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Regulatory B Cell Therapy in Kidney Transplantation

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In the context of kidney injury, the role of Bregs is gaining interest. In a number of autoimmune diseases, the number and/or the function of Bregs has been shown to be impaired or downregulated, therefore restoring their balance might be a potential therapeutic tool. Moreover, in the context of kidney transplantation their upregulation has been linked to tolerance. However, a specific marker or set of markers that define Bregs as a unique cell subset has not been found and otherwise multiple phenotypes of Bregs have been studied. A quest on the proper markers and induction mechanisms is now the goal of many researchers. Here we summarize the most recent evidence on the role of Bregs in kidney disease by describing the relevance of *in vitro* and *in vivo* Bregs induction as well as the potential use of Bregs as cell therapy agents in kidney transplantation.

Keywords: regulatory B cells, kidney transplantation, graft tolerance, cell therapy, immunosuppressive therapy

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INTRODUCTION

B cells are traditionally described to show a primarily effector phenotype: antibody-producing cells with the capacity to present antigen and stimulate T cells through cytokine production (Janeway et al., 1987; Ochsenbein et al., 1999; Harris et al., 2000). However, nowadays it is widely accepted the existence of B cell subsets with regulatory phenotypes (Bregs) involved in suppressing the immune response, inducing tolerance and maintaining homeostasis (Wang et al., 2020). Immunomodulatory functions of Bregs could be mediated by the action of soluble molecules such as IL-10, IL-35, TGF-β or Granzyme B or by cell contact-dependent apoptosis-inducing mechanisms such as PD-L1, FasL or TIGIT (Flores-Borja et al., 2013; Tang et al., 2016; Cai et al., 2019; Chesneau et al., 2020).

Despite essential roles in modulating several diseases, Bregs so far are not known to have a unique or exclusive marker that defines them as a population, but they constitute a heterogeneous cell population that possess a regulatory phenotype and can be found at different stages of B-cell development as reviewed in (Rosser and Mauri, 2015; Oleinika et al., 2019; Long et al., 2021). However, several markers have been proposed as enriched or identifiers of Breg populations. Breg are commonly identified by their expression of IL-10, with transitional phenotypes, $CD19^{+}CD24^{Hi}CD38^{Hi}$, as the most abundant phenotype in peripheral blood. Nevertheless, since the initial description of IL-10 + Breg, other populations such as plasmablast ($CD19^{+}CD27^{Hi}CD38^{+}$), regulatory B1 cells ($CD19^{+}CD25^{+}CD71^{+}CD73^{+}$) and memory IL-$10^{+}$ B cells ($CD19^{+}CD24^{Hi}CD27^{+}$IL-$10^{+}$) have been described as Breg subsets, and different effector molecules have been linked to regulatory B cells identification and function, such as Tim-1, CD5, CD1d, CD25, GMZB, FasL, CD71, etc. as summarized in **Table 1**.

The classic conception of the role of B cells in the field of transplantation was called into question in the last decade, following the publication of two simultaneous studies in 2010, highlighting the

TABLE 1 | Breg Human Cellular markers and Effector molecules.

