

## T REGULATORY CELLS IN ALLERGY

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The progressive understanding of the nature and mechanisms of T regulatory (Treg) cells in the last decade has changed the concept of immune tolerance, that is no longer considered as a mere lack of immune reactivity but as a finely regulated process that requires specific activity of cells, adhesion and secreted molecules. Tregs play a key role in maintenance of self-tolerance and induction of tolerance against ubiquitous innocuous non-self antigens, so preventing the onset of autoimmune diseases and allergies. This review will focus on the Treg response in allergy that is characterized by a down-regulation of allergen specific T cell proliferation and inhibition of both Th1 and Th2 cytokines production. Hence, Treg cells suppress allergen-specific Th1 and Th2 cell responses playing an important role in the physiological immune response to allergens. Further, Treg cells are able to suppress IgE production by B lymphocytes and directly or indirectly inhibit the activity of allergic inflammation effector cells, namely eosinophils, basophils and mastcells. Finally, increasing evidence suggests that Treg cells are also implicated in chronicity development of inflammatory diseases. This appears to happen through a fine interaction they entertain with resident tissue cells and has been particularly highlighted in the study of airways remodeling in asthma. The understanding of the mechanisms underlying allergen tolerance has brought new interest in the development of new allergy treatment, able to target Treg cells, both in allergy prevention and in the therapy of established allergy.

### Introduction

The development of adaptive immune responses is orchestrated by the activity of CD4 T cells, which play a critical role both in physiological and pathological processes, including allergic reactions. In the mature immune response, two main different phenotypes of Th cells, Th1 and Th2, have been identified on the bases of the cytokine pattern they secrete (1, 2). Th1 cells mainly produce IL-2, TNF $\alpha$ , IFN $\gamma$ , important for macrophage activation and clearance of intracellular pathogens. These cells play a pathogenetic role in the chronicity of autoimmune diseases, delayed type hypersensitivity and allograft rejection (3). Th2 cells secrete IL-4, IL-5 and IL-13, proved to be critical for IgE production, eosinophil recruitment and clearance of extracellular parasites. Thus, they are involved in allergic inflammation, both IgE mediated reactions and late phase eosinophils recruitment (4). Finally, the identification of IL-23 led to the definition of a new IL-23 responsive Th cells subset, namely Th17

cells, that produce several cytokines including IL-17, IL-22 and IL-21. This latter T cell subset appears involved in autoimmune diseases and plays a role in immune responses against extracellular bacteria and fungi (5). Formerly, the pathogenesis of autoimmune and allergic diseases has been explained as a dysregulation in the Th1/Th2 balance. However, this paradigm has been revised with the description of a new subset of CD4 T cells known as regulatory T (Treg) cells (6,7). These cells play a key role in maintenance of self-tolerance and induction of tolerance against ubiquitous innocuous non-self antigens (8). The progressive understanding of the nature and mechanisms of Treg cells in the last decade has changed the concept of immune tolerance, that is no longer considered as a mere lack of immune reactivity but as a finely regulated process that requires specific activity of cells, adhesion and secreted molecules (9,10).

Treg cells are further divided in two subsets exerting different phenotypes and mechanisms of action, namely

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naturally occurring CD4<sup>+</sup>CD25<sup>+</sup> FoxP3<sup>+</sup> Treg cells (nTreg) and inducible or adaptive IL-10 or TGF $\beta$ -secreting Treg cells known as Tr1 and Th3 respectively (11,12). Adaptive or inducible Treg cells originate from the thymus as single-positive CD4 cells. They eventually differentiate into CD25 and FoxP3 expressing Tregs (iTregs) following adequate antigenic stimulation in the presence of specialized immunoregulatory cytokines such as TGF- $\beta$ , IL-10, and IL-4 (11,12). Moreover, subsets of CD8<sup>+</sup> T cells (13),  $\gamma\delta$  T cells (14), CD4-CD8<sup>-</sup> T cells (15), IL-10 producing B cells (16), IL-10 producing dendritic cells (17) and IL-10 producing NK cells (18), as well as subsets of macrophages (19) have been attributed suppressive properties, eventually contributing to suppressive and regulatory events.

