[Frontiers in Bioscience, Scholar, 5, 167-180, January 1, 2013]

Experimental advances in understanding allergic airway inflammation

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1. ABSTRACT

Asthma is largely an inflammatory disease, with the development of T cell mediated inflammation in the lung following exposure to allergen or other precipitating factors. Currently, the major therapies for this disease are directed either at relief of bronchoconstriction (ie beta-agonists) or are non-specific immunomodulators (ie, corticosteroids). While much attention has been paid to factors that regulate the initiation of an inflammatory response, chronic inflammation may also be due to defects in regulatory mechanisms that limit or terminate immune responses. In this review, we explore the elements controlling both the recruitment of T cells to the lung and their function. Possibilities for future therapeutic intervention are highlighted.

2. INTRODUCTION

Asthma is a chronic inflammatory disease of the airways affecting approximately 23 million Americans. Exacerbations are often triggered by inhalation of environmental agents that precipitate an inflammatory response, leading to the hallmark symptoms of airway hyperresponsiveness and excess mucous production. Thus, understanding mechanisms that control inflammatory responses *in vivo* are key to understanding the pathogenesis of asthma.

Murine models have been an important tool in dissecting the pathogenesis of asthma as they recapitulate some of the key features of the disease, including a characteristic CD4-dependent Th2-mediated immune

response (1-5). In this review we will explore current therapies aimed at regulation of T cell function and other targets that may promote the resolution of allergic airway inflammation, comparing and contrasting data from murine model systems with that obtained from human studies.

Inflammation can be characterized by three distinct phases: (a) initiation, (b) effector and (c) resolution. Regulation and manipulation of the initiation and effector phases has been the subject of intense research resulting in many new therapies for immunologically based disorders. More recently, increased emphasis has been placed on understanding how immune responses are terminated, with the hope of developing new therapeutic targets (6-9). Such an approach may be beneficial in the treatment of asthma, as patients are typically encountered only after initial sensitization, limiting the ability to intervene at earlier phases.

Both activating and inhibitory receptors modulate the T cell response throughout the inflammatory response. For example, we and others have shown in a murine model that engagement of CD28 and other activating receptors such as Inducible Costimulator (ICOS) are required to initiate and maintain allergic airway inflammation (3, 10-12). Inhibitory receptors including Cytotoxic T-lymphocyte antigen 4 (CTLA4), programmed death receptor (PD-1) and B and T lymphocyte attenuator (BTLA) function after initial activation, determining the intensity and duration of inflammation (6, 8, 13-14). Thus the persistent inflammation observed in asthmatic patients could potentially be due to either aberrant initial T cell activation and persistent positive signaling driving inflammation, or alternatively due to a failure of the normal homeostatic mechanisms that govern the resolution of inflammation.

3. CHEMOKINES AND CHEMOATTRACTANTS IN T CELL MIGRATION INTO THE LUNG

The recruitment of T cells to the lung is an essential early step in allergic lung inflammation. This process is regulated by chemokines, lipid chemoattractants, and their ligands expressed both on T lymphocytes and by parenchymal cells of the lung. These same classes of molecules are important during the resolution phase of inflammation, coordinating the egress of T lymphocytes out of the lung. Chemokines and chemoattractants have been the subject of extensive studies (15-18). Here we will specifically review the chemokines and chemoattractants which are important for T cell migration in murine models of allergic airway inflammation. Targeting of these molecules is a possible strategy for limiting allergic airway inflammation by altering cell trafficking.

CCR1 is a chemokine receptor expressed on multiple cell types, including: neutrophils, monocytes, lymphocytes, and eosinophils. It binds three chemokines: macrophage inflammatory protein-1-alpha (MIP-1-alpha, CCL3), regulated upon activation, normal T-cell expressed and secreted (RANTES, CCL5), and monocyte specific chemokine -3 (MCP-3, CCL7). There is conflicting data as to the importance of this chemokine receptor in airway inflammation. In comparison to wild type controls, CCR1-deficient mice had decreased Th2 cytokines and airway remodeling following challenge with *Aspergillus fumigates*, although no difference in airway hyperresponsiveness or cell composition of the bronchoalveolar lavage (BAL) was observed (19). In contrast, using CCR1 antagonist in wild type mice resulted in a decrease in airway hyperresponsiveness and no change in cytokine production after challenge (20). Thus, the importance of this pathway remains unclear.