Human regulatory B cell markers		
Breg subsets and molecules	**Markers**	**Reference**
Transitional or Immature B10 cells	$CD19^{+}CD24^{Hi}CD38^{Hi}IL\text{-}10^{+}$	Blair et al. (2010); Zhang et al. (2012); Flores-Borja et al. (2013); Khoder et al. (2014); Liu et al. (2016)
$CD1d^{Hi}$ B10 B cells	$CD19^{+}CD1d^{Hi}CD5^{+}IL\text{-}10^{+}$	Yanaba et al. (2008); Bankoti et al. (2012); Zhang et al. (2012); van der Vlugt et al. (2014); Khan et al. (2015a)
Memory B10 Cells	$CD19^{+}CD24^{Hi}CD27^{+}IL\text{-}10^{+}$	Iwata et al. (2011); Salomon et al. (2017); Hasan et al. (2019)
Br1 Cells	$CD19^{+}CD25^{+}CD71^{+}CD73^{low}$	Kubo et al. (2012); Kim et al. (2016)
Plasmablasts	$CD19^{+}CD27^{Hi}CD38^{+}$	Matsumoto et al. (2014); Shen et al. (2014)
TIM-1^{+} B cells	$CD19^{+}$ TIM-1^{+}(TIM-1^{+} B cells present in different B cell subsets)	Ding et al. (2011); Xiao et al. (2012); Aravena et al. (2017); Cherukuri et al. (2021)
$GMZB^{+}$ B cells	$CD19^{+}GMZB^{+}$($GMZB^{+}$ B cells present in different B cell subsets)	Hagn and Jahrsdörfer (2012); Hagn et al. (2012); Lindner et al. (2013); Chesneau et al. (2015); Durand et al. (2015); Zhu et al. (2017)
$CD9^{+}$ B cells	$CD19^{+}$ $CD9^{+}$($CD9^{+}$ B cells present in different B cell subsets)	Sun et al. (2015); Brosseau et al. (2018a), Brosseau et al. (2018b); Mohd Jaya et al. (2021)
Circulating B cells	$CD19^{+}CD25^{Hi}$ $CD27^{Hi}CD1d^{Hi}CD86^{Hi}$	Kessel et al. (2012)
$TIGIT^{+}$ memory B cells	$CD24^{Hi}$ $CD27^{+}$ $CD39^{Hi}$ $IgD^{-}IgM^{+}CD1c^{+}$ $TIGIT^{+}$	Hasan et al. (2021)

Human Regulatory B Cell Effector Molecules		
Breg subsets and molecules	**Key Features**	**Reference**
IL-10	Induce Treg, maintain NKT homeostasis, supress effector T cells Modulates plasmacytoid dendritic cells and macrophage and function CD9 and Tim-1 are strongly associated to IL-10 production	Yanaba et al. (2009); Mauri and Bosma (2012); Lykken et al. (2015); Lighaam et al. (2018)
IL-35	Promotes IL-35 and Il-10 production by Treg and Breg Inhibits pathogenic Th1 and Th17 responses	Shen et al. (2014); Wang et al. (2014); Choi and Egwuagu (2021)
PD-L1	Inhibits T cell activation and differentiation by binding PD-1	Khan et al. (2015b); Wang et al. (2019)
FASL	Induces T cell apoptosis by binding FAS	Lundy and Boros (2002); Lundy and Fox (2009); Tang et al. (2016); Wang et al. (2017)
TGF-β	Enhances Treg and Breg induction Inhibits Th1 differentiation by inhibiting STAT4	Natarajan et al. (2012); Lee et al. (2014)
GZMB	Induces T cell apoptosis and strongly suppress T cell proliferation by degradation of the T-cell receptor ζ-chain Present in several B cell subsets, in peripheral, most commonly found in plasmablasts	Hagn and Jahrsdörfer (2012); Hagn et al. (2012); Lindner et al. (2013); Durand et al. (2015); Zhu et al. (2017); Chesneau et al. (2020)
CD73	Supresses effector T cell function by producing adenosine. CD73 catalyses the dephosphorylation of adenine to adenosine	Saze et al. (2013); Kaku et al. (2014)
IDO	Promotes Treg and Breg differentiation	Nouël et al. (2015)

Breg: Regulatory B cell, Br1: Type 1 Regulatory B cell, B10: IL-10-producing regulatory B cells, GZMB: Granzyme B, IDO: indoleamine 2,3-dioxygenase.

relevance of B cells in the development of tolerance in renal transplantation. Both studies involved transplant recipients who had developed spontaneous tolerance and stable patients receiving immunosuppressive therapy. The results obtained in "spontaneously tolerant" patients showed the presence of a higher percentage of B cells in peripheral blood, especially naïve and transitional B cells. At the same time, a higher expression of genes involved in B-cell development was also detected in these tolerant patients compared to stable patients on immunosuppressive therapy (Newell et al., 2010; Sagoo et al., 2010).

