Human Immunology 76 (2015) 615–621

Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/humimm

Review

Regulatory B cell: New member of immunosuppressive cell club

Tingting Ding [a,b,c,d], Fan Yan [a,c,d], Shui Cao [b,c,d,*], Xiubao Ren [a,b,c,d,*]

[a] Department of Immunology, Tianjin Medical University Cancer Institute and Hospital, Tianjin 300060, China
[b] Department of Biotherapy, Tianjin Medical University Cancer Institute and Hospital, Tianjin 300060, China
[c] Key Laboratory of Cancer Immunology and Biotherapy, Tianjin 300060, China
[d] National Clinical Research Center of Cancer, China

ARTICLE INFO

Article history:
Received 25 March 2015
Revised 17 August 2015
Accepted 12 September 2015
Available online 15 September 2015

Keywords:
Regulatory B cells
Immuno-suppressive environment
Tumor immunology
B cell-based therapy

ABSTRACT

Historically, the pivotal role of B cells or B lymphocytes in immunity has been attributed to the production of antibodies. They were also demonstrated to present antigens to T cells and to secrete cytokines, thereby acting as positive regulators in immune responses. A series of studies on autoimmune diseases, however, led researchers to find a unique subset of B cells, later described as "regulatory B cells" (Bregs), that has the ability to suppress immune responses. Bregs occur not only in autoimmune diseases, but also in inflammation and transplantation. Furthermore, recently published literatures suggested that Bregs contributed to the growth and metastasis of certain cancers. In this review, we will discuss these unique subsets of B cells in different kinds of disorders, with particular emphasis on the mechanisms of their immunoregulatory role that were collected from mice and humans.

Contents

Abbreviations: Bregs, regulatory B cells; tBregs, tumor-evoked Bregs; Tregs, regulatory T cells; EAE, experimental autoimmune encephalomyelitis; CIA, collagen-induced arthritis; MZ, marginal zone; T2-MZP, transitional 2 marginal zone precursor; Tim-1, T-cell Ig domain and mucin domain protein 1; GrB, Granzyme B; TLR, toll like receptor; LPS, lipopolysaccharide; GITRL, glucocorticoid-induced tumor necrosis factor ligand; GITR, TNFR family-related protein; LIT, local inhalational tolerance; HLN, hilar lymph node; DMBA/TPA, 7,12-dimethylbenz[α]anthracene/12-O-tetradecanoylphorbol 13-acetate; GAL-1, Galectin-1; 5-LO, 5-lipoxygenase; FLAP, 5-lipoxygenase-activating protein; LTB4, leukotriene B4; PPARa, peroxisome proliferator–activated receptor a; STAT3, Signal Transducer and Activator of Transcription 3; IDO, indoleamine-2,3-dioxygenase; HCC, hepatocellular carcinoma; cGVHD, Chronic Graft Versus Host Disease; tolDC, tolerogenic dendritic cell.

* Corresponding authors at: Department of Biotherapy, Tianjin Medical University Cancer Institute and Hospital, Tianjin 300060, China.
E-mail addresses: caoshui9999@163.com (S. Cao), renxiubao@tjmuch.com (X. Ren).

http://dx.doi.org/10.1016/j.humimm.2015.09.006
0198-8859/

1. Introduction

The first clues indicating B cells as immune suppressor by producing "inhibitory antibodies" were found decades ago [1], but significant researches on these negative regulators did not occur until 1996, when Wolf and colleagues proposed that B cells might contribute to the immune deviation from Th1 to Th2 cytokines in murine acute experimental autoimmune encephalomyelitis (EAE) model [2]. Mizoguchi et al. suggested that murine B cells played a suppressive role in the development of colitis by secreting auto-antibodies to clear apoptotic cells in the colon (epithelial cells and lamina propria cells), preventing tissue damage caused by the harmful exposure to self antigens [3]. Mature B cells in mice also functioned by directly eliminating pathogenic $CD4^+TCR\alpha^-\beta^+$ T cells or suppressing their proliferation through co-stimulatory molecule interactions such as CD40–CD154 and CD86–CD28, thus inhibited the development of colitis [4]. In the ensuing years after these initial studies, a considerable evidence gathered from various diseases, including autoimmune disorders [5,6], inflammation [7,8] and transplantation [9,10], had reinforced the theory of B cells as potential negatively regulatory cells in immune response.

Though seemly different, cancers and autoimmune diseases are both outcomes of dysfunction of immune regulatory machinery that should be in precise control of protecting oneself and attacking the enemies-lack of immune regulation facilitates autoimmune diseases, while over-suppression of immune effectors results in cancer development [11]. The extensive set of evidence confirmed the negative role of B cells in immune-related diseases in both mice and humans. Whether suppressive B cells are hijacked by cancer cells to defeat anti-tumor immune responses remains to be established. There were clinical observations that B cell infiltration was correlated with poor outcome in metastatic ovarian carcinoma [12]. B-cell knockout mice also showed enhanced anti-tumor immunity after challenge with certain tumors [13], suggesting that B cells can function as negatively regulatory cells in some tumor settings. What's more, recent data from BALB/c murine model first showed the existence of a unique subset of B cells that can promote breast cancer lung metastasis [14]. In this review, we will highlight the phenotypes, origin, possible roles and mechanisms of regulatory B cells (Bregs) in autoimmune diseases, inflammation, transplantation and cancers in mice and humans.

