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Mechanism of Regulatory T Cells During Allergen-Specific Immunotherapy: from the Past to Future

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Abstract

Allergen-specific subcutaneous immunotherapy (SCIT) has been effective used for the treatment choice for allergic rhinitis and asthma. Although it is clear that SCIT reduces the symptoms of allergic disease and can alter the natural course of allergic disease, however, the basic immunologic mechanisms involved in the amelioration of the allergic symptoms are still unknown. Recent studies suggest that the induction of $CD4^+CD25^+$ $Foxp3^+$ Treg cells and IL-10-secreting type 1 Treg cells might be associated with suppression of allergic responses in patients after successful SIT. IL-10 and TGF-β from $CD4^+$ Treg cells have proven essential roles in the maintenance of immunological self-tolerance in the $CD4^+$ T cell compartment and inhibit Th2 cytokines releasing and differentiation. Evidences suggest that the shift from Th2 to Th1 induced by SIT might be mediated by induction of the apoptosis in mite allergen-responder $CD4^+IL\text{-}4^+$ Th2 cells in asthmatic children. We noted a significant increase in $CD8^+Foxp3^+$ Treg cells population expressing intracellular IL-10 and granzyme B can be generated by continuous allergen stimulation following six months of SCIT. We further demonstrated that $CD8^+$ Treg cells, but not CD4+ Treg cells, can enhance $CD4^+CD45ROhi^+$ cell apoptosis. TLR2 agonist stimulates endogenous $CD4^+CD25hi^+$ Treg cells to produce IL-10, and may support another mechanism for the treatment of allergic disease. Future perspectives are required to clarify the precise Treg subsets involved SIT and develop clinical efficacious and safer allergen vaccines by utilizing the Treg cells functions.

Keywords: Immunotherapy; Allergen-specific subcutaneous immunotherapy (SCIT); $CD4^+CD25^+$ Foxp3+ Treg Cells; TGF-B; GATA-3; $CD8^+CD25^+Foxp3^+$; $CD4^+CD25hi^+$ Treg Cells

Abbreviations: Der p: *Dermatophagoides pteronyssinus*; Treg: Regulatory T; SCIT: Subcutaneous Immunotherapy; SIT: Specific Immunotherapy; SLIT: Sublingual Immunotherapy

Introduction

Since the first trial reported by Noon about a century ago [1], allergen-specific immunotherapy (SIT) by repeated subcutaneous administration of increased doses of allergen extracts has a long-lasting effect on immunologic tolerance to common environmental allergens [2-4]. Allergen-specific subcutaneous immunotherapy (SCIT) has been effectively used for the treatment choice for allergic rhinitis and asthma [5,6]. It is clear that SCIT reduces the symptoms of allergic disease and can alter the natural course of allergic disease, however, the basic immunologic mechanisms involved in the amelioration of the allergic symptoms are becoming better understanding in recent years.

For decades it has been postulated that allergen-specific IgG presents in serum and secretions may block allergen before it interacts with cell-bound IgE. This blocking activity is likely to have some relevance in the protective effect of venom SIT but is unlikely to be a major mechanism with inhalant allergens [7]. Several changes in cytokines profiles of T cells, such as increased production of IFN-γ and a reduction of IL-4 in atopic patients undergoing SIT, suggest that a shift in the balance between the lymphocyte responses from Th2 to Th1 is involved in the SIT mechanism [2-4]. However, some studies failed to show any changes in Th1 cytokine production by SIT [8]. The Th1 and Th2 balance thesis has been abandoned after the description of the regulatory T cells (Treg), recent accumulating evidences suggest that the induction of $CD4^+$ regulatory T cells might be associated with suppression of allergic responses in patients after successful SIT [9-11].

Functional Treg cells in asthma

Subsets of Treg cells with distinct phenotypes have received particular attention: the naturally thymus-selected $CD4^+CD25^+Foxp3^+$ Treg cells [12] and the inducible type 1 IL-10 secreting Treg cells (Tr1 cells) and TGF β- secreting Th3 cells [13], which are generated in the periphery under various tolerogenic conditions. Regulatory T cells (Treg) are clearly pivotal for maintenance of immune self-tolerance, including unresponsiveness of T cells to exogenous allergen or active peripheral tolerance induction [12-14]. Various evidences revealed Treg cells play important roles in the control of autoimmune diseases, allergic disorders, infections and cancer development [15-17].

$CD4^+CD25hi^+$ regulatory T cells was a minor fraction (approximately 10%) of $CD4^+$ T cells that play a critical role in the maintenance of self-tolerance during allergy. $CD4^+CD25^+$ T cells have been shown to inhibit the development of airway eosinophilia and CD4+CD25+ T cells could suppress immune responses through direct cell-cell contact in a process that is dependent on signaling via secretion of TGF-β and IL-10 [18]. Treg cells modulate allergen-specific antibody production, suppress IgE production and directly or indirectly suppress effector cells of allergic inflammation such as mast cells, eosinophils

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and basophils [19,20]. Treg cells also down-regulate the expression of CD80/CD86 on dendritic cells and inhibiting the pro-inflammatory effects [21,22].

