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Brief Reviews

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Friend or Foe: The Protective and Pathological Roles of Inducible Bronchus-Associated Lymphoid Tissue in Pulmonary Diseases

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Inducible bronchus-associated lymphoid tissue (iBALT) is a tertiary lymphoid structure that resembles secondary lymphoid organs. iBALT is induced in the lung in response to Ag exposure. In some cases, such as infection with *Mycobacterium tuberculosis*, the formation of iBALT structure is indicative of an effective protective immune response. However, with persistent exposure to Ags during chronic inflammation, allergy, or autoimmune diseases, iBALT may be associated with exacerbation of inflammation. iBALT is characterized by well-organized T and B areas enmeshed with conventional dendritic cells, follicular dendritic cells, and stromal cells, usually located surrounding airways or blood vessels. Several of the molecular signals and cellular contributors that mediate formation of iBALT structures have been recently identified. This review will outline the recent findings associated with the formation and maintenance of iBALT and their contributions toward a protective or pathogenic function in pulmonary disease outcome. ***The Journal of Immunology*****, 2019, 202: 2519–2526.**

Secondary lymphoid organs (SLOs) are immune structures distributed throughout the human body that serve as localized reservoirs of immune cells poised to be primed and activated quickly upon infection or inflammatory insult (1). SLOs, such as lymph nodes and Peyer patches, are seeded during embryonic development in the absence of infectious or inflammatory stimuli. These structures are formed as part of a highly ordered series of events, guided by lymphoid tissue inducer cells that require lymphotoxin α (LTα), and occur early during embryonic development (2–4).

Inducible bronchus-associated lymphoid tissue structure and function

Inducible bronchus-associated lymphoid tissue (iBALT) is a tertiary lymphoid organ (TLO) specifically induced by antigenic stimuli. These stimuli can be from infectious exposures, environmental insults, self-antigens, or other sources. Although several cell types and molecular signals function similarly in SLOs and TLOs, the anatomical feature that makes iBALT unique is its localization, which is generally near major bronchi but often during inflammation or infection may also localize within the perivascular or interstitial areas of the lung (5, 6). Additionally, iBALT is also unique in that it is induced after antigenic or inflammatory stimulation, and Ag- or pathogen-specific factors often skew the characteristics of iBALT.

Endothelial, epithelial, and stromal cells are thought to secrete the initial inflammatory signals that trigger the initiation of iBALT and TLO formation (7, 8). Dendritic cells (DCs) and macrophages, which are among the first immune cells that seed the nascent iBALT, further propagate the cascade of proinflammatory cytokines and chemokine signals to initiate the recruitment of more DCs, B cells, and T cells (9). As iBALT formation progresses, the nascent structure becomes more organized, with segregated B and T cell zones forming sustained germinal center (GC)–like structures (9), a marker of iBALT. LTα and TNF-α are key signals required for the maintenance of SLOs (1, 10), but, in the context of iBALT, are known to play a role only in some models of infection and chronic inflammation (5, 11, 12). IL-1α is also required for induction of iBALT formation, as IL-1α deficiency is correlated with a decreased frequency of conventional DCs (cDCs) and failure to induce iBALT during viral infection, and iBALT formation could be reversed by exogenous IL-1α administration (11, 13). IL-1α is produced during the early stages of pulmonary influenza infection by stromal

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Abbreviations used in this article: cDC, conventional DC; COPD, chronic obstructive pulmonary disease; DAMP, damage-associated molecular pattern; DC, dendritic cell; FDC, follicular DC; GC, germinal center; iBALT, inducible bronchus-associated lymphoid tissue; LTα, lymphotoxin α; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; RA, rheumatoid arthritis; *sigH*, sigma-H factor; SLO, secondary lymphoid organ; TB, tuberculosis; Tfh, T follicular helper; TLO, tertiary lymphoid organ; Treg, T regulatory cell.

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cells and is required for control of viral replication and iBALT formation through the induction of CXCL13, which is also driven by LTα (13).

