Regulatory T Cells in Asthma and Airway Hyperresponsiveness

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Keywords: Treg; Asthma; Aging; Gender

Introduction

Regulatory T cells, or Tregs, have been shown to play a major role in reducing Th2 cell proliferation, potentially reducing (often significantly) airway-associated inflammation seen in airway diseases, such as asthma. These cells are characterized as a sub-population of T cells that maintain peripheral tolerance through a variety of biological mechanisms. Although Treg make up only 5-10% of peripheral CD4+ T cells, these cells are nonetheless very potent suppressors of the inflammation, airway hyperresponsiveness, and airway remodeling. This review will discuss the history of Treg, the role Tregs play in the reduction of asthma and lung inflammation, and age- and gender-associated differences in Treg.

Regulatory T Cells

In the late 1960s it was noted that certain CD4+ T cells in normal mice exhibited suppression against autoimmunity [1]. In 1971 Gershon and Kondo [2] noted that the transfer of splenocytes from tolerized but otherwise normal mice induced tolerance in athymic mice. The following year, these cells were termed “suppressor T cells” by Gershon et al. [3]. As the technology of that era did not allow for phenotypic analysis due to a lack of an identifiable marker for these then-term supressor cells, these findings were not explored. Nearly a quarter of a century later Sakaguchi’s group noted that a distinct population of CD4+ T cells that expressed the alpha chain of the IL-2 receptor (CD25) also prevented autoimmunity [4]. Not long after, Sakaguchi’s lab and Shevach’s group independently demonstrated that CD4+CD25+ T cells, anergic upon stimulation, were able to suppress IL-2 production as well as cellular proliferation of activated CD4+ T cells in vitro [5-6] in a cell-to-cell contact-dependent manner. As a result, CD25 became a reliable and widely-used surface marker of these suppressor cells. In the ensuing decades these cells became known as regulatory T cells, or Tregs.

The high-affinity IL-2 receptor, CD25, has been widely used as a surface marker for the identification of Tregs. However, while Treg express this surface marker, so do recently-activated T cells. A more definitive marker for Tregs was needed to distinguish these cells from recently-activated T cells. As early as 1982 immune dysregulation polyendocrinopathy enteropathy x-linked syndrome, or IPEX, was described in humans [7]. This disease, which manifests itself as a severe, multisystem autoimmune and inflammatory disease, generally arises during prenatal stages. A similar disease in mice, Scurfy, was described in 1991 [8]. Both conditions are due to a deficiency in the gene expression of a transcription factor, known as forkhead box protein 3, or Foxp3 [9-11]. In 2001 Schubert demonstrated that this transcription factor Foxp3 and differentiates into an iTreg. Initially it was thought that iTregs were functionally and phenotypically identical to nTregs. However, it has recently been shown that the transfer of nTregs into Foxp3-deficient mice increases survival, indicating functional differences between natural and peripherally-induced Tregs. These cells differ in other ways. While nTregs are strongly biased towards autoreactive TCR-specifications, express Foxp3 constitutively [27,28], and require TNF-a signaling for in vivo function, inducible Tregs do not [29]. Other populations of Treg have been identified in recent years, including CD8+ suppressor cells [30], IL-10-producing Treg (known as ‘Tr1’ cells) [31], and transforming growth factor-β-producing (or ‘TGF-β-producing’) Treg [32]. Although not classified as a “regulatory cell” there are other cell populations that can exhibit suppressive and/or regulatory functions, such as dendritic cells [33], gamma delta T cells [34], NK cells [35], and CD4-CD8- T cells [36-40].

