# Role of iBALT in Respiratory Immunity


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## Contents



**Abstract** Pulmonary respiration inevitably exposes the mucosal surface of the lung to potentially noxious stimuli, including pathogens, allergens, and particulates, each of which can trigger pulmonary damage and inflammation. As inflammation resolves, B and T lymphocytes often aggregate around large bronchi to form inducible Bronchus-Associated Lymphoid Tissue (iBALT). iBALT formation can be initiated by a diverse array of molecular pathways that converge on the activation and differentiation of chemokine-expressing stromal cells that serve as the scaffolding for iBALT and facilitate the recruitment, retention, and organization of leukocytes. Like conventional lymphoid organs, iBALT recruits naïve lymphocytes from the blood, exposes them to local antigens, in this case from the airways, and supports their activation and differentiation into effector cells. The activity of iBALT is demonstrably beneficial for the clearance of respiratory pathogens; however, it is less clear whether it dampens or exacerbates inflammatory responses to non-infectious agents. Here, we review the evidence regarding the role of iBALT in pulmonary immunity and propose that the final outcome depends on the context of the disease.

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## 1 Introduction

Lymph nodes (LNs) are small, bean-shaped organs found along lymphatic vessels that drain the parenchyma of non-lymphoid organs. Like other secondary lymphoid organs (SLOs), LNs have a characteristic lymphoid architecture, with segregated B and T cell domains organized by distinct stromal cell types (Fletcher et al. 2011; Gentek and Bajenoff 2017). This structure facilitates the encounter of rare, antigen-specific lymphocytes with antigen-bearing dendritic cells (DCs) and thereby supports primary immune responses (Flajnik 2002; Neely and Flajnik 2016). LN formation occurs during late embryogenesis according to a developmental program that proceeds independently of antigen or inflammation (Luther et al. 2003). However, lymphocytes can also encounter antigen outside of LNs, as shown in reptiles and birds (species that lack LN), and in experimental mice that lack SLOs (Moyron-Quiroz et al. 2004). In these cases, T and B cells aggregate in the parenchyma of peripheral non-lymphoid organs and even form distinct B and T cell domains similar to those in conventional SLOs. Because these lymphoid aggregates do not occur as part of a developmental program and are only formed after local inflammation, they are termed tertiary lymphoid organs (TLO) (Hwang et al. 2016; Cupedo et al. 2004).

Three types of TLOs are found in the lung: nodular inflammatory foci (NIF), composed of clusters of myeloid cells and $CD8^+$ T cells (Stahl et al. 2013); granulomas, such as those formed during *Mycobacterium tuberculosis* infection, characterized by a central core of infected macrophages surrounded by B cells and T cells (Cadena et al. 2017); and inducible Bronchus-Associated Lymphoid Tissue (iBALT), which most closely resembles the architecture of conventional SLOs and is found in the perivascular space surrounding large blood vessels and along the airways of the lung (Hwang et al. 2016; Fleige and Forster 2017). iBALT formation occurs in response to numerous inflammatory conditions, using a variety of molecular pathways. In this chapter, we will summarize the current understanding of the steps leading to iBALT development and briefly review the impact of iBALT on pulmonary immune responses against microbial infections, allergens, and self-antigens.

## 2 Mechanisms Leading to iBALT Formation: A Rainbow of Options

The spatial distribution of lymphocytes in TLOs resembles that in SLOs, with the caveat that TLOs occur in places normally devoid of lymphocyte aggregates. iBALT typically forms on the basal side of the bronchial epithelium, often in the perivascular space of major blood vessels and consists minimally of a B cell follicle, sometimes with an active germinal center (GC) (Holt 1993). A variety of B cell phenotypes are observed in iBALT, including resting, naïve B cells,

isotype-switched memory B cells, germinal center B cells, and antibody-secreting plasma cells (GeurtsvanKessel et al. 2009; Halle et al. 2009; Rangel-Moreno et al. 2006). T cells and DCs are located along the bronchial epithelium and typically surround the B cell follicle (Fig. 1a) (Halle et al. 2009).

The organization, maintenance, and survival of leukocytes in iBALT require the presence of specialized stromal cells. For example, $CD31^{+}PNAd^{+}$ high endothelial venules (HEVs) form near the outer edges of the B cell follicle and serve as entry portals for recirculating lymphocytes (Ager 2017; Otsuki et al. 1989; Sato et al. 2000). Newly formed $Thy1^{+}$ lymphatic endothelial cells (LECs) appear in the lungs after an inflammatory response, particularly surrounding areas of iBALT, where they support T cell recruitment and survival by secreting the chemokines, CCL21 and CCL19, as well as the cytokines, IL-7 and IL-33 (Baluk et al. 2009, 2014a). In SLOs, the formation of B cell follicles depends on the secretion of CXCL13 by a network of follicular dendritic cells (FDCs) that attract $CXCR5^{+}$ B cells (Carlsen et al. 2002; Yu et al. 2002). However, two types of B cell follicles are described in iBALT—a classic follicle with $CD35^{+}CXCL13^{+}$ FDCs (Rangel-Moreno et al. 2011) and non-classical B cell follicle that lacks FDCs and instead uses podoplanin $(PDPN)^{+}CD35^{-}CD31^{-}CXCL12^{+}$ fibroblast-like stromal cells to maintain the B cell

