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Regulatory T Cells in Asthma and Airway Hyperresponsiveness

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Introduction

Regulatory T cells, or T_{regs}, 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 T_{regs} 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 T_{regs}, the role of T_{regs} play in the reduction of asthma and lung inflammation, and age- and gender-associated differences in T_{regs}.

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-termed suppressor 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 T_{regs}.

The high-affinity IL-2 receptor, CD25, has been widely used as a surface marker for the identification of T_{regs}. However, while T_{regs} express this surface marker, so do recently-activated T cells. A more definitive marker for T_{regs} 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 regulated T cell activation [12]. Two years later it was demonstrated that Foxp3 is required for the development and function of T_{regs} [13]. Indeed, forced expression of Foxp3 in conventional T cells imparts a T_{reg}-phenotype [14,15]. The nuclear protein Foxp3 soon emerged as the most reliable marker for T_{regs}. Although T_{regs} 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 T_{regs} will certainly proliferate *in vivo* [18,21].

Since the re-discovery of these cells, a number of subpopulations of T_{regs} have been identified. Natural T_{regs} (or nT_{regs}) are $CD4^+Foxp3^+$ cells that originate in the thymus [22] during ontogeny and enter the periphery as fully-functional T_{regs}. In the thymus, the T_{reg} 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 are still able to develop T_{regs}, indicating that T_{reg} commitment can also take place in the cortex [24]. A second group of T_{regs} known as adaptive, or induced T_{regs} (iT_{reg}) acquire Foxp3 in the periphery [25]. In this case a naïve ($CD4^+CD25$-) T cell acquires the transcription factor Foxp3 and differentiates into an iT_{reg}. Initially it was thought that iT_{regs} were functionally and phenotypically identical to nT_{regs}. However, it has recently been shown that while the transfer of nT_{regs} into Foxp3-deficient mice increases survival, iT_{regs} (generated *in-vitro*) fail to do so [26], indicating functional differences between natural and peripherally-induced T_{regs}. These cells differ in other ways. While nT_{regs} are strongly biased towards autoreactive TCR-specifications, express Foxp3 constitutively [27,28], and require TNF-α signaling for *in vivo* function, inducible T_{regs} do not [29]. Other populations of T_{regs} have been identified in recent years, including CD8+ suppressor cells [30], IL-10-producing T_{regs} (known as 'Tr1' cells) [31], and transforming growth factor-β-producing (or 'TGF-β-producing') T_{regs} [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 degranulation of mast cells followed by cytokine, leukotrienes, and prostaglandin production. The sequence of events leading to the development of immediate hypersensitivity involves the production

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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 FcεRI 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 (FcεR1) or low-affinity (FcεRII) 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_{regs} 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_{regs}, 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, FcεR1 (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_{regs}, 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_{regs} 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_{regs} can effectively suppress inflammatory IgE as well as effector cells and the development of allergic Th2 responses [61] during allergic inflammation. Indeed, T_{regs} 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 [61,63-65], 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_{regs} 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_{regs} can reduce or prevent Th2-associated inflammation in the lung following allergen challenge. However, the mechanism(s) underlying $Foxp3^+$ T_{reg} suppression is not conclusive.

T_{regs} 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 cytoplasmic cAMP [74]. Cell cycle arrest may occur when T_{regs}, which exhibit a high level of CD25 (the IL-2α 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 preferentially expressed on T_{regs} significantly reduces both mouse and human T_{reg} suppressive function [73]. T_{regs} may also kill responder cells in a granzyme- and/or perforin- dependent manner via upregulation of intracellular cAMP (which leads to inhibition of T cell and/or IL-2 proliferation); by generation of pericellular adenosine (catalyzed by CD39 and CD73); or through interactions with B7 (CD80/86) expressed on responder T cells [75]. Activated T_{regs} may inhibit the upregulation, or perhaps the down-modulation, of CD80/86 expression on antigen presenting cells (APCs), which may stimulate DCs to express the enzyme indoleamine 2,3-dioxygenase (IDO), which catabolizes the conversion of tryptophan to kynurenime; kynurenime is toxic to DCs through a mechanism dependent upon the expression of CTLA-4 (CD152) [75] which is abundant on T_{regs}. Toll-like receptor 2 (TLR2) also plays a role in T_{reg} and/or Foxp3 function and expression, in that TLR2 signaling can temporarily abrogate T_{reg}-mediated suppression and downregulate Foxp3 expression. Indeed, TLR2-/- mice have decreased T_{reg} numbers, as mice treated with TLR2 agonists induce T_{reg} proliferation [76]. The co-stimulatory receptor ICOS has also been shown to play a role in T_{reg}- mediated immunosuppression. While both ICOS+ and ICOS- T_{regs} were both found to be anergic, $ICOS^+Foxp3^+$ cells were shown to use IL-10 to suppress dendritic cell function and TGF-β to suppress T cell

function, while ICOS-Foxp3$^+$ cells were found to use only TGF-β [77]. It has been shown that IL-10 secretion by T_{regs} plays a major role in T_{reg}-mediated suppression [78,79]. IL-10, secreted in large amounts by T_{regs}, counter-regulates antigen-specific IgE production as well as IgG4 antibody synthesis [51,80], while TGF-β plays a number of roles in T_{reg}-mediated suppression and regulation.

