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Review Article

Regulatory T Cells and the Control of the Allergic Response

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The study of immune regulation and tolerance has been traditionally associated with self/nonself-discrimination. However, the finding that dominant tolerance, a model that puts in evidence the active role of regulatory T cells, can develop to nonself-antigens suggests that the imposition of tolerance can be context dependent. This paper reviews the emerging field of acquired immune tolerance to non-self antigens, with an emphasis on the different subsets of induced regulatory T cells that appear to specialize in specific functional niches. Such regulatory mechanisms are important in preventing the onset of allergic diseases in healthy individuals. In addition, it may be possible to take advantage of these immune regulatory mechanisms for the induction of tolerance in cases where pathological immune responses are generated to allergens occurring in nature, but also to other immunogens such as biological drugs developed for medical therapies.

1. Introduction

For many decades the self/nonself-discrimination by the immune system was assumed to be a consequence of clonal selection of effector T cells. Compelling evidence has, however, imposed a revised view of self/nonself-discrimination: dominant regulatory mechanisms, where regulatory T (Treg) cells play a central role, are essential for maintenance of self-tolerance [1]. But recently it is becoming apparent that the importance of dominant regulation goes beyond the discrimination of self and nonself: it also discriminates between harmful and innocuous. In fact, cellular mechanisms, as detailed below, persistently patrol the organism preventing the onset of inflammation, namely, allergic inflammation. The biological significance of this active tolerance-imposing mechanism is well demonstrated by the severity of the allergic and autoimmune syndrome that arises in individuals that lack these ability to tolerate self- and harmless antigens.

Indeed, the organism is constantly exposed to non-pathogenic antigens that, in healthy individuals, are tolerated. It is, however, common (and becoming increasingly frequent) that an overzealous immune system will activate and develop effector responses to such harmless antigens developing allergy and other inflammatory diseases. Over the last decades allergic diseases, including allergic asthma, atopic dermatitis, and food allergy, have become a major health problem in developed countries [2]. Despite the advances in the understanding of the pathophysiology of allergy and in its clinical management, allergic pathology remains a significant burden on the quality of life and economy of western society. Several strategies have been devised to overcome the pathological immune response by inducing immune tolerance. This paper reviews the impact of dominant regulatory mechanisms in the maintenance of tolerance to foreign antigens, including allergens.

A major cellular mechanism in maintaining immune tolerance is the population of natural (or thymic-derived) Foxp3$^+$ Treg cells [3, 4]. Indeed these have been clearly implicated as potent inducers of a nonresponsive state in several immune-mediated pathologies like autoimmunity, transplantation, graft-versus-host disease, and allergy [5–9]. It has been shown, in allergy, that regulatory T cells can be transferred conferring specific tolerance to subsequent challenges with the allergen [10, 11]. In addition, depletion of the regulatory T cells can have a detrimental effect in allergic airway hyperreactivity [12]. Importantly Foxp3 deficiency, in

mice and human beings, leads to a severe immune disregulation syndrome characterized by allergic and autoimmune manifestations that are rapidly fatal [13]. In addition to the important role of natural Foxp3$^+$ Treg cells (nTreg) in preventing autoimmunity, it has become established that Foxp3 expression can be peripherally induced following T-cell activation in presence of TGF-β [14]. These peripherally induced Treg cells (iTreg) are believed to be important for tolerance induction to nonselfantigens, including allergens [14].