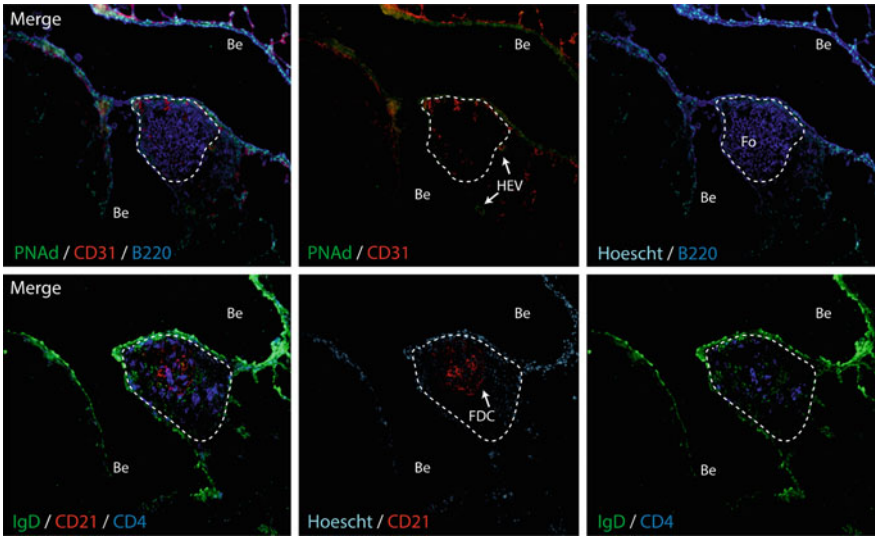
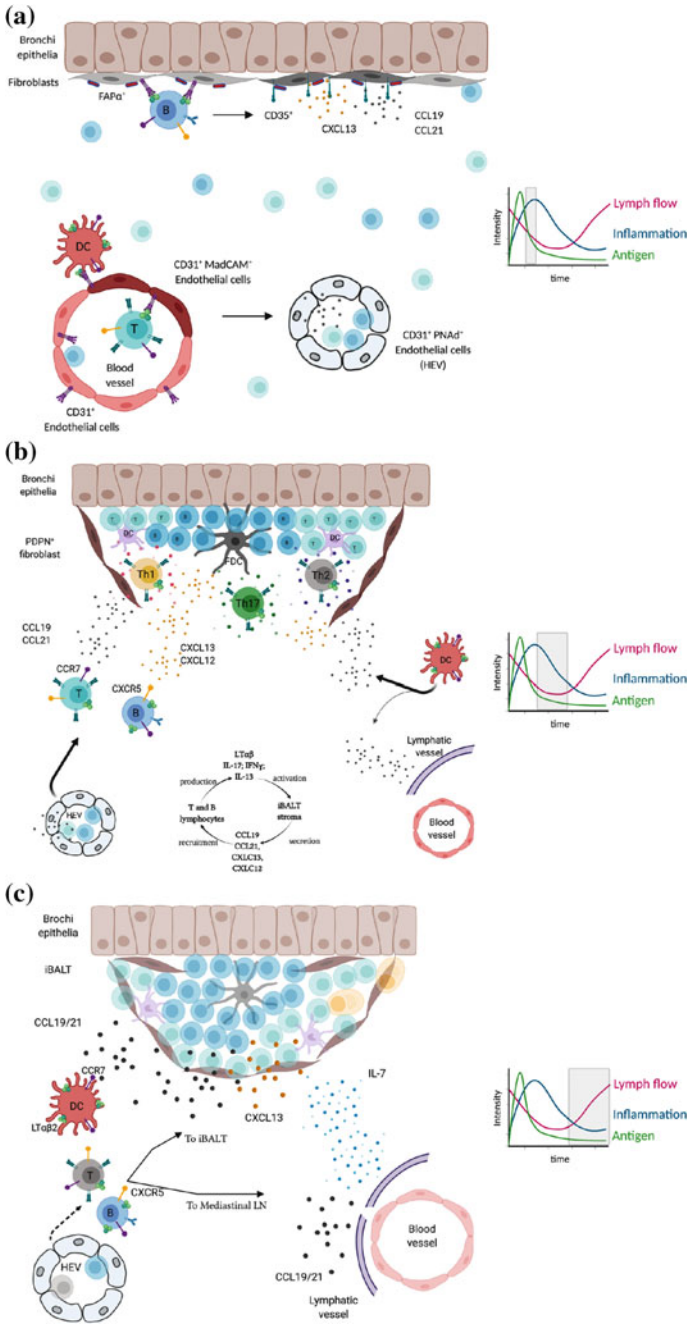



