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Regulatory B cells in respiratory health and diseases

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Abstract

B cells are critical mediators of humoral immune responses in the airways through antibody production, antigen presentation, and cytokine secretion. In addition, a subset of B cells, known as regulatory B cells (Bregs), exhibit immunosuppressive functions via diverse regulatory mechanisms. Bregs modulate immune responses via the secretion of IL-10, IL-35, and tumor growth factor-β (TGF-β), and by direct cell contact. The balance between effector and regulatory B cell functions is critical in the maintenance of immune homeostasis. The importance of Bregs in airway immune responses is emphasized by the different respiratory disorders associated with abnormalities in Breg numbers and function. In this review, we summarize the role of immunosuppressive Bregs in airway inflammatory diseases and highlight the importance of this subset in the maintenance of respiratory health. We propose that improved understanding of signals in the lung microenvironment that drive Breg differentiation can provide novel therapeutic avenues for improved management of respiratory diseases.

KEYWORDS
airway inflammation, B cells, IL-10, immune regulation, infection, lung

1 | INTRODUCTION

B cells are an essential part of humoral immune responses in the airways through antibody production, antigen presentation, and cytokine secretion.[1] Although these functions are pivotal in the clearance of invading pathogens and the development of long-term immunity, unrestrained inflammation can cause irreversible damage to tissues.[1] To prevent this, we require mechanisms of suppression that prevent exaggerated immune responses and maintain tissue homeostasis.

In addition to well-established effector functions, a subset of immunosuppressive B cells, known as regulatory B cells or Bregs, contribute to preventing uncontrolled inflammation.[2] Bregs, as negative regulators of the immune system, suppress inflammatory responses via the production of IL-10 and other anti-inflammatory mediators, as well as via direct cell contact. Depending on the disease context, Bregs can be either pathogenic or beneficial; whereas an expansion of Bregs is advantageous in autoimmunity and other chronic inflammatory conditions, increased Breg frequencies can cause detrimental immune suppression in infectious diseases and cancers.[3]

The signals required for the induction of Bregs include a combination of toll-like receptor (TLRs) ligands, CD40-ligand (CD40-L), antigens activating the B cell receptor (BCR), co-stimulatory molecules (CD80, CD86), and inflammatory cytokines.[2,4] Majority of these stimuli can be found in the lung microenvironment,[1,5] supporting an expansion of Bregs in the airways. Moreover, numerical and functional abnormalities in Bregs have been associated with various

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immune-related lung pathologies,[6-9] highlighting the importance of this B cell subset in mounting an appropriate immune response in the airways. For these reasons, there is an increased interest in understanding the role of Bregs in respiratory health and disease settings. This review summarizes the role of immunosuppressive Bregs in airway inflammatory diseases, including lung cancer, respiratory infections, allergy, pulmonary fibrosis, and autoimmune pulmonary manifestations, thus emphasizing the importance of this subset in the maintenance of respiratory health.

2 | OVERVIEW OF BREG INDUCTION, PHENOTYPE, AND FUNCTION

Over the past decade, studies in experimental animal models and patients with autoimmune diseases have identified multiple Breg subsets exhibiting diverse mechanisms of immune suppression.[3] Evidence suggests that the environmental milieu plays a pivotal role in the induction of Bregs. In addition to TLR, BCR, and CD40 signaling, as well as CD80 and CD86 activation, inflammatory cytokines have been shown to play an important role in expanding immunosuppressive Bregs.[4] For example, exposure to inflammatory cytokines IL-1β and IL-6 has been shown to induce Breg differentiation in a mouse model of arthritis.[10] Moreover, mice with B cell-specific deletion of IL-1R1 or IL-6R displayed reduced Bregs and exacerbated arthritis. Interestingly, the production of IL-1β and IL-6 is modulated by gut bacteria, highlighting an indirect role for microbiota in Breg induction.[10] Other inflammatory cytokines, such as type I interferons (IFN-I), IL-21 and B cell-activating factor (BAFF) have also been shown to play a role in Breg differentiation.[11-14] Although anti-inflammatory cytokine IL-35 has been shown to expand IL-10- and IL-35-producing Bregs,[15] evidence suggests that IL-35 is itself induced in response to inflammatory stimuli.[16] Of note, activation of STAT3 is important for induction of IL-10 expression by B cells, as inhibition of STAT3 has been shown to abrogate IL-10$^+$ B cells.[17] Taken together, the expansion of suppressive Bregs in response to inflammatory signals appears to be a mechanism that has evolved to prevent excessive inflammation and tissue damage.

In addition to inflammatory stimuli, recent studies have identified aryl hydrocarbon receptor (AhR) as an important transcription factor involved in Breg differentiation.[18,19] Ahr has been shown to regulate the transcription of IL-10 by B cells while actively repressing the transcription of pro-inflammatory mediators.[18] In a mouse model of arthritis, the lack of Ahr expression by B cells has been demonstrated to increase Th1/Th17 responses, decrease regulatory T cells (Tregs), and lead to exacerbated arthritis as a result of impaired IL-10-producing Breg differentiation.[18] Interestingly, Blimp1, a transcription factor critical for plasma cell differentiation,[20] has also been shown to play a role in IL-10$^+$ Breg function; as Bregs lacking Blimp-1 expression fail to efficiently suppress naïve CD4$^+$ T cell proliferation.[21] Furthermore, evidence suggests that Bregs have the ability to differentiate into IL-10-producing plasmablasts and plasma cells in vitro and in vivo.[22,23] Although antibody-producing plasmablasts/plasma cells are largely associated with pro-inflammatory responses,[24] a subset of IL-10$^+$ regulatory plasmablasts have been shown to suppress immune responses while producing antibody.[25,26] These findings suggest that B cells at any stage of development can exhibit a regulatory phenotype.

