Wheezing and itching
The requirement for STAT proteins in allergic inflammation

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Abbreviations: AAD, allergic airway disease; AD, atopic dermatitis; ASM, airway smooth muscle; CCL, C-C chemokine ligand; IL, interleukin; LPS, lipopolysaccharide; OVA, ovalbumin; SNP, single nucleotide polymorphism; Th, CD4+ T helper cell subset; WT, wild-type

The development of allergic inflammation requires the orchestration of gene expression from the inflamed tissue and from the infiltrating immune cells. Since many of the cytokines that promote allergic inflammation signal through hematopoietic family receptors, the Signal Transducer and Activator of Transcription (STAT) family have obligate roles in pro-allergic cytokine-induced gene regulation in multiple cell types. In this review, we summarize work defining the contribution of each of the STAT family members to the development of allergic inflammation, using data from mouse models of allergic inflammation, studies on patient samples and correlations with single nucleotide polymorphisms in STAT genes.

Inappropriate immune responses to otherwise innocuous allergens result in the development of inflammatory disease.¹,² Hyper-sensitivity responses to allergens lead to a variety of allergic diseases, including asthma, rhinitis, atopic dermatitis, intestinal anaphylaxis and eosinophilic esophagitis. The incidence of allergic disease is growing in Western society, creating considerable health care costs. Following initial allergen exposure, epithelial cells at the environmental interface such as keratinocytes and airway epithelial cells, secrete cytokines that recruit innate and adaptive immune cells to the site of exposure, initiating the induction of an allergen-specific immune response. Dendritic cells prime the development of effector T cells that produce cytokines including IL-4, IL-5, IL-9, IL-13 and IL-17 to promote inflammation.³,⁴ Although Th2 cells are thought to be the major cells involved in allergic inflammation, roles for Th1, Th9 and Th17 cells have been demonstrated. Cytokines produced by T helper cells stimulate allergen-specific antibody production, particularly IgE that sensitizes mast cells for degranulation upon subsequent exposure to allergen. Allergen challenge results in the recruitment of a variety of cells to the site including T cells, B cells, dendritic cells, eosinophils and neutrophils. Inflammation may be transient, but chronic exposure to allergens results in disease such as asthma characterized by pulmonary inflammation, mucus production, tissue remodeling and airflow hyperreactivity (AHR). At various stages in the development of allergic inflammation, the generation of T helper subsets and the responses of resident cells in the inflamed target organs rely upon cytokine stimulation and the subsequent activation of Signal Transducer and Activator of Transcription (STAT) proteins.

In this review we focus on the role of STAT proteins in the development of allergic inflammation. We review data both from biological samples from patients and single nucleotide polymorphisms supporting a role for STATs in human disease (summarized in Table 1). We also summarize the evidence from a number of models of asthma that have been developed in mice, collectively referred to here as allergic airway disease (AAD), and models of other allergic diseases that demonstrate a requirement for STAT family members in the pathogenesis of allergic inflammation.

STAT1 and STAT2

STAT1 is primarily activated by type I and type II interferons, although stimulation with a number of other cytokines can result in STAT1 activation. In contrast, STAT2 activation is restricted to type I interferons. Interferons are often considered antagonists of Th2 development and allergic inflammation, though there is evidence that active STAT1 may also contribute to inflammation.

Levels of activated STAT1, but not other transcription factors such as STAT3, NFκB or AP-1, are increased in airway epithelial cells of asthmatic patients compared with non-asthmatic subjects or patients with chronic bronchitis.⁵ Similarly, levels of phospho-STAT1, but not phospho-STAT3 or STAT5, are increased in peripheral CD4+CD161+ T cells isolated from asthmatic patients compared with healthy subjects.⁶ Consistent with an anti-allergic function of STAT1, the presence of the STAT1 SNP rs3771300 is inversely related to total serum IgE levels in a population of German children and may be protective for atopic sensitization,⁷ and there is a significant association between STAT2 SNP rs2066807 and asthma in Chinese and Taiwanese children.⁸ IFN-γ has been shown to suppress murine AAD in a STAT1-dependent manner. Upon continuous exposure to allergen, IFN-γ

