REVIEW ARTICLE

WILEY | Journal of Cutaneous Immunology and Allergy

IL-10–producing regulatory B cells in skin diseases

Hiraku Suga MD, PhD (iD) | **Shinichi Sato MD, PhD**

Department of Dermatology, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

Correspondence
Shinichi Sato, Department of Dermatology, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
Email: satos-der@h.u-tokyo.ac.jp

Abstract

B cells are generally considered to regulate immune responses positively because they differentiate into plasma cells and produce antigen-specific antibodies. However, specific B-cell subsets have been reported to regulate immune responses negatively and have been termed regulatory B cells. Accumulating evidence has shown that regulatory B cells play an important role in a variety of inflammatory and autoimmune diseases. Among several regulatory B-cell subsets, IL-10–producing regulatory B cells are the most widely investigated. This review focused on the role of regulatory B cells in autoimmune and inflammatory skin diseases. The frequency of IL-10–producing B cells in the peripheral blood from patients with systemic sclerosis was decreased compared to healthy controls. In addition, the function of regulatory B cells was impaired in patients with systemic sclerosis. As for systemic lupus erythematosus, the frequency of regulatory B cells was increased in the peripheral blood, while their regulatory function was impaired. In inflammatory skin diseases including psoriasis and atopic dermatitis, the number of IL-10–producing B cells was decreased compared to healthy controls. Similarly, patients with cutaneous T-cell lymphoma showed decreased number of IL-10–producing B cells. Taken together, regulatory B cells would play important roles in suppressing the disease onset, whose dysfunction might lead to worsening the disease symptoms. Revealing the mechanisms of human regulatory B cells in skin diseases could lead to the development of novel therapies targeting regulatory B cells.

KEYWORDS
atopic dermatitis, cutaneous T-cell lymphoma, IL-10, regulatory B cell, systemic sclerosis

1 | INTRODUCTION

B cells have been considered to regulate humoral immune responses positively because of their ability to produce antigen-specific antibodies and to activate T cells through antigen presentation.[1] B cells can also serve as antigen-presenting cells, leading to optimal antigen-specific CD4^{+} T-cell expansion, memory formation, and cytokine production (Figure 1).[1–4] Furthermore, co-stimulatory molecules including CD80, CD86, and OX40 ligand expressed on B cells are also important for optimal T-cell activation.[5,6] Thus, B cells can positively regulate cellular immune responses in addition to producing antibodies.

Specific B-cell subsets, however, negatively regulate immune responses and have been termed regulatory B cells.[7–9] There is accumulating evidence demonstrating that regulatory B cells play an important role in a variety of mouse models of inflammation and autoimmunity.[10–15]

Among several regulatory B-cell subsets described in mice, IL-10–producing regulatory B cells are the most widely investigated.[15,16] Human regulatory B cells, also predominantly identified based on their production of IL-10, exhibited a phenotypic and functional heterogeneity similar to that of mouse IL-10–producing regulatory B cells.[17-19] Human regulatory B cells were enriched in CD24^{hi}CD38^{hi} transitional B cells and CD24^{hi}CD27^{+} memory B cells.[18,19] CD24^{hi}CD38^{hi} transitional B cells inhibited proinflammatory cytokine production by CD4^{+} T cells, dependent on IL-10, CD80, and CD86, but not transforming growth factor-β.[18] Human CD25^{hi}CD86^{hi}CD1d^{hi} B cells could also suppress the proliferation of CD4^{+} T cells and enhance Forkhead box protein 3 and cytotoxic T-lymphocyte antigen 4 expression in regulatory T cells by producing IL-10 and transforming growth factor-β.[20] Moreover, IL-10 production was also enriched in CD27^{hi}CD38^{hi} plasmablast B-cell compartments.[21] Taken together, it is possible that human regulatory B cells do not belong to a single B-cell subset (Figure 2). Matsumoto et al[22] investigated what happened to immature, naïve mature, and memory B cells after in vitro stimulation with combinations of CpG, IL-2, IL-6, and interferon (IFN)-α. They showed that these four stimuli used all together induced naïve immature B cells to develop into IL-10–expressing CD27^{int}CD38^{+} plasmablast-like cells. Furthermore, there was more IL-10 expression by plasmablast-like cells that developed from immature naïve B cells than by plasmablasts that developed from mature or memory B cells.[22] These data suggested that naïve immature B cells had ability to produce more IL-10 after appropriate stimulation compared to proliferated B cells including memory cells and plasma cells.

Regardless of the different markers used to identify human regulatory B cells, the majority of protective effects of human regulatory B cells are dependent on IL-10. Although studies of human regulatory B cells are limited, there have been emerging data proposing the importance and potential future therapeutic application of peripheral blood regulatory B cells in human diseases.[23] The present review focused on the role of regulatory B cells in autoimmune and inflammatory skin diseases (Table 1).