Several Breg subsets with overlapping markers and functions have been identified in mice and humans.[3] In animal models, Bregs suppress allergic airway inflammation,[27] promote tolerance in transplantation,[28,29] and improve experimental autoimmune diseases.[22,30,31] Among the different subsets, IL-10-producing B cell subpopulations that constitute ~10% of circulating human B cells are the most studied in different disease settings.[3,32] These subsets include CD1d^{hi}CD5$^+$ B10 Bregs,[33] CD21$^+$CD23$^-$CD24^{hi} marginal zone (MZ) Bregs,[34,35] CD1d^{hi}CD21^{hi}CD23^{hi}CD24^{hi} T2-MZP Bregs,[30,36] and CD138$^+$CD44^{hi} plasmablasts.[22] In addition, T cell immunoglobulin and mucin-domain-containing protein (Tim-1) has been identified as a marker for IL-10-producing B cells in mice and is expressed by multiple Breg subsets.[37,38] Importantly, B cell-specific Tim-1 deletion results in spontaneous multi-organ tissue inflammation, supporting a role for this Breg subset in maintaining self-tolerance and restraining tissue inflammation.[19,38] Other Breg populations include MZ-like and MZ-progenitor B cells that express programmed cell death-ligand 1 (PD-L1) molecule in mice.[39] Immune suppression by PD-L1^{hi} Bregs is independent of IL-10 and mediated by the PD-1/PD-L1 pathway that can regulate follicular T-helper (Tfh) cell responses.[39]

Due to the limited access to human lymphoid tissues, majority of human Bregs identified thus far are in the peripheral blood. The characterized human Breg subsets include CD24^{hi}CD38^{hi} transitional B cells,[32] CD24^{hi}CD27$^+$ human B10 cells,[40] CD25^{hi}CD71^{hi}CD73^{lo} regulatory B1 (Br1) cells,[41] CD27^{int}CD38^{hi} plasmablasts,[22] CD38$^+$CD1d$^+$IgM$^+$CD147$^+$granzymeB (GzmB)$^+$ B cells,[42] and CD39$^+$CD73$^+$B cells.[43,44] Similar to mouse models, Tim-1$^+$ B cells that co-express IL-10 have also been reported in humans.[45] The different Breg subsets, their mechanisms of suppression, and role in different disease settings have been described in detail elsewhere,[3,4,46] and summarized here in Table 1.

Inhibitory mechanisms of Bregs are best described by their secretion of the anti-inflammatory cytokine, IL-10.[2] Breg-derived IL-10 can convert CD4$^+$T cells into Tregs and type I regulatory T (Tr1) cells,[47] inhibit Th1/ Th17 differentiation,[32,48] suppress TNF-α production by monocytes,[40] and maintain the number and function of immunosuppressive invariant natural killer (iNKT) cells.[49,50] IL-10-producing Bregs also suppress the production of IFN-α, an antiviral cytokine that is secreted by plasmacytoid dendritic cells (pDCs),[11] thereby implicating a role for Bregs in preventing hyper-inflammation and tissue damage caused by unresolved infections. Bregs also act through the secretion of other anti-inflammatory cytokines like tumor growth factor-β (TGF-β) and IL-35. Breg-derived IL-35 induces Treg expansion and inhibits Th1 and Th17 differentiation,[15,23] whereas TGF-β induces CD8$^+$T cell anergy and apoptosis of effector CD4$^+$ T cells.[51,52] Furthermore, a subset of induced Bregs (iBregs, induced by CTLA-4$^+$T cells) expand Tregs in a TGF-β and indoleamine 2,3 dioxygenase (IDO)-dependent manner[53]). Another subset of

TABLE 1 Phenotype and function of Breg subsets

Subset	Phenotypic markers	Mechanism of action	Functions	References
B10 cells	$CD1d^{hi}CD5^{+}$ (mouse) $CD1d^{+}CD24^{hi}CD27^{+}$ (human)	IL-10	Inhibits Th17 cells, effector $CD4^{+}$ T cells, macrophages and DCs, expands Tregs and Tr1 cells	18,33,40,47,48
Tim-1 B cells	$Tim\text{-}1^{+}$ (mouse and human)	IL-10, TGF-β	Expands Tregs and reduces Th1 cells, increases allograft tolerance	19,37,38,45
T2-MZP B cells	$CD1d^{hi}CD21^{hi}CD23^{hi}CD24^{hi}$ (mouse)	IL-10	Promotes Treg differentiation, inhibits Th1/ Th2 cells, suppresses effector $CD4^{+}$ and $CD8^{+}$ T cells	30,36,48
MZ B cells	$CD5^{+}CD21^{+}CD23^{-}$ $CD1d^{+}CD24^{hi}IgM^{hi}IgD^{lo}$ (mouse)	IL-10	Suppresses effector $CD4^{+}$ and $CD8^{+}$ T cells, promotes Treg differentiation	34,35
Plasma cells	$CD138^{hi}CD1d^{+}$ $IgM^{+}B220^{+}TACI^{+}$ $CXCR4^{+}$ $Tim1^{\pm}$ (mouse)	IL-10, IL-35	Inhibits NK cells, Th cells, macrophages, and neutrophils, promotes antigen presentation	15,23
Plasmablasts	$CD138^{+}CD44^{hi}$ (mouse) $CD27^{hi}CD38^{hi}$ (human)	IL-10	Suppresses DCs ability to expand effector T cells	22,25,26
Br1 cells	$CD25^{hi}CD71^{hi}CD73^{lo}$ (Human)	IL-10, IgG4, PD-L1	Secretes anti-inflammatory IgG4, reduces differentiation of Th cells	41
Transitional/ Immature B cells	$CD24^{hi}CD38^{hi}$ (human)	IL-10, PD-L1, CD86	Suppresses Th1/ Th17, $TNF\alpha^{+}$ monocytes, virus-specific $CD8^{+}$ T cells, expands Tregs and iNKT cells	32,48-50
$GzmB^{+}$ B cells	$CD5^{+}CD27^{+}CD138^{+}$ (human)	Granzyme-B	Induces $CD4^{+}$ T cell apoptosis, inhibit proliferation of $CD4^{+}$ T cell	42
iBregs	-	TGF-β, IDO	Differentiates T cells into IL-10- and TGF-β-producing Tregs	53
$PD\text{-}L1^{high}$ B cells	$PD\text{-}L1^{hi}Blimp1^{lo}$ $CD138^{lo}B220^{hi}$ (mouse)	PD-L1	Inhibits Tfh expansion, suppress T cell differentiation	39
$CD39^{+}CD73^{+}$ B cells	$CD39^{+}CD73^{hi/lo}$ (mouse and human)	5′-AMP, ADO	Inhibits proliferation of $CD4^{+}$ and $CD8^{+}$ T cells	43,44