**Fig. 1 Structure of iBALT**. Immunofluorescence staining was performed on serial sections of lungs from 3-week-old mice after treatment with LPS during the first week after birth. Top row shows B cell follicle in iBALT ($B220^{+}$ cells in blue delimited by the dotted line) and associated HEV structures ($PNAd^{+}$ in green and $CD31^{+}$ n red) indicated by arrows. $CD31^{+}$ blood vasculature is observed in the whole field. Bronchi epithelia (Be) are indicated with arrowheads. The bottom row shows $IgD^{+}$ B cells inside the B cell follicle of iBALT ($IgD^{+}$ in green) and the associated FDC network that supports B cell aggregation ($CD35^{+}$ cells in red). Scattered CD4 T cells can be seen within and near the outer edges of the B cell follicle Be indicates bronchial epithelium


(a)
Bronchi epithelia
Fibroblasts
FAPα+
B
CD35+
CXCL13
CCL19
CCL21
DC
T
Blood vessel
CD31+ Endothelial cells
CD31+ MadCAM- Endothelial cells
CD31+ PNAd+ Endothelial cells (HEV)
Lymph flow
Inflammation
Antigen
Intensity
time
(b)
Bronchi epithelia
PDPN+ fibroblast
DC
FDC
Th1
Th2
Th17
CCL19
CCL21
CXCL13
CXCL12
CCR7
CXCR5
T
B
HEV
LTαβ
IL-17; IFNγ; IL-13
production
activation
T and B lymphocytes
iBALT stroma
recruitment
secretion
CCL19
CCL21,
CXLC13,
CXLC12
Lymphatic vessel
Blood vessel
Lymph flow
Inflammation
Antigen
Intensity
time
(c)
Brochi epithelia
iBALT
CCL19/21
CCR7
DC
LTαβ2
CXCL13
IL-7
To iBALT
T
B
CXCR5
To Mediastinal LN
HEV
CCL19/21
Lymphatic vessel
Blood vessel
Lymph flow
Inflammation
Antigen
Intensity
time

◂**Fig. 2 Sequential development of iBALT**. **a** Early stage of iBALT formation requires the differentiation and activation of stromal cells that segregate B cells and T cells. CXCL13 producing FDCs arise from the activation of FAP∝+ fibroblastic cells in a LTαβ dependent manner. **b** Local inflammation is required to amplify the activation of newly developed stromal cells and the recruitment of activated lymphocytes and dendritic cells. During IAV infection model, this stage would correspond to the lymphocyte aggregates observed right after clearance of the virus around 14 days post-infection. **c** iBALT structures perdure after the peak of the inflammatory response. At this stage, the feedback loop between stromal cells and the recruitment of LTαβ-bearing lymphocytes is controlled by the frequency of recruitable $LT\alpha\beta^{+}$ lymphocytes

area (Fleige et al. 2014). Recruitment of B cells toward the $PDPN^{+}CXCL12^{+}$ cells requires the expression of CXCR4 by B cells, similar to that described in the dark zones of germinal centers in conventional SLOs (Rodda et al. 2015). While it remains to be elucidated whether the two types of B cell follicles in iBALT are functionally different, the differentiation of $CXCL12^{+}PDPN^{+}$ stroma requires IL-17 signaling (Fig. 1b).

A wide range of stimuli trigger iBALT formation including viruses (Moyron-Quiroz et al. 2004; GeurtsvanKessel et al. 2009; Rangel-Moreno et al. 2007), bacteria (Baluk et al. 2014a; Fleige et al. 2014), fungi (Eddens et al. 2017), helminths (Venturiello et al. 2007; Gentilini et al. 2011), microbial products, particulates, and other inflammatory stimuli (Kuroda et al. 2016; Gregson et al. 1979; Noble and Zhao 2016). iBALT formation also occurs in mice that overexpress (Botelho et al. 2013; Furtado et al. 2014) or lack (Kocks et al. 2007; Das et al. 2006; Bouton et al. 2012) particular genes, each of which gives us insight into the mechanisms that lead to TLO formation. In general, the development of iBALT parallels the embryonic development of SLOs (Fig. 2). The first step of iBALT development entails the activation and differentiation of stromal cell precursors into iBALT supporting stroma—FDCs, HEVs, LECs, and $CXCL12^{+}PDPN^{+}$ fibroblasts (Fig. 2a). In the second step, leukocyte-mediated inflammation increases the recruitment of B and T cells around the activated stroma, leading to the maturation of the iBALT structure (Fig. 2b). In the third step, inflammation resolves and iBALT is maintained by homeostatic interactions between leukocytes and stromal cells, which supports the recruitment and organization of leukocytes from the blood (Fig. 2c).

The differentiation of each stromal cell type uses distinct molecular pathways (Lu and Browning 2014; Girard et al. 2012). For example, the formation of LECs depends on the secretion of IL-1β, which leads to VEGF expression and signaling through VEGFR2 and VEGFR3 (Baluk et al. 2009, 2013, 2014a, b). Although the formation of iBALT and the appearance of new lymphatic vessels occur at the same time and are closely associated, the formation of new lymphatic vessels is independent of iBALT development (Baluk et al. 2014a). The role of LTβR signaling is not clear since LTβ-deficient mice develop more lymphatic vessels than LTα-deficient and WT mice when infected with *Mycoplasma pulmonis* (Mounzer et al. 2010). However, the ectopic expression of LTα promotes TLO development (Mounzer et al. 2010), including the formation of new lymphatic vessels,

suggesting that $LT\alpha_3$ is sufficient to trigger the generation of new lymphatic vessels and TLO. In contrast, the differentiation of FDCs, $PDPN^+$ fibroblasts, and HEVs heavily depends on LTβR signaling (Lu and Browning 2014), although in some cases (i.e., LTαβ-deficient mice), it can be bypassed by the overexpression of TNFα (Furtado et al. 2014; Guedj et al. 2014), suggesting that other members of the TNF superfamily can act as triggers of FDC and $PDPN^+$ fibroblast differentiation (Ciccia et al. 2017; Ding et al. 2016; Berrih-Aknin et al. 2013).