Since the emergence of these breakthrough results in 2010, the effect of Breg on the development of tolerance has been described several times as reviewed in (Peng et al., 2018; Cherukuri et al., 2021; Long et al., 2021).

The putative tolerance-inducing power of Bregs makes them an interesting target for the development of therapies to combat transplanted kidney rejection. Among the possible treatment strategies that could be considered, two main groups can be distinguished: those aimed at boosting the natural population of Bregs in the donor and, alternatively, therapy based on the transfer of previously expanded or modified Breg *in vitro*. Here we summarize the most recent evidence on the role of Bregs in kidney transplantation by describing the relevance of *in vitro* and *in vivo* induced Breg (iBreg) as well as the potential use of Bregs as cell therapy agents.

IN VIVO BREGS INDUCTION

Several therapeutic strategies have been proposed or found to induce Breg *in vitro* and *in vivo* in human patients, both in preclinical and clinical trials, despite the aforementioned difficulty of accurately identify Breg. In the following section we discuss the different drugs and therapies involved in Breg induction *in vivo*.

Pharmacological Interventions

The use of immunosuppressive regimes combining different drugs has become a staple of clinical transplantation. For the most part, classical immunosuppressive interventions have little to no effect over B cells, and they have shown not to be active inductors of Breg cells with few exceptions.

Starting from classical immunosuppressive regimes, corticosteroids and calcineurin inhibitors (CNI) mildly reduce the number of total naïve and transitional B cells in renal transplant patients, with the exception of tacrolimus having no effect on B cell subsets (Latorre et al., 2016; Rebollo-Mesa et al., 2016; Tebbe et al., 2016; Bottomley et al., 2017).

In patients with IgA vasculitis that had impaired Breg function, the treatment with glucocorticoid prednisolone, promoted an increase in $CD5^+CD1d^+$, $CD5^+CD1d^+$ IL-10^+, and IL-10^+ B cell subsets, accompanied by an increase in the serum IL-10 concentration (Hu et al., 2016). However, in Lupus Nephritis patients, same treatment with prednisolone correlated with lower percentages of $IL10^+$ B cells (Heinemann et al., 2016).

While low to medium doses of mycophenolate mofetil increase Breg subsets, high doses of mycophenolate reduce both B cell IL-10 and CD80/86 expression on B cells in kidney transplant patients. (Matz et al., 2012; Joly et al., 2014; Rebollo-Mesa et al., 2016; Bottomley et al., 2017).

The effect of mTOR inhibitors over Breg subsets has not been clearly stablished. In kidney transplanted patients sirolimus reduced Transitional B cell populations, while in another report in liver transplant patients, it was described to induce Breg when patients were converted to sirolimus from a tacrolimus based regime (Latorre et al., 2016; Song et al., 2020).

Also the effect of the 6-mercaptopurine analog, Azathioprine, on Bregs has been studied, and it's know to reduce total, naïve and transitional B cells (Rebollo-Mesa et al., 2016; Bottomley et al., 2017).

The B cell depleting agent rituximab induces rapid depletion of $CD20^+$ B cells after administration in a dose-dependent manner, lasting as long as 6 months, followed by a slow recovery (Bergantini et al., 2020). Breg frequencies decrease after administration of the drug, while long term effect of rituximab seems to indirectly stimulate bone marrow to produce transitional B cells when B cells are depleted, coupled with a substantial reduction in $CD27^+$ B (memory) cells at long-term follow-up (Moller et al., 2009; Rehnberg et al., 2009).

The costimulation blocker Belatacept has shown promising results in kidney transplanted patients regarding Breg induction. Belatacept increases IL-10 expression and transitional populations, while reducing plasmablast differentiation (Leibler et al., 2014; Xu et al., 2020).

Finally, common induction therapies, such as basiliximab (chimeric anti-CD25) and Thymoglobulin (anti-thymocyte globulin) show no effect over transitional B cells (Longshan et al., 2014; Alfaro et al., 2021) while CAMPATH-1H (anti-CD52) increased transitional B cells and reduced memory B cells (Thompson et al., 2010; Heidt et al., 2012; Cherukuri et al., 2021).

Other immunomodulatory drugs have been described to induce Breg, such as tocilizumab (anti-IL-6) (Assier et al., 2010; Snir et al., 2011), Fingolimod (sphingosine-1-phosphate receptors modulator) (Grützke et al., 2015) and Laquinimod (quinolone-3-carboxiamide) (Toubi et al., 2012).

Cell and Extracellular Vesicles Therapies

Cell therapies earned a lot of interest as a new approach to induce immunosuppression and tolerance, with an increased presence in clinical trials during the last decade.

Mesenchymal stromal/stem cells (MSC) therapy has been at the forefront of cell therapies in the field of transplantation due to their immunomodulatory and regenerative properties (Pittenger et al., 2019). MSC interact with several cell types, including B cells, inducing regulatory B cells while abrogating plasmablast induction, B cell terminal differentiation and inhibiting antibody production (Comoli et al., 2007; Asari et al., 2009; Guo et al., 2013; Franquesa et al., 2015; Gupte et al., 2017; Perico et al., 2018; Chen et al., 2019, 23). The effect and mechanisms of MSC immunomodulatory action on Bregs has been extensively reviewed (Liu et al., 2020).

A promising alternative to MSC cell therapies are extracellular vesicles (MSC-EVs), reviewed in (Gomzikova et al., 2019; Gowen et al., 2020). EVs emulate parental cell properties, MSC-EVs stimulate tissue regeneration and immune modulation and have been proposed to tackle many diseases including kidney diseases and kidney graft rejection. MSC-EVs have been described *in vitro* to be mediators of Breg induction in a dose dependent manner (Budoni et al., 2013). However, MSC-EV involvement in Breg induction is a complex topic as the EV isolation method used might produce opposite effects as we previously described (Carreras-Planella et al., 2019). Highly purified MSC-EV displayed reduced immunomodulatory capabilities on B cells compared to MSC soluble protein enriched fractions.

In addition to MSC, other cell therapies have been tested and described to induce Breg. Regulatory T cells (Treg) therapy using autologous T cells in kidney transplant patients has been associated with a long-lasting dose-dependent increase of marginal B zone B cells, which are associated with IL-10 production and regulation (Harden et al., 2021). In a different study in a mouse model, CAR-Treg specific to the B cell marker CD19 (Imura et al., 2020) suppressed IgG antibody production and differentiation of B cells in a TGF-β–dependent manner. Regulatory T and B cells work in harmony to stablish homeostasis, and both promote each other induction and expansion as seen in different mouse models (Lee et al., 2014; Wang et al., 2015; Chien and Chiang, 2017) *via* IL-10 and TGF-β.

Tolerogenic Dendritic cells (tolDC) are essential for the induction of Breg in humans and their administration has been described to induce Breg (Boldison et al., 2020). No clinical trials have been performed in kidney transplant patients, but in a phase one safety study in diabetic patients, tolDC increased the frequency of regulatory B cells (Giannoukakis et al., 2011).

Indirect Intervention: The Role of Microbiota

Previous methods described to induce Bregs focus on tackling the specific either cellular or molecular pathways involved in the maintenance or induction of Breg, but a different approach with

growing interest during recent years is to promote balanced stress-free metabolic and immune balance.

In this context, an alternative approach to promote graft tolerance and improve patients' quality of life, most likely in combination with previous drug interventions and/or cell therapies, would be focus on metabolic interventions by modulation of gut microbiota or other metabolic pathways.

Gut microbiota and dysbiosis are linked to adverse events, reduced quality of life, and an increase of graft rejection in kidney transplanted patients (Lee et al., 2019; Swarte et al., 2020; Pacaud et al., 2021). Gut microbiota interacts with the immune system generating a balance of inflammatory and regulatory responses that maintain the homeostasis with metabolic and immune system effects outside the gut, including the generation of Bregs. B cells have the capability to recognize different bacterial and viral elements by the BCR and TLRs (Gallego-Valle et al., 2018; Mu et al., 2020; Pacaud et al., 2021) and also cytokines and metabolites derived from these microbes, such as short chain fatty acids (SCFAs) (Rosser et al., 2020; Daïen et al., 2021; Pacaud et al., 2021; Zou et al., 2021) expanding Breg subsets. Recent studies have elucidated the role of the SCFA pentanoate in the modulation of mTOR activity, leading to a significant boost of IL-10 production by LPS or CpG stimulated Breg, and a substantial reduction of B cell apoptosis, in addition to reducing expression of IL-17A in effector T cells by inhibiting HDAC (histone deacetylase) activity *via* epigenetic modulation (Luu et al., 2019). In a different study, direct inhibition of HDAC by Entinostat, an HDAC inhibitor, increased IL-10 production by LPS-stimulated B cells. Entinostat activity prevented HDAC binding to the proximal region of the IL-10 expression promoter, increasing binding of NF-κB p65, and enhancing IL-10 expression (Min et al., 2021).

IBREG CELL THERAPY: IS IT FEASIBLE

Cell therapy is not a new concept anymore and protocols and clinical trials are being set up to promote tolerance in autoimmune diseases and transplantation in the absence or in a minimized immunosuppressive regime. MSC therapy has taken the lead in this area with several clinical trials already published. In parallel, regulatory immune cell types such as Tregs or tolDCs are the main not-modified immune cell types being studied and used for cell therapy in immune mediated diseases and regenerative approaches. Therefore, the idea of a cell therapy product involving Bregs might sound promising although, to this moment, there are no trials on the use of Breg as a cell therapy. The incomplete knowledge on Breg induction and or expansion, stability, and functional potential and the lack of a consensus Breg signature are just some of the hurdles to be bypassed to generate a safe and efficient cell product. Moreover, we might be dealing with different subsets of Breg depending on the induction cocktail and system used that might present different stability and functionality. We are going in depth on it in the next *In Vitro Breg induction (iBregs)*.

Another matter of concern is the antigen specificity of Breg. Recent studies provide evidence for an essential role of antigen recognition by B cells to generate allograft tolerance in murine models (Kimura et al., 2020; Mohib et al., 2020) and in this line, the critical role of BCR and CD40 expression for Breg development and in transplant models is proven. On the other hand, TGF-β seems to mediate a prominent role in allograft survival (Kimura et al., 2020) while IL-10 essentiality in mediating Breg tolerogenic action is questioned. Insight in the role of Breg antigen specificity may bring the development of chimeric antigen receptor (CAR)-lymphocyte generation to produce cellular therapies with targeted Bregs.

Bregs have also been shown to represent a significant source of serum IgM and IgG during adoptive transfer experiments, and produce antigen-specific, polyreactive and autoreactive antibody specificities (Lo-Man, 2011). However, their role in solid organ transplantation still needs to be defined and new technical advances in nanosciences might bring new opportunities into that area.

The effect that donor or recipient-derived Breg could have in modulating the immune reaction remains unknown if we envision a therapy with autologous or allogeneic Breg in autoimmune diseases or organ transplantation. And as in every cell therapy donor origin (autologous or allogeneic) needs to be carefully considered. The age of the patient appears to be a relevant factor in the capacity of Bregs to produce IL-10 since it is impaired in $CD38^{Hi}CD24^{Hi}$ B cells from old individuals (Duggal et al., 2013). Also, autoimmune diseases have been related to disfunctional Bregs where patient's Breg numbers are normal but they lack the immunomodulatory properties related to this cell "subset" and furthermore, Bregs isolated from patients who had suffered renal graft rejection lost their inhibitory capacity (Nouël et al., 2014). This might be a major problem if we think of autologous cell treatment. There are other mechanistic issues that would have to be addressed such as the time needed to produce enough Breg, infusion timing and dosage, route of administration, and GMP compliance.

In Vitro Breg Induction (iBregs)

The implementation of a reliable and reproducible method of *in vitro* Breg induction and expansion from human B cells is highly required for the development of Breg-based cell therapies. The application of a standardized *in vitro* induction method which generates a well-characterized subset of induced Bregs could compensate for the absence of a human Breg biomarker.

Traditional mechanisms of iBregs induction are mostly based on the stimulation of Toll-like receptors 4 and 9 (TLR4 and TLR9) by bacterial-derived LPS and CpG molecules and the ligation of B-cell antigen receptor (BCR) and CD40 to agonist molecules. In this sense, signaling pathways triggered by TLRs and CD40 accompanied by BCR stimulation might lead to IL-10 production, a conventionally used cytokine for the assessment of *in vitro* Breg induction, *via* activation of transcription factors such as STAT3 (Baba et al., 2015). However, there is also evidence of B cell activation towards effector and/or memory phenotypes when using such strong stimulation methods, and therefore inflammatory cytokines should also be carefully monitored in these induction systems (Lighaam et al., 2018).

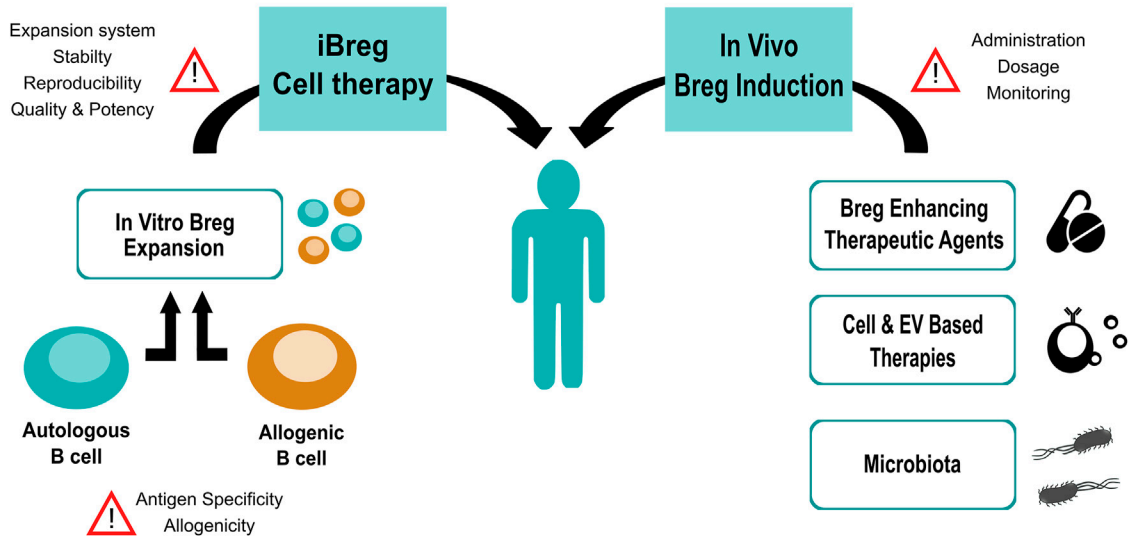

FIGURE 1 | Summarized workflow of Breg-based therapy for kidney transplanted patients, steps and points of concern.

Besides IL-10, several groups have described other molecules as key mediators of iBreg regulatory potential. Several "non-classic" Breg markers have been explored, such as the Granzyme B (GZMB) molecule. Currently, the population of GZMB-expressing B cells is represented as a particular subset of Bregs. In addition, a reproducible protocol for the *in vitro* expansion of this cell subset is already reported in the literature (Chesneau et al., 2020).

As we mentioned in *Indirect Intervention: The Role of Microbiota*, the use of SCFAs is being developed in an attempt to mimic the gut microbiota action. This method would be considered an additional novel form of *in vitro* Breg induction as an alternative to boosting the patient's natural gut microbiota.

Leaving aside the traditional methods and the use of bacterial compounds, our group described the co-culture of tonsil derived-B cells and MSCs from subcutaneous fat as a method of inducing the development of Bregs (Franquesa et al., 2015; Luk et al., 2017).

Common to all the aforementioned methodology, it would be necessary to establish a protocol for the generation of iBregs with a stable phenotype over time. In this regard, the Breg marker CD9 has already been shown to be highly modulated (Mohd Jaya et al., 2021). Therefore, phenotypic and functional stability is a challenge considering the transient nature of some of the Breg phenotypes described (**Table 1**).

DISCUSSION

In this mini-review we aimed to summarize the most relevant and recent evidence on the role of Bregs in kidney disease by discussing the relevance of *in vitro* and *in vivo* Breg induction as well as the potential use of Bregs as cell therapy agents (**Figure 1**). Bregs have been described as major drivers of tolerance in kidney transplantation and in autoimmune diseases. Their upregulated expression has been related to spontaneous tolerant kidney transplant patients, while impaired function and low numbers of Bregs have been associated to several autoimmune diseases.

Breg homeostasis appears to be a cornerstone for immune regulation and tolerance, so several tactics are being approached to reestablish the equilibrium lost in several pathological situations.

One approach is to boost natural Breg populations in patients. Regardless of the limited knowledge of markers, there is already a description of the effect of every immunosuppressant used in kidney transplantation and other anti-inflammatory drugs on Breg populations, allowing for a possible optimization of Breg-induced tolerance. In this line, some immunosuppressants such as Belatacept or Campath, have shown to boost Breg in kidney transplant patients.

Such Breg boosting therapies could be coadjuvant of cellular therapies with MSC or Tregs which have shown capacity to induce Bregs in kidney transplant patients. TolDC have shown similar results in diabetic patients, but have not been tested in clinical trials for kidney transplant. Furthermore, indirect metabolic interventions are slowly gaining track on the field, with increasing publications about the role of gut microbiota and dysbiosis in the maintenance of homeostasis and immune balance, opening new fields of research and clinical research.

On the other hand, Breg application as adoptive cellular therapy is a contentious topic, with no clinical trials on the horizon, due to their difficult identification and expansion. In human, Breg are niche populations in peripheral blood with low expression, with most of them being localized in the spleen, so

in vitro expansion would be necessary to achieve significant therapeutic effects. The lack of consensus on several key points such as; Breg signature, antigen specificity, alloreactivity, expansion system, stability after administration and dosage, would be critical in the efficacy of such therapy.

In recent years, there has been extensive progress in the understanding of Bregs, many researchers are pursuing the definitive human Breg signature, however this seems rather utopic. Many different markers have been associated to Bregs as reviewed in (Rosser and Mauri, 2015; Shang et al., 2020; Catalán et al., 2021), highlighting the fact that they are found across all B cell subsets.

The differences in phenotype and in secreted factors is not just a make-up signature but it affects Bregs' mechanism of action, claiming for proper read-outs for the regulatory activity of Bregs. For long time, IL-10 has been the gold-standard to discern between regulatory and non-regulatory B cells, but evidence has shown that, on one hand IL-10 alone is not enough to truly describe Bregs and iBregs, as IL-10 is also an activation marker, and the ratio between inflammatory markers and IL10 (anti-inflammatory cytokine) might be the real hallmark of Bregs. On the other hand, other secreted factors such as GZMB or the expression of FasL or PD-L1 have also been described as key markers of Bregs and iBregs, opening new doors for their mechanistic paths of regulation.

However, the development of improved *in vitro* Bregs induction systems from human B cells, such as the use of SCFAs or MSCs, opens up the possibility of re-educating the patient's B cells towards a regulatory phenotype and presents a small ray of hope in the context of adoptive Bregs therapy. The ideal *in vitro* induction system should generate, from donor B cells, a sufficient number of iBregs with a stable phenotype and a demonstrable immunodulatory capacity.

AUTHOR CONTRIBUTIONS

SGG, NS-H, and MF summarized the literature and drafted the manuscript. All authors reviewed and approved the final manuscript.

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