Regulatory T Cells and Asthma

Asthma is a chronic respiratory disease characterized by recurrent attacks of impaired breathing of differing intensities and results from an inappropriate response to otherwise normally harmless stimuli. Characterized by wheezing, chest tightness, and dyspnea, one of the hallmarks of asthma is reversible airway narrowing and/or airway hyperresponsiveness (AHR) to bronchoconstrictor stimuli [41,42]. Asthma presents itself in two separate stages. The first (acute stage, or early-phase) response occurs within seconds to minutes following exposure to an allergen. Histamine is released which leads to the degradation of mast cells followed by cytokine, leukotrienes, and prostaglandin production. The sequence of events leading to the development of immediate hypersensitivity involves the production of Treg-phenotype [14,15]. The nuclear protein Foxp3 soon emerged as the most reliable marker for Treg. Although Treg exhibit anergy in vitro, these cells rapidly proliferate upon encountering a cognate ligand [16-19] or upon adoptive transfer into lymphopenic mice in vivo [16,20]; antigen-specific Treg will certainly proliferate in vivo [18,21].

Since the re-discovery of these cells, a number of subpopulations of Treg have been identified. Natural Treg (or nTreg) are CD4+Foxp3+ cells that originate in the thymus [22] during ontogeny and enter the periphery as fully-functional Treg. In the thymus, the Treg repertoire is thought to be shaped largely in the medulla, where the bulk of Foxp3+ cells are found (few Foxp3+ cells are found in the cortex [23]). However, it has been shown that in mice that express MHCII in the cortex exclusively still are able to develop Treg, indicating that Treg commitment can also take place in the cortex [24]. A second group of Treg known as adaptive, or induced Treg (iTreg) acquire Foxp3 in the periphery [25]. In this case a naïve (CD4+CD25−) T cell acquires the transcription factor Foxp3 and differentiates into an iTreg. Initially it was thought that iTregs were functionally and phenotypically identical to nTregs. However, it has recently been shown that while the transfer of nTreg into Foxp3-deficient mice increases survival, iTreg (generated in-vitro) fail to do so [26], indicating functional differences between natural and peripherally-induced Treg. These cells differ in other ways. While nTreg are strongly biased towards autoreactive TCR-specifications, express Foxp3 constitutively [27,28], and require TNF-a signaling for in vivo function, inducible Treg do not [29]. Other populations of Treg have been identified in recent years, including CD8+ suppressor cells [30], IL-10-producing Treg (known as ‘Tr1’ cells) [31], and transforming growth factor-β-producing (or ‘TGF-β-producing’) Treg [32]. Although not classified as a “regulatory cell” there are other cell populations that can exhibit suppressive and/or regulatory functions, such as dendritic cells [33], gamma delta T cells [34], NK cells [35], and CD4-CD8- T cells [36-40].

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Received August 29, 2011; Accepted October 03, 2011; Published November 14, 2011


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of immunoglobulin E (IgE) antibodies in response to the allergen, followed by the production and binding of specific IgE antibodies [43] and high-affinity FceRI receptors on pulmonary sub-mucosal mast cells [44]. Mast cell activation leads to a multitude of signaling pathways which in turn cause immediate hypersensitivity reactions. When degranulated, mast cells stimulate the release of inflammatory mediators (e.g. histamine) that increase mucus secretion and tissue permeability and an increased contraction of airway smooth muscle tissue [45]. Although antigen-specific IgE plays a major role in the early phase, particularly in bronchoconstriction, the main role of IgE is immediate hypersensitivity through IgE binding to high-affinity IgE (FccRI) or low-affinity (FccRII) receptors on a number of cells, including mast cells [46].