There is growing evidence of the role Treg cells, namely CD4<sup>+</sup>CD25<sup>+</sup> and Tr1 cells, play in regulating peripheral tolerance to allergens in experimental models (20).

Treg cells response is characterized by a down-regulation of allergen specific T cell proliferation and inhibition of both Th1 and Th2 cytokines production (21). Hence, Treg cells suppress allergen-specific Th1 and Th2 cell responses playing an important role in the physiological immune response to allergens (22). Further, Treg cells are able to suppress IgE production by B lymphocytes (23) and, directly or indirectly, inhibit the activity of allergic inflammation effector cells, namely eosinophils, basophils and mastcells (24). Finally, increasing evidence suggests that Treg cells are also implicated in chronicity development of infectious and other inflammatory diseases as well as in the induction of tumor tolerance (25). This appears to happen through a fine interaction they entertain with resident tissue cells and has been particularly highlighted in the study of airways remodeling in asthma (26).

The aforementioned functions appear largely mediated by IL-10 and TGF $\beta$ . For this reason peripheral adaptive Treg cells are thought to play a major role in the establishment and maintenance of allergen tolerance in healthy subjects whereas natural Treg cells appear mainly involved in the preservation of self-tolerance, protecting the organism from autoimmune aggressions.

Understanding the interactions between immunologic effector cells and T regulatory cells is crucial in order to identify new possible targets for the treatment of allergic diseases and is already clarifying how specific immunotherapy (SIT) is able to re-establish immunologic homeostasis and tolerance towards allergens (27).

The aim of this review is to outline the role of Treg cells in the regulation of allergic responses. They can act through five major ways: interaction with antigen presenting cells; inhibition of Th cell activity; modulation

of B cell antibody production; suppression of effector cells (mastcells, basophils and eosinophils); interaction with resident tissue cells. (Tab 1)

### *1. Interactions between Treg cells and antigen presenting cells (Tab 2)*

Dendritic cells (DCs) appear to have a crucial role in the induction of peripheral tolerance to allergens. Depending on the maturation stage and ontogenetic subset as well as on the microenvironment, different DCs exert tolerogenic functions. For instance, DCs in the lamina propria of the small intestine are able to induce the expression of Foxp3 in naive T cells in presence of TGF $\beta$  and the subset of DCs expressing CD103 are able to do so even in the absence of exogenous factors (28,29). This finding is crucial in understanding the onset of food allergen tolerance. Moreover, DCs found in tumor or chronic infection microenvironment were proved to be able to induce Treg cells hence favoring the onset of tumor tolerance and infection persistence, in the physiological attempt to limit tissue damage (30).

It has been observed that immature DCs induce peripheral tolerance through the differentiation of Treg cells, namely Tr1 cells, with subsequent inhibition of inflammatory reactions (31). In particular, antigen presentation promoted by immature IL-10 expressing DCs was found to induce Tr1 cells in the lung (32). Thus, DCs could have a key role in pulmonary immune responses to non-self antigens and, whether immunity or tolerance are established, asthma can be prevented or develops.

On the other hand, iTreg cells are able to suppress the activity of APCs. IL-10 down-regulates the expression of MCH class II and costimulatory molecules on monocytes/macrophages and dendritic cells. By limiting their antigen-presenting capacity, IL-10 further inhibits the generation of effector T cells, both Th1 and Th2 (33). Related to this observation, iTreg cells appear to modify both antigen-presenting cells and T cell responses (34) in allergic patients treated with specific immunotherapy (SIT), IL-10 is also responsible for the inhibition of DCs maturation and mediates a downregulation of inflammatory DCs, whereas it enhances the proliferation of IL-10 producing DCs, which further contribute to the suppressive effects of IL-10 (32).

