

## B cells with regulatory properties in transplantation tolerance

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### Abstract

Induction of tolerance remains a major goal in transplantation. Indeed, despite potent immunosuppression, chronic rejection is still a real problem in transplantation. The humoral response is an important mediator of chronic rejection, and numerous strategies have been developed to target either B cells or plasma cells. However, the use of anti-CD20 therapy has highlighted the beneficial role of subpopulation of B cells, termed regulatory B cells. These cells have been characterized mainly in mice models of auto-immune diseases but emerging literature suggests their role in graft tolerance in transplantation. Regulatory B cells seem to be induced following inflammation to restrain excessive response. Different phenotypes of regulatory B cells have been described and are functional at various differentiation steps from immature to plasma cells. These cells act by multiple mechanisms such as secretion of immuno-suppressive cytokines interleukin-10 (IL-10) or IL-35, cytotoxicity, expression of inhibitory receptors or by secretion of non-inflammatory antibodies. Better characterization of the development, phenotype and mode of action of these cells seems urgent to develop novel approaches to manipulate the different B cell subsets and the response to the graft in a clinical setting.

**Key words:** Regulatory B cells; Suppression; Immuno-suppressive cytokines interleukin-10; Antibodies; Tolerance

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**Core tip:** Regulatory B cells have been characterized mainly in auto-immune diseases but emerging literature suggests their role in graft tolerance in transplantation. Regulatory B cells exhibit different phenotypes and act by multiple mechanisms such as secretion of immuno-

suppressive cytokines, cytotoxicity, expression of inhibitory receptors or secretion of non-inflammatory antibodies. Better characterization of the development, phenotype and mode of action of these cells seems urgent to develop novel approaches to manipulate the different B cell subsets and the response to the graft in a clinical setting.

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## INTRODUCTION

The major goal in the field of transplantation is to prevent allograft rejection due to the response of recipient's immune system against alloantigen. Despite strong advances in immuno-suppression regimens that allow the control of acute rejection, chronic rejection subsists and the lack of antigen specificity leads to increased risks for infectious diseases and malignancies<sup>[1,2]</sup>. Achievement of long-term immunologic tolerance, defined as long-term graft function in the absence of immunosuppression is difficult to achieve in humans. Nevertheless, operational tolerance has been reported in some liver and in more rare cases of kidney transplantations<sup>[3,4]</sup>. Therefore, understanding the mechanisms of tolerance in these patients and in animal models is of great importance for subsequent breakthroughs in the transplantation field. Last decades, research in transplantation has focused mostly on T cell-directed therapy. Nevertheless, the role of B cells in transplantation and especially in chronic rejection with their production of deleterious antibodies has recently pushed the immunologist to develop more B cell-targeted therapies. However, recent literature demonstrates that B cells can also be beneficial for the grafted tissue by the secretion of anti-inflammatory cytokines or by the production of protective antibodies. Among these populations, different subsets of regulatory B cells have been described. These findings have generated great interest and urge immunologists to modulate B cell-directed therapies to target specifically effector B cells while sparing regulatory B cells.

### **B cells are important actors of transplant rejection**

B cells play an important role in graft rejection by stimulating directly CD4<sup>+</sup> T lymphocytes to produce cytokines including interferon- $\gamma$  (IFN $\gamma$ ) interleukin-4 (IL-4) and IL-6<sup>[5]</sup>. B cells infiltrate allografts and locally stimulate effector T cells. Indeed, it has been demonstrated the presence of ectopic germinal centers in the transplanted tissue, called tertiary lymphoid tissues<sup>[6,7]</sup>.

The most deleterious role of B cells in transplantation is due to their differentiation in plasma cells producing high level of alloantibodies<sup>[8,9]</sup>. The mode of action of

these alloantibodies depends mainly of two mechanisms. The first is the activation of the complement proteolytic cascade and the second, the antibody dependent cellular cytotoxicity. These cytotoxic mechanisms are triggered by the fixation of alloantibodies on donor class I and II MHC molecules expressed especially by endothelial cells of the graft.

Classical pathway of complement activation (antibody-dependent) is induced by the fixation of the C1 component to the Fc fragment of antibodies bound to their antigen. The enzymatic complement cascade leads to the formation of an attack membrane complex (C5b, 6, 7, 8, 9) which forms a channel in the cell membrane and damages the endothelium<sup>[10]</sup>. Activated endothelial cells produce then pro-inflammatory cytokines such as IL-1, IL-8 and MCP-1 that attract neutrophils and monocytes in the graft, promote vascular permeability and the secretion of procoagulant factors. This cascading event results in bleeding, vascular thrombosis and causes ischemia and graft rejection<sup>[11]</sup>. The C4d resulting from the hydrolysis of C4b deposits on the graft cells and is a marker for activation of the humoral response<sup>[12]</sup>. Therefore, similarly to the presence of donor-specific antibodies, the C4d deposit detection on cells of the graft is usually a bad prognostic. It can provide an indication of graft outcome and the mechanisms involved in rejection. The deleterious effect of donor-specific antibodies can vary according to their concentration, affinity, isotype and their glycans groups at their Fc fragment<sup>[13,14]</sup>.