Abbreviations: 5′-AMP, adenosine 5′-monophasphate; ADO, adenosine; Br1, B regulatory 1 (Br1) cells; DC, dendritic cell; GzmB, Granzyme B; IDO, indoleamine 2,3 dioxygenase; iNKT, inducible natural killer T cell; MZ, marginal zone; NK, natural killer cell; PD-L1, programmed cell death-ligand 1; T2-MZP, transitional-2 marginal zone precursor; Tim-1, T cell immunoglobulin and mucin-domain-containing protein 1; Tregs, regulatory T cells.

Bregs, known as Br1 cells, secrete IL-10 and allergen-specific IgG4 antibodies that regulate tolerance to allergic reactions and suppress allergen-specific T cell proliferation.[41] Additionally, a population of $CD39^{+}CD73^{+}$ B cells suppress inflammatory reactions by inhibiting the proliferation of $CD4^{+}$ and $CD8^{+}$ T cells, via the production of adenosine 5′-monophosphate (5′-AMP).[43,44] Other mechanisms of Breg immune suppression include co-stimulatory interactions with T cells, iNKT cells, and DCs that involve CD80, CD86, CD1d CTLA-4, PD-L1, and MHC class II.[4] $PD\text{-}L1^{hi}$ Bregs inhibit the expansion of Tfh cells in spleen/ lymph nodes and suppress effector T cell differentiation by modulating downstream signaling pathways.[39] Figure 1 summarizes the mechanisms of suppression by Bregs.

3 | B CELLS IN THE RESPIRATORY SYSTEM

The respiratory tract is designed with immune structures to protect the body against a wide range of potentially harmful external airborne antigens.[1,54] B cells are rarely found in the lungs of healthy humans; their presence in the lung is almost exclusively associated with lung injury, usually infection or chronic inflammation.[1] B cells are typically located within tertiary or ectopic lymphoid tissues (ELTs) in the lung, like the inducible bronchus-associated lymphoid tissue (iBALT).[1,5] Unlike well-organized secondary lymphoid organs, ELTs are loosely organized, poorly defined aggregates of lymphoid cells that develop rapidly in response to infection, chronic inflammation, or autoimmunity.[55] ELTs have separate B and T cell-rich zones, Tfh cells, a network of follicular dendritic cells (FDCs), stromal mesenchymal cells, and high endothelial venules, and can vary depending on the type of pathogen or inflammatory condition that triggered their formation.[5,55,56] Importantly, they display localized expression of CXCL12 and CXCL13 (a strong homing signal for $CXCR5^{+}$ B cells[57]) that promote naïve B cell recruitment to the ELTs[58]; recruited B cells then produce lymphotoxin-β that further sustain the ELT.[59,60] Tfh cells also express CXCR5 that allows them to stay in close contact with B cells within the ELT.[61-63] Thus, ELTs contain functional germinal centers (GCs) for local B

