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REVIEW

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Regulatory T cells induced by B cells: a novel subpopulation of regulatory T cells

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Abstract

Regulatory T cells play a crucial role in the homeostasis of the immune response. In addition to $CD4^+Foxp3^+$ regulatory T cells, several subsets of $Foxp3^-$ regulatory T cells, such as T helper 3 (Th3) cells and type 1 regulatory T (Tr1) cells, have been described in mice and human. Accumulating evidence shows that naïve B cells contribute to tolerance and are able to promote regulatory T cell differentiation. Naïve B cells can convert $CD4^+CD25^-$ T cells into $CD25^+Foxp3^-$ regulatory T cells, named Treg-of-B cells by our group. Treg-of-B cells express LAG3, ICOS, GITR, OX40, PD1, and CTLA4 and secrete IL-10. Intriguingly, B-T cell-cell contact but not IL-10 is essential for Treg-of-B cells induction. Moreover, Treg-of-B cells possess both IL-10-dependent and IL-10-independent inhibitory functions. Treg-of-B cells exert suppressive activities in antigen-specific and non-antigen-specific manners in vitro and in vivo. Here, we review the phenotype and function of $Foxp3^+$ regulatory T cells, Th3 cells, Tr1 cells, and Treg-of-B cells.

Keywords: Regulatory T cells, Lymphocyte-activation gene 3, Programmed cell death protein 1, Inducible T-cell co-stimulator, Interleukin 10, Cytotoxic T lymphocyte-associated antigen-4, Treg-of-B cells

Background

Regulatory T cells are a therapeutic strategy for immune dysregulated diseases and a potential target for cancer immunotherapy. In addition to $CD4^+Foxp3^+$ regulatory T (Treg) cells, studies have emphasized the roles of $CD4^+Foxp3^-$ regulatory T cells, such as TGF-β-producing T helper 3 (Th3) cells, IL-10-producing type 1 regulatory T (Tr1) cells, and others. Accumulating evidence demonstrate that naïve B cells possess the ability to promote naïve $CD4^+$ T cells into $CD25^+$ $Foxp3^-$ regulatory T cells with the expression of lymphocyte activation gene-3 (LAG3, CD223), inducible co-stimulator (ICOS, CD278), programmed cell death protein 1 (PD1, CD279), and glucocorticoid-induced TNFR family-related protein (GITR). B-cell-induced $CD4^+Foxp3^-$ regulatory T cells exert the inhibition through both IL-10-independent and cell-cell contact-dependent mechanisms, although they also show IL-10-mediated suppression. Furthermore, these B cell-induced regulatory T cells protect mice from several immune disorders, including graft-versus-host disease, experimental allergic asthma, collagen-induced arthritis, and inflammatory bowel disease. Here, we review the phenotypes and functional mechanisms of thymus-derived and peripherally derived $CD4^+Foxp3^+$ regulatory T cells, Th3 cells, Tr1 cells, B-cell-induced $Foxp3^-$ regulatory T cells, and B-cell-induced $Foxp3^+$ regulatory T cells. The present article focuses on B-cell-induced $CD4^+Foxp3^-$ regulatory T cells, which we have named Treg-of-B cells.

Main text

$CD4^+Foxp3^+$ regulatory T cells

Sakaguchi et al. demonstrated that $CD4^+CD25^+$ T cells contributed to maintaining self-tolerance in a non-antigen-specific manner [1]. Immune dysregulation, polyendocrinophathy, enteropathy X-linked (IPEX) syndrome is a recessive immune disorder. Reports showed that IPEX is caused by mutations of *FOXP3* gene, which is orthologouse of the *Foxp3* gene mutated in scurfy mouse [2–4]. Further studies demonstrated that Foxp3 expressed predominantly in $CD4^+CD25^+$ T cells than $CD4^+CD25^-$ T and $CD19^+$ B cells. Moreover, retroviral transduction of Foxp3 in naïve $CD4^+CD25^-$ T cells converted these cells toward Treg cells phenotype. Thus, Foxp3 has been identified as the master transcription factor of Treg cells [5].