A common mesenchymal stromal cell precursor in the LN gives rise to marginal reticular cells (MRC), fibroblastic reticular cells (FRC), some FDCs, and CRCs, but not HEVs (Denton et al. 2019a). This mesenchymal stromal cell precursor expresses the fibroblast activation protein alpha (FAPα), VCAM, CXCL13, and LTβR and is found in the perivascular region as lymphoid tissue inducer cells are being recruited to the LN anlagen (Denton et al. 2019a). A similar fibroblastic $FAP\alpha^+$ cell is found in the lungs of mice infected with influenza, one of the stimuli that promotes iBALT formation (GeurtsvanKessel et al. 2009; Denton et al. 2019a, b). Fate-mapping shows that $FAP\alpha^+$ mesenchymal cells are the precursors of $CD35^+FAP\alpha^+$ FDC-like cells in the B cell follicles of iBALT (Denton et al. 2019a). Unlike in the LN anlagen, however, the differentiation of $FAP\alpha^+$ precursors into mature stromal cells does not require the subset of innate lymphoid cells known as lymphoid tissue inducer (LTi) cells (Denton et al. 2019a), most likely because of numerous cell types, including activated B cells, T cells and DCs, can express LT and promote stromal cell maturation (Rangel-Moreno et al. 2011; Furtado et al. 2014; Marinkovic et al. 2006).

In conventional SLOs, the transition of $CD31^+MadCAM^-PNAd^-$ blood endothelial cells (BECs) to $CD31^+MadCAM^+PNAd^-$ immature HEVs and to $CD31^+MadCAM^-PNAd^+$ mature HEVs requires signaling through the LTβR and the activation of the canonical (RelA, p52) and non-canonical (RelB) NF-kB pathways (Ager 2017). In adult mice, LN HEVs need to be maintained by the constant influx of homeostatically activated DCs arriving from the afferent lymphatics (Herzog et al. 2013; Baratin et al. 2015; Astarita et al. 2015). In fact, any interruption of lymph flow (Mebius et al. 1991a, b), DC influx (Moussion and Girard 2011; Wendland et al. 2011), or LTβR/NF-kB signaling (Martinet et al. 2013; Browning et al. 2005) leads to the rapid involution of HEVs into flattened endothelial cells that lack PNAd expression. Similar pathways regulate iBALT-associated HEVs that surround the B cell follicle (Weinstein and Storkus 2016; Sato et al. 2011; Drayton et al. 2003).

Interestingly, a wide variety of signals can trigger the initial differentiation of stromal cells and start the process of iBALT formation. For example, the administration of LPS to neonatal mice leads to a strong IL-17 response, which turns on CXCL13 and promotes iBALT formation (Rangel-Moreno et al. 2011). In fact, IL-17 seems to be involved in the formation of iBALT and other TLOs in numerous contexts (Rangel-Moreno et al. 2011; Fleige et al. 2012, 2014; Eddens et al. 2017). Another Th17-related cytokine, IL-22, which is involved in epithelial repair and TLO formation in other tissues (Aujla and Kolls 2009; Barone et al. 2015; Pociask et al. 2013; Rendon et al. 2013), may also play a role in iBALT formation, as B cell

follicles are mildly reduced in size and number in the lungs of *M. tuberculosis*-infected IL-22-deficient mice (Khader et al. 2011).

Th17-related molecules are not the only inducers of iBALT formation, as mice infected with modified Vaccinia Ankara develop iBALT in an IL-17-independent fashion (Fleige et al. 2012, 2014). Mice infected with influenza also develop iBALT. In this case, however, type I IFN signaling is responsible for CXCL13 expression by lung fibroblasts and subsequent formation of B cell aggregates (Denton et al. 2019b). Similarly, mice infected with *Pneumocystis murina* develop iBALT in response to a mixed Th2 (IL-13) and Th17 (IL-17A) response, in which CXCL13 expression by lung $PDPN^+$ fibroblasts is dependent on the synergistic effects of IL-13 and IL-17 on IL-6 (Eddens et al. 2017). The pulmonary administration of particulates like alum triggers iBALT formation via macrophage cell death and IL-1α release (Kuroda et al. 2016). Similarly, the IL-1-related cytokines, IL-36 and IL-18, promote the formation of TLOs in colorectal cancer (Weinstein et al. 2019) and iBALT formation in COPD patients (Briend et al. 2017). Taken together, these data suggest that the first step of iBALT development depends on the differentiation of stromal cells capable of recruiting and organizing leukocytes via the production of chemokines like CXCL13 and that subsequently, the accumulation of activated, LT-expressing lymphocytes generate a positive feedback loop that maintains the structure.

