B cell-regulated immune responses in tumor models and cancer patients

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The essential role played by T cells in anticancer immunity is widely accepted. The immunosuppressive functions of regulatory T cells are central for tumor progression and have been endowed with a robust predictive value. Increasing evidence indicates that also B cells have a crucial part in the regulation of T-cell responses against tumors. Although experiments reporting the production of natural antitumor antibodies and the induction of cytotoxic immune responses have revealed a tumor-protective function for B cells, other findings suggest that B cells may also exert tumor-promoting functions, resulting in a controversial picture. Here, we review recent evidence on the interactions between B and T cells in murine models and cancer patients and their implications for cancer immunology.

Introduction

The important role of T cells in antitumor immune responses is widely accepted and has been extensively studied. However, tumor-specific immune responses appear to be much more complex than other mechanisms of defense against pathogens, as demonstrated by the clinical inefficacy of T cell-based anticancer vaccines. As early as in 1956, Thomas and Burnet proposed the theory of immunosurveillance in humans, suggesting that lymphocytes act as sentinels that continuously eliminate neo-transformed cells to prevent the manifestation of overt neoplasms. Although this theory has been challenged several times, data accumulating in the late 1990s led to the widespread acceptance of its original formulation.¹,²

B cells are mainly known for being in charge of the production of antibodies against a broad range of antigens. The discovery of B cells occurred in the mid-1960s, together with that of T cells. Cooper and Good demonstrated the functional distinction between cells in the chicken bursa of Fabricius (B cells), which were responsible for the secretion of antibodies, and cells that required an intact thymus (T cells), being associated with delayed-type hypersensitivity responses.³,⁴ Initially, B cells were defined as lymphocytes expressing clonally diverse cell-surface immunoglobulin receptors capable of recognizing specific antigens. In 1948, plasma cells were suggested to be the main source of antigen-specific antibodies.⁵

Besides their role in antibody generation, however, B cells mediate and regulate numerous other functions that are essential for immune homeostasis. Of crucial importance for T-cell immunity, B cells, regulatory B cells, T cells, Tregs, tumor-specific immune responses

B-Cell Immunology in Murine Tumor Models and Cancer Patients

Although during the last decade the field of oncoimmunology was largely focused on T cells, research has also been conducted to evaluate the potential involvement of B cells in carcinogenesis and tumor progression. To the knowledge of the authors, however,
a systematic study of B cells in cancer patients has not been performed yet. Rather, most of the studies dissecting the regulatory functions of B cells relied on mouse models of autoimmune diseases or in vitro settings. Thus, it has been shown that T cell-mediated autoimmune responses can be prevented by a small subset of IL-10-producing B cells, which were characterized as CD1d<sup>high</sup>CD5<sup>+</sup> B cells. Along similar lines, mice can be protected from chronic colitis by B1b (CD5<sup>−</sup>CD1d<sup>high</sup>B220<sup>−</sup>CD11b<sup>+</sup>IgM<sup>+</sup>) regulatory cells, while CD19<sup>+</sup>CD24<sup>−</sup>CD38<sup>−</sup>B cells are associated with a protection from systemic lupus erythematosus in humans.<ref>19,20</ref>

As early as in 1978, a tumor-promoting role was proposed for B cells in C57BL/6 mice injected with fibrosarcoma cells. Tumor growth and metastatic spread were indeed significantly reduced in mice depleted of B cells by an anti-IgM monoclonal antibody. These early findings have been supported by data from murine xenograft models collected throughout the 1990s, although the precise functions of B cells in antitumor immunity remained unclear.<ref>22</ref> Seminal studies by Qin et al. based on wild-type and nude C57BL/6 mice subjected to the depletion of B cells by means of an anti-CD20 antibody revealed that the repertoire of CD4<sup>+</sup> helper T cells is limited in the presence of B cells, resulting in reduced antitumor immune responses.<ref>23</ref> More recently, Inoue et al. provided additional insights into the mechanisms mediating such an immunosuppressive function of B cells.<ref>24</ref> To this aim, the authors screened tumors for their susceptibility to B cell-deficient immune networks by culturing splenic cells from wild-type or B cell-deficient C57BL/6 mice with irradiated tumor cells. Upon stimulation, the production of interferon γ (IFNγ) from CD8<sup>+</sup> T cells and natural killer (NK) cells was found to be markedly increased in the B cell-deficient as compared with wild-type conditions. IFNγ production could be correlated directly with the expression of the CD40 ligand on the surface of cancer cells and inversely with IL-10 production by B cells. Confirming the findings described above, in a two-step model of skin carcinogenesis (as induced by the sequential administration of 7,12-dimethylbenz[a]anthracene and 12-O-tetradecanoylphorbol-13-acetate in the context of adoptive B-cell transfer), tumor necrosis factor α (TNFα) was identified as a key immunosuppressive mediator, owing to its ability to promote the accumulation of regulatory B cells (Bregs) (Fig. 1).<ref>26</ref>