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Thymus-derived Foxp3$^+$ regulatory T cells

In addition to Foxp3, thymus-derived CD4$^+$CD25$^+$Foxp3$^+$ regulatory T (tTreg) cells highly expressed Helios, cytotoxic T lymphocyte-associated antigen-4 (CTLA4, CD152), neuropilin-1, GITR, galectin-1, IL-10, and granzyme B [6]. tTreg cells could be activated in an antigen-specific fashion and exerted suppressive activity in a non-antigen-specific fashion [7]. tTreg cells produced many inhibitory cytokines, including TGF-β1, IL-10, and IL-35, to downregulate immune responses [8]. Furthermore, tTreg cells exhibited cell-cell contact-dependent suppression via latency-associated peptide (LAP) [9], CD39 (ectonucleoside triphosphate diphosphohydrolase-1, ENTPD1) and CD73 (ecto-5′-nucleotidase) [10], and cytosolic cyclic adenosine monophosphate (cAMP) [11]. Reports showed that tTreg cells induced effector T cell apoptosis via various pathways, including deprivation of IL-2 and IL-7 [12], disruption of effector cell membrane integrity by granzyme B [13], galectin-1-induced apoptosis [14], and the engagement of TNF-related apoptosis inducing ligand (TRAIL)-death receptor 5 (DR5) [15]. Additionally, tTreg cells inhibited effector T cell activation via downregulation of costimulatory molecules on DCs through CTLA4 [16] and LAG3 [17]. These studies indicate that tTreg cells are a polyclonal population, and the above mentioned complicated mechanisms result in maximal immunosuppression during homeostasis.

Peripherally derived Foxp3$^+$ regulatory T cells

Foxp3$^+$ regulatory T cells induced in vivo are called peripherally derived regulatory T (pTreg) cells and those generated in vitro are called in vitro-induced regulatory T (iTreg) cells [18]. Studies demonstrated that CD4$^+$Foxp3$^-$ T cells differentiated into Foxp3$^+$CD25$^+$CD45RB^{low} anergic T cells with suppressive functions in the presence of TGF-β1 in vitro as well as in vivo [19] and rescue Foxp3-deficient scurfy mice [20]. In the absence of tTreg cells, oral antigen administration induced the generation of CD4$^+$CD25$^+$Foxp3$^+$ regulatory T cells in a TGF-β1-dependent manner [21]. Gut-associated lymphoid tissue CD103$^+$ DCs played an important role in the *de novo* conversion of naïve T cells into pTreg cells, and retinoic acid facilitates that process [22]. Additionally, lung-resident tissue macrophages expressed retinal dehydrogenases, and TGF-β1 promoted pTreg cell induction under steady-state conditions [23]. Evidence has shown that the tumor environment induced pTreg cell generation to escape immune clearance [24]. One report demonstrated that tTreg and pTreg cells shared similar phenotypes, and neuropilin-1 serving as a surface marker to distinguish tTreg cells from pTreg cells [25].

CD4$^+$Foxp3$^-$ regulatory T cells

The most well-defined Foxp3$^-$ regulatory T cells are Th3 cells and Tr1 cells. Th3 cells have been identified as TGF-β-producing CD4$^+$LAP$^+$ T cells exhibiting TGF-β-mediated suppression [26]. Tr1 cells have been characterized by the higher production of IL-10 and IL-10-mediated suppressive functions [27].

T helper 3 cellsl

Th3 cells were first found in mesenteric lymph node CD4$^+$ T cells as single cell clones producing TGF-β1 after oral administration of self-antigen [28]. Oida et al. found that primary purified CD4$^+$CD25$^-$LAP$^+$ regulatory T cells protected mice from T-cell-induced colitis in a TGF-β1-dependent manner [29]. Tumor environment CD4$^+$CD25$^-$CD69$^+$Foxp3$^-$LAP$^+$ T cells expressed IL-2 receptor β chain, produced TGF-β1, and exerted TGF-β1-mediated functional activity [30]. Gandhi et al. showed that human peripheral CD4$^+$LAP$^+$Foxp3$^-$CD69$^+$ T cells exhibited TGF-β1- and IL-10-dependent suppression in the periphery in healthy individuals [31]. Furthermore, human CD4$^+$CD25$^+$LAP$^+$Foxp3$^-$ T cells in colorectal tumors expressed LAG3 and exhibited inhibitory functions through TGF-β1 and IL-10 [32]. To date, the specific transcription factor for Th3 cells remains to be identified.

