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Review

Humoral autoimmunity: A failure of regulatory T cells?

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ABSTRACT

Regulatory T cells (Tregs) are essential in maintaining tolerance to self. Several lines of evidence indicate that Tregs are functionally impaired in a variety of autoimmune diseases, leading to inefficient regulation of autoimmune T cells. Recent findings also suggest that Tregs are essential in controlling autoreactive B cells. The recently identified follicular regulatory T cell subset (T_{FR}) is thought to regulate the production of autoantibodies in the germinal center (GC) response. Here we provide an update on the role of Tregs in controlling the GC response, and whether defective control over B cell tolerance contributes to autoimmunity.

Contents

Abbreviations: CTLA-4, cytotoxic T lymphocyteantigen-4; DCs, dendritic cells; FDC, follicular dendritic cells; FoxP3, Foxheadbox3P; GARP, Glycoprotein A Repetitions Predominant; GC, germinal center; GITR, glucocorticoid-induced TNFR-related protein; IL, interleukin; LN, lymph node; NFAT, nuclear factor of activated T cells; PD-1, programmed death 1; SLO, secondary lymphoid organs; pTregs, peripherally-derived Tregs; Teff, effector T cells; TGF-β, transforming growth factor-β; T_H, helper T cells; Tregs, regulatory T cells; tTregs, thymic-derived regulatory T cells; T_{FH}, follicular helper T cells; T_{FR}, follicular regulatory T cells.

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1. Introduction

The immune system is dependent on various checkpoints to both ensure an optimal recognition and elimination of foreign antigens and to maintain tolerance against self-antigens. While negative selection of self-specific immune cells occurs during early differentiation, additional peripheral control mechanisms are in place to further ensure tolerance to self. Regulatory T cells (Tregs) are central in controlling peripheral tolerance and are characterized by the expression of the transcription factor Foxheadbox3P (Foxp3). Deletion of *Foxp3* in mice [1] or mutations in the *FOXP3* gene in humans [2] lead to multi-organ autoimmunity, inflammatory disease and allergy [3]. Tregs can be classified according to their origin [4]. Thymus-derived Tregs (tTregs) originate in the thymus and migrate to secondary lymphoid organs (SLO) and inflamed tissue sites, as conventional $CD4^+$ T cells do. Other Tregs, known as peripherally-derived Treg (pTreg), are induced in the periphery, where the functional evidence is strongest for control over mucosal immunity. Accumulating evidence suggests that the induction by commensal bacteria in the gut is the major source of pTregs [5,6]. Intracellular Foxp3 expression identifies Tregs, but given the obvious limitation other markers have been used to characterize Tregs such as $CD25^{hi}CD127^{lo}$, CD39, cytotoxic T lymphocyte antigen-4 (CTLA-4) [7], and more recently Glycoprotein A Repetitions Predominant (GARP), TIGIT and Helios [8–11] (for an elaborate overview of Treg markers see [11]).

The maturation and differentiation of the humoral immune response are T cell-dependent and occur in the germinal centers (GCs) of SLO. The GC response is mainly orchestrated by three types of cells: B cells, follicular helper T cells (T_{FH}) and follicular dendritic cells (FDC). After naïve T and B cells bind their cognate antigen, both cell types migrate towards the border of the T–B cell zone as a result of upregulation and downregulation of certain chemokine receptors (e.g. CXCR5 and CCR7, respectively) [12,13]. The T cell differentiates into a T_{FH} and interacts with the antigen-activated B cell, leading to the formation of an extrafollicular focus, where short-lived plasmablasts thrive, or the development of a GC. T_{FH} and B cells migrate to the center of the follicle where T_{FH} cells further stimulate B cell survival and maturation, including B cell expansion, isotype switching, immunoglobulin affinity maturation and selection [14–16]. In turn, B cells stimulate T_{FH} cells (by presenting antigen) to expand and further develop, as well as, conversely, also negatively regulating T cells to keep the response in check [17,18]. Eventually, the GC response results in the formation of long-lived plasmablasts and memory B cells [19]. The GC response requires exquisite regulation to ensure the production of antibody-producing and memory B cells and to minimize unwanted autoreactive or low affinity antibodies. The cellular characteristics of Tregs identify them as ideal candidates for the regulation of this complex and delicate process, with the ability to migrate to sites of T and B cell accumulation and a suppressive effect on both cell types. A specialized subset of regulatory T cells, named the follicular regulatory T cells (T_{FR}) was recently found to be indispensible for the regulation of the GC response [20–23].

