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Novel regulatory Th17 cells and regulatory B cells in modulating autoimmune diseases

Bhagirath Singh[a,b,c,*], Kelly L. Summers[a,b,d], Steven M. Kerfoot[a,b]

[a] Centre for Human Immunology, University of Western Ontario, London, ON, Canada
[b] Department of Microbiology and Immunology, University of Western Ontario, London, ON, Canada
[c] Robarts Research Institute, University of Western Ontario, London, ON, Canada
[d] Lawson Health Research Institute, London, ON, Canada

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ABSTRACT

Pathogenic lymphocytes aberrantly recognize and mount an immune response against self-antigens, leading to the destruction of healthy cells, tissues and organs. Recent studies have shown that both B and T lymphocytes contribute to the development, prevention and modulation of various autoimmune diseases. Regulatory T and B cell subsets appear to play a prominent role in the prevention of autoimmune diseases. The recent identification of novel regulatory Th17 cells, termed as Treg17 cells, has expanded the scope of regulatory T lymphocytes (Treg cells) in the prevention of autoimmune diseases. Similarly, novel regulatory B cell subsets, termed as Breg cells, acting on their own or by inducing Treg cells have extended the role of B lymphocytes in the prevention and regulation of autoimmune diseases. We suggest that Treg17 cells and Breg cells have an important immunoregulatory role in autoimmune diseases.

1. Introduction

Autoimmune diseases generally result from the breakdown of the immunoregulatory mechanisms that control autoreactive T and/or B lymphocytes that escape negative selection in the thymus or the bone marrow, respectively, during development [1–5]. Both self-reactive T cells and B cells can cause autoimmune diseases with other cell types such as NK cells, dendritic cells (DC) and monocytes contributing to this process. Previous studies have shown that autoreactive regulatory $CD4^+$ $CD25^+$ T cells have the ability to prevent autoimmune disease *in vivo* and, upon antigenic stimulation, suppress the activation/proliferation of other T cell subsets *in vitro*. $CD4^+$ $CD25^+$ regulatory T cells develop in the thymus as a functionally distinct subpopulation of T cells [4]. These naturally produced regulatory T cells are anergic and suppressive and play a critical role in immune tolerance. B lymphocytes are produced in the bone marrow where autoreactive B cells are normally purged. Nevertheless, auto-antibodies produced by B cell-derived plasma cells can contribute to autoimmune pathology, and recent studies suggest that B cells can also modulate autoimmunity by producing regulatory cytokines that primarily induce regulatory T cells [5].

1.1. *Regulatory cells and autoimmunity*

The crucial role of regulatory cells in self-tolerance and autoimmunity has been established in many autoimmune diseases. Much focus has been placed on thymically derived Treg cells, given that the depletion of these cells results in the spontaneous development of autoimmune diseases in several animal models [3]. These naturally occurring Treg cells functionally mature in the thymus and exert their immunosuppressive effect in both a contact-dependent or contact-independent manner [6]. Two major subsets of CD4+ regulatory T cells have been identified that suppress immune responses, including the cells that cause autoimmune diseases. These are FoxP3+ Treg cells and FoxP3 − Treg cells. The transcription factor Forkhead-Box-Protein P3 (FoxP3) is critical for Treg cell function. Both thymus-derived (nTreg) cells and peripherally induced (iTreg) regulatory T cells express FoxP3. During the immune response, these immunosuppressive Treg cells are induced [7] as well as cells that do not express FoxP3, including TGF-β-producing T helper 3 (Th3) cells [8], IL-10-producing type 1 regulatory T (Tr1) cells [9] and invariant natural killer T (iNKT) cells [10]. The role of B cells in regulating autoimmunity was discovered in B cell deficient mice [11,12]. Recent studies have identified regulatory B cell subsets (Breg cells) that induce naïve CD4+ T cells into regulatory T cells that prevent autoimmunity. Bregs are identified by their

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* Corresponding author at: Department of Microbiology & Immunology, University of Western Ontario, London, ON, Canada.
E-mail address: bsingh@uwo.ca (B. Singh).

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Table 1
Regulatory T and B cells with immunoregulatory function in autoimmunity.

