

T Regulatory Cells in Allergy and Health: A Question of Allergen Specificity and Balance

Alison Taylor · Johan Verhagen · Cezmi A. Akdis · MÜbecce Akdis

Swiss Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland

Key Words

T regulatory cells · Immunotherapy · Tolerance · Anergy · IgE · T cells

Abstract

Anergy, tolerance and active suppression may not be independent events, but rather involve similar mechanisms and cell types in immune regulation. Induction of allergen-specific regulatory/suppressor T cells (T_{Reg}) seems essential for the maintenance of a healthy immune response to allergens. Allergen-specific immunotherapy can induce specific T_{Reg} cells that abolish allergen-induced proliferation of T helper 1 (Th1) and Th2 cells, as well as their cytokine production. T_{Reg} cells utilize multiple suppressive mechanisms, interleukin-10 (IL-10) and transforming growth factor- β (TGF- β) as secreted cytokines and CTLA-4, PD-1, mTGF- β , mIL-10, TGF- β R and IL-10R as surface molecules. An important aspect of T_{Reg} cells is the regulation of antibody isotypes and suppression of proinflammatory cells. IL-10 and TGF- β secreted by T_{Reg} cells skew production of IgE towards the noninflammatory isotypes, IgG4 and IgA, respectively. Furthermore, T_{Reg} cells may directly or indirectly suppress effector cells of allergic inflammation such as basophils and eosinophils. In conclusion, induction of

antigen-specific T_{Reg} cells may redirect an inappropriate immune response against allergen or autoantigens with the help of a broad range of suppressor mechanisms.

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Introduction

During the last decade, the study of tolerance/anergy within immunological research has become extensively popular and elaborate, suggesting a link between the mechanisms of anergy, tolerance and active suppression, possibly involving the same molecular events. T cell tolerance is characterized by induced unresponsiveness of surviving T cells when subject to antigen encounter. Immunological tolerance is observed when antigen exposure occurs before the immune response develops, specifically abrogating the response to that antigen thereafter [1, 2]. Anergy entails a process by which presentation of antigen to T cell clones in the absence of professional antigen-presenting cells (APC) results in the induction of a hyporesponsive state affecting interleukin-2 (IL-2) production and proliferation upon restimulation [3]. Anergic T cells can be characterized by their reversible functional limitations, including cell division, cell differentiation, and cytokine production [4, 5]. It is important to note that in

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Correspondence to: Dr. MÜbecce Akdis
Swiss Institute of Allergy and Asthma Research (SIAF)
Obere Strasse 22
CH–7270 Davos (Switzerland)
Tel. +41 81 4100848, Fax +41 81 4100840, E-Mail akdis@siaf.unizh.ch