Interestingly, the impairment of lymphatic drainage from the lungs is sufficient to trigger the formation of iBALT (Reed et al. 2019). Because the lymphatic vessels in the lungs of humans and mice lack smooth muscle cells in the lymphangions responsible for collecting lymph (Reed et al. 2019), the lymph flow from the lung depends on changes in the thoracic pressure produced by respiration. However, mice with a platelet-specific deletion of CLEC2, a ligand for PDPN and highly expressed on platelets, have impaired lymphatic flow from the lungs and spontaneously develop iBALT (Reed et al. 2019). Moreover, the ablation of $CD11c^+$ cells, presumably DCs, leads to the dissolution of iBALT structures (GeurtsvanKessel et al. 2009). Although $CD11c^+$ cell depletion affects cells other than DCs, including activated B cells (Zhang et al. 2019; Winslow et al. 2017; Naradikian et al. 2016) and some FDCs (Aziz et al. 1997), these studies suggest that DCs are important for the homeostatic maintenance of iBALT. Consistent with this idea, the loss of CCR7 on $CD11c^+$ cells leads to iBALT formation (Halle et al. 2009; Fleige et al. 2018), perhaps because activated DCs accumulate in the lung. Together these data suggest that DCs help maintain iBALT by providing LT signals to stromal cells (Muniz et al. 2011). Interestingly, CCR7 also regulates the trafficking of regulatory $CD4^+$ T cells (Tregs), which are important for limiting inflammatory responses (Georgiev et al. 2019). Neonatal mice lacking CCR7 spontaneously form iBALT due to impaired Treg migration and loss of inflammatory control (Foo et al. 2015; Cowan et al. 2013). However, once iBALT is formed, it recruits $FoxP3^+$ Tregs (Li et al. 2019; Trujillo et al. 2010; Siemeni et al. 2019), which help limit local inflammatory responses. These data indicate that once formed, iBALT is maintained by homeostatic mechanisms similar to those that maintain conventional SLOs.

## 3 Role of iBALT in Immunity Against Infectious Diseases

The structure of iBALT suggests that it should promote primary immune responses against pulmonary antigens. In fact, antigen-specific T cell and B cell responses are initiated in iBALT, leading to B and T cell activation, germinal center formation, and the differentiation of plasma cells and effector T cells (Halle et al. 2009; Gregson et al. 1979; Shilling et al. 2013). The functional outcomes of these responses are often dependent on the type of pathogen or antigen as well as the quality of the resulting immune response. Below, we will summarize what we know about the role of iBALT in regulating immunity to different classes of pathogens.

a. **Mycobacterial and other bacterial infections**

The development or expansion of iBALT is often associated with bacterial infections (Baluk et al. 2014a; Khader et al. 2011; Jupelli et al. 2013; Chiavolini et al. 2010; Linge et al. 2017). For example, rats infected with *Pseudomonas aeruginosa* develop iBALT (Iwata and Sato 1991), as do pigs infected with *Salmonella oranienburg*, *Mycoplasma granularum,* or hemolytic *streptococcus* (Jericho et al. 1971a, b). In mice, pulmonary infection with *Pseudomonas aeruginosa* or *Staphylococcus aureus* promotes the development of iBALT, in part via the expression of CXCL12, CXCL13, and IL-17A (Frija-Masson et al. 2017), similar to that seen in other models.

A consistent feature of most bacterial infections is the recruitment of neutrophils, which likely enhance iBALT formation in a variety of ways. For example, neutrophils express cytokines like APRIL that activate B cells (Tecchio et al. 2014). Moreover, neutrophils secrete proteases and reactive oxygen species that trigger epithelial and mesenchymal cell activation (Meyer-Hoffert and Wiedow 2011). In fact, serine proteases made by neutrophils promote iBALT formation by causing damage and triggering the expression of inflammatory chemokines (Solleti et al. 2016). Activated neutrophils also produce neutrophil extracellular traps (NETs), which consist of granular components precipitated on ejected chromatin (Kaplan and Radic 2012). The NETs help trap and kill bacteria, but also cause damage and inflammation that facilitate iBALT formation (Sørensen and Borregaard 2016; Zhao et al. 2015).

iBALT formation is also associated with infection by *Mycobacterium tuberculosis*, the causative agent of pulmonary tuberculosis, which kills more than a million people per year worldwide and is rapidly acquiring antibiotic resistance (Orme et al. 2015). The course of disease is characterized by a temporary paralysis of DC migration to the lung-draining lymph nodes (Curtis et al. 2015; Vanessa et al. 2015; Lai et al. 2014; Roberts and Robinson 2014), which delays the generation of Th1 and Th17 responses (Doz et al. 2013; Demangel et al. 2002), thereby allowing the bacilli to accumulate in infected macrophages (Khan et al. 2019; Kang et al. 2011; Blomgran et al. 2012). Even when protective Th1 and Th17 responses are generated, *M. tuberculosis* survives, but is contained in a granuloma—a type of inducible lymphoid structure with a central area of infected macrophages surrounded by

activated T cells and B cells (Cadena et al. 2017). These activated B and T cells often form iBALT surrounding the granulomas in *M. tuberculosis*-infected humans (Zhang et al. 2011; Ulrichs et al. 2004), non-human primates (Ganchua et al. 2018), and mice (Khader et al. 2011; Slight et al. 2013). Importantly, the presence of iBALT is associated with the maintenance of latency and containment of infection, whereas the absence of iBALT is associated with active disease (Ulrichs et al. 2004; Slight et al. 2013).