Cells	Cellular Phenotype	Transcription Factors	Major Cytokines Produced	References
Treg	CD4+ FoxP3+	FoxP3+	IL-10, TGF-β	[3]
Treg17	CD4+ FoxP3+	RORγt, FoxP3, AhR	Il-10, IL-17	[20,21]
Treg-of-B	CD4+ FoxP3-	?	IL-10	[53]
Th3	CD4+ FoxP3-	?	TGF-β	[8]
Tr1	CD4+ FoxP3-	?	IL-10	[9]
Breg	?	?	IL-10, IL-35, TGF-β	[5,44,55]

production of IL-10, IL-35 and TGF-β. They suppress autoimmunity by blocking the differentiation of proinflammatory cells and pathogenic T cells [5]. In addition, cells of the innate immune system such as NK cells, DCs and macrophages also play an important role in the regulation of autoimmune immune responses [13]. The role of regulatory cells in autoimmunity is complex and is growing field of investigation both at the molecular and cellular level (Table 1).

2. Th17 cells and autoimmunity

IL-17-producing Th17 cells play an important role in the host defense against extracellular infections and in the regulation of the commensal microbiota [14,15]. There appears to be a reciprocal relationship between gut microbiota and Th17 cells [16]. They also participate in the pathogenesis of multiple inflammatory and autoimmune disorders [17]. The dual nature of Th17 cells allows these cells to be pathogenic in inflammatory disorders and also act as an intestinal barrier to maintain its integrity [18].

Th17 cells mainly produce the proinflammatory IL-17 cytokines, IL-17A and IL-17F, however they also produce regulatory cytokines such as IL-10, IL-21, IL-22, and GM-CSF. Recently, pathogenic and regulatory subsets of Th17 cells have been characterized based upon the cytokines they produce and factors required for their differentiation [19,20]. Depending upon the priming conditions, Th17 cells can alter their differentiation program giving rise to either proinflammatory (pathogenic) or protective (regulatory) cells. We found that Th17 differentiation by TGF-β plus IL-6 induced non-pathogenic regulatory Th17 cells, while IL-23 plus IL-6 induced pathogenic Th17 cells [20,21]. Transcriptomic studies [19] have suggested that Th17 responses might be shaped by the magnitude and duration of cytokine responses and/or by environmental stimuli that sustain these cells [22]. This may reflect pathogenic versus beneficial responses as determined by environmental factors that keep these cells in homeostatic balance in the intestine, such as in inflammatory bowel disease.

It is likely that various subsets of Th17 cells are induced by priming cytokines through intermediate cells such as FoxP3+ Th17 cells [23]. The pathogenic Th17 cells differentially express IL-22, whereas regulatory Th17 cells, referred to as Treg17 [20] or rTh17 cells [24], express IL-21 and IL-10. The differentiation of Th17 cells is controlled by the transcription factor retinoid orphan receptor (RORγT) whereas T-bet regulates Th1 differentiation. There is linkage between Th1 and Th17 cells and Th17 cells co-express cells the transcription factors T-bet and RORγt and secrete both IL-17 and IFN-γ. These double IFN-γ and IL-17-producing Th17 cells have a role in the pathogenesis of autoimmune disease [17] and can be found in arthritic joints [25]. The IFN-γ+ IL-17+ cells can switch from Th17 to Treg or Th1 cytokine profiles under certain environmental conditions [22,26]. There is evidence that Th17 cells up-regulate IFN-γ and also downregulate IL-17 in response to IL-12 or IL-23 in the absence of TGF-β *in vitro* [27]. Therefore, Th17 cells can actively develop into pathogenic Th1 cells in certain autoimmune diseases. In Type 1 diabetes (T1D) there is evidence that the Th1 cells [28] and pathogenic Th17 cells [21,29] both contribute to the disease as they secrete proinflammatory cytokines such as IFN-γ or IL-17 leading to autoimmune disease [1,2]. The high degree of plasticity of Th17 cells likely results in their dual pathogenic and protective roles in autoimmune diseases [18,22].

The developmental similarities between Treg cells and Th17 cells could allow for the differentiation of Treg cells into Th17 cells [22,23]. The conversion of Foxp3+ Treg cells into pathogenic Th17 cells appears to have an important role in the pathogenesis of autoimmunity [18,22].

2.1. Regulatory Th17 (Treg17) cells and autoimmune diseases

We have found that the Th17 subset differentiated with IL-23 and IL-6 are pathogenic [21,29]. These cells produce IL-17, large amounts of IL-22, and induce T1D in young NOD mice upon adoptive transfer [20,21]. Conversely, polarizing the Th17 subset with TGF-β and IL-6 led to non-pathogenic regulatory (Treg17) cells. These cells produce IL-17 and express high levels of aryl hydrocarbon receptor (AhR) and IL-10, but produced significantly reduced levels of IL-22 [21,30]. These cells did not induce T1D upon adoptive transfer into young NOD mice and suppressed diabetogenic Th17 cells efficiently *in vivo*. Based upon our results, we suggest that both pathogenic Th17 cells and non-pathogenic Treg17 cells can be generated from CD4+ T cells under appropriate polarization conditions [20]. The IL-17-producing Treg17 cells offer a novel regulatory T cell population for the modulation of autoimmunity.