The inhibitory function IL-10 exerts both on APCs and T effector cells has been related to the immunoregulatory effects of histamine through the Histamine Receptor (HR)2 pathway (35). In fact HR1, 3 and 4 found both on T cells and APCs exert proinflammatory activities such as increase antigen-presentation capacity and proinflammatory cytokines production. Differently, HR2 is a suppressive molecule that down-regulates antigen presentation and IL-12 production in maturing dendritic

cells as it enhances IL-10 production in both DCs and T cells (36). An increase in T cell susceptibility to TGF $\beta$  by histamine was also observed (37). Hence, histamine appears as an important enhancer of Treg cells suppressive capacity through HR2, representing an alternative regulatory mechanism of allergen-specific T cells.

Similarly, inhibition of APCs function is also induced by nTreg cells. Activated Tregs downregulate the expression of CD80 and CD86 on APCs and stimulate DCs to express the enzyme indoleamine 2,3-dioxygenase (IDO) (38). IDO enhances the conversion of the essential amino acid tryptophan to kynurenine, which is toxic to T cells neighboring the DCs (39). These APC-modifying pathways depend on the Treg expression of CTLA-4 which binds CD80 and CD86. In mice models, activated nTregs can also kill APCs including B cells through a cell to cell contact pathway, with upregulation of perforine and granzymes (40).

In conclusion, specific subsets of DCs are required to drive Treg cells differentiation. On the other hand, an important inflammatory downregulation process is exerted by Treg cells through the inhibition of effector T cells priming by DCs and by promoting the development of tolerogenic DCs.

## 2. Treg cells suppress effector Th cells (Tab 3)

Treg cells abolish allergen-induced proliferation of Th1 and Th2 cells, as well as their cytokine production (21) through multiple suppressor mechanisms. Both soluble and membrane-bound factors are implicated in the process, in particular IL-10, TGF $\beta$ , CTLA4, Program death receptor- (PD)1 and HR2, all exerting synergistic effects in immunologic suppression (22). Additionally, it has been demonstrated that nTreg suppress Th17-mediated lung inflammation, regulating neutrophilic inflammation (41).

IL-10 and TGF $\beta$  inhibitory mechanisms have been closely related to allergen tolerance. Indeed, peripheral blood T cells isolated from allergic patients treated with SIT were able to suppress allergen-specific cell proliferation in vitro. This response appeared strongly dependent on IL-10 and TGF $\beta$  as neutralizing antibodies directed against these cytokines abrogated T cell suppression (34).

IL-10 inhibits effector T cells proliferation blocking CD2, CD28 and inducible costimulator (ICOS) costimulatory pathways (42). In particular, upon IL-10 binding to its receptor, the CD2 tyrosine phosphatase, which contains a SHP-1 domain, rapidly binds and dephosphorylates CD28 and ICOS. As a result, the binding of phosphatidylinositol 3-kinase to either costimulatory molecule no longer occurs and the signaling transduction cascade is inhibited. Moreover, as forementioned, IL-10 broadly suppress T cells priming downregulating APC

activity.

The suppressive effects exerted by TGF $\beta$  on Th cells are still to be fully elucidated. However, TGF $\beta$  is known to inhibit activated Th1, Th2 and Th17 cells, it is able to induce naïve CD4+CD25- T cell conversion into CD4+CD25+ T cells through the induction of Foxp3 and, further, its signaling is required for in vivo expansion and suppressive capacity of these cells (43).

The inhibition of Th2 development and proliferation minimizes the production IL-4, IL-5, IL-9 and IL-13, which are essential for the onset and maintenance of allergic reactions. These cytokines act as chemoattractants for Th2 cells itself as well as other effector cells such as eosinophils, basophils and mast cells. Thus, a reduction of Th2 cytokine production prevents the amplification of a Th2 reaction and the further recruitment of effector cells (44). Moreover, Th2 cytokines are also responsible for IgE production and mucous production which are hence inhibited. Additionally, Treg cells were observed to exert a suppressive activity on effector Th1 cells, thus reducing keratinocytes and bronchial epithelial cells apoptosis (45,46), preventing tissue damage.

In conclusion, Treg cells are able to directly and indirectly inhibit immunogenic functions of effector Th cells. By doing so, they suppress the orchestration of various immune responses, preventing the onset of both autoimmunity and allergy. However, the downregulation of Th cells eventually leads to disease spreading as observed in tumor immune responses or chronic infections.