Although protective immunity against *M. tuberculosis* is mediated by IFNγ-producing Th1 cells, more recent data suggest IL-17A is also required (Khader et al. 2007, 2011; Doz et al. 2013; Martínez-Barricarte et al. 2018). IFN-γ activates macrophages and kills the bacilli, whereas IL-17A increases CXCL13 expression, which is required for the recruitment and organization of cellular infiltrates (Khader et al. 2007, 2011; Martínez-Barricarte et al. 2018; Gopal et al. 2013). Immune responses that deviate from these pathways fail to effectively control disease, as shown in mice previously exposed to *Schistosoma mansoni* egg antigen (SEA), which triggers a mixed Th1/Th2 response and thereby shifts the leukocyte infiltrate from B cell follicles to perivascular T cells and ultimately fails to control *M. tuberculosis* (DiNardo et al. 2016; Monin et al. 2015). Thus, effective immunity to *M. tuberculosis* requires the proper spatial positioning of cells in the lung consistent with iBALT formation.

Given the apparent protective effects of iBALT in the context of pulmonary infections, it makes sense to develop pulmonary vaccines that also trigger iBALT formation (Sanchez-Guzman et al. 2019). For example, pulmonary vaccination with *Francisella tularensis* LPS as a vaccine antigen and recombinant Porin B as an adjuvant promotes iBALT formation and germinal center development, leading to significant titers of LPS-reactive IgG and IgM that, together with iBALT, protect the immunized mice from subsequent challenge infection (Chiavolini et al. 2010). Similarly, the pulmonary administration of protein nanoparticles promotes iBALT formation in an antigen-non-specific fashion, leading to improved immune outcomes following pulmonary infection with the intracellular bacteria *Coxiella burnetii* (Wiley et al. 2009). Thus, the formation of iBALT in response to antigen-specific and antigen-non-specific stimuli provide subsequent protection from bacterial infections.

b. **Viral infections**

Pulmonary infection with viruses, including influenza (GeurtsvanKessel et al. 2009; Denton et al. 2019b; Richert et al. 2013), MVA (Fleige and Forster 2017; Fleige et al. 2018; Mzinza et al. 2018), respiratory syncytial virus (RSV) (Auais et al. 2003), SARS coronavirus (Channappanavar et al. 2014) and adenovirus (Jericho et al. 1971b), is often associated with the formation of iBALT. In mice, influenza infection promotes iBALT formation, which supports germinal center responses and the local differentiation of influenza-specific plasma cells (GeurtsvanKessel et al. 2009; Rangel-Moreno et al. 2011), many of which differentiate locally, as the disruption of iBALT two weeks after infection reduces local IgA production (GeurtsvanKessel et al. 2009). Moreover, influenza-specific memory B cells in the

lung are more broadly reactive against numerous strains of influenza (Adachi et al. 2015), suggesting that the BCR selection process in the germinal centers of iBALT is qualitatively different than that in LNs. Moreover, mice with pre-existing iBALT experience an accelerated, influenza-specific antibody response in the lung (Rangel-Moreno et al. 2011; Wiley et al. 2009) and perform better than control mice in terms of weight loss and viral titers. Interestingly, iBALT also forms in the lungs of influenza-infected adult monkeys, but not in influenza-infected infants (Holbrook et al. 2015), leading to poor antibody responses and increased pulmonary damage in infants.

The presence of iBALT also provides a beneficial effect with SARS coronavirus, which is cleared more rapidly in mice with iBALT by an accelerated antibody response (Wiley et al. 2009). Similarly, mice that have iBALT induced as a result of neonatal LPS exposure lose less weight and clear pneumovirus faster than mice without iBALT (Foo et al. 2015). Importantly, $CD4^+$ T cell response to pneumovirus is accelerated in mice with iBALT (Foo et al. 2015), suggesting that the presence of iBALT in the lung leads to faster, more efficient pulmonary immune responses that promote rapid viral clearance and reduce morbidity after infection.

Although a faster more robust immune response may be desirable for immunity to many pathogens, some viruses elicit immune responses that are themselves the primary cause of pathogenesis. For example, RSV causes acute bronchiolitis in children and is linked to recurrent wheezing and asthma (Munywoki et al. 2013). Interestingly, infection of CCR7-deficient mice with RSV leads to enhanced production of IL-17 and IL-13 by $CD4^+$ T cells and excessive mucus production (Kallal et al. 2010). RSV-infected LTα-deficient mice, which lack conventional lymphoid organs, also experience excessive IL-17 and IL-13 expression and increased mucus production in the lung, suggesting that local immune responses in iBALT are responsible for pathology (Kallal et al. 2010). Similar exacerbations of pulmonary pathology are linked to the presence of iBALT in RSV-infected humans (Johnson et al. 2007). The combination of a pulmonary allergic response and RSV infection is particularly damaging in guinea pigs, which develop exacerbated iBALT hyperplasia, goblet cell metaplasia, and airway hypersensitivity (Robinson et al. 1997). Thus, in the context of RSV and perhaps other Th2-driven pulmonary conditions, the presence of iBALT may exacerbate disease simply by driving bigger, better faster immune responses that are more pathologic than protective.