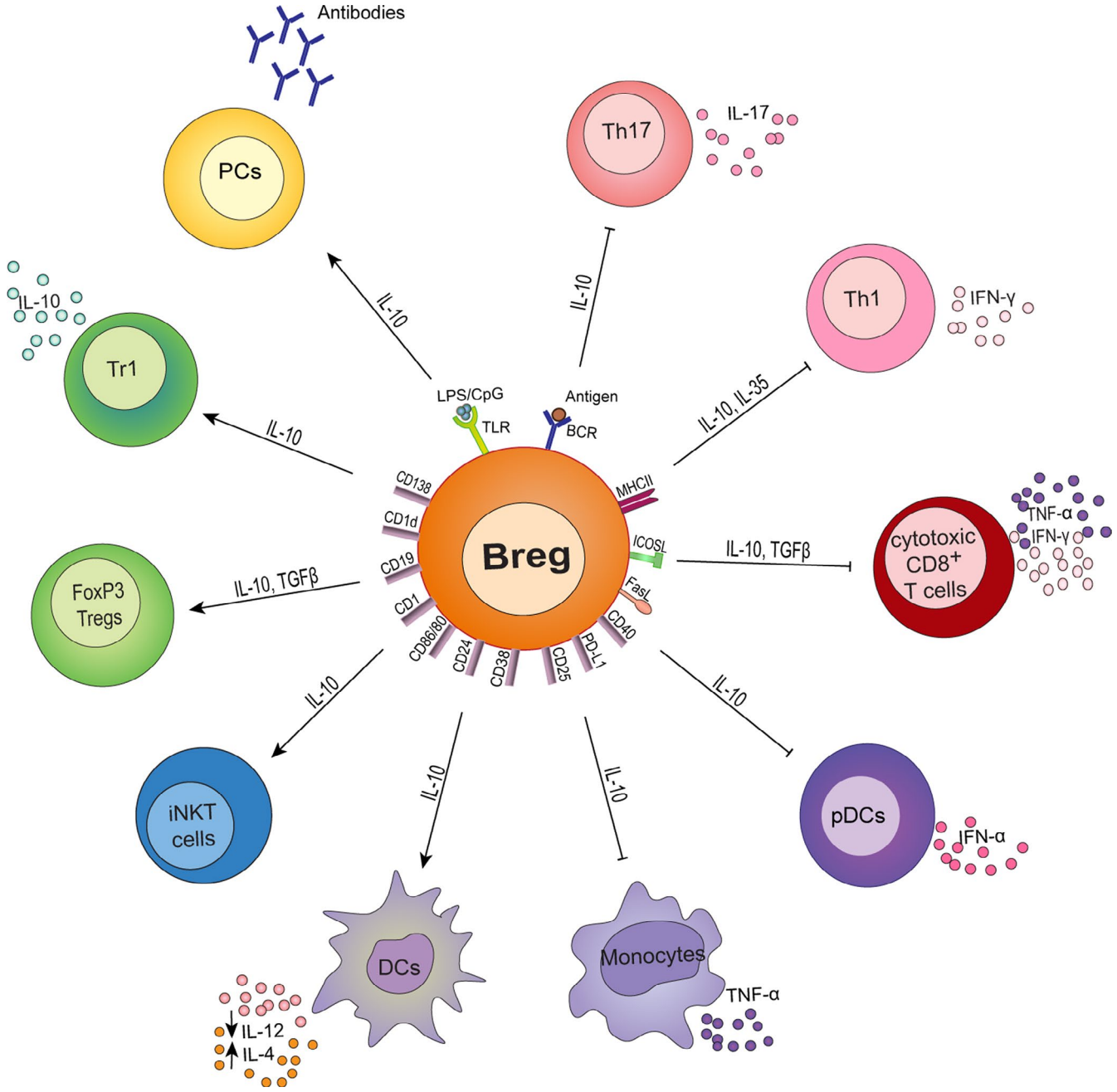

FIGURE 1 Mechanisms of immune suppression by Bregs. Human Bregs suppress Th1 and Th17 responses, and inhibit cytotoxic activity by $CD8^+$ T cells. They also induce the differentiation of $CD4^+$T cells into $FoxP3^+$ Tregs and $IL\text{-}10^+$ T regulatory-1 (Tr1) cells. In addition to modulating T cell responses, they suppress TNFα production by monocytes, IFN-α production by plasmacytoid dendritic cells (pDCs) and IL-12-producing DCs. Breg-mediated suppression of the immune response is achieved predominantly via the production of IL-10, and to an extent by TGF-β and IL-35 production. Further, immune suppression by Bregs can be mediated via co-stimulatory interactions with T cells, invariant natural killer T (iNKT) cells and DCs. Bregs support iNKT cell homeostasis by presenting lipid antigens via CD1d to the invariant T cell receptor (iTCR)

cell differentiation, expansion, somatic hypermutation, and antibody production.[55,64] It is noteworthy that resident memory B cells (BRM) are a common feature of antigen-experienced lungs, and have been shown to play an important role in acquired antiviral and anti-bacterial lung immunity.[65,66] Like the gut, B cells in the airways secrete antibodies that act both locally and at mucosal surfaces.[1,5] These antibodies are predominantly IgA and IgM that bind to glandular epithelial and mucosal surfaces and help in expelling antigens out of the body.[1,67-69] Similar to B cells activated in Peyer's patches, B cells that are activated in airway lymphoid tissues also differentiate into IgA-secreting PCs that predominantly act in the airway.[70,71] Current understand of B cell homing and class switching in the airway remains limited, with CCR10-CCL28 and α4β7-VCAM-1 interactions suggested to play an integral role

in B cell homing in the airway,[72-75] and CXCR3 found to uniquely identify BRMs.[76]

Studies of airway inflammatory diseases have recently demonstrated the involvement of B cells in disease pathology.[1] B cells act as both pro- and anti-inflammatory agents via secretion of antibodies and cytokines, as well as by antigen presentation to Th cells. Airway inflammatory diseases such as hypersensitivity, chronic obstructive pulmonary disease (COPD), asthma, sarcoidosis, idiopathic fibrosing alveolitis, lung transplant rejection, and autoimmune diseases have been strongly linked with dysfunctional B cells and their products.[1,5] For instance, B cells promote overall inflammation, Th2 responses, and eosinophilia in allergic diseases typically via the production of IgE.[77] Increased progenitor B cell subsets (pre- and pro-B cells) in the lung are capable of proliferating, resisting apoptosis and expressing chemotaxis markers (CCR10 and CXCR4) in allergic airways reactions.[78] In asthmatic lungs, an increased accumulation of tissue-resident memory B cells, IgG1-secreting cells, and BAFF levels have been associated with severe disease.[79,80] Furthermore, COPD patients display elevated levels of autoantibodies (predominantly IgG1) as well as increased numbers of B cells and ELTs in the adventitia of small airways of patients compared to controls that associate with disease severity.[81,82] Concentration of BAFF is also observed to increase in the advanced forms COPD and patients with emphysema.[83] Several phenotypes of emphysema have been linked with B cell-rich lymphoid follicles that contribute to clonal proliferation in the emphysematous lung[84,85] and associate with increased B cell signaling.[83] Similarly, lymphoid tissues with increased B cell aggregates are commonly seen in lung biopsies of patients with idiopathic pulmonary fibrosis (IPF); however, the precise role of B cells in this disease is not well demonstrated.[86,87]

