

INVITED REVIEW

Regulatory B cells in respiratory health and diseases

Madhvi Menon  | Tracy Hussell | Halima Ali Shuwa

Lydia Becker Institute of Immunology and Inflammation, Division of Infection, Immunity & Respiratory Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

Correspondence

Madhvi Menon, Lydia Becker Institute of Immunology and Inflammation, Division of Infection, Immunity & Respiratory Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Room 2.16, Core Technology Facility, 46 Grafton Street, Manchester M13 9PL, UK.
Email: madhvi.menon@manchester.ac.uk

Funding information

Petroleum Technology Development Fund, Grant/Award Number: SHS/1327/18

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

This article is part of a series of reviews covering Novel Frontiers in regulatory B cells appearing in Volume 299 of *Immunological Reviews*.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. *Immunological Reviews* published by John Wiley & Sons Ltd.

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-1 β 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-1 β 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 manner⁵³). 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-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 ⁺ (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 α ⁺ 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-L1 ^{high} B cells	PD-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'-monophosphate; ADO, adenosine; Br1, B regulatory 1 (Br1) cells; DC, dendritic cell; GzmB, Granzyme B; IDO, indoleamine 2,3 dioxigenase; 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-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 cells⁵⁷) that promote naïve B cell recruitment to the ELTs⁵⁸; 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

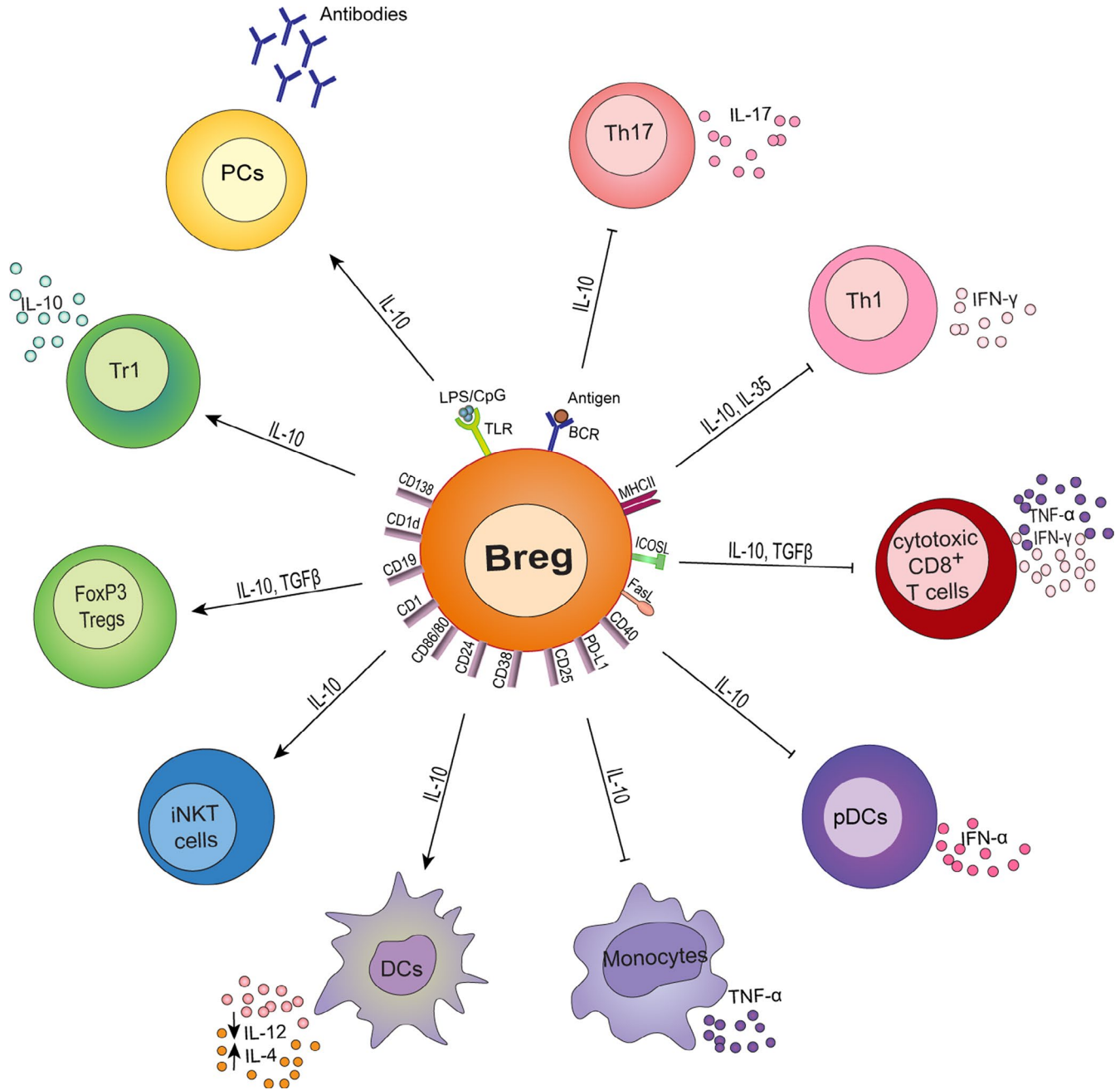


FIGURE 1 Mechanisms of immune suppression by Bregs. Human Bregs suppress Th1 and Th17 responses, and inhibit cytotoxic activity by CD8⁺ T cells. They also induce the differentiation of CD4⁺ T cells into FoxP3⁺ Tregs and IL-10⁺ T regulatory-1 (Tr1) cells. In addition to modulating T cell responses, they suppress TNF α 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 (iTTCR)