The second stage is termed the late-phase response and involves an inflammatory cascade of macrophages and leukocytes (T cells, lymphocytes, eosinophils, and neutrophils) following the release of the above inflammatory cascade (leukotrienes, prostaglandins, and cytokines as well as chemokines, eosinophil chemoattractant factors, adhesion molecules, and matrix metalloproteinases). The cells produced typically contain a high proportion of lymphocytes, in particular eosinophils. While Th1 cells may be involved in the effector phase in allergic disease, they may also dampen allergic inflammation; in contrast Th2 cells, via the cytokines IL-4, -5, 9, and -13, recruit eosinophils and cause smooth muscle contraction and IgE synthesis via B cells [47]. T_{reg} are able to regulate B-cell antibody production [48] and have been shown to inhibit these Th2 responses [49]. It is thought that an increase in IgG4 isotype antibodies can block IgE-facilitated allergy[50] and that the generation of allergy-specific T_{reg} along with IL-10 and TGF-β [51], are very important early events during the allergic response. Due to the levels of IgE production and the accompanying eosinophilia evident following an attack, asthma is considered to be a Th2-mediated disease [52]. Several hours following the acute (early phase) response, leukocytes migrating to the bronchi lead to chronic allergic inflammation due to increased Th2 cells and cytokines (IL-4, IL-5). The end result is airway hyperresponsiveness (AHR) [53] which over time can lead to airway remodeling and negative and irreversible changes in lung function. During airway remodeling in asthma, the airway wall is characterized by increased thickness, and thus a reduction in the airway diameter and difficulty breathing [47].

Dendritic cells (DCs) play a major role in the development and persistence of allergic asthma. In addition to the cytokine environment and the type and concentration of allergen, DCs can direct host responses to an allergen. Lying below the surface of the epithelial layer, DCs extend their processes through epithelial cells where they survey the airway lumen. Dendritic cells identify and process antigens then migrate to the draining lymph node, where they act as potent antigen presenting cells. Here they present antigen to naïve T cells on major histocompatibility complex class II (MHCII) molecules. As is the case with airway epithelial cells, DCs are capable of recognizing pathogens and initiating innate responses. In individuals that have been previously sensitized to an allergen, FcɛRI (the high-affinity IgE receptor) on DCs aid in processing the allergen bound by IgE. While DCs can drive Th1, Th2, Th17, and T_{reg} responses, in the case of allergy DCs preferentially mobilize a Th2-type response [54]. It is the interaction between naïve T cells and DCs that drive the allergic response. Mature DCs and DCs from myeloid precursors preferentially drive Th2-type responses, and the presence of pro-Th2 cytokines also drives the Th2 response [55]. Airway mucosal DCs derived from myeloid precursors [56] capture and traffic antigen to the draining lymph nodes, where they stimulate naïve T cells [57], although plasmacytoid DCs are also more likely to promote tolerance than are myeloid DCs [58].

In addition to activation of Th2 cells during the allergic response, DCs can also activate T_{reg}, inducing a tolerogenic response rather than an inflammatory one [59], with low antigen doses more likely initiating a tolerogenic response than high-level doses [58]. Low DC activation levels and low levels of MHCII and co-stimulatory molecules on DC surfaces can also shift the response to a T_{reg}-mediated response rather than Th2 response[45,58]. The presence of IL-10, which has been shown to be transiently produced by pulmonary DCs, can also stimulate regulatory cells [60]. T_{reg} in turn have been shown to mitigate the allergic response by interfering with the function of DCs and preventing their activation of Th2 cells [59], thus potentially reducing inflammation.

T_{reg} can effectively suppress inflammatory IgE as well as effector cells in the development of allergic Th2 responses [61] during allergic inflammation. Indeed, T_{reg} are able to suppress airway inflammation in sensitized mice prior to an inhaled-antigen challenge [62]. An imbalance between Th2 and T_{reg} cell responses may underlie the development and progression of asthma [63,65-65], as the CD4+CD25+Foxp3+ T_{reg} population has been implicated in allergen-induced airway responses [8] and has been shown to suppress Th2 responses in vivo [66]. Indeed, Foxp3+ T cells accumulate in nasal mucosa of allergic patients after a challenge [67], and the transfer of T_{reg} prior to an inhaled-allergen challenge reduces inflammation and hyperresponsiveness in the lungs and airways of mice [68,69]. This supports the hypothesis that T_{reg} can reduce or prevent Th2-associated inflammation in the lung following allergic challenge. However, the mechanism(s) underlying Foxp3+ T_{reg} suppression is not conclusive.