Abnormalities in both circulating and tissue-resident B cell subsets have been implicated in the pathophysiology of autoimmune diseases that include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), and Sjögren's syndrome. These abnormalities include defects in B cell activation, cytokine production, induction of other immune cells, increased autoantibody production, and lymphoid organogenesis.[88-91] ELTs are thought to be a site for generating autoreactive B cells that are frequently found in the airways of patients with RA and Sjögren's syndrome.[1] Furthermore, interstitial lung disease (ILD) is a common feature of RA, SSc, and Sjögren syndrome, where lung biopsies from patients show increased B cell infiltration, B cell hyperactivation and formation of B cell-rich BALT with elevated CXCL13 and CCL21 expression (not observed in healthy individuals).[92-94] Activated B cells produce IL-6 and TGFβ that can further contribute to lung fibrosis in SSc patients.[95] In other diseases such as chronic lung transplant rejection, B cells have been shown to be key drivers of rejection via antibody production,[96,97] where secreted IgGs bound to allo-antigens activate macrophages and NKT cells through the FcγR.[96] Although not conclusively established in sarcoidosis, altered antibody responses are suspected to be one of the major drivers of disease pathogenesis, as observed by the increased IgG and IgA-secreting B cells in lung biopsies from patients compared to controls.[98,99]

Importantly, abnormalities in immunosuppressive Breg numbers and function have also been linked to various lung pathologies, highlighting the importance of Bregs in modulating airway inflammation and maintaining tissue homeostasis.[6-8,100] While Bregs are well recognized as important modulators of the airway inflammatory responses, specific signals in the lung microenvironment that induce Bregs currently remain unknown. Inflammatory signals that play an important role in Breg induction are upregulated in the lung microenvironment in infections and chronic inflammatory conditions, suggesting their potential involvement in Breg induction.[101-105]

4 | ROLE IN DISEASE

4.1 | Lung cancer

Lung cancer is currently the leading cause of cancer deaths worldwide, with a complex pathophysiology that is not well understood.[106] Bregs play an important role in suppressing anti-tumor responses and driving tumor progression by attenuating cytotoxic $CD8^+$ T cells and NK cells while promoting functions of Tregs, myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs).[105] Tumor-infiltrating Bregs have been shown to mediate immunosuppression by secreting anti-inflammatory cytokines IL-10 and TGF-β, and by upregulating expression of regulatory ligands CTLA4 and PD-L1.[107-109] Several phenotypically distinct Breg subsets have been identified in tumor settings, including $CD24^{hi}CD27^+$ memory, $CD24^{hi}CD38^{hi}$ transitional, and $CD138^+IgA^+$ or $CD147^+IgM^+$ plasma cell phenotypes.[110] A growing body of evidence suggests that tumor-infiltrating B cells are not intrinsically suppressive and that the induction of Bregs is likely upon exposure to the lung microenvironment. The expansion of $IL\text{-}10^+$ tumor-evoked Bregs has been associated with inflammatory signals derived either directly from the tumor or indirectly from tumor-infiltrating cells in the surrounding microenvironmental milieu.[110]

Studies from mouse models have provided substantial evidence supporting a role for Bregs in tumor immunity. Tumor-evoked Bregs have been shown to expand $FoxP3^+$ Tregs, induce the regulatory activity of myeloid-derived dendritic cells (MDSCs), and inhibit the tumoricidal activity of NK cells and effector T cells in a TGF-β-dependent manner.[110-113] These Bregs were found to express high levels of CD40, CD80, and CD86, suggesting the involvement of additional mechanisms of cell-contact-mediated suppression. More recently, tumor-infiltrating $PD\text{-}L1^{hi}CD80^{hi}CD86^{hi}CD69^{hi}$ B cells have been shown to suppress Th17 cell differentiation via the PD-1/PD-L1 pathway, in a model of lung cancer.[109] Interestingly, in mouse models of lung metastasis, STAT3-expressing Bregs have also been reported to promote tumor angiogenesis via the induction of vascular endothelial growth factor (VEGF); a feature strongly associated with B cells in human tumors.[114]

Albeit limited, a new wave of evidence has also implicated a role for human Bregs in lung cancer progression. Increased frequencies of peripheral IL-10-producing $CD27^+CD24^{hi}$ Bregs and

tumor-infiltrating IL-10$^+$CD19 B cells have been reported in patients with lung cancers, compared to healthy controls.[6] Together with data from murine models, these data implicate a role for Bregs in the suppression of anti-tumor immune responses. However, it is still unclear whether Bregs directly or indirectly influence the progression of lung cancer. Improved understanding of Breg induction and function in lung tumors could lead to the development of Breg-targeted therapies to enhance anti-tumor immunity.