In this review, we describe how Tregs control the humoral immune response and prevent humoral autoimmune responses and disease. First, we provide an overview of Treg involvement in controlling B cell immunity. Specific attention is paid to the T_{FR} specialized subset of Tregs. Second, we review recent data on the role of T_{FR} in autoimmunity. Finally, we consider the immunological function of circulating T_{FR} in light of recently published data on human circulating T_{FH}.

2. Regulatory T cells control the maturation of B cells

The primary physiological function of Tregs is the regulation of effector T cells (Teff). Nonetheless, Tregs are also capable of controlling other immune cells, such as B cells (Fig. 1). Early evidence showed that murine Tregs were able to directly inhibit B cell proliferation, proving their ability to modulate the maturation of B cells in vivo [24]. This suppression of proliferation was explained by an increase in cell death of antigen-presenting B cells, thereby contributing to a reduction in T helper (T_H) cell activity. The mechanisms that induced B cell apoptosis were dependent on the secretion of perforin and granzymes [25]. In humans, Tregs were shown to suppress IgG and IgA production by B cells in a T cell-independent manner. Furthermore, Tregs suppressed class-switching and affinity maturation of B cells, independent of the presence of T_H cells [26]. Of note, this suppression was dependent on cell–cell contact, and blockade of TGF-β and CTLA-4 abolished suppression. It is worth mentioning that regulatory B cells can also, in return, regulate T cells (reviewed in [27]), thus constituting an elaborate regulatory network.

2.1. Regulatory T cells control the germinal center response

During B cell maturation an enormous number of somatically mutated B cells emerge in the GC. To maintain self-tolerance, regulatory pathways need to be employed (Fig. 1). A regulatory T cell subtype with capacities to migrate towards the T cell zone in SLO in humans was discovered 10 years ago [28]. Lim et al. found that highly suppressive $CD4^+CD25^+CD69^-$ Tregs are able to regulate the GC-T_H cell-dependent IgG synthesis. These cells were considered to be regulatory based on expression of TGF-β, CD62L, GITR and FOXP3. They also showed that Tregs in human tonsils are able to suppress B cells in a T_{FH}-independent manner, regulating class-switching [26].

Several research groups have added or depleted Tregs (or essential Treg genes) in vivo to demonstrate the effect on the GC response. Fields et al. used adoptive transfer of labeled Tregs in vivo to assess the time point of Treg intervention in the GC response. They showed that Tregs block the maturation but not the initiation of autoantibodies and did not interfere with the initial follicular entry or activation of T_H or B cells [29]. In the reciprocal experiment, depletion of Tregs by anti-glucocorticoid-induced tumor necrosis factor receptor-related protein (GITR) monoclonal antibodies leads to increased GC B cells with an increased proportion of class-switched B cells [30]. In addition, Treg-deficient mice show expansion of GC-T_{FH} cells [31]. Furthermore, blocking TGF-β or IL-10 results in enhanced GCs [30]. Constitutive signaling of TGF-β inhibits T_{FH} cell accumulation and B cell autoreactivity, confirming the latter [32]. Recently, the phosphatase PTEN was identified as a crucial element in governing the stability of Tregs in suppressing T_{FH} responses in mice [33]. In summary, Tregs are essential to regulate the GC response during B cell maturation to obtain an optimal humoral response.

2.2. Follicular regulatory T cells

The GC response is a highly sensitive and delicate temporary process where a high number of dying cells are present, thereby provisioning an arsenal of potential self-antigens. Selection mechanisms, such as competition between maturing B cells for crucial T_{FH} support, have been demonstrated in the GC [21,22]. During this process T_{FH} cells select B cells depending on their ability to bind and present specific antigen [34]. A limiting number of T_{FH} cells are required to enable competition in a 'survival of the fittest'-like mechanism and thereby eliminating undesirable (self-reactive) B cells. Yet, the factors that are responsible for limiting the availability of T_{FH} cells remained to be elucidated. In 2012, three research groups independently identified and characterized a new subset of regulatory T cells, the follicular regulatory T cells (T_{FR})(Fig. 1). The T_{FR} control the normal GC response and preventing emergence of auto-reactive B cells. T_{FR} are characterized by phenotypic overlaps with the surface profile of T_{FH} cells ($CD4^+CXCR5^+PD\text{-}1^+ICOS^+BCL\text{-}6^+$), but also express Foxp3, CD25, CTLA-4, GITR and IL-10, which are characteristic markers for activated Tregs [21–23].

To address the question of the origin of T_{FR}, adoptive transfer models and Helios expression were used [21,22]. These studies