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B10 Cells: A Functionally Defined Regulatory B Cell Subset

Thomas F. Tedder

B cells are commonly thought to enhance inflammatory immune responses. However, specific regulatory B cell subsets recently were identified that downregulate adaptive and innate immunity, inflammation, and autoimmunity through diverse molecular mechanisms. In both mice and humans, a rare, but specific, subset of regulatory B cells is functionally characterized by its capacity to produce IL-10, a potent inhibitory cytokine. For clarity, this regulatory B cell subset has been labeled as B10 cells, because their ability to downregulate immune responses and inflammatory disease is fully attributable to IL-10, and their absence or loss exacerbates disease symptoms in mouse models. This review preferentially focuses on what is known about mouse B10 cell development, phenotype, and effector function, as well as on mechanistic studies that demonstrated their functional importance during inflammation, autoimmune disease, and immune responses. The Journal of Immunology, 2015, 194: 1395–1401.

B cells are generally thought to augment immune responses. However, B cells also can suppress immune responses in a variety of mouse models of autoimmunity and inflammation. Mizoguchi et al. (1, 2) first coined the term regulatory B cell to describe B cells that suppress disease in a mouse inflammatory bowel disease (IBD) model. Similarly, the absence or loss of B cells with regulatory activities exacerbates disease symptoms in models of experimental autoimmune encephalomyelitis (EAE) (3–7), type 1 diabetes (8), collagen-induced arthritis (9–11), contact hypersensitivity (12, 13), lupus (14–16), and allergy (17). The identification and evolving characterization of regulatory B cells and their potential mechanisms of action were comprehensively reviewed elsewhere (18–22). Therefore, this review specifically focuses on mouse regulatory B cells that produce IL-10, a potent inhibitory cytokine with pleiotropic activities in vitro and in vivo, whereas it is appreciated that monocytes, T cell subsets, and other cells also can produce IL-10 (23).

Regulatory B cells

Because the existence of regulatory B cells is well documented, the current challenge is to comprehend the diversity of B cell subsets with regulatory function that have been described, particularly those that influence immune responses through mechanistically distinct pathways. In many cases, regulatory B cells inhibit inflammation and disease through the production of either IL-10 alone or in combination with other immunomodulatory cytokines or cell surface receptors. However, IL-10 expression by B cells is not always necessary to suppress inflammation, and multiple regulatory B cell subsets and mechanisms for reducing inflammation are likely to exist. The complexity of this issue was well demonstrated in studies of IBD. Mizoguchi et al. (24) first showed that regulatory B cells from the mesenteric lymph nodes of TCRα−/− mice and their Ab products suppress colitis by enhancing the clearance of apoptotic cells. Ab blockade of the CD40 or B7-2 costimulatory molecules on adoptively transferred B cells also eliminates their suppressive regulatory effects on pathogenic T cells (1). This group subsequently showed that IL-10 production by CD1dhigh B cells within the mesenteric lymph nodes of TCRα−/− mice inhibits chronic intestinal inflammation (2). However, they also demonstrated a regulatory role for peritoneal cavity B1 cells from TCRα−/− mice during chronic colitis, possibly through natural Ab generation in response to microbial flora (25). In studies by other investigators, mesenteric lymph node B cells in combination with CD8+ T cells protect mice from colitis induced by Gαi2−/− CD4+ T cells by instigating the formation of immunosuppressive T cells (26). Whether these regulatory activities and mechanisms of action are attributable to a single B cell subset or functionally diverse B cell populations during IBD is unresolved.

Wolf et al. (3) first demonstrated a requirement for B cells during recovery from EAE, with mice rarely returning to normal in the absence of B cells. Dittel and colleagues (27) subsequently demonstrated that B cell deficiency and the absence of B7 expression delayed the emergence of Foxp3+ regulatory T cells (Tregs) and IL-10 in the CNS during EAE. However, most recently, they demonstrated a novel IL-10−/−, B7−, and MHC class II–independent regulatory role for B cells in suppressing autoimmunity by the maintenance of Tregs via GITR ligand (28). In contrast, B cell IL-10 production dramatically modulated EAE resolution in a separate study (4). IL-10–competent B cells control EAE initiation (6), whereas Tregs and IL-10–competent B cells independently influence EAE resolution (7, 29, 30). Thus, functionally distinct B cell subsets may regulate autoimmune responses at different times.