## 3. Treg cells suppress B cells production of allergen-specific IgE and induce IgG4 and IgA (Tab 4)

It has been demonstrated that T reg cells can negatively regulate T cell-dependent antibody production by B cells in mice (47). Later, IL-10 was identified as a core mediator able to regulate antigen specific IgE and IgG4 synthesis (23). Indeed, IL-10 exerts two major effects on B cells: it decreases  $\epsilon$ -transcript expression and therefore IgE production induced by IL-4, when early added to PBMCs culture while enhancing g4 transcript expression and IgG4 production (48). Hence, Tr1 cells not only mediate peripheral T cell tolerance, but also regulate specific isotype formation redirecting specific IgE mediated responses to predominantly IgG4 mediated ones.

In sera of healthy individuals, antibody response to allergens, such as Der p 1, is characterized by specific IgA and IgG4 production, small amounts of IgG1 and almost undetectable IgEs (49). A similar pattern with significant increase in specific IgA, IgG1 and IgG4 was observed after SIT in allergic patients (49,50). In particular, the increase of specific IgA and IgG4 in serum was associated to an

Table 1

| <b>T REGULATORY CELLS CONTROL OF ALLERGEN-SPECIFIC IMMUNE RESPONSES</b>                                                                                                                                                                                                                                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ol style="list-style-type: none"> <li>1) Suppression of antigen presenting cells</li> <li>2) Suppression mechanism of Th2 and Th1</li> <li>3) Regulatory function on B cells and allergen-specific antibody production</li> <li>4) Suppression of mast cells, basophils and eosinophils</li> <li>5) Interaction with resident tissue cells and remodelling</li> </ol> |

Table 2

| <b>INTERACTIONS BETWEEN T REGULATORY CELLS AND APCs</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• IL-10 downregulates the expression of MHC class II and that of costimulatory molecules on APCs</li> <li>• IL-10 downregulates s differentiation and activation of inflammatory dendritic cells (DC)</li> <li>• IL-10 enhances the differentiation of IL-10 producing DCs</li> <li>• nTreg cells, through the interaction between CTLA4 and CD80 and CD86, up-regulate IDO and induce production of kynurenine by DCs, toxic for T cells</li> <li>• nTreg cells can induce APCs apoptosis through cell to cell contact (in mice).</li> </ul> |

Table 3

| <b>T REGULATORY CELLS SUPPRESSION OF EFFECTOR TH CELLS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• IL-10 inhibits Th cells proliferation blocking CD8, CD28 and ICOS costimulatory pathways</li> <li>• IL-10 suppresses Th cells priming down-regulating APCs activity</li> <li>• TGF<math>\beta</math> inhibits activated Th cells and induces Foxp3 expression in peripheral T cells</li> <li>• Neutralizing antibodies against IL-10 and TGF<math>\beta</math> abrogate T cell suppression</li> <li>• nTreg suppress Th17-mediated lung inflammation</li> </ul> |

increase in TGF $\beta$  and IL-10 production from allergen-specific Treg cells, respectively (49,51). These findings have been related to the onset of peripheral mucosal immune responses to allergens in healthy individual (23).

Based on these findings the determination of IgE/IgG4 ratio and the observation of its decrease during SIT has been proposed as a parameter that reflects the change from allergen specific Th2 to Treg cells predominance (52).

It is worth mentioning that IgG4 presents a non-inflammatory role that depends on their unique molecular structure (52). Indeed, they have low affinity for certain Fc $\gamma$  receptors

and do not activate the complement. Moreover, IgG4 can exchange Fab arms among them, with subsequent formation of bispecific antibodies (54). IgG4 hence are able to inhibit immune complexes formation, presenting unique anti-inflammatory properties.