For cellular cytotoxicity mechanism, the Fc fragments of alloantibodies attached on the target cells are thus recognized by Fc fragment receptors on natural killer cells and macrophages. This recognition will lyse target cells *via* granzyme/perforin pathway and induces the production of pro-inflammatory mediators such as NO, ROS and TNF.

Different strategies have been developed to reduce the level of donor-specific antibodies in transplanted patients. One approach is to induce the depletion of B cells using depleting antibodies such as anti-CD20 (Rituximab) or anti-CD22. Rituximab is a glycosylated immunoglobulin G (IgG) chimeric mouse/human antibody. Rituximab binds to the CD20 antigen present at the cell-surface of the pre-B cells to terminally differentiated plasma cells. However, pro-B cells or mature plasma cells that produce about 90% of circulating IgG do not express CD20. Therefore, Rituximab is not able to prevent the regeneration of B cells from precursors, and does not directly prevent immunoglobulin productions<sup>[15]</sup>. Rituximab is efficient to treat auto-immune diseases and lymphoma<sup>[16]</sup>, however, in clinic, no convincing benefit was found so far as induction therapy in renal transplantation. However, in conjunction with other treatment it has been reported to have a beneficial effect on antibody production in chronic antibody-mediated rejection<sup>[17]</sup>. CD22 corresponds to an Ig superfamily glycoprotein that acts as an inhibitory receptor. In mice, anti-CD22 treatment, has been shown to deplete B cells in spleen, bone marrow, lymph nodes and peripheral

blood and since CD22 is also expressed on CD138<sup>+</sup> plasma cells, it decreases antibody production<sup>[18]</sup>. Thus, this antibody has been reported to reduce the anti-donor immune response in some mouse models of islet transplantation<sup>[19]</sup>. In Human, Epratuzumab, a humanized anti-CD22 antibody, has been shown to induce depletion of both naive and transitional B cells, to inhibit B cell activation and proliferation leading to a beneficial effect for treatment of systemic lupus erythematosus<sup>[20]</sup>. Other strategical approach has been to modulate the B cell response by targeting B-cell survival, proliferation and maturation. In this regard, to modulate the B-cell-activating factor (BAFF) pathway is promising<sup>[21]</sup>. BAFF belongs to the tumor necrosis factor family and is produced by monocytes, macrophages and dendritic cells. The three BAFF receptors, BAFF-R, transmembrane activator and calcium modulator and cyclophyllin ligand interactor and B-cell-maturation antigen (BCMA) are expressed on B cells (follicular, germinal centre and memory), with BCMA preferentially expressed on plasma cells<sup>[22]</sup>. *In vivo* BAFF neutralization has been shown to be efficient in experimental models of auto-immune diseases such as diabetes<sup>[23]</sup>. In transplantation, BAFF-deficient recipients exhibit prolongation of allograft survival in a murine cardiac model<sup>[24]</sup>. In addition, in an islet allograft model, BAFF blockade in conjunction with immunosuppression allowed long-term allograft survival<sup>[25]</sup>. In Human, BAFF-blockade has been used as strategy in the treatment of autoimmune diseases<sup>[26]</sup> such as systemic lupus erythematosus (SLE)<sup>[27]</sup>, and must now be tested in combination with immunosuppressive agents. Other strategies, such as plasmapheresis or injection of polyclonal intravenous immunoglobulins (IVIGs) allow a more rapid elimination of circulating donor-specific antibodies. The IVIGs treatment consists in injection of high doses of human purified IgG from many healthy donors. It is suggested that the immunosuppressive effect of these Ig involves their attachment to the donor-specific antibodies hindering their function but also through regulatory mechanisms induced by the fixation of their Fc fragment on Fc receptors present on many cells, such as B cells, dendritic cells and macrophages<sup>[28]</sup>. Bortezomib, a proteasome inhibitor blocking the production of antibodies and inducing apoptosis of plasma cells<sup>[29,30]</sup>, in combination with dexamethasone, is commonly used in multiple myeloma patients and represents a promising strategy. A humanized monoclonal antibody targeting the C5 complement compound (Eculizumab) and donor-specific antibodies function is also under study and provides encouraging results. It inhibits the formation of attack membrane complex, thus preventing the full complement activation<sup>[31]</sup>.

### **Emerging role of regulatory B cells**

As mentioned, B cells play a crucial role in graft rejection and auto-immune diseases by their ability to induce

inflammatory immune response through their role of antigen-presenting cells and their unique ability to produce and secrete deleterious antibodies. Therefore, numerous strategies have been developed to target these B cells or the produced antibodies.

However the last years, numerous studies have also reported regulatory properties of B cells<sup>[32,33]</sup>. Existence of B cells with suppressive properties has originally been highlighted in the 60 s. Authors observed that transfer into naive syngeneic mice of antibody-secreting cells from spleen of mice immunized with sheep red blood cells suppressed the antibody production against these sheep cells<sup>[34]</sup>. Then, concept of suppressive B cells was confirmed in 1974 in a model of guinea pig delayed hypersensitivity<sup>[35,36]</sup>. First report that described precisely the existence of regulatory B cells was in a model of experimental autoimmune encephalomyelitis (EAE) in mice. They showed that ( $\mu$ MT) B-cell deficient mice, developing EAE following myelin oligodendrocyte glycoprotein immunization, were not able to spontaneously enter in remission compared to wild-type mice<sup>[37]</sup>. Then, the regulatory properties of B cells have been described in mice in other models of autoimmune diseases, such as rheumatoid arthritis<sup>[38]</sup>, SLE<sup>[39]</sup>, diabetes<sup>[40]</sup>, colitis<sup>[41]</sup>, as well as more recently in infectious diseases and cancer<sup>[42-44]</sup>.