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 $\alpha 4\beta 7$ -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 TGF β 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 Fc γ R.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-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-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 Bregs³²) mirrored by an expansion of extra-follicular 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 patients¹²⁰; 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 lungs⁵; 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 role 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 be 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 infiltrate 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-1 β , 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-1 α) in lung-epithelial cells under non-hypoxic conditions.¹⁵² In addition to activating innate immune responses in the lung,¹⁵³ systemic hypoxia and HIF-1 α 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-1 α display reduced IL-10-producing B cells, and as a consequence exacerbated collagen-induced arthritis and experimental autoimmune encephalomyelitis. Thus, HIF-1 α 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 IFN α 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-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.

ACKNOWLEDGMENT

We thank PA Blair and EC Rosser for her comments on the manuscript. HA Shuwa is funded by Petroleum Technology Development Fund (SHS/1327/18).

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.

ORCID

Madhvi Menon  <https://orcid.org/0000-0003-2516-9438>

REFERENCES

- Kato A, Hulse KE, Tan BK, Schleimer RP. B-lymphocyte lineage cells and the respiratory system. *J Allergy Clin Immunol*. 2013;131:933-957.
- Mauri C, Bosma A. Immune regulatory function of B cells. *Annu Rev Immunol*. 2012;30(1):221-241.
- Mauri C, Menon M. The expanding family of regulatory B cells. *Int Immunol*. 2015;27(10):479-486.
- Mauri C, Menon M. Human regulatory B cells in health and disease: therapeutic potential. *J Clin Invest*. 2017;127(3):772-779.
- Polverino F, Seys LJM, Bracke KR, Owen CA. B cells in chronic obstructive pulmonary disease: moving to center stage. *Am J Physiol Lung Cell Mol Physiol*. 2016;311(4):L687-L695.
- Zhou J, Min Z, Zhang D, Wang W, Marincola F, Wang X. Enhanced frequency and potential mechanism of B regulatory cells in patients with lung cancer. *J Transl Med*. 2014;12:304.
- Zhang M, Zheng X, Zhang J, et al. CD19(+)/CD1d(+)/CD5(+) B cell frequencies are increased in patients with tuberculosis and suppress Th17 responses. *Cell Immunol*. 2012;274(1-2):89-97.
- Vlugt LE, Mlejnek E, Ozir-Fazalalikhani A et al. CD24(hi)CD27(+) B cells from patients with allergic asthma have impaired regulatory activity in response to lipopolysaccharide. *Clin Exp Allergy*. 2014;44(4):517-528.
- Mavropoulos A, Simopoulou T, Varna A, et al. Breg cells are numerically decreased and functionally impaired in patients with systemic sclerosis. *Arthritis Rheumatol* Hoboken NJ. 2016;68(2):494-504.
- Rosser EC, Oleinika K, Tonon S, et al. Regulatory B cells are induced by gut microbiota-driven interleukin-1 β and interleukin-6 production. *Nat Med*. 2014;20(11):1334-1339.
- Menon M, Blair PA, Isenberg DA, Mauri C. A regulatory feedback between plasmacytoid dendritic cells and regulatory B cells is aberrant in systemic lupus erythematosus. *Immunity*. 2016;44(3):683-697.
- Schubert RD, Hu Y, Kumar G, et al. IFN- β treatment requires B cells for efficacy in neuroautoimmunity. *J Immunol Baltim Md 1950*. 2015;194(5):2110-2116.
- Yoshizaki A, Miyagaki T, DiLillo DJ, Matsushita T, Kountikov EI. Regulatory B cells control T-cell autoimmunity through IL-21-dependent cognate interactions. *Nature*. 2012;491(7423):264-268.
- Yang M, Sun L, Wang S, et al. Novel function of B cell-activating factor in the induction of IL-10-producing regulatory B cells. *J Immunol Baltim Md 1950*. 2010;184(7):3321-3325.
- Wang R-X, Yu C-R, Dambuzza IM, et al. Interleukin-35 induces regulatory B cells that suppress CNS autoimmune disease. *Nat Med*. 2014;20(6):633-641.
- Li X, Mai J, Virtue A, et al. IL-35 is a novel responsive anti-inflammatory cytokine—a new system of categorizing anti-inflammatory cytokines. *PLoS One*. 2012;7(3):e33628.
- Liu B-S, Cao Y, Huizinga TW, Hafler DA, Toes REM. TLR-mediated STAT3 and ERK activation controls IL-10 secretion by human B cells. *Eur J Immunol*. 2014;44(7):2121-2129.
- Piper CJM, Rosser EC, Oleinika K, et al. Aryl hydrocarbon receptor contributes to the transcriptional program of IL-10-producing regulatory B cells. *Cell Rep*. 2019;29(7):1878-1892.e7.
- Xiao S, Bod L, Pochet N, et al. Checkpoint receptor TIGIT expressed on Tim-1+ B cells regulates tissue inflammation. *Cell Rep*. 2020;32(2):107892.
- Shapiro-Shelef M, Lin K-I, McHeyzer-Williams LJ, Liao J, McHeyzer-Williams MG, Calame K. Blimp-1 is required for the formation of immunoglobulin secreting plasma cells and pre-plasma memory B cells. *Immunity*. 2003;19(4):607-620.
- Wang Y-H, Tsai D-Y, Ko Y-A, et al. Blimp-1 contributes to the development and function of regulatory B cells. *Front Immunol*. 2019;10:1909.
- Matsumoto M, Baba A, Yokota T, et al. Interleukin-10-producing plasmablasts exert regulatory function in autoimmune inflammation. *Immunity*. 2014;41(6):1040-1051.
- Shen P, Roch T, Lampropoulou V, et al. IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases. *Nature*. 2014;507(7492):366-370.
- Pioli PD. Plasma cells, the next generation: beyond antibody secretion. *Front Immunol*. 2019;10:2768.
- Fehres CM, van Uden NO, Yeremenko NG, et al. APRIL induces a novel subset of IgA+ regulatory B cells that suppress inflammation via expression of IL-10 and PD-L1. *Front Immunol*. 2019;10:1368.
- Fillatreau S. Natural regulatory plasma cells. *Curr Opin Immunol*. 2018;55:62-66.
- Amu S, Saunders SP, Kronenberg M, Mangan NE, Atzberger A, Fallon PG. Regulatory B cells prevent and reverse allergic airway inflammation via FoxP3-positive T regulatory cells in a murine model. *J Allergy Clin Immunol*. 2010;125(5):1114-1124.e8.
- Lal G, Nakayama Y, Sethi A, Singh AK, Burrell BE, Kulkarni N. Interleukin-10 from marginal zone precursor B-cell subset is required for costimulatory blockade-induced transplantation tolerance. *Transplantation*. 2015;99(9):1817-1828.
- Alhabbab R, Blair P, Elgueta R, Stolarczyk E, Marks E, Becker PD. Diversity of gut microflora is required for the generation of B cell with regulatory properties in a skin graft model. *Sci Rep*. 2015;5:11554.
- Evans JG, Chavez-Rueda KA, Eddaoudi A, et al. Novel suppressive function of transitional 2 B cells in experimental arthritis. *J Immunol*. 2007;178(12):7868-7878.
- Watanabe R, Ishiura N, Nakashima H, et al. Regulatory B Cells (B10 Cells) have a suppressive role in murine lupus: CD19 and B10 cell deficiency exacerbates systemic autoimmunity. *J Immunol*. 2010;184(9):4801-4809.
- Blair PA, Norena LY, Flores-Borja F, Rawlings DJ, Isenberg DA, Ehrenstein MR, Mauri C. CD19(+)/CD24(hi)CD38(hi) B cells exhibit regulatory capacity in healthy individuals but are functionally impaired in systemic lupus erythematosus patients. *Immunity*. 2010;32(1):129-140.
- Sheng JR, Soliven SQB. IL-10 derived from CD1dhiCD5(+) B cells regulates experimental autoimmune myasthenia gravis. *J Neuroimmunol*. 2015;289:130-138.