The understanding of the establishment of mucosal tolerance or immunologic ignorance through the upregulation of mucosal IgA still remains to be clarified. While neither IL-10 secreting Tr1 nor CD4<sup>+</sup> CD25<sup>+</sup> Treg cells were shown to directly influence IgA production, it has been demonstrated that IgA synthesis is strongly

Table 4

| T REGULATORY CELLS INTERACTIONS WITH B CELLS                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>• IL-10 decreases <math>\epsilon</math>-transcript expression in B cells while enhancing <math>\gamma 4</math> transcript</li><li>• IL-10 and TGF<math>\beta</math> might contribute to upregulation of mucosal IgA</li><li>• IgG4 antibodies present anti-inflammatory properties and sIgA are protective for the development of allergy in children</li></ul> |

Table 5

| T REGULATORY CELLS SUPPRESSION OF EFFECTOR CELLS                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>• Treg cells modulate the threshold for mast cells and basophils activation</li><li>• IL-10 reduces proinflammatory cytokines release from mast cells</li><li>• IL-10 interferes with mast cells survival and proliferation in peripheral tissues</li><li>• Tregs directly inhibit IgE-dependent mast cells degranulation via OX40-OX40L interaction</li><li>• IL-10 directly downregulates eosinophils activation and suppresses IL-5 production</li></ul> |

Table 6

| T REGULATORY CELLS INTERACTION WITH RESIDENT TISSUE CELLS                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>• TGF<math>\beta</math> promotes fibroblast and myofibroblast function and production of extracellular matrix proteins</li><li>• TGF<math>\beta</math> dependent fibroblasts activation favours the thickening of subepithelial lamina reticularis in bronchial asthma</li><li>• TGF<math>\beta</math> promotes recruitment of inflammatory cells in the airways</li><li>• Anti- TGF<math>\beta</math> treatment in mice significantly reduced airway remodelling</li></ul> |

dependent on the innate immune system, specifically on Toll-like receptor (TLR)7 and TLR9 activation of B cells (55). In a mouse model of food allergy, it was observed that antigen-specific secretory IgA antibodies in the gut were significantly decreased suggesting a role of IgA in the establishment of peripheral tolerance to foods. In Payer's patches CD3+ cells were involved in the enhancement of IgA production through the secretion of IL-10 and TGF $\beta$ , whereas low production of IL-10 favored the onset of food allergy (56). It has been observed that allergen-specific secretory IgA has a protective role for the development of allergy symptoms in sensitized children throughout the first two years of life, thus suggesting a possible preventing role of mucosal IgA against the development of allergy (57).

In conclusion, the described findings suggest that IL-10 strongly suppresses both total and allergen specific IgE production while enhancing IgG4 and likely IgA production (20,23).

4. *Treg cells suppress mastcells, basophils and eosinophils (Tab 5)*

Treg cells seem to directly and indirectly downregulate effector cells in allergy inflammation both in early and in late phases (24). Indeed, mast cells, basophils and eosinophils require T-cell cytokines for priming, survival and activity (58), which are not efficiently provided by Tregs suppressed Th2 cells.

During the early phase, Treg cells modulate the thresholds for mastcell and basophil activation,

hence decreasing IgE mediated histamine release (59, 60). In addition, through IL-10, Treg cells reduce proinflammatory cytokine release from mast cells (61). IL-10 was also found to be an homeostatic regulator for mast cells (62) in peripheral tissues, where it is able to regulate their number and functions affecting their survival and proliferation. Moreover, although demonstrated on a model of myocarditis, IL-10 gene transfer resulted in a reduction of mast cells density and growth, local histamine concentration and overall prevention of mast cell degranulation (63).

As previously mentioned, histamine released by allergy effector cells is also able to promote peripheral tolerance induced by Treg cells through the interaction with HR2 (64). This interaction indeed results in the enhancement of TGF $\beta$  suppressive effects on Th2 cells (37) and favors the production of IL-10 by DCs and Th2 cells (36, 65).

Recently, allergen-specific basophil suppression has been associated with clinical tolerance in patients with milk allergy. Basophils from heath denatured milk-tolerant subjects were significantly less responsive to milk allergenic stimulation than basophils from allergic reactive individuals (66). The mechanisms underlying this specific outcome still remain to be defined although it was widely demonstrated that immunoregulation established after SIT is characterized by a decrease in IgE-mediated histamine release and histamine-induced tolerogenic effects through HR2 (67).

