaccine that can provide long-lasting and cross-reactive immunity against a broad-spectrum of influenza viral strains. It is argued that an "all-inclusive" approach, i.e., the induction of concerted immune responses, including both strong memory B and T cell responses, is needed to provide protective immunity against a wide ranges of influenza viruses [145]. Due to the nature of mucosal B_{RM} and T_{RM} responses, a mucosal vaccine that can induce strong cross-reactive B_{RM} and T_{RM} responses is more than likely a viable strategy for universal vaccine development. Since T_{RH} cells are able to provide local "help" for the development and/or maintenance of robust mucosal B and CD8 T cell responses,

we argue that the promotion of T_{RH} responses by future mucosal vaccines will be key to develop successful universal influenza vaccines.

The current mRNA vaccines against SARS-CoV2 infection induce robust systemic immunity, thereby providing strong protection against viral infection and severe disease development [146]. It is still unknown whether SARS-CoV2 mRNA vaccines are able to induce effective mucosal antibody and/or B/T cell responses in humans. However, based on data generated using mouse immunization models, it seems unlikely that systemic immunization of mRNA-encoded antigens would generate strong mucosal memory T and B cells against SARS-CoV2 infection. Despite the current success of SARS-CoV2 mRNA vaccines, emerging data have suggested that the mRNA vaccine induced protective immunity may be dampened against newer variants of the SARS-CoV2 virus, particularly the delta strain [147,148]. Thus, there is still room for improvement with the development of better and broader protective SARS-CoV2 vaccines. To this end, a SARS-CoV2 vaccine capable of inducing both strong humoral and cellular (i.e., B_{RM} and/or T_{RM} development) immunity in the respiratory mucosa may ultimately meet the needs for long-lasting protection against a variety of SARS-CoV2 strains. In this case, the induction of robust respiratory T_{RH} responses again may be a pre-requirement for the success of such a vaccine.

7. Concluding Remarks

Memory lymphocytes establish tissue residency in the respiratory tract following pulmonary viral infection and/or mucosal vaccination. Here we reviewed the developmental cues and molecular mechanisms regulating the formation of CD4 and CD8 T_{RM} and B_{RM} cells in mucosal tissues. We put forward a T_{RH}-centric model, modulating the concerted development of mucosal B and T cell memory responses following mucosal infection and immunization. We believe that the induction of a strong T_{RH} response is key to protective mucosal immunity generated by future universal vaccine candidates. Conversely, dysregulated T_{RH} responses may contribute to the development pulmonary inflammation in various disease conditions including asthma or long-term chronic sequelae following respiratory viral infections [149,150].

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