4.2 | Infections

In addition to their effector functions, B cells also produce IL-10 that limits excessive inflammation and suppresses potential pro-inflammatory cytokine over-production. B cell-derived IL-10 acts as an immunoregulator, inhibiting pro-inflammatory responses and preventing tissue damage resulting from exacerbated innate and adaptive immune responses.[115] Here, we focus on the role of Bregs in the immune response during respiratory infections. The role of Bregs in other infection settings has been described in detail elsewhere.[115]

Respiratory viruses, such as H1N1 influenza and SARS-CoV-2 coronavirus, are a cause of severe pneumonia and acute respiratory distress syndrome (ARDS).[116,117] The virus-triggered immune response is capable of resolving an infection in a majority of individuals; however, a subset of patients generate a dysfunctional immune response resulting in severe immune-mediated lung pathology and systemic hyper-inflammation. Recent evidence suggests that the uncontrolled inflammation may be partly due to abnormalities in immunosuppressive Bregs. Critically ill COVID-19 patients display a significant decrease in peripheral CD24^{hi}CD38^{hi} transitional B cells (precursors to human Bregs[32]) mirrored by an expansion of extrafollicular B cells, compared to patients with mild disease.[118] Further, B cells from acute COVID-19 patients display a reduction in IL-10 production mirrored by an expansion of IL-6, in response to TLR activation, in comparison with healthy B cells.[119] This suggests an imbalance in circulating B cells from COVID-19 patients toward a more pro-inflammatory phenotype. The reduced IL-10$^+$ Bregs are possibly a result of impaired type I interferon (IFN-I) responses previously reported in critically unwell COVID-19 patients[120]; antiviral IFN-I is a key signal for IL-10$^+$ Breg differentiation.[11] Remarkably, IL-10$^+$ Breg frequencies, but not IL-6 expression, are normalized in COVID-19 patients upon recovery.[119] In contrast, respiratory syncytial virus (RSV) causing lower respiratory tract infections in infants is associated with an increased infiltration of pulmonary neonatal Bregs (nBregs) that secrete IL-10 in response to RSV and dampen Th1 function. The frequencies of RSV-infected nBregs have been shown to correlate with increased viral load and predict severity of acute bronchiolitis disease, suggesting that nBregs are detrimental to host response in early life.[121] While the expansion of Bregs in neonates inhibits generation of an effective immune response to the virus, the lack of functional Bregs appears to contribute to severe disease and ARDS in older adults. This is supported by multiple studies reporting an age-related numerical and functional decline in transitional Bregs that might contribute toward "inflammaging" or the chronic inflammation observed with aging.[36,122] Reduced frequency of transitional B cells as well as impaired STAT3 phosphorylation and IL-10 production in response to TLR/ CD40 activation has been reported in healthy older donors (>60 years old) compared to healthy younger donors (20-40 years old). Of note, no age-associated changes in CD80 and CD86 were observed, suggesting that contact-dependent suppressive capacity of Bregs might remain intact with age.[122]

Parasitic infections of the lung may affect the respiratory system by causing pulmonary alveolar hemorrhage, bronchiolitis, and pneumonitis.[123] Bregs suppress damaging inflammation in parasitic airway infection via the production of IL-10 and TGF-β, thus playing an essential immunosuppressive role in various helminth infections, including *Ascaris*, *Toxocara*, *Onchocerca*, *and Trichuris*.[124] In addition, IL-10-producing CD1d^{hi} Bregs were shown to induce immunomodulation by influencing FoxP3$^+$ Tregs in S *mansoni* and H *polygyrus* infections.[125,126] In contrast, studies in other infection settings have implicated a role for Breg expansion in hindering pathogen clearance. For instance, in bacterial infections such as tuberculosis (TB), caused by *Mycobacterium tuberculosis*, CD19$^+$CD1d$^+$CD5$^+$ Bregs suppress IL-22 secretion (vital in combating TB infection) and selectively inhibit Th17 responses.[7,127] Furthermore, response to TB treatment has been associated with a decrease in CD19$^+$CD1d$^+$CD5$^+$ Bregs and an increase in IL-22 production, thereby emphasizing the detrimental effects of Bregs in this infection.[127] Another unique subset of lung-resident IL-10-producing CD19$^+$B220$^-$ B cells has been shown to exacerbate *Streptococcus pneumoniae* infection.[128] Similarly, in fungal infections such as pneumocystis pneumonia (PCP), an increase in IL-10-producing Bregs has been associated with the inhibition of Th1/Th17 responses and effective pathogen clearance.[129] Overall, it appears that immunosuppressive functions of Bregs can be either detrimental or beneficial depending on the disease context.

4.3 | Allergic airway inflammation

Asthma is chronic inflammation of the airway characterized by heightened reactivity and sensitivity of the airway to a variety of inhaled stimuli.[130] Bregs play a protective role against hyperresponsive airway inflammation, where IL-10-producing B cells significantly suppress inflammatory reactions.[131] Functional impairments in Bregs have been associated with enhanced asthma-like inflammation and airway hyperresponsiveness. In mouse models of disease, adoptive transfer of CD9$^+$ Bregs suppress all asthma-related features by inhibiting effector T cells in an IL-10-dependent manner.[132] In addition, IL-10-producing CD5$^+$CD21^{hi}CD1d^{hi} Bregs can reverse allergic airway inflammation by actively recruiting immunosuppressive Tregs to the lungs.[133] Interestingly, infection with *Schistosoma mansoni* worms has been shown to protect against ovalbumin-induced allergic airway inflammation by inducing IL-10-producing T2-MZP Bregs.[134]

In contrast with hypersensitivity, pathology in chronic obstructive pulmonary disorder (COPD) is a result of proteolytic destruction

of the extracellular lung matrix by the immune response.[135] The main symptoms of COPD include chronic coughing, sputum production, and breathing difficulties. COPD patients have elevated frequencies of B cells and ELTs in their lungs[5]; however, the role of Bregs in disease pathogenesis remains unknown. Unpublished studies from our laboratory identify an expansion of Tim-1$^+$ and IL-10$^+$ Bregs in the lung of COPD patients, supporting a plausible for Bregs in modulating inflammation in disease.