T_{reg} are known to exert suppressive function in a number of ways, including direct contact with effector cells [70], release of perforin [71] and granzyme B [72,73], and possibly through the release of cytotoxic cAMP [74]. Cell cycle arrest may occur when T_{reg}, which exhibit a high level of CD25 (the IL-2a receptor), compete with effector T cells for IL-2 [73] and essentially ‘starve’ effector cells metabolically. Galectin-1 may also play a role, as blocking this molecule which is present on DC surfaces can also shift the response to a T_{reg}-mediated response rather than an inflammatory one [59], with low antigen doses more likely inducing a tolerogenic response rather than an inflammatory one [59], with low antigen doses more likely initiating a tolerogenic response than high-level doses [58]. Low DC activation levels and low levels of MHCII and co-stimulatory molecules on DC surfaces can also shift the response to a T_{reg}-mediated response rather than Th2 response[45,58]. The presence of IL-10, which has been shown to be transiently produced by pulmonary DCs, can also stimulate regulatory cells [60]. T_{reg} in turn have been shown to mitigate the allergic response by interfering with the function of DCs and preventing their activation of Th2 cells [59], thus potentially reducing inflammation.
function, while ICOS-Foxp3+ cells were found to use only TGF-β [77]. It has been shown that IL-10 secretion by Tregs plays a major role in Treg-mediated suppression [78,79]. IL-10, secreted in large amounts by Tregs, counter-regulates antigen-specific IgE production as well as IgG4 antibody synthesis [51,80], while TGF-β plays a number of roles in Treg-mediated suppression and regulation.

TGF-β, first described in the mid-1980s [81,82], plays a number of major roles in Treg development and function, although how TGF-β promotes Foxp3 expression is not yet fully clear and the detailed pathway(s) in TGF-β/T cell signaling has yet to be determined [83]. TGF-β-induced Treg, which have been reported to lose Foxp3 expression upon in vitro stimulation [84] and following adoptive transfer into mice [85], appear to be similar both phenotypically and functionally as nTreg [86]. Mediation of TGF-β is greatly controlled by Smad proteins [87,88], as TGF-β fails to suppress IL-2 production in mice lacking the R-Smad3 gene [89]. TGF-β also inhibits CD122 upregulation [89], which in turn limits Th1 effector cell numbers. TGF-β not only regulates Treg differentiation, but also that of Th-17 [90]. In addition, TGF-β can inhibit differentiation of both Th1 and Th2 cells by inhibiting the transcription factors GATA-3 [91] and T-BET [92]; this inhibition of Th1 and Th2 polarization can then lead to the generation of Treg [93].

While TGF-β induces the expression of Foxp3+ in vivo, it is also required to induce ROR-γt, the essential transcription factor for Th17 cells [94]. Th-17, as well as IL-6, has further been shown to compete with regulatory T cells [95]. This could occur in a number of ways, including IL-6 inhibiting TGF-β from driving expressions of Foxp3 [96] or, in the absence of IL-6, TGF-β joining with IL-21 to induce Th17 cells [97]. TGF-β also induces expression of CD103; CD103+ DCs have been shown to induce adaptive Treg cells due to their ability to produce retinoic acid, which has been shown to be required to induce naïve T cells to differentiate into Foxp3+ Treg [98]. Aside from its role(s) in Treg expression, maintenance, development, and function, TGF-β alone can modulate IgE and FcεRI expression and acts as a class switch factor [99], which if induced can induce peripheral tolerance. In vitro studies indicate direct cell-to-cell contact via membrane-bound TGF-β rather than cytokine production is essential for Treg activity [100].