CCR3 and CCR4 are Th2 associated chemokine receptors. CCR3 is essential for the recruitment of eosinophils to the lung during allergic airway inflammation (21-22). While not directly responsible for recruiting T cells to the lung, CCR3 may still be an important target in dampening airway inflammation because of its role in recruitment of eosinophils (23-24). Conflicting results exist when examining the relationship between CCR4 and allergic airway inflammation. Some studies using CCR4-deficient animals (25) or antibodies against the ligand of CCR4, (26) led to decreases in eosinophilia and Th2 cytokines in the BAL. However, in other studies, deficiency or blockade of CCR4 did not affect allergic airway inflammation (27-28). Interestingly, CCR4 is also expressed on allergen-specific regulatory T cells (Tregs) and may modulate inflammation via these cells (29). Using two adoptive transfer models, Mikhak *et al* demonstrated that CCR4 expression on Th2 cells was important for homing to the lung and inflammation independent of its expression on Tregs (30). However, this study did not examine the role of CCR4 on the trafficking of Tregs to the lungs. Thus, while CCR4 may be important for recruitment of Th2 lymphocytes during allergic airway inflammation, its function on Tregs will need to be clarified prior to therapeutic targeting.

CCR6, which binds CCL20, is expressed on immature dendritic cells, B cells, and memory T cells (31-33). Acutely after allergen challenge, CCR6 and CCL20 were increased in the lung and draining lymph nodes (17). Further supportive of a role for CCR6, mice deficient in the receptor have decreased serum IgE, airway resistance, eosinophilia, IL-5, and fewer CD4+ T cells and B220+ B cells, in the lung following challenge (34). Another group has shown that deficiency of TNF-related apoptosis-inducing ligand (TRAIL) leads to a decrease in CCL20 production, resulting in fewer myeloid dendritic cells (mDC) and memory T cells recruited through CCR6 and a concomitant decrease in airway inflammation (35).

Natural Killer (NK) cells, B cells and activated T cells all express CXCR3 (36). Though upregulated in mice following allergen challenge, (37) CXCR3 deficiency had no effect on the migration of Th2 cells to the lung (30). CXCR3 and its ligands, CXCL9 and CXCL10, have been associated predominantly with Th1 responses and explored as a potential mechanism to skew T cell populations in the lungs towards a Th1 response as opposed to a Th2 response. Using a neutralizing antibody, Thomas *et al* showed that loss of CXCL9 caused a decrease in CXCR3 expressing T cells, but also led to increased inflammation (38). Conversely, addition of exogenous CXCL9 reduced

inflammation and production of Th2 cytokines (38). Manipulation of CXCL10 has led to conflicting results (39-41). Thus, the effect of manipulation of this pathway on airway inflammation is difficult to predict and likely dependent on the specifics of the inflammatory response.

Lipid mediators also regulate the trafficking of cells to the lung. BLT1 is found on Th1 and Th2 cells and binds leukotriene B4 (LTB4). Mice deficient in BLT1 have fewer Th2 cells and altered kinetics of neutrophil and eosinophil recruitment to the airways (42-43). Prostaglandin D2 (PGD2) binds CRTh2, also known as DP2, which is expressed on Th2 lymphocytes, neutrophils and eosinophils, and has been associated with allergic inflammation. Activation of CRTh2 through the agonist 13,14-dihydro-15-keto-PGD_2, resulted in increased eosinophilia in the BAL after allergen challenge (18, 44). However, somewhat discrepant results have been reported in the analysis of CRTh2 deficient mice. Deletion of CRTh2 resulted in decreased allergic skin inflammation, while in an airway model, enhanced eosinophilia and inflammatory cytokine production was observed (45-46). CRTh2 is found exclusively on Th2 cells in humans, while it can be expressed on both Th1 and Th2 cells in mice. Nonetheless, various small molecules antagonists to CRTh2 have been successfully tested in murine models and result in attenuation of allergic airway inflammation, suggesting this may be a viable therapeutic strategy (47-49).