Since then, numerous studies in humans and rodents demonstrated common features of suppression by these cells in these different models. However, a single phenotype of regulatory B cells common to the different species is at present not yet identified.

### **Regulatory B cells in transplantation**

In transplantation, implication of B cells as inductors of tolerance has been demonstrated in several experimental models. In mouse pancreatic islet and cardiac MHC mismatched allograft models, administration of allogenic donor B cells together with CD40 ligand blockade prior transplantation induced prolongation of allograft survival<sup>[45,46]</sup>. In rat, B cells from donor administrated at the time of transplantation induce long-term kidney graft acceptance<sup>[47]</sup>. By CD45 immunosuppressive targeted therapy, that modulated T cell development and activation, it has been shown that tolerance was lost in ( $\mu$ MT) B cell-deficient mice and was restored by B cell transfer, demonstrating that tolerogenic effect requires host B cells<sup>[48]</sup>. These host B cells require the costimulatory molecules CD80, CD86 and CD40 to exert their suppression suggesting cooperation with T cells.

Ding *et al.*<sup>[49]</sup> demonstrated in mice that T-cell immunoglobulin and mucin domain 1 (Tim1) represents a cell-surface phenotypic marker of IL-10<sup>+</sup> enriched regulatory B cells and that enhancement of this population by anti-Tim1 antibody treatment prolong islet and cardiac allograft survival. In this model, depletion of CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells before transplantation leads to allograft rejection demonstrating that tolerance induction is dependent on interaction between regulatory

**Table 1** Phenotypes of different subpopulations of regulatory B cells identified in different compartments in mice according to the literature

Peritoneal cavity	Periarteriolar lymphoid sheaths	FO	MZ
Mature B1a cells: CD19 <sup>+</sup> CD11b <sup>+</sup> CD5 <sup>+</sup> IgM <sup>high</sup> CD23 <sup>-</sup> CD21 <sup>-</sup>	T1 B cells: CD19 <sup>+</sup> CD24 <sup>+</sup> IgM <sup>high</sup> IgD <sup>+</sup> CD23 <sup>-</sup> CD21 <sup>-</sup> Pro B10 cells: CD19 <sup>+</sup> CD1d <sup>+</sup> CD5 <sup>+</sup>	T2 FO B cells: CD19 <sup>+</sup> CD24 <sup>+</sup> IgM <sup>high</sup> IgD <sup>+</sup> CD23 <sup>+</sup> CD21 <sup>-</sup>  FO B cells: CD19 <sup>+</sup> CD24 <sup>+</sup> IgM <sup>int</sup> IgD <sup>+</sup> CD23 <sup>+</sup> CD21 <sup>int</sup>  Plasma cells: CD19 <sup>+</sup> CD138 <sup>high</sup> IgM <sup>high</sup> IgD <sup>low</sup> CD1d <sup>int</sup> CD43 <sup>hi</sup> CD44 <sup>hi</sup>	T2 MZP B cells: CD19 <sup>+</sup> CD24 <sup>+</sup> IgM <sup>high</sup> IgD <sup>+</sup> CD23 <sup>int</sup> CD21 <sup>+</sup> CD1d <sup>+</sup> B10 B cells: CD19 <sup>+</sup> CD1d <sup>+</sup> CD5 <sup>+</sup> IL10 <sup>+</sup> MZ B cells: CD19 <sup>+</sup> CD24 <sup>+</sup> IgM <sup>high</sup> IgD <sup>+</sup> CD23 <sup>-</sup> CD21 <sup>+</sup> CD1d <sup>+</sup> CD5 <sup>+</sup>

FO: Follicle; MZ: Marginal zone; MZP: Marginal zone precursor.

B and regulatory T cells<sup>[50]</sup>.

We previously demonstrated a model of cardiac allograft tolerance in rat induced by a short-term treatment with the immuno-suppressor LF15-0195, a deoxyspergualin analog<sup>[51,52]</sup>. In this model, we observed after treatment cessation an accumulation of B cells in the blood over-expressing inhibitory molecules and B cells from spleen were able to transfer allograft tolerance to new recipients demonstrating the presence of regulatory B cells<sup>[53]</sup>. In the graft, we observed cluster of mature B cells that in contrast to the ones from chronically rejected recipients do not express IgG suggesting B cells blocked at the switch recombination process<sup>[53]</sup>.

