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Regulatory B-cells: immunomodulating mechanisms and important cellular targets underlining immunotherapy by immunoregulation

Zaman I. L. Al-Kaabi[1,*]

[1]Department of Clinical Laboratory Sciences, College of Pharmacy, University of Babylon, Hillah, Iraq

***Corresponding author:** Zaman I. L. Al-Kaabi, Department of Clinical Laboratory Sciences, College of Pharmacy, University of Babylon, Hillah, Iraq; Tel.: +964-(0)7825372592
E-mail: zaman_medicalmsc@yahoo.com

Abstract

Regulatory B-cells (Breg cells) represent as an important modulator of the immune system and their role is unique in autoimmunity, infection, tolerance to transplants, allergy, and cancer. Several regulatory mechanisms exist by which Breg cells can control the function of other immune cells through two main pathways: the secretion of soluble molecules and the use of cell surface-expressed molecules. Anti-inflammatory cytokine interleukin-10 acts as the hallmark of Breg cell function; other cytokines with a similar role include the transforming growth factor-beta and interleukin-35. Breg B cells also release the cytotoxic granzyme B that mediates cell apoptosis. Cell surface-expressed proteins include FasL, CD80, CD86, CD73, CD1d, and PD-L1. The present article reviews the immunosuppressive pathways in order to understand how they emerge and are induced to evoke their regulatory activities, and how we can benefit from them in the field of immunotherapy.

KEYWORDS

immunosuppressive mechanisms, regulatory B-cells, IL-10, TGF-β, PD-L1

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1. INTRODUCTION

B-cells do not only act as antibody producers and antigen-presenting cells (APCs), but also act as positive regulators of immune responses. Many previous studies have shown that certain subsets of B-cells have a regulatory function and that these subsets of B-cells could suppress the immune reaction independently of the antibody production. These cells can be divided into many subsets differing in phenotype, location, and functional style; all of them can inhibit the progression and/or enhance the recovery from acquired immune-mediated inflammatory responses and can induce immune tolerance [1]. The regulatory function of the regulatory B-cells (Breg cells) may be achieved through a variety of mechanisms that involve multiple soluble effectors: (i) through the production of immunoregulatory cytokines such as interleukin (IL)-10 (IL-10), the transforming growth

factor-beta (TGF-β), and IL-35, which have bidirectional effects on the immune cells with both pro-inflammatory and immunosuppressive activities, and (ii) through the secretion of immunoregulatory enzymes such as granzyme B and indoleamine 2,3-dioxygenase (IDO/IDO1). A direct cell-cell contact mechanism is also used by Breg cells in order to suppress effector immune cells and promote immune tolerance *via* the expression of membrane proteins and/or receptors such as CD80/CD86, FasL (CD95L), PD-L1, GITRL, CD1d, T2-MZP, TIM-1, the ectoenzyme CD73, and CD39. Important cellular targets include CD4+ T-cells, CD8+ T-cells, regulatory T-cells (Treg cells), monocytes, natural killer (NK) cells, Th17 cells, APCs, and even effector B-cells [2].

2. SOLUBLE EFFECTOR-DEPENDENT MECHANISMS

Immunoregulatory cytokines: IL-10 is an important anti-inflammatory and immunosuppressive cytokine, and the most secreted effector across Breg cell subsets. IL-10 inhibits T-cell activation by inhibiting the expression of CD54 (ICAM-1; the ligand for LFA-1), CD80, and CD86, which function as important costimulatory molecules for T-cell activation. This leads to a reduction of the antigen-presenting capacity of monocytes. IL-10 inhibits the secretion of proinflammatory cytokines (IL-1, IL-6, IL-8, and of the granulocyte-macrophage colony-stimulating factor) from type-1 helper T-cells, monocytes/macrophages, and polymorphonuclear leukocytes. Furthermore, IL-10 downregulates class II major histocompatibility complex expression on monocytes, dendritic cells, and Langerhans cells. IL-10, in the absence of professional APCs, has direct effects on CD4+ T-cells by suppressing IL-2 and tumor necrosis factor-alpha (TNF-α) secretion [3]. In addition to inhibiting antigen-specific responses, IL-10 induces long lasting antigen-specific anergy in human CD4+ T-cells. IL-10 is also responsible for the lack of cytotoxic activity by specific CD8+ T-cell clones, in which the blocking of endogenous IL-10 production can restore their cytotoxic activity. NK cells secreting interferon-gamma (IFN-γ) are also inhibited because of the IL-10 double action: by inhibiting IL-12 (a NK-cell-stimulating factor) production by APCs, and through its direct action on NK cells [4] (Figure 1).