3.1. The role of chemokines and chemoattractants in human asthmaStudies on humans with asthma have suggested an important role for chemokines and chemoattractants. Expression of the ligands for CCR3, CCR4, CCR5, CXCR1/2, CXCR3, and CRTh2 has been observed, suggesting that these chemoattractants play a role in both normal homeostasis as well as recruiting T lymphocytes to the lung in response to inflammation (50-56). Here we briefly review the role of these pathways on T cell migration to the lung in human asthma (Figure 1).

In humans, CCR3 is expresssed on multiple cell types including eosinophils, neutrophils, and Th2 cells (57). The expression of the chemokine eotaxin, the ligand of CCR3, is found to be increased in the airways of asthmatics (58-60). It has been hypothesized that CCR3 contributes to the migration of Th2 cells to the lungs during asthma and may therefore make a good therapeutic target. CCR3 antagonists have been used by a number of groups in allergic airway inflammation models in mice and non-human primates. These antagonists have effectively blocked eosinophil, neutrophil, and lymphocyte migration into the lungs of these animals (61-64). Further studies are needed to understand their potential efficacy in humans.

Like CCR3, CCR4 is a Th2 associated chemokine receptor. CCR4 binds the chemokines CCL17 and CCL22, which are both found to be upregulated in the airway epithelial cells of asthmatics after allergen challenge (50, 65-66). Multiple studies have demonstrated CCR4 expression on T cells in asthmatics isolated from both the blood and the airways (67). Furthermore, using a CCR4 antagonist, it has been demonstrated that *ex vivo* allergen stimulated bronchial biopsies resulted in CCR4-dependent T cell chemotaxis. Interestingly, corticosteroid use in asthmatics has been shown to reduce the number of CCR4+ T cells (68). It should be noted that human Tregs also express CCR4 (69). As will be discussed later in this review, Tregs may be important for controlling allergic airway inflammation, and therefore any therapies targeting CCR4 will have to take into account potential effects on Tregs

Little is known about the role of CRTh2 in human asthma. It is well established, however, that the lipid mediator PGD2, which binds to CRTh2, is elevated in asthmatic patients (70). One study reports a significant difference in the percentage of CRTh2+ T cells in the BAL of asthmatics versus normal patients, however the percentage of cells expressing this receptor was low (71). Engagement of CRTh2 on Th2 cells by PGD2 induced cell migration (72) and stimulation of human Th2 cells *in vitro* with the CRTh2 agonist 13,14-dihydro-15-keto-PGD2 induced Th2 type cytokine production (73).

Manipulation of the migration of T lymphocytes into and/or out of the lung tissue provides an attractive potential for the development of new therapeutic reagents for asthma and other inflammatory diseases. By affecting the rate or ability of T lymphocytes to traffic to the lung, one should affect the overall evolution of the inflammatory response and thereby interrupt disease pathogenesis. While conflicting results in pre-clinical studies remain the rule, some potential drugs have been shown to have beneficial effects in animal models, although their effect in humans remains to be seen (47-49). Targeting individual chemokines, chemoattractants, and their ligands may allow for possible intervention that could affect only a subset of T cells. However, unintended immune suppression or other detrimental side effects remain a possibility.

4. T LYMPHOCYTE INHIBITORY RECEPTORS AND ALLERGIC AIRWAY INFLAMMATION

Specific receptor mediated pathways inhibit both the initiation of T cell function, as well as promote the resolution of an established inflammatory response. The major inhibitory receptors on T cells include: CTLA4 (CD152), PD-1 (CD279), and BTLA (CD272). Aberrant expression or function of these pathways could lead to a failure to normally limit ongoing T cell activation, and thereby result in chronic inflammation. We will more fully explore the function of each of these ligands and their possible roles in allergic airway inflammation.