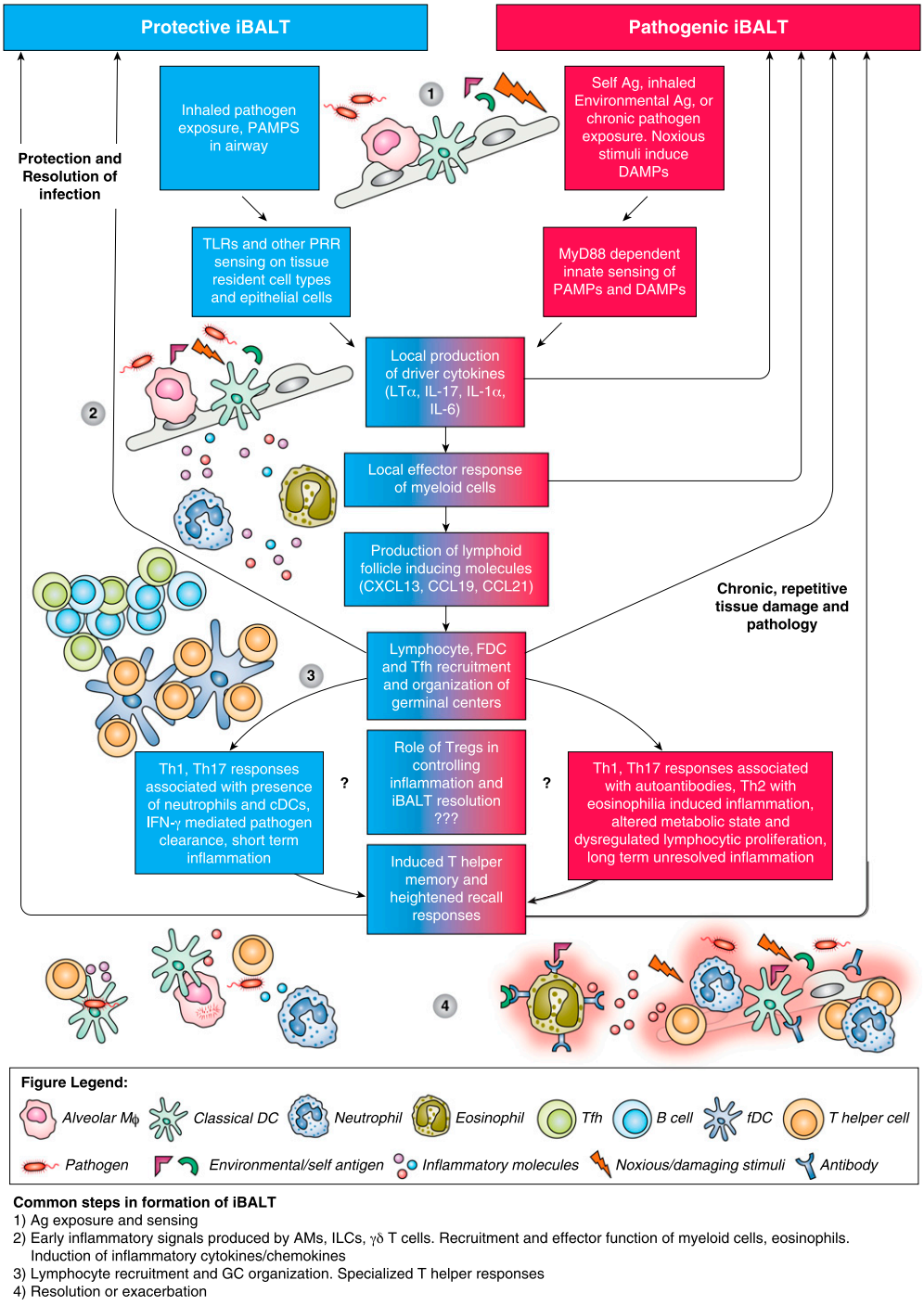
Early production of IL-23, IL-17, and IL-22 also constitutes critical cytokine signals required for iBALT formation during infections such as *Mycobacterium tuberculosis* (14–16) by inducing the secretion of chemokines associated with the recruitment of T and B cells to the nascent iBALT (17). Of the homeostatic chemokines, CCL19, CCL21, CXCL12, and CXCL13 and their receptors CCR7, CXCR4, and CXCR5 are associated with the structural organization of iBALT (12, 18, 19). CCL19 and CCL21, constitutively expressed by stromal cells and follicular DCs (FDCs), recruit CCR7-expressing cDCs as well as naive, Ag-specific, and memory T cells to the nascent T cell zones of the iBALT structure (5, 18). Accordingly, recruited cDCs and T cells can localize around the tightly packed B cell follicles (5, 20, 21). During infection with bacterial pathogens such as *M. tuberculosis*, absence of CCR7 and CCL19/CCL21 deficiency resulted in delayed Ag presentation and T cell priming, poorly formed B cell follicle formation, and increased susceptibility to infection (22, 23), supporting a nonredundant role for the CCR7-CCL19/CCL21 axis in iBALT induction and function. CCL21, along with CXCL13, can maintain iBALT even in the absence of LTα (5). CXCL13, produced mainly by FDCs, follicular B cells, and other stromal cells within iBALT (5), can mediate the homing of CXCR5-expressing B and T cells (including a subset of T follicular helper [Tfh] cells) to the follicular compartment of iBALT (5, 24). Accordingly, CXCL13 or CXCR5 deficiency coincided with defects in T and B cell homing into iBALT structures, thus impacting the control of bacterial infections such as *M. tuberculosis* (24).