2 | SYSTEMIC SCLEROSIS

Systemic sclerosis (SSc) is a connective tissue disorder characterized by fibrosis in the skin and various internal organs, with an autoimmune background. More than 90% of patients with SSc carry autoantibodies such as anti-DNA topoisomerase I, anticentromere, and anti-RNA polymerase antibodies (Abs).[24] In addition, B-cell activating factor was present at elevated levels in patients with SSc and correlated with disease severity.[25] Thus, B cells are considered to play a pathogenic role in SSc.

Clinical study using peripheral blood B cells from patients with SSc showed a decreased number of CD19^{+}IL-10^{+} B cells in the blood of patients with SSc when cells were stimulated with lipopolysaccharide (LPS) for 24 hours with the additional phorbol-12-myristate-13-acetate (PMA) and ionomycin compared to healthy controls.[26] Similarly, the frequency of CD24^{hi}CD27^{+} regulatory B cells was significantly lower in patients with SSc than in healthy controls.[26] Furthermore, the frequency of regulatory B cells negatively correlated with the titer of anti-topo I Ab and anticentromere Ab in patients with SSc.

Consistently, Mavropoulos et al[27] demonstrated that regulatory B cells were phenotypically and functionally impaired in patients with SSc. Percentages of CD24^{hi}CD38^{hi} B cells were decreased in patients with early SSc, established SSc, and with SSc-associated pulmonary fibrosis compared to healthy controls.[27] Furthermore, expression of IL-10 by regulatory B cells after stimulation with CpG was impaired in patients with SSc, particularly those with SSc-associated pulmonary fibrosis. Activation of signal transducer and activator of transcription 3 and p38 mitogen-activated protein
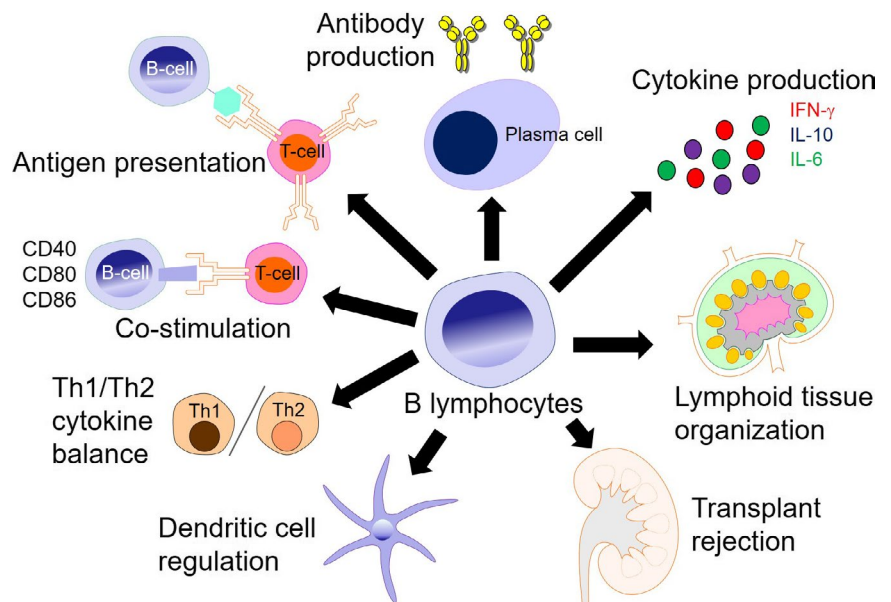