In vivo, McGee and Agrawal have demonstrated that adoptive transfer of either nTreg or iTreg reversed airway inflammation and airway hyperresponsiveness (AHR) in an in vivo asthma model (methacholine challenge) [101] and that this effect lasted for at least four weeks. Ostroukhova demonstrated that adoptive transfer of Foxp3-expressing cells (cells which also expressed membrane-bound TGF-β) from mice that were repeatedly exposed to low-dose allergen prevented allergic sensitization [102]. Interestingly, a similar study that used a higher dose of inhaled allergen stimulated an IL-10-dominant Treg population [103], demonstrating that strength of stimulation affects the type of Treg response. Lowder et al. [104] showed that exercise-training during ovalbumin-induced asthma challenge significantly increases both in vivo Foxp3+ Treg expression and in vitro Treg-mediated suppressive function in a TGF-β-independent manner. Interestingly, this study also showed that when Treg were co-cultured with CD4+ effector T cells, in vitro production of both IL-17 and IL-6 (cytokines that compete with Treg) was significantly decreased.

In humans, it has been shown that generation of allergen-specific Treg are essential events that occur early on in asthma [75,49,51]. Adoptive transfer of antigen-specific Treg suppresses airway hyperreactivity and allergic inflammation in an IL-10-dependent manner [105] and prevents airway remodeling [106]. Depleting Treg prior to sensitization has the opposite effect, with enhanced inflammation and airway hyperresponsiveness seen in the lung of subsequently sensitized mice [107]. Both iTreg and nTreg induced in an antigen-specific manner can reduce asthma severity in an IL-10-dependent [108] or IL-10 and TGF-β-dependent [52] manner. To this list of cytokines that act either as suppressive on their own, or with Treg, we must include IL-35, as ectopic expression of this cytokine instilled a regulatory activity on naïve T cells via suppression of in vitro T cell proliferation [109].

**Aging, Asthma, and Treg**

Although asthma is often considered to be a disease more prevalent in younger individuals, asthma is not only prevalent in the elderly, but is thought to be under-diagnosed and under-treated. In spite of maintaining Treg numbers during the aging process, these cells seem to be lower in number in asthmatics compared to healthy elderly individuals [110]. While serum IgE decreases with age, individuals with high IgE levels relative to their age-matched counterparts are still at greater asthma risk [111,112]. Elderly individuals may in fact be more prone to asthma upon exposure to indoor allergens [112]. In one group of elderly individuals it was found that three-quarters of asthmatics tested positive on a skin-prick test for at least one common indoor allergen [113]. This sensitization to environmental allergens has been found to be much greater in elderly asthmatics than in healthy elderly individuals [114]. This could be due in part to the normal course of aging as the regulation of inflammation appears to be compromised in elderly individuals [115]. While increases in tumor rates and infections (both of which are prevalent in the elderly) are an indication of decreased immunocompetence and a reduced acute inflammatory response [115,116], diseases associated with inflammation gain in prevalence in the aged population such as osteoarthritis, atherosclerosis, type II diabetes. An increased level of C-reactive protein, as well as in increase in the inflammatory cytokines IL-6 and TNF-α, are often the result of chronic inflammation concomitant with aging [115,117].

Thymic involution occurs during the aging process, which is accompanied by a decrease in the number of naïve T cells [114]. As a result the immune profile changes during aging, with significantly more memory cells and fewer naïve cells. In humans, CD4+CD25+ Foxp3+ Treg have a long survival in vivo in the elderly, are more resistant to apoptosis, and have suppressive activity on par with younger counterparts [118]. In spite of the lack of thymic development of nTreg in the elderly, both aged animal and human studies have been shown to have either equal or higher numbers of Treg when compared to their younger counterparts [112,119-122]. Why we see these differences in Treg expression is not known; it is possible that as the thymus involutes and fewer T cells enter the periphery, Treg accumulate and become long-lasting memory Treg as an increase in the number of CD4+CD25+Foxp3+ T cells has been shown to accompany advanced aging, with an accumulation of CD45RO (memory) Treg, accounting for much of this increase [123]. iTreg production (naïve CD4+ T cells that become Foxp3+ Treg in the periphery) accounts for a large portion of Treg in the elderly, as thymic involution restricts the number of naïve T cells, including nTreg, from entering the periphery from the thymus [115]. Mota-Pinto et al. determined that T cells with regulatory function(s) played a limited role in controlling chronic asthma in elderly patients aged > 65 [110]. Treg from this study group were found to be within normal ranges or reduced in asthmatic patients compared to normal (non-asthmatic) patients and 80% of asthmatics were classified as mild-moderate asthma as determined by forced expiratory volume while a significant increase in CD4+ T cells were seen in mild-moderate asthmatics.