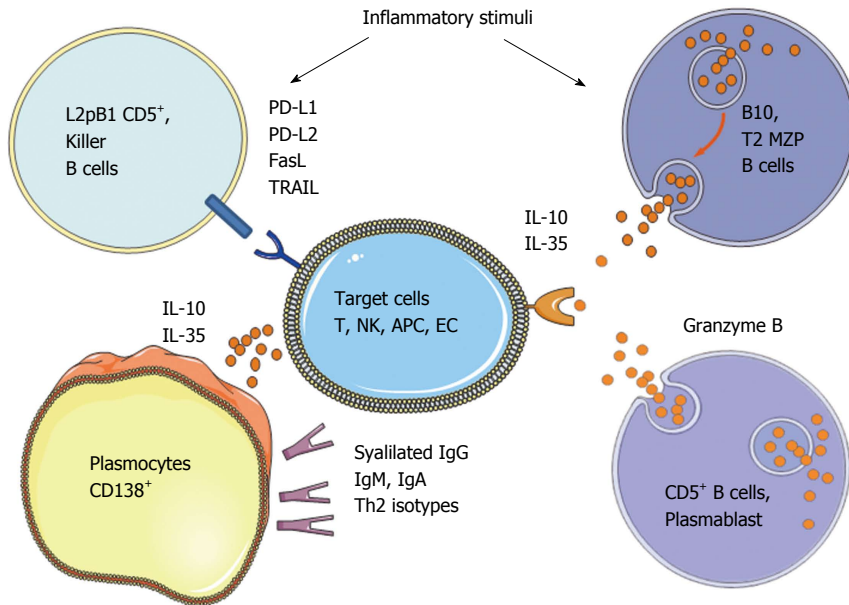
Interestingly, several research groups have demonstrated a B cell gene signature in blood of patients that spontaneously developed operational tolerance to kidney transplant after immuno-suppressive treatment cessation<sup>[54-56]</sup>. These patients exhibit higher mRNA expression of immunoglobulin light chains, CD20 and proliferation and cell cycle genes<sup>[55]</sup>. Moreover, B cells from tolerant patients expressed more of the inhibitory receptors Fcgr2b and of the CD40 signaling modulator BANK-1 (B-Cell Protein Scaffold With Ankyrin Repeats)<sup>[54]</sup>. This signature is associated with increased or at least preserved pool of CD19<sup>+</sup> CD24<sup>high</sup> CD38<sup>high</sup> IL10<sup>+</sup> B cells<sup>[54-56]</sup>. The precise mechanisms of this suppression mediated by B cells remains elusive but it has been suggested that transforming growth factor (TGF) could play a function since a third of the modulated genes in the blood are target of TGF<sup>[57]</sup>. More recently, the same team shows that B cell from operationally tolerant patients cells have a defect in their *in vitro* differentiation into CD38<sup>+</sup> CD138<sup>+</sup> plasma cell and a more important susceptibility to apoptosis at late differentiation step<sup>[58]</sup>. In addition, these B cells secrete more IL-10 following *in vitro* stimulation. Interestingly, during pregnancy that corresponds to a particular state of tolerance to alloantigens, a population of CD19<sup>+</sup> CD27<sup>+</sup> CD24<sup>high</sup> regulatory B cells is induced to maintain tolerance to the fetus<sup>[59]</sup>. These B cells present in the mother produce high amounts of IL-10 and suppress in co-culture the production of TNF $\alpha$  by effector T cells. Consistent with a regulatory function for B cells in human transplantation,

a clinical trial has shown an increased risk for acute cellular rejection following depletion of B cells prior to transplantation that could be due to a loss of regulatory B cells<sup>[60]</sup>. Therefore, all these results suggest a role of regulatory B cells in the induction or maintenance of tolerance in these operationally tolerant patients.

**Regulatory B cells phenotype**

Regulatory B cells cannot be defined based on a phenotype composed of conventional B cell-surface markers. Therefore, characterization has relied exclusively on assessing their suppressive activity. Although several regulatory B cell subsets have been described in Humans and mice, most of them share the ability to express the anti-inflammatory cytokine IL-10. IL-10 producing cells have been identified in the immature, naive, CD27<sup>+</sup> memory as well as the plasmablast/plasma B cell subpopulations<sup>[61-64]</sup>. In mice, regulatory B cells are described in the CD19<sup>+</sup> CD1d<sup>high</sup> CD5<sup>+</sup> subset in the spleen and may present as CD21<sup>high</sup> IgM<sup>high</sup> either with or without expression of CD23 (Cf Table 1 representing different phenotype of regulatory B cells in different compartment in mice). In humans, regulatory B cells were identified in CD19<sup>+</sup> CD24<sup>high</sup> subsets of both CD27<sup>-</sup> CD38<sup>high</sup> immature and CD27<sup>+</sup> memory B cell compartments highlighting the diversity of these cells<sup>[65-68]</sup>.

The most recurrent phenotype for identifying murine regulatory B cells is probably the secretion of IL-10. These regulators B lymphocytes are then called B-10. Apart from this particular property, many studies have described subpopulations of murine regulatory B cells with different phenotypes. The B1a cells, present in the peritoneal cavity were one of the first sub-population identified as IL-10-secreting B cells<sup>[69]</sup>. B cells of the marginal zone of the spleen and having a CD19<sup>+</sup> CD21<sup>+</sup> CD23<sup>-</sup> CD24<sup>+</sup> CD1d<sup>+</sup> IgM<sup>+</sup> phenotype secrete IL-10 following CpG (TLR9 agonist) stimulation and are able to regulate the immune response in a model of lupus<sup>[39]</sup>. Mauri *et al*<sup>[38]</sup> describe precursors of these cells, called transitional 2-marginal zone precursor (T2-MZP), in a mouse model of collagen-induced arthritis. These B cells produce IL-10, have a CD19<sup>+</sup> CD21<sup>high</sup> CD23<sup>+</sup> CD93<sup>+</sup> CD24<sup>high</sup> phenotype and their adoptive transfer



**Figure 1** Different subpopulations and mechanisms described for regulatory B cells according to the literature. NK: Natural killer; MZP: Marginal zone precursor; APC: Antigen presenting cells; EC: Endothelial cells; IL: Interleukin; PD-L: Programmed death receptor ligand; TRAIL: Tumor necrosis factor-related apoptosis inducing-ligand; FasL: Fas ligand.

in immunized mice prevents the development of the disease by IL-10 dependent mechanisms, since B cells deficient for IL-10 are inefficient<sup>[38,61]</sup>.