4.1. CTLA4

CTLA4 is a homolog of CD28 and has been shown to inhibit T cell function. Not expressed on resting T cells, CTLA4 expression on the cell surface is detected following initial activation. Both CD28 and CTLA4 are able to bind B7-1 (CD80) and B7-2 (CD86) on antigen presenting cells (APCs). However, CTLA4 binds both B7 molecules with a higher affinity than CD28. A critical role for CTLA4 in the regulation of T cell activation and the maintenance of T cell-mediated immune responses has

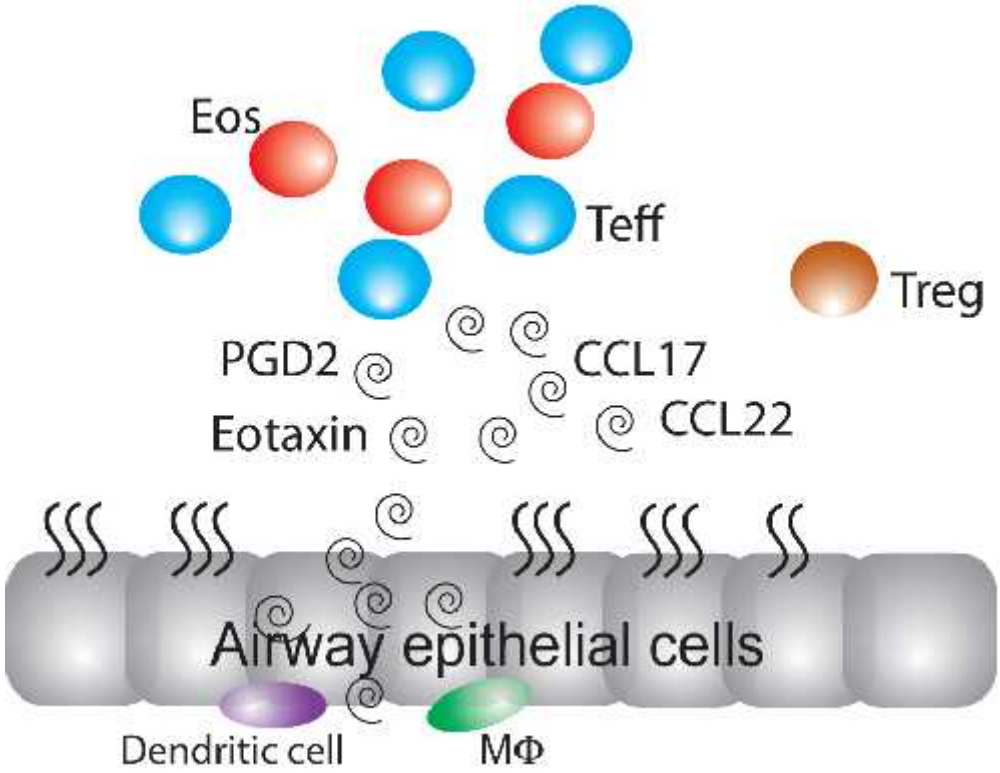

Figure 1. Migration of T lymphocytes to the airways. In response to allergen challenge, airway epithelial cells and other cells in the lungs upregulate production of chemokines. These chemokines (black swirls) then attract Th2 cells (blue) to the lungs in order to clear the allergen, and this results in inflammation. Also attracted to the lungs by some of the same cytokines are eosinophils (red), which exacerbates the inflammation, and regulatory T cells (brown), which may be one mechanism by which inflammation can be resolved.

been demonstrated. CTLA4-deficient mice display a rapid development of severe lymphoproliferation, which results in lethality at 3-4 weeks of age (74-75). *In vitro*, T cells deficient in CTLA4 have increased proliferation and cytokine production. The role of this inhibitory receptor during allergic airway inflammation has been studied. Treatment of mice with a CTLA4 blocking antibody during sensitization led to increased eosinophil infiltrates and antigen specific IgE production (76). However, it was also shown that blockade of CTLA4 during only the challenge phase resulted in no change in the inflammation. These results suggest that CTLA4 may function to regulate early responses in naïve T cells, but may not be as critical for regulation of already activated T cells in allergic airway inflammation.

CTLA4Ig is a fusion protein of an Fc fragment and the extracellular portion of CTLA4. It is able to effectively block CD28 ligation by B7 molecules through competitive inhibition. Studies in which CTLA4Ig was administered before and during antigen challenge, consistently prevented allergic airway inflammation, measured by both eosinophilic infiltration and cytokine production (77-82). While showing that the activation of allergic airway inflammation is dependent on the B7:CD28 signaling pathway, these studies did not address whether or not CTLA4Ig could be used to ablate already established inflammation. Using a model in which mice are deficient in both CD28 and the inhibitory receptor, BTLA, we established that CTLA4Ig can not only prevent inflammation, but can promote the resolution of established airway inflammation. Surprisingly, we found that this is through a mechanism independent of CTLA4Ig's ability to prevent CD28 engagement of B7-1 and B7-2 (83). While there is currently no literature on the use of CTLA4Ig in humans as a therapeutic drug during asthma, it is currently approved for use in rheumatoid arthritis (abatacept, Orencia™, Bristol Myers Squibb Corporation) (84).

