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Review

T-cell–B-cell collaboration in the lung

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Collaboration between T and B cells in secondary lymphoid organs is a crucial component of adaptive immunity, but lymphocytes also persist in other tissues. Recent studies have examined T-cell–B-cell interactions in nonlymphoid tissues such as the lung. CD4+ T- resident helper cells (TRH) remain in the lung after influenza infection and support both resident CD8 T cells and B cells. Multiple lung-resident B-cell subsets (B-resident memory (BRM)) that exhibit spatial and phenotypic diversity have also been described. Though not generated by all types of infection, inducible bronchus-associated lymphoid tissue offers a logical place for T and B cells to interact. Perturbations to BRM and TRH cells elicit effects specific to Immunoglobulin A (IgA) production, an antibody isotype with privileged access to mucosa. Understanding the interplay of lymphocytes in mucosal tissues, which can be insulated from systemic immune responses, may improve the design of future vaccines and therapies.

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Introduction

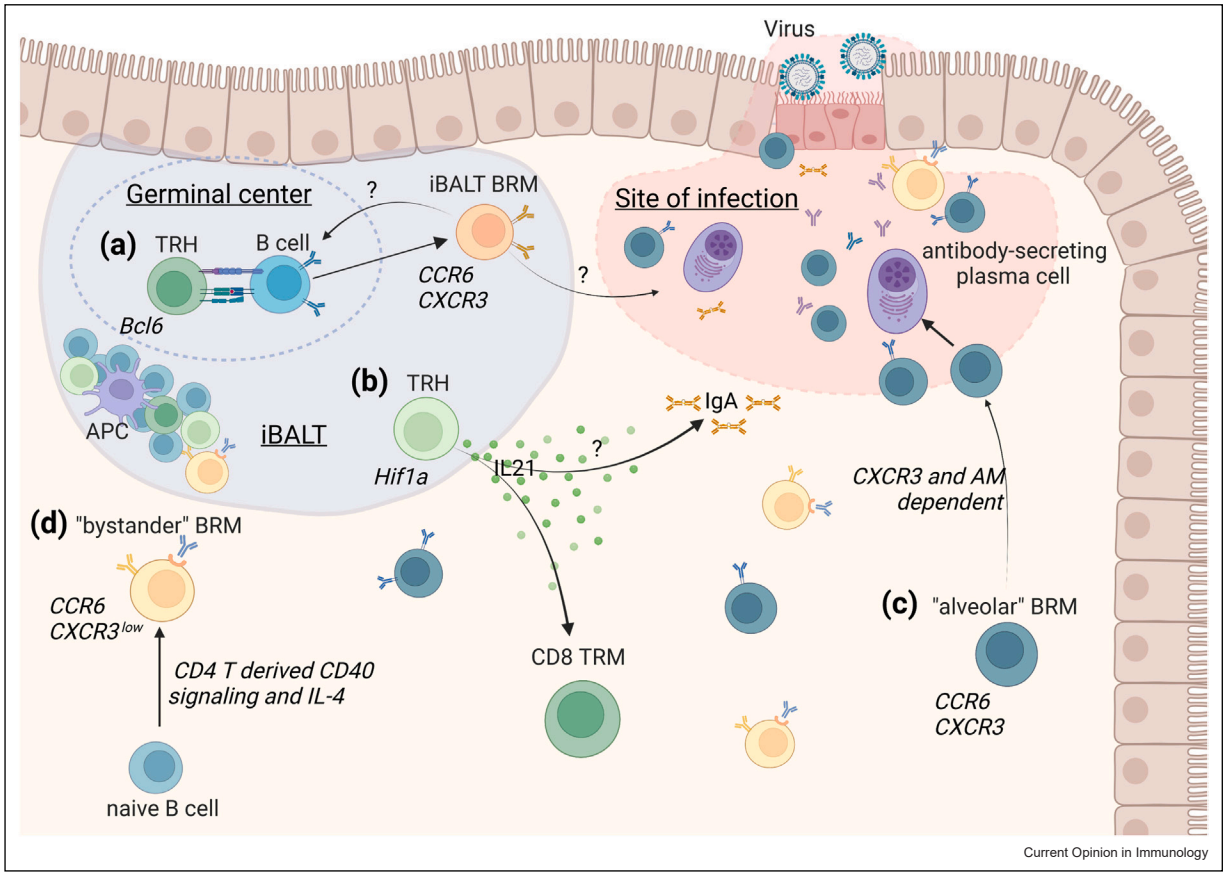
T-follicular helper (TFH) cells provide growth, differentiation, and survival signals to developing B cells and are essential for antibody production in a variety of immune contexts [1]. TFH cells also support the development of B memory cells (Bmem) and are thus a crucial component of long-lasting, antipathogen immunity. Over the past ten years, there has been a growing appreciation for TFH cell heterogeneity, based on distinct transcription factor and cytokine profiles that differentially shape their localization, plasticity, and functional impact on both effector and memory B-cell responses [2–4]. Although TFH cells are generally considered lymphoid-resident, circulating memory CD4 T cells with transcriptional and repertoire similarities to TFH cells have also been identified in the blood [5–7]. Following reactivation, circulating TFH cells rapidly home to lymphoid organs to participate in germinal center reactions, while TFH cells already localized in the lymph node support early plasma cell generation [8,9]. More recently, noncirculating TFH have been identified in a number of tissues, including lung, gut, salivary gland, synovial tissue, and tumors, where they are frequently found in tertiary lymphoid structures (TLS) together with B cells [10,11]. The specific functions of these T-resident helper cells (TRH), along with the heterogeneous array of tissue-resident B cells they often accompany, are just beginning to be uncovered. This review will primarily highlight advances in our understanding of T- and B-cell interactions in the lung following viral infection.