Migration into nascent iBALT and the specific localization of T and B cells within iBALT, driven by the aforementioned chemokines, represent the initial steps in the development of bona fide iBALT structures in lung. The unique localization of iBALT near the airways raises the possibility that iBALT samples Ag effectively and rapidly because of this unique anatomical localization. With time, the developing iBALT becomes more structured, with organized, segregated B and T cell zones (9) interspersed with FDC, cDC, and stromal cells. FDCs and cDCs likely provide Ag, survival, and costimulatory signals to activate and sustain iBALT-harbored T and B cells (9, 25). Previously activated T and B cells can infiltrate iBALT, and naive T and B cells may also be activated by local APC or by direct Ag recognition within iBALT structures (26). Activated T cells, such as Th1, Th2, Th17, or even T regulatory cells (Tregs), along with DCs within the iBALT can produce effector molecules, including cytokines and chemokines, required to control pathogens and may contribute directly to the outcome of the disease (25, 27). T cells and DCs can also provide help for Ab production by B cells that may act systemically or locally during infections (25, 28). Whether T cells differentiate within iBALT or whether they migrate into iBALT once they are differentiated in SLOs is not fully understood. However, T cells actively participate in the protective immune responses against pathogens in protective iBALT or can drive dysregulated pathological responses associated with persistent inflammation during chronic pulmonary conditions such as chronic obstructive pulmonary disease (COPD), autoimmune diseases, or allergy.

The protective and pathogenic roles of iBALT

iBALT structures can maintain a pool of locally activated, Ag-specific lymphocytes able to induce a rapid and effective immune response (5, 29). As such, the presence of iBALT has important implications in the progression and outcome of pathogen exposures and chronic inflammation. The triggers that induce protective versus pathological outcomes for iBALT are just beginning to be characterized but likely implicate the type of Ag, the type of T cell response induced, and the chronicity of the stimulation conditions. Understanding the initial seeding events that drive iBALT formation may explain the distinct roles of iBALT during infection and inflammation. In this study, we explore the key differences between protective and pathogenic iBALT and their effects on health and disease (Fig. 1).

Protective iBALT. A proposed function of protective iBALT is to harbor a local supply of B and T cells within the lung, resulting in a rapid, localized immune response and sustained and rapid activation of Ag-specific lymphocytes in the tissue (29). The initial response to microbial pathogens occurs through the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) on immune cells. This interaction can lead to the induction of specific, polarizing cytokine and chemokine cascades, thus allowing the immune system to tailor the response to effectively contain and neutralize the pathogen through the recruitment of specialized myeloid populations and T helper subsets. The specific PAMPs and PRRs that are required for the formation of iBALT are not fully defined; although, we hypothesize that the type of PAMP and PRR involved will impact subsequent immune response and skew the initial production of chemokines and molecules required for the recruitment of immune cells to allow formation of the iBALT. In line with this hypothesis, Fleige et al. (19) demonstrated that the type of pathogen determines which key factors are required for the formation and maturation of iBALT. Specifically, by comparing modified vaccinia virus Ankara and *Pseudomonas aeruginosa* pulmonary infection models, some of the initial interactions with host receptors that can alter the characteristics of iBALT were defined. In the case of *P. aeruginosa*, TLR signaling through MyD88 was shown to drive the formation of FDC-lacking iBALT and required the production of IL-17. In contrast, modified vaccinia virus Ankara–induced iBALT was highly organized, with FDCs surrounding densely packed B cell follicles, and did not require IL-17 signaling (19). Thus, characteristics of iBALT during infection are dictated by early cellular interactions, inflammatory signals, and the type of pathogen. In response to, and in conjunction with, cytokines induced by PRRs, early signals from infected myeloid cells, epithelial cells, Th17 helper T cells, type 3 innate lymphoid cells, and γδ T cells likely induce the inflammatory cascade of cytokines (including IL-23, IL-22, IL-17, TNF-α, and LTα) that drive and maintain iBALT formation during pulmonary infections (29, 30). These tissue-resident cells likely produce the signals that drive the earliest immune responses, even before the recruitment and activation of monocytes, DCs, B cells, and T helper cells occur. These early signals, specifically IL-17 and LTα, are known to be upstream drivers of CXCR5 and CXCL13 (15, 17, 31), required for iBALT formation and organization of B cell follicles (5, 10, 14, 22, 24, 32, 33), and play important protective roles in host immune responses