2. Induction of Regulatory T Cells

The study of peripheral induction of Treg cells was greatly facilitated with the use of *Rag*-insufficient TCR-transgenic mice, with the TCR specific for a nonselfantigen. In these mice nTregs cannot be formed in the thymus due to the absence of a selecting thymic antigen. In 2003 it was shown that conventional T cells can be converted into iTreg *in vitro* when activated in presence of TGF-β [15]. In addition those iTreg cells were fully capable of controlling airway hyperreactivity (AHR) in previously sensitized mice [15–19]. It was subsequently found that reducing or blocking the available amount of TGF-β exacerbates AHR [20, 21], while the local delivery of this cytokine or adoptive transfer of T cells engineered to express latent TGF-β rescue mice from antigen sensitization and therefore prevent AHR [22, 23]. Interestingly, suboptimal TCR signaling together with TGF-β greatly enhances iTreg conversion [24], which is in agreement with *in vivo* data showing that repeated low doses of allergen exposure promotes the emergence of Foxp3$^+$ iTregs expressing TGF-β on the membrane [25]. Under suboptimal TCR stimulation, which can be obtained by using a low dose of plate bound anti-CD3 or DCs pulsed with a low dose of agonist peptide or with downmodulation of the TCR with nondepleting anti-CD4, iTreg conversion is promoted in the absence of exogenous TGF-β [26]. Under those conditions Foxp3 expression still requires TGF-β, but the T cells can produce TGF-β and benefit from the presence of this cytokine for conversion to Treg [26].

In addition to the importance of TGF-β for iTreg conversion, some studies showed that TGF-β can directly inhibit GATA3 expression thus impairing Th2 differentiation [27–29]. Because the Th2 response is impaired, the production of IL-4 is diminished, and this has a direct impact on B-cell class switch preventing IgE and favoring IgA production [30].

It is also becoming apparent that the environment influences the outcome of T-cell activation and the decision to induce Foxp3 and regulatory properties. Several reports have shown that the mucosal surfaces have a role in establishing an iTreg population: alveolar epithelial cells have been reported to participate in iTreg induction in a mechanism dependent of MHC class II expression and TGF-β [31]. Both alveolar and gut epithelia have been shown to depend on retinoic acid together with TGF-β to induce tolerance [32, 33]. It was also found that retinoic acid in the presence of TGF-β impaired STAT6 binding to the Foxp3 promoter therefore enhancing histone acetylation and reverting the repressive effect of IL-4 on the Foxp3 promoter [34].

Despite the critical role of TGF-β in iTreg induction and henceforth tolerance, this cytokine can also have some adverse effects since it is instrumental in the differentiation of Th17 and Th9 together with IL-6 and IL-4, respectively [35, 36]. Note that although Treg cells can prevent allergic autoimmune encephalomyelitis (EAE), mice with T cells with a dominant negative receptor for TGF-β1 do not develop EAE as Th17 cells are not induced [37]. Moreover, TGF-β has also been implicated in tissue remodeling, by induction of collagen expression in fibroblasts, as well as goblet cell proliferation and mucus production [38].

3. Regulatory T Cells and IL-10

Although TGF-β is the major known driver of iTreg differentiation, IL-10 has been shown to be another key player that has been vastly described in protection from allergic diseases [39].

Studies with bee venom-specific immunotherapy have shown that tolerance to the allergen can be induced in a process that is IL-10 mediated [40]. In addition, respiratory exposure tolerance induction to OVA relied on antigen specific CD4$^+$ regulatory cells that produced IL-10 [41]. Tolerance was transferrable and abrogated when IL-10 or ICOS ligand was blocked. Interestingly, those regulatory cells shared some features with effector Th2 cells: both populations expressed IL-4 and IL-10 although in different amounts. While the regulatory cells primarily release IL-10, the effectors rely on IL-4 as the main cytokine. It has been suggested that different types of effector cells, including Th2, produce IL-10 at the end of the immune response in a mechanism that is important in limiting their inflammatory behavior [42]. IL-10 producing T cells has been described able to control the late response in allergic asthma by reducing neutrophilia [43]. It has been suggested that Foxp3-negative IL-10 producing T cells can be induced following activation in presence of IL-10 and constitute a population of regulatory cells different from Foxp3$^+$ Tregs that are named TR1 [44, 45]. TR1 cells have been identified in mice and humans, and there are currently clinical trials [9, 46]. There are several other lines of evidence demonstrating the crucial role of IL-10 in the prevention of airway inflammation: IL-10-deficient mice have an exacerbated allergic airways response with high levels of proinflammatory cytokines like IL-5 and IFN-γ in the BAL [47]. Furthermore, intranasal administration of rmIL-10, concurrently with OVA, inhibited both airway neutrophilia and eosinophilia [48]. It was also shown that allergen-specific CD4$^+$CD25$^+$ Tregs can suppress allergic airway disease *in vivo* through an IL-10-dependent mechanism [18]. In this study, adoptive transfer of Treg cells reduced AHR, Th2 and eosinophil recruitment into the airways, and secretion of Th2-type cytokines. The effect was IL-10 mediated, since neutralizing anti-IL-10R abrogated suppression. In addition, these effects were independent of IL-10 production by the CD4$^+$CD25$^+$ regulatory cells themselves [18].