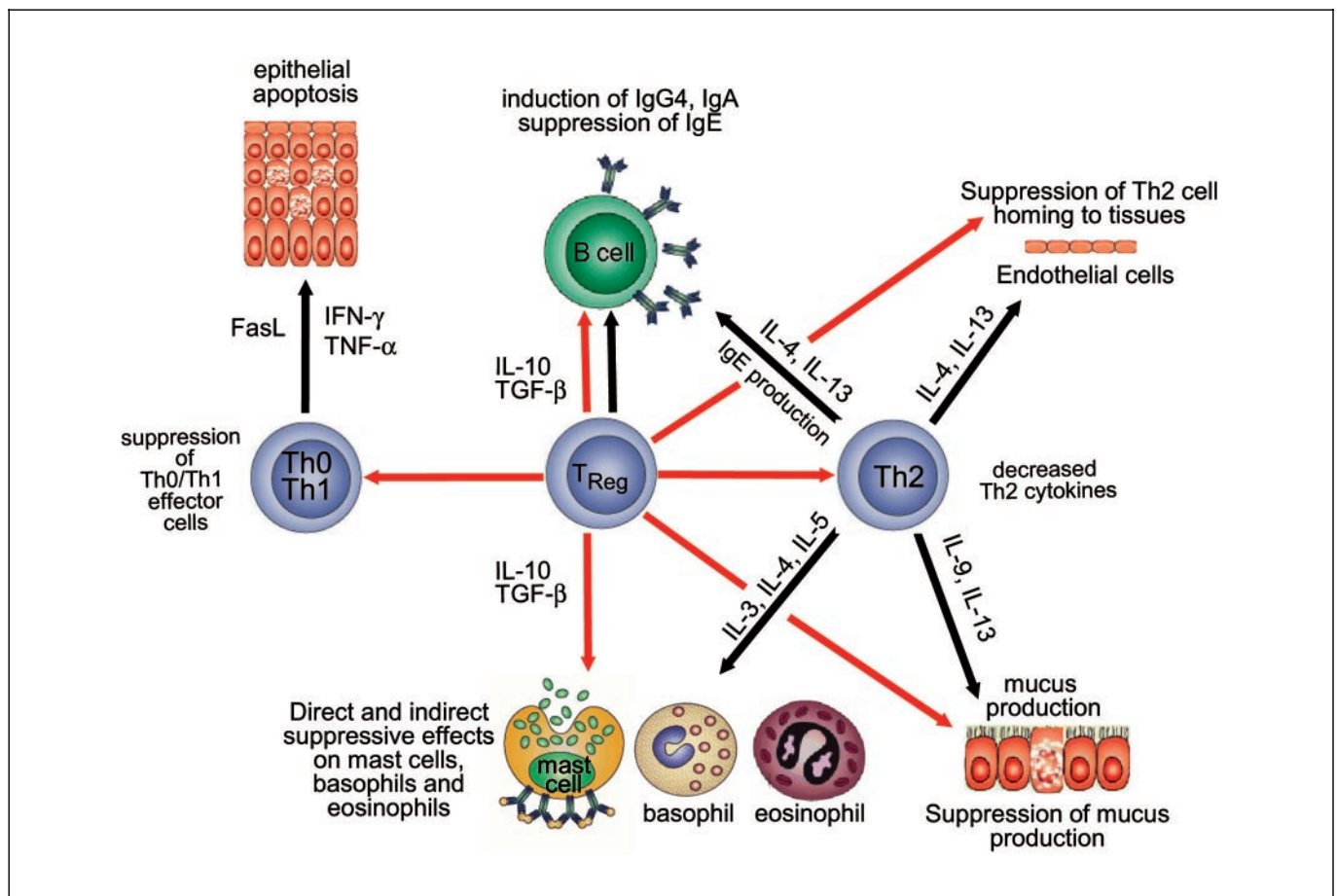


Fig. 1. Induction of immune deviation towards T_{Reg} cell response leads to peripheral tolerance in allergen SIT and healthy immune response. T_{Reg} cells utilize multiple suppressor factors to regulate undesired activity of effector cells. IL-10 and TGF- β suppress IgE production and induce noninflammatory Ig isotypes IgG4 and IgA, respectively. Furthermore, these two cytokines directly suppress allergic inflammation induced by effector cells such as mast cells, basophils and eosinophils. In addition, T_{Reg} cells inhibit Th2 cells,

which can no longer provide cytokines such as IL-3, IL-4, IL-5 and IL-9. These cytokines are required for the differentiation, survival and activity of mast cells, basophils, eosinophils and mucus-producing cells, as well as for the tissue homing of Th2 cells. Moreover, suppression of the induction of Th0/Th1 cells abrogates tissue injury mechanisms, such as apoptosis of keratinocytes and bronchial epithelial cells, via IFN- γ , TNF- α and Fas ligand (FasL) (red line: suppression, black line: stimulation).

earlier studies, which provide a basis for the definition of anergy/tolerance, functional unresponsiveness was analyzed by nonsophisticated assays such as antigen-induced [³H]-thymidine incorporation, IL-2 and total IgG production. Furthermore, until recent years, the antigens used within mouse models contained high amounts of impurities, such as LPS and other innate immune response-stimulating substances, which may have influenced experimental outcomes.