Even deeper insights into the mechanisms accounting for B cell-mediated immunosuppression have been provided by de Visser et al. (Table 1).<ref>27</ref> These authors used a model of human papillomavirus type 16 (HPV-16)-induced skin carcinoma and observed a reduced infiltration of immune cells in B cell-deficient mice as compared with wild-type animals. In line with this notion, the adoptive transfer of B lymphocytes into B cell-deficient mice restored the infiltration of innate immune cells into premalignant tissues. Although only low numbers of B cells infiltrate premalignant lesions, B cells may exert a distant effect on oncogenesis by secreting antibodies that are deposited at the tumor site in the form of immune complexes. Upon the binding of activating Fcγ receptors (FcγRs) to such immune complexes, myeloid cells including macrophages can be recruited to neoplastic lesions and become primed to exert tumor-supporting functions by secreting pro-angiogenic factors and immunosuppressive cytokines (Fig. 1). We have extended these findings to a clinical setting and demonstrated the presence of tumor-specific T-cell responses in the bone marrow of 40% breast carcinoma patients, correlating with an improved prognosis, as opposed to tumor-specific natural antibodies, which were detectable in approximately 50% of the patients and correlated with both the absence of bone marrow tumor-specific T cells and advanced tumor stage.<ref>25,21</ref>

It is widely accepted that several distinct immunogenic cancers are driven by a chronic inflammatory milieu that, at least in part, may be maintained by B cells. Some cancers such as hepatocellular carcinoma and prostate cancer have indeed been epidemiologically linked to chronic inflammation.<ref>32–35</ref> In line with this notion, chronic inflammation was identified as a key etiological mechanism, independent of carcinogen exposure, also in a mouse model of lung cancer.<ref>36</ref>

Although inflammation is generally linked to tumor progression, it may also stimulate antitumor response and can be harnessed for the immunotherapy of cancer patients.<ref>27,37,38</ref> Since B cells have a major impact on the basic physiology of inflammatory responses to pathogens, numerous disorders are regulated by B cells. In the course of autoimmune diseases and antibody dependent cellular cytotoxicity (ADCC) reactions, B cells are indeed considered a command center interacting with other immune cells within a complex cytokine network (Fig. 1).<ref>15,39,40</ref> Moreover, Ammirante et al. demonstrated the T cell- and complement-independent, lymphotoxin-mediated inhibition of prostate carcinoma by B cells.<ref>29</ref> In this context, a link could be made with the activation of inhibitor of κB kinase α (IKKα), which stimulates metastasis by an NFκB-independent, cell-autonomous mechanism. Ammirante et al. first demonstrated that immunoglobulins in the tumor stroma elicit at least 2 pro-inflammatory pathways, namely, by activating the complement system and by engaging FcγRs on the surface of immune cells.<ref>29</ref> The stimulation of FcγRs in B cells was found to be a prerequisite to establish a tumor-promoting stroma. The authors reported a transient increase in the infiltration of tumors regressing upon castration by immune cells, including B cells. In this context, the production of lymphotoxin α/β by B cells was responsible for the androgen-independent activation of IKKα and signal transducer and activator of transcription 3 (STAT3) in tumor cells, which promoted relapse (Table 1). Thus, FcγRs are responsible for a functional link between adaptive and innate immune responses against developing tumors providing a platform for the interaction between circulating immunoglobulins and innate immune cells.<ref>41</ref> Moreover, immunoglobulins can serve as a carrier for TGFβ and thereby exert suppressive effects on cellular immune responses.<ref>26</ref> In a different study based on the mouse mammary adenocarcinoma 4T1 model, a population of CD19<sup>+</sup>B220<sup>−</sup>CD25<sup>−</sup> B lymphocytes was also implicated in cancer progression.<ref>42</ref> It should be noted that CD25 might simply identify activated cells, as it is upregulated on all activated T and B lymphocytes and expressed at high levels by thymic regulatory T cells (Tregs). Nonetheless, the abovementioned study demonstrated that the subcutaneous
The study mentioned above showed that CD19+B220+CD25+ B cells are able to inhibit T-cell proliferation and induce the conversion of CD4+ T cells into regulatory T cells (Tregs), both in vitro and in vivo, thus favoring metastasis (Fig. 1). The authors also demonstrated that conversion of CD4+ T cells into Tregs was dependent on physical contacts between T and B cells, as well as on the secretion of TGFβ by the latter. However, the molecular components involved in such a contact-dependent T-cell inhibition by B cells remain to be identified. The implication of TGFβ is in contrast with previous observations on Bregs, showing that the immunosuppressive functions of these cells is TGFβ-independent. Finally, the authors did not report a crucial role for IL-10, as recently confirmed by Zhang and colleagues.
in a similar experimental setting. Thus, the cytofluorometric characterization of Bregs based on standardized markers will be a major challenge for future research.