While the majority of T cells in the elderly are of memory phenotype,
elderly asthmatics have been shown to have even lower numbers of naïve cells than do healthy elderly individuals [114], along with decreases in CD95 (an apoptosis marker, indicating a decreased ability to clear senescent or effete cells). Whether or not we see a decrease in T\(_{\text{reg}}\) in elderly asthmatics versus elderly non-asthmatics requires further investigation. While the number of nT\(_{\text{reg}}\) decreases, an increase in iT\(_{\text{reg}}\) generated in the periphery may be the reason for the overall increase in T\(_{\text{reg}}\) numbers in the elderly [121]. Nishioka et al. [120] identified a significant increase in the proportion of Foxp3\(^+\) cells in aged mice as compared to young mice. While the number of CD4\(^+\)CD25\(^{hi}\) Foxp3\(^+\) cells remained constant across age groups, aged mice had a significantly higher proportion of CD4\(^+\)CD25 Foxp3\(^+\) suppressive T cells.

Although the number of T\(_{\text{reg}}\) tends to increase concomitantly with age, there appears to be little or no difference in T\(_{\text{reg}}\) function between old and younger counterparts [112,122]. It has been proposed that T\(_{\text{reg}}\) function decreases with age [121], while others have shown no impairment due to aging [112,120,122]. Using a mouse model, Nishioka et al. demonstrated that the number of CD4\(^+\)CD25\(^{hi}\) Foxp3\(^+\) T cells was similar and that these cells maintained the same level of suppressive function as the cells from younger mice [120]. Interestingly, another study demonstrated that T\(_{\text{reg}}\) from aged humans suppressed the production of IL-10 by CD4\(^+\)CD25 effector cells better than did T\(_{\text{reg}}\) from younger counterparts [115]. This is of particular interest in asthma as IL-10-secreting Type 1 T\(_{\text{reg}}\), which are allergen-specific, are found in lower numbers in individuals with allergic rhinitis [124]. The levels of some TH2-type cytokines, such as IL-10 and IL-4, have been shown to be elevated in the elderly compared to younger counterparts [125].

**Gender Differences**

Asthma, as with other inflammatory diseases, is more prevalent in females than in males [126-132]. Because of their role in maintaining immune homeostasis and regulating the immune system, gender differences in T\(_{\text{reg}}\) may contribute to this discrepancy between males and females due to the interplay between the sex hormones (e.g., estrogen, progesterone, and testosterone) and T\(_{\text{reg}}\). The incidence of asthma is higher during the female's reproductive years, when these hormones are at their highest levels of production, and then declines during menopause [126]. Indeed, the number of T\(_{\text{reg}}\) changes throughout the menstrual cycle as well as throughout pregnancy [127,123,134]. Multiple investigators have determined that estrogen helps to drive T\(_{\text{reg}}\) expansion and a reduction in or amelioration of various diseases [131,133,135,136]. Arruvito found T\(_{\text{reg}}\) numbers to be highest during the late follicular phase (when estrogen levels are at their peak) and lowest during the luteal phase, while Wegienka's group found a steady increase in T\(_{\text{reg}}\) during pregnancy [133]. Both Tai and Polanczyk found that estrogen treatment increased Foxp3 expression and the number of CD25\(^+\) cells; however, this effect was absent in mice deficient of the estrogen receptor, indicating the significant role that sex hormones play in maintaining immune homeostasis [131,134]. Female mice sensitized with ovalbumin (OVA) had lower initial numbers of T\(_{\text{reg}}\) in the lung [130] despite no differences in T\(_{\text{reg}}\) number or function after OVA challenge [129,130]. While sex hormones and their effect(s) on T\(_{\text{reg}}\) may be involved in the gender differences in asthma prevalence, they do not account for all of the differences in the differences seen between males and females [128]. Women tend to have higher B cell-mediated immunity and higher CD4:CD8 ratios than do males and these differences may also extend to T\(_{\text{reg}}\) numbers.