The reason for allergen exposure causing atopic disorders in some individuals but not others involves the interaction of environmental and genetic factors. The initial

event responsible for the development of allergic diseases is the generation of allergen-specific CD4⁺ T helper cells. The current view is that IL-4-influenced naive T cells differentiate into T helper 2 (Th2) cells when activated by APC [6, 7]. Several regulatory and effector functions are then mediated by IL-4, IL-5 and IL-13 production by these effector Th2 cells (fig. 1). These functions include allergen-specific IgE production by B cells, eosinophil development and recruitment, mucus production and smooth muscle contraction, as well as tissue homing of Th2 cells [6–10]. Chronic allergic inflammation may result from type I hypersensitivity, which involves IgE-

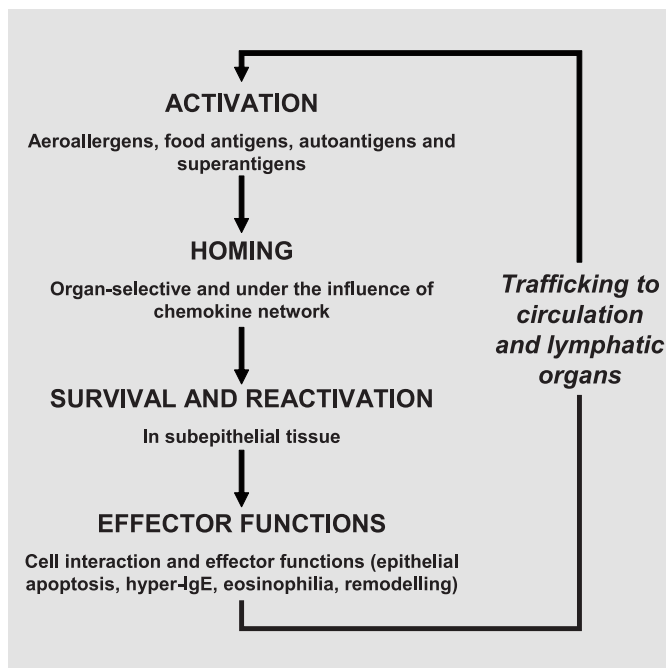


Fig. 2. The four sequential processes characterizing allergic inflammation. Various antigens or still unidentified factors activate T cells; these cells then undergo organ-selective homing according to the influence of organ-related chemokine networks. T cells within subepithelial tissues show increased survival and are continuously stimulated. These activated T cells then trigger effector functions, including apoptosis, hyper-IgE and eosinophilia. These four events can be summarized as shown.

mediated cross-linking of receptors, resulting in the degranulation of mast cells and basophils. Th1 cells, on the other hand, may contribute to chronicity and the effector phase in allergic disease [11–13]. These two distinct T cell subpopulations are able to counterregulate each other [7]. A further subset of T cells termed regulatory/suppressor T cells (T_{Reg}), with a distinct immunosuppressive function and cytokine profile to that of Th1 or Th2 cells, has been described [14, 15]. Like Th1 cells, T_{Reg} cells are able to inhibit the development of allergic Th2 responses [16, 17] and play an important role in allergen-specific immunotherapy (SIT) [18, 19] (fig. 1).