Recently, Treg17 cells have been shown to depend on the activation of the transcription factor Stat3 to suppress immune responses [31,32]. Moreover, the pathogenic Th17 cells are the major target of Treg17 cells in autoimmunity [31,33]. In addition, IL-10 receptor signaling allows Treg17-mediated suppression of pathogenic Th17 cells. Therefore IL-10 secretion by Treg17 cells controls the Th17 development *via* direct and indirect mechanisms [34]. It has also been shown that cannabidiol enhanced the development of Treg17 cells *in vivo* [33]. In addition, serotonin elevated the level of Treg17 cells in multiple sclerosis patients [35].

The commensal bacteria in the gut have a significant impact on the maturation of the gut immune system [36,37] whereby intestinal colonization contributes to combined effector and regulatory T cell responses. Alteration of gut microbiota has been implicated in the imbalance between Th17 and Treg cells. Regulatory Th17 cells suppress pathogenic T cells in the gut via IL-10 signaling [38]. Commensal bacteria can induce expression of IL-25 in intestinal epithelial cells that inhibits their production of IL-23, a major survival factor for pathogenic Th17 cells [39].

We have shown that injection of adjuvants containing Mycobacterium, such as complete Freund's adjuvant (CFA) or bacillus Calmette-Guérin (BCG), can prevent T1D in NOD mice [40]. We found that IL-17-producing Th17 cells were induced in the draining lymph nodes and spleen of these mice following *in vitro* restimulation with or without IL-17-polarizing cytokines [41]. Mice receiving CFA had a concomitant rise in the level of IL-17, IL-22, IL-10, and IFN-γ in the draining lymph node and spleen. Adoptive transfer of these cells delayed the development of diabetes in recipient mice. Injection of CFA also changed the cytokine profile of cells in pancreatic tissue by increasing IL-17, IL-10, and IFN-γ cytokine gene expression. We suggest that the rise in the level of IL-17 after adjuvant therapy in NOD mice has a protective effect on type 1 diabetes development because of the induction of the Treg17 cells [41].

3. Regulatory B cells and regulation of autoimmune diseases

The pathogenic contributions of B cells to autoimmune disease is well recognized for a long time [5]. Through the production of antibodies targeting self-antigen, B cells and their plasma cell progeny are considered the primary drivers of diseases such as systemic lupus erythematosus (SLE) and myasthenia gravis. Recently, the success of B cell-depleting therapies in multiple sclerosis (MS) and rheumatoid arthritis (RA) has revealed pathogenic roles for B cells in diseases previously considered to be driven predominantly by T cells. Demonstrations of a regulatory role for B cells in autoimmunity has relied largely on animal models of disease. Several investigators have shown that experimental allergic encephalomyelitis (EAE) is less severe in mice genetically deficient in B cells [11,42,43]. Similar observations have been made in a mouse model of arthritis [12]. However, compared to our understanding of Treg biology, our grasp of immune regulation by B cells is much less known. Unlike for the different subsets of Tregs, no reliable surface markers or master regulators have been identified for regulatory B cells, and therefore the Breg cells themselves remains elusive and may be more conceptual than an independent lineage [5].

As with Tregs, IL-10 production has been identified as a primary regulatory mechanism for B cells in autoimmunity. Indeed, mice with B cell-specific deficiencies in IL-10 production largely mimic the phenotype of pan-B cell deficient mice in their resistance to developing autoimmune disease [43,44]. Breg cells have been variously defined as IL-10-producing B cells with several B cell subsets identified with this capacity in both mice and humans, including B-1 ($CD5^+$ $CD1d^{hi}$) cells [45,46], marginal zone (MZ) B cells, naïve phenotype B cells and others [5]. However, the assays used in these studies primarily relied on *ex vivo* mitogenic stimulation of isolated subsets in order to measure IL-10, and it is not clear that the capacity to produce IL-10 under these conditions reflects actual production of IL-10 *in vivo*. Using a fluorescent reporter of IL-10 production [47], it was demonstrated that $CD138^+$ plasmablasts were the primary producers of IL-10 in autoimmunity, while $B220^+$ B cell subsets expressed very little, if any. Indeed, investigations of the activation requirements to induce IL-10 production by B lineage cells have shown that a combination of BCR, CD40, and TLR stimulation is required for optimal induction *in vitro* [48]. This combination closely aligns with B cell activation in T cell-dependent responses, which result in rapid plasmablast differentiation and downstream induction of a germinal center response. Importantly, mice specifically deficient in *Irf4* and *Prdm1*, both required for early plasmablast differentiation, develop exacerbated EAE, while this is not the case for mice deficient in Bcl-6, which is required for the germinal center pathway [47].