Unlike TGF-β, IL-10 does not directly influence B-cell class switch [49]. However, it is possible that indirectly, by inhibiting the inflammatory response, IL-10 shapes the

humoral outcome. Indeed, it was proposed that IL-10 may favor the ratio of IgG4/IgE ratio [50]. In fact immunotherapy studies show that Th2 responses can be suppressed by IL-10 secreting regulatory cells accompanied by an increase of circulating IgG4 [51, 52].

4. Different Subsets of Regulatory T Cells

Foxp3$^+$ Treg cells, despite an apparent phenotypic uniformity and immunosuppressive function, can have different subtypes with distinct genetic signatures. The first major division was identified between nTreg and iTreg, where the first are enriched in Helios, a transcription factor that is primarily expressed in T-lineage cells and early precursors [53, 54]. While nTreg cells have epigenetic mechanisms that stabilize Foxp3 expression allowing them to be a stable differentiated cell lineage, TGF-β induced Tregs lack those mechanisms having incomplete demethylation [55]. Therefore, although iTreg cells have high levels of Foxp3, the expression of Foxp3 is less stable [55–57]. In addition, conserved noncoding DNA sequence (CNS) elements at the Foxp3 locus encode information defining the size, composition, and stability of the Treg cell population [58]. CNS3, which binds c-Rel, has a drastic effect on the frequency of Treg cells generated in the thymus. Contrary to CNS3, CNS1 has no effect on thymic generation of Treg cells but is essential for induction of iTregs [58]. CNS1 contains a TGF-β-NFAT response element, so these results could represent the requirement of TGF-β and NFAT for Treg induction in the periphery [58–60]. Although CNS2-deficient T cells can acquire Foxp3 expression, they fail to maintain Foxp3 expression on their progeny due to the failure on recruitment of Foxp3-Runx1-Cbf-β complexes to CNS2 after demethylation of the CNS2 CpG island [58, 61]. Interestingly CNS1 deficient mice had no lymphoproliferative disorder. However, it can be argued that these animals kept in clean facilities have a minimal exposure to foreign antigens and thus nTreg may be sufficient to maintain homeostasis in such conditions. In effector T cells, GATA-3 is a hallmark of the Th2 cells, but Treg cells can also express GATA-3, that binds both to the Th2 cell locus and to the CNS2 of Foxp3 locus [62]. In fact, there is a dramatic increase of GATA-3 binding to CNS2 compared to conventional T cells, suggesting that GATA-3 regulates CNS2 activity in Treg cells [62].

There is strong evidence that the CCR7-dependent continuous migration of DC from the lung to its draining LNs is required for the transport of inhaled Ag and thereby for the proper composition of APCs in the LN. These processes are essential to induce peripheral tolerance of T cells [63]. The costimulation with ICOS, crucial for regulatory phenotype polarization in allergy [64], promotes the downregulation of CCR7 and CD62L after activation, leading to a reduced return of activated CD4 T cells to the lymph nodes and a more efficient entry into the lungs [65]. Regulatory T cells express CCR4 and CD103 induced by antigen-driven activation in the lymph nodes. In addition, the accumulation of Tregs in the skin and lung airways is impaired in the absence of CCR4 expression [66]. Mice without CCR4 in the Treg compartment develop lymphocytic infiltration and severe inflammatory disease in the skin and lungs [66]. Some studies suggest that CCR4 has a prominent role in effector Th2 homing [67]. Despite their differences it seems both regulatory and effector T cells share the response to homing factors [68, 69].