TGF-β, first described in the mid-1980s [81,82], plays a number of major roles in T_{reg} development and function, although how TGF-β promotes Foxp3 expression is not yet fully clear and the detailed pathway(s) in TGF-β/T_{reg} signaling has yet to be determined [83]. TGF-β-induced T_{regs}, 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 nT_{regs} [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 T_{reg} 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 T_{regs} [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 T_{reg} 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$^+$ T_{regs} [98]. Aside from its role(s) in T_{reg} expression, maintenance, development, and function, TGF-β alone can modulate IgE and FcεRI expression and acts as a class switch factor [99], which by itself 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 T_{reg} activity [100] .

In vivo, McGee and Agrawal have demonstrated that adoptive transfer of either nT_{regs} or iT_{regs} 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 T_{reg} population [103], demonstrating that strength of stimulation affects the "type" of T_{reg} response. Lowder et al. [104] showed that exercise-training during an ovalbumin-induced asthma challenge significantly increases both *in vivo* Foxp3$^+$ T_{reg} expression and *in vitro* T_{reg}-mediated suppressive function in a TGF-β-independent manner. Interestingly, this study also showed that when T_{regs} were co-cultured with CD4$^-$ effector T cells, *in vitro* production of both IL-17 and IL-6 (cytokines that compete with T_{regs}) was significantly decreased.

In humans, it has been shown that generation of allergen-specific T_{regs} are essential events that occur early on in asthma [75,49,51]. Adoptive transfer of antigen-specific T_{regs} suppresses airway hyperreactivity and allergic inflammation in an IL-10-dependent manner [105] and prevents airway remodeling [106]. Depleting T_{regs} prior to sensitization has the opposite effect, with enhanced inflammation and airway hyperresponsiveness seen in the lung of subsequently sensitized mice [107]. Both nT_{regs} and iT_{regs} 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 T_{regs}, 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 T_{regs}

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 T_{reg} 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 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^{high} T_{regs} 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 nT_{regs} in the elderly, both aged animal and human studies have been shown to have either equal or higher numbers of T_{regs} when compared to their younger counterparts [112,119-122]. Why we see these differences in T_{reg} expression is not known; it is possible that as the thymus involutes and fewer T cells enter the periphery, T_{regs} accumulate and become long-lasting memory T_{regs} as an increase in the number of CD4$^+$CD25^{high} T cells has been shown to accompany advanced aging, with an accumulation of CD45RO (memory) T_{regs} accounting for much of this increase [123]. iT_{reg} production (naïve CD4$^+$ T cells that become Foxp3$^+$ T_{regs} in the periphery) accounts for a large portion of T_{regs} in the elderly, as thymic involution restricts the number of naïve T cells, including nT_{regs}, 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]. T_{regs} 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_{regs} in elderly asthmatics versus elderly non-asthmatics requires further investigation. While the number of nT_{regs} decreases, an increase in iT_{regs} generated in the periphery may be the reason for the overall increase in T_{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 $CD4^+CD25^{high}$ $Foxp3^+$ 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_{regs} tends to increase concomitantly with age, there appears to be little or no difference in T_{reg} function between old and younger counterparts [112,122]. It has been proposed that T_{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 $CD4^+CD25^{high}$ $Foxp3^+$ 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_{regs} from aged humans suppressed the production of IL-10 by $CD4^+CD25^-$ effector cells better than did T_{regs} from younger counterparts [115]. This is of particular interest in asthma as IL-10-secreting Type 1 T_{regs}, 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_{regs} 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_{regs}. 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_{regs} changes throughout the menstrual cycle as well as throughout pregnancy [127,133,134]. Multiple investigators have determined that estrogen helps to drive T_{reg} expansion and a reduction in or amelioration of various diseases [131,133,135,136]. Arruvito found T_{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_{regs} 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_{regs} in the lung [130] despite no differences in T_{reg} number or function after OVA challenge [129,130]. While sex hormones and their effect(s) on T_{regs} 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_{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/cJ 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_{reg} response [104]. Few studies have examined how exercise training affects T_{regs} in humans. Yeh 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 $CD4^+CD25^+$ regulatory T cells, and finally the finding that the nuclear protein and transcription factor forkhead box P3 (Foxp3), research in the field of T_{regs} 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_{regs}, depending on the system (*in vivo* versus *in vitro*), model (mouse, human, cell line), or even severity of disease (moderate versus severe asthma). Though we now know that an enhanced T_{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_{regs} in the elderly. The number of T_{regs} 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_{regs} 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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