Department of Immunology, Duke University Medical Center, Durham, NC 27710

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Address correspondence and reprint requests to Dr. Thomas F. Tedder, Box 3010, Department of Immunology, Room 353 Jones Building, Research Drive, Duke University Medical Center, Durham, NC 27710. E-mail address: thomas.tedder@duke.edu

Abbreviations used in this article: B10pro, progenitor B10 cell; EAE, experimental autoimmune encephalomyelitis; IBD, inflammatory bowel disease; PIM, PMA, ionomycin, and monensin; TIM-1, T cell Ig domain and mucin domain protein 1; Treg, Foxp3+ regulatory T cell.

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The reality that diverse molecular mechanisms and cell subsets contribute to regulatory B cell suppression of disease has created confusion, which is exacerbated by the different experimental approaches, phenotypes, and assays used to describe these cells. In particular, most studies fractionated B cells into subsets using phenotypic markers and then characterized these B cell subsets based on their level of regulatory activity in different disease models (21). An alternative approach was used that specifically characterizes regulatory B cell subsets based on their functional capacity. In particular, we focused on characterizing the B cells that selectively produce IL-10, regardless of their cell surface phenotype or tissue location. For clarity, this IL-10–producing regulatory B cell subset was labeled as B10 cells to highlight that IL-10 predominantly accounts for their regulatory function during inflammation, autoimmune disease, and other adaptive and innate immune responses (6, 7, 13, 15, 31–33), as well as to distinguish them from other regulatory B cell subsets that function through different molecular pathways. This review highlights our current understanding of mouse B10 cell function with remarks on tolerance regulation and therapeutic potential.

**B10 cell identification by function**

Currently, there are no phenotypic, transcription factor, or lineage markers that are unique to B10 cells. Therefore, B10 cells in mice and humans are functionally defined and enumerated by their competence to express measurable IL-10 following 5 h of ex vivo stimulation with PMA and ionomycin (13, 32, 34). This combination of stimuli induces and enhances lymphocyte translation of cytokine genes that are in an accessible configuration for transcription, resulting in measurable IL-10 protein production and secretion by B10 effector cells (Fig. 1A). Monensin is included in these cultures to enhance cytoplasmic IL-10 staining by blocking protein effector cells (35, 40). IL-10 reporter B-Green mice also express IL-10 during 5-h assays (Fig. 1A). However, B10+B10pro cells functionally mature into B10 cells following ex vivo PIM stimulation, but it persists on B cells from naive mice, while B10+B10pro cells respond <0.2% of total B cells in naive mice, but GFP expression mimics cytoplasmic IL-10 induction following PIM stimulation ex vivo. 10BiT mice have multiple bacterial artificial chromosome transgene insertions that drive Thy1.1 expression under the control of *il10* regulatory elements (39). Cell surface Thy1.1 expression is not measurable on B cells from naive mice and is delayed relative to IL-10 expression following ex vivo PIM stimulation, but it persists on the cell surface following the termination of IL-10 expression, allowing for the surveillance of B10 effector cells post–IL-10 production (38). B10 cell frequencies increase 2–4-fold in Tiger and 10BiT mice following in vivo stimulation (38). Only 1% of peritoneal cavity B cells from Tiger mice express GFP ex vivo, whereas up to 3% express GFP following intestinal injury, demonstrating that gut inflammation induces B10 effector cells (35, 40). IL-10 reporter B-Green mice also have GFP sequences inserted into the *il10* gene downstream of the translation stop site (41). However, GFP+ B cells are only measurable in B-Green mice following *Salmonella* infection. Vert-X mice carry an IRES-GFP reporter inserted between the endogenous *il10* gene stop codon and the poly(A) attachment signal sequence (42). In naive Vert-X mice, 1.1% of spleen B cells express GFP ex vivo, whereas 14% express GFP after LPS exposure. Thus, B10 effector cells are found at low frequencies in mouse models of intestinal injury or infection where B10 cells are known to regulate disease severity.

