Main Submission

Regulatory B cells: The new cells on the block to modulate allergic inflammation.

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Despite its heterogeneity, common clinical manifestations of allergic disease include redness, itchiness and swelling of the affected areas. In those with allergic disease, the exposure to allergens (e.g. antigens that healthy individuals normally have no reaction to, such as pollen and animal dander) can induce IgE-mediated inflammatory processes. The allergic response is canonically mediated by IgE antibodies against allergens, whereby cross-linking of IgE bound on the surface of effector cells propagate the allergic pathways. This can result in the maturation of cluster of differentiation 4^+ ($CD4^+$) T cells into T helper type-2 (Th2) cells and an increase in eosinophilia (1). Eosinophilia, a hallmark of allergic disease manifestation, is the infiltration of the granulocytic cell known as eosinophils, mediated by an increase in Interleukin (IL)-5. Overall, the allergic inflammatory response is facilitated by the release of type 2 cytokines, such as IL-4 and IL-13, which further induce the maturation of IgE-producing B cells (2; Figure 1).

It is thought that the induction of immunological tolerance can mitigate allergic inflammation through the desensitization of the immune system to allergens. Establishing tolerance involves the interplay of regulatory T cells (Tregs), the immunosuppressive IL-10 cytokine, and the process of T cell anergy where pro-inflammatory responses towards allergic substances are weakened (2).

Currently, there is a renewed interest in B cells as an integral component of both tolerance and the allergic disease framework. While B cells are normally associated with allergy pathogenesis through the production of IgE and other Th2 cytokines, evidence suggests that a subset of B cells (known as regulatory B cells or Bregs) have a regulatory role in suppressing allergen-induced inflammation (2). This review will discuss the inhibitory capacity of Bregs in allergic disease, their mechanism of inhibitory action, and their identification and role in allergen tolerance in human allergies.

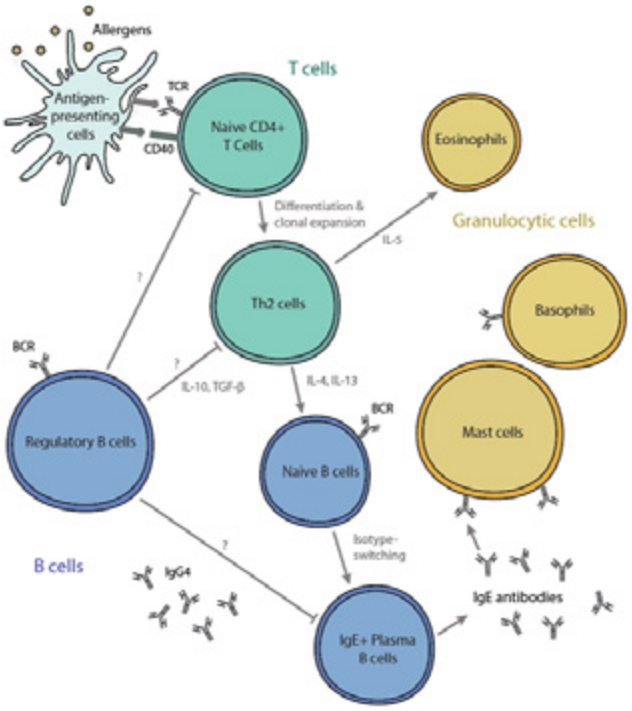

Figure 1. Pathogenesis of the allergic inflammatory cascade in asthma.

The Role of Regulatory B Cells in Allergic Disease

After the initial characterization of B cells with inhibitory properties by Katz et al. (3), several studies directly showed that the transfer of B cells induced tolerance and attenuated inflammation in mouse models of allergic airway disease, anaphylaxis, and contact hypersensitivity through IL-10 (4–7). Furthermore, IL-10-producing Bregs have been shown in humans at similar frequencies compared to Bregs in mice (5).

The Mechanistic Function of Regulatory B cells

Bregs are capable of attenuating inflammation at sites

of immune activation through the secretion of IL-10 (Br1) and TGF-β (Br3). IL-10 has been shown to have an immunosuppressive effect through the suppression of Th2 inflammatory processes by binding to T cell receptors and blocking co-stimulatory signaling. Meanwhile, TGF-β binds T cell receptors to encourage the maturation of Tregs, which have the capacity to inhibit the activation of effector T cells. The disruption of TGF-β receptor signaling has been shown to increase an individual's susceptibility to develop allergic asthma. While TGF-β has been implicated in mouse allergen tolerance, IL-10 has been implicated in that of humans; however further research needs to be done to determine whether B cell production of TGF-β also has allergen tolerance effects in humans. In addition, the inhibitory immunoglobulin, IgG4, is secreted by Bregs to induce a protective effect against IgE by interfering with allergen-IgE interactions and binding to excess allergen (2).

Currently there is interest in the application of Bregs in the field of allergy immunotherapy to achieve an induced state of tolerance and higher levels of IL-10, TGF-β, and IgG4-specific antibodies, thus modulating allergic inflammation (2).

Characterization of Regulatory B cell Phenotypes

CD19 is considered to be a pan B cell surface marker in both mouse and human models. However, Breg identification is difficult in humans due to a lack of a universal phenotypic characterization. Fortunately, there have been parallels between human and mouse phenotypic characterization of Bregs (5). Common phenotypes in literature used to identify Bregs include: $CD1d^{+}CD5^{+}$, $CD5^{+}FoxP3^{+}$, $CD24^{+}CD38^{+}$ and $CD24^{+}CD27^{+}$ (5, 10-11), which have been shown to exert their modulatory role through IL-10 production. Furthermore, it has been shown that these Breg phenotypes express forkhead box 3 (FoxP3), a transcription factor important for regulating the development and function of regulatory T cells. Although the current understanding of Breg development and differentiation into Br1 and Br3 is limited due to a lack of mouse and human studies of allergic inflammation (8), several studies are being conducted to elucidate the complexities of Bregs.

In humans it has been shown that levels of $CD5^{+}FoxP3^{+}$ Bregs were lower in the blood but higher in the airways of allergic asthmatics compared to healthy controls (9–11). These findings were supported by a higher proportion of $IL\text{-}10^{+}$ Bregs present in the airways of allergic asthmatics compared to healthy controls (10). Taken together, these findings suggest the possibility that Bregs may be trafficking to sites of inflammation to elicit immunomodulatory processes, however their suppressive roles may not be enough to overcome the chronic allergic inflammation experienced in allergic asthmatics.

Conclusion

While evidence shows that the primary mode of action of Bregs may occur at local sites of allergic inflammation in an IL-10-dependent manner, TGF-β and IgG4 antibodies may also play crucial immunosuppressive roles. Overall, further investigation into the functions and phenotypic identification of regulatory B cells will help build on the complex framework of the pathobiology of allergic disease with the goal of identifying novel drug targets for future therapeutic strategies. ■

List of abbreviations

Ag- Antigen, Br1 - IL-10-producing regulatory B cell, Br3 - TGF-β- producing regulatory B cell, Breg - Regulatory B cell, CD - Cluster of differentiation, FoxP3- forkhead box P3, Ig - Immunoglobulin, IL– Interleukin, TGF-β - Transforming Growth Factor β, Th2 - T helper type-2, Treg - Regulatory T cell

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