The combination of four sequential processes characterize allergic inflammation (fig. 2), the first being the activation of memory/effector T cells and other effector cells (mast cells, eosinophils and basophils) by aeroallergens, food antigens, autoantigens and bacterial superantigens [20, 21]. This process is followed by organ-selective homing, whereby cells are influenced by the network of chemokines in the skin, nose and lung [22, 23]. The third

stage is classified by prolonged survival of inflammatory cells, which interact with resident cells and become reactivated within the allergic organs [24, 25]. Finally, there are the effector roles of T cells, which result in the induction of hyper-IgE, eosinophil survival and mucus hyperproduction and remodeling [20, 25, 26], all of which are important factors in atopic dermatitis and asthma. Furthermore, activated T cells induce apoptosis of bronchial epithelial cells and keratinocytes as main/essential tissue injury events [11, 27]. As all of these pathological events require activated T cells, peripheral T cell tolerance is seen to be vital for a healthy immune response and represents a mechanism to overcome allergic inflammation and successfully treat allergic disorders [18, 19, 28, 29].

Regulatory Cell Types

In the early 1970s, T cells that were able to suppress the immune response were first described [30]. Unfortunately, this area of research was abandoned in the 1980s, when the mechanisms underlying immune suppression could not be clarified [31]. Exploration into the concept of T cell-mediated immune suppression was focused upon once more in the mid 1990s. Currently, the idea of T_{Reg} cells suppressing immune responses via cell-cell interactions and/or the production of suppressor cytokines is well established. However, many aspects behind these mechanisms remain to be unraveled [15, 18, 28, 32].

Type 1 T Regulatory Cells (Tr1) (table 1)

Tr1 cells, which are also called inducible T_{Reg} cells, are defined by their ability to produce high levels of IL-10 and transforming growth factor- β (TGF- β) [15, 32]. Tr1 cells specific for a variety of antigens arise in vivo, but may also differentiate from naive CD4⁺ T cells. It has been reported that stimulating naive CD4⁺ T cells in the presence of IL-10, interferon- α (IFN- α) or a combination of IL-4 and IL-10 leads to the in vitro generation of a Tr1 cell subset [15, 32]. A combination of vitamin D₃ and dexamethasone has been demonstrated to induce human and mouse naive CD4⁺ T cells to differentiate in vitro into Tr1 cells [33], which, in contrast to the previously described in vitro derived CD4⁺ T cells, only produce IL-10, but not IL-5 and IFN- γ . It is now clear that IL-10- and/or TGF- β -producing Tr1 cells in humans are generated in vivo during the early course of allergen SIT, implying that high and increasing doses of allergens induce Tr1 cells [18, 19, 34]. These Tr1 cells downregulate allergen-specific Th1 and Th2 responses [17]. The foreseeable future

Table 1. Subsets of T_{Reg} cells

T _{Reg} cells	Suppressor mechanism	References
Tr1	IL-10, TGF- β	14, 15, 18, 19, 28, 32–35, 43
Th3	TGF- β	14, 37, 50
CD4+CD25+ T _{Reg}	IL-10, TGF- β , CTLA-4, PD-1, GITR	39–42, 44, 45
CD8+CD25+CD28– T _{Reg}	Same as CD4+CD25+	47, 48, 51
Qa-1-dependent CD8+	Qa-1-specific TCR	49
CD4–CD8– T _{Reg}	Induction of apoptosis	52, 53
TCR $\gamma\delta$ T _{Reg}	IL-10, TGF- β	54–57

entails the use of Tr1 cells in the identification of novel targets for developing new therapeutic agents, and as a cellular therapy for peripheral tolerance modulation in allergy and autoimmunity [28, 35, 36].

Th3 Cells

There are similarities between Tr1 cells and Th3 cells. Th3 cells produce high levels of TGF- β , with variable amounts of IL-4 and IL-10 upon activation with an appropriate antigen or anti-CD3 antibody [14, 37]. In vivo, these cells were found to suppress encephalitis induction with myelin basic protein. TGF- β and IL-10 seemed to play a crucial role, as neutralizing antibodies abrogated the disease-protective effects of these cells. Furthermore, Th3 cells have been shown to exert bystander immune suppression in vitro [37].