Idiopathic pulmonary fibrosis (IPF) is a rare form of chronic and progressive fibrosing lung disease that is characterized by an increase in collagen deposition in the lung parenchyma; it is a type of interstitial lung disease (ILD).[136] In IPF, inhaled environmental pollutants (organic and inorganic dust) and toxins from cigarette smoke (CS) are implicated factors in the disease etiology, since by-products of these factors are frequently identified in the lungs of patients with this disease.[136] Ectopic lymphoid structures are commonly seen in lung biopsies of patients with IPF; however, the role of B cells in disease pathogenesis remains ill-defined.[86] Recent evidence suggests there is a significant decrease in CD24^{hi}CD27$^+$Bregs in IPF patients, mirrored by an increase in Tfh cells and levels of BAFF in the lungs and in circulation.[137] This suggests that a lack of Breg-mediated immunosuppression and expansion of effector B cells (Beffs) likely contribute to disease pathogenesis.

4.4 | Autoimmunity

Autoimmune diseases, including SLE, RA, SSc, and Sjogren's syndrome, can often result in pulmonary manifestations.[138] Multiple studies have identified increased infiltration of B cells in lung tissues of patients, indicating a plausible role for B cells in disease pathogenesis.[1] Although the involvement of Bregs in lung pathology remains largely uninvestigated, numerical and functional defects in circulating Bregs have been reported in patients with SLE, SSc, RA and Sjogren's syndrome, and found to associated with disease severity.[9,32,48,139] Whether the defects in Bregs are a cause or consequence of chronic inflammation remains to be addressed.

In systemic autoimmune diseases, such as SLE and SSc, reduced frequencies of circulating CD24^{hi}CD27$^+$ and CD24^{hi}CD38^{hi} Bregs have been reported in patients compared to controls.[9,32] Numerical defects are accompanied by compromised Breg functions with a significant decrease in IL-10 expression. Importantly, B cells infiltrates have been identified in the lung of SSc patients with ILD and in mouse models of pulmonary lupus.[93,140] Increased infiltration of CD20$^+$ B cells and plasma cells have also been reported in lung biopsies of RA patients with interstitial pneumonia, compared to normal lungs.[141] While the phenotype of lung-infiltrating B cells remains unknown, reduced frequencies of circulating IL-10$^+$ Breg subsets have been reported in RA patients compared to controls and found to correlate with disease severity.[48,142] These defects are associated with an expansion of pro-inflammatory effector B and T cells leading to exacerbated disease symptoms.

Due to the multiple abnormalities in the B cell compartment, patients with SLE, SSc, and RA with pulmonary manifestations are often treated with rituximab (anti-CD20) or B cell depletion therapy. Rituximab has shown success in the treatment of early and refractory pulmonary hemorrhage in patients with SLE,[143,144] as well as in improving lung function in patients with RA and SSc with ILD.[145,146] Long-term remission after B cell repopulation in rituximab-treated patients has been associated with a higher immature-to-memory B cell ratio, suggesting that repopulation of immunosuppressive CD24^{hi}CD38^{hi} Bregs might be associated with improved clinical outcomes.[147,148] This is further supported by studies reporting an expansion of CD24^{hi}CD38^{hi} Bregs with restored STAT3 activation and IL-10 production in patients responding to rituximab therapy.[11] Further, the expansion of repopulated Bregs corresponded with normalization of pDC activation and iNKT cell function.[11,49] However, it is important to note that not all patients respond to rituximab,[149] and to date, there is no strategy to predict which patients will respond to rituximab. One possible explanation is that an incomplete depletion of "pathogenic" B cells infiltrating the lung or/ and other tissue sites contributes to the lack of clinical response. A second possibility is that repopulating B cells in non-responding patients are being skewed toward pro-inflammatory Beffs and not suppressive Bregs by environmental milieu. Another scenario is that rituximab depletes beneficial tissue-resident Bregs that suppress inflammation, and therefore exacerbates disease. Overall, the underlying mechanisms that determine clinical response to rituximab remain to be ascertained.

5 | CHALLENGES AND OUTSTANDING QUESTIONS

The role of Bregs as negative regulators of the immune response is now well established. More recently, it has become evident that Bregs play a role in the pathophysiology of respiratory diseases such as lung cancer, asthma, autoimmunity, and IPF. While alterations in Breg numbers and function have been identified as contributors to disease pathology, the precise role of Bregs in disease pathogenesis remains to be ascertained. There are several aspects of Breg phenotype and function that must be addressed in order to exploit their therapeutic potential.