TGF-β suppresses the immune system through many pathways. TGF-β downregulates the activating receptor NKG2D, which is expressed on NK cells and CD8+ T-cells and is considered as the master switch in determining the activation status of NK cells. Moreover, TGF-β promotes the apoptosis of CD8+ T-cells during the clonal expansions that occur during and after infection. Lipopolysaccharide (LPS)-activated B cells (LPS-B cells) express a significantly higher level of TGF-β1 on their surface. These regulatory cells failed to induce significant levels of proliferation, cytokine secretion (IFN-γ, TNF-α, IL-2, and IL-6), and cytotoxic ability of CD8+T cells. This hypo-responsiveness of CD8+ T-cells when activated by LPS-B cells was significantly rescued by anti-TGF-β1 antibodies. TGF-β-expressing Breg cells were reported to trigger anergy in CD4+ and CD8+ T-cells. In addition to that, TGF-β alone could drive naive T-cells into inducible-Treg (iTreg) cells and enhance the differentiation of Th17 from CD4+ T-cells through the synergistic effect of both TGF-β and IL-6. TGF-β appears to block the activation of lymphocytes and monocyte-derived phagocytes, and to mediate effective class switching to IgA upon CD40 activation and in the presence of IL-10 (Figure 1).

IL-35 secreted by Breg cells is an anti-inflammatory cytokine with immunosuppressive activities that stimulates the expansion of IL-10+ Breg cells and the generation of IL-35-secreting B cells. It can also promote tumor growth and metastasis, and block the development of Th1 and Th17 cells by limiting early T-cell proliferation. Moreover, IL-35 has a role in infection and autoimmunity, and can lower the expression of the vascular endothelial growth factor and of TNF-α [5] (Figure 1).

Immunoregulatory enzymes: Breg cells, in addition to secreting immunoregulatory cytokines, secrete immunoregulatory enzymes such as indoleamine 2,3-dioxygenase (IDO/IDO1) and granzyme B. Granzyme B is a member of the cytotoxic serine proteases group that mediates target cell apoptosis upon entering the cytoplasm after perforin-mediated membrane disruption. Granzyme B also plays a role in controlling the inflammatory process, and it has a role in tissue remodeling by cleaving a number of extracellular matrix components. Secretion of IDO dampens T-cell activation by catabolizing the essential amino-acid tryptophan, and the secretion of granzyme B kills T-cells, while Breg cells that secret granzyme B can inhibit CD4+ T-cell proliferation and the responses of both Th1 and Th17 cells [4] (Figure 1).

3. CELL CONTACT-DEPENDENT MECHANISMS

A cell-to-cell contact-dependent mechanism involving membrane proteins and/or receptors is known to promote immune tolerance by activating cell death markers or costimulatory molecules involving CD80, CD86, CD40-CD40L, and FasL. It is known that the glucocorticoid-induced TNFR-related protein (GITR) is activated by its ligand

(GITRL). GITRL+ Breg cells promote Treg cell expansion *via* GITRL. CD1d+T2-MZP Breg cells support the development and function of immunosuppressive invariant NK cells through the presentation of lipids on CD1d. Moreover, the binding of TIM-1 on TIM-1+ Breg cells induces their expansion [6]. Like Treg cells, CD73+CD39+ Breg cells can convert immunostimulatory ATP and ADP into immunosuppressive adenosine *via* the ectoenzymes CD73 and CD39.