CD4+CD25+ T_{Reg} Cells

Besides the expression of CD4 and CD25, these cells are also associated with the transcription factor FOXP3 [38]. This distinct subset of T_{Reg} cells, which are also called constitutive T_{Reg} cells, accounts for 5–10% of peripheral CD4+ T cells and has been shown to inhibit the activation of effector T cells in the periphery [39–43]. The mechanism of suppression by CD4+CD25+ T_{Reg} cells has been shown to function via the inhibition of IL-2R α chain in target T cells, which is induced by the combined activity of cytotoxic T lymphocyte antigen 4 (CTLA-4) [44] and membrane-bound TGF- β 1 [45].

PBMC from atopic and nonatopic donors proliferate in response to allergen in culture, but differ in Th2 cytokine production. In PBMC of nonatopic donors, regulatory CD4+CD25+ T cells normally inhibit Th2 cytokine expression and proliferation in response to allergen. The suppressive ability of these cells has been shown to be associated with the control of allergic diseases [46].

During SIT and in normal immunity to mucosal allergens, IL-10 and TGF- β were shown to induce T cell suppression. SIT induced antigen-specific suppressive activity in CD4+CD25+ T cells of allergic individuals and this suppression can be blocked partially by the neutralization of secreted or membrane-bound IL-10 and TGF- β [19]. It is tempting to speculate that CD4+CD25+ T cells in humans may represent a whole repertoire of single antigen/allergen-specific Tr1 cells.

Elimination of CD4+CD25+ T cells leads to the spontaneous development of various autoimmune diseases: arthritis, diabetes and the X-linked immune dysregulation, polyendocrinopathy and enteropathy syndrome, indicating the presence of a population of professional T_{Reg} cells.

Other T_{Reg} Cells

It has been proposed that, in addition to CD4+ T cells, CD8+ T_{Reg} cells may have a role in oral tolerance [47–50]. Furthermore, CD8+ T_{Reg} cells have been described to control proliferation of CD4+ T cells in a Qa-1-dependent (HLA-E in humans) manner [49]. CD8+CD28–FOXP3+ T suppressor cells have recently been reported to induce tolerogenic endothelial cells [51], by the induction of inhibitory receptors and the downregulation of costimulatory and adhesion molecules.

Several studies on autoimmune disease describe double-negative (CD4–CD8–) TCR $\alpha\beta$ + T_{Reg} cells that mediate tolerance [52]. This effect was mainly attributed to Fas-mediated apoptosis of alloreactive T cells [53].

A population of tumor-infiltrating $\gamma\delta$ T_{Reg} cells, with a cytokine profile reminiscent of Tr1 cell clones, may play a role in the inhibition of immune responses against tumors [54, 55]. Furthermore, they have been shown to play a role in the induction of tolerance against aerosol-delivered protein antigen [54] and ovalbumin [56], but are not essential in IgE unresponsiveness [57].

Other Cells with Regulatory Function

IL-10-secreting B cells have recently been proposed to prevent the development of arthritis [58]. It is generally accepted that immature dendritic cells (DC), which cannot appropriately activate T cells, may induce tolerance [59]. In normal immunity, DC should not have any restriction in maturation due to sufficient signals from the surroundings of the antigen, T cells and other tissue cells, innate immune response stimulating (i.e. Toll-like receptor triggering) substances and via costimulatory ligands and cytokines. However, IL-10 inhibits the full maturation of DC, which induces a state of anergy in alloantigen-specific CD4⁺ T cells [60]. Furthermore, there are some indications that mature DC can induce peripheral T cell tolerance. Pulmonary DC from mice exposed to respiratory antigen transiently produce IL-10 [61]. These phenotypically mature pulmonary DC, which were B7^{hi}, stimulate the development of CD4⁺ Tr1-like cells. Adoptive transfer of IL-10^{+/+}, but not IL-10^{-/-} pulmonary DC of mice exposed to respiratory antigen induced antigen-specific unresponsiveness in recipient mice. This study shows that phenotypically mature DC_{Reg} may exist under certain circumstances.