FIGURE 1 Multifunctional attributes of B cells. Selected examples of how B cells regulate immune homeostasis are shown
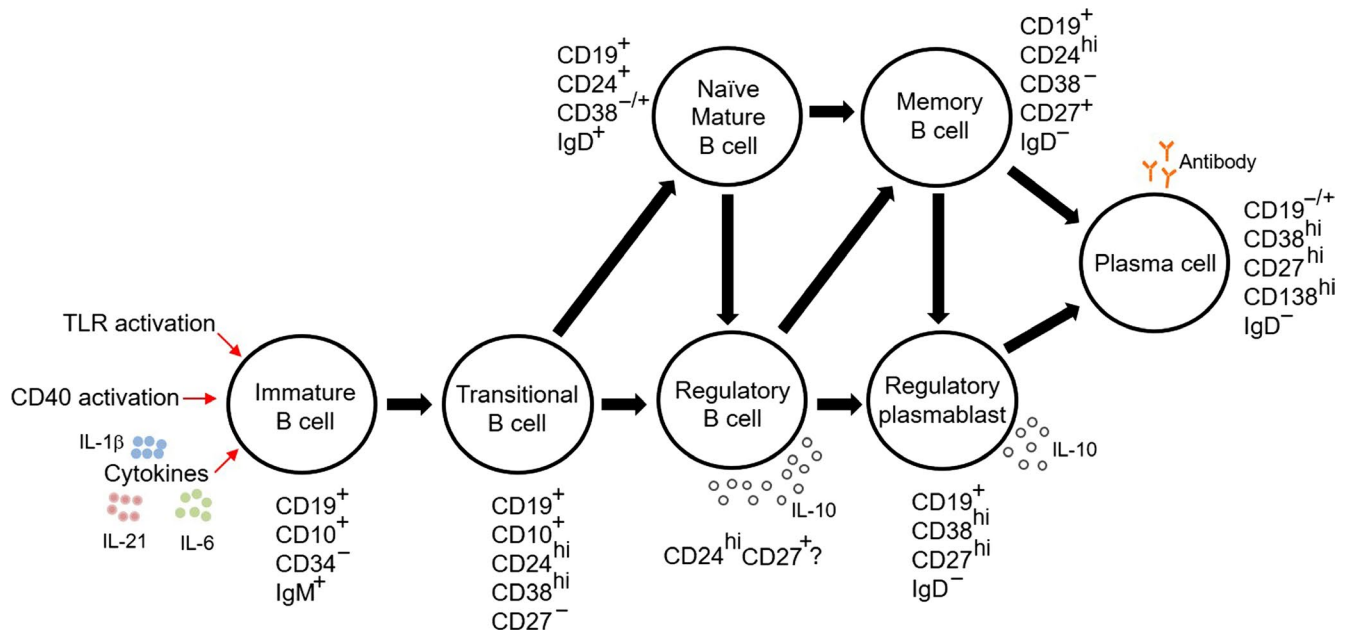
FIGURE 2 Hypothesis of regulatory B-cell development. After Toll-like receptor (TLR) activation, CD40 activation, and activation with cytokines, immature B cells differentiate into transitional B cells, then into IL-10–producing regulatory B cells, naïve B cells, and mature B cells. Plasmablasts, which develop from IL-10–producing regulatory B cells or memory B cells, retain their ability to produce IL-10. All regulatory B-cell types terminally differentiate into antibody-producing plasma cells

kinase was impaired in naïve and memory B cells from patients with SSc after stimulation with CpG.[27] These findings supported the idea of B-cell autoaggression acting as an immunopathogenic mediator in SSc. Taken together, regulatory B cells were numerically decreased and functionally impaired in patients with SSc.

3 | SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by the production of antinuclear Abs and abnormalities in T-cell and B-cell function. Internal organ systems are involved, and renal involvement is one of the most serious complications of SLE.

A clinical study using peripheral blood B cells showed that the frequencies of IL-10–producing B cells in the peripheral blood were significantly higher in patients with several autoimmune diseases including SLE, rheumatoid arthritis, Sjögren syndrome, bullous diseases, and multiple sclerosis compared with normal controls when stimulated with LPS or CpG in the presence of CD40 ligation for 48 hours with additional PMA and ionomycin.[19] Similarly, Yang et al[28] showed an increase in CD19^{+}IL-10^{+} B cells in the blood of patients with SLE when the cells were stimulated with LPS for 24 hours with the additional PMA and ionomycin.

Recently, the dysfunction of regulatory B cells in patients with SLE was reported by demonstrating functional impairment of CD24^{hi}CD38^{hi} regulatory B cells in the peripheral blood.[18] After CD40 stimulation, CD24^{hi}CD38^{hi} regulatory B cells suppressed IFN-γ and tumor necrosis factor (TNF)-α production from CD4^{+} T

cells in normal controls, whereas they did not have the inhibitory effect in patients with SLE. This effect was partially dependent on IL-10.[18] CD24^{hi}CD38^{hi} regulatory B cells isolated from peripheral blood of patients with SLE were unresponsive to CD40 stimulation and produced less IL-10 than those from normal controls.[18] Another study showed that FSC[hi] fractions of B cells from patients with SLE stimulated with IL-2 and *Staphylococcus aureus* Cowan 1 for 72 hours had less suppressive effects on T-cell proliferation compared to those from normal controls.[29] Collectively, although regulatory B cells were increased in the peripheral blood of patients with SLE, the function of those cells was impaired.

4 | PEMPHIGUS

Pemphigus is another organ-specific autoimmune disease, which is characterized by severe blistering condition of the skin and mucosa caused by autoantibodies directed against two desmosomal proteins involved in keratinocyte adhesion: desmoglein (DSG) 1 and DSG 3.[30,31] These autoantibodies block keratinocyte adhesion, resulting in intraepidermal blistering of mucosa membranes and skin.[30,31] Although high doses of corticosteroids along with immunosuppressants are the first-line treatment,[32] relapses are frequent, so long-term treatment is necessary. Therefore, new treatment with rituximab based on B-cell depletion has been reported in severe pemphigus cases and efficacy of rituximab in patients with pemphigus has been confirmed in both short and long term.[33–36] The underlying mechanism of rituximab's effectiveness has gradually become clear. In most cases, B-cell reconstitution

TABLE 1 A summary of human studies on regulatory B cells in patients with skin diseases