4.2. PD-L1, PD-L2 and PD-1

PD-1 is an inhibitory receptor that is a member of the CD28 superfamily (85). Activated B, T, and myeloid cells express PD-1 (86-87). In mice, deficiency of PD-1 leads to a lupus-like autoimmune disease, which suggests an inhibitory role for PD-1 in the immune response *in vivo* (87). Analogous to CD28, PD-1 has two ligands B7-H1 (PD-L1) and B7-DC (PD-L2) which have differing expression patterns. PD-L1 is expressed on B and T lymphocytes, dendritic cells, macrophages, and non-lymphoid cells (88-89). In contrast, PD-L2 is expressed only on macrophages and dendritic cells. To date, PD-L1 and PD-L2 have been implicated in both the activation (90) and inhibition (91) of T cell function. While these contradictory results have not been fully explained, they

could be due to the presence of an ITSM in the cytoplasmic tail of PD-1. This switch domain may result in either activating or inhibitory signaling. Alternatively there may be a second receptor for PD-L1 and PD-L2 (92). Interestingly, it has recently been demonstrated that PD-L1 is important for the maintenance of some Treg populations (93). Expression and engagement of PD-L1 on this suppressive cell type may explain some of the existing contradictory results from different studies exploring the role of the PD-1 in allergic airway inflammation. Studies examining this pathway in allergic airway inflammation, have suggested that PD-L2 is upregulated during such inflammation (94). It was also shown that administration of the fusion protein PD-L2-Fc resulted in increased lung inflammation, suggesting that the binding of this protein to PD-1 may be activating in nature. Alternatively, the PD-L2-Fc may be binding to a ligand that is currently unidentified.

Other studies have found that treatment with PD-L2 neutralizing antibodies at the time of allergen challenge resulted in decreased Th1 and increased Th2 cytokine production, accompanied by an increase in eosinophilia and airway hyperreactivity (95). These results suggest that PD-1/PD-L2 signaling is critical for the downregulation of allergic lung inflammation. Though these two studies used similar allergic airway models, the results were contradictory. One suggests that PD-1/PD-L2 signaling is important for activating allergic airway inflammation, while the other suggests that the receptor/ligand binding is important for termination of such inflammation. Thus, further studies are required to fully elucidate the function of the PD-1/PD-L1/PD-L2 pathway in the regulation of allergic airway inflammation.

4.3. BTLA and HVEM

BTLA is an inhibitory receptor that is a member of the Ig- superfamily (96). BTLA can be found on B and T lymphocytes, macrophages, dendritic cells, and NK cells (96-97). It is expressed at higher levels on activated versus naïve T cells (97-98). The cytoplasmic tail of BTLA has an ITIM, ITSM, and a third tyrosine containing motif. The ITIM and ITSM are associated with SHP-1 and SHP-2, while the third motif has been shown to bind Grb-2 (96, 99-100). The presence of the ITIM and ITSM motifs suggests that BTLA is an inhibitory molecule. Studies have shown that engagement of BTLA is able to partially inhibit IL-2 secretion and BTLA-deficient T lymphocytes exhibit increased proliferation (96). In a murine model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), BTLA-deficiency led to increased severity of and prolonged disease (96). Further suggesting an inhibitory role, *in vivo* studies have shown that BTLA-deficient mice reject partially mismatched cardiac allografts faster than their wild type counterparts (101).BTLA has been shown to also have an inhibitory role in allergic airway inflammation. Mice deficient in BTLA exhibit prolonged inflammation after allergen challenge (6). Further, it has been demonstrated that BTLA is responsible for increased Th2 cytokines during allergic airway inflammation (102). In contrast to all of the studies suggesting an inhibitory role for BTLA, one recent study suggests an activating function for this molecule. In a graft versus host disease (GVHD) model, $BTLA^{-/-}$ donor cells that were transferred into wild type hosts, failed to survive (103). Similar effects were demonstrated using an antibody that blocks BTLA binding to its ligand. Taken together, these studies suggest a complicated role for BTLA in the immune response.