T-resident helper cells in the lung

The lung is a mucosal barrier tissue whose large surface area is constantly exposed to airborne microbes and environmental pollutants. Inflammation or infection of the lung can elicit the development of TLS near major bronchi known as inducible bronchus-associated lymphoid tissue (iBALT) [12]. Lung iBALT consists of aggregated T- and B-cell areas together with antigen-presenting cells and an underlying network of stromal cells (Fig. 1). In chronic lung conditions such as asthma and allergic sensitization, the role of iBALT is enigmatic. While iBALT acts as a niche for the survival of pathogenic memory Th2 cells during allergic airway inflammation in mice, pre-established iBALT can delay the accumulation of lung Th2 cells, and correlates with reduced lung pathology [13]. Given that allergic sensitization also elicits Th2-skewed TFH cells in the lung [14], these observations raise the possibility that colocalization of T cells with B cells in iBALT reduces detrimental T-cell–epithelial cell interactions [13].

iBALT is also generated in response to a number of respiratory pathogens, including influenza, *Mycobacterium tuberculosis*, and *Pneumocystis*, and is often correlated with host protection [15–17]. At relatively late stages after

Figure 1



Function of lung TRH and BRM upon infection with a respiratory virus. **(a)** TRH cells expressing the transcription factor *Bcl6* provide help to naive B cells in germinal center reactions to produce BRMs. Some of these iBALT-located CCR6+CXCR3+ BRM might undergo further maturation in germinal centers or contribute in clearing the virus upon secondary infection. **(b)** iBALT-located TRH cells expressing *Hif1a* secrete IL-21 to help maintain CD8 TRMs and possibly also the production of protective IgA from antibody-secreting cells. **(c)** 'Alveolar' CCR6+CXCR3+ BRMs are scattered throughout the alveoli and rapidly migrate toward sites of infection upon rechallenge to become antibody-secreting plasma cells. The migration is dependent on CXCR3 and help from alveolar macrophages. **(d)** Naive B cells need CD4-derived IL-4 and CD40 signaling to develop into CCR6+CXCR3^{low} 'bystander' BRMs. It is not yet clear where that help is provided. Figure was created using BioRender.