The question as to whether the use of different tumor cells in the same animal model may confirm the hypothesis that B cells exert major tumor-promoting functions was first addressed by Shah et al.28 These authors evaluated the immune responses to primary tumors of mice genetically engineered to lack B cells, finding the growth of EL4 thymomas and MC38 colon carcinomas to be significantly reduced. In contrast, the growth of B16 melanomas was significantly enhanced in B-cell-deficient as compared with wild-type mice. These results have been subsequently confirmed by several other investigators using the same model.30 Also Sorrentino et al. were able to show that the absence of B cells promotes the growth of lung cancers in mice.44 By contrast, in B cell-deficient C57BL/6J mice implanted with metastatic B16-F10 melanoma cells, the adoptive transfer of B cells activated by CpG-oligodeoxynucleotides (ODNs), a Toll-like receptor 9 (TLR9) agonist, blocked the growth and induced the apoptotic demise of lung metastases. Along similar lines, the depletion of mature CD20+ B cells increased tumor growth in both CpG ODN-treated C57BL/6J and nude mice. In summary, these data demonstrate at least some degree of antitumor activity for CpG ODN-activated B cells. Many studies of this type, however, were performed using mice in which the immune system had developed in the complete absence of B cells (Table 1). These hosts harbor therefore a limited T-cell repertoire, lack follicular DCs as well as several macrophage subsets and show enhanced IL-12 production by DCs, which can skew Th1 responses.53–55 Besides the (partially controversial) findings described above, other potential mechanisms of B-cell malfunction or abnormalities in the B-cell compartment of cancer patients have not been characterized to date. For instance, a preferential loss of CD27+ and CD19+ B cells in patients bearing advanced melanomas and other solid tumors has been reported, but the mechanisms underlying this phenomenon still await elucidation.48,49

### Crosstalk Between B and T Lymphocytes in the Course of Antitumor Immune Responses

The mutual interaction between immune cells through physical contacts, cell surface receptors, and soluble mediators represents the basic mechanism for the generation of immune responses. To this aim, the same evolutionarily perfected protocol of defense against a multitude of enemies, including malignant cells, is used. Thus, via a specific T-cell receptor (TCR), T cells recognize a peptidic fragment of the antigen in association with MHC molecules presented on the surface of APCs. Following this interaction, T cells massively proliferate and differentiate into effector T cells. The efficient priming of naïve CD8+ T cells depends on distinct signals by APCs (Fig. 1). First, APCs should present a peptidic fragment of the antigen in association with MHC molecules on the surface of APCs. Following this interaction, T cells massively proliferate and differentiate into effector T cells. The efficient priming of naïve CD8+ T cells depends on distinct signals by APCs (Fig. 1). First, APCs should present a peptidic fragment of the antigen in association with MHC molecules on the surface of APCs. Following this interaction, T cells massively proliferate and differentiate into effector T cells. The efficient priming of naïve CD8+ T cells depends on distinct signals by APCs (Fig. 1). First, APCs should present a peptidic fragment of the antigen in association with MHC molecules on the surface of APCs. Following this interaction, T cells massively proliferate and differentiate into effector T cells. The efficient priming of naïve CD8+ T cells depends on distinct signals by APCs (Fig. 1). First, APCs should present a peptidic fragment of the antigen in association with MHC molecules on the surface of APCs. Following this interaction, T cells massively proliferate and differentiate into effector T cells. The efficient priming of naïve CD8+ T cells depends on distinct signals by APCs (Fig. 1). First, APCs should present a peptidic fragment of the antigen in association with MHC molecules on the surface of APCs. Following this interaction, T cells massively proliferate and differentiate into effector T cells. The efficient priming of naïve CD8+ T cells depends on distinct signals by APCs (Fig. 1). First, APCs should present a peptidic fragment of the antigen in association with MHC molecules on the surface of APCs. Following this interaction, T cells massively proliferate and differentiate into effector T cells. The efficient priming of naïve CD8+ T cells depends on distinct signals by APCs (Fig. 1). First, APCs should present a peptidic fragment of the antigen in association with MHC molecules on the surface of APCs. Following this interaction, T cells massively proliferate and differentiate into effector T cells.
epitopes independent of their B-cell receptor (BCR) specificity but also can promote MHC class I cross-presentation.

