

EDITORIAL

Clinical & Experimental Allergy

Is there a place for B cells as regulators of immune tolerance in allergic diseases?

This editorial discusses the findings of the article in this issue by L. E. P. M. van der Vlugt et al. [16] pp. 517–528.

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B-lymphocytes have long been relegated to the periphery when it comes to their role in airway inflammation. Despite being the cell that synthesizes IgE, the primary initiator of allergic inflammation, B cells have not achieved as prominent place in either the pathophysiology or the regulation of asthma as T cells or dendritic cells, as examples. Early studies using B cell-deficient mice suggested that in murine models of allergic airways disease, both B cells and potentially IgE played little role in asthma pathogenesis. However, these observations appeared to be highly dependent on the model used and the methods of sensitization [1]. Our understanding of the role of B-lymphocytes as effector cells in inflammation has vastly increased. This was initiated by work from the Lund laboratory and others [2], determining that B cells were active cytokine-producing cells in parasitic inflammation, and coining the terms Be1 and Be2 for B-effector cells capable of synthesizing Th1 or Th2 cytokines. Work from our own laboratory demonstrated that human mucosal B cells, stimulated by antigen, were capable of producing IL-13 [3]. This pointed to B cells having the potential to be important effectors of allergic response beyond their primary occupation as antibody-secreting cells.

A novel role implicating B cells in the regulation of auto-immune and inflammatory responses has been gathering momentum. Regulatory B cells, or B-reg, are

now implicated as key players in the co-ordination of immune responses in systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis and other severe inflammatory diseases. Murine models of experimental allergic encephalitis are much more severe if B cells are absent. Moreover, the defect can be corrected with a specific B cell subset, B10 cells which are regulatory B cells that produce IL-10 [4]. Patients with MS have fewer regulatory B cells that produce IL-10, compared to effector B cells that produce lymphotoxin [5]. During MS remissions, the ratio of IL-10/LT producing B cells becomes more favourable. In allergy, B10 cells have been found to be regulators of inflammation in murine models of hypersensitivity dermatitis [6]; moreover, studies using helminth-derived products have been used to induce B10 cells and in allergic airways diseases [7].

What do regulatory B cells look like? The definition of B-reg remains a matter of debate, as do the cytokines they release. The majority of the evidence implicates IL-10 as a key immune-regulatory cytokine produced by B cell, but non-IL-10-related regulatory pathways have also been demonstrated, including many IgG-mediated regulatory pathways [8–11]. Phenotypically, the current definition of murine B10 cells are cells that secrete or exhibit intracellular IL-10 following stimulation with LPS, phorbol-ester and ionomycin in the presence of a Golgi blocker such as Brefeldin. The predominant B cell subset that can secrete IL-10 under these conditions is characterized by expression of surface CD5 and CD1d [4, 6]. However, in humans, the most common definition of B-reg includes cells characterized by the combination of surface antigens CD19+ CD38+ CD24+ and intracellular IL-10+. The combination of CD38 and CD24 suggests that the IL-10-secreting B cells are activated, mature B cells. To date, there have been few studies that address this newly defined cell population in diseases, with recent

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Cite this as: B. Mazer, *Clinical & Experimental Allergy*, 2014 (44) 469–471.

publications demonstrating the potential for B-regs playing a role in autoimmunity associated with ageing, in pregnancy and in graft tolerance [12–15]. There is clearly a lack of mechanistic studies and studies that clearly define the functional role of these cells.

In the accompanying paper by van der Vlugt, the authors examine peripheral B cell subsets in a small cohort of asthmatic subjects ($n = 13$) [16]. The key findings of the paper include lower numbers of B cells that produce IL-10 in response to LPS compared to healthy individuals, but no differences in responses to B cell receptor signalling or stimulation through TLR-9 (via CPG). These patients also showed lower numbers of CD24⁺ CD27⁺ B cells and lower IL-10 production by T and B cell co-culture in response to house dust mite allergen. This led the authors to conclude that impaired IL-10 responses by B cells may lead to the dysregulation seen in allergic asthma. The authors have extensive experience in the study of B cells and IL-10-related regulatory events, especially in the context of parasitic diseases [17, 18]. The extrapolation of the regulatory events in host defence to parasites to that of allergic disease is a logical extension of Th2 immunity; both rely on inflammatory events initiated via STAT6-related production of IL-4 and IL-13, and both utilize IgE as the key antibody that mediates the humoral response against unwanted pathogens or allergens. Key B and T cell-related regulatory events are similar in both allergy and parasitic defence. This type of paradigm has been a mainstay of some of the purveyors of the hygiene hypothesis such as Rook [19]. Although the focus of regulatory events has largely been on adaptive T cell responses, the recent increase in evidence of the important role of B cells as regulators of inflammatory responses provides an important avenue for exploration of the role of B cells in allergic diseases such as asthma.

There are many things that need to be clarified as we move forward on the study of regulatory B cells. In the paper by van der Vlugt, the asthma cohort is small, and by definition needed to be mild, as they stopped all

inhaled corticosteroids or combination medications for 2 weeks prior to the study of their peripheral B cells. The application of this finding to larger cohorts that include more severe asthmatics is important and may show even greater discrepancies in regulatory cells. In future studies, it will be important to be mindful, as the authors were, of the effect of medications on circulating B cells. Secondly, the most prominent human B-reg population is proposed to be CD19⁺ CD24⁺ CD38⁺; this in fact was elevated in the asthmatic cohort, whereas CD24⁺ CD27⁺ B cells, which represent an activated, memory subset, were significantly decreased compared to controls. These cells were also less responsive to LPS than healthy controls in producing IL-10, whereas the IL-10 production by CD38⁺ CD24⁺ B cells was comparable in asthmatics and controls. Importantly, the authors demonstrate that their B cell responses to LPS were robust, which is not always the case for experiments using human B cells compared to murine studies.

Allergic diseases are initiated by IgE, a unique B cell product. B-lymphocytes autoregulate antibody production, and it is clear that IgG molecules not only are effector molecules but are regulatory molecules, possibly via different glycosylation enzymes activated in B cells during different stages of immune responses [11, 20]. The concept that B cells could regulate inflammation is highly plausible, and CD38⁺ and CD27⁺ B cells are prominent in both lung and gut mucosa [1, 18, 21]. The studies by van der Vlugt et al. [16] point towards a more important role for B cells not only as producers of IgE but in potentially mediating both B and T cell IL-10 production. Clearly, more studies are needed evaluating peripheral B cell subsets in both asthma and in food allergies. Despite the small cohort, the current study gives food for thought in designing approaches to determine the emerging role of B cells in immune regulation in allergic diseases.

Conflict of interest: The author declares no conflict of interest.

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