The regulatory role of B10 cells (CD19<sup>+</sup> CD5<sup>+</sup> CD1d<sup>+</sup>) was identified in various autoimmune models such as EAE, inflammatory bowel disease, collagen-induced arthritis and lupus<sup>[70]</sup>. B10 cells, share phenotypic markers with B1a cells, T2-MZP and marginal zone B cells and correspond to less than 2% of B cells from the spleen of naive mice. The Tedder team demonstrates the existence of rare B10 enriched in the subpopulation of CD1d<sup>high</sup> CD5<sup>+</sup> B cells in the spleen of naive mice and secreting large quantities of IL-10 in response to strong stimulation<sup>[71]</sup>. In addition, another study demonstrated that this subpopulation of CD5<sup>+</sup> CD1d<sup>+</sup> IL-10<sup>+</sup> B cells could, *in vitro*, be substantially increased following stimulation with the B cell activating factor BAFF and help to reduce following transfer the development of collagen-induced arthritis<sup>[72]</sup>. Indeed, BAFF is required for transition from T1 immature to T2 transitional stage of B cells and is essential for marginal zone B cell development<sup>[73]</sup>.

Interestingly, the TIM-1 protein has been identified as expressed by a large part of IL10<sup>+</sup> regulatory B cells in mice. Transfer of these TIM-1<sup>+</sup>IL-10<sup>+</sup> cells, obtained from any B cell subpopulation of the spleen can directly induce tolerance to islet allograft<sup>[49]</sup>. However, some studies described regulatory B cells exerting their suppressive role through IL-10 independent mechanisms<sup>[74]</sup>.

The existence of regulatory B cells in humans has been suggested by different teams. As for the mouse, the phenotype of these cells varies depending on the study. Duddy *et al*<sup>[75]</sup> observed a decrease in IL-10 secreting B cells in multiple sclerosis patients. The team of Mauri highlighted in patients with SLE, a decreased in

the subpopulation of immature CD19<sup>+</sup> CD24<sup>high</sup> CD38<sup>high</sup> cells defined as secreting large amounts of IL-10 and suppressing TNF and IFN secretion by autologous T cells<sup>[65]</sup>. Subpopulations of regulatory B cells equivalent to murine B10 were also identified in humans. Indeed, although most publications described regulatory B cells with a transitional/naive phenotype, some teams identify them in humans among the pool of memory B cells with the CD27 or CD148 markers<sup>[66,68]</sup>. In addition, CD19<sup>+</sup> CD24<sup>high</sup> CD38<sup>high</sup> CD5<sup>high</sup> IgD<sup>+</sup> B cells with suppressive properties and inducing an expansion of regulatory T cells *in vitro* were also identified<sup>[76]</sup>.

Taken together, all these studies suggest that the development of B cells with regulatory functions described at different B-cell differentiation step and in several compartments may depend on the microenvironmental factors and may not derived from a single lineage population.

### Regulatory B cell mode of action

Suppressive mechanisms appear to be diverse and can act by the production of anti-inflammatory antibodies, the secretion of immunosuppressive agents, or by the cell surface expression of inhibitory receptors (Figure 1).

**Natural antibodies:** It has been shown in Humans and mice that B cells from neonates expressed a basal level of IgM named natural antibodies or non-immune antibodies generated by the B-1 cells, derived from a small portion of precursors capable of self-renewing<sup>[77]</sup>. IgM produced have restricted repertoire, low affinity and respond to T-independent signals by cross-reactivity. They play a role in the removal of apoptotic cells by inducing the recruitment of complement component that will following complex phagocytosis prevents

excessive immune activation<sup>[78]</sup> and induces Th2-deviation<sup>[79]</sup>.

