Review Article

Regulatory T cells and B cells: implication on autoimmune diseases

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Abstract: The regulatory T (Treg) cells play an important role in the maintenance of homeostasis and the prevention of autoimmune diseases. Although most studies are focusing on the role of Treg cells in T cells and T cells-mediated diseases, these cells also directly affect B cells and other non-T cells. This manuscript updates the role of Treg cells on the B cells and B cell-mediated diseases. In addition, the mechanisms whereby Treg cells suppress B cell responses have been discussed.

Keywords: Treg, Foxp3, B cells, antibodies, autoimmune diseases

Introduction

Accumulated evidence has indicated that regulatory T (Treg) cells play an essential role in the maintenance of homeostasis and prevention of autoimmune responses [1-5]. Most of these cells are CD4+ cells that express CD25, an IL-2 receptor alpha chain and other Treg cells related molecular markers [6-8]. Foxp3, a transcript factor, has been recognized to be a key factor for Treg cell development and function. Foxp3 has also been considered as a specific marker to define and identify Treg cells from other T cell subpopulations although this has been challenged on its specificity in human Treg cells [9-12]. In addition to CD4+ Treg cells, CD8+ Treg cells represent another cell population and Foxp3 may not be so crucial for their development and function when compared to CD4+ Treg cells [13-15].

Treg cells originate from thymus, being called natural Treg cells. These cells move to periphery to exert their roles. In the periphery, these cells can be emigrated from thymus or differentiated in the local places. Thus, Treg cells can be classified into natural and induced Treg cells. It is unclear what percentages of Treg cells are natural or induced Treg cells in the periphery since both Treg populations share similar phenotypes and functional characteristics, and no specific molecular marker can distinguish natural Treg from induced Treg cells so far. Although recent efforts have demonstrated that neuropilin-1 and helios could be valuable to distinguish two populations [16-18], however, other studies have also demonstrated that their specificity may not be what we previously expected since helios is also highly expressed on Th2 and T follicular helper cells and is associated with the differentiation of these cells [4, 19].

Induced Treg cells can be induced ex vivo from non-Treg cells [20-23]. During this induction, TGF-β and TGF-β receptor signal pathway is essential for the development and differentiation of induced Treg cells [24-26]. Other factors, like IL-2 and all-trans retinoic acid (atRA), can promote Treg cell development and function [27-32]. These iTreg cells not only mostly share the phenotypic and functional characteristics with nTreg cells, but also display some advantageous features. For example, these cells are
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more stable in the inflammatory conditions than natural Treg cells, demonstrating their superior capacity on treating inflammatory and autoimmune diseases [33-37].

B cells and immune responses

Both B- and T-lymphocytes consist of important players in this adaptive immune response. B-cells exert their effect through the production of antibodies, antigen-presenting ability and cytokines production.

B cells usually need the help provided by T cells to get activated upon encountering antigens to differentiate into effector plasma cells. Plasma cells produce or secrete antibodies that subsequently circulate in the blood, lymph, and tissues where they can target specific antigens or pathogens and promote their elimination [38]. B cells can also be activated independent upon T cells, as B cells express Toll-like receptors (TLRs), primarily TLR4 and TLR9, which recognize additional signals in the form of microbial viral components, to affect like innate immune cells [39].

Like dendritic cells (DCs), B cells have also antigen-presenting cell ability. B cell receptor expressed on B cell surface can bind specific antigen containing major histocompatibility complex (MHC). When MHC is presented to T cell surface, B cells have elicited T cell immune-mediated response. Unlike DCs, B cells present low loses of antigens whereas DCs present high levels of antigens that both may have a concordant role in presenting antigens to T cells [38, 40].

Additionally, B cells also produce cytokines, for example, activated B cells can produce IL-4, IL-6, IL-10, IL-21, IL-23, TNF-α, and lymphotoxin. These cytokines further regulates innate and adaptive immune responses [38, 40].

B cells and autoimmune diseases

Aside from their role in immune defense, the dysfunction of B cells also contributes three classes of B-cells diseases: congenital immunodeficiencies, autoimmunity, and leukemia and lymphoma [41, 42].

B lymphocytes have been classically recognized to contribute to the pathogenesis of autoimmune diseases through autoantibody production [40]. Self-reactive B cells are responsible for the autoantibody production and autoimmunity. Self-reactive B cells are mostly eliminated in the bone marrow through a process termed negative selection. Nonetheless, some of self-reactive B cells escape negative selection in the bone marrow and migrate to periphery. These self-reactive B cells are kept under check by other mechanisms including deletion, anergy and immune modulation in the periphery [38, 40]. Genetic defects may promote a loss of B cell tolerance [43]. Dysregulated apoptotic genes increase B-cell lifespans and thereby promote survival of self-reactive B-cell clones, leading to autoantibodies and multiple autoimmune syndromes [44]. Treg cells play an important role in controlling the immune responses of these self-B and self-T cells and then prevention of autoimmune diseases. Dysfunction of Treg cells contributes autoimmune responses.