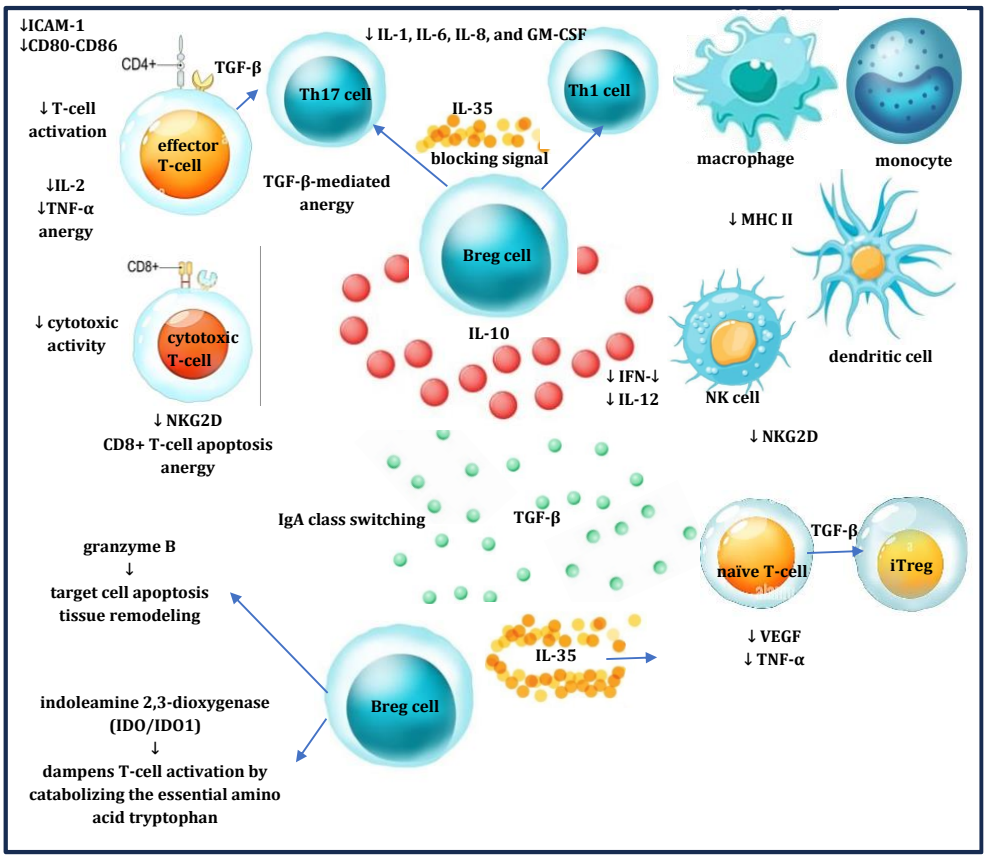

Figure 1. Common pathways of regulatory B-cell (Breg cell) soluble effector-mediated immune regulation. Abbreviations used: GM-CSF, granulocyte-monocyte colony stimulating factor; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; MHC II, major histocompatibility complex type II; NK, natural killer; NKG2D, natural killer receptor group 2, member D; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor.

PD-1 is a type I transmembrane receptor expressed in activated monocytes, dendritic cells, NK cells, B-cells, and T-cells [7]. Through the binding of PD-1/PD-L1, PD-L2 delivers inhibitory signals that downregulate receptor-triggered cell survival, differentiation, and the secretion of proinflammatory cytokines. Studies have observed that PD-1+ and PD-L1+ Breg cells have a role in promoting IL-10 expression, suppress CD4+ T-cell activity and CD8+ T-cell cytotoxicity, induce Tr1 cells, dampen TNF production by macrophages and T-cells, and maintain peripheral tolerance [8].

4. REGULATORY B-CELL-BASED IMMUNOTHERAPY

The use of Breg cells in immunotherapy is still controversial and requires further research so as to realize a fully effectiveness of Breg cells in the field of immunotherapy. Breg cells can have multifaceted roles in tumor immunity, autoimmunity, and hypersensitivity. Breg cells help in clearing tumors by both direct and indirect mechanisms. The direct pathway is where B-cells differentiate into plasma cells and produce antibodies. Tumor-specific anti-

bodies against neoantigens are a powerful way to kill tumor cells in a specific manner, and they have considerably fewer side-effects. In the indirect pathway, B-cells help T-cells to carry out their anti-tumorigenic activity [9]. Infiltrating B-cells in a tumor can help CD4+ helper T-cells and CD8+ cytotoxic T-cells undergo activation and expansion. Breg cells acts as a form of cell immunotherapy for autoimmune disorders. What hasn't been clear to date, however, is how the Breg cell-induced IL-10 production and regulation of antigen-specific immune responses are controlled *in vivo* without inducing systemic immunosuppression. It has now been shown that the IL-10+ Breg cell expansion and maturation into functional IL-10-secreting effector cells that can inhibit autoimmune disease *in vivo* requires a stimulation by IL-21 as well as CD40-dependent cognate interactions with T-cells. These cells are produced in millions of copies and can be introduced back into someone with an autoimmune disease, thereby shutting down the disease [10]. In hypersensitivity, TGF-β+, IL-10+, and Foxp3+ Breg cell subsets seem to be able to negatively regulate allergic diseases, including contact dermatitis, asthma, anaphylaxis, and non-IgE-mediated food allergies related to atopic dermatitis.

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CONFLICT OF INTEREST STATEMENT
The author declares no conflicts of interest.

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