Type 1 regulatory T cells

The first study on Tr1 cells reported that naïve T cells repeated stimulation with peptide-pulsed splenocytes in the presence of IL-10 induced IL-10-producing CD4$^+$ T cells with suppressive ability and hypoproliferative ability [33]. Akbari et al. demonstrated that bronchial DCs promoted Tr1 cells in vitro in an IL-10-and ICOS/ ICOS ligand (ICOSL)-dependent manner in the context of nasal tolerance [34]. By microarray analysis Tr1 and Th0 cell clones, CD49b, LAG3, and CD226 have been identified as the surface markers of Tr1 cells [35].

It has been shown that c-Maf transactivated IL-10 expression under CD4$^+$ Th17 polarization conditions [36]. Aryl hydrocarbon receptor (AhR) and c-Maf facilitated IL-10 production in CD4$^+$ T cells in an IL-27-dependent fashion [37, 38]. Another study reported that c-Maf, IL-21, and ICOS were essential for IL-27-induced Tr1 cell generation [39]. Consistent with these observations, Awasthi et al. showed that CD4$^+$Foxp3$^+$ regulatory T cell-educated DCs produced IL-27 and promoted Tr1 cell generation [38]. Nasal anti-CD3ε antibody treatment induced the expression of IL-10, IL-27, and TGF-β in nasal tolerogenic DCs, which further facilitated Tr1 cell generation through c-Maf, IL-21, and AhR [40]. Orally antigen treated tolerogenic Peyer's patch DCs increased the production of IL-10 and IL-27 and promoted the induction of Tr1 cells [41]. Carrier et al. reported that

constitutive ectopic expression of GITR ligand (GITRL) on MHCII$^+$ APCs increased IL-27 production and further upregulated the expression of c-Maf and IL-10 in T cells [42].

In addition to cytokines, reports have demonstrated that Tr1 cells could be induced by different proteins, different APCs, and different types of T cells. Galectin-1 promoted IL-10 expression in CD4$^+$ T cells in an APC-independent pathway by binding to CD45 on T cells and inducing the expression of c-Maf and AhR [43]. In vitro activation of CD4$^+$CD44^{hi}Foxp3$^-$ T cells through anti-CD3/CD28 antibodies and IL-2 generated CD49b-, LAG3-, c-Maf-, and AhR-expressing Tr1 cells [44]. Nie et al. found that long-term stimulation of lipopolysaccharide (LPS) conferred ICOSL expression in bone marrow-derived mast cells through NF-κB, subsequently promoting Tr1 cell development [45]. These reports suggest that the generation mechanisms for Tr1 cells consist of a fine-tuning program.

B cells in tolerance induction

B cells have been shown to have a role in the fine equilibrium for immune tolerance. Genetically B-cell-deficient mice delayed recovery from experimental autoimmune encephalomyelitis and suggested B cells might contribute to immune modulation [46]. Collagen fragments expressed on B cell MHC class II sufficiently delayed the onset and decreased the severity of arthritis [47]. The role of B cells in oral tolerance has been investigated because B-cell-deficient mice exhibit a defective oral tolerogenic response characterized by lower levels of IL-10 and TGF-β in the spleen and gut-associated lymphoid tissues [48]. Gutgemann et al. showed that B cells interacted with T cells at the B-T border in the spleen after 4 h of oral administration of proteins [49]. Furthermore, orally antigen treated B cells have an enhanced ability to induce CD4$^+$ regulatory T cells in vitro [50]. Anterior chamber-associated immune deviation was characterized by antigen-specific downregulation of the immune response to antigen occurs in the anterior chamber of the eye [51], and this phenomenon was abrogated in the absence of B cells [52]. Studies suggested that splenic B cells presented antigens derived from ocular APCs and induced CD4$^+$CD25$^+$ regulatory T cells via IL-10 and MHC class II [52, 53]. These evidence emphasize the role of B cells in the induction and maintenance of self-tolerance.