Interestingly, the ligand of BTLA, herpesvirus entry mediator (HVEM), is a member of the tumor necrosis factor receptor (TNFR) superfamily (104-105). Expression of HVEM on T cells is fluctuating; it is high on naïve cells, downregulated upon activation, and then upregulated near the end of the activation phase (106). HVEM is also able to bind to LIGHT and interactions with this receptor result in a costimulatory signal for T cells (107). Conversely, engagement of BTLA by HVEM leads to inhibition of T cell proliferation (105). Targeting the interactions between BTLA and HVEM as a means for controlling allergic airway inflammation will need to be carefully monitored. Not only does signaling occur through both molecules, but the ability of BTLA's ligand, HVEM, to bind the costimulatory molecule LIGHT will provide for potentially complicated outcomes.

Expression of the ligands of T cell inhibitory receptors has been detected in lung tissue. Expression of CD80, CD86, PD-L1, and PD-L2, can be induced on airway epithelial cells from humans (108-109). Furthermore, in mice CD86 expression is upregulated in alveolar macrophages, and expression of CD86 and PD-L1 is upregulated in lung tissue after allergen challenge (110-111). Interaction between the inhibitory receptors on T cells and their ligands in the lung tissue under normal homeostatic conditions may lead to the resolution of inflammation (Figure 2). Use of a drug, such as CTLA4Ig, may be able to resolve this aberrant airway inflammation.

Of these three major inhibitory receptors of T cell activation, CTLA4 is currently the most promising target for resolution of allergic airway inflammation. Both PD-1 and BTLA are found on multiple cell types, as are their ligands. More research must be completed in order to determine their mechanisms of action during allergic airway inflammation and if monoclonal antibodies against these ligands would be able to inhibit inflammation. Particularly agonists of these inhibitory pathways may help to speed the resolution of inflammation.

5. REGULATORY T CELLS AND ALLERGIC AIRWAY INFLAMMATION

Tregs are a subset of T lymphocytes that can suppress immune responses. The most well characterized subset of these cells are CD4+ T cells, with high levels of CD25 expressed on their surface and expression of the transcription factor Foxp3. Not only may these cells play an important role in immunological tolerance within the lungs of normal individuals, but their role as an effector cell in limiting allergic airway inflammation has been explored. Tregs may control inflammation through suppression of effector T cells, APCs, or both. Suppression by Tregs has been shown *in vitro* through production of IL-