Furthermore, it was recently demonstrated that Treg cells can influence immediate hypersensitivity response of mast cells not only through secreted molecules but also by cell to cell contact. Gri et al demonstrated that T reg cells can directly inhibit the Fc $\epsilon$ RI-dependent mast cell degranulation via OX40-OX40L interaction between Treg cells and mast cells (68). In the same experiment the *in vivo* depletion of Treg cells was related to anaphylactic response enhancement. Thus, not only Treg cell direct interaction with mast cells controls their degranulation, but the loss of this interaction might contribute to the severity of allergic responses.

Treg cells also appear critical to the inhibition of late phase allergic reactions that typically involve the recruitment and activation of eosinophils and T effector cells. Indeed, IL-10 downregulates eosinophil function and activity and suppresses IL-5 production by human resting Th0 and Th2 cells (69,70). Related to these observations, during birch pollen SIT, a reduction in serum eosinophil cationic protein and chemotactic factors for eosinophils and neutrophils correlated with a decreased in bronchial hyperreactivity and clinical improvement (71). The same authors observed the ability of SIT to inhibit seasonal increase in eosinophil priming (72).

### 5. Treg cells interaction with resident tissue cells and their role in remodelling (Tab 6)

Tregs may not always be responsible for beneficial effects, in fact, several studies have shown that they could favor chronicity of infections and tumor tolerance (25) and in allergic asthma may favor airway remodeling (73).

In fact, Treg cytokines, TGF $\beta$  in particular, are potent regulators of fibroblast and myofibroblast function and control the production of several extracellular matrix protein, including collagens, proteoglycans and tenascin (74).

In allergic asthma, airway remodeling includes deposition of several extracellular matrix proteins in the basement membrane and bronchial mucosa, increase in airway smooth muscle mass, goblet cell hyperplasia and new blood vessel formation (73).

The thickening of subepithelial lamina reticularis in bronchial asthma has been related to an increase in fibroblasts in correlation to TGF $\beta$  expression (75). Moreover, TGF $\beta$  stimulates recruitment and proliferation of other cell types including eosinophils, macrophages, mast cells, neutrophils and epithelial cells (76). Therapeutic treatment of mice with anti-TGF $\beta$  antibody significantly reduced peribronchiolar extracellular matrix deposition, airway smooth muscle proliferation and mucus production in the lung (77).

There is clear evidence that lamina reticularis thickening begins very early, even at the time of first diagnosis (78), suggesting that a barrier between activated epithelium or mucosal allergens and inner tissues (i.e. immune system cells) may contribute to downregulate allergen-induced inflammatory responses.

Taken together, increased subepithelial lamina reticularis thickness and mucosal IgA production against allergens could be promoted by Treg cells in the attempt to decrease the amount of allergen exposure and favor immunologic ignorance (79).

Remodelling in asthma hence appears both as an attempt to limit tissues contact with allergens and as the consequence of excessive repair processes after repeated airway injury to which Treg cells contribute. However, this results in permanent bronchial wall thickening and airway caliber reduction eventually leading to progressive loss of lung function.

## CONCLUSION

It has been widely demonstrated that Treg cells are involved in the establishment of healthy immune responses towards self antigens and noninfectious non-self antigens, preventing autoimmunity and allergy. As described above, the study of peripheral immune tolerance

in healthy individuals and the mechanisms underlying the establishment of allergen tolerance after SIT have led to the acknowledgment that inducible Treg cells and their cytokines appear as master regulators of allergen specific responses.

The understanding of the mechanisms underlying allergen tolerance has brought new interest in the development of new allergy treatment, able to target Treg cells, both in allergy prevention and in the therapy of established allergy. The identification of new adjuvants, that selectively stimulate Treg cells, might eventually be added to SIT vaccines in order to increase and further accelerate tolerance restoration. Early approaches might also be appointed in order to prevent the onset of allergy, even before the occurrence of sensitization. Finally, allergic diseases can serve as a model to understand interactions between Treg cells and effector cells. This will eventually lead to further advance in understanding and treatment of autoimmunity, tumor cell growth, chronic infections, graft-vs-host disease and parasite survival and clearance.

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