**Phenotype/lineage/profession**

A variety of cell surface markers have been proposed for different regulatory B cell subsets (21, 22). The generalized ex vivo phenotype of B10 cells from untreated mice is IgM<sup>high</sup>IgD<sup>low</sup>CD1<sub>1d</sub>><sup>high</sup>CD5<sup>CD19<sub>high</sub>CD23<sub>low</sub>CD22<sub>high</sub>, with <10% coexpressing IgG or IgA (13, 15, 35, 38). Thereby, spleen B10 cells share surface markers with multiple phenotypically defined B cell subsets, including transitional, marginal zone, marginal zone precursor, memory, and B1 cells (6, 11, 13–15, 38, 41, 43, 44). Spleen B10 cells are enriched within the CD1<sub>1d</sub><sup>high</sup>CD5<sup>CD19<sub>high</sub>subpopulation (Fig. 2), where 15–20% are B10 cells, and up to 50% are B10+B10pro cells (6, 13, 15, 29). Small numbers of B10 cells are also found within other spleen B cell fractions. The phenotype of B10pro cells after culture reflects their in vitro activation more than their subset of origin. For example, most mouse and human B cells upregulate CD5 expression following CD40 stimulation in...
vitro (31, 32). Spleen IL-10+ B cells are also enriched within the T cell Ig domain and mucin domain protein 1 (TIM-1)+ compartment, and TIM-1+B cells are enriched in the CD1dhighCD5+ compartment (45). However, IL-10+ B cells are also present in the TIM-1− compartment, and TIM-1+B cells are present in the non-CD1dhighCD5+ compartment. Thereby, intracellular IL-10 staining remains the only way to visualize the entire B10 cell subset.

Although the developmental relationships between phenotypically defined B cell subsets are undoubtedly complex, spleen IL-10+ B cells are also enriched within the T cell Ig domain and mucin domain protein 1 (TIM-1)− compartment, and TIM-1+ B cells are enriched in the CD1dhighCD5+ compartment (45). However, IL-10+ B cells are also present in the TIM-1− compartment, and TIM-1− B cells are present in the non-CD1dhighCD5+ compartment. Thereby, intracellular IL-10 staining remains the only way to visualize the entire B10 cell subset.

B10 cells can be isolated using commercial cytokine-capture assays following activation with PMA and ionomycin to induce IL-10 secretion (31). That B10 and B10pro cells preferentially localize within the CD1dhighCD5+ B cell fraction also provides a convenient means to isolate a spleen population enriched in unstimulated B10 cells for functional and adoptive-transfer experiments. However, the CD1dhighCD5+ subset predominantly contains non-B10 cells that may have diverse functions. To control for this, it is critical to demonstrate that IL-10 production fully accounts for the regulatory activities of the cells being studied by using comparable B cells from IL-10−/− mice, as one example. IL-10−/− mice have normal numbers of spleen B cells and normal frequencies of CD1dhigh and CD5+ B cells (7, 31), peritoneal cavity B1a, B1b, and B2 cells (35), and IgM-secreting B cells (38), and they develop normal T cell–dependent Ab responses (47) prior to their development of inflammation and disease. Moreover, autocrine IL-10 is not required for B10 cell development (38), although IL-10 is reported to have an autocrine effect on mouse B1 cells (48).

Using the size of the CD1dhighCD5+ B cell compartment or other phenotypic subsets as surrogate markers for B10 cell expansion are not justifiable, because phenotype and IL-10 competence are not synonymous. For example, most B10 cells are CD5+, but B10 cells only represent a subset of CD5+. Additional experiments are required to confirm that the B10 cell is a distinct subset of B cells with unique functional properties.

**FIGURE 1.** Models for mouse B10 cell function. (A) The functional development of B10 and B10pro cells. B10 cells are functionally defined by their ability to express measurable cytoplasmic IL-10 after 5 h of PIM stimulation. Ex vivo stimulation induces B10pro cells to acquire IL-10 competence, while B10 effector cells (B10eff) cells actively secrete IL-10. B10pro and B10 cells within the spleen predominantly display a CD1dhighCD5+ cell surface phenotype. B10pro and B10 cells variably express CD5 and high CD1d depending on their tissue of origin. BCR signals are required for B10pro cell development; thereafter, CD40 signals, LPS or IL-21 can induce their functional maturation and ability to become B10eff cells. IL-10 reporter Tiger or 10BiT mice express GFP or Thy1.1 with delayed kinetics relative to IL-10, with the expression of GFP and Thy1.1 serving as more durable markers than IL-10 expression. After terminating IL-10 production, a small fraction of B10eff cells can differentiate into Ab-secreting plasma cells in vivo that secrete germline Abs with polyreactive, autoreactive or Ag-specific reactivity. (B) Model for B10 cell regulation of Ag-specific immunity. Some B cells capture select Ags that trigger appropriate BCR transmembrane signals (lightning bolt, step 1) and promote B10pro cell generation. During immune responses, B10pro cells present peptides to Ag-specific T cells through cognate MHC-class II (MHC II) interactions (step 2) that induce T cell activation and CD40/CD154 interactions, thereby inducing B10 cell IL-10 competence (step 3). Activated T cells then produce IL-21 locally, which binds to proximal B10 cell IL-21R (step 4). IL-21R signals induce B10 cell IL-10 production and effector function (step 5), which suppresses the activation of proximal Ag-specific T cells (step 6, ref. 29) and innate macrophage function (step 7, ref. 52). Absence of the correct BCR, CD40, MHC-class II, IL-21R, CD4+ T cells or IL-10 eliminates B10 effector cell function in vivo.
wedge sizes denote relative B cell numbers of each subset. B cells (Fig. 2). Additionally, CD5⁺ or CD1d⁺CD5⁺ B cell frequencies do not predict B10 cell frequencies in different models of disease, strains of mice, or lines of transgenic mice (31). Although most B cells in NOD and SJL mice are CD5⁺, only a few have the capacity to express IL-10 ex vivo or following in vitro stimulation. Thus, B10 cells represent a functionally programmed B cell subset that pursues a regulatory “profession” through their capacity to express IL-10.