34. Bankoti R, Gupta K, Levchenko A, Stager S. Marginal zone B cells regulate antigen-specific T cell responses during infection. *J Immunol.* 2012;188(8):3961-3971.
35. Miles K, Heaney J, Sibinska Z, Salter D, Savill J, Gray D. A tolerogenic role for toll-like receptor 9 is revealed by B-cell interaction with DNA complexes expressed on apoptotic cells. *Proc Natl Acad Sci USA.* 2012;109(3):887-892.
36. Blair PA, Chavez-Rueda KA, Evans JG, et al. Selective targeting of B cells with agonistic anti-CD40 is an efficacious strategy for the generation of induced regulatory T2-like B cells and for the suppression of lupus in MRL/lpr mice. *J Immunol.* 2009;182(6):3492-3502.
37. Ding Q, Yeung M, Camirand G, et al. Regulatory B cells are identified by expression of TIM-1 and can be induced through TIM-1 ligation to promote tolerance in mice. *J Clin Invest.* 2011;121(9):3645-3656.
38. Xiao S, Brooks CR, Sobel RA, Kuchroo VK. Tim-1 is essential for induction and maintenance of IL-10 in regulatory B cells and their regulation of tissue inflammation. *J Immunol.* 2015;194(4):1602-1608.
39. Khan AR, Hams E, Floudas A, Sparwasser T, Weaver CT, Fallon PG. PD-L1 hi B cells are critical regulators of humoral immunity. *Nat Commun.* 2015;6(1):5997.
40. Iwata Y, Matsushita T, Horikawa M, et al. Characterization of a rare IL-10-competent B-cell subset in humans that parallels mouse regulatory B10 cells. *Blood.* 2011;117(2):530-541.
41. Veen W, Stanic B, Yaman G, Wawrzyniak M, Sollner S, Akdis DG. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. *J Allergy Clin Immunol.* 2013;131(4):1204-1212.
42. Lindner S, Dahlke K, Sontheimer K, et al. Interleukin 21-induced granzyme B-expressing B cells infiltrate tumors and regulate T cells. *Cancer Res.* 2013;73(8):2468-2479.
43. Kaku H, Cheng KF, Al-Abed Y, Rothstein TL. A novel mechanism of B cell-mediated immune suppression through CD73 expression and adenosine production. *J Immunol.* 2014;193(12):5904-5913.
44. Saze Z, Schuler PJ, Hong C-S, Cheng D, Jackson EK, Whiteside TL. Adenosine production by human B cells and B cell-mediated suppression of activated T cells. *Blood.* 2013;122(1):9-18.
45. Aravena O, Ferrier A, Menon M, et al. TIM-1 defines a human regulatory B cell population that is altered in frequency and function in systemic sclerosis patients. *Arthritis Res Ther.* 2017;19(1):8.
46. Baba Y, Saito Y, Kotetsu Y. Heterogeneous subsets of B-lineage regulatory cells (Breg cells). *Int Immunol.* 2020;32(3):155-162.
47. Chien C-H, Chiang B-L. Regulatory T cells induced by B cells: a novel subpopulation of regulatory T cells. *J Biomed Sci.* 2017;24(1):86.
48. Flores-Borja F, Bosma A, Ng D, Reddy V, Ehrenstein MR, Isenberg DA. CD19+CD24hiCD38hi B cells maintain regulatory T cells while limiting TH1 and TH17 differentiation. *Sci Transl Med.* 2013;5:173.
49. Bosma A, Abdel-Gadir A, Isenberg DA, Jury EC, Mauri C. Lipid-antigen presentation by CD1d(+) B cells is essential for the maintenance of invariant natural killer T cells. *Immunity.* 2012;36(3):477-490.
50. Oleinika K, Rosser EC, Matei DE, et al. CD1d-dependent immune suppression mediated by regulatory B cells through modulations of iNKT cells. *Nat Commun.* 2018;9(1):684.
51. Parekh VV, Prasad DV, Banerjee PP, Joshi BN, Kumar A, Mishra GC. B cells activated by lipopolysaccharide, but not by anti-Ig and anti-CD40 antibody, induce anergy in CD8+ T cells: role of TGF-beta 1. *J Immunol.* 2003;170(12):5897-5911.
52. Tian J, Zekzer D, Hanssen L, Lu Y, Olcott A, Kaufman DL. Lipopolysaccharide-activated B cells down-regulate Th1 immunity and prevent autoimmune diabetes in nonobese diabetic mice. *J Immunol Baltim Md 1950.* 2001;167(2):1081-1089.
53. Nouël A, Pochard P, Simon Q, et al. B-Cells induce regulatory T cells through TGF-β/IDO production in a CTLA-4 dependent manner. *J Autoimmun.* 2015;1(59):53-60.