Disease	Regulatory B-cell subsets (compared to healthy controls)	Supernatant IL-10 levels from B cells (compared to healthy controls)	Function (compared to healthy controls)	Stimulus for IL-10 assay	References
SSc	Decreased CD24^{hi}CD27^{+} B cells Decreased CD19^{+}IL-10^{+} B cells	ND	ND	LPS + PI	26
	Decreased CD24^{hi}CD38^{hi} B cells	ND	Impaired	CpG + PI	27
SLE	Similar CD24^{hi}CD38^{hi} B cells Decreased IL-10^{+} B cells	ND	Impaired	CD40L + PI	18
	Increased CD1d^{hi}CD5^{+} B cells Increased IL-10^{+} B cells	Increased	ND	LPS + PI	28
	Similar FSC^{hi} B cells	Similar	Impaired	IL-2 + SAC	29
	Increased IL-10^{+} B cells	ND	ND	CpG + CD40L + PI	19
Pemphigus	Increased CD24^{hi}CD38^{hi} B cells Similar IL-10^{+} B cells	ND	Impaired	CpG + CD40L + PI	37
Psoriasis	Decreased CD24^{hi}CD27^{+} B cells Decreased CD24^{hi}CD38^{hi} B cells Decreased IL-10^{+} B cells	ND	Impaired	CpG + PI	39
	Decreased IL-10^{+} B cells	ND	ND	CpG + CD40L + PI	40
Atopic Dermatitis	Similar CD24^{hi}CD27^{+} B cells Decreased IL-10^{+} B cells	ND	ND	CpG + CD40L + PI	45
CTCL	Decreased CD24^{hi}CD27^{+} B cells, Decreased CD24^{hi}CD38^{hi} B cells Decreased IL-10^{+} B cells	ND	ND	CpG + PI	51

Note. Abbreviations: CD40L, CD40 ligand; CTCL, cutaneous T-cell lymphoma; IBD, inflammatory bowel disease; LPS, lipopolysaccharide; ND, not done; PI, PMA + ionomycin; SAC, *Staphylococcus aureus* Cowan 1.

began 6 to 9 months after rituximab infusion, and the patients in complete remission had a fourfold higher number of transitional B cells and IL-10–producing B cells than those who had incomplete remission. These results suggested that newly emerging B cells with transitional phenotype could give rise to IL-10–producing B cells, leading to the decrease in DSG-specific circulating B cells and disease remission.[36]

Another clinical research regarding regulatory B-cell involvement in pemphigus revealed the up-regulated frequency of CD24^{hi}CD38^{hi} regulatory B cells in peripheral blood of patients with pemphigus.[37] Moreover, regulatory B cells from patients with pemphigus had a lower capacity to produce IL-10 after 48 hours of stimulation with CpG and CD40 ligand compared to those from normal controls.[37] In addition, these regulatory B cells failed to suppress IFN-γ production from CD4^{+} T cells, as was the case with SLE.[18] Thus, regulatory B-cell function may be impaired in patients with pemphigus, and recovery of functional regulatory B cells after rituximab may contribute to remission of the disease.

5 | PSORIASIS

Psoriasis is a cutaneous disorder characterized by widespread erythematous plaques with adherent scales that affect ~2% of the general population.[38] Mavropoulos et al[39] analyzed peripheral blood regulatory B cells from 60 patients with psoriatic arthritis (PsA), 50 patients with psoriasis, and 23 healthy volunteers. CD19^{+}CD27^{+}CD24^{hi} and CD19^{+}CD24^{hi}CD38^{hi} regulatory B cells were decreased in PsA and psoriasis compared to healthy controls. In patients with psoriasis, the frequency of CD19^{+}CD27^{+}CD24^{hi} regulatory B cells inversely correlated with disease severity score. IL-10^{+} B cells were also decreased and inversely correlated with IL-17A^{+}CD3^{+} and IFN-γ^{+}CD3^{+} T cells.[39] Furthermore, B cells from patients with PsA and psoriasis exhibited impaired activation of p38 mitogen-activated protein kinase and signal transducer and activator of transcription 3. These results demonstrated that regulatory B cells were numerically decreased and functionally impaired in the patients with PsA and psoriasis.

Another study using clinical samples from patients with psoriasis reported a decrease in IL-10–producing regulatory B cells but did not find a correlation with disease severity score.[40] In a mouse model of psoriasis induced by imiquimod, splenic IL-10–producing regulatory B cells were greatly reduced.[41] In this model, depletion of regulatory B cells resulted in more severe skin inflammation, while adoptive transfer of IL-10–producing B cells from wild-type mice to imiquimod-treated CD19-knockout animals reduced skin inflammation and IFN-γ and IL-17A production in inflamed skins.[41] In humans, IL-10 administration appears to have a favorable effect on PsA and psoriasis.[42] Subcutaneous IL-10 administration for 28 days in patients with PsA in a double-blind study improved psoriasis and decreased T-cell and macrophage infiltrations in synovial tissue.[42] Collectively, regulatory B cells could be regulators in the pathogenesis of psoriasis.

