**B Cells: Regulatory (Bregs)**

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**B cells provide innate immunity**

B lymphocytes (or B cells) are white blood cells that are produced in the bone marrow of mammals. Traditionally, B cells were thought to predominantly play a role in **positively regulating** the immune system by antigen presentation to CD4+, but not CD8+, T cells, which in turn feedback to activate B cells, conferring humoral immunity. The interaction between B cell and T helper cell is important, as demonstrated by B-cell deficient or depleted mice having a decreased immune response upon challenge with a pathogen.

Although the positive regulatory role of B has been established for many years, it is now recognised that certain B-cell lineages can play a role in **negatively regulating** immune responses, such as reducing inflammation in autoimmune conditions. When B cells are depleted in animal models, there is an increased manifestation of autoimmune disease, suggesting certain B-cell lineages regulate inflammation. These B-cell lineages are referred to as **regulatory B cells (Bregs)**. Various phenotypic variants of cells that appear to negatively regulate immune responses have been identified, with all the variants sharing the ability to produce **IL-10**, which is not secreted by other B cell subsets. IL-10 is a cytokine that inhibits production of pro-inflammatory cytokines, such as IL-2, IL-3, IFN-γ and TNF-α, and inhibits responses from T-helper type 1 cells (Th1), suggesting that this cytokine functions as the primary molecule by which Bregs elicit a response. A unique CD1dhiCD5+CD19hisubset, identified in spleens of naïve wild-type mice, is suggested as the Breg lineage that contributes to the majority of B cell IL-10 production, once activated by stimulation *in vitro*. Due to the fact that this novel B-cell subset only produces IL-10, they have been named **B10 cells**.

**Function of regulatory B cells**

Unlike T cells, which respond to antigen following cleavage of peptides, B cells can respond directly to naïve antigen, due to the presence of the **B-cell receptor (BCR)**. This suggests an earlier involvement of Bregs in an immune response, when compared to regulatory T cells. However, as a result, the Breg response is also shorter lived than the regulatory T-cell response.

In humans, Bregs represent a very low proportion of the B-cell population (=0.5% in healthy individuals). However there is substantial proof that Bregs are very important B-cell subsets. Treatment of many autoimmune conditions by B-cell depletion has shown disappointing results. This could be due to depletion of Bregs, in addition to normal B-cells, removing the protective anti-inflammatory effects provided by the Bregs and counterbalancing the positive effects from B-cell depletion. When B cells are depleted in mice, autoimmune diseases can spontaneously develop, providing support for this theory of Breg depletion. As stated above, these protective properties are derived from production of **IL-10**. It is believed that IL-10 production is activated upon stimulation of **Toll-like receptors (TLRs)** in mice, or CD40 and TLRs, in the case of Humans. The result following activation is the inhibition of cell subsets that are involved in inflammatory responses, such as T cells or dendritic cells. Bregs can also trigger change in T-cell behaviour via interaction with T-helper cells. Due to their ability to interact with a vast array of other immune subsets, and inhibit pro-inflammatory signals, Bregs could be used as a novel therapeutic in autoimmune diseases.

*Figure 1. Suggested interactions between B10 cells and other immune cells. IL-10 regulates activation of various immune cell-subsets including dendritic cells (DC), macrophages, plasma cells (PC), T-helper cells (Th) and B-cells.*
In spite of the evidence for the role of Bregs in the literature, there are still many questions over the origin of Bregs; IL-10-competent B cells seem to respond to stimulus from the BCR. A reduction in the number of IL-10 competent B cells is seen in mice when CD19, a strong positive regulator of BCR signalling, is knocked out. Furthermore, preliminary results suggest that both CD40 and lipopolysaccharide (LPS) stimulation promote production of IL-10 competent B cells. Collectively this suggests that stimulation, mainly in the form of BCR stimulation, is required for IL-10 competence in B cells. Consequently, the question arises whether Bregs are found as a unique subset, or are produced from B cells exposed to correct stimuli. In various studies with mouse models, where B cells with a regulatory role are identified, a unique, consistent phenotype is not observed between the studies. IL-10-producing B cells have been identified in humans; however variable results with regards to the identity of the B cell subset responsible for the IL-10 production are also seen, as with the mouse models. The overall consequence is that the origin, and the overall role, of Bregs in humans still remains unclear.