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www.landesbioscience.com JAK-STAT
induces apoptosis of airway epithelial cells, leading to the eventual resolution of Ag-induced goblet cell hyperplasia.19-21 IFN-γ-STAT1 signaling can impair IL-4-induced STAT6 phosphorylation and production of eotaxin, an eosinophil chemoattractant, through the induction of SOCS-1.13 Studies using mouse embryonic fibroblasts have shown that IFN-γ/STAT1 signaling can impair IL-4-induced STAT6 phosphorylation and production of eotaxin, an eosinophil chemoattractant, through the induction of SOCS-1.13

In contrast, STAT1 can also promote allergen-induced AAD in mice when Th1 cells contribute to the inflammation. Administration of STAT1-specific decoy oligonucleotides to the airways of allergic mice results in reduced lung expression of the co-stimulatory molecule, CD40 and adhesion molecule, VCAM-1, of allergic mice results in reduced lung expression of the co-stimulatory molecule, CD40 and adhesion molecule, VCAM-1, which correlates with reduced pulmonary lymphocytic infiltrate along with reduced AHR.14 STAT1-deficient mice display limited recruitment of adoptively transferred Ag-specific Th1 cells to their lungs and airways after local allergen challenge. STAT1 induces the expression of the CXCR3 ligands CXCL9, CXCL10, and CXCL11 in the lung whose expression is important for the Ag-induced recruitment of CXCR3-expressing Th1 cells.15 Upon exposure to lipopolysaccharide (LPS) and ovalbumin (OVA), mice that have received adoptively transferred Ag-specific Th1 cells display increased IFN-γ and STAT1-dependent expression of KC and MIP-2, two CXCR2 ligands, which correlates with enhanced pulmonary recruitment of CXCR2-expressing neutrophils.16 Taken together, STAT1 may inhibit or promote the development of AAD depending on the cells involved in a particular state of inflammation.

**STAT3**

STAT3 is activated by a large number of cytokines present in the pro-allergic milieu. Moreover, it is expressed in multiple cell types including epithelial cells, airway smooth muscle cells and immune cells. Thus, it is a critical component in multiple aspects of allergic disease.

Although not associated with classical atopic disease, heterozygous mutations in the DNA binding, SH2, linker and trans-activation domains of STAT3 have been identified as the primary molecular cause of autosomal-dominant Hyper-IgE syndrome (HIES), and this has been extensively reviewed elsewhere.17-20 An examination of B cells isolated from control and HIES patients demonstrated that STAT3 is required for IL-23-stimulated IgE production and thus, IgE production in response to IL-21 was decreased in B cells from HIES patients.21 However, a later report found that the STAT3 mutations identified in HIES were not responsible for elevated serum IgE levels in asthmatic patients.22 It is not clear whether SNPs in the STAT3 gene are associated with allergic phenotypes in patients. Three STAT3 polymorphisms (rs2306581, rs957971, rs1026916) are strongly associated with decreased lung function in asthmatic adults and children.23 In contrast, an analysis of 25 STAT3 SNPs demonstrated no association of any of the STAT3 polymorphisms with asthma, lung