Loss of Treg cells function appears to be a critical factor in the pathogenesis of human allergic asthma. Cumulative evidences show defective immunoregulation in $CD4^+$ regulatory T cells (Treg) function to control allergic inflammation in asthmatic subjects [11,23]. Evidence from pediatric asthmatic subjects demonstrated $CD4^+CD25hi^+$ Treg cells are decreased in the bronchoalveolar lavage fluid and fail to inhibit pulmonary Th2 responses, suggesting the functional defective recruitment of Treg cells to the site of airway inflammation [24]. Attention has been focused on defects of natural occurring $CD4^+CD25^+$ Treg cells to regulate inflammatory response in asthmatic subjects, however, the adaptive regulatory T (Tr1) cells and $CD8^+$ regulatory T cells, which secrete the immunosuppressive cytokines, may also play cardinal role to maintain immune tolerance with allergen in asthma [25-27]. The identification and isolation of highly purified, functional Tregs can be challenging and time-consuming for cutting-edge Treg research. The present used conventional Treg markers, such as CD25 and CTLA-4, are not fully specific to represent inducible Tregs, such as TGF β- secreting Th3 and Tr1 cells. Although that, further studies are needed to understand all of the signals that differentially affect Th2 and T regulatory cells development and the relationship of tolerance to the pathogenesis of allergic disease and asthma.

Conventional $CD4^+$ Treg cells during SIT

Allergen specific immunotherapy (SIT), which induces the generation of Treg cells to maintain allergen tolerance, has emerged as the most reasonable approach in the management of allergic disorders. Recent studies suggest that the induction of CD4+CD25+ Foxp3+ Treg cells and IL-10-secreting type 1 Treg cells might be associated with suppression of allergic responses in patients after successful SIT [2-4]. SIT improved the symptoms of asthma and decreased airway inflammation by the induction of $CD4^+CD25^+$ regulatory T (Treg) cells with anti-inflammatory cytokines such as IL-10 and TGF-β [28].

Evidences suggest IL-10 and TGF-β have proven essential roles in the maintenance of immunological self-tolerance in the $CD4^+$ T cell compartment during SIT [29]. Peripheral T cell tolerance after SIT is characterized by decreased Th2 cytokine release and suppressed antigen-driven proliferative T cell responses in an IL-10-dependent manner [30]. The mechanism of action by IL-10 from Treg cells during IT was observed including, suppresses allergen-specific IgE, induces allergen-specific IgG4 and blocks CD28-costimulatory molecule signaling pathway of antigen presenting cells [10,19-22,29]. In addition, TGF-β induces the expression of Foxp3, which promotes the induction of Treg cells with potent regulatory property [31-33]. It also inhibits the differentiation of Th2 cells by inhibiting the expression of transcription factors GATA-3 [34].

Asthma is characterized by chronic airway inflammation with several increased inflammatory cytokines. The transcription factor NF-κB subunits, p65 and p50, play an important role in immune and inflammatory responses. We further noted that *Dermatophagoides pteronyssinus* (Der p) SIT could induce anti-inflammatory cytokines, IL-10, TGF-β and sCD14, correlated with improved pulmonary function by inhibiting nuclear NF-κB/p65 expression. The finding of a correlation between improved lung function and the various anti-inflammatory cytokines raises interesting questions about whether strategies that can achieve a higher level of Treg cells with IL-10 or TGF-β during SIT might be more effective therapy for asthma [11].

Emerging roles of $CD8^+$ Treg cells during SIT

While the majority of research is focus on $CD4^+$ Treg function, less known about the role of $CD8^+$ Treg cells during asthma. $CD8^+$ Treg cells with regulatory function expressing transcription factor Foxp3 and Involvement of $CD8^+$ Tregs in maintaining self-tolerance has recently been identified [35-37]. Human $CD8^+$ Treg cells are implicated in various infectious diseases [38,39] and autoimmune disorders [40,41].

With numbers of $CD8^+$ Tregs cells are relatively small in peripheral blood, $CD8^+CD25^+Foxp3^+$ T cells can be generated by continuous antigen stimulation and T cell receptor stimulation [42,43]. $CD8^+$ Tregs cells can suppress cellular proliferation of $CD4^+$ naïve and effector T cells via cell–cell contact lysis or soluble factors like IL-10 and TGF-β [44-46]. Systemic immunization with allergen in mice induces $CD8^+$ Treg cells that can inhibit the development of allergic diarrhea, suggesting $CD8^+$ Treg cells may play a pivotal role in limiting allergic disease [47]. Der p SIT by repeated antigen stimulation may augment $CD8^+$ Terg population and amplify the mechanism of immune tolerance. We noted a significant increase in $CD8^+Foxp3^+$ Treg cells population expressing intracellular IL-10 and granzyme B following 6 months of SIT [27].

Functional $CD8^+$ Treg cells induced Th2 apoptosis during SIT

Apoptosis, a specific morphological feature of activation-induced cell death, can maintain T-lymphocytes homeostasis [48]. In allergic asthma, the over-activation of lymphocytes and eosinophils were found to accumulate in the airway inflammation tissues, partly because of their prolonged survival [49].