In addition to IL-10 production, B cells have been demonstrated to produce the immunoregulatory and anti-inflammatory cytokines IL-35 and TGF-β [5,49]. The primary effect of these cytokines is to influence the T cell response and in particular the development of Treg cells [44]. Indeed, B cell deficiency results in reduced levels of Treg cells [50], a phenotype that is also observed with B cell-specific IL-10 deficiency [4].

B cells are also capable of presenting antigen to T cells. This is best understood in the context of T cell-dependent B cell responses that result in the formation of a germinal center and the development of high affinity antibody responses to the specific antigen. In this scenario, B cells internalize antigen bound to their specific BCR for subsequent processing and presentation to T cells, resulting in so-called “cognate” interactions in which the interacting T cell/B cell pairs are specific for the same antigen [51]. While these provide necessary signals for proper B cell activation, they may provide feedback signals to the T cells that influence T cell activation. Evidence for B cells acting as antigen-presenting cells (APCs) to induce Treg cells comes largely from *in vitro* studies. T cells activated with anti-CD3/CD28 in the presence of follicular B cells [52] or B1a cells [43] converted into CD25+ Foxp3-regulatory T cells through an IL-10-independent, contact-dependent process, which were shown to have suppressive activity in an inflammatory colitis model [53]. *In vivo*, molecules required to facilitate antigen presentation to T cells are required for Breg cell activity [5], but it is not clear if this is necessary for the suppressive mechanism of Breg cells. Alternatively, APC interaction may be necessary for the activation of B cells to aquire regulatory capacity through a T cell-dependent pathway. Interestingly, B cell deficient mice are also defective in natural, thymic-derived Treg cells, and thymic B cells may induce their development through antigen presentation [54]. It is not clear whether these interactions are cognate, or otherwise related to those T cell/B cell interactions that underpin the germinal center response. Indeed, while antigen-specific activation can induce Breg cell activity and IL-10 production, it is not clear if their regulatory activity is limited to specific antigen.

In summary, there is growing evidence that Breg cells play an important role in immune tolerance and autoimmunity. To determine their therapeutic potential to block autoimmunity, further studies are needed to better understand how Breg cells are induced to evoke their regulatory activities and how they function *in vivo* [5,55]. Recent analysis suggests that IL-10-capable Breg cells preferentially reappearance following anti-CD20-mediated B cell depletion in MS, suggesting that the balance between pathogenic and protective B cell subsets is particularly important to the progression of disease and that there is an opportunity for more selective targeting of one function over the other for improved therapeutic outcome [56].

4. Conclusion

Th17 and Treg cells have both been implicated in the regulation of inflammatory and autoimmune diseases. Pathogenic Th17 cells are involved in the induction and propagation of pathologies, whereas regulatory Treg17 and Treg cells inhibit autoimmunity and are responsible for tolerance induction to self-antigens. Th17 and Treg cells share common differentiation factors, such as TGF-β, that affect their development and generation. The balance between inflammation (Th17 cells) and tolerance (Treg17 and Treg cells) may influence pathology and disease outcomes in autoimmune diseases [57]. Autoimmune disease could be significantly enhanced when there is bias in favor of the pathogenic Th17 and Th1 cells and against regulatory Treg17 or Treg cells. Therefore, when developing new therapeutic approaches it is essential to retain an appropriate balance between pathogenic Th17 and Th1 cells and regulatory Treg17 and Treg cells to prevent the development and progression of autoimmune and inflammatory diseases.

B cells and their plasmablast/plasma cell progeny are generally considered to be important mediators of the immune response due to their role in producing antibodies. Autoantibodies targeting self-antigen are important pathological contributors to some autoimmune diseases. B cells can also serve as APCs to T cells and through this function can exert several modulatory functions in immune responses. Regulatory cytokine production by Breg cells or plasmablasts negatively regulate the immune response, including autoimmune responses. While these have been globally defined as Breg cells, unlike Treg cells it is not clear that these represent a separate differentiation pathway or lineage. At present no definitive phenotype has emerged for B cell subsets that has the regulatory potential; nevertheless the regulatory function of B cell lineage cells has been demonstrated in several autoimmune diseases. We conclude that both regulatory B and T cell subsets have a potential to modulate and regulate immune responses including autoimmune diseases. Further studies are clearly needed to elucidate the role of Treg17 cells and Breg cells in autoimmunity.

5. Conflict of interest

The authors have no financial conflict of interest to declare.

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