6 | ATOPIC DERMATITIS

Atopic dermatitis (AD) is one of the allergic diseases characterized by high IgE levels, and IgE-mediated mechanisms are thought to play an important role in the pathogenesis of this disease. Mechanisms promoting allergic inflammation are caused by Th2-polarized immune response. One of the significant causes of allergic inflammation development is an alteration in the immune regulatory processes.[43]

The first experiment demonstrating the regulatory function of B cells in AD-like mouse model was performed in 2015.[44] The frequency of IL-10–producing B cells in the spleen CD19^{+} B cells was decreased in the mice of AD group compared to the control group after stimulation with LPS for 5 hours with additional PMA and ionomycin.[44] The regulatory function of IL-10–producing B cells on IgE production was investigated by sorting these cells. Purified IL-10–producing cells sorted from AD or control mice were cultured with peripheral blood mononuclear cells for 72 hours and with additional LPS, PMA, and ionomycin for the last 5 hours. Interestingly, IL-10–producing B cells from control mice effectively inhibited IgE secretion, whereas the suppressive function of IL-10–producing B cells from the AD mice was significantly decreased, which was similar to that observed in the group without IL-10–producing B cells. These results suggested that the frequency of IL-10–producing B cells was decreased in the AD group and that these cells showed a defective regulatory function on IgE secretion.

Quite recently, the frequency of IL-10–producing regulatory B cells in patients with AD was examined.[45] Lower numbers of IL-10–producing B cells were found in patients with severe AD than in healthy controls and patients with mild AD.[40] Moreover, the frequency of IL-10–producing B cells was negatively correlated with both the disease severity skin score and serum CCL17 levels in patients with AD. Thus, the frequency of IL-10–producing B cells negatively correlated with disease severity in patients with AD. These results suggest that impaired function of IL-10–producing B cells may induce uncontrollable allergic inflammation, resulting in severe allergic diseases.

The frequency and function of IL-10–producing regulatory B cells in patients with asthma were also examined recently.[46] Lower numbers of IL-10–producing CD24^{hi}CD27^{+} B cells were found in asthma patients when B cells were cultured with LPS for 48 hours with additional PMA and ionomycin.[46] When CD4^{+} T cells activated with the dust-mite allergen were co-cultured with LPS-stimulated B cells, they produced less IL-10 in asthma patients compared to those in healthy controls, suggesting defective function of regulatory B cells in patients with asthma.[46] Another group also showed the decreased frequency of CD24^{hi}CD27^{+} B cells in allergic rhinitis patients.[47]

Taken together, regulatory B cells would contribute to the suppression of allergic diseases including AD and asthma.

7 | CUTANEOUS T-CELL LYMPHOMA

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL).[48] MF is characterized by malignant proliferation of neoplastic CD4^{+}CD45RO^{+} T cells that preferentially traffic to the skin and has a classically prolonged clinical course. Limited cases progress over years through patch, plaque, and tumor stages, followed by lymph node and visceral involvement.[49,50] It was reported that IL-10–producing B cells were decreased in peripheral blood of advanced MF patients, and that CD19^{+}CD24^{hi}CD27^{+} memory B cells and CD19^{+}CD24^{hi}CD38^{hi} transitional B cells, in which IL-10–producing B cells were enriched, were also decreased in advanced MF.[51] The frequency of IL-10–producing B cells, memory, and transitional B cells inversely correlated with serum soluble IL-2 receptor levels and serum lactate dehydrogenase levels, which were disease severity markers of CTCL.[52] These results demonstrated that decrease in regulatory B cells might have an important role in the progression of advanced MF.

Similarly, the frequency of regulatory T cells in lesional skin was decreased in patients with advanced MF, compared to that in patients with early MF, and a high frequency of regulatory T cells was associated with a better clinical course.[53,54] Although mechanisms for this phenomenon are still unknown, it was hypothesized that infiltrating regulatory T cells in lesional skin might suppress the propagation of the tumor cells.[55] In this situation, the decreased number of regulatory T cells could promote disease progression. In the same way, it is possible that regulatory B cells might suppress the activity of tumor cells in blood, considering that clonal tumor cells exist in peripheral blood in MF.[56] In addition, the frequency of clonal tumor cells in blood was increased as the disease progressed,[56] which was consistent with the fact that the amount of regulatory B cells inversely correlated with disease severity. Therefore, decreased number of regulatory B cells might be associated with disease progression as well as regulatory T cells in CTCL.

8 | MALIGNANT MELANOMA

There has been no paper that investigated the function of human regulatory B cell in the tumor microenvironment of malignant melanoma so far. Transitional 2-marginal zone precursor (T2-MZP) B cells have previously been associated with a regulatory function, as transplantation of these cells reduced autoimmune diseases.[57] In a mouse model of melanoma, phenotypic characterization of lymphocytes in mice bearing B16-F10 melanomas identified preferential accumulation of T2-MZP B cells in the tumor-draining popliteal lymph nodes.[58] B-cell–deficient and immunocompetent mice reconstituted with T2-MZP B cells but not with other B-cell subsets displayed accelerated tumor growth, demonstrating that T2-MZP B cells possessed regulatory activity in tumor-bearing mice. These findings demonstrated that regulatory B cells would play some roles in generating an immunosuppressive environment to permit tumor growth and metastasis.