Apoptosis of allergen-specific Th2 cells during SIT represents a unique down-regulatory mechanism that prevents the continuous activation of Th2 immune responses by allergen. Some evidence suggested allergen induced apoptosis of T lymphocytes in allergen specific IT treated atopic patients [50]. Guerra et al. reported that peripheral blood mononuclear cells (PBMC) culture of 48 h with grass allergen induced apoptosis of Th2 cells from grass IT treated patients [51]. Our previous results indicated that the shift from Th2 to Th1 induced by allergen-specific IT might be mediated by induction of the apoptosis in mite allergen-responder $CD4^+IL\text{-}4^+$ Th2 cells in asthmatic children [52]. We further demonstrated that $CD8^+$ Treg cells, but not $CD4^+$ Treg cells, can enhance $CD4^+CD45ROhi^+$ cell apoptosis. Cell contact with $CD8^+$ Treg cells expressing increased granzyme B may induce cell apoptosis of $CD4^+CD45RO^+$ memory T cells during SIT [27].

Sublingual allergen-specific IT and Treg cells

The clinical efficacy of sublingual specific allergen immunotherapy (SLIT) as an alternative to subcutaneous immunotherapy has been confirmed in evidence practice [53]. Elevated levels of recent evidences suggest SLIT induces IL-10-producing T regulatory cells to maintain allergen- specific T-cell tolerance and immune deviation [54-56]. The mechanisms of SLIT to induction of Treg cells are not fully understood, the mucosal dendritic cells play a potential role in the induction of allergen-specific tolerance and may prime $Foxp3^+$ Treg cells to produce IL-10, TGF–β [57-59].

Toll like receptors enhance Treg cells may benefit in SIT

To further increase efficacy of SIT, a novel therapeutic strategy is to

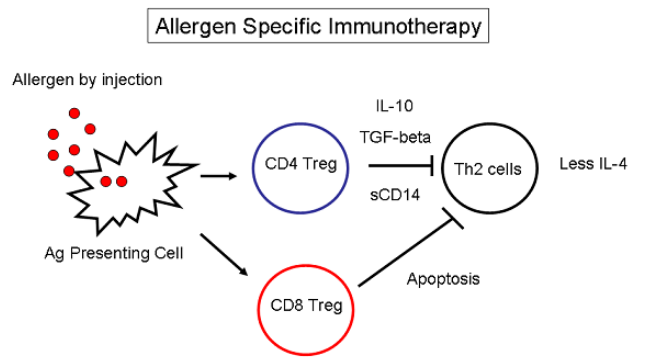

Figure 1: Brief summary of the mechanism of Treg cells to maintain immune tolerance during immunotherapy. Our results indicated that Th2 cells anergy and the relationship of immune tolerance during IT might be mediated by induction of $CD4^+$ Treg cells and $CD8^+$ Treg cells with anti-inflammatory cytokine that produced soluble CD14, IL-10, and TGF-β. $CD8^+CD25^+$ Tregs, but not $CD4^+CD25^+$ Tregs, directly induced allergen induced CD4+CD45ROhi+ cells apoptosis.

develop combined adjuvant vaccine with Toll like receptors (TLR) via promoting expansion and function of Treg cells. TLRs, when responding to microbial signals, may have an important role in the development of allergy [60]. A number of future forms of immunotherapy may provide better alternatives to the currently available SCIT or SLIT, including combination of conventional SCIT with CpG (a synthetic TLR 9 ligand) [61,62] and Pam3CSK4 (a synthetic TLR receptor 2 ligand) [27,63].

TLR2 agonist stimulate endogenous $CD4^+CD25hi^+$ Treg cells to produce IL-10, and may support another mechanism for the treatment of allergic disease [64]. It has been demonstrated that TLR2 synthetic agonist Pam3CSK4 has therapeutic potential to decrease mite allergen-induced Th2 immune response and thus may be useful as adjuvant in immunotherapy for allergic disease [63,65]. Co-stimulation of PBMCs with Pam3CSK4 and Der p 2 expanded the $CD8^+CD25^+Foxp3^+$ Treg population and inhibited Der p 2-induced IL-4 production may benefit in SIT [27].

Brief Summary of Treg cells during SIT

Functional $CD4^+$ Treg cells play important roles in reducing Th2-mediated allergic inflammation and modulate allergen induced tolerance during SIT. However, the interaction between the two subsets of $CD4^+$ and $CD8^+$ Treg cells that protect against allergy remains unclear. Th2 cells anergy and the relationship of immune tolerance during SIT might be mediated by induction of $CD4^+$ Treg cells and $CD8^+$ Treg cells with anti-inflammatory cytokine. $CD8^+Foxp3^+$ Treg cells can induce apoptosis of Der p-2 induced $CD4^+CD45ROhi^+$ cells and suppress $CD4^+$ T cells proliferation by cell-contact inhibition may benefit the immune tolerance during SIT (as summary in Figure 1). Future perspectives are required to clarify the precise Treg subsets involved SIT and develop clinical efficacious and safer allergen vaccines by utilizing the Treg cells functions.

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