### Table 1. Correlations of allergic disease with SNPs in STAT genes

| Gene Polymorphism | Disease/Phenotype | Population | References |
|-------------------|-------------------|------------|------------|
| STAT2 rs2066807   | Associated with asthma | Chinese and Taiwanese | 8 |
| STAT3 rs2306581, rs957971, rs1026916 | Associated with decreased lung function | Caucasian | 23 |
| STAT4 T90099C     | Associated with risk of mite allergen IgE production in asthmatics | Korean | 37 |
| STAT6 rs2d401      | Inconsistent findings with asthma correlation | Japanese, Swedish, Finnish | 38, 39, 65, 67-69 |
| STAT6 rs32d4015    | No association with bronchial asthma, atopic dermatitis, food-related anaphylaxis, serum IgE | Japanese | 65, 67 |
| STAT6 rs32d4015    | Associated with susceptibility to nut allergy | British Caucasian | 66 |
| STAT6 rs32d4011    | Associated with increased IgE levels | German and Swedish | 69, 73, 74 |
| STAT6 rs32d4011    | Association with recurrent wheezing but not asthma susceptibility | Slovene | 72 |
| STAT6 rs1059913    | Associated with increased IgE levels and bronchial responsiveness to methacholine | German and Swedish | 69, 74 |
| STAT6 rs302d4074   | Associated with improved lung function | Chinese | 76 |
| STAT6 rs20d4071, rs8d4715, rs167768, rs703817 | Associated with AD patients with viral skin infections (eczema herpeticum) | Caucasian | 77 |
| STAT6 GT repeat in exon 1 (A1 allele, GT1 repeat) | Increased frequency in patients with bronchial asthma, atopic dermatitis, and/or food-related anaphylaxis | Japanese | 67 |
| STAT6 GT repeat A1-A5 (GT17, GT12) | No correlation with asthma, serum IgE or bronchial responsiveness | German and Swedish | 69 |
| STAT6 GT repeat A4 (GT11) | Associated with increased numbers of peripheral eosinophils | German and Swedish | 69 |
| STAT6 GT repeat A1 allele (GT10) | Associated with atopic asthma and elevated serum IgE | Americans and British Caucasians | 71 |
| STAT6 GT repeat A3 allele (GT12) | Associated with asthma but not elevated serum IgE | North Indian | 70 |
function, high levels of total or specific serum IgE, or elevated eosinophil counts. Hypothesis: In human airway smooth muscle (ASM) cells, STAT3 expression is required for the expression of eotaxin-1/CCCA11 following IL-9, IL-17A, and Oncostatin M stimulation, VEGF expression following Oncostatin M stimulation and IL-6 and IL-6/IL-11 cytokine production following TSLP stimulation. PDGF-stimulated proliferation of ASM cells requires STAT3 to regulate cyclin D3 and p27 expression. STAT3 expression in epithelial cells and CD4+ T cells is essential for the development of allergic inflammation in mice. A chronic model of murine AAD, continuous local exposure to allergen induces STAT3 activation in the epithelium, smooth muscle, and surrounding cells of the airway in wild type (WT) mice. STAT3 expression in lung epithelial cells is necessary for the induction of the chemokines TARC and KC, and mice that lack STAT3 expression in their lung epithelial cells display impaired recruitment of eosinophils and Th2 cells into their lungs, which correlates with reduced pulmonary inflammation and AHR. In addition, it has recently been shown that STAT3 cooperates with STAT6 to promote the development of Th2 cells and Th2-mediated allergic inflammation. In an OVA-induced model of AAD, mice with a T cell specific deletion of STAT3 (Stat3Cd4−/−) display decreased pulmonary inflammation and eosinophilia along with reduced levels of Th2 cytokines and IL-17A in their airways. Since STAT3 is important for the development of both Th2 and Th17 cells, these observations cannot be solely attributed to Th2 cells, and the role of STAT3 in Th2-mediated allergic inflammation was further assessed through crossing Stat3−/− mice to mice that express a constitutively active Stat6 (Stat6VT) in T cells. STAT3-sufficient Stat6VT mice are characterized by IL-4-dependent spontaneous pulmonary and skin inflammation and blepharitis. STAT3-deficient T cells do not develop spontaneous pulmonary and skin inflammation nor do they develop blepharitis, demonstrating that STAT3 expression in T cells is important for the development of Th2-mediated allergic inflammation. Thus, STAT3 expression in multiple cell types is critical for the development of allergic inflammation.