The frequency of IL-10–producing B cells in blood was reported to be increased in patients with various solid malignancies; for example, the frequency of CD19^{+}CD24^{hi}CD27^{+} B cells was increased in patients with colorectal cancer.[59] Furthermore, patients with

esophageal cancer showed increased number of IL-10–producing B cells as the disease progressed.[60] Also in gastric cancer, there was an increase in the frequency of IL-10–producing B cells and they suppressed the secretion of IFN-γ and TNF-α by CD4^{+} helper T cells.[61] On the other hand, in patients with hepatocellular carcinoma, the frequency of IL-10–producing B cells is decreased compared to normal controls.[62] These previous reports suggested that the development of IL-10–producing B cells would be altered in patients with malignancies and that the directions of changes might be different, depending on the types of malignancies.

9 | CONCLUSION

In this review, studies on regulatory B cells in a wide variety of skin diseases have been reviewed. Studies of the role of regulatory B cells were relatively limited compared to regulatory T cells. Moreover, the number of articles regarding the function of regulatory B cells in inflammatory diseases and malignancies was smaller than that of autoimmune diseases. On the basis of the previous reports, regulatory B cells would play an important role in preventing the disease onset or suppressing the disease symptoms. As several reports showed regulatory B-cell dysfunction in skin diseases, revealing the mechanism of immune regulation by regulatory B cells would bring us a scientific basis for developing a new treatment strategy targeting regulatory B cells.

CONFLICT OF INTEREST

ORCID

Hiraku Suga https://orcid.org/0000-0002-4212-8278

REFERENCES

1. LeBien TW, Tedder TF. B lymphocytes: how they develop and function. Blood. 2008;112(5):1570–80.
2. Linton PJ, Harbertson J, Bradley LM. A critical role for B cells in the development of memory CD4 cells. J Immunol. 2000;165(10):5558–65.
3. Crawford A, Macleod M, Schumacher T, Corlett L, Gray D. Primary T cell expansion and differentiation in vivo requires antigen presentation by B cells. J Immunol. 2006;176(6):3498–506.
4. Bouaziz JD, Yanaba K, Venturi GM, Wang Y, Tisch RM, Poe JC, et al. Therapeutic B cell depletion impairs adaptive and autoreactive CD4 + T cell activation in mice. Proc Natl Acad Sci U S A. 2007;104(52):20878–83.
5. O'Neill SK, Cao Y, Hamel KM, Doodes PD, Hutas G, Finnegan A. Expression of CD80/86 on B cells is essential for autoreactive T cell activation and the development of arthritis. J Immunol. 2007;179(8):5109–16.
6. Linton PJ, Bautista B, Biederman E, Bradely ES, Harbertson J, Kondrack RM, et al. Costimulation via OX40L expressed by B cells is sufficient to determine the extent of primary CD4 cell expansion and Th2 cytokine secretion in vivo. J Exp Med. 2003;197(7):875–83.
7. DiLillo DJ, Matsushita T, Tedder TF. B10 cells and regulatory B cells balance immune responses during inflammation, autoimmunity, and cancer. Ann N Y Acad Sci. 2010;1183:38–57.
8. Fillatreau S. Novel regulatory functions for Toll-like receptor-activated B cells during intracellular bacterial infection. Immunol Rev. 2011;240(1):52–71.
9. Mauri C. Regulation of immunity and autoimmunity by B cells. Curr Opin Immunol. 2010;22(6):761–7.
10. Fillatreau S, Gray D, Anderton SM. Not always the bad guys: B cells as regulators of autoimmune pathology. Nat Rev Immunol. 2008;8(5):391–7.
11. Mizoguchi A, Bhan AK. A case for regulatory B cells. J Immunol. 2006;176(2):705–10.
12. Mauri C, Ehrenstein MR. The 'short' history of regulatory B cells. Trends Immunol. 2008;29(1):34–40.
13. Lund FE. Cytokine-producing B lymphocytes-key regulators of immunity. Curr Opin Immunol. 2008;20(3):332–8.
14. Bouaziz JD, Yanaba K, Tedder TF. Regulatory B cells as inhibitors of immune responses and inflammation. Immunol Rev. 2008;224:201–14.
15. Yanaba K, Bouaziz JD, Matsushita T, Magro CM, St Clair EW, Tedder TF. B-lymphocyte contributions to human autoimmune disease. Immunol Rev. 2008;223:284–99.
16. Mauri C, Bosma A. Immune regulatory function of B cells. Annu Rev Immunol. 2012;30:221–41.
17. Correale J, Farez M, Razzitte G. Helminth infections associated with multiple sclerosis induce regulatory B cells. Ann Neurol. 2008;64(2):187–99.
18. Blair PA, Noreña 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):129–40.
19. Iwata Y, Matsushita T, Horikawa M, Dilillo DJ, Yanaba K, Venturi GM, et al. Characterization of a rare IL-10-competent B-cell subset in humans that parallels mouse regulatory B10 cells. Blood. 2011;117(2):530–41.
20. Kessel A, Haj T, Peri R, Snir A, Melamed D, Sabo E, et al. Human CD19(+)CD25(high) B regulatory cells suppress proliferation of CD4(+) T cells and enhance Foxp3 and CTLA-4 expression in T-regulatory cells. Autoimmun Rev. 2012;11(9):670–7.
21. de Masson A, Bouaziz JD, Le Buanec H, Robin M, O'Meara A, Parquest N, et al. CD24(hi)CD27^{+} and plasmablast-like regulatory B cells in human chronic graft-versus-host disease. Blood. 2015;125(11):1830–9.
22. Matsumoto M, Baba A, Yokota T, Nishikawa H, Ohkawa Y, Kayama H, et al. Interleukin-10-producing plasmablasts exert regulatory function in autoimmune inflammation. Immunity. 2014;41(6):1040–51.
23. Miyagaki T, Fujimoto M, Sato S. Regulatory B cells in human inflammatory and autoimmune diseases: from mouse models to clinical research. Int Immunol. 2015;27(10):495–504.
24. Matsushita T, Kobayashi T, Mizumaki K, Kano M, Sawada T, Tennichi M, et al. BAFF inhibition attenuates fibrosis in scleroderma by modulating the regulatory and effector B cell balance. Sci Adv. 2018;4(7):eaas9944.
25. Matsushita T, Hasegawa M, Yanaba K, Takehara K, Sato S. Elevated serum BAFF levels in patients with systemic sclerosis: enhanced BAFF signaling in systemic sclerosis B lymphocytes. Arthritis Rheum. 2006;54(1):192–201.
26. 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 (Oxford). 2016;55(2):263–7.