Further evidence on the involvement of B cells in the induction of optimal CD4+ and CD8+ T-cell response against tumors has been provided by DiLiLo et al. Thus, in a murine B16 melanoma transfer model, the authors depleted mature B cells from wild-type adult mice by means of an anti-CD20 monoclonal antibody. In B cell-depleted hosts, tumor growth was markedly increased along with a significant impairment in CD4+ and CD8+ T-cell induction. Carpenter et al. demonstrated that B cells from patients with advanced stage solid tumors display a reduced ability to activate T cells to secrete IFNγ and IL2, while Blair et al., investigating the immunosuppressive functions of Bregs, could demonstrate that CD40-stimulated human B cells do suppress the differentiation of T H1 cells as partially mediated by IL-10 but not TGFβ. Such an immunosuppressive activity was reversed by means of anti-CD80 and anti-CD86 monomolecular antibodies. In a mouse model of lung cancer, Chapoval et al. demonstrated NK and T lymphocytes to be required for optimal responses to chemotherapy, while B cells appeared to suppress its antitumoral effects. Accordingly, B cell-deficient mice were manifested a significant improvement in survival rates. In additional support of the immunosuppressive capacity of B cells, Perricone et al. reported an enhanced efficacy of melanoma-targeting vaccines in the absence of B lymphocytes. The vast majority of these studies has focused on how activated B cells can be used as effective APCs for T-cell priming. While lipopolysaccharide (LPS)-activated B cells have been reported to enhance the expansion of tumor-infiltrating lymphocytes in a culture system involving anti-CD3 monoclonal antibodies and IL-2, the adoptive transfer of LPS-activated B cells exposed to anti-CD3 antibodies to B16 melanoma-bearing mice induced the regression of lung metastases. Although the mechanisms whereby adoptively transferred B cells mediated antitumoral effects require further clarification, an involvement of B cell-T cell interactions is likely.

Along similar lines, the presence of CD20+ tumor-infiltrating B cells (TIBCs) and Ig κ chains (IGKC)s within the tumor bed has been positively correlated with metastasis-free survival and response to chemotherapy in patients affected by a variety of malignancies including breast, ovarian, head and neck, non-small cell lung, and colorectal carcinoma as well as melanoma. The mechanisms underlying TIBC antitumor immunity may involve a role of B cells as APCs in that they can bind tumor-associated antigens via their BCR, process them, and then present the corresponding peptides to T cells in the context of MHC molecules. Moreover, by secreting lymphotoxin, TIBCs orchestrate the generation of local tertiary lymphoid structures, consisting of CD20+ B cells co-residing with CD8+ T cells in loose aggregates within and adjacent to tumor cell islets. Finally, effector TIBCs can produce cytokines IFNγ and IL-4 that may polarize T cells toward a T H1, T H2, or alternative functional phenotype. These observations might have strong implications for the development of prognostic tests based on TIBCs and inform the design of ever more effective anticancer immunotherapies.