It has been clearly demonstrated that natural killer cells, epithelial cells, macrophages, and glial cells express suppressor cytokines such as IL-10 and TGF- β . Although their role has not been classified as professional regulatory cells, these cells may have an involvement in the generation and suppression of an immune response [62–67].

Tr1 Cell-Mediated Peripheral T Cell Tolerance in Allergen SIT and the Healthy Immune Response to Allergens

Allergen SIT has been most successfully applied in the treatment of insect venom allergy and allergic rhinitis in clinical practice during the last century [68–70]. A more long-term solution/treatment is provided by allergen SIT, specifically restoring normal immunity against allergens rather than a temporary suppression of mediators and immune cells provided by antihistamines, antileukotrienes, β_2 -adrenergic receptor antagonists and corticosteroids [71, 72]. Successful allergen SIT is associated with an increase in allergen blocking IgG antibodies (mainly IgG4) [73], the generation of IgE-modulating CD8⁺ T cells [74] and a decline in the number of mast cells and eosinophils as well as the release of mediators [75]. Furthermore, an affiliation with a shift in the Th2 cytokine profile toward decreased levels of IL-4 and IL-5 produc-

tion [76–78] and an increase in IFN- γ production in allergen SIT of the allergy to bee venom, wasp venom, grass pollen and house dust mite [76, 79] were demonstrated. The induction of peripheral T cell tolerance plays a crucial role in allergen SIT (fig. 1) [18, 19, 28, 29]. T cell tolerance is initiated by the autocrine action of IL-10 and TGF- β , which are increasingly produced by antigen-specific T cells [18, 19, 28]. Reactivation of tolerized T cells can result in the distinct production of either Th1 or Th2 cytokine profiles depending on cytokines present in the tissue microenvironment, and can therefore direct allergen SIT towards either successful or unsuccessful treatment [29] (fig. 1).

Another elegant approach in immunotherapy for the investigation of peripheral T cell tolerance in humans involves the use of non-IgE binding, but T cell epitope-containing peptides (PIT). At present, two types of allergy have been targeted by PIT in clinical trials [80–82]. For the major cat allergen Fel d 1, studies with relatively long peptides of 27 and 35 amino acids or a mixture of peptides spanning the whole protein sequence resulted in the induction of tolerance in IL-4-producing cells in the late phase response. The observed effect was closely associated with an upregulation of IL-10 production [81, 82]. In bee venom allergy, a mixture of short peptides directly representing the T cell epitopes (17, 12, 11) of the major bee venom allergen, phospholipase A₂, was used [36]. The study demonstrated modulation of the immune response against the whole allergen, inducing specific T cell tolerance and a decline in the specific IgE:IgG4 ratio [36].

Analysis of responses to various food and inhalant antigens has shown the healthy immune response to mucosal antigens to have a similar mechanism of active regulation to that which can maintain immunological unresponsiveness [17]. IL-10-secreting allergen-specific T cells are predominant in healthy individuals in comparison to IL-4-secreting T cells. In contrast, this is reversed in allergic individuals [17].

A recent study has been performed using IFN- γ -, IL-4- and IL-10-secreting allergen-specific CD4⁺ T cells that resemble Th1-, Th2- and Tr1-like cells, respectively. Healthy and allergic individuals exhibit all three subsets, but in different proportions. In healthy individuals Tr1 cells represent the dominant subset for common environmental allergens, whereas a high frequency of allergen-specific IL-4-secreting T cells (Th2-like) is found in allergic individuals. Hence, a change in the dominant subset may lead to either the development of allergy or recovery [17].

Tr1 cells have many suppressive mechanisms, including secretion of suppressive cytokines IL-10 and TGF- β , as well as the surface molecules CTLA-4 [44] and programmed death 1 (PD-1) [83, 84]. It has been shown *ex vivo* that blocking these suppressor activities of Tr1 cells or increasing the Th2 cell frequency enhances allergen-specific Th2 cell activation [17].