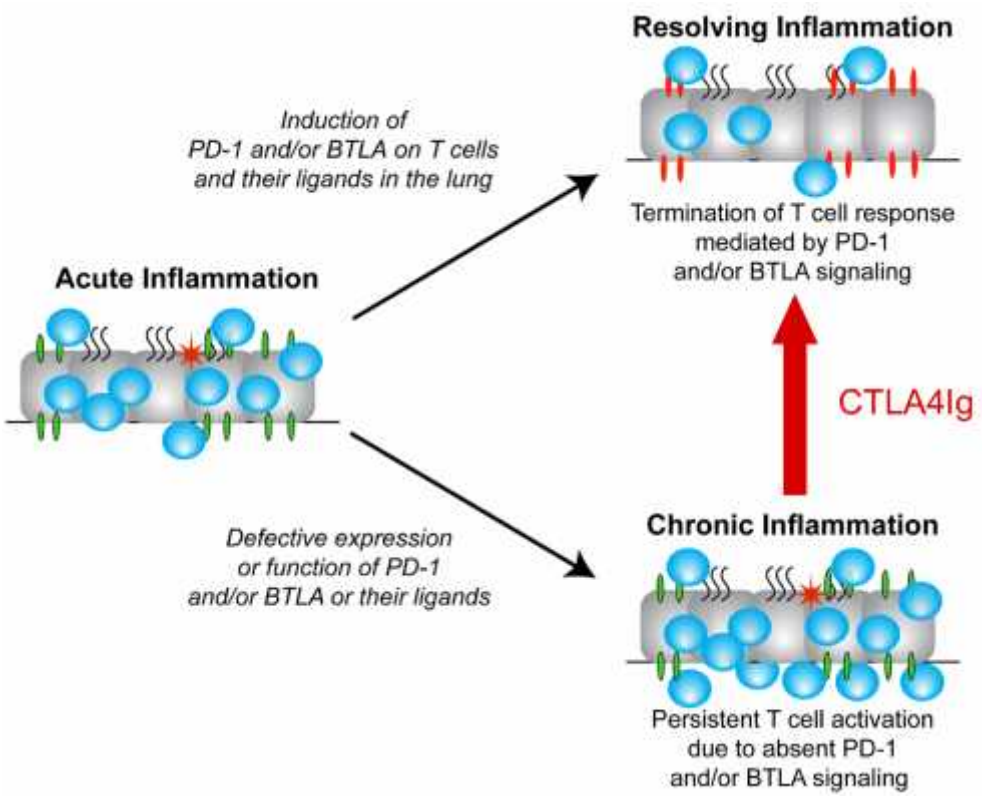

Figure 2. Resolution of the inflammatory response. Following activation of inflammation within the airways, inhibitory receptors and ligands are upregulated on T lymphocytes and other cells in the lung environment. Engagement of these inhibitory receptors leads to resolution of inflammation. When there is defective expression or function of these receptors, chronic inflammation may ensue. This chronic inflammation may then be resolved through the use of the drug CTLA4Ig.

10 and through the inhibitory receptors CTLA4, PD-1, and BTLA (112). Optimization of the number or function of these suppressive cells may be a potential therapeutic target in allergic airway inflammation. Though the exact mechanisms of action remain unclear, we will briefly review here, the role of Tregs in limiting allergic airway inflammation.

5.1. Regulatory T cells in murine models of allergic airway inflammation

In murine models, it has been shown that the number of Foxp3+ cells increases during airway inflammation, suggesting that it may be a natural mechanism by which organisms limit or resolve lung inflammation (113) . Depletion of Tregs prior to antigen challenge can lead to increased inflammation, airway hyperresponsiveness, eosinophilia, and Th2 cytokine production (114-115). Conversely, adoptive transfer of Tregs inhibits airway inflammation (116-119). While these studies have shown the importance of Tregs in regulating allergic airway inflammation, there is no consensus on the precise mechanism of action. Pathways implicated by these studies include, PD-1, increased pulmonary mDCs, as well as IL-10 dependent and -independent pathways.

Interestingly, some evidence suggests that current therapies for asthma may work in part by effecting Tregs. Treatment of mice with corticosteroids and IL-2 led to an increase in Foxp3+ Tregs in spleens which were able to suppress proliferation of CD4+CD25- T cells *in vitro* (120). Vitamin D can inhibit proinflammatory responses and has recently been used in combination with glucocorticoids in order to determine their combined effect on Tregs. *In vitro* stimulation of CD4+ T cells with Vitamin D and dexamethasone led to production of Tregs, determined by both the production of IL-10 and the ability to prevent EAE *in vivo* (121).

5.2. Regulatory T cells in human asthma

Tregs have been implicated as a possible suppressor of allergic airway inflammation in humans. In atopic children and adults, CD4+CD25hi T cells isolated from the blood have a reduced ability to suppress CD4+CD25- cells, as compared to controls (122-127). While comparison of nonatopic controls with asthmatics showed no significant difference in the percentages of CD4+CD25hi T cells in the blood, a decrease of Foxp3 expression was shown (126). Furthermore, one study suggested there may be a decrease in Tregs in the broncoalveolar lavage fluid (BALF) of asthmatic children (128). Another study comparing asthmatic and healthy individuals showed a greater number of Tregs in healthy individuals, while asthmatics had a higher percentage of Th2 cells (129). When these IL-10 producing Tregs, which

expressed CTLA4, PD-1 and IL-10R, were expanded *ex vivo* and cultured with peripheral blood mononuclear cells (PBMCs), there was an antigen-specific suppression of proliferation.