There is accumulating evidence demonstrating that specific B cell subsets modulate immune responses named as regulatory B (Breg) cells by Mizoguchi et al. [54]. Breg cells dampened immune responses though the secretion of IL-10, TGF-β, directly interact with activated CD4$^+$ T cells, and the production of antibody that neutralized harmful soluble molecules [55]. Several Breg cells have been described in mice and IL-10-producing Breg cells are the most widely studied [56]. IL-10 produced by a variety of Breg cells suppressed inflammatory cytokines and promoted regulatory T cell differentiation [57, 58]. These indicate that B cells contribute to the maintenance of tolerance.

In addition, naïve B cells functioned as antigen-presenting cells presented antigen and resulted in T cell tolerance to antigen [59]. Raimondi et al. demonstrated that adoptive transfer of antigen-presenting B cells four times in a week lead to antigen-specific CD4$^+$ T cells tolerance independent of naïve or activated B cells [60, 61]. Antigen-presenting follicular B, marginal zone B, and B-1a cells rendered antigen-specific T cells hyporesponsiveness without Foxp3$^+$ Treg cells induction [62]. One study reported that B cells contributed to Treg cells homeostasis and cooperated with Treg cells to ameliorate inflammation [63]. These findings suggest that B cells play a role in immune modulation and might through the manipulation of CD4$^+$ Treg cells.

B-cell-induced CD4$^+$Foxp3$^-$ Treg-of-B cells

Naïve splenic B2 cells, peritoneal B-1a cells, and mucosal Peyer's patch B cells have been shown to induce CD4$^+$CD25$^+$Foxp3$^-$ regulatory T cells, which named Treg-of-B cells by our group, without additional cytokines or molecules [50, 64]. Naïve splenic B cells and naïve splenic CD4$^+$CD25$^-$ T cells formed a stable immunological synapse and promoted CD62L^{hi}CD25$^+$Foxp3$^-$ regulatory T cell generation [65]. In our reports, transwell insertion during B-T coculture abrogated Treg-of-B cell induction suggesting that cell-cell contact between B and T cells was essential. By applying blocking antibodies during B-T coculture, both CD80 and CD86 on splenic B cells were required to induce functional Treg-of-B [64]. In consistent with above, Etemire et al. demonstrated that addition of anti-CD28 antibody to the B-T cell co-culture decreased the suppressive activity of Treg-of-B cells. Lower activity of the PI3K/AKT pathway was associated with Foxp3$^-$ regulatory T cell generation [66]. IL-10-deficient Treg-of-B cells and Treg-of-B cells induced in the presence of anti-IL-10 neutralizing antibody remained their suppressive function suggesting that IL-10 was not critical for their induction [64, 67, 68]. These results suggest that the interaction between B-T cells is indispensable for the differentiation of Treg-of-B cells.

Treg-of-B cells differ from well-known Treg cells

To date, several molecules have been identified for their strong association with Treg-of-B cells that are conserved in single peptide-induced and anti-CD3/CD28 antibodies-induced methods. Treg-of-B cells expressed higher levels of LAG3, ICOS, PD1, GITR, OX40 (CD134), and CTLA4 compared to those on naïve CD4

$^{+}CD25^{-}$ T cells (Fig. 1). Another group demonstrated that antigen-presenting B cells facilitated naïve T cells to convert into $CD4^{+}CD25^{+}CD62L^{+}Foxp3^{-}$ IL-10-producing regulatory T cells [65]. Our published and unpublished data showed that Treg-of-B cells did not express Foxp3, Helios, or neuropilin-1 [67, 69], and these also confirmed by using Foxp3-GFP reporter mice [64]. These evidence differentiates Treg-of-B cells from Foxp3-expressing Treg cells (Table 1).