2. Various phenotypes of Bregs

Until recently, the exact surface molecules of Bregs have been elusive. Various markers, alone or combined with others, were used to identify Bregs in immune-related diseases. Previous studies in mice identified Bregs as $CD5^+$ B1a cells, $CD21^+CD23^-$ marginal zone (MZ) cells or $CD1d^+CD21^+CD23^+IgM^{hi}$ transitional 2 marginal zone precursor (T2-MZP) B cells [15]. Later an IL-10-producing Breg subpopulation with a phenotype of $CD1d^{hi}CD5^+CD19^+$, termed as B10 cells, was demonstrated to be suppressive in the study of mice models [16]. In humans, $CD19^+CD24^{+/int}CD38^{+/int}$ [17–20] and $CD24^{hi}CD27^+$ [21–24] were widely used as markers for Bregs. Other rarely reported Breg subsets included $CD1d^{hi}CD19^+$ B cells [25], $CD19^+CD25^+$ B cells [26], $CD19^+CD5^+Foxp3^+$ B cells [27,28] and $CD25^+CD71^+CD73^-$ B cells [29] in human peripheral blood. Since the definition of Bregs was based on their suppressive function mostly mediated by IL-10, intracellular IL-10 staining became a more straight-forward way to identify these cells in the present [30]. Meanwhile, novel surface markers, which could facilitate viable purification, remained in the hot spot for further functional study of Bregs. Ding et al. demonstrated that in mice, over 70% $CD19^+IL\text{-}10^+$ splenic B cells were T-cell Ig domain and mucin domain protein 1 (Tim-1) positive [31]. Moreover, Tim-1-mutant mice showed a profound defect in IL-10 production by Bregs and developed spontaneous autoimmunity associated with hyperactive T cells, indicating a critical role of Tim-1 in maintaining Breg function [32]. Given that $CD25^+Foxp3^+$ is believed to be the determinative and also functional marker for regulatory T cells (Tregs) [33], it is reasonable to speculate that combination of intracellular molecules and surface makers would be a better way to accurately identify Bregs.

In contrast with Breg-mediated suppression in the immune response, cancer related Bregs remained elusive for their existence and phenotypes. Shimabukuro-Vornhagen and colleagues detected tumor-infiltrating B cells in colorectal cancer. Results showed that frequency of $CD19^+CD24^{hi}CD38^{hi}$ B cells were low in primary tumors, but significantly higher in the metastatic tissues, indicating that this B cell subset as Bregs which contributed to tumor metastasis [34]. However, despite providing candidate markers for Bregs in colorectal cancer, they did not further investigate their function. To date, there are only two subsets of B cells that have been demonstrated to exert immunosuppressive effect in certain cancers, namely $CD25^{hi}B220^+CD19^+$ tumor-evoked Bregs (tBregs) in mice breast cancer [14]and $CD19^+CD38^+CD1d^+IgM^+CD147^+$ Granzyme B (GrB)-producing Bregs in the microenvironment of various human solid tumors [35].

3. Origin of Bregs

Mauri et al. proposed that Bregs arised from a common progenitor, named T2-MZP B cells, as they encompass most of the indicated markers for Bregs [36]. T2-MZP B cells are at immature developmental stage and highly responsive to BCR engagement [37,38]. In the presence of toll like receptor (TLR) ligands, they released first wave of IL-10 [36,39]. As inflammation cascade ensued, B cells received BCR, CD40, or CD80/CD86 activating signals, and robustly enhanced IL-10 production [16,36,40]. IL-10 played an essential role in inducing immunoregulatory phenotype of B cells that exerted substantial anti-inflammatory and immunosuppressive functions [41].

However, some of the identified Breg subsets physiologically exist as part of normal immune system. $CD25^{hi}CD27^{hi}CD86^{hi}$-$CD1d^{hi}IL\text{-}10^{hi}TGF\text{-}\beta^{hi}$ Bregs isolated from peripheral blood of healthy donors have been demonstrated to be suppressive without *ex-vivo* stimulation [26]. $CD21^+$ B cells were constitutive in sheep Peyer's patches of normal intestinal tissues. They spontaneously secreted IL-10 and directly suppressed the effects of IFN-γ, IFN-α and IL-12 [42]. Therefore, as its counterpart Tregs [43], Bregs are also comprised of innate subpopulations which spontaneously secreted inhibitory cytokine IL-10, and induced subsets that needed extra stimuli to produce and secret IL-10 [44].

4. Function and mechanisms of Breg in immune-related diseases

Since the discovery of suppressive B cells, scientists have begun to unravel how Bregs suppress immune responses. Different laboratories have confirmed that the production of IL-10 represented the main mechanism of heterogeneous Bregs' actions.

4.1. IL-10

So far, studies on Bregs have demonstrated the essential role of IL-10 in Breg-mediated immunosuppression [25,45,46]. Data from independent groups were in agreement with these observations. In experimental arthritis mice, Evans et al. confirmed that T2-MZP B cells suppressed disease and pro-inflammatory cytokines IFN-γ production by T cells via the release of IL-10 [47]. In EAE mice,