54. Salvi S, Holgate ST. Could the airway epithelium play an important role in mucosal immunoglobulin A production? *Clin Exp Allergy J Br Soc Allergy Clin Immunol.* 1999;29(12):1597-1605.
55. Carragher DM, Rangel-Moreno J, Randall TD. Ectopic lymphoid tissues and local immunity. *Semin Immunol.* 2008;20(1):26-42.
56. Barone F, Gardner DH, Nayar S, Steinthal N, Buckley CD, Luther SA. Stromal fibroblasts in tertiary lymphoid structures: a novel target in chronic inflammation. *Front Immunol.* 2016;7:477.
57. Carlsen HS, Baekkevold ES, Johansen F-E, Haraldsen G, Brandtzaeg P. B cell attracting chemokine 1 (CXCL13) and its receptor CXCR5 are expressed in normal and aberrant gut associated lymphoid tissue. *Gut.* 2002;51(3):364-371.
58. Nerviani A, Pitzalis C. Role of chemokines in ectopic lymphoid structures formation in autoimmunity and cancer. *J Leukoc Biol.* 2018;104(2):333-341.
59. Alsughayyir J, Pettigrew GJ, Motalebzadeh R. Spoiling for a fight: B lymphocytes as initiator and effector populations within tertiary lymphoid organs in autoimmunity and transplantation. *Front Immunol.* 2017;8:1639.
60. Tang H, Zhu M, Qiao J, Fu Y-X. Lymphotoxin signalling in tertiary lymphoid structures and immunotherapy. *Cell Mol Immunol.* 2017;14(10):809-818.
61. Rasheed A-U, Rahn H-P, Sallusto F, Lipp M, Müller G. Follicular B helper T cell activity is confined to CXCR5(hi)ICOS(hi) CD4 T cells and is independent of CD57 expression. *Eur J Immunol.* 2006;36(7):1892-1903.
62. Rao DA. T cells that help B cells in chronically inflamed tissues. *Front Immunol.* 2018;9:1924.
63. Stebegg M, Kumar SD, Silva-Cayetano A, Fonseca VR, Linterman MA, Graca L. Regulation of the germinal center response. *Front Immunol.* 2018;9:2469.
64. Jones GW, Jones SA. Ectopic lymphoid follicles: inducible centres for generating antigen-specific immune responses within tissues. *Immunology.* 2016;147(2):141-151.
65. Allie SR, Bradley JE, Mudunuru U, et al. The establishment of resident memory B cells in the lung requires local antigen encounter. *Nat Immunol.* 2019;20(1):97-108.
66. Barker KA, Shenoy AT, Stauffer-Smith N, et al. Lung resident memory B cells are a common and functionally significant component of lung adaptive immunity. *J Immunol.* 2020;204(1 Supplement):85.8.
67. Brandtzaeg P. Mucosal immunity: induction, dissemination, and effector functions. *Scand J Immunol.* 2009;70(6):505-515.
68. Corthésy B. Role of secretory immunoglobulin A and secretory component in the protection of mucosal surfaces. *Future Microbiol.* 2010;5(5):817-829.
69. Kaetzel CS, Robinson JK, Chintalacheruvu KR, Vaerman JP, Lamm ME. The polymeric immunoglobulin receptor (secretory component) mediates transport of immune complexes across epithelial cells: a local defense function for IgA. *Proc Natl Acad Sci.* 1991;88(19):8796-8800.
70. Kiyono H, Fukuyama S. NALT- versus Peyer's-patch-mediated mucosal immunity. *Nat Rev Immunol.* 2004;4(9):699-710.
71. Brandtzaeg P, Johansen F-E. Mucosal B cells: phenotypic characteristics, transcriptional regulation, and homing properties. *Immunol Rev.* 2005;206(1):32-63.
72. Morteau O, Gerard C, Lu B, et al. An indispensable role for the chemokine receptor CCR10 in IgA antibody secreting cell accumulation. *J Immunol Baltim Md 1950.* 2008;181(9):6309-6315.
73. Kunkel EJ, Butcher EC. Plasma-cell homing. *Nat Rev Immunol.* 2003;3(10):822-829.
74. Cook-Mills JM. VCAM-1 signals during lymphocyte migration: role of reactive oxygen species. *Mol Immunol.* 2002;39(9):499-508.
75. Xu B, Wagner N, Pham LN, et al. Lymphocyte Homing to Bronchus-associated Lymphoid Tissue (BALT) is mediated by L-selectin/PNAd, α4β1 Integrin/VCAM-1, and LFA-1 adhesion pathways. *J Exp Med.* 2003;197(10):1255-1267.