Th3 cells are well-known that they exert TGF-β-dependent inhibition and express LAP on surface [26]. Although Treg-of-B cells produced TGF-β compared with naïve $CD4^{+}CD25^{-}$ T cells [68, 69], TGF-β did not play a role in their suppressive mechanism [64]. In our unpublished data, Treg-of-B cells did not express LAP. These indicate that Treg-of-B cells are different from Th3 cells.

Tr1 cells are characterized by IL-10-mediated suppression and the higher production of IL-10 [27]. In recent years, CD49b, LAG3, and CD226 were identified as the surface markers for human and mouse Tr1 cells [35]. In our results, Treg-of-B cells produced a higher amount of IL-10 compared with naïve $CD4^{+}CD25^{-}$ T cells [50, 64]. Repeated stimulation of B cells induced long-term Treg-of-B cells with higher expression of ICOS, CTLA4, CD49b, and c-Maf, but not CD226. In addition to the difference in surface marker, IL-10 seems to be dispensable in the inhibitory mechanism of Treg-of-B cells and these would be described in the later section. These observations suggest that this Treg-of-B cell is a new type of regulatory T cells and different from Tr1 cells.

In addition to regulatory T cells, Treg-of-B cells did not share characteristics with follicular T helper (T_{FH}) cells. T_{FH} cells expressed BCL-6, CXCR5, ICOS, PD1, and c-Maf and CXCR5 conferred T_{FH} cells migration to B follicles [67, 70]. Although Treg-of-B cells expressed ICOS, PD1 and c-Maf, they did not express the critical molecule BCL-6 and CXCR5 (data not shown). These indicate that Treg-of-B cells could not migrate into follicle to facilitate B cell as T_{FH} cells did.

Furthermore, Treg-of-B cells were hypoproliferative to stimulation and did not express T-bet, GATA3, or ROR-γt ([64] and our unpublished data). Treg-of-B cells produced higher level of IL-10, TGF-β, and IL-4 and lower or no IL-2, IFN-γ, IL-17, or tumor necrosis factor (TNF)-α [68, 69, 71]. These data confirm that Treg-of-B cells have anergic characteristics and are not proinflammatory T helper cells.

Application of Treg-of-B cells

The therapeutic effects of $CD4^{+}Foxp3^{-}$ Treg-of-B cells has been described in several murine disease models (Fig. 2). Adoptive transfer of Treg-of-B cells prevented mice from graft-versus-host disease in a murine model of heart transplantation [65]. Peyer's patch B-cell-induced ovalbumin (OVA)-specific Treg-of-B cells