influenza infection, iBALT plays a role in maintaining plasma cells in the lung and bone marrow, and promotes the development of cross-reactive memory B cells capable of neutralizing viral escape variants [16,18]. In a macaque model, infection with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) was also shown to induce iBALT, although the relative importance of lymphoid versus local antibody responses is not yet clear [19,20]. While functional antigen-specific T and B cells can be recovered from the bronchoalveolar lavage fluid of COVID-19 convalescents, dysregulated tissue remodeling and iBALT have also been associated with exhausted TFH-like cells that might contribute to prolonged disease [21,22].

The discovery of lung TFH-like cells that persist after the resolution of infection has added a new perspective on barrier immune memory [15,23,24]. Two recent studies described a subset of TRH cells that express both tissue residency and follicular helper markers and persist to at least four months after infection [25,26]. TRH cells colocalize with B cells in lung iBALT, depend on intrinsic expression of Bcl6 for their development, and are essential for the optimal induction of lung-resident Bmem cells (Fig. 1a). Moreover, sustained TRH and B- cell interactions are important for host protection during rechallenge: late deletion of Bcl6 in CD4 T cells impaired their retention in iBALT, ultimately leading to decreased mucosal antibodies and increased viral load. Importantly, adoptive transfer experiments demonstrated that TRH cells retain the ability to differentiate into Th1 effectors and have the capacity to contribute to both tissue and lymphoid responses following secondary challenge [25]. These observations may indicate that TRH cells can undergo retrograde migration as has been reported for CD8 T cells [27,28]. In contrast to TRH cells, lung-

resident Th1 cells almost exclusively home back to the lung and, similar to their lymphoid counterparts, have more limited plasticity and expansion [4,29].

The flexibility of TRH cell fate could be key for maintaining diverse tissue-localized CD4 T-cell subsets with the capacity to influence multiple arms of the immune response. Consistent with this idea, a substantial fraction of the TRH population produces Interleukin 21 (IL-21), which contributes to the maintenance of lung-resident CD8 T cells in an epitope-specific manner [26] (Fig. 1b). Similarly, IL-21 produced by TFH-like cells supports the differentiation of functional brain-resident CD8 T cells during viral infection, underlining the linkage between tissue-resident CD4 and CD8 cells in multiple immune settings [30]. In lymphoid organs, IL-21 was recently shown to promote CD4 T-cell expansion and the subsequent magnitude of GC B-cell responses independently of cognate T-cell–B-cell interactions and, at very high levels of bioavailability, plasma cell differentiation [31]. CD4 T-cell production of IL-21 has previously been linked to the transcription factor HIF-1a, which is also enriched within a distinct subset of lung TRH cells [25,32]. *Hif1a*-expressing TRH cells express higher levels of tissue-associated genes, while *Bcl6*-expressing TRH cells have higher expression of lymphoid-associated genes, indicating that these subsets may occupy distinct lung niches. Taken together, these observations raise the possibility that *Hif-* and *Bcl6*-expressing TRH subsets perform distinct functions, perhaps akin to lymphoid responses in which TFH cells discriminated by their production of IL-21 and IL-4 localize to distinct areas of the B-cell follicle where they have non-overlapping impact on the germinal center and antibody responses [31,33–35].