76. Onodera T, Takahashi Y, Yokoi Y, et al. Memory B cells in the lung participate in protective humoral immune responses to pulmonary influenza virus reinfection. *Proc Natl Acad Sci U S A*. 2012;109(7):2485-2490.
77. Hamelmann E, Vella AT, Oshiba A, Kappler JW, Marrack P, Gelfand EW. Allergic airway sensitization induces T cell activation but not airway hyperresponsiveness in B cell-deficient mice. *Proc Natl Acad Sci*. 1997;94(4):1350.
78. Samitas K, Malmhäll C, Rådinger M, et al. Precursor B cells increase in the lung during airway allergic inflammation: a role for B cell-activating factor. *PLoS One*. 2016;11(8):e0161161.
79. Turner DL, Verter J, Turner R, Cao M. Tissue resident memory B cells established in lungs in allergic asthma. *J Immunol*. 2017;198(1 Supplement):71.3.
80. Habener A, Behrendt A-K, Skuljec J, Jirmo AC, Meyer-Bahlburg A, Hansen G. B cell subsets are modulated during allergic airway inflammation but are not required for the development of respiratory tolerance in a murine model. *Eur J Immunol*. 2017;47(3):552-562.
81. Kirkham PA, Caramori G, Casolari P, et al. Oxidative stress-induced antibodies to carbonyl-modified protein correlate with severity of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2011;184(7):796-802.
82. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(26):2645-2653.
83. Faner R, Cruz T, Casserras T, et al. Network analysis of lung transcriptomics reveals a distinct B-Cell signature in emphysema. *Am J Respir Crit Care Med*. 2016;193(11):1242-1253.
84. Baraldo S, Turato G, Lunardi F, et al. Immune activation in α 1-antitrypsin-deficiency emphysema. Beyond the protease-antiprotease paradigm. *Am J Respir Crit Care Med*. 2015;191(4):402-409.
85. van der Strate BWA, Postma DS, Brandsma C-A, et al. Cigarette smoke-induced emphysema: A role for the B cell? *Am J Respir Crit Care Med*. 2006;173(7):751-758.
86. Todd NW, Scheraga RG, Galvin JR, et al. Lymphocyte aggregates persist and accumulate in the lungs of patients with idiopathic pulmonary fibrosis. *J Inflamm Res*. 2013;6:63-70.
87. Xue J, Kass DJ, Bon J, et al. Plasma B lymphocyte stimulator and B cell differentiation in idiopathic pulmonary fibrosis patients. *J Immunol Baltim Md 1950*. 2013;191(5):2089-2095.
88. Feng Y, Yang M, Wu H, Lu Q. The pathological role of B cells in systemic lupus erythematosus: From basic research to clinical. *Autoimmunity*. 2020;53(2):56-64.
89. Bugatti S, Vitolo B, Caporali R, Montecucco C, Manzo A. B cells in rheumatoid arthritis: from pathogenic players to disease biomarkers. *BioMed Res Int*. 2014;2014:681678.
90. Yoshizaki A. Pathogenic roles of B lymphocytes in systemic sclerosis. *Immunol Lett*. 2018;195:76-82.
91. Nocturne G, Mariette X. B cells in the pathogenesis of primary Sjögren syndrome. *Nat Rev Rheumatol*. 2018;14(3):133-145.
92. Rangel-Moreno J, Hartson L, Navarro C, Gaxiola M, Selman M, Randall TD. Inducible bronchus-associated lymphoid tissue (iBALT) in patients with pulmonary complications of rheumatoid arthritis. *J Clin Invest*. 2006;116(12):3183-3194.
93. Lafyatis R, O'Hara C, Feghali-Bostwick CA, Matteson E. B cell infiltration in systemic sclerosis-associated interstitial lung disease. *Arthritis Rheum*. 2007;56(9):3167-3168.
94. Salomonsson S, Jonsson MV, Skarstein K, et al. Cellular basis of ectopic germinal center formation and autoantibody production in the target organ of patients with Sjögren's syndrome. *Arthritis Rheum*. 2003;48(11):3187-3201.
95. Sakkas LI, Bogdanos DP. Systemic sclerosis: New evidence re-enforces the role of B cells. *Autoimmun Rev*. 2016;15(2):155-161.
96. Levine DJ, Glanville AR, Aboyoun C, et al. Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant*. 2016;35(4):397-406.