**The secretion of suppressive cytokines:** The most described and studied mechanism of suppression employed by the regulatory B cells is the secretion of IL-10, which is one of the most potent anti-inflammatory cytokine to control inflammation. The importance of IL-10 in suppression by B cells has been demonstrated only in the last decade with the identification of a subpopulation of B cells producing high level of IL-10 and over-expressing CD1d molecule in the gut-associated lymphoid tissues in a chronic intestinal inflammation model<sup>[80]</sup>. Moreover, remission of multiple sclerosis in mice correlates with the presence in the spleen of B cells producing IL-10 following stimulation<sup>[81]</sup>. Interestingly, they found that IL-10 producing B cells can reduce the severity of the disease following adoptive transfer, while B cells from mice deficient for IL-10 could not. In the following years, other studies have shown that the IL-10 secreting B cells regulate autoimmunity in different mouse models including models of arthritis<sup>[38]</sup>, diabetes<sup>[40]</sup> and systemic lupus erythematosus<sup>[82]</sup>. Recently, the TIM-1 protein (T-cell Ig and mucin domain domain protein 1) has been described to identify the two-thirds of IL-10 producing B cells, making it the most specific cell-surface marker identified to date<sup>[49]</sup>. The treatment of mice with anti-TIM-1 antibody induced an increase of the TIM-1 B cell pool producing IL-10 and improved the tolerance to an allograft, suggesting that TIM-1 is also involved in the function of these cells and not only a cell-surface marker. These results suggest that targeting TIM-1 could be a new therapeutical approach for enhancing the expansion of these regulatory B cells in transplantation or auto-immune disease fields. It is suggested that the IL-10<sup>+</sup> expressing B cells (called B10 cells) are not T2-MZP B cells<sup>[83]</sup>. It is also possible that the production of IL-10 appears indifferently in the various subpopulations of B cells, depending on the activation or differentiation state. The action of IL-10 appears to be closely linked to the one of another cytokine less described, IL-35. Indeed, mice deficient in p35 or EB13, the two subunits of IL-35 and specifically in B cells exhibit an exacerbation of EAE compared to control mice<sup>[63]</sup>. In addition, culture of B cells in the presence of IL-35 induced an increase in the B cell subpopulation expressing IL-35, called IL-35<sup>+</sup> regulatory B cells, and half of them expressed IL-10. Similarly, in *in vivo* experiments, although IL-35 inhibits the proliferation of conventional B cells, it selectively induces the expansion of CD19<sup>+</sup> CD5<sup>+</sup> B220<sup>low</sup> B10 regulatory B cells. These B10 cells are capable upon transfer to limit established uveitis in mice, and 60% of B10 found in the spleen also express IL-35. This urges the importance to better knowledge these mechanisms, which could then represent new therapeutic targets for autoimmune disorders and infectious diseases.

Interestingly, studies in genetically modified mice expressing eGFP linked to *IL-10* gene, so as IL10

reporter, have shown that the cells that express the most IL10 have the plasma cell marker CD138, suggesting that the most potent regulatory B cells are plasma cells<sup>[67]</sup>. Similarly, a 2014 study showed following infection with Salmonella, the emergence of IL-10 and IL-35 producing B cells enriched in the pool of IgM<sup>+</sup> CD138<sup>++</sup> BLIMP1 plasma cells<sup>[84]</sup>. Furthermore, after PCR analysis, transcripts for Ebi3 and p35 were co-expressed by the CD138<sup>high</sup> B cells, also expressing high levels of Blimp-1 and IRF4 transcripts and corresponding to the most efficient antibodies secreting cells. EB13 and p35 proteins were found as expressed by CD138<sup>+</sup> plasma cells and not by CD19<sup>+</sup> CD138<sup>-</sup> B cells in mice following infection with Salmonella or during EAE. B cells depend on IRF4 and BLIMP-1, which are required for plasma cell differentiation, to provide regulatory functions *in vivo*. These data, although referenced in 2014 by Dang *et al.*<sup>[64]</sup> and Ries *et al.*<sup>[85]</sup>, suggest that plasma cells have roles other than the one of antibodies producers, such as the secretion of immunosuppressive cytokines able to modulate many immune responses. Indeed, B1 cells were demonstrated to be able to differentiate into CD19<sup>+</sup> CD138<sup>+</sup> IgM<sup>+</sup> plasma cells producing GM-CSF in a mouse model of septic shock<sup>[86]</sup>. Similarly, plasma cells expressing iNOS and TNF were found in the lamina propria of the intestine in mice<sup>[87]</sup>. In normoglycemic NOD mice, which do not develop diabetes, islet-infiltrating B cells were identified as more antigen-experienced IL-10<sup>+</sup> cells with more diverse B-cell receptor repertoires compared to those of hyperglycemic mice. In addition, healthy individuals showed increased numbers of IL-10<sup>+</sup> B cells compared to type 1 diabetic patients<sup>[88]</sup>. Therefore, cytokine production is also an important aspect of B cell biology. Further work is therefore required to identify the additional signals that specify the differentiation of B cells into "regulatory plasma cells" producing anti-inflammatory cytokines.

**The expression of cytotoxic mediators:** Expression of the cytotoxic component Granzyme B by B cells was first described in chronic leukemia patients whose B cells undergo apoptosis following stimulation with TLR agonist and IL-21<sup>[89]</sup>. Such cells were then identified following Epstein-Barr virus transformation, but also in patients developing psoriasis, rheumatoid arthritis or lupus (SLE)<sup>[89-91]</sup>. Although the existence of B cells expressing Granzyme B was confirmed in humans, there is nothing in the mouse. Indeed, in different mouse strains, B cells are not capable of expressing Granzyme B even with strong stimuli (IL-21, anti-BCR, LPS, CpG-ODN) or after viral infection, unlike cytotoxic T cells for which the level of expression is significantly increased<sup>[92]</sup>. Recently, it has been shown that untreated human immunodeficiency virus (HIV) patients display CD4<sup>+</sup> T cells with enhanced IL-21 expression and high *in vivo* frequencies of regulatory B cells over-expressing the Granzyme B<sup>[93]</sup>. These cells may contribute significantly to immune dysfunction in HIV patients, and may also explain ineffective antibody

responses after vaccination. In transplantation, kidney-transplanted tolerant recipients exhibited a higher number of Granzyme B expressing B cells with a plasma cell phenotype and that required IL-21 production<sup>[94]</sup>. Granzyme B - expressing CD19<sup>+</sup> IgA<sup>+</sup> CD27<sup>+</sup> CD138<sup>high</sup> CD20<sup>-</sup> plasma cells with cytotoxic properties have also been described in the normal intestinal mucosa, and were significantly more frequent in both Crohn's disease and ulcerative colitis<sup>[95]</sup>. Granzyme B expression by B cells has been shown to act by limiting T-cell proliferation by degradation of the T-cell receptor  $\zeta$ -chain<sup>[96]</sup>.