Allergen-Specific Peripheral T Cell Tolerance Is Associated with Antibody Isotype Regulation and Effector Cell Suppression

Although peripheral tolerance was demonstrated in specific T cells, the ability of B cells to produce specific IgE antibodies was not eliminated during SIT [29]. In fact, during the early phase of treatment, specific serum levels of both IgE and IgG4 antibodies increase. However, the increase in antigen-specific IgG4 was more striking and the ratio of specific IgE to IgG4 decreased by 10- to 100-fold. Also the *in vitro* production of PLA-specific IgE and IgG4 antibodies by PBMC changes in parallel to the serum levels of specific isotypes. A similar change in specific isotype ratio was observed in SIT of various allergies [76, 78, 79, 85]. Moreover, IL-10 which is induced and progressively secreted during SIT appears to counterregulate antigen-specific IgE and IgG4 antibody synthesis [18]. IL-10 potently suppresses both total and allergen-specific IgE, whereas it simultaneously increases IgG4 production [18, 86]. Therefore, IL-10 not only generates T cell tolerance, it also regulates specific isotype formation and skews the specific IgE response towards an IgG4-dominated phenotype (fig. 1). The healthy immune response to Der p 1 demonstrated high levels of specific IgA and IgG4, low amounts of IgG1 and barely detectable levels of IgE antibodies in serum [19]. After 70 days of house dust mite SIT treatment of allergic patients, specific IgE levels did not significantly change; however, a marked increase in specific IgA, IgG1 and IgG4 was observed [19]. The increase of specific IgA and IgG4 in serum coincides with increased TGF- β and IL-10, respectively. This may account for the role of IgA and TGF- β as well as IgG4 and IL-10 in mucosal immune responses to allergens in healthy individuals [18, 87].

An obvious decrease in IgE antibody levels and IgE-mediated skin sensitivity normally requires several years of SIT; however, most patients are already protected against bee stings at an early stage of bee venom SIT. The reason for this could be that the effector cells (mast cells, basophils and eosinophils) require T cell cytokines for

priming, survival and activity [88, 89], which cannot be sufficiently provided by suppressed Th2 and T_{Reg} cells (fig. 1). SIT efficiently modulates the mast cell and basophil activation thresholds and decreases IgE-mediated histamine release [90, 91]. In addition, IL-10 has been shown to reduce proinflammatory cytokine release from mast cells [92], downregulate eosinophil function and activity, and suppress IL-5 production by resting human Th0 and Th2 cells [93].

Since IL-13 and IL-4 have been shown to induce the upregulation of vascular adhesion molecule-1 (VCAM-1) expression on human endothelial cells [9, 10], suppression of Th2 cells may prevent the recruitment of inflammatory cells (eosinophils, macrophages and T cells) to the site of allergic inflammation (fig. 1). CD8+CD28-FOXP3+ T cells upregulate the inhibitory receptors, immunoglobulin-like transcripts (ILT)3 and ILT4 and downregulate costimulatory molecules, which results in the suppression of T cell activation. Furthermore, these cells can prevent the adhesion and transmigration of Th2 cells [51].

T Regulatory Cells in a Clinical Aspect

In humans, circumstantial evidence suggests that T_{Reg} cells play a major role in the inhibition of allergic disorders. Studies have shown lower levels of IL-10 in the bronchoalveolar lavage fluid of asthmatic patients than in healthy controls, and that T cells produce less IL-10 mRNA in asthmatic children than in healthy children [94, 95]. These findings indicate that a decrease in allergic reactions is associated with an increase in IL-10 production. Since T_{Reg} cells are a major source of IL-10, it is hypothesized that they play a role in the suppression of allergic Th2 responses in humans, which is supported by several human allergen SIT studies [18, 36, 96].