97. Roux A, Bendib Le Lan I, Holifanjaniaina S, et al. Antibody-mediated rejection in lung transplantation: clinical outcomes and donor-specific antibody characteristics. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2016;16(4):1216-1228.
98. Hunninghake GW, Crystal RG. Mechanisms of hypergammaglobulinemia in pulmonary sarcoidosis. Site of increased antibody production and role of T lymphocytes. *J Clin Invest*. 1981;67(1):86-92.
99. Kamphuis LS, van Zelm MC, Lam KH, et al. Perigranuloma localization and abnormal maturation of B cells. *Am J Respir Crit Care Med*. 2013;187(4):406-416.
100. Matsushita T, Hamaguchi Y, Hasegawa M, Takehara K, Fujimoto M. Decreased levels of regulatory B cells in patients with systemic sclerosis: association with autoantibody production and disease activity. *Rheumatology*. 2016;55(2):263-267.
101. Su D-L, Lu Z-M, Shen M-N, Li X, Sun L-Y. Roles of pro- and anti-inflammatory cytokines in the pathogenesis of SLE. *J Biomed Biotechnol*. 2012;2012:347141.
102. Vazquez MI, Catalan-Dibene J, Zlotnik A. B cells responses and cytokine production are regulated by their immune microenvironment. *Cytokine*. 2015;74(2):318-326.
103. Mohd Jaya FN, Garcia SG, Borràs FE, Chan GCF, Franquesa M. Paradoxical role of Breg-inducing cytokines in autoimmune diseases. *J Transl Autoimmun*. 2019;1(2):100011.
104. Landskron G, De la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA. Chronic inflammation and cytokines in the tumor microenvironment. *J Immunol Res*. 2014;2014:149185.
105. Patel AJ, Richter A, Drayson MT, Middleton GW. The role of B lymphocytes in the immuno-biology of non-small-cell lung cancer. *Cancer Immunol Immunother*. 2020;69(3):325-342.
106. Miller YE. Pathogenesis of lung cancer: 100 year report. *Am J Respir Cell Mol Biol*. 2005;33(3):216-223.
107. Xiao X, Lao X-M, Chen M-M, et al. PD-1hi identifies a novel regulatory B-cell population in human hepatoma that promotes disease progression. *Cancer Discov*. 2016;6(5):546-559.
108. Varn FS, Wang Y, Cheng C. A B cell-derived gene expression signature associates with an immunologically active tumor microenvironment and response to immune checkpoint blockade therapy. *Oncoimmunology*. 2019;8(1):e1513440.
109. Zhang Y, Morgan R, Chen C, et al. Mammary-tumor-educated B cells acquire LAP/TGF- β and PD-L1 expression and suppress anti-tumor immune responses. *Int Immunol*. 2016;28(9):423-433.
110. Sarvaria A, Madrigal JA, Saudemont A. B cell regulation in cancer and anti-tumor immunity. *Cell Mol Immunol*. 2017;14(8):662-674.
111. Wang WW, Yuan XL, Chen H, et al. CD19+CD24hiCD38hiBregs involved in downregulate helper T cells and upregulate regulatory T cells in gastric cancer. *Oncotarget*. 2015;6(32):33486-33499.
112. Bodogai M, Moritoh K, Lee-Chang C, et al. Immunosuppressive and prometastatic functions of myeloid-derived suppressive cells rely upon education from tumor-associated B cells. *Cancer Res*. 2015;75(17):3456-3465.
113. Olkhanud PB, Damdinsuren B, Bodogai M, et al. Tumor-evoked regulatory B cells promote breast cancer metastasis by converting resting CD4⁺ T cells to T-regulatory cells. *Cancer Res*. 2011;71(10):3505-3515.
114. Yang C, Lee H, Pal S, et al. B cells promote tumor progression via STAT3 regulated-angiogenesis. *PLoS One*. 2013;8(5):e64159.
115. Dai Y-C, Zhong J, Xu J-F. Regulatory B cells in infectious disease (Review). *Mol Med Rep*. 2017;16(1):3-10.
116. Tang X, Du R-H, Wang R, et al. Comparison of hospitalized patients with ARDS caused by COVID-19 and H1N1. *Chest*. 2020;158(1):195-205.
117. Torres Acosta MA, Singer BD. Pathogenesis of COVID-19-induced ARDS: implications for an ageing population. *Eur Respir J*. 2020;56(3):2002049.