An additional, incompletely understood effect of IL-21 in the lung is the augmentation of IgA responses. Although IL-21 receptor blockade did not appear to impact local Immunoglobulin G (IgG) titers in response to influenza, T-cell-dependent IL-21 has been linked to IgA in chronic lung disease, food allergy, and immune responses to intestinal microbiota [36–38]. Relatedly, we have detected higher expression of IL-21 in *Hif1a*-expressing TRH cells and reduced titers of mucosal IgA following deletion of *Hif1a* in CD4 T cells (unpublished data) (Fig. 1b). An overarching open question is whether IgA class switching occurs in the draining lymph node, the lung mucosa, or both. Notably, TRH cells continue to express IL-21 at relatively late time points after influenza infection, raising the possibility that the relative abundance of TRH-derived IL-4 and IL-21 in the lung selectively expands or sustains distinct B-cell isotypes. Interestingly, in human naive B cells, IL-4 and IL-21 synergistically increase IgG1 B cells in vitro, while IL-4 alone completely abrogates switching to IgA [39]. Although a temporal role for these cytokines has not yet been assessed in the tissue, future studies will determine if distinct TRH subsets can be leveraged to elicit distinct types of B-cell responses in the lung mucosa.

B-resident memory cells in the lung

The formal recognition of tissue-resident B cells in mice is also quite recent. In a seminal study by Randall and colleagues, influenza-specific B-resident memory (BRM) cells were shown to require local antigen recognition and retained the ability to rapidly differentiate into plasma cells during rechallenge [40]. Subsequent transcriptional analyses of tissue and lymphoid influenza-specific B cells confirmed that lung-resident B cells acquire a distinct residency signature and can arise continuously from germinal center reactions taking place in peripheral lymphoid organs [23,41–44]. Importantly, a comprehensive comparison of Bmem cells in mouse and human tissues confirmed the shared expression of many residency markers across the species [45,46].

Spatial heterogeneity of lung B-resident memory cells

A 2022 report using two-photon microscopy of mouse lungs after influenza infection revealed that CXCR3+ BRM are scattered throughout the alveoli and exhibit relatively sessile behavior [43]. Following rechallenge, 'alveolar' CXCR3+ BRMs rapidly relocate to infected sites where they differentiate into plasma cells (Fig. 1c). This process is facilitated by alveolar macrophages recruiting IFNg-producing NK cells, which in turn induce the expression of CXCR3 ligands such as CXCL9 and CXCL10. It is also clear that BRMs can localize within lung iBALT [43,44,47]. Whether or not iBALT-localized BRM have a similar capacity to generate plasma cells on recall or whether they might be predisposed to undergo further maturation in germinal center reactions is unknown (Fig. 1(a)). It is also possible that iBALT provides a niche for the recruitment of circulating naive or memory lymphocytes [48]. In peripheral lymphoid organs, secondary germinal centers are mainly repopulated by naive B cells with minimal participation of Bmem, although naive B-cell recruitment can be modulated by the affinity of antibodies generated in the primary response [49,50]. Whether a similar paradigm exists within the tissue and specifically within lung iBALT remains to be seen.

Importantly, BRMs are also described following pulmonary infection with *S. pneumococcus* that, unlike influenza, does not elicit iBALT in mice [46]. In this model, BRM cells were detected within bronchovascular bundles located close to the airways of the lung interstitium, and their depletion led to reduced protection during heterotypic challenge.

Phenotypic heterogeneity of lung B-resident memory cells

Aside from spatial heterogeneity, several new studies have highlighted the phenotypic diversity of lung BRM cells. While the majority of influenza-specific BRM cells express CCR6, CXCR3 is expressed on only a subset (approximately 30–50% of lung Bmem and 20% of lymphoid Bmem) [47]. Mixed bone marrow chimera experiments indicated that while neither CCR6 or CXCR3 are strictly required for BRM cell seeding in the lung, CCR6 deficiency leads to impaired tissue homing and/or maintenance of BRM cells, as well as their decreased differentiation into IgG+ mucosal plasma cells following challenge. Notably, while CXCR3 deficiency had no impact on secondary IgG production in this model, another study showed that CXCR3 is indispensable for the induction of IgA+ BRM and plasma cells [42].