Ag regulates B10 cell development

B10pro and B10 cell development is not stochastic, because their numbers are reduced dramatically in transgenic mice with a fixed BCR (31) and in mice with decreased BCR signaling, such as CD19-deficient (CD19⁻/⁻) mice, whereas CD19 overexpression expands B10 cell numbers (13, 31). The absence of B10 cells in CD19⁺/⁺ mice leads to exacerbated inflammation and disease symptoms during contact hypersensitivity, EAE, and IBD (6, 13, 40). In contrast, increasing CD40 signaling by CD22 deficiency and ectopic B cell CD154 expression in transgenic mice increases B10+B10pro cell numbers 10-fold in vivo (46). The calcium sensors STIM1 and STIM2 are also required for B cell IL-10 production after BCR stimulation (49). Thus, BCR signaling pathways appear to drive B cell acquisition of IL-10 competence, thereby selecting for Ag-specific B10 cells in vivo.

Ag-driven BCR signaling during B10 cell development likely explains why B10 cell regulation of inflammation and autoimmunity appears to be Ag specific under physiologic in vivo conditions (4, 6, 13, 29). In vivo selection by Ag also explains why B10 cells are primed to proliferate rapidly in response to mitogenic stimulation in vitro compared with other B cells (31, 35). Human B10 and B10pro cells are found within the CD27⁺ memory compartment, consistent with the concept of in vivo Ag experience (32). Like B10 cells, spleen marginal zone and B1 B cells are more responsive to mitogenic signals than other B cells (50), but it is not possible to delineate these three subsets because of their overlapping phenotypes. Despite Ag simulation in vivo, B10 cells express diverse germine BCRs with only rare mutations (35, 38). Therefore, low-affinity or chronic Ag–BCR stimulation may drive IL-10 competence in vivo, because strong BCR signals may actually divert intracellular signaling and induce B10pro cells to progress down a different functional pathway. In support of this, potent B cell stimulation with mitogenic anti-IgM Ab inhibits B10pro cell acquisition of IL-10 competence during in vitro cultures (31, 32, 35). Thus, BCR specificity and signaling intensity are likely developmental checkpoints that allow B10 cells to respond rapidly to self- or foreign Ags as a first line of defense to protect against vigorous immune responses that could lead to autoantibody production and tissue pathology.

Cognate interactions regulate B10 cell effector function in vivo

At the cellular level, B10 cell–derived IL-10 inhibits T cell activation, as well as IFN-γ and Th17 cell cytokine responses in vivo (29). B10 cells are not able to inhibit polyclonal T cell activation or proliferation following CD3 and CD28 ligation in vitro, but they do suppress Ag-specific CD4⁺ T cell IFN-γ and TNF-α responses and Th17 cell differentiation (7, 51). Nonetheless, B10 cells are present in T cell–deficient nude mice (31). Likewise, B cell MHC class I, MHC class II, CD1d, CD40, or intrinsic IL-10 expression is not required for B10 cell development (31, 38). However, MHC class II– and CD40-dependent cognate interactions between B10 cells and CD4⁺ T cells are essential for B10 effector cell function during T cell–driven autoimmunity (29). The requirement for Ag-specific interactions between CD4⁺ T cells and B10 cells to generate B10 effector cells suggests a regulatory-feedback loop whereby localized B10 effector cell IL-10 secretion preferentially downregulates Ag-specific T cell responses during cognate B10:T cell interactions, although IL-10 suppression of Ag presentation by dendritic cells and macrophages is also possible (Fig. 1B). Either way, Ag specificity ultimately regulates B10 cell effector function.