FasL (CD178) expression by human B cells has been observed first following strong *in vitro* stimulation<sup>[97]</sup>. Since then, different teams demonstrated the expression of FasL by human and murine B cells<sup>[98,99]</sup>, and was suggested in the cases of malignancy, to be a way to increase the virulence of the tumor by promoting apoptosis of the T cells<sup>[100]</sup>. B cells expressing FasL were also found in various types of viral infections including Epstein-Barr virus<sup>[101]</sup>, HIV<sup>[102]</sup> and virus murine leukemia virus<sup>[103]</sup>, and also by leading to T cell apoptosis lead to persistent infections. B cells expressing FasL were demonstrated to suppress the induction of autoimmune diabetes in NOD mice<sup>[104]</sup> and were found at high levels in a mouse model of lupus<sup>[105]</sup>. In a minor mismatch transplantation model in mice, injection of splenic purified B cells is sufficient to prevent graft rejection, whereas the one from FasL deficient mice does not<sup>[106]</sup>.

The role of tumor necrosis factor-related apoptosis inducing-ligand (TRAIL) or CD253 in B cell mediated immunosuppression is less characterized. Expression of TRAIL by B cells was described in human lines and murine B lymphoma<sup>[107,108]</sup>. TRAIL has also been detected in cases of leukemia and myeloma and in non-transformed human and murine B cells<sup>[107-109]</sup>.

The programmed death receptor 1 (PD-1), and its two ligands, PD-L1 and PD-L2 are important regulator of tolerance<sup>[110]</sup>. PD-L1 is expressed by numerous resting immune cells and regulates Th1 responses<sup>[111]</sup>. In contrast, PD-L2 is more restricted to activated antigen-presenting cells<sup>[112]</sup>, and regulates Th2 responses, such as asthma<sup>[113]</sup>. It has been demonstrated PD-L2 expression on half of a subpopulation of peritoneum CD5<sup>+</sup>, the L2pB1 cells in mice<sup>[114]</sup>. Recently, it has been shown the presence of regulatory B cells in a model of human-therapy-resistant prostate cancer. The crucial immunosuppressive B cells that infiltrate the tumors are plasma cells that express IgA, IL-10 and PD-L1. Their appearance depends on TGF $\beta$  receptor signaling and their elimination allows CTL-dependent eradication of oxaliplatin-treated tumours<sup>[115]</sup>.

### Immunosuppressive IgG antibodies and deviation of the response:

During an effective immune response, high-affinity IgG antibodies are produced to recognize epitopes from pathogens and their Fc fragment binds to the Fc receptors expressed on immune cells, thus altering their activation and phagocytosis property<sup>[116]</sup>.

Particular glycoforms of IgG have been identified to alter binding of IgG to Fc receptors<sup>[117]</sup>. In addition, IgG glycoforms having a sialic acid group at terminal position showed an anti-inflammatory activity<sup>[128,118]</sup>. These glycoforms suppress inflammation by binding to specific intracellular adhesion molecule 3 grabbing nonintegrin homolog-related 1 (SIGN-R1)<sup>[119]</sup>, leading to induction of an immunosuppressive Th2 response<sup>[120]</sup>. The events involved in sialylation of IgG are currently unknown and surprisingly, pro-inflammatory stimuli induced *in vitro*, rather than a decrease, an increase in sialylation<sup>[121]</sup>.

Inhibition or deviation of the Th T cell response and induction of regulatory T cells by B cells have been demonstrated in numerous *in vitro* and *in vivo* studies and may implied direct interactions or act through the mechanisms described early. Antigen specific immunosuppressive T cells can be expanded *in vitro* by co-cultures with regulatory B cells isolated in a transplantation tolerance model in mice<sup>[122]</sup>. *In vivo*, following adoptive transfer, regulatory B cells induced the expansion of regulatory T cells *via* IL-10 and were able to regulate autoimmune<sup>[123]</sup> and infectious diseases<sup>[124]</sup>. In addition, various studies have demonstrated that allogeneic T cells with suppressive properties could be induced *in vitro* with the only presence of naive B cells<sup>[125,126]</sup>.

Other interesting aspect of the properties of antibody in transplantation is the phenomenon called accommodation. Indeed, in some models of allo-and xenotransplantation, it is possible to observe the presence of donor-specific antibodies without functional deterioration of the tissue or the graft<sup>[127]</sup>. Accommodation is associated with the expression of cytoprotective molecules such as HO-1, IDO, NO, Bcl-2 and Bcl-XL that protect graft endothelial cells by regulating immune response, inflammation and apoptosis<sup>[128-134]</sup>. It is suggested that these antibodies with particular isotype would not be harmful but rather protective toward the graft and could be the source of the expression of protective molecules.