Sakaguchi et al. were the first to stimulate an interest in Tregs by identifying a population of CD4+ T cells specifically expressing the transcription factor FOXP3 and preventing autoimmunity in a murine model. Subsequently, numerous reports enlightened major aspects of the biology of Tregs, by characterizing different T-cell subpopulations with regulatory properties, including naturally occurring CD4+CD25high Tregs, induced Tregs (e.g., T H1 and T H3 cells) as well as CD4+CD25high Tregs developing in the periphery upon the conversion of CD4+CD25− T cells. All these T-cell populations with regulatory functions co-exist and contribute to immune suppression in the course of oncogenesis as well as in several other pathophysiological settings.

Tregs suppress in a rather potent way T H1 immune responses as well as other CD8+ cytotoxic lymphocytes, hence favoring tumor growth. In line with this notion, CD4+CD25highFOXP3+ T regulatory cells are mainly characterized by an anergic state and by the capacity to actively inhibit CD4+CD25− T cells, CD8+ T cells, DCs, NK cells, natural killer T (NKT) cells, and B cells in a contact-and-dose-dependent manner. Moreover, CD4+CD25highFOXP3+ Tregs are characterized by a phenotypic profile of antigen-experienced memory T cells. Recent evidence shows the Tregs can suppress the activity of plasma cells even without an intervention of helper T cells. In this context, it is important to note the distinct effects of Tregs on different B-cell subsets. Cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and glucocorticoid-induced TNFR-related protein (GITR) are among the most prominent cell-surface markers associated with the phenotype and function of Tregs. In addition, IL-10 and TGFβ, although rarely expressed in vitro, might be functionally relevant for Tregs in vivo, especially in settings of B cell-mediated immunosuppression (Fig. 1). Although Tregs have been intensively investigated during the last decade, it is still unclear whether these cells are prominently primed in the thymus or rather emerge in the periphery upon antigen-specific stimulation. In this respect, the work of Valzasina et al. supports the thymus-independent expansion of Tregs, as the inoculation of malignant cells to mice resulted in the expansion of CD4+CD25− T cells even in thymectomized animals and independently of pre-existing CD25+ T cells (which had been removed by specific monoclonal antibodies).

The first line of evidence demonstrating the regulation of Tregs by B cells in a murine model was provided by Wei et al., describing the B cell-mediated protection from colitis resulting from the conversion of naïve T cells into Tregs. The protective potential of Tregs in autoimmune diseases has been unveiled long time ago, but the underlying mechanisms, including the conversion of T cells and the involvement of specific and rather small subsets of B cells, have only recently begun to emerge.

Kessel et al. have studied the effects of Bregs on T cells in human samples, with particular attention to the role of IL-10 and TGFβ, finding that the co-culture of Bregs (defined as CD25highCD79αhighCD86highCD1dhighIL-10highTGFβhigh) with stimulated autologous CD4+ T cells significantly decreased the proliferative properties of the latter. Furthermore, FOXP3 and CTLA-4
expression by Tregs were enhanced by non-stimulated (and even more by CD40L-stimulated) Bregs. The Treg-regulatory activity of Bregs was essentially dependent on direct cell-to-cell contacts as well as on TGFβ, but not IL-10. The recruitment of Tregs by B cells mainly relies on the secretion of chemokine (C-C motif) ligand 4 (CCL4), operating as a potent chemotractant.42 Primary B lymphocytes are also capable of actively converting naïve T cells into FOXP3+ Tregs.79,80 Interestingly, in a murine 4T1 breast carcinoma model, Olkhanud et al. could demonstrate that so-called “tumor-evoked Bregs” promote the metastatic spread to the lung of breast cancer cells by converting resting CD4+ T cells into Tregs.42 Upon further analysis, such a metastatic spread turned out to require a chemokine (C-C motif) receptor 4 (CCR4)-mediated chemotactic response on both tumor cells and Tregs, which directly inactivated pulmonary NK cells.81 Olkhanud et al. speculate that Tregs and tumor-evoked Bregs may also functionally interact with myeloid-derived suppressor cells (MDSCs), which can further potentiate the Treg response, hence exerting immunosuppressive effects and promoting disease progression.42 Finally, Tadmor et al. compared tumor growth as well as the number and function of Tregs in wild-type immunocompetent and B cell-deficient mice.82 Mice were either naïve or had received EMT-6 mammary adenocarcinoma cells. Tumor growth was substantially inhibited in B cell-deficient mice as compared with wild-type animals. Tregs expanded in wild-type mice upon EMT-6 cell inoculation, a phenomenon that was much less pronounced in B cell-deficient animals. The percentage and absolute number of Tregs found in the spleen, tumor-draining lymph nodes, and within neoplastic lesions were significantly reduced in tumor-bearing B cell-deficient mice as compared with their wild-type counterparts, and so were Treg functions.82