IL-21 is a key cytokine for regulating B cell effector functions. Nonetheless, IL-21 is not required for B10 cell generation, and IL-21 exposure does not induce most B cells to express IL-10, despite their IL-21R expression (29). However, IL-21 and its receptor are necessary for B10 cell expansion and the induction of IL-10–secreting B10 effector cells during the induction of autoimmunity. In contrast, TGF-β and IFN-γ inhibit B10pro cell maturation in vitro (29). Thus, different cytokines may elicit or inhibit B10 cell expansion and IL-10 secretion in vivo.

B10 cells suppress dendritic cell activation, cytokine production, and their ability to present Ag (7). B10 cells also suppress macrophage activation, cytokine and NO production, and phagocytosis in an IL-10–dependent manner (6, 33). Although serum IL-10 increases with inflammation, cognate B10 cell:T cell interactions are required to regulate monocyte activation during Listeria infection (Fig. 1B) (52). This reveals the potent effects of IL-10 in vivo and reinforces the need for multiple checkpoints in the control of B10 effector cell function during both innate and adaptive immune responses. These checkpoints are likely to restrict B10 cell IL-10 production within the local microenvironment and selectively inhibit local macrophage and Ag-specific T cell function during inflammation and autoimmunity without inducing immunosuppression.

B10 cells respond to innate signals

LPS induces mouse B10pro cells to mature and become B10 effector cells, whereas CpG oligonucleotides induce B10 cells...
to produce IL-10 (Fig. 1A) (31). IL-33 and B cell–produced IL-35 also were reported to enhance B10 cell numbers (53–57). TLR signals, infection, and apoptotic cells can also significantly expand B10 and B10 effector cell numbers in vivo (38, 42, 52, 58). Nonetheless, MyD88, environmental pathogens, and gut–associated flora are not required for normal B10 cell development in vivo (31). Therefore, BCR-associated signals appear to preferentially program B10 cell IL-10 competence, whereas overlapping adaptive and innate signaling pathways can induce B10 cell activation, proliferation, and effector function. Undoubtedly, IFNs, ILs, and cytokines that generally regulate B cell function are also likely to influence B10pro and B10 cells. Thus, there is no reason to partition B10 cells into adaptive or innate subsets because they respond like most other B cells to both signals.

**B10 effector cell function and therapeutic potential**

The rapid in vivo expansion of B10 cells in disease models suggests acute Ag-specific B10 cell expansion and/or B10pro cell maturation into B10 cells during disease initiation. In either case, overall B10 cell numbers remain relatively low. Nonetheless, even small numbers of B10 cells among purified CD1d
high
CD5
+ B cells, peritoneal cavity B cells, or other subsets can significantly inhibit disease initiation and subsequent pathology in adoptive-transfer models of contact hypersensitivity (13), EAE (4, 6, 7), lupus (15, 16), IBD (35, 40), and graft-versus-host disease (59), whereas comparable B cells isolated from IL-10
−/− mice are without therapeutic effect. B10 cells isolated from Ag-primed mice or mice with inflammation or autoimmunity are more potent than comparable naive cells, consistent with disease driving the clonal expansion of Ag-specific B10 cells before their adoptive transfer. Ex vivo B10 cell activation before adoptive transfers further enhances their regulatory efficacy in vivo (7). Therefore, B10 cells in relatively small numbers can have potent suppressive effects in vivo, particularly during Ag-specific responses.

The therapeutic potential of B cells induced to express IL-10 was first demonstrated in landmark studies by the Londei laboratory, where agonistic CD40 mAbs effectively treated mice with collagen-induced arthritis (9, 60). Total spleen B cell populations from in vitro culture systems that stimulate through CD40 or Ag sensitization also were shown to be therapeutic during disease initiation and progression (10, 11, 51). The therapeutic potential of purified B10 cells also was validated in studies in which B10 effector cells were expanded ex vivo by a million-fold in a CD40- and IL-21–dependent culture system (29). Remarkably, B10 effector cells purified from these cultures dramatically suppressed both EAE initiation and established disease. Thus, B10 cells are regulatory during early inflammatory responses but also are functional during the course of disease in concert with other regulatory cells (7). Translation of these studies into humans may provide a novel immunotherapy for patients with complex disease that does not respond to current treatments.