Common steps in formation of iBALT
1) Ag exposure and sensing
2) Early inflammatory signals produced by AMs, ILCs, γδ T cells. Recruitment and effector function of myeloid cells, eosinophils. Induction of inflammatory cytokines/chemokines
3) Lymphocyte recruitment and GC organization. Specialized T helper responses
4) Resolution or exacerbation

FIGURE 1. The common and distinct mechanisms of protective and pathogenic iBALT formation. 1) Protective iBALT is induced in response to PAMPs recognized by PRR expressed on innate immune cells or epithelial cells. Pathogenic iBALT is induced in response to chronic pathogen exposure, self-antigens, or environmental Ags, which induce DAMPs and inflammation. 2) The sensing of PAMPs and DAMPs results in the production of iBALT-driving cytokines that induce the local response of myeloid cells, production of inflammatory molecules, and recruitment of more myeloid cells, lymphocytes, FDCs, and Tfh. 3) These signals and associated cellular recruitment drive the formation and organization of GC. 4) In protective iBALT, responses are associated with early recruitment of neutrophils and cDCs, IFN-γ–mediated pathogen clearance, and short-term inflammation. In pathogenic iBALT, responses are associated with autoantibodies and uncontrolled inflammation, with some diseases specifically highlighted by eosinophilia-induced inflammation. Other changes include altered metabolic state and dysregulated lymphocyte proliferation with subsequent long-term unresolved inflammation.

to a variety of viral (31, 34) and bacterial infections (35–40) (Table I). Early IL-17 is required for protective immunity against the highly pathogenic H5N1 influenza virus infection demonstrated by a mechanism involving induction of CXCL13 and recruitment of $CXCR5^+$ B cells into the lung tissue (31). Accordingly, $IL\text{-}17^{-/-}$ mice had increased inflammation and decreased total B cells in the lung (19, 31), and in vitro, IL-17 axis blockade led to defects in chemotaxis of human B cells (41). These findings suggest that localization and organization of B cells in follicles were likely impaired without IL-17 signaling in these models. Beyond their roles in acute infection, IL-17, IL-22, and IL-23 are also required for the long-term control of *M. tuberculosis*, and deficiency of these cytokines correlated with reduced B cell follicle formation and a failure to control

Table I. Published studies describing the protective and pathogenic roles of iBALT in pulmonary diseases

Agent/Disease	Cellular Drivers	Molecular Signature	References
		Protective Function	
M. tuberculosis	Tfh, FDCs, GC B cells,	Th17, CXCL13, CCL19, CCL21, IL-23, IL-17, IL-22	(14–16, 22–24, 49, 51, 52)
Pneumocystis	Th2, Th17	CXCL13, IL-13, IL-17, LTα	(12)
Viral infections	$CD11c^+$ DCs, lung stromal cells, GC, B cells	IL-17, CXCL13, CCL19, CCL21, LTα, IL-1α	(5, 13, 25–27, 31)
P. aeruginosa	Neutrophils, B and T cells	CXCL12, CXCR4, IL-17	(47, 48)
		Pathogenic Function	
RA	Autoreactive T cells, B cells, FDCs	CCL19, CCL21, LTβ	(21)
Inhalation allergy/asthma	Eosinophils, B cells, FDCs, Th2, endothelial cells	IL-1α, IgE, CCL19, CCL21	(11, 57, 68)
COPD	DCs, autoimmune B cells	CCL20, CCR7, CXCL13, LTα, IL-1β, IL-18, IFN-γ	(64, 69, 72, 73, 75, 76)
Pulmonary arterial hypertension	T cells, B cells, DCs	CXCL13, CCL20, LTα,	(65, 66)