STAT4

Among the STAT proteins, STAT4 is the only one that shows a tissue-restricted pattern of expression, primarily in lymphoid and myeloid cells. STAT4 is required for all known IL-12 biological responses, including IFN-γ production and the differentiation of Th1 cells. STAT4 also mediates some responses to type I IFNs and to IL-23. Considerably more work has been done to define a role for STAT4 in mouse models than has been reported for disease in patients. In humans, a STAT4 SNP (T90089C) is positively associated with risk of production of mite allergen-specific IgE in asthmatic Korean patients, although no association to asthma is found in Korean or Finnish populations. A later study on the same STAT4 polymorphism identified a significant positive association with asthma in a Chinese population. As was noted for STAT1, STAT4 can have both positive and negative roles in the development of allergic inflammation. The obligate requirement for STAT4 in IFN-γ-producing Th1 cells, which can inhibit Th2-mediated inflammation, provides a mechanism for negative regulation. IFN-γ-induced negative regulation of AAD is dependent on IL-12 and STAT4 signals, as STAT4-deficient mice, or WT mice exposed to IL-12 neutralizing antibodies, display attenuated pulmonary inflammation, cytokine responses and AHR. In addition, the combination of IL-2 and IL-18, which increases IL-12 and IFN-γ in the airways, can reduce pulmonary inflammation and AHR in OVA-sensitized mice and these effects are dependent on local IL-12 and STAT4-induced IFN-γ production from NK cells. Based on its role in Th1 cells, the demonstration that STAT4 is required for allergic inflammation is somewhat counter-intuitive. Several mechanisms have been proposed to explain this phenomenon. In a cockroach allergen model, STAT4-deficient mice, and WT mice treated with anti-IL-12, display reduced inflammation that correlates with decreased pulmonary chemokine production. These defects cannot be rescued by adoptive transfer of WT sensitized splenocytes, suggesting that there may be dominant repressive factors present in the STAT4-deficient environment. In an OVA-induced model, two possible, and not mutually exclusive, mechanisms have been defined for decreased allergic inflammation in the absence of STAT4. The first is based on the observation that IL-17 is required for allergic inflammation in this model, and that IL-17 production from lymphocytes isolated from sensitized and challenged STAT4-deficient mice is decreased compared with control mice. It is possible that IL-17 plays an important role in the development of STAT4-dependent AAD, perhaps by recruiting neutrophils to the airways of challenged mice. Parallel studies also implicate IL-12 and STAT4 in limiting the development of inducible Tregs during the development of allergic inflammation. Mechanistically, STAT4 may mediate this effect by inducing repressive chromatin modifications at the Foxp3 locus and impairing STAT5 binding to Foxp3. STAT4 also contributes to AAD when LPS is used as an adjuvant. Mice exposed to high or low doses of LPS during airway allergen sensitization develop allergic inflammation associated with Th1 or Th2 responses, respectively, after local Ag-challenge. When administered during the induction of AAD, high-dose LPS results in an increase in serum IgE and IgG2a, pulmonary IL-12 production, and enhanced AHR that is associated with pulmonary infiltration of macrophages, lymphocytes and neutrophils but not eosinophils. Importantly, the responses induced by high-dose LPS are dependent on STAT4. Thus, the pro-inflammatory role of STAT4 in many autoimmune diseases extends to the development of allergic inflammation in the lung.