### c. **Fungal infections**

Mice infected with the opportunistic fungal pathogen, *Pneumocystis*, often generate a mixed Th17/Th2 response. Importantly, the combination of IL-13 and IL-17 synergistically promotes the differentiation of pulmonary fibroblasts and their expression of CXCL13, ultimately leading to iBALT formation (Eddens et al. 2017). Activated DCs also accumulate in the lungs of *Pneumocystis*-infected mice and potentiate T cell priming to other pulmonary antigens (Swain et al. 2011). In fact, prior infection with *Pneumocystis* enhances subsequent immunity to the influenza virus, leading to the accelerated appearance of influenza-specific antibodies and reduced expression of inflammatory cytokines in the bronchoalveolar

lavage fluid, thereby reducing morbidity and accelerating viral clearance (Wiley and Harmsen 2008). Thus, the formation of iBALT in response to one pathogen enhances immunity to unrelated pathogens.

## 4 Role of iBALT in the Immune Response Against Non-infectious Agents

a. **Allergens**

Allergic or atopic immune responses are mediated by inappropriate Th2 and/or Th17 responses against non-pathogenic, environmental antigens, such as food antigens (peanut, egg), arthropods (house dust mite, cockroach), and plant components (pollen). The frequency of individuals developing severe allergies or asthma is rapidly increasing for unknown reasons (Jappe et al. 2019). Allergic responses typically involve a sensitization phase, in which allergen exposure primes T cells, but does not cause symptoms (Pizzolla et al. 2016; Shilovskiy et al. 2019), and a challenge phase, in which exposure to the same allergen caused an atopic inflammatory response (Shinoda et al. 2017; Gregory and Lloyd 2011). In the lung, chronic allergic responses promote airway remodeling, goblet cell hyperplasia and excessive mucus production, ultimately leading to reductions in lung function (Elieh Ali Komi and Bjermer 2019; Holt and Sly 2007) and obstructive leukocyte infiltration (Lainez et al. 2019; Maselli and Hanania 2019).

Chronic or repetitive exposure to allergens can trigger iBALT formation (Guest and Sell 2015). Hypersensitivity pneumonitis (sometimes called farmer's lung) is a classic example, in which repeated exposure to molds or other antigens in barn dust leads to lung disease, in which iBALT features prominently (Suda et al. 1999). The inflammatory milieu of allergic responses supports iBALT formation via numerous mechanisms, including the combined expression of IL-13 and IL-17 that promote stromal cell differentiation (Eddens et al. 2017). Moreover, Th2-related cytokines like IL-5 promote the recruitment of eosinophils, which likely accelerate iBALT formation by releasing granular contents including proteases and cytokines that in turn cause damage and support cellular differentiation (Lee et al. 1997a; b). In fact, this process can be mimicked by the overexpression of IL-5 in club cells (Lee et al. 1997a), which promotes eosinophil accumulation and iBAT formation in the absence of exogenous antigen.

The presence of iBALT in the lungs might contribute to the development of allergies by preferentially recruiting Th2 memory cells into the lung (Fleige et al. 2018; Shinoda et al. 2016), by increasing the concentration of IL-33 due to the differentiation of new lymphatic endothelial cells (Shinoda et al. 2016, 2017), or by supporting germinal centers that produce $IgE^+$ or $IgG1^+$ plasma cells (Chvatchko et al. 1996). In fact, iBALT may generally exacerbate atopic inflammation by supporting bigger, better, faster (albeit inappropriate) immune responses in the lung. One way to accomplish this goal would be to recruit $Gata3^+CXCR5^+$ T

follicular helper (Tfh13) cells to iBALT (Noble and Zhao 2016). Tfh13 cells strongly produce IL-4, IL-5, and IL-13, but not IL-21, conditions that support B cell differentiation into antibody-secreting cells that make IgG1 or high-affinity IgE (Gowthaman et al. 2019).

Although repeated allergen exposure can lead to eosinophil recruitment, mucus production, and IgE secretion, thereby promoting allergic inflammation and pathology, these same activities should help control parasitic infection. In fact, mice pre-sensitized with house dust mite extract developed iBALT areas, recruited eosinophils, and expressed high levels of IL-4, IL-13, and IL-33 in the lungs, which together acted to prevent the maturation of *Ascaris* larvae, whereas mice not pre-sensitized with house dust mite failed to prevent larval development (Gazzinelli-Guimaraes et al. 2019). These data suggest that although Th2-driven iBALT formation may enhance atopic responses and promote pulmonary inflammation, it may also be beneficial in the clearance of pulmonary parasites.