bacterial replication during later stages of infection (15). These studies are supported by a role for IL-22 in driving the development of TLOs (8, 15), possibly because of their effects on stromal cells, which express IL-22R and mediate downstream signaling events for induction of CXCL-13 and CXCL-12 (15). Additionally, $LT\alpha^{-/-}$ mice showed defective B and T cell follicle organization, lower numbers of proliferating B cells, and lower IgG serum titers during *Pneumocystis jirovecii* infection, although these mice were still able to clear the infection and did have smaller, but persistent, iBALT (12). These findings suggest that LTα, although not required for iBALT induction, is required for the organization and long-term maintenance of iBALT structures. Together, IL-17 and IL-22 modulate the recruitment of B, Tfh, and other $CXCR5^+$ cells to nascent iBALT, thus providing critical early signals for formation and organization of protective iBALT (Table I).

Without early signals from IL-17 and IL-22, chemokine signals are dysregulated or abrogated, leading to defective or inappropriate recruitment and organization of myeloid and lymphoid cells required for protection against pathogen exposure. Proper migration and specific localization of B and T cells into iBALT occur through CXCL13/CXCR5 and CCL19/CCL21/CCR7 signaling (14, 18, 22, 24, 42). Particularly, CCL19 and CCL21 are important for not only pulmonary recruitment of naive $CD4^+$ T cells but also $CD11c^+$ cDCs, Ag-specific IFN-γ–producing T cells, and development of iBALT within granulomas during *M. tuberculosis* infection (22). Beyond inducing migration of naive cells or already differentiated T and B cells, early secreted chemokines also induce the differentiation of naive T cells toward specific T helper subsets. CCL19 by itself can enhance T cell proliferation by inducing maturation of DCs and specifically program DCs to induce Th1 responses (43).

T cells are crucial for iBALT formation, as treatment with anti-CD4 Ab resulted in the reduction of lymphoid follicles within iBALT in several infection models (12, 44). Recruited or locally differentiated T helper subsets in iBALT may include Th1, Th2, Th17, Tregs, and Tfh cells, which are poised to exert their effector functions to provide a rapid local recall response (5, 26, 29) or control exacerbated inflammation (45, 46). Induction of particular T helper subsets determines the type of immune response occurring in iBALT and impacts the outcome of the disease. For instance, Th1, Th17, and Tfh-like cells expressing CXCR5 in the lung were associated with iBALT formation, control of *M. tuberculosis* infection, and host survival (17, 24, 39). Similarly, the Th1 immune response induced in iBALT during influenza infection correlated with improved viral clearance, decreased lung pathology, increased survival rates, and sustained memory responses, even in the absence of SLOs (5, 26, 27). Furthermore, Th2 and Th17 cells were required to control *Pneumocystis* infection and induction of protective iBALT in a CXCL13-dependent manner (12). Early induction of iBALT correlated with increased recruitment of T and B cells during chronic infection with *P. aeruginosa.* Interestingly, as infection progressed, cellular infiltration and associated inflammation decreased, suggesting that iBALT may also serve to regulate or dampen the local immune response during chronic pulmonary infections (47, 48), most likely through the recruitment of IL-10–producing Tregs. iBALT may contribute to the induction of long-term memory B cell responses by maintaining plasmablasts and long-lived plasma cells, which migrate to the bone marrow, suggesting that the presence of long-term memory and recall responses during influenza virus infection partially depends on sustained input of B cells migrating from iBALT in the lung (25). As such, the presence of iBALT correlates with an increased recall response after secondary Ag exposure, thus improving the outcome of repeated exposure to the same infection. The presence of preexisting iBALT can also improve the outcome following challenge with other pulmonary infections, regardless of the initial Ag that seeded it (28). This is done by sustaining the activation of a local pool of $CD4^+$ T cells with different Ag specificities and can be maintained even in the absence of the triggering Ag (9). Furthermore, it was shown that secondary immune responses initiated in iBALT induced less inflammation and were potentially less damaging to the host than the immune response induced systemically (5). Taken together, in the context of secondary infection, the presence of iBALT is generally considered to be protective by inducing an improved recall response. In the nonhuman primate model of tuberculosis (TB), a model that closely mimics human TB, the presence of B cell follicles correlates with protection during TB (49, 50), as iBALT structures are prominent in lungs of latently infected primates and negligible in cavitary lung lesions of *M. tuberculosis*–infected primates and patients with acute pulmonary TB (51, 52). These findings highlight the importance of iBALT in protective immune responses against *M. tuberculosis*,