27. Mavropoulos A, Simopoulou T, Varna A, Liaskos C, Liaskos C, Bogdanos DP. Breg cells are numerically decreased and functionally impaired in patients with systemic sclerosis. Arthritis Rheumatol. 2016;68(2):494–504.

28. Yang X, Yang J, Chu Y, Xue Y, Xuan D, Zheng S, et al. T follicular helper cells and regulatory B cells dynamics in systemic lupus erythematosus. PLoS One. 2014;9(2):e88441.

29. Gao N, Dresel J, Eckstein V, Gellert R, Storch H, Venigalla R, et al. Impaired suppressive capacity of activation-induced regulatory B cells in systemic lupus erythematosus. Arthritis Rheumatol. 2014;66(10):2849–61.

30. Stanley JR. Autoantibodies against adhesion molecules and structures in blistering skin diseases. J Exp Med. 1995;181(1):1–4.

31. Amagai M. Pemphigus: autoimmunity to epidermal cell adhesion molecules. Adv Dermatol. 1996;11:319–52; discussion 353.

32. Meurer M. Immunosuppressive therapy for autoimmune bullous diseases. Clin Dermatol. 2012;30(1):78–83.

33. Joly P, Mouquet H, Roujeau JC, D'Incan JC, Gilbert D, Jacquot S, et al. A single cycle of rituximab for the treatment of severe pemphigus. N Engl J Med. 2007;357(6):545–52.

34. Mouquet H, Musette P, Gougeon ML, Jacquot S, Lemerier B, Lim A, et al. B-cell depletion immunotherapy in pemphigus: effects on cellular and humoral immune responses. J Invest Dermatol. 2008;128(12):2859–69.

35. Cianchini G, Lupi F, Masini C, Corona R, Puddu P, De Pita O. Therapy with rituximab for autoimmune pemphigus: results from a single-center observational study on 42 cases with long-term follow-up. J Am Acad Dermatol. 2012;67(4):617–22.

36. Colliou N, Picard D, Caillot F, Calbo S, Le Corre S, Lim A, et al. Long-term remissions of severe pemphigus after rituximab therapy are associated with prolonged failure of desmoglein B cell response. Sci Transl Med. 2013;5(175):175ra130.

37. Zhu HQ, Xu RC, Chen YY, Yuan HJ, Cao H, Zhao XQ, et al. Impaired function of CD19(+) CD24(hi) CD38(hi) regulatory B cells in patients with pemphigus. Br J Dermatol. 2015;172(1):101–10.

38. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med. 2009;361(5):496–509.

39. Mavropoulos A, Varna A, Zafiriou E, Liaskos C, Alexiou I, Roussaki-Schulze A, et al. IL-10 producing Bregs are impaired in psoriatic arthritis and psoriasis and inversely correlate with IL-17- and IFNγ-producing T cells. Clin Immunol. 2017;184:33–41.

40. Hayashi M, Yanaba K, Umezawa Y, Yoshihara Y, Kikuchi S, Ishiuji Y, et al. IL-10-producing regulatory B cells are decreased in patients with psoriasis. J Dermatol Sci. 2016;81(2):93–100.

41. Yanaba K, Kamata M, Ishiura N, Shibatta S, Asano Y, Tada Y, et al. Regulatory B cells suppress imiquimod-induced, psoriasis-like skin inflammation. J Leukoc Biol. 2013;94(4):563–73.