**Exercise and Asthma**

Therapeutic treatment of asthma is two-fold: that of reducing the risk for a severe attack and minimizing symptoms during an attack [137]. Asthma treatment has traditionally included inhaled corticosteroids, β2 adrenergic receptor agonists, and cholinergic antagonists. However, none of these prevent asthma, and not all asthmatics benefit from their use. As such, alternative means treating asthma are worth investigating. One approach to enhancing immune function in asthmatics is exercise. Exercise training has been shown to ameliorate many negative effects of asthma in both human [138-141] and murine [104,142-144] models. Pastva et al. investigated the effects of exercise in Balb/c mice, a strain susceptible to OVA-induced IgE responses [145,146] and demonstrated that aerobic exercise training reduces lung inflammatory responses (leukocyte infiltration, cytokine/chemokine production, adhesion molecule expression, structural airway remodeling) in OVA-sensitized mice [147,148], later demonstrating that these responses are at least in part due to an enhanced T\(_{\text{reg}}\) response [104]. Few studies have examined how exercise training affects T\(_{\text{reg}}\) in humans. Few et al. found increased TGF-β and IL-10 production following antigenic stimulation in healthy adults that performed 12wks of Tai Chi [149], significant as IL-10 can suppress airway inflammation [150-151]. Ramel et al. found that resistance training reduced peripheral T suppressor cell numbers [152]. However, these values were recorded in healthy (non-asthmatic) individuals.

**Summary and Future Directions**

Since the discovery of suppressor T cells in the early 1970s, their re-emergence as CD4\(^+\)CD25\(^{hi}\) regulatory T cells, and finally the finding that the nuclear protein and transcription factor forkhead box P3 (Foxp3), research in the field of T\(_{\text{reg}}\) has exploded. Defects or absence of this highly-specialized sub-population of T cells has been implicated in numerous diseases in both humans and mice. It has been shown that TGF-β, IL-10, and IL-2 can be essential, required, non-essential, or not required for proper maintenance and function of T\(_{\text{reg}}\) depending on the system (in vivo vs. in vitro), model (mouse, human, cell line), or even severity of disease (mild versus severe asthma). Though we now know that an enhanced T\(_{\text{reg}}\) response may reduce asthma severity and airway hyperresponsiveness in both human and animal models, we do not have a means in which to directly enhance this response in individuals suffering from asthma.

Few studies have examined the relationship between asthma and T\(_{\text{reg}}\) in the elderly. The number of T\(_{\text{reg}}\) tends to increase with age, and these cells maintain their suppressive function; however, the regulation of the immune system seems to be compromised with age, and there is an indication for a reduced number of T\(_{\text{reg}}\) in asthmatic elderly individuals. Elderly asthmatics, in particular, have been shown to have even fewer naïve than healthy age-matched individuals. With a large population rapidly approaching senior status, and an increase in respiratory and lung diseases on the rise, it is critical to know what roles regulatory T cells play in the aging lung.

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This article was originally published in a special issue, Airway Inflammation and Hyperresponsiveness handled by Editor(s). Dr. John F. Alcorn, Children's Hospital of Pittsburgh, USA.