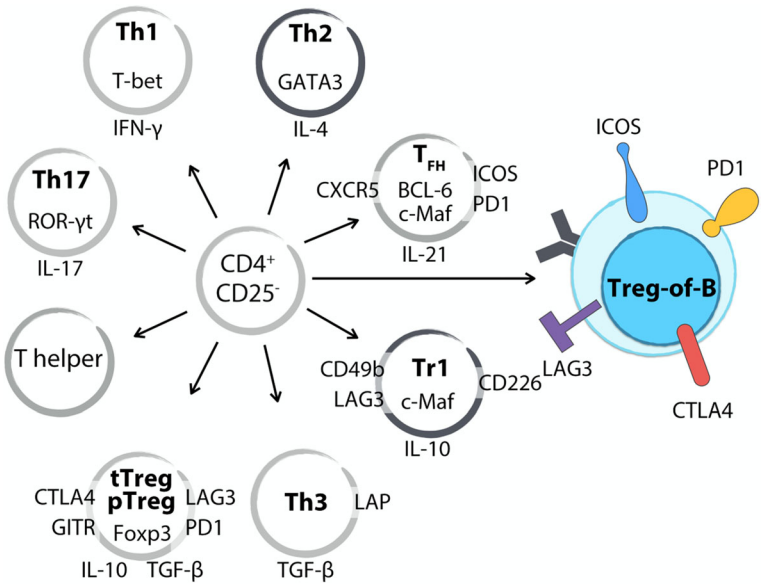

Fig. 1 Treg-of-B cells differ from well-known regulatory T cells and T helper cells. With regard to transcription factors, Treg-of-B cells do not express Foxp3, ROR-γt, T-bet, or BCL-6. Repeated stimulation increased the expression of c-Maf in long-term Treg-of-B cells. Treg-of-B cells produce a higher amount of IL-10 and TGF-β and lower amounts of IL-17 and IFN-γ. Several Treg-associated molecules have been described in Treg-of-B cells, including LAG3, PD1, ICOS, CTLA4, and GITR. Long-term cultured Treg-of-B cells express CD49b but do not express CD226 as Tr1 cells. Treg-of-B cells do not express ROR-γt as Th17 cells do, do not express T-bet as Th1 cells do, do not express CXCR5 or BCL-6 as T_{FH} cells do, and do not express LAP as Th3 cells do. These indicate Treg-of-B cell is a new type of $CD4^{+}$ regulatory T cells

Table 1 The differences between Treg-of-B cells and the well-known Treg cells, including Foxp3$^+$ Treg, Th3, and Tr1 cells

Treg cells	Biomarkers	Effector molecules	Transcription factors	Assisted cell types
Treg-of-B	$CD4^+CD25^+Foxp3^-LAG3^+ICOS^+PD1^+GITR^+OX40^+$	Majorly contact-dependent IL-10, LAG3, and CTLA4 has reported in reference	Undefined	B cells
Foxp3$^+$ Treg	$CD4^+Foxp3^+$ Helios has reported in reference	IL-10, TGF-β, IL-35, LAP, CD39/CD73, cAMP, CTLA4, LAG3, IL-2/IL-7 consumption, granzyme B, galectin-1, DR5…etc	Foxp3	DCs, macrophages, B cells
Th3	$CD4^+Foxp3^-LAP^+$	Majorly TGF-β IL-10 has reported in reference	Undefined	DCs
Tr1	$CD4^+Foxp3^-CD49b^+$ $LAG3^+$ $CD226^+$	Majorly IL-10 TGF-β, CTLA4, and CD226 has reported in reference	Undefined c-Maf, AhR has reported in reference	DCs, macrophages, B cells, mast cells…etc

protected mice from Th2-cell-mediated airway hyperresponsiveness (AHR), airway inflammation, and IgE hyperproduction in allergic asthma in an antigen-specific fashion [50]. In addition, splenic B-cell-induced OVA-specific Treg-of-B cells shared several characteristics with oral antigen administration activated $CD4^+CD25^+$ T cells, including elevated expression levels of ICOS, PD1, and CTLA4 and enhanced non-antigen-specific suppressive functions [69]. Monoclonal antibody-induced Treg-of-B cells prevented mice from osteolysis and joint inflammation in collagen-induced arthritis [71]. Prophylactic transfer of Treg-of-B cells also protected mice from T-cell-induced Th1- and Th17-dominant inflammatory bowel disease [68]. Taken together, naïve B cell without cytokines or chemical supplements is able to induce functional $CD4^+Foxp3^-$ regulatory T cells and that B-cell-induced regulatory T cells is an economical strategy for cellular therapy for different T-helper-cell-dominant inflammatory diseases.

Treg-of-B cells possess both IL-10-dependent and IL-10-independent suppressive functions

IL-10 as an anti-inflammatory cytokine is an issue in Treg-of-B cells suppressive function. As described above, IL-10 does not play a crucial role in Treg-of-B cells differentiation. Chen and Chu et al. reported that LAG3 $^+$Treg-of-B cells produced higher amount of IL-10 and both IL-10 and LAG3 play the roles in their inhibitory mechanisms [71, 72]. Long-term Treg-of-B cells increased expression levels of CTLA4 and IL-10, both of which were involved in their suppressive functions [67]. IL-10-deficient mice were used to confirm the role of IL-10 in the regulation; however, IL-10-deficient Treg-of-B cells remained suppressive activities [64, 68]. IL-10 seems to be dispensable in the inhibitory mechanism of Treg-of-B cells. Although IL-10 plays a more important role in long-term Treg-of-B cells than in short-term Treg-of-B cells, three-day short-term culture is sufficient