The study of Tregs in asthmatics is complicated by the prevalent use of corticosteroids, which may alter Tregs by affecting both IL-10 production and Foxp3 expression (122-125). In one study where patients used corticosteroids, moderate/severe asthmatics had an increase in CD4+Foxp3+ cells in the BAL as compared to healthy adults (130). The authors attributed this increase to a combination of the use of corticosteroids and increased airway inflammation. A study of pediatric patients with asthma and allergic rhinitis found there to be a lower percentage of CD4+CD25hi cells in the blood, though Foxp3 mRNA levels were increased as compared to control patients (131). Again, in this study, these patients received steroids, which may alter Foxp3 expression. Similarly, Hartl *et al* demonstrated that administration of corticosteroids increased the number of CD4+CD25hi cells in the BALF and the suppressive capabilities of these cells (128). In another study, the numbers of CD4+CD25hiFoxp3+ cells in the peripheral blood were found to be the same between asthmatics and control patients (132). However, the decreased expression of Foxp3 in the CD4+CD25hi T cells of asthmatics patients was less pronounced in those treated with glucocorticoids. Additionally, Vitamin D may influence the generation of IL-10 producing Tregs, an effect that may synergize with glucocorticoids (121, 133). It has been proposed that Vitamin D may increase the effectiveness of corticosteroid therapy in some steroid resistant asthmatics (133-135). Thus, Tregs have an important, if not yet well defined, role in regulating the asthmatic phenotype.

6. CONCLUSION

Asthma is a chronic inflammatory disease of the airways. In this review we have explored three possible categories of targets for controlling asthma and its debilitating symptoms. Though many similarities exist between murine models of allergic airway inflammation and human asthma, there are differences in expression and function of individual molecules which are important for the pathogenesis of this disease. The first set of possible targets reviewed includes chemoattractant receptors which regulate T cell trafficking into the lung during an immune response. Currently, it seems that targeting the trafficking of T lymphocytes during allergic airway inflammation may provide the most complicated strategies of the three categories discussed in this review. All of the receptors discussed are associated with multiple cell types and in many locations. To date, no lung-specific chemoattractant and receptor pair have been identified. Targeting any individually known molecule important for the trafficking of T cells may lead to a variety of outcomes.

The second category of targets reviewed was inhibitory receptors expressed on T cells. As with targeting T cell trafficking, a central issue with targeting these inhibitory receptors is that they are general T cell receptors and may dampen other aspects of the immune system, with the accompanying potential for deleterious outcomes. Last, we examined the function of Treg cells as a mechanism for ablating allergic airway inflammation. Use of Tregs in this capacity encompasses aspects of both the trafficking of these cells into the lungs and inhibitory ligands as possible mechanisms of suppression. The potential ability of glucocorticoids to increase the numbers and function of Tregs, including through enhanced upregulation of inhibitory receptors, may provide a new clinical endpoint for optimizing the use of already approved treatments for asthma. Studies altering the way that glucocorticoids are administered to optimize effects on Tregs may be key to understanding "natural" suppression of allergic airway inflammation. Though the three main topics reviewed here are broad, they are all complicatedly intertwined. Studies of the trafficking of T cells, the mechanisms of T cell inhibitory receptors, and Tregs cells may lead to exciting new therapies to aid in the control of asthma.

7. ACKNOWLEDGEMENTS

The authors thank Jonathan Boomer and Traci Bricker for discussion and review of the manuscript.

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Abbreviations: APC, antigen presenting cell; BAL, bronchoalveolar lavage; BALF, bronchoalveolar lavage fluid; BTLA, B and T lymphocyte attenuator; CTLA4, cytotoxic T-lymphocyte antigen 4; EAE, experimental autoimmune encephalomyelitis; GVHD, graft versus host disease; HVEM, herpes virus entry mediator; ICOS, inducible costimulator; LTB4, leukotriene B4; MCP-3, monocyte specific chemokine-3; mDC, myeloid dendritic cell; MIP-1-alpha, macrophage inflammatory protein-1-alpha; NK, natural killer; PBMC, peripheral blood mononuclear cell; PD-1, programmed death receptor; PGD2, prostaglandin D2; RANTES, Regulated upon activation, normal T-cell expressed and secreted; TNFR, tumor necrosis factor receptor; TRAIL, TNF-related apoptosis-inducing ligand;

Key Words: Asthma, T cells, Inflammation, Lung, Review

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