influenza, and other infections, suggesting iBALT as an important local source of cellular and humoral effectors to mediate local immunity in the lung. It is also possible that iBALT functions as a protective feature by limiting infected cells within the lymphoid follicle and preventing dissemination to other organs (53).

Delineating the protective role of iBALT and identifying the mechanisms of protection will be major steps forward in developing therapies or vaccines for pulmonary infections. The initial seeding and the early host- and pathogen-specific factors that induce iBALT are not well understood. Broader knowledge of the PAMPs and damage-associated molecular patterns (DAMPs) that can trigger iBALT formation will provide new insights into the development of molecule-based therapies or vaccines to induce iBALT. In a recent study performed by Griffiths et al. (44), pulmonary delivery of *M. tuberculosis* Ag-primed DCs led to increased and rapid iBALT formation, near-sterilizing immunity, and improved disease outcome, suggesting that early Ag acquisition, delivery, and rapid Ag presentation may be key to protection against TB. In the context of vaccination, one could potentially administer an attenuated version of a pathogen to induce protective, long-lasting iBALT, as was done by Kaushal et al (49). Pulmonary delivery of an attenuated strain of *M. tuberculosis* lacking functional sigma-H factor (*sigH*) (*M. tuberculosis*Δ*sigH*), a master regulator of *M. tuberculosis* oxidative stress responses, induced effective and long-lasting iBALT structures (49). Upon subsequent lethal challenge with aerosolized *M. tuberculosis*, *M. tuberculosis*Δ*sigH*–vaccinated macaques demonstrated increased iBALT formation, decreased inflammation, improved recruitment of T cells, and superior *M. tuberculosis* control when compared with the macaques vaccinated with the currently used vaccine, *Mycobacterium bovis* bacillus Calmette-Guérin (49). Similar approaches with other attenuated strains or different pathogens could induce the local proliferation of iBALT in the lung, providing long-lasting immunity to specific pathogens. Furthermore, the induction of iBALT using intranasally delivered nanoparticles was shown to accelerate the immune response to influenza and other infections, increasing IgG and IgA production, reducing lung pathology, and protecting mice against a spectrum of respiratory viral pathogens (28). Delivery of mucosally administered nanoemulsion-based vaccines for TB induced IL-17 responses and iBALT containing lymphoid follicles in the lung and protected mice upon *M. tuberculosis* challenge (54). These findings suggest that targeting specific cytokines such as IL-17 could induce iBALT structures as a potential therapeutic strategy and should be included in combination with current or new vaccines to improve vaccine-mediated protection to a broader variety of pathogens.

Pathogenic iBALT. Although it is believed that iBALT in the context of long-term inflammatory responses is detrimental to the host, the mechanisms associated with iBALT induction and maintenance are less understood for pulmonary chronic inflammatory conditions. During pulmonary chronic inflammatory conditions, it is thought that different Ag classes can trigger iBALT, including inhaled particulates, allergens, self-antigens, and DAMPs (11, 55, 56). Whether iBALT contributes to exacerbating inflammation during chronic conditions or is induced as a consequence of an already established inflammatory condition remains unclear. However, the presence of iBALT correlates with worsened lung disease rather than resolution of inflammation in chronic inflammatory diseases.