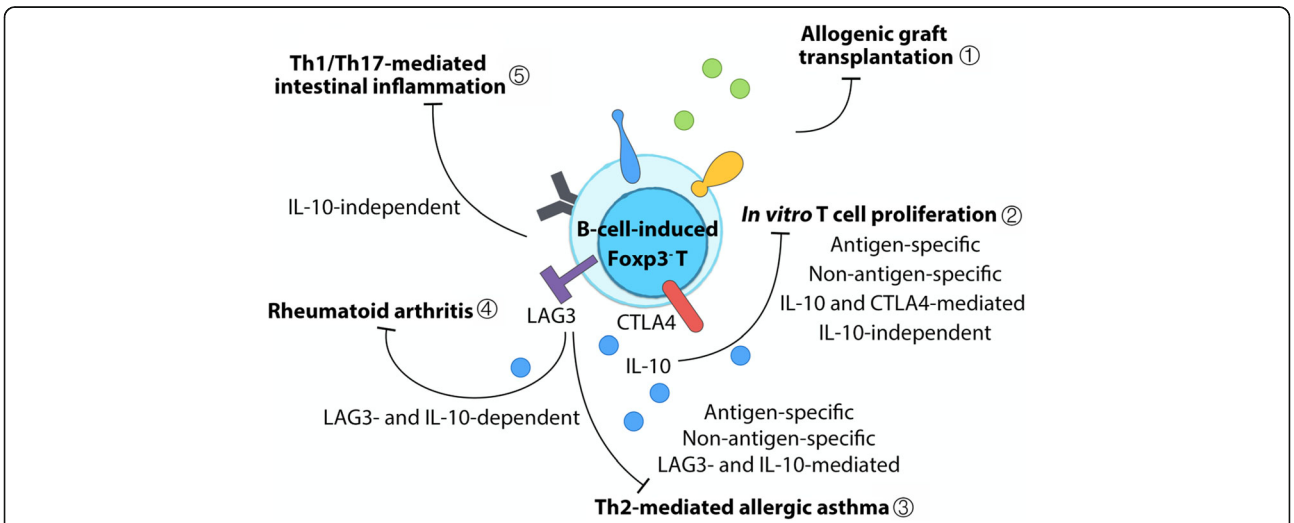

Fig. 2 B-cell-induced $CD4^+Foxp3^-$ regulatory T cells treatment in disease models. Treg-of-B cells have been used for therapy in several animal models. Pre-treated Treg-of-B cells prevented allogeneic heart transplantation-induced tissue rejection ①. Treg-of-B cells inhibited antigen-specific and non-antigen-specific T cell proliferation in vitro through IL-10-mediated and IL-10-independent mechanisms. Both IL-10 and CTLA4 play roles in long-term Treg-of-B cells suppressive functions ②. In vivo treatment with Treg-of-B cells protected mice from Th2-mediated allergic asthma in an antigen-specific manner and in a non-antigen-specific fashion ③. Both LAG3 and IL-10 may play roles in the protection of mice from allergic asthma and rheumatoid arthritis ④. IL-10-deficient Treg-of-B cells prevented mice from T-cell-mediated intestinal inflammation ⑤

for the generation of Treg-of-B cells. These suggest that there might be unknown inhibitory factors in Treg-of-B cells suppressive functions.