b. **Self-antigens: the good and the bad, can we tell them apart?**

TLOs, including iBALT, are often formed around tumors, in transplanted organs and in the target organs of autoimmune responses. For example, the presence of iBALT near tumor nests in patients with non-small-cell lung cancer (NSCLC) correlates with a better prognosis (Dieu-Nosjean et al. 2016). Within iBALT, higher numbers of DCs in close proximity to tumor cells (Dieu-Nosjean et al. 2008), the presence of $Tbet^{+}CD4^{+}$ T cells (Goc et al. 2014), and the frequency of $CD161^{+}CD4^{+}$ T cells (Braud et al. 2018), all indicate an active anti-tumor response and correlate with better clinical outcomes. For some tumors, including breast cancer (Peske et al. 2015), ovarian cancer (Kroeger et al. 2016; Truxova et al. 2018), and NSCLC (Germain et al. 2014), the presence of TLOs is associated with a favorable prognosis, whereas in tumors like colorectal cancer, the chronic inflammation associated with TLO formation is also linked to tumorigenesis (Weinstein et al. 2019).

TLO development is initially triggered inflammatory responses that promote the activation and differentiation of mesenchymal cells and trigger the expression of CXCL13. In tumor that lack microbial components, inflammatory signals might come from the release of danger-associated molecular patterns (DAMPs), such as IL-1α (Kuroda et al. 2016), IL-18 (Briend et al. 2017), or IL-36γ (Weinstein et al. 2017). Increased CXCL13 expression and the recruitment of LT-expressing lymphocytes promote the expression of ICAM, VCAM, PNAd, and CCL21 in blood endothelial cells (BEC) and reinforce the recruitment of more LT-bearing cells. The continuous signaling of LTαβ-LTβR activates the non-canonical NF-kB pathway and leads to the differentiation of BEC into $PNAd^{+}$ HEV (Ager 2017). Can the process of HEV development be exploited to improve immune responses against tumor cells? In this regard, VEGFR2 blockade prevents angiogenesis in tumors, but also induces PD-L1 expression by tumor cells, thus impairing anti-tumor immunity. However, the combined blockade of VEGFR2 and PD-L1 antibody maintained anti-tumor immunity and promoted the differentiation of BEC into HEVs by the constant influx of activated LT-expressing lymphocytes (Allen et al. 2017). Thus,

the mechanisms that regulate lymphocyte recruitment and TLO formation can be exploited for therapeutic benefit.

In contrast to the beneficial effect of local immunity against tumors, local immune responses against organ transplants, including transplanted lungs, can lead to graft rejection (Kumar et al. 2018). Not surprisingly the formation of iBALT with active germinal centers is indicative of an ongoing immune response against transplanted lungs and is associated with the development of antibody-mediated rejection (Gauthier et al. 2019; Shenoy et al. 2012; Hasegawa et al. 1999). Interestingly, this process can be prevented by the recruitment of Tregs, which suppress germinal center formation in iBALT and prevent allo-antibody production (Li et al. 2019). The switch from immunity to tolerance is mediated by the blockade of costimulatory signals through CD40 and CD28. Moreover, once Tregs are recruited to iBALT areas in the transplanted lung, it can be re-transplanted to another recipient without rejection (Li et al. 2019)! Importantly, $CXCR5^+$ Tregs in limiting lung rejection after chronic GVHD were demonstrated in B10.BR mice receiving lungs from C57BL/6 donors (McDonald-Hyman et al. 2016). In the recipient B10.BR mice, lung transplants improved their function and reduced the number of T follicular helper cells when receiving a passive transfer of $CXCR5^+$ Tregs but not with $CXCR5^-$ Tregs. Overall these studies suggest that iBALT facilitates the entry and interaction of $CXCR5^+$ lymphocytes and that the type of local immune response depends on the lymphocyte subsets recruited (Li et al. 2019; McDonald-Hyman et al. 2016; Flynn et al. 2014).

Furthermore, in autoimmune diseases like rheumatoid arthritis (RA) and Wegener's granulomatosis (WG), iBALT can develop in the lungs and its occurrence is associated with a chronic and worsening status of the disease (Shilling et al. 2013). For instance, in RA increased concentration of serum rheumatoid factor (IgM antibodies directed against IgG Fc portion) correlates with the appearance of rheumatoid pulmonary vasculitis and TLO in the lungs (Rangel-Moreno et al. 2006). In Wegener's granulomatosis (WG), lymphocytes in the lungs can form diffuse infiltrates, but also can form structured iBALT and form germinal centers (Shilling et al. 2013). The pronounced infiltration of granulocytes is characteristic of a Th17-driven disease and is consistent with the role of IL-17 in promoting iBALT formation.

## 5 Conclusion

Like many tertiary lymphoid organs, iBALT forms in response to a variety of inflammatory stimuli that converge on the differentiation of specialized stromal cells, the expression of homeostatic chemokines and the recruitment and organization of activated lymphocytes. Once formed, iBALT participates in local, pulmonary immune responses by collecting antigen and APCs and supporting B and T cell responses. The biological outcome of those immune responses is on the type of antigen or pathogen and may be modified by the presence of iBALT by changing

the kinetics or magnitude of the resulting immune response, which may be beneficial or harmful depending on the context. Thus, understanding the mechanisms that control iBALT formation and function should give us insights into ways to improve immunity to pathogens and malignancy and to dampen atopic or inflammatory diseases.

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