Interestingly, beekeepers who have a long-term tolerance to bee venom allergens have a subpopulation of CD25<sup>high</sup> CD71<sup>high</sup> regulatory B cells which produces the specific antibody isotype IgG4<sup>[135]</sup>. Indeed, the bee venom-based vaccines induce the production of IgG4 antibodies specific to allergen and capable to inhibit the interaction IgE/allergen and to promote the expansion of regulatory T cells<sup>[136]</sup>. It is necessary to identify the conditions responsible for the production of protective antibodies to the graft to adapt immunosuppressive treatment and therapy protocols targeting B cells or antibodies.

### Clinical relevance

Although largely described as involved in the prevention of auto-immune diseases, the importance of CD19<sup>+</sup> CD24<sup>high</sup> CD38<sup>high</sup> immature B cells in kidney transplantation in a clinical setting, has been highlighted by their increased frequencies in operationally tolerant patients after immunosuppressive treatment

cessation<sup>[55,56]</sup>. The proof as to their direct role in this phenomenon is still lacking but these studies suggest the relevance of these cells as biomarkers of tolerance. In this sense, a recent longitudinal prospective study aiming to track the relationship between these cells and clinical events demonstrates that transitional B cell frequencies (but not “regulatory” T cells) were associated with protection from acute rejection<sup>[137]</sup>. Another study demonstrates in the cases of chronic antibody-mediated rejection, a reduced ratio of activated to memory B cells and an impaired immunosuppressive activity<sup>[138]</sup>. Therefore, these clinical studies highlighted the potential utility of these cells as biomarkers of predictive graft outcome, to adapt immunosuppressive treatment.

According to immuno-suppression protocols, there constitution of the B cell compartment in the presence of alloantigens could create a favorable environment for the development and maintenance of tolerance towards antigens of the graft. Indeed, Parsons *et al.*<sup>[139]</sup> demonstrated in mice that depletion of the B cell compartment at the time of transplantation induces tolerance by depleting allo-reactive B cell clones and reshaping the B cell repertoire. Following some immunosuppressive treatments, the B cell compartment is recolonized by B cell populations exhibiting a phenotype of regulatory B cells. For example, following an induction treatment with Alemtuzumab (anti-CD52), the authors observed a temporary increase in the proportion of transitional B cells, described as regulatory B cells<sup>[140]</sup>. It has also been shown that Alemtuzumab in contrast to Basiliximab (anti-CD25) induced the expansion of a novel peripheral lymphocyte phenotype, although clinical outcomes were similar. This appearance of naive, transitional and regulatory B-cell subtypes was associated with more stable graft function and is due to homeostatic repopulation following lymphocyte depletion<sup>[141]</sup>. Furthermore, similar results were obtained in non-human primates following depletion of B cells with Rituximab (anti-CD20). Indeed, the reconstitution of the compartment by immature and transitional B cells was associated with long-term graft survival of pancreatic islets<sup>[142]</sup>. In a model of diabetes in mice, anti-CD22 treatment also demonstrated the generation of a pool of immature reemerging B220<sup>+</sup> CD93<sup>+</sup> CD23<sup>+</sup> IgM<sup>low</sup> B cells, unable to present efficiently antigens, and that can regulate at long-term the autoimmune response by establishing tolerance toward autoantigens<sup>[18]</sup>.

Moreover, a novel role of CD24<sup>high</sup> CD27<sup>+</sup> and IL-10<sup>+</sup> plasmablast B cells has been suggested in the regulation of human chronic graft-versus-host disease<sup>[143]</sup>. Therefore, depletion of B cells as the central strategy for preventing rejection is a paradigm. Depleting strategy at the induction phase may help to reshape the immune B cell repertoire and the re-emergence of regulatory immature B cells but at a latter phase or for the treatment of antibody-mediated rejection, although prevent the donor-specific antibody formation, may be deleterious for the pre-existing regulatory B cell population. The exact therapeutical narrow

of depletion and the beneficial effect of combined immunosuppressive regimens are now urgent to evaluate in the setting of transplantation. Another aspect to consider is the potential adverse side effects of B-cell modulation in the development of infections. Indeed, as such for immunosuppressive regimens, B cell depletion and emergence of regulatory B cells could lead to infectious complications and reactivation of some virus notably following B cell transfer<sup>[144]</sup>.

## CONCLUSION

This review highlighted the recent literature suggesting that B cells can also act as beneficial players in organ transplantation by controlling inflammation and promoting long-term regulatory mechanisms leading to operational tolerance. They exhibit various phenotypes and mode of action that may depend on their localization and their induction. They seem to expand following inflammation to restrain immune response and are therefore involved in the maintenance of the fine-tune balance equilibrium between effector and regulatory cells. Mechanisms exert by these cells are diverse and have mostly been described in auto-immune diseases. However, recent literature data suggests similar mechanisms in transplantation. They can act through the production of anti-inflammatory cytokines, protective antibodies or by depleting effectors or inducing other types of regulatory cells. The depletion of B cells as the central strategy for preventing antibody-mediated rejection should be reconsidered since this therapy deplete also B cells displaying regulatory activity and consequently could impact badly the graft outcome.

Therefore, it is crucial to better characterize the temporal expansion of these cells, the stimuli that activate them, their precise phenotype and mode of action to develop new strategies in a clinical setting.

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