5.1 | Signals inducing Breg differentiation in the lung

The environmental milieu is known to play an important role in the induction of Bregs; however, specific signals in the lung microenvironment that induce Bregs remain ill-defined. In addition to TLR, BCR, and CD40 signaling, exposure to inflammatory cytokines IFN-α, IFN-β, IL-1β, IL-6, IL-21 and BAFF has been shown to enhance Breg differentiation.[2,4] These signals are upregulated in the lung microenvironment in infections and chronic inflammatory

conditions,[102,150] suggesting their involvement in Breg induction in the airways. For instance, studies from mouse models of lung cancer suggest that Breg differentiation occurs in response to the lung tumor microenvironment.[110]

The lung can experience hypoxia in pathological but sometimes also physiological situations, with associated alveolar hypoxia.[151] Moreover, cigarette smoke (CS) and CS extract activate hypoxia-inducible factor 1 (HIF-1α) in lung-epithelial cells under non-hypoxic conditions.[152] In addition to activating innate immune responses in the lung,[153] systemic hypoxia and HIF-1α could play a role in the expansion of Bregs in the lungs. Hypoxia is considered a critical factor for the induction of IL-10 by B cells and the expansion of $CD1d^{hi}CD5^{+}$ Bregs.[154] Importantly, mice with B cell-specific deletion of HIF-1α display reduced IL-10-producing B cells, and as a consequence exacerbated collagen-induced arthritis and experimental autoimmune encephalomyelitis. Thus, HIF-1α expression by B cells could play a protective role in tissue injury, and further studies are needed to determine whether or not the net effects of HIF-1 α in the context of inflammatory disease is beneficial.

As detailed above, AhR is a key transcription factor involved in Breg differentiation.[18,19] AhR and its ligands exhibit important immunomodulatory properties and can modulate the respiratory immune response.[155] On the one hand, AhR ligands have been shown to suppress allergic airway inflammation and prove beneficial in models of asthma.[156] On the other hand, the pathogenesis of COPD has been attributed to various cell populations expressing AhR. AhR has been shown to be a master regulator of inflammatory responses in innate immune cells and T cells, critical in driving COPD pathology.[157] The precise role of AhR in modulating respiratory disease appears to be disease and context-dependent. Further research is required to understand the multifaceted role of AhR in inflammatory lung diseases. Other signals that modulate Breg differentiation include commensal bacteria.[10] The importance of microbiota in the expansion of Bregs was confirmed by the treatment of mice with antibiotics; antibiotic-treated mice displayed reduced Bregs in comparison with untreated mice. Improved understanding of signals driving Breg differentiation in the lung could provide new therapeutic strategies.

5.2 | Plasticity and stability of Bregs in the lung

Another critical question is whether Bregs remain stable over time. Although abnormalities in Breg numbers and function have been associated with various respiratory diseases, the stability of lung-infiltrating Bregs remains unknown. Bregs have been identified at various stages of B cell development, and thus far, no lineage-specific transcription factor has been identified.[3] It remains unknown whether Bregs remain suppressive cells or whether they differentiate into Beffs upon exposure to chronic inflammatory conditions. Although pro-inflammatory cytokines induce Breg differentiation, the level of exposure is crucial in determining B cell fate. Whereas low-moderate concentrations of IFN-α simultaneously induce Breg and plasmablast differentiation, high concentrations have been shown to preferentially skew B cell differentiation toward Beffs and fail to expand Bregs.[11] In patients with SLE, increased IFNα signaling is associated with an expansion of autoantibody-secreting plasmablasts and a loss of Bregs, linked to alterations in STAT1/ STAT3 phosphorylation downstream of the IFN-α/β receptor. As a result, chronic exposure of B cells to increased levels of pro-inflammatory signals, such as in autoimmune diseases, could impair Breg function and enhance Beff differentiation. Although IL-10-secreting plasmablasts exhibiting immunosuppression have been identified in models of autoimmune diseases,[22] an independent study has shown that Bregs transiently secrete IL-10 and terminally differentiate into antibody-secreting cells.[158] This is further supported by studies reporting a role for plasma cell-specific transcription factor Blimp1 in the generation and function of IL-10-producing Bregs.[21] Further investigations on Breg plasticity and stability are necessary to understand the possibility of generating a prolonged Breg phenotype.

5.3 | Therapies targeting Bregs

Current therapies for various respiratory diseases focus on disease management rather than offer a cure and become toxic and ineffective over a period of time. Highly targeted immunotherapies offer several advantages over conventional steroid and immunosuppressants and have proven highly effective in the treatment of pulmonary diseases.[159,160] The use of rituximab for the treatment of pulmonary manifestations in autoimmune diseases has shown some success.[143-146] While targeting aberrant B cells is beneficial, the lack of clinical response in some patients could be associated with the depletion of immunosuppressive Bregs. Therapies targeting specific subsets of Bregs could be advantageous in different disease settings. For instance, increased infiltration of $PD\text{-}L1^{hi}$Bregs in lung tumors has provided the rationale for PD-L1 and PD-1 blockade.[161] Remarkably, studies show that targeting the PD-1/PD-L1 pathway can improve the survival of patients with advanced lung cancer.[162] Several strategies to isolate, expand, or deplete Bregs to treat various immune-related pathologies have been discussed elsewhere.[4] Taken together, these reports suggest that a better understanding of lung-infiltrating Bregs could provide novel therapeutic targets for improved management of various respiratory diseases.

6 | CONCLUSIONS

A balance in effector and regulatory responses is necessary to maintain proper immune surveillance in the lungs, while at the same time preventing chronic inflammation, fibrosis, and autoimmunity. The various airway inflammatory diseases resulting from abnormalities in Breg function emphasize the importance of immunosuppressive Bregs in maintaining immune homeostasis. Notably, the identification of multiple phenotypically distinct Breg subsets at different stages of B cell development suggest that any B cell can become regulatory upon exposure to specific environmental stimuli and

exhibit suppressive capacity. Further research into the biology of lung-infiltrating Bregs and the signals that drive Breg differentiation could provide novel therapeutic avenues for improved management of respiratory diseases.

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CONFLICT OF INTEREST

There is no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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