42. McInnes IB, Illei GG, Danning CL, Yarboro CH, Crane M, Kuroiwa T, et al. IL-10 improves skin disease and modulates endothelial activation and leukocyte effector function in patients with psoriatic arthritis. J Immunol. 2001;167(7):4075–82.

43. Soyer OU, Akdis M, Ring J, Behrendt H, Crameri R, Lauener R. Mechanisms of peripheral tolerance to allergens. Allergy. 2013;68(2):161–70.

44. Li J, Shen C, Liu Y, Li Y, Sun L, Jiao L, et al. Impaired function of CD5 + CD19 + CD1dhi B10 cells on IgE secretion in an atopic dermatitis-like mouse model. PLoS One. 2015;10(8):e0132173.

45. Yoshihara Y, Ishiuji Y, Yoshizaki A, Kurita M, Hayashi M, Ishiji T, et al. IL-10-producing regulatory B cells are decreased in patients with atopic dermatitis. J Invest Dermatol. 2019;139(2):475–8.

46. van der Vlugt LE, Mlejnek E, Ozir-Fazalalikhan A, Janssen Bonas M, Dijksman TR, Labuda LA, 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):517–28.

47. Kamekura R, Shigehara K, Miyajima S, Jitsukawa S, Kawata K, Yamashita K, et al. Alteration of circulating type 2 follicular helper T cells and regulatory B cells underlies the comorbid association of allergic rhinitis with bronchial asthma. Clin Immunol. 2015;158(2):204–11.

48. Willemze R, Jaffe ES, Burg G. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105(10):3768–85.

49. Girardi M, Heald PW, Wilson LD. The pathogenesis of mycosis fungoides. N Engl J Med. 2004;350(19):1978–88.

50. Kim EJ, Hess S, Richardson SK, Newton S, Showe LC, Benoit BM, et al. Immunopathogenesis and therapy of cutaneous T cell lymphoma. J Clin Invest. 2005;115(4):798–812.

51. Akatsuka T, Miyagaki T, Nakajima R. Decreased IL-10-producing regulatory B cells in patients with advanced mycosis fungoides. Eur J Dermatol. 2018;28(3):314–9.

52. Wasik MA, Vonderheid EC, Bigler RD. Increased serum concentration of the soluble interleukin-2 receptor in cutaneous T-cell lymphoma. Clinical and prognostic implications. Arch Dermatol. 1996;132(1):42–7.

53. Gjerdrum LM, Woetmann A, Odum N, Burton CM, Rossen K, Skovgaard GL, et al. FOXP3 + regulatory T cells in cutaneous T-cell lymphomas: association with disease stage and survival. Leukemia. 2007;21(12):2512–8.

54. Zhang QA, Chen ZQ, Chen MH, Xu ZD. The number of regular T cells and immature dendritic cells involved in mycosis fungoides is linked to the tumor stage. Eur Rev Med Pharmacol Sci. 2014;18(4):553–8.

55. Krejsgaard T, Odum N, Geisler C, Wasik MA, Woetmann A. Regulatory T cells and immunodeficiency in mycosis fungoides and Sézary syndrome. Leukemia. 2012;26(3):424–32.

56. Delfau-Larue MH, Laroche L, Wechsler J. Diagnostic value of dominant T-cell clones in peripheral blood in 363 patients presenting consecutively with a clinical suspicion of cutaneous lymphoma. Blood. 2000;96(9):2987–92.

57. Evans JG, Chavez-Rueda KA, Eddaoudi A, Mayer-Bahlburg A, Rawlings DJ, Ehrenstein MR, et al. Novel suppressive function of transitional 2 B cells in experimental arthritis. J Immunol. 2007;178(12):7868–78.

58. Ganti SN, Albershardt TC, Iritani BM, Ruddell A. Regulatory B cells preferentially accumulate in tumor-draining lymph nodes and promote tumor growth. Sci Rep. 2015;5:12255.

59. Shimabukuro-Vornhagen A, Schlößer HA, Gryschok L, Malcher J, Wennhold K, Garcia-Marquez M, et al. Characterization of tumor-associated B-cell subsets in patients with colorectal cancer. Oncotarget. 2014;5(13):4651–64.

60. Qian L, Bian GR, Zhou Y. Clinical significance of regulatory B cells in the peripheral blood of patients with oesophageal cancer. Cent Eur J Immunol. 2015;40(2):263–5.

61. Wang WW, Yuan XL, Chen H, Xie G, Ma Y, Zheng Y, et al. CD19 + CD24hiCD38hiBregs involved in downregulate helper T cells and upregulate regulatory T cells in gastric cancer. Oncotarget. 2015;6(32):33486–99.

62. Chen T, Song D, Min Z, Wang X, Gu Y, Wei B, et al. Perioperative dynamic alterations in peripheral regulatory T and B cells in patients with hepatocellular carcinoma. J Transl Med. 2012;10:14.