In most cases, regardless of the Ag or triggering signals, a sustained inflammatory response with an influx of granulocytes, such as neutrophils, eosinophils, and basophils as well as inappropriately activated T and B cells, yields detrimental consequences for the host (6, 56–58). During chronic inflammatory conditions, IL-17 and LTα likely play a similar early role in driving iBALT induction as during protective iBALT formation. However, prolonged production of these drivers can lead to sustained inflammatory cytokine and chemokine production, thus rendering inflammatory iBALT over time. These events favor dysregulated inflammatory responses and result in maintenance of activated lymphocytic and myeloid cell accumulation, thus leading to tissue damage and the development of autoimmune diseases. For instance, contrasting the protective role of IL-17 in early induction of iBALT during acute influenza, *M. tuberculosis*, and *Pneumocystis* infection (12, 15, 23, 32), heightened Th17 responses can cause inflammation during respiratory syncytial virus infection and influenza (59, 60) (Table I). These findings highlight a dichotomous role for this cytokine axis that may be dependent on time and pathogen persistence. The increased inflammation over time correlates with an enhanced influx of neutrophils and IL-13 production that promotes the activation of Th2 lymphocytes and excessive mucus production (61). In alum or silica exposure models of airway inflammation, alveolar macrophages underwent cell death and produced IL-1α, which acts as a DAMP that can trigger iBALT, thus inducing further allergic responses associated with IgE Ab production (11). High levels of IL-6 and TNF-α in bronchoalveolar lavage fluid were also found following environmental exposure to crystalline silica in mice. Respiratory exposure to crystalline silica induced a robust inflammatory response associated with eosinophilia, increased production of Igs, and proinflammatory cytokines and chemokines in bronchoalveolar lavage fluid, corresponding with systemic lupus erythematous–type autoimmune response (62). Because systemic lupus erythematous is a systemic disease, the persistence of iBALT structures resulted in dysregulated inflammatory responses, suggesting that iBALT structure may serve as a platform for triggering systemic autoimmune responses (62).

Because of chronic stimuli, several chronic inflammatory conditions containing iBALT eventually lead to exacerbation and tissue damage by driving the production of autoreactive Abs by activated B cells present in iBALT. Increased production of molecules associated with B cell follicles, such as B cell activating factor of the TNF family (BAFF), ICOS-ligand, and LTα, correlated with increased numbers of iBALT structures in patients with pulmonary complications associated with rheumatoid arthritis (RA) (21), COPD (63), and Sjögren syndrome (21). In patients with COPD, LTα was associated with disease by driving enhanced expression of CXCL13 and B cell recruitment within iBALT, yielding hallmarks of the disease, such as production of autoantibodies and exacerbated inflammation (64). Furthermore, in RA patients, clinical parameters of disease, such as the presence of anticyclic citrullinated peptide Abs, correlated with the presence of iBALT and increased lung tissue damage, supporting a pathogenic role for B cells and iBALT during chronic inflammation (21). In situ production of autoantibodies (65)

against fibroblasts or epithelial cells in iBALT was reported in patients with pulmonary arterial hypertension (66). Induction of pulmonary hypertension also correlated with increased number and size of iBALT (66), resulting in increased local inflammation and autoantibody production. Therefore, strategies targeting reduction in iBALT formation during these chronic conditions may be effective approaches to prevent or reverse pulmonary hypertension.

As previously mentioned, signals and Ags driving the initial seeding of iBALT may also skew the T helper responses and the mechanisms underlying chronic disease. CCL19 and CCL21 produced by lymphatic endothelial cells in the lung may mediate iBALT formation during chronic allergic inflammation (57), possibly because of the recruitment of $CCR7^+$ cDCs and T cells (55). Furthermore IL-5 and IL-7 produced by lymphatic endothelial cells within iBALT are required for the maintenance of pathogenic Th2 memory T cells, which are present in many chronic inflammatory diseases, such as allergy and asthma (57, 67). In chronic allergic inflammation, iBALT sustains enhanced memory Th2 responses with local production of environmental-reactive IgG1, IgA, and IgE in the lungs, which further worsens inflammation after Ag exposure (11, 57, 68). Overall, the production of Abs in this model is thought to be MyD88- and IL-18 independent, although IgE was specifically driven by IL-4 secreted by Tfh cells (11). The pathogenic consequences of enhanced local production of IgE involve induction of eosinophilia, mononuclear cell infiltration, and airway hyperreactivity to Ag exposure, suggesting a detrimental role for IgE-producing B cells in iBALT during the allergic response (68) (Table I).