A recent report indicated the increased allergic inflammation seen after blocking CTLA-4, to be clearly associated with decreased TGF- β levels within the bronchoalveolar lavage fluid [97]. Furthermore, experimental tracheal eosinophilia was inhibited due to the induction of CD4+ T cells secreting TGF- β [98].

Currently, the relationship between different T_{Reg} cell populations with respect to their development and activation is not clear. However, numerous animal studies have shown that, *in vivo*, T_{Reg} cells can actively suppress the development of autoimmune and allergic responses, by suppression of both Th1 and Th2 responses. Mouse studies have shown protection from the development of aller-

gen-induced Th2 responses after the application of in vitro engineered allergen-specific T_{Reg} cells [99].

CD4+CD25+ T cells have been found to inhibit lethal graft versus host disease in rodents. In vitro, CD4+CD25+ T cells act antigen-nonspecifically; however, when these cells are isolated from naive mice and activated by allergenic APC they induced long-term tolerance to bone marrow grafts; protection of target bone marrow occurred simultaneously to rejection of third-party bone marrow, indicating CD4+CD25+ T cells to work antigen-specifically in vivo [100].

Tumor antigens are an important group of autoantigens and the depletion of T_{Reg} cells should result in an enhanced immune response to tumor vaccines. Several studies have demonstrated the induction of tumor immunity to be facilitated by the antibody-mediated depletion of CD25+ T cells [101, 102].

In pregnancy, maternal CD4+CD25+ T cells suppress allogenic responses against the fetus, in addition to autoimmune responses. To analyze in vivo existence of human T_{Reg} cells, lymphocyte populations in human lymph nodes have been investigated with emphasis on CD4+CD25+ T_{Reg} cells [103]. As found in T_{Reg} cells from peripheral blood, T_{Reg} cells from the lymph node are anergic and efficiently inhibit proliferation of other CD4+ and CD8+ lymphocytes in vitro [103].

Further clinical studies are required to demonstrate whether in vivo generation or adoptive transfer of T_{Reg} cells and/or their related suppressive cytokines may alter the progression of allergy and asthma. Small molecular weight compounds generating T_{Reg} cells or increasing their suppressive properties provide important targets not only for use in allergy and asthma, but in transplantation and autoimmunity as well.

Although suppression of an immune response may have a beneficial effect in the case of such hypersensitivity reactions, it may be harmful in the event of cancer, chronic infection or tissue remodeling [104–109]. Suppression of effector T cells could lead to the uncontrolled growth of potentially harmful target cells and therefore aggravate the disease. For this reason, care should be taken with the long-term induction of T_{Reg} cells by SIT.

Conclusion

The key mechanism in healthy immune responses to noninfectious, nonself antigens is peripheral T cell tolerance. This hypothesis is clinically well documented in allergy, transplantation, tumor and infection. There is

substantial and increasing evidence to support the role of T_{Reg} cells and/or immunosuppressive cytokines in mediating allergen SIT and healthy immune responses (fig. 1). Development of prophylactic vaccines to induce allergen-specific T_{Reg} cells should be considered in addition to the treatment of established allergy. Balancing Th2 responses with the aid of T_{Reg} cells has been shown to be an important mechanism in successful SIT. Furthermore, increased activity could be an adequate measure for the suppression of allograft rejection, graft versus host disease and autoimmunity. However, caution should be taken concerning the overactivation of T_{Reg} cells, since several studies show that they may be responsible for the chronicity of infections and tumor tolerance, and are not always a healthy response. In addition, the strong fibrogenic capacity of regulatory cytokine TGF- β may be responsible for the incorrect remodeling in the lungs [110].

Although difficult, it has been proven possible to grow, expand and clone T_{Reg} cell populations, in vitro, while preserving their suppressor function. Taking this into consideration, recent advances in the knowledge of peripheral tolerance mechanisms may lead to the development of a safer treatment of immune-mediated diseases in the future.

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