But GATA-3 is not the only transcription factor characteristic of effector T-cell responses that can be expressed by Foxp3$^+$ Treg cells. Under the influence of IFN-γ, Foxp3$^+$ Treg cells can express the Th1-defining transcription factor T-bet [70]. T-bet expression by Foxp3$^+$ Treg cells induces the expression of the chemokine receptor CXCR3, necessary for these Treg cells to accumulate at the site of type 1 inflammation. T-bet expression was thus required for the homeostasis and function of Treg cells during type-1 inflammation [70].

It is likely that the regulation of different types of immune response requires the participation of specialized subsets of regulatory cells. This way, iTreg cells induced in an environment favorable to Th1 or Th2 type of immune responses require the appropriate chemokine receptors to give them access to the same locations as effector T cells (Figure 1).

Th17 cells that have been implicated in autoimmunity and allergy share with iTreg cells the need for TGF-β to differentiate [71]. The decision of antigen-stimulated cells to differentiate into either Th17 or iTreg depends on the cytokine balance of IL-6, IL-21, and IL-23 that relieve Foxp3-mediated inhibition of RORγt [72]. These results indicate that Foxp3 and RORγt are transcription factors that antagonize each other in the lineage differentiation.

Another subset of T cells, the follicular T helper cells (Tfh), is mostly spatially confined to secondary lymphoid organs, more precisely to the B-cell follicles [73]. Tfh cells express high levels of the transcription factor Bcl-6, that impairs the expression and function of other transcription factors specific for other CD4 subsets: Tbet, GATA3, and RORγt, thereby regulating cytokine production by Tfh cells [74, 75]. Tfh cells differentiate under the influence of ICOS:ICOSL and IL-21 but independently of any other cytokine [76]. In addition, the characteristic anatomical distribution of Tfh cells is dependent of CXCR5 that endows access to the B-cell follicle [73, 77, 78]. We and others have recently found that also this subset of effector T cells has a specialized regulatory counterpart [69, 79, 80]. It was found that Foxp3$^+$ Treg cells can be found within the B-cell follicle [81], sharing many characteristics of Tfh and Treg cells [69, 79, 80]. Importantly, Bcl-6 can be coexpressed with Foxp3 as it seems Foxp3 expression is not inhibited by Bcl-6. These follicular regulatory T cells (Tfr) are immunesuppressive and can control de magnitude of the germinal center response [69, 79, 80]. In addition, they exhibit a CTLA4^{hi}GITR^{hi}IL-10^{hi} phenotype that is the characteristic of activated Tregs [69, 79, 80]. However, the Tfr origin is quite distinct from the other induced Treg cells previously described. Tfr cells do not derive from the commitment of conventional CD4 T cells, but result from acquisition of "follicular" characteristics (viz. Bcl-6 expression) by natural Foxp3$^+$ Treg cells [69, 79, 80]. In fact sorted Tfh cells