COPD is associated with a mixture of Th1, Th2, and Th17 responses, which contribute to worsened disease condition and are exacerbated in the presence of iBALT in both human and mice models (56, 58, 69–71). Particularly, IL-18, a proinflammatory cytokine derived mainly from epithelial cells and myeloid cells, was shown to be associated with worsened lung pathology during COPD by a mechanism involving induction of high levels of IFN-γ–producing Th1 cells, which contributed to exacerbated inflammation and disease severity (72). IL-17–producing Th17 cells, along with IL-1β, are thought to be the main drivers of neutrophilic inflammation in COPD (58, 71, 73) by a mechanism involving upregulation of the B cell– and T cell–attracting chemokine CXCL12. Furthermore, high serum levels of IL-17 correlated with exacerbated disease and increased numbers of circulating neutrophils in COPD patients (73). Although the identification of the triggering Ag in COPD is not clear, lung infections, which are common in these patients (74), may contribute to disease severity (75). More recent evidence suggests that genetic and metabolic factors can also impact iBALT formation and progression. Mutations in serpin family E member 2 (SERPINE2), an extracellular matrix–associated glycoprotein, is associated with COPD development (76). SERPINE2 deficiency was associated with enhanced production of molecules associated with iBALT induction and inflammation, including IL-17, TNF-α, LTα, CXCL13, IFN-γ, IL-2, and spontaneous mononuclear cell infiltration, thus boosting formation of iBALT in the lungs (76). Furthermore, using a mouse model of COPD, Jia et al. (77) reported that oxysterol metabolism of cholesterol drove iBALT formation and the induction of COPD, similar to what occurs in SLOs. Increased production of a cholesterol-derived metabolite, 7a,25-hydroxy cholesterol, enhanced B cell recruitment into iBALT by interacting with EBV-induced G protein–coupled receptor 2 (EBI2), a G protein–coupled receptor also expressed in lymphocytes and DCs. Pharmacological inhibition of the involved oxysterol pathway was shown to resolve this observed B cell–driven iBALT and abrogated associated emphysema in mice (77), presenting a new possible therapeutic target to treat patients with this clinical condition. Thus, different signals have been described to induce or maintain iBALT structures in the context of chronic inflammatory diseases. The ability to block signals or DAMPs associated with the formation of pathogenic iBALT could lead to less autoreactivity associated with autoimmune diseases and the ability to resolve pathogenic iBALT and unwanted inflammation, which would be a potential step forward in treatment.

Conclusions

Although the signals and cellular components present in protective and pathological iBALT may be somewhat similar, the impact on pathogen exposure, infection, or inflammation can be distinct. For example, some of the requirements for B cell– and T cell–associated chemokines CXCL13, CCL19, and CCL21; Tfh and FDC signals; and the signals driving GC formation are ubiquitous across both protective and pathological iBALT structures. However, as discussed above, distinct differences in Ag exposure, duration of Ag exposure, early cytokine signals, and downstream soluble and cellular inflammatory mediators may drive distinct cellular differences in the structure and function of protective versus pathological iBALT structures. For example, although IL-17 is critical for initiation of early chemokine signals to seed iBALT formation, sustained and prolonged IL-17 production might lead to detrimental accumulation of macrophages and neutrophils, resulting in chronic inflammation. Thus, it is likely that iBALT formation is a short-term protective solution for pathogen control, but if left unresolved, it may result in long-term localized pathological iBALT. Another possible difference in protective versus pathological iBALT is likely the type of Th response induced by the Ag. Although early Th1 and Th17 responses appear to be involved in protective iBALT formation and function, prolonged Th17 and Th2 responses are associated with environmental or self-reactive IgE and IgA. As a downstream event, the effect of chronic Th17 and Th2 responses on lung epithelia and sustained presence of granulocytes are also likely major determinants of the function of protective versus pathological iBALT structures. Finding immunological targets that can limit pathological iBALT while promoting protective iBALT structure may provide novel therapeutic strategies to drive immunity during pulmonary infections while alleviating chronic pulmonary symptoms in allergy, asthma, COPD, and even autoimmune diseases. Potential targets would likely be cytokines involved in iBALT initiation and formation, such as IL-17, IL-22, LTα, and the associated chemokines CXCL13 and CXCL12. However, because the molecules and pathways associated with pathogenic and pathological iBALT formation largely overlap, targeting specific molecules to abrogate formation or maintenance needs to be carefully interrogated to avoid potential undesired effects or compromised immunity. Additional studies addressing the mechanisms of persistence of

iBALT, Ag presentation, and Th differentiation within iBALT and the local immunity within iBALT could open up a new field of host-directed immunotherapeutics targeting iBALT formation.

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