A better quantification of human Ag–specific B10 cells is needed to understand their relative contributions during human disease. B10 and B10pro cell numbers are generally normal or elevated in patients with autoimmune disease (32). However, disease may progress when IL-10–producing regulatory B cells are inadequate, as suggested for some patients with lupus and rheumatoid arthritis (61, 62). Tregs with the capacity to limit collateral tissue damage are also present at sites of inflammation in active human autoimmune diseases, but they are too few in number to adequately control disease (63). Alternatively, autoimmune disease and inflammatory cytokine production may impact B10 cell maturation and/or functional capacity in vivo. Therefore, the ex vivo expansion of a patient’s B10 cells in the absence of inflammatory factors before reinfusion may offer great promise for treating autoimmunity, allergy, and transplant rejection.

The in vivo depletion of all mature B cells, which includes B10 cells, can have therapeutic, as well as detrimental, effects in mouse models of human disease. Specifically, disease symptoms during contact hypersensitivity, EAE, and skin transplant rejection can be more severe in B cell–depleted mice (6, 13, 64). Likewise, the depletion of B10 cells using a mAb that predominantly spares other B cell subsets results in enhanced cellular, innate, and humoral immune responses and exacerbates autoimmune disease (7, 46, 52). Therefore, future interventions that decrease B10 cell numbers may prove beneficial in cancer therapy, infectious disease, and vaccine responses.

**B10 effector cell differentiation**

IL-10 is not required for B cell or B10 cell development, differentiation, or Ab production in mice (38). However, a small fraction of B10 effector cells can differentiate into Ab-producing cells in vivo and in vitro as they lose the capacity to express IL-10 (Fig. 1A). B10 cells express the plasma cell–associated transcription factors blimp1, xbp1, and irf4, with downregulated pax5 and bcl6 transcripts relative to follicular B cells, likely due to chronic BCR selection and activation in vivo (38). Even so, B10 effector cells from naive or LPS-treated mice are not themselves plasmablasts/plasma cells, but they can differentiate into Ab-secreting cells at low frequencies. IL-10 reporter mice provide a means to identify B10 effector cells after transient IL-10 expression, where the phenotype of spleen B10 cells and IL-10 reporter
B cells remains predominantly IgM
high
CD1d
high
CD5
+CD19
high
CD23
low
B220
high
, even after in vivo LPS treatment (35). Variable low frequencies of B10 effector cells express the CD43, GL7, and CD138 activation markers, and rare CD138
high
B220
int
/low
 cells have been identified among IL-10 reporter
B cells in naive, LPS-treated, and infected mice (38, 41, 42). However, <0.1% of reporter
B cells isolated from LPS-treated 10BiT mice are Ab-secreting cells (38). Thus, like most B cells, some B10 effector cells can differentiate into plasma cells. In contrast, other investigators report that Ab-secreting cells, at least in some cases, are the major source of B cell–derived regulatory IL-10 and IL-35 in vivo (53, 65). The fate of most other B10 effector cells and whether they become memory cells or regain the capacity to express IL-10 are unknown.

Plasma cells that derive from B10 cells secrete autoreactive, polyreactive, and Ag-specific IgM, as well as IgG reactive with T cell–dependent Ags (Fig. 1), reflecting their diverse BCR sequences (35, 38). Despite their ability to switch isotypes, B10 cell BCRs are predominantly germline and without somatic hypermutation, arguing against a germlinal center origin. However, connectivity maps from multiparameter analyses of human B cell phenotypes, function, and gene expression profiles suggest that IL-10–secreting B cells may undergo specific differentiation toward a germlinal center fate.
function beyond what is currently known for B10 cell regulatory B cell subsets will be identified. Thus, the extraordinary unanticipated functional diversity within the B cell pool, which has yet to be fully explored. It is likely that additional regulatory B cells exist in mice. B10 pro and B10 cell development are likely to be cleared by Abs coming from B10 cell-derived plasma cells, potentially providing a regulatory checkpoint that meters B10 cell development and peripheral tolerance.

Conclusions

Historically, although B cell subsets have been studied based on their phenotype, B10 cells demonstrate a clear case where function trumps phenotype, because their only unique phenotypic characteristic is their capacity to express IL-10. It is likely that additional regulatory B cells have a suppressive role in murine lupus: CD19 and B10 cell deficiency exacerbates systemic autoimmunity. J. Immunol. 184: 4868–4877.


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BRIEF REVIEWS: MOUSE REGULATORY B10 CELLS


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