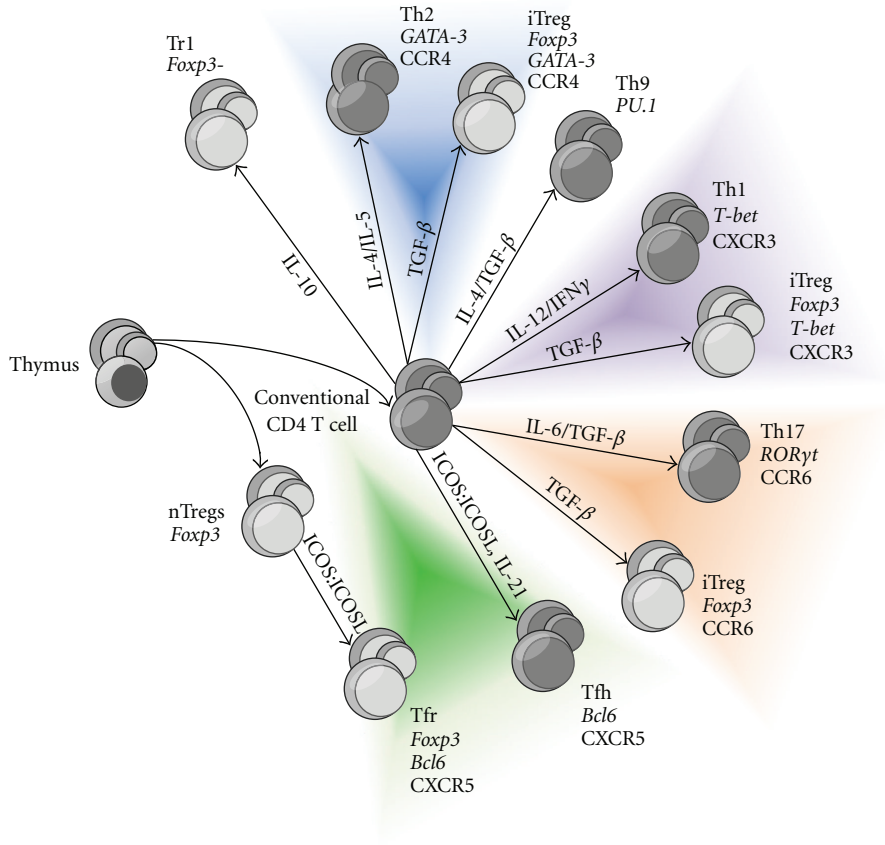

Figure 1: Functional specialization of effector and regulatory T cells. Different types of immune responses carry different cytokine microenvironments that can influence both effector and regulatory T-cell differentiation. In the same way effector T cells when activated in specific cytokine environment acquire specialized functions, induced regulatory cells (iTreg) can also activate the expression of different transcription factors (italics) that endow them access to different anatomic compartments on the basis of the chemokine receptors they express. Follicular regulatory cells (Tfr) represent an exception among peripherally induced Foxp3$^+$ cells, as they are derived from natural regulatory cells (nTreg) that acquire Bcl-6 expression, rather than from conventional CD4 T cells.

exposed to optimal conditions to induce Foxp3 expression in conventional T cells (including TGF-β) resist conversion to Tfr [79]. Given the importance of the germinal center response for allergy, it is likely that Tfr cells can play an important role in regulating IgE production.

Besides conventional T cells, also natural killer T (NKT) cells are important players in defining the outcome of immune responses. Notably, invariant NKT (iNKT) cells were found able to help B-cell differentiation, germinal-center formation, affinity maturation, and immunoglobulin response that was uniquely dependent on iNKT cell-derived IL-21, although the GCs maintain a small size throughout the reaction [82, 83]. This contribution of iNKT cells for humoral responses can be added to their ability to contribute to allergic airways diseases by producing IL-4 and IL-13 [84, 85], or IL-17 [86, 87]. But iNKT cells can also have a regulatory role, namely, in preventing EAE following administration of its TCR agonist [88, 89]. We and others recently described that activation of murine or human iNKT cells in presence of TGF-β induces Foxp3 expression and acquisition of suppressive function [88, 90].

5. Influencing Regulatory T Cells in Allergy

The understanding of the mechanisms involved in regulatory T-cells generation and function may lead to novel strategies to restore immune tolerance where it has been lost. As TGF-β and IL-10 play a crucial role in tolerance induction, several studies on immune tolerance induction took advantage of environments rich in those anti-inflammatory cytokines. To our advantage the mucosa itself is an anatomical location rich in these immune mediators [91].