Studies have demonstrated that ICOS controls IL-10 production and functional CTLA4 expression in Treg cells [73–75]. PD1 recruits SHP-1 and SHP-2 to intrinsically downregulate T cell receptor signaling, which maintains an anergic phenotype in Treg cells [76, 77]. Mouse Treg cells constitutively expressed GITR and OX40 and involved the tTreg cells development as well as their functions [78–80]. All regulatory-T-related molecules on Treg-of-B cells, including IL-10, TGF-β, LAG3, CTLA4, ICOS, PD1, GITR, and OX40, might confer partial suppressive activities to compensate for single blockage or neutralization. The critical molecules controlling Treg-of-B cell phenotype and regulatory mechanisms remain priorities for investigation. The inhibitory functions of Treg-of-B cell depend on the suppressive molecules on the surface or soluble mediators that require short distance.

B-cell-induced $CD4^+Foxp3^+$ regulatory T cells

Reports have revealed the role of B cells in the development of Treg cells. Naïve primary B cells preferentially induced the expansion of allogenic $CD4^+Foxp3^+$ T cells rather than $CD4^+Foxp3^-$ T cells [81, 82]. Splenic B cells converted allogenic naïve T cells into $Foxp3^+$ regulatory T cells in the presence of TGF-β and IL-2, and peritoneal B cells induce Th17 cells [83]. Human CD40-activated B cells induced the differentiation of $CD25^+Foxp3^+CD62L^+$ regulatory T cells more efficiently than immature DCs [84, 85]. In contrast, reports demonstrated that murine CD40-activated B cells promoted $CD4^+$ T cell proliferation and effector functions [86, 87]. Furthermore, the frequency of intrathymic B cells correlated with that of tTreg cells, and B cells colocalized with tTreg cells in the thymus [88, 89]. Intrathymic B cells expressed autoimmune regulator (Aire), increased the levels of MHC class II and CD80, and contributed to T cell negative selection for central T cell tolerance [90, 91]. Taken together, there are unknown criteria, such as MHC class II-TCR signaling, the B cell activation status, and different types of tissue resident B cells, that may fine-tune the expression of Foxp3 in B-cell-induced regulatory T cells.

Conclusions

To date, we know that naïve antigen-presenting B cell is sufficient to induce $CD4^+Foxp3^-$ regulatory T cells without additional cytokines or chemicals in an IL-10- and IL-27-dispensable and cell-cell contact-dependent manner. The expression levels of characteristic molecules differentiate Treg-of-B cells from well-known T helper and regulatory T cells as a brand-new type of $CD4^+Foxp3^-$ regulatory T cells (Fig. 1). Treg-of-B cells possess IL-10-depedent, IL-10-independent, and cell-cell contact-dependent suppressive abilities in antigen-specific and non-antigen specific fashions. Compared to long-term Treg-of-B cells, short-term Treg-of-B cells act through multiple suppressive pathways, and thus a blockade strategy would be more easily overcome through compensation by other pathways. Treg-of-B cells exhibit immunomodulatory effects in Th2-, Th1-, and Th17-medated diseases and even allogeneic transplantation. Nevertheless, the physiological conditions or cues necessary for Treg-of-B cell generation remain unknown. What is the fine-tuning mechanism for B cells to induce $CD4^+Foxp3^-$ or expand $CD4^+Foxp3^+$ T cells? What factors determine the kinetics, memory, and maintenance? And, most importantly, how could we use Treg-of-B cells in immunotherapy?

Abbreviations

Breg: Regulatory B; Foxp3: Forkhead box P3; ICOS: Inducible T-cell co-stimulator; IL-10: Interleukin 10; iTreg: in vitro-induced Treg; LAG3: Lymphocyte-activation gene 3; PD1: Programmed cell death protein 1; pTreg: Peripherally derived regulatory T; TGF-β: Transforming growth factor-β; Th3: Type 3 helper; Tr1: Type 1 regulatory T; Treg: Regulatory T; Treg-of-B: B cell-induced regulatory T; tTreg: Thymus-derived regulatory T

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Authors' contributions

C-H C performed the literature reviewed and drafted the manuscript. B-L C supervised and critically reviewed the manuscript. Both authors read and approved the final manuscript.

Authors' information

None.

Ethics approval and consent to participate

Not applicable.

Consent for publication

None.

Competing interests

The authors declare that they have no competing interests.

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