Conclusions and Clinical Perspectives

Although increasing evidence indicates that B cells play a significant role in antitumor immune responses, the identification of distinct B-cell subsets and associated markers has been challenging, for several reasons. First, B cells are extraordinarily sensitive to isolation methods commonly used to purify other immune cells, e.g., T cells. Second, tumor progression seems to be a critical factor for the ever more pronounced malfunctioning of B cells. Therefore, the precise identification and clear distinction of protumor vs. anti-tumor B-cell subsets will be a central goal for the forthcoming research. Going one step further, only a few translational approaches have been made in order to explore B cell-modulatory drugs in murine tumor models and cancer patients. In this regard, rituximab—a chimeric monoclonal antibody targeting CD20—has been shown to exert promising therapeutic activity in patients affected by some hematologic malignancies, including leukemia and lymphoma. Chronic lymphocytic leukemia patients, for example, significantly benefited in terms of overall and progression-free survival when receiving chemotherapy plus rituximab as compared with chemotherapy alone.83 The same held true in elderly patients with diffuse large B-cell lymphomas, as the addition of rituximab to the standard therapeutic regimen (as the addition of cyclophosphamide, doxorubicin, vincristine and prednisone, CHOP) substantially enhanced the rate of complete responses and prolonged event-free and overall survival in the absence of a clinically significant increase in toxicity.84 Second-generation antibodies targeting CD20 (e.g., ofatumumab, veltuzumab, and ocrelizumab) are currently under clinical evaluation.85 Anti-CD20 antibodies also attracted interest for the treatment of solid tumors. Aklili et al. reported that the depletion of circulating B cells by rituximab in combination with IL-2-based immunotherapy did not increase the response rate of patients with metastatic renal cell carcinoma or melanoma.86 On the other hand, in a pilot clinical trial including patients with metastatic unresectable colon cancer, a reduction of tumor burden was observed in 5 out of 8 patients upon partial B-cell depletion with rituximab plus conventional chemotherapy.87 This said, some Breg subsets may escape anti-CD20 immunotherapies.87,88 Thus, the meticulous characterization of distinct Breg subsets might become crucially important in the future to finely tune targeted anticancer immunotherapies.

Another field of interest has been opened up by TIBCs strongly expressing IGKCs, in that the levels of IGKCs proved to constitute a single, robust immune biomarker predicting an improved metastasis-free survival and favorable responses to chemotherapy in patients affected by various solid tumors (see above).64,89 Due to such a reliable association with clinical endpoints, IGKC levels might therefore serve as an immunological biomarker of disease outcome in future clinical trials.70 Furthermore, a recently developed method for cloning and immortalizing TIBCs may prove instrumental for unraveling the actual relevance of these cells in tumor progression and response to therapy.90 Finally, even B cell-based antitumor therapies might be envisioned now that isolation and expansion procedures for tumor-infiltrating and antigen-specific B cells are available.66

Recently, increasing attention has been attracted by signal transducers operating downstream of the BCR, which regulate multiple processes including B-cell development and survival. Bruton tyrosine kinase (BTK) is positioned in a rather apical position within the BCR signaling cascade, thus presenting an attractive target for the selective inhibition of B cells.92 Accordingly, in a Phase I clinical trial, ibrutinib—a selective and irreversible small-molecule inhibitor of BTK—has been shown to exert substantial therapeutic activity in patients affected by a variety of B-cell malignancies.92 Another small-molecule inhibitor of BCR signaling is dasatinib, which interferes with the enzymatic activity of SRC family tyrosine kinases. Interestingly, in a Phase I/II trial involving patients with castration-resistant prostate cancer, dasatinib administered in combination with docetaxel, an established anti-mitotic chemotherapeutic agent, has been associated with a favorable toxicity and some partial responses, although the question of clinical efficacy remains to be clarified in randomized studies.93

In spite of several open questions, accumulating evidence suggests that B cells not only excel in antibody production but also play a critical role as part of the complex cast regulating cellular immune responses.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.
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