Airborne antigens can be transferred from the mother to the newborn through milk [92]. Breastfeeding-induced tolerance was found to be mediated by induced Foxp3$^+$ Treg cells and dependent on TGF-β [92]. It has been proposed that metallomatrix proteases, derived from commensal bacteria in the gut, can facilitate the conversion of latent TGF-β to its active form, thus favoring iTreg differentiation [93]. In addition, CD103$^+$ dendritic cells in the mucosa-draining lymph nodes have been shown effective in promoting conversion of iTregs in the gut, mediated by TGF-β and the synthesis of retinoic acid, a powerful inducer of Foxp3 expression [32, 94, 95]. Furthermore, vitamin D receptor

deficient mice were associated with a reduction in tolerogenic $CD103^+$ dendritic cells favoring the development of effector type T cells [96]. Vitamin D3 can be used to induce human and mouse naive $CD4^+$ T cells to differentiate *in vitro* into regulatory cells that produced only IL-10, but no IL-5 and IFN-γ, and furthermore retain strong proliferative capacity [97]. Several other studies put vitamin D3 in relevance as acting directly on T cells to induce IL-10^+ regulatory cells and also influencing levels of TGF-β [98–100]. These data suggest that the mucosa, in particular the gut, has several mechanisms that can favor immune tolerance. Sublingual immunotherapy (SLIT) and oral immunotherapy (OIT) are becoming more relevant as effective tolerance-inducing strategies to treat inhalant as well as food allergies [101].

Allergen specific immunotherapy (SIT) which comprehends SLIT, OIT, and subcutaneous immunotherapy (SCIT) has been in clinical use for around 100 years [102] and consists on the administration of increasing doses of an allergen [103]. It has been shown that both $Foxp3^+$ and IL-10 positive regulatory T cells can be induced during the course of SIT protocols [104, 105]. Furthermore, allergen-specific TR1 cells, in healthy individuals, have been suggested to play a key role in preventing pathologic responses [52, 102, 106]. While the presence of IL-10 leads B cells to produce IgG4 in detriment of IgE [107, 108], TGF-β drives B cells to switch to IgA production [106]. Another approach to direct the organism towards a tolerant state arises from the results that suggest that reduced TCR stimulation favors the induction of a regulatory phenotype on the T cells [26, 109, 110]. Blockade of molecules involved in the immune synapse has been suggested as an approach to achieve suboptimal TCR activation [26, 110]. Blockade of CD4 was shown a robust approach to achieve Treg-mediated dominant tolerance in transplantation [111–113]. We recently showed that a nondepleting anti-CD4 monoclonal antibody can induce in mice robust, antigen-specific tolerance to house dust mite, even in presensitized animals [16]. In addition, a similar strategy was effective to prevent peanut-induced anaphylaxis in mice [114]. Costimulation blockade was also shown effective in preventing allergic sensitization in mice [115]. Based on previous studies of tolerance induction to alloantigens following costimulation blockade, it is likely the mechanism also relies on Treg cells [116, 117]. Regarding the different modalities for costimulation blockade, on one hand CTLA4Ig was shown able to greatly reduce the secretion of IL-4 but not enough to impair Th2 response [118]. On the other hand, treatment with OX40L-blocking mAbs inhibited to some extent allergic immune responses induced by TSLP in the lung and skin, preventing Th2 inflammatory cell infiltration, cytokine secretion, and IgE production in mice and nonhuman primate models of asthma [119].

6. Final Remarks

The realization that active regulatory mechanisms, such as the ones mediated by Treg cells, can prevent pathological immune responses to harmless antigens is changing the way immunotherapy is perceived. In very diverse fields of immunology, ranging from cancer immunotherapy to autoimmunity and allergy, regulatory mechanisms need to be considered when therapeutic interventions are designed to boost or dampen the immune response. The realization that different subsets of regulatory T cells exist may offer the possibility to fine tune such interventions in order to achieve optimal therapeutic benefit with limited immunosuppressive consequences in unrelated immune responses.

At a time when therapeutic interventions rely increasingly on potentially immunogenic drugs, such as recombinant proteins to correct genetic diseases or monoclonal antibodies, where even the human antibodies can be immunogenic due to their unique idiotypes [120, 121], the issue of tolerance induction to nonselfantigens will not be restricted to allergy and transplantation, but a growing concern for drug efficacy.

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