STAT5

STAT5 is activated by a number of γc receptor cytokines on various cells that contribute to the development of AAD, including IL-2 and IL-9. STAT5 is activated by thymic stromal lymphopoietin, a cytokine critical for the development of allergic
inflammation, in T cells and dendritic cells. STAT5 plays an important role in mast cell and eosinophil responses, both of which are important for the development of inflammatory diseases, such as AAD. Studies using STAT5-deficient mice have shown that STAT5 is critical for mast cell proliferation, survival, and function. STAT5 is rapidly activated in response to IL-4 and Ag-mediated FcεRI cross-linkage in WT bone marrow mast cells and STAT5-deficient mast cells display impaired IL-4-mediated degranulation and decreased leukotriene and cytokine secretion. IL-5-induced STAT5A and STAT5B signaling is important for murine eosinophilopoiesis and eosinophil chemotaxis and can also induce the development of IL-4-producing eosinophils. Upon induction of AAD, STAT5A-deficient and STAT5B-deficient allergic mice proliferate less than those from WT mice when stimulated with relevant antigen, suggesting that STAT5 may be important for the priming of Ag-specific T cells during allergic inflammation. Furthermore, while STAT6 is critical for the development of Th2 cells and allergic inflammation, STAT6-independent Th2 differentiation can occur in a STAT5A-dependent manner. Allergic mice deficient in STAT5A or STAT6 display reduced pulmonary lymphocytic and eosinophilic infiltration as well as lower levels of IL-5 in their airways in comparison to WT allergic mice. In addition, splenocytes from STAT5A-deficient and STAT5B-deficient allergic mice proliferate less than those from WT mice when stimulated with relevant antigen, suggesting that STAT6 may be important for the priming of Ag-specific T cells during allergic inflammation. Nevertheless, while STAT6 is critical for the development of Th2 cells and allergic inflammation, STAT6-independent Th2 differentiation can occur in a STAT5A-dependent manner. Allergic mice deficient in STAT5A or STAT6 display reduced pulmonary lymphocytic and eosinophilic infiltration in comparison to WT mice, whereas in the absence of both STAT5A and STAT6, pulmonary inflammation is nearly abolished. Together, these data show that STAT5-induced signals are important for the normal development and function of mast cells and eosinophils and allergen-induced responses in murine AAD.

**STAT6**

STAT6 has been the focus of extensive research in allergic inflammation and atopic disease. It is activated by IL-4 and IL-13, cytokines that are critical for the differentiation of Th2 cells, and responses to Th2 cytokines by resident tissue cells. Considerable evidence supports a central role for STAT6 in human and murine allergic inflammation.

**Patient samples.** An examination of patients with allergic rhinitis revealed that STAT6 expression (nuclear and cytoplasmic) in the nasal mucosa increases following allergen challenge, but steroid treatment prevented the allergen-induced increase in STAT6. Similarly, baseline levels of phospho-STAT6 in CD4+CD161+ peripheral T cells are higher in atopic asthmatics, but treatment with oral corticosteroids decreased levels of phospho-STAT6. Interestingly, the corticosteroids were specifically targeting STAT6 since baseline levels of phospho-STAT5 (which are also increased in asthmatics) were not decreased following steroid treatment. Increased numbers of STAT6+ cells are present in bronchial epithelial cells from atopic asthmatic patients compared with non-atopic asthmatics and control patients, and similarly, the number of cells expressing STAT6 as well as c-Maf and GATA-3, Th2-associated transcription factors, in the sputum of asthmatic patients is significantly higher than that of healthy subjects. However, neither protein levels nor DNA-binding activity of STAT6 in peripheral blood monocytes is different between patients with asthma or elevated serum IgE and nonatopic subjects. An examination of bronchial epithelium from patients with mild asthma, severe asthma or non-atopic controls demonstrated that STAT6 expression is significantly higher in bronchial epithelial cells from patients with severe asthma, but not in patients with mild asthma, compared with non-atopic subjects, and following allergen challenge. An increased number of phosphorylated STAT6+ fibroblasts are observed in the bronchial tissue of atopic asthmatics as compared with control subjects.

**SNPs** Polymorphisms of the STAT6 gene are associated with various aspects of asthma and atopy (Table 1). In an examination of British and Japanese populations, a single nucleotide polymorphism (STAT6 G2296A; rs324015) is associated with mild atopic asthma, but not atopy or elevated serum IgE levels, in a Japanese population, but not in a British population. While this SNP is associated with the susceptibility and severity of nut allergy in an atopic British population, other studies found no association of the polymorphism with asthma in Japanese, German, Swedish, and Chinese populations nor with serum IgE levels in a Finnish population. A dinucleotide polymorphism (GT 13–17 repeats) in exon 1 of STAT6 has also been studied for its potential link to atopic disorders. The A1 allele (GT 13 repeat) is found more frequently in Japanese children with allergic diseases (bronchial asthma, atopic dermatitis, and/or food-related anaphylaