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IL-10-producing regulatory B cells and plasmocytes: molecular mechanisms and disease relevance

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Abstract

It has long been assumed that the functions of B cells reflected the roles of antibodies. However, B cells also decisively influence immunity via antibody-independent mechanisms including the presentation of antigen to T cells and the secretion of cytokines. In fact, B cell depletion therapy improves the course of autoimmune diseases such as multiple sclerosis by removing pro-inflammatory cytokine-producing B cells rather than by reducing autoantibody levels. Remarkably, B cells can also produce anti-inflammatory cytokines, and subsequently suppress immunity, providing protection from autoimmune diseases while interfering with beneficial responses against pathogens and cancers. A major mediator of this B cell regulatory function is their secretion of IL-10. There is considerable interest in identifying the mechanisms inducing the expression of IL-10 in B cells during the course of their activation. Here, we review the molecular mechanisms controlling IL-10 expression in B cells, and the evidence that IL-10-producing B cells play a protective role in human autoimmune diseases, underlying the relevance of this immunosuppressive axis for therapy.

Keywords: B cell, plasma cell, cytokine, IL-10, autoimmune disease

1. Introduction

B cells are the unique precursors of antibody-secreting plasmablasts and plasma cells, which provide antigen-specific humoral immunity. B cells and plasma cells are also important sources of pro- and anti-inflammatory cytokines through which they can modulate directly a multitude of cell types, including stromal cells and hematopoietic cells [1, 2]. These cytokine-mediated B cell functions have been associated with the pathogenesis of autoimmune, infectious, and malignant diseases [1, 2]. For instance, the lack of interleukin(IL)-10 production by B cells leads to the marked exacerbation of autoimmune disease [3], while an increased provision of this cytokine was found to impair anti-microbial immunity [4] and anti-tumor responses [5]. There is therefore considerable interest in understanding how B cells acquire this suppressive function upon activation, how this activity is provided in diseases, and how it is affected by therapies. This review details the molecular mechanisms implicated in the acquisition of IL-10 expression by B cell upon activation, since B cells need to be activated to secrete IL-10, and the implication of IL-10 producing B cells in three human diseases (multiple sclerosis, osteoarthritis, and bullous pemphigoid). IL-10 expression in B cells has been directly observed in these diseases, without any *ex vivo* re-stimulation, which enabled the characterization of some of their molecular properties, and allowed interpreting results obtained with therapeutic interventions, which altogether supported the concept that IL-10-producing B cells provide protection from human autoimmune diseases.

2. Molecular mechanisms controlling IL-10 expression in B cells

Naïve B cells do not constitutively express IL-10, and several receptors have been implicated in their production of this cytokine, including TLR, BCR, CD40, and the receptors for the cytokines IL-1 β , IL-6, IL-21, IL-33, IFN- γ , and APRIL [3, 6-11]. Several of these

pathways play non-redundant roles since a defect in any of them is sufficient to alter the suppressive function of B cells *in vivo* [3, 6, 10].

These receptors also induce other functions in B cells, including their secretion of other cytokines and their differentiation into antibody-secreting cells (ASC). This section reviews the signaling pathways, transcription factors, post-transcriptional regulators, and epigenetic processes implicated in IL-10 expression in B cells, in an attempt to distinguish the mechanisms selectively controlling the acquisition by B cells of suppressive functions from those globally involved in their activation.

2.1. Signaling pathways implicated in IL-10 production by B cells

TLRs play a critical role in initiating IL-10 expression in naïve B cells, which cannot be elicited via BCR and/or CD40 engagement [6]. This TLR function involves phosphatidylinositol 3-kinase (PI3K) because inhibitors of PI3K and Akt reduce IL-10 secretion by TLR-activated B cells, while in contrast, increasing PI3K-Akt signaling through the genetic deletion of phosphatase and tensin homolog (*Pten*) augments the amount of IL-10 produced [12]. Accordingly, mice with a *Pten* deficiency restricted to B cells display increased IL-10-mediated B cell regulatory activity leading to reduced T cell functions. Thus, these mice are protected from T cell-mediated severe contact hypersensitivity [12], and are more permissive to melanoma growth because of reduced anti-tumor effector CD8⁺ T cell responses [13].

There are three classes of PI3K in mammals, which comprise a total of 8 isoforms [14]. The PI3K class 1 p110 δ isoform is important for IL-10 production by B cells [15]. B cells from mice carrying a p110 δ hyper-active mutant, mimicking in mice the mutation found in patients with activated PI3K δ Syndrome (APDS), display an increased IL-10 expression upon stimulation [16]. However, p110 δ signaling also induces B cell secretion of IL-6 and differentiation into ASC, indicating that this pathway contributes globally to B cell activation

[15]. It nonetheless imparts a degree of specificity to B cell differentiation depending on its signaling strength. At high level this signaling preferentially promotes ASC differentiation [17], while at low level it favors germinal center formation [18].

The TLR-mediated induction of IL-10 expression in B cells additionally requires the signaling adaptor B cell linker protein (BLNK), also known as SLP65 and BASH [19]. This adaptor is the major activator of the Bruton Tyrosine Kinase (BTK), which promotes IL-10 expression by activating the transcription factor STAT3 [19]. The BTK-STAT3-IL-10 axis is active in several B cell tumors including LMP2A-expressing B cell lymphomas [20], diffuse large B cell lymphoma (DLBCL) [21], and chronic lymphocytic leukemia (CLL) [22].

The involvement of PI3K and BLNK in the production of IL-10 by TLR-activated B cells underscores the importance of the cross-talk between TLR and BCR in this B cell activity. Indeed, the activation of AKT upon TLR engagement occurs only if B cells express a BCR at their surface, and depends on the proximal BCR signaling adaptor SYK while being independent of MyD88 [23]. TLRs thus employ in B cells unique signaling pathways that recruit BCR signaling components. This might explain why BTK and phospholipase C (PLC) γ 2 participate in TLR4 signaling in B cells [24-26]. However, TLR4 engagement does not stimulate the entire BCR response since it does not elicit a calcium flux [23]. This cross-talk between TLR and BCR provides a link between the innate functions of B cells and their antigen reactivity. The quality of TLR signaling in individual B cells might thus depend on the degree of tonic signaling and autoreactivity of their BCR. This notion is consistent with the observation that B cells with regulatory functions have a distinct BCR repertoire [4]. The molecular mechanism underlying this cross-talk is not fully understood, but might involve the actin cytoskeleton that is engaged upon both TLR4 and BCR activation [27].

A remarkable impact of TLR signaling on naïve B cells is that it confers to these cells the capacity to produce IL-10 upon subsequent re-stimulation via other receptors, such as BCR and CD40, which themselves cannot induce IL-10 in naïve B cells [6]. The production of IL-10 by B cells primed first by TLR and then re-stimulated via the BCR involves calcium signaling [28]. The BCR engagement activates PLC- γ 2, leading to the generation of inositol-

1,4,5-triphosphate that, upon binding to its receptor on the endoplasmic reticulum (ER) membrane, provokes a transient Ca^{2+} release from ER stores into the cytosol. This subsequently induces the opening of Ca^{2+} channels at the plasma membrane, which allows a sustained influx of extracellular Ca^{2+} inside the cytoplasm and provokes the activation of the serine/threonine protein phosphatase calcineurin leading to the activation of the transcription factor NFAT [29]. This pathway depends on the transmembrane protein stromal interaction molecule 1 (STIM-1) and its homolog STIM-2, which are localized in the ER, and link the depletion of ER Ca^{2+} stores to the activation of the store-operated Ca^{2+} (SOC) influx at the plasma membrane [28]. B cells lacking STIM1 and STIM2 are defective in IL-10 production after priming via TLR and re-stimulation via BCR [28]. This calcium-mediated signaling is important to the regulatory functions of B cells *in vivo* because mice with B cells deficient in *Stim1* and *Stim2* develop an exacerbated experimental autoimmune encephalomyelitis (EAE) compared to controls, which reflects their increased autoreactive T cell responses of $\text{T}_{\text{H}1}$ and $\text{T}_{\text{H}17}$ types [28]. The PLC- γ 2-STIM1/STIM2-calcineurin pathway might be uniquely important for the suppressive functions of B cells *in vivo*, because mice with B cells deficient in *Stim1* and *Stim2* displayed normal antibody responses after immunization with either T cell-dependent or T cell-independent antigens [28].

The IL-10 expression induced in B cells upon TLR stimulation can be modulated through the provision of co-signals. For instance, IFN- γ modulates IL-10 production by B cells in a manner that depends on the TLR engaged, having no effect on TLR4-stimulated B cells while increasing strongly the secretion of IL-10 by TLR7/8- and TLR9-activated B cells [8]. This potentiating effect of IFN- γ involves the mitogen activated protein (MAP) kinases p38 and JNK, and is independent of ERK1/2 [8]. It also correlates with a reduced expression of the mRNA coding for the MAPK phosphatase MKP1 (also known as DUSP1) that can inactivate p38, JNK, and ERK1/2 [8, 30].

2.2. Transcription factors associated with IL-10 production in activated B cells

The *Il10* gene contains well characterized regulatory sequences, and transcription factors important for *Il10* expression in macrophages, dendritic cells, and CD4⁺ T cells have been identified [31]. B cells rely on such transcription factors to express IL-10.

STAT3 binding sites are present in the *Il10* promoter, and STAT3 binds to these sites in B cell lines [32, 33]. STAT3 is important for IL-10 expression in B cells, including for TLR-stimulated human B cells [34]. Activation conditions leading to higher STAT3 activation result in higher IL-10 secretion [10]. STAT3 is also important for B cell differentiation into ASC, but is dispensable for their IL-6 production [34-36].

IRF4 is another transcription factor important for IL-10 production by B cells and their differentiation into ASC [37-39]. B cells deficient in *Irf4* secrete less IL-10 than controls after activation by TLR and then BCR [38]. Conversely, IRF4 ectopic expression is sufficient to induce IL-10 expression in a B cell lymphoma line [40]. IRF4 directly stimulates *Il10* transcription by binding to the conserved non-coding sequence 9 (CNS-9) of this gene [38]. B cells critically depend on IRF4 to exert suppressive function *in vivo* because mice lacking *Irf4* selectively in B cells develop an exacerbated EAE compared to controls [38]. This transcriptional mechanism is used by the murine gammaherpes virus 68 (MHV68) that resides in a latent state in memory B cells [40]. The re-activation of MHV68 involves the viral protein M2 [41], which induces IRF4 and subsequently promotes IL-10 production and ASC differentiation [40, 42].

NFAT also contributes to IL-10 expression in naïve B cells first activated via TLR and then via BCR [28]. This two-step B cell stimulation activates the phosphatase calcineurin, which dephosphorylates NFAT1 that promotes IL-10 expression [28]. NFAT and IRF4 might cooperate to promote *Il10* transcription in B cells because IRF4 is a weak DNA binding protein on its own that has been shown to cooperate with NFAT to activate *Il10* transcription in T cells [43, 44]. Noteworthy, NFAT transcription factors however have complex roles in IL-10 expression in B cells: NFATc1 α /A, a short isoform of NFATc1 harboring a particular N-terminal domain, suppressed *Il10* transcription in B cells by binding to an intronic site of the

Il10 gene [45]. Mice with a deficiency in *Nfatc1* selectively in B lymphocytes displayed increased B cell-mediated regulation, and a less severe EAE compared to controls [45]. Further work is required to clarify how NFAT transcription factors control B cell activities at a comprehensive level.

Further underlining the participation of transcription factors previously identified to play a role in *Il10* transcription in other cell types, c-Maf also contributes to IL-10 expression in B cells [46-48]. In T cells, c-Maf promotes IL-10 expression by interacting with the aryl hydrocarbon receptor (AhR), suggesting that the latter might also contribute to *Il10* transcription in B cells.

2.3. miRNA modulating IL-10 expression in B cells

miRNA can modulate IL-10 expression by targeting *Il10* mRNA, mRNA coding for transcription factors controlling *Il10* expression, or epigenetic regulators that affect the *Il10* locus chromatin status.

miR-21 directly impairs IL-10 expression in TLR-stimulated B cells [49]. It is predicted to target *Il10* mRNA by the miRWalk program, and reducing miR-21 levels in B cells using specific inhibitory antagomir increased the frequency of IL-10-producing B cells as well as the amount of IL-10 secreted by activated B cells [49]. Remarkably, B cell subsets competent to produce high amounts of IL-10 upon TLR stimulation including CD1d^{hi}CD5⁺ and Tim-1⁺ B cells express less miR-21 than their CD1d^{lo} and Tim-1⁻ counterparts, suggesting that miR-21 is directly responsible for the phenotypic differences between these B cell subsets [49]. This also highlights the importance of post-transcriptional mechanisms in defining subset-specific B cell functions. B cells isolated from mice that were treated with a miR-21 antagomir mediated stronger IL-10-driven suppression in recipient mice upon adoptive transfer, underlining the *in vivo* relevance of this molecular mechanism [49]. miR-21 has however more complex effects on IL-10 expression because it also inhibits the expression of proteins acting as inhibitors of IL-10 production such as programmed cell death 4 (PDCD4) [50, 51].

The miRNA miR-16 targets *Stat3* mRNA, which codes for STAT3 that is important for IL-10 expression in B cells, and reduces STAT3 as well as IL-10 expression in B cells [52]. Conversely, the lack of miR-16 resulted in an increased expression of IL-10 [52]. Noteworthy, a deficit in miR-16 was also associated with a higher expression of the cell surface receptor T cell Ig and mucin domain-1 (TIM-1) [52], which identified a B cell subset with IL-10-dependent suppressive function [53, 54], suggesting that miR-16 and possibly STAT3 expression regulates the formation of these cells.

miR-155 regulates IL-10 production by B cells indirectly. The levels of miR-155 and *IL10* mRNA increased in parallel in TLR9-stimulated human B cells, suggesting a possible interaction between these two factors. Indeed, enforced expression of a miR-155 mimic augmented IL-10 expression in B cells, and in contrast, miR-155 antagonists reduced their IL-10 secretion [55]. miR-155 modulates IL-10 expression by down-modulating the epigenetic regulator Jarid2, whose mRNA contains several miR-155 seed sequences. Jarid2 is a DNA-binding protein that silences gene expression by recruiting the polycomb repressive complex 2 to specific sites leading to histone 3 lysine 27 (H3K27) trimethylation [56]. The *IL10* gene is directly targeted by Jarid2, which inhibits IL-10 expression in CD4 T cells [57]. IL-10-secreting B cells isolated from activated B cell cultures expressed markedly lower levels of Jarid2 than B cells not secreting IL-10, and B cells in which Jarid2 expression was reduced using a knock-down approach expressed higher level of IL-10 [55]. Of note, miR-155 is also important for B cell differentiation into ASC [58, 59]. Interestingly, miR-155 expression is up-regulated by STAT3 and IRF4, illustrating the various ways these two transcription factors control B cell differentiation and IL-10 production [57, 60].

2.4. Epigenetic regulation of IL-10 expression in activated B cells

The *IL10* locus methylation differs between B cells producing IL-10 or not after stimulation [61]. The mouse B cells producing IL-10 within 5 hours after stimulation have a lower level of CpG methylation at the CNS-9, CNS-4.5, and CNS+1.65 regions. The B cells

expressing IL-10 at later time points after activation only display a lower methylation at the CNS-9 region [61]. The CNS-4.5 methylation status therefore identifies cells competent for “immediate” IL-10 expression, while low methylation at CNS-9 is generally associated with IL-10 expression [61]. This region is bound by the transcription factors NFAT1 and IRF4, which are implicated in IL-10 expression [43].

IL-10-producing human B cells also display a lower level of DNA methylation at the CNS-12.5 region, which corresponds to CNS-9 in mice [61]. The CNS-12.5 region also shows a low level of methylation in germinal centre B cells, memory B cells, and plasma cells, suggesting that these cells are competent for IL-10 production. No region has been identified so far for human B cells that indicates a distinctive capacity for rapid IL-10 production.

Some human B cell tumors also display a low methylation at the CNS-12.5 region, including CLL and some multiple myeloma [61]. The epigenome is an important defining feature of CLL [62, 63]. CLL can be divided into two subtypes depending on the mutation status of their immunoglobulin heavy chain variable region. Unmutated CLL (U-CLL) derive from pre-germinal centre CD5⁺ B cells, and have a worse prognosis than mutated CLL (M-CLL), which originate from post-germinal centre CD5⁺ B cells [64]. The *IL10* gene is within the top 1% of the most highly differentially methylated genes between U-CLL and M-CLL, being hypomethylated in M-CLL [22]. Accordingly, M-CLL produce more IL-10 than U-CLL following TLR stimulation [22, 65]. Two regions show particularly strong methylation differences, a region located in the first intron at position +200 to + 500 bp, and another one in the gene body at position +1300 to +1800. This second region contains a STAT3 binding site whose capacity to bind STAT3 depends on its methylation status [22]. This is essential for IL-10 expression in CLL since inhibiting STAT3 suppresses *IL10* transcription. CLL produce IL-10 in lymph nodes, which are also the primary sites of CLL proliferation [66, 67]. The production of IL-10 by CLL might contribute to the immunocompromised status of these patients, who display an increased susceptibility to severe infections [68, 69]. In keeping with

this, the IL-10 produced by CLL in mice facilitated the development of this tumor by inhibiting the anti-tumor T cell response, while having little effect on the CLL growth *per se* [70].

3. IL-10 production by B cells in autoimmune conditions

IL-10 production by B cells is impaired in several human pathologies. We discuss below the examples of multiple sclerosis (MS), osteoarthritis (OA), and bullous pemphigoid (BP).

B cells from MS patients showed a reduced IL-10 production compared to cells from healthy individuals across several stimulation conditions implicating TLR9, BCR, or CD40 [71, 72]. The underlying molecular defect must extend beyond autoreactive B cells because these cells are too few to impose a noticeable phenotype in polyclonal cultures of peripheral blood B cells. Strikingly, this anomaly is already apparent at disease onset: patients with clinical features preceding MS, such as a radiologically-isolated syndrome or a clinically-isolated syndrome, had a higher propensity to progress towards MS within the next 6 months if they displayed a reduced abundance of IL-10-expressing B cells [73]. In patients with established disease, an impairment of IL-10 production by B cells is found during phases of remission and relapse [74]. However, distinct B cell subsets (CD27⁺ or CD27^{hi}) are the main IL-10 producers during remission and relapse, respectively [74]. Since either CD27⁺ or CD27^{hi} B cells have been reported to be the major IL-10 producers depending on the mode of peripheral blood B cell stimulation [75], MS relapses might be associated with the provision of distinct systemic B cell activation signals. This might involve augmented levels of systemic TLR agonists during disease flares. Endogenous TLR agonists have been identified in MS lesions [76], including the high mobility group box chromosomal protein 1 (HMGB1) that can stimulate TLR2 and TLR4 [77].

MS patients display a lower concentration of several serum factors that have been implicated in IL-10 production by B cells compared to healthy individuals. These patients have reduced serum levels of both vitamin A and its metabolic derivative retinoic acid (RA),

which inversely correlates with MS activity [78-81]. The exogenous addition of RA increases IL-10 expression in B cells *in vitro* [82-84]. The serum of these patients also contained reduced amounts of thymosin- α 1, a peptide produced by the thymus that increases the production of IL-10 by B cells *in vitro* [85]. Collectively, these results suggest that the deficit in IL-10 production by B cells in MS reflects impairments in the level of systemic factors that affect B cell functional status globally, which is consistent with the fact that this phenotype is observed across various B cell stimulation conditions. Although IL-10 production by B cells is reduced in MS, some activated B cells express this cytokine. In particular B cells terminally differentiated into plasma cells are a major source of IL-10, together with astrocytes, in the central nervous system of MS patients [86]. The treatment of MS patients with a drug blocking the plasma cell survival factors APRIL and BAFF, namely atacicept, underwent a severe aggravation of disease activity, which led to the premature termination of this trial [87], suggesting that IL-10-producing plasma cells limit MS progression. This effect was most likely due to the neutralization of APRIL because the blockade of BAFF had no significant effect in MS patients (<https://clinicaltrials.gov/ct2/show/NCT00882999>)[88]. Noteworthy, memory B cell survival is independent of APRIL and BAFF [89], suggesting that in the ATAMS clinical trial memory B cells were not targeted. Memory B cells from MS patients produce elevated amounts of pro-inflammatory cytokines such as IL-6 and GM-CSF, which stimulate pathogenic T and myeloid cells, respectively [90, 91]. This disbalance between protective and pathogenic B cell functions might explain why B cell depletion therapy (BCDT) is beneficial in MS. Accordingly, BCDT rebalances these antagonistic B cell activities [90, 91].

In human diseases, IL-10 production by activated B cells can take place in the target tissue, as mentioned above with the example of IL-10 producing plasma cells in the central nervous system of MS patients [86]. IL-10-producing B cells have also been found in the joints of patients suffering from OA, which is the most common form of arthritis. Remarkably, about 20% of the B cells present in the synovial fluid of the affected knee joints constitutively expressed IL-10, while almost no IL-10-expressing B cells were found in blood unless *ex vivo*

stimulated [92]. In the synovial fluid, IL-10-expressing B cells displayed a CD27^{hi}IgM⁺ phenotype evoking IgM memory B cells [93]. These cells inhibited T cell proliferation and T_H1 differentiation in an IL-10-dependent manner *in vitro*, suggesting that they were endowed with regulatory activity [92]. In keeping with this, the patients with the most severe disease displayed a lower frequency of IL-10-expressing B cells in the joint [92]. This is intriguing because OA is, unlike rheumatoid arthritis, usually not considered as an autoimmune disease. Considering these observations in OA and MS, it appears that activated B cells and plasma cells might be able to influence their microenvironment in the inflamed targeted organ through the production of IL-10 irrespectively of their antigen specificity.

The antigen-specificity of cytokine-expressing B cells during human disease is often undefined, reflecting in many cases the lack of knowledge of the disease relevant autoantigens. It has however been shown in a study of bullous pemphigoid (BP) that autoreactive human B cells can express pro- and anti-inflammatory cytokines, with important consequences for disease progression [94]. BP involves the targeting of two proteins of the hemi-desmosome, BP180 and BP230, by autoantibodies, which provoke the local activation of complement and the recruitment of eosinophils and neutrophils, ultimately causing the disruption of the skin basement membrane and its blistering [95, 96]. BP can be treated by BCDT, which usually leads to disease improvement, and a drop of autoantibody levels in the majority of patients [94]. This reduction of autoantibody levels seems important for the maintenance of disease improvement, because patients who had no major decrease in autoantibody levels after BCDT relapsed around day 100 post-treatment [94]. Some patients can achieve complete remission after BCDT, often being maintained on minimal steroid therapy, with a few patients achieving off-therapy remission [94]. Patients in remission distinctively displayed a marked decrease in autoantibody levels, and the remodeling of cytokine gene expression in autoreactive B cells [94]. At 24 months post BCDT, only patients in remission displayed the expression of IL-10 and IL-1RA, and an almost complete loss of IL-6, in autoreactive BP180-specific B cells [94]. Taken together, these data indicate that the long-term establishment of disease remission requires a switch in cytokine expression away

from pro-inflammatory mediators towards anti-inflammatory factors in autoreactive B cells in addition to the reduction of autoantibody levels.

In summary, these clinical observations demonstrate the existence of IL-10-producing B cells in human, because these cells were observed directly in clinical samples without having recourse to artificial *ex vivo* stimulation. These cells could be found in the targeted tissue such as the brain in MS, or the joint in OA, where they displayed plasmocyte and IgM memory B cell phenotypes, respectively. The elimination of these cells might lead to an aggravation of disease pathogenesis, as suggested by the case of MS patients treated with atacicept. Noteworthy, autoreactive B cells transcribing the *IL10* gene can also be found in blood, as documented in the case of BP, and their appearance following therapeutic intervention seems to be associated with a better disease outcome since *IL10*-expressing autoreactive B cells were only observed in BP patients who achieved complete remission at 2 years after BCDT.

4. Conclusion

Our knowledge of the molecular mechanisms controlling IL-10 expression in B cells has greatly increased with the identification of signaling pathways, transcription factors, epigenetic processes, and post-transcriptional regulators implicated in this process. This knowledge now provides molecular signatures associated with this B cell activity that can be used to address the presence of this B cell function in human diseases. This is all the most relevant that IL-10-producing B cells have now been observed directly in chronic human diseases, as illustrated here with the examples of plasmocytes in MS and IgM memory B cells in OA, and that there is evidence accumulating that they play a protective role. Indeed, their loss is associated with a worsening of the disease (MS), while their presence seems to facilitate remission (BP). The observation that blood B cells from patients with chronic autoimmune diseases display a reduced provision of IL-10 upon polyclonal stimulation using agonists of BCR, CD40, or TLR, indicates that this B cell function is influenced by systemic

factors such as the vitamin A metabolite retinoic acid. The identification of agents that increase this B cell function without globally augmenting B cell activation might provide unique opportunities to harness this B cell regulatory activity therapeutically in autoimmune diseases.

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Declaration of interest

S.F. performed consultancy work for Novartis International AG and Galapagos NV. C.C. and B.M. have no conflict of interest to declare.

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