B cells to the rescue: regulatory B cells are a promising therapeutic target for autoimmune disease

Immune cells are indispensable for protecting us from microbial infections. They recognize specific patterns on microbes to mount robust cellular and molecular immune responses for the clearance of pathogens. Intriguingly, development and function of these cells is tightly regulated through a multistep processes, which allows them to discriminate between self and nonself. This tolerance mechanism allows them to recognize and attack only invading pathogens but not our own cells. Unfortunately, genetic and environmental factors and other causes, which are mostly unknown, might breakdown this regulation. Failed tolerance leads to the generation of self-reactive immune cells that attack our own cells damaging various organs. This manifests in the development of autoimmunity such as multiple sclerosis (central nervous system), arthritis (joints), and type 1 diabetes (pancreas).
As of now, there are no effective cures for autoimmune diseases. A promising line of approach for the treatment of autoimmunity are the use of specialized cells of the immune system termed regulatory immune cells. These cells, unlike their pathogenic counterparts, are uniquely endowed with the ability to thwart an immune response. Lymphocytes are immune cells that are essential for mounting immune responses. These include T and B cells, both of which contain cell subsets that possess regulatory properties. These are called regulatory T cells (Treg) and regulatory B cells (Breg). Treg and Breg efficiently control autoimmunity in mouse models and are thought to be important for preventing autoimmune diseases in humans. One of the best studied mechanisms of Breg function is secretion of interleukin-10 (IL-10), an immunosuppressive molecule, which has the capability to dampen immune responses, including autoimmunity. Interestingly, we were the first to identify an IL-10-independent mechanism of Breg function. We found that Breg were involved in expansion and homeostatic maintenance of Treg, resulting in the resolution of disease in the mouse model of multiple sclerosis. We also reported that Breg-Treg interactions were important for attenuating colitis severity in mice. Other researchers have also identified IL-10-independent Breg mechanisms and reported the existence of varied populations of Breg.

For therapeutic purposes, it is absolutely necessary to have a complete understanding of the different Breg subsets and their mechanism of action. In this article, we extensively reviewed the identity and the modus operandi of IL-10-independent regulatory B cell subsets in the context of different autoimmune diseases and transplantation models. Interestingly, some subsets of Breg exhibit overlapping phenotypic and functional identity. This suggests that some Breg populations could potentially control multiple autoimmune diseases. Moreover, drawing knowledge from the current literature, we discussed the possible interplay between some of the reported mechanisms of Breg function. Hence, we proposed that Breg, depending on the context, utilize cooperative muti-mechanistic approaches for successfully extinguishing a self-directed inflammatory response for preventing autoimmunity. A thorough knowledge of the different Breg subsets and their mechanism of action, as reviewed in this article, will be beneficial for effectively exploiting the diverse arsenal of Breg for the development of therapeutics for autoimmune diseases.
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