118. Woodruff M, Ramonell R, Cashman K, et al. Dominant extrafollicular B cell responses in severe COVID-19 disease correlate with robust viral-specific antibody production but poor clinical outcomes. *medRxiv*. 2020;2020.04.29.20083717.
119. Shuwa HA, Shaw TN, Knight SB, et al. *Long-Lasting Alterations in T and B Cell Function in Convalescent COVID-19 Patients* [Internet]. Rochester, NY: Social Science Research Network; 2020 Oct [cited 2020 Nov 22]. Report No.: ID 3720301. Available from: <https://papers.ssrn.com/abstract=3720301>
120. Acharya D, Liu G, Gack MU. Dysregulation of type I interferon responses in COVID-19. *Nat Rev Immunol*. 2020;20(7):397-398.
121. Zhivaki D, Lemoine S, Lim A, et al. Respiratory syncytial virus infects regulatory B cells in human neonates via chemokine receptor CX3CR1 and promotes lung disease severity. *Immunity*. 2017;46(2):301-314.
122. Duggal NA, Upton J, Phillips AC, Sapey E, Lord JM. An age-related numerical and functional deficit in CD19(+) CD24(hi) CD38(hi) B cells is associated with an increase in systemic autoimmunity. *Aging Cell*. 2013;12(5):873-881.
123. Cheepsattayakorn A, Cheepsattayakorn R. Parasitic pneumonia and lung involvement. *BioMed Res Int*. 2014;2014:874021.
124. McSorley HJ, Chayé MAM, Smits HH. Worms: Pernicious parasites or allies against allergies? *Parasite Immunol*. 2019;41(6):e12574.
125. Wilson MS, Taylor MD, O'Gorman MT, et al. Helminth-induced CD19+CD23hi B cells modulate experimental allergic and autoimmune inflammation. *Eur J Immunol*. 2010;40(6):1682-1696.
126. van der Vlugt LEPM, Labuda LA, Ozir-Fazalalikhani A, et al. Schistosomes induce regulatory features in human and mouse CD1d(hi) B cells: inhibition of allergic inflammation by IL-10 and regulatory T cells. *PLoS One*. 2012;7(2):e30883.
127. Loxton AG. Bcells and their regulatory functions during Tuberculosis: Latency and active disease. *Mol Immunol*. 2019;1(111):145-151.
128. Stark A-K, Chandra A, Chakraborty K, et al. PI3K δ hyper-activation promotes development of B cells that exacerbate Streptococcus pneumoniae infection in an antibody-independent manner. *Nat Commun*. 2018;9(1):3174.
129. Rong H-M, Li T, Zhang C, et al. IL-10-producing B cells regulate Th1/Th17-cell immune responses in Pneumocystis pneumonia. *Am J Physiol-Lung Cell Mol Physiol*. 2018;316(1):L291-301.
130. Murdoch JR, Lloyd CM. Chronic inflammation and asthma. *Mutat Res*. 2010;690(1-2):24-39.
131. Habener A, Happel C, Skuljec J, et al. B cells are crucial in the regulation of airway hyperreactivity in an experimental model of asthma. *Eur Respir J*. 2019;54(suppl 63):PA4362.
132. Brosseau C, Durand M, Colas L, et al. CD9+ regulatory B cells induce T cell apoptosis via IL-10 and are reduced in severe asthmatic patients. *Front Immunol*. 2018;9:3034.
133. Tedder TF, Matsushita T. Regulatory B cells that produce IL-10: a breath of fresh air in allergic airway disease. *J Allergy Clin Immunol*. 2010;125(5):1125-1127.
134. Fallon PG, Mangan NE. Suppression of TH2-type allergic reactions by helminth infection. *Nat Rev Immunol*. 2007;7(3):220-230.
135. MacNee W. Pathogenesis of chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2005;2(4):258-266.
136. Sgalla G, Iovene B, Calvello M, Ori M, Varone F, Richeldi L. Idiopathic pulmonary fibrosis: pathogenesis and management. *Respir Res*. 2018;19(1):32.
137. Asai Y, Chiba H, Nishikiro H, et al. Aberrant populations of circulating T follicular helper cells and regulatory B cells underlying idiopathic pulmonary fibrosis. *Respir Res*. 2019;20(1):244.
138. Cojocar M, Cojocar IM, Silosi I, Vrabie CD. Pulmonary manifestations of systemic autoimmune diseases. *Mædica*. 2011;6(3):224-229.
139. Lin W, Jin L, Chen H, et al. B cell subsets and dysfunction of regulatory B cells in IgG4-related diseases and primary Sjögren's syndrome: the similarities and differences. *Arthritis Res Ther*. 2014;16(3):R118.
140. Singh RR, Prasad P, Fishbein M, Valera I. II-07 Pathogenesis of pulmonary lupus and vasculitis: trafficking of innate B1 B cells to the lungs as a novel mechanism. *Lupus Sci Amp Med*. 2018;5(Suppl 2):A63.