CXCR3 was also recently shown to delineate two transcriptionally distinct lung BRM subsets [44]. In contrast to the study above that identified both CXCR3-positive and -negative cells within the tetramer-binding, antigen-specific BRM compartment, this study used CXCR3 to discriminate antigen-specific BRM from CXCR3^{low} 'bystander' BRM cells. Intriguingly, bystander BRM cells had no discernable specificity for major viral antigens, despite having undergone more extensive somatic hypermutation. The development of bystander BRM cells was shown to require TFH cell-derived IL-4 and CD40 signaling, and increased IL-4 availability led to a more permissive germinal center reaction and the accumulation of bystander BRM cells (Fig. 1d). However, given that bystander BRMs were detected in both tissue and lymphoid compartments, it is not yet clear where the required T-cell help is being provided. Importantly, bystander BRMs were also shown to express high levels of the IgE and IgM Fc receptors (*Fcer2a* and *Fcmr*), which the authors propose allows these cells to capture exogenous immune complexes, potentially furthering local antigen presentation. Surprisingly, however, the authors also noted that deletion of CCR6 or Fcmr in the B-cell compartment specifically impacted lung IgA but not IgG responses following secondary infection. Although CCR6 deletion did not prevent recruitment of B cells into the lung, CCR6- deficient B cells were predominantly localized on the periphery of iBALT structures.

As most of these studies have focused on the lung, it will be important to understand if these observations extend to the upper respiratory tract, which is most proximal to initial pathogen exposure. In response to inhaled antigen, nasal-associated lymphoid tissue failed to support naive CD8 T-cell priming likely because these structures are excluded from routine surveillance by circulating T cells [51]. Nevertheless, secondary infection selectively recruits protective CXCR3+ memory CD8 T cells, with clear implications for boosting immunity through intranasal vaccination. Additional contexts in which circulating lymphocytes have limited access to tissues remain to be discovered, but a blood–endothelial barrier was similarly shown to exclude circulating antibodies from the olfactory mucosa [52]. In this study, upper airway protection required antibody secretion by tissue-resident plasma cells in the olfactory mucosa. Similar to plasma cells in the lung, olfactory plasma cells depended on both CXCR3 and CD4 T-cell help and were inefficiently generated by common vaccination strategies. Taken together, these BRM studies open several new lines of investigation into how distinct resident lymphocyte subsets contribute to protection against both heterologous and recall infections. Furthermore, the requirements for T-cell help, potentially from TRH cells, are as yet unclear for the various spatially and phenotypically distinct BRM subsets identified so far.

Conclusions

Recent studies have shown that the elegant interplay of T and B cells that characterizes the adaptive immune response in secondary lymphoid organs is at least partly reflected in the mucosal barrier tissue of the lung. Upon infection, B cells and helper T cells collaborate in the lung tissue, whether within or outside of iBALT, to effect pathogen clearance and seed the tissue with memory cells that provide enhanced responses upon reinfection. These resident lymphocytes are phenotypically and spatially diverse in ways that are only beginning to be understood, but which include differential capacities for homing, differentiation, cytokine secretion, antigen presentation, and antibody isotype switching.

While the efficient systemic surveillance provided by the lymphatic system is crucial for ameliorating many forms of disease, it is not as effective at preventing infection in the mucosa, which would be an ideal vaccine feature. For example, an intranasally administered protein-based influenza vaccine was superior to intramuscular or intraperitoneal administration in establishing tissue-resident memory B cells and mucosal IgA [53]. Similarly, boosting primary parenteral vaccination with an adjuvanted intranasal spike protein led to the development of tissue-resident T- and B-cell responses capable of protecting against lethal SARS-CoV-2 infection in mice [54]. Future work in this area will deepen our understanding of the important functions and interactions of resident lymphocytes in a variety of infection contexts and will hopefully pave the way to the development of vaccines and therapeutics that reduce the global burden of respiratory disease.

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Given her role as Guest Editor, Carolyn King had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Stuart Tangye.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data were used for the research described in the article.

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Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.coi.2023.102284.

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