Although B cells are generally considered to be crucial for the pathogenesis of autoimmune diseases, it actually has an extent difference of role in the pathogenesis of various autoimmune diseases. In general, systemic lupus erythematosus (SLE) appears to be highly dependent upon B cells for their development. Using MRL/lpr animal model of SLE, B cells are crucial for the lupus pathogenesis since B-cell-deficient MRL/lpr mice have no pathology at an age whereas B-cell-intact MRL/lpr mice have an evident disease [45]. Conversely, in other autoimmune diseases, such as rheumatoid arthritis (RA), systemic sclerosis (SSc), multiple sclerosis (MS), and type 1 diabetes (T1D), B cells may play an adjuvant role in their development. Additionally, B cells play an important role in the early stage of diseases during the initiation of T-cell activation and the generation of the autoreactive long-lived plasma cells, thus using therapy on B-cell depletion should be considered on initial phase of diseases but not late stage of diseases.

A major role B cell played is the production of autoantibodies. When the disease is initiated, the self-reactive B cells recognize self-tissues and produce autoantibodies. For example, the levels of anti-dsDNA, anti-ANA, anti-SM, anti-phospholipid, anti-cardioplin, anti-Ro antibodies are elevated and corrected the clinical features of disease activity in SLE [46]. These autoantibodies are also indicative of diagno-
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Autoantibodies will bind to self-antigens to form an immune complex in tissues that locally activate the complement cascade and induce type III immune complex reactions with inflammation [40].

B cells also contribute autoimmune diseases through their function as cellular adjuvants for CD4+ T cell activation and differentiation. Additionally, B cells secrete many cytokines that also regulate T cell function and inflammation. Thus, B cells regulate multiple aspects of humoral and cellular function in the immune system and autoimmune diseases.

**Treg cells control B cells and autoantibodies**

The major target for Treg cells is T cells, therefore, Treg cells play an important role in controlling T cell-mediated diseases (Figure 1). Nonetheless, recent studies have also demonstrated that Treg cells also exert their effects on other cells including DCs, macrophages, mast, B cells and osteoclast [35, 47-52].

To determine the impact of Tregs on the establishment of human early B-cell tolerance checkpoints, Kinnunen et al have recently cloned and expressed in vitro recombinant antibodies from single B cells from IPEX patients who lack Foxp3+ Treg cells, and compared their reactivity to those derived from healthy donors. They observed that characteristics and reactivity of antibodies expressed by new emigrant/transitional B cells from IPEX patients were similar to those from healthy donors, demonstrating that defective Treg function does not impact central B-cell tolerance. Conversely, they also observed that FOXP3 deficiency resulted in the accumulation of autoreactive clones in the mature naive B-cell compartment of IPEX patients, providing direct evidence for the role of Tregs in maintaining peripheral B-cell tolerance in humans [56].

Lim et al first identified that Treg cells locate on B cell-rich area. Using immunohistochemical staining combining anti-Foxp3, anti-CD4 and anti-IgD antibodies, and three-color confocal...
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microscope technique in human tonsils, they found while most human Foxp3+ cells locate on T cell zone, they also observed that significant numbers of Foxp3+ cells distribute on T-B border area including mantle zones and germinal center areas. These Foxp3+ cells are T cells but not B cells. They further demonstrated that these Foxp3+ Treg cells suppress B cell activities, including B cell activation, proliferation, IgG production and switch. Moreover, the inhibitory effect of Treg on B cells is independent upon T cells since it still works in T cell-free condition [57].

Using transgenic mice expressing model antigens in the kidney, Gotot et al demonstrated that Treg cells are essential to suppress autoreactive B cells in an antigen-specific manner and to prevent them from producing autoantibodies. This suppression requires PD-1 expression on autoreactive B cells and expression of the two PD-1 ligands on Treg cells. These findings demonstrate in vivo that Treg cells use PD-1 ligands to directly suppress autoreactive B cells [58].

Zhao et al used an in vitro culture system to demonstrate that mice Treg cells can directly suppress B cell activation and proliferation [49]. This suppression needs cell to cell contact but not suppressive cytokines. They further found that activated T cells kill B cells through the emancipation of perforin and granzyme B by Treg cells. Iikuni et al further found that Treg cells also can suppress B cell activity and Ig production from SLE patients. Moreover, they also conducted an in vivo experiment to document Treg can suppress B cell immune responses. Similarly, they confirmed that perform and granzyme B released from Treg cells are responsible for B cell killing and suppression in patient with SLE [59].

Given the significant differences between natural and induced Treg cells exist, we also studied whether induced Treg cells suppress B cell immune responses. Like natural Treg cells, induced Treg cells also directly suppress B cell activities in vitro and in vivo. Unlike natural Treg cells, induced Treg cells suppress B cells not through cell killing but suppressive cytokines. Using granzyme B and perforin deficient mice, we found that induced Treg cells lacking these killing molecules still suppressed B cell responses [Liu and Zheng, manuscript under review]. The significance of the mechanism's difference between natural and induced Treg cells on B cell suppression needs further investigation.

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Disclosure of conflict of interest

None.

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