141. Atkins SR, Turesson C, Myers JL, et al. Morphologic and quantitative assessment of CD20+ B cell infiltrates in rheumatoid arthritis-associated nonspecific interstitial pneumonia and usual interstitial pneumonia. *Arthritis Rheum*. 2006;54(2):635-641.
142. Ma L, Liu B, Jiang Z, Jiang Y. Reduced numbers of regulatory B cells are negatively correlated with disease activity in patients with new-onset rheumatoid arthritis. *Clin Rheumatol*. 2014;33(2):187-195.
143. Narshi CB, Haider S, Ford CM, Isenberg DA, Giles IP. Rituximab as early therapy for pulmonary haemorrhage in systemic lupus erythematosus. *Rheumatology*. 2010;49(2):392-394.
144. Pinto LF, Candia L, Garcia P, et al. Effective treatment of refractory pulmonary hemorrhage with monoclonal anti-CD20 antibody (Rituximab). *Respiration*. 2009;78(1):106-109.
145. Mohammed AGA, Alshihre A, Al-Homood IA. Rituximab treatment in patients with systemic sclerosis and interstitial lung disease. *Ann Thorac Med*. 2017;12(4):294-297.
146. Fui A, Bergantini L, Selvi E, et al. Rituximab therapy in interstitial lung disease associated with rheumatoid arthritis. *Intern Med J*. 2020;50(3):330-336.
147. Palanichamy A, Barnard J, Zheng B, et al. Novel human transitional B cell populations revealed by B cell depletion therapy. *J Immunol Baltim Md 1950*. 2009;182(10):5982-5993.
148. Anolik JH, Barnard J, Owen T, et al. Delayed memory B cell recovery in peripheral blood and lymphoid tissue in systemic lupus erythematosus after B cell depletion therapy. *Arthritis Rheum*. 2007;56(9):3044-3056.
149. Crickx E, Weill J-C, Reynaud C-A, Mahévas M. Anti-CD20-mediated B-cell depletion in autoimmune diseases: successes, failures and future perspectives. *Kidney Int*. 2020;97(5):885-893.
150. Didierlaurent A, Goulding J, Hussell T. The impact of successive infections on the lung microenvironment. *Immunology*. 2007;122(4):457-465.
151. Sarkar M, Niranjana N, Banyal P. Mechanisms of hypoxemia. *Lung India Off Organ Indian Chest Soc*. 2017;34(1):47-60.
152. Daijo H, Hoshino Y, Kai S, et al. Cigarette smoke reversibly activates hypoxia-inducible factor 1 in a reactive oxygen species-dependent manner. *Sci Rep*. 2016;29(6):34424.
153. Harris AJ, Thompson AR, Whyte MK, Walmsley SR. HIF-mediated innate immune responses: cell signaling and therapeutic implications. *Hypoxia*. 2014;24(2):47-58.
154. Meng X, Grötsch B, Luo Y, et al. Hypoxia-inducible factor-1 α is a critical transcription factor for IL-10-producing B cells in autoimmune disease. *Nat Commun*. 2018;9(1):251.
155. Beamer CA, Shepherd DM. Role of the aryl hydrocarbon receptor (AhR) in lung inflammation. *Semin Immunopathol*. 2013;35(6):693-704.
156. Chang Y-D, Li C-H, Tsai C-H, Cheng Y-W, Kang J-J, Lee C-C. Aryl hydrocarbon receptor deficiency enhanced airway inflammation and remodeling in a murine chronic asthma model. *FASEB J Off Publ Fed Am Soc Exp Biol*. 2020;34(11):15300-15313.
157. Chiba T, Chihara J, Furue M. Role of the arylhydrocarbon receptor (AhR) in the pathology of asthma and COPD. *J Allergy*. 2012;2012:372384.
158. Maseda D, Smith SH, DiLillo DJ, et al. Regulatory B10 cells differentiate into antibody-secreting cells after transient IL-10 production in vivo. *J Immunol Baltim Md 1950*. 2012;188(3):1036-1048.
159. Picard C. The lungs and immunosuppressants: practical problems. *Rev Pneumol Clin*. 2011;67(4):226-232.

160. Massarelli E, Papadimitrakopoulou V, Welsh J, Tang C, Tsao AS. Immunotherapy in lung cancer. *Transl Lung Cancer Res*. 2014;3(1):53-63.
161. Sun X, Zhang T, Li M, Yin L, Xue J. Immunosuppressive B cells expressing PD-1/PD-L1 in solid tumors: A mini review. *QJM Mon J Assoc Physicians*. 2019; Epub ahead of print. <https://doi.org/10.1093/qjmed/hcz162>
162. Schulze AB, Schmidt LH. PD-1 targeted Immunotherapy as first-line therapy for advanced non-small-cell lung cancer patients. *J Thorac Dis*. 2017;9(4):E384-E386.

How to cite this article: Menon M, Hussell T, Ali Shuwa H. Regulatory B cells in respiratory health and diseases. *Immunol Rev*. 2021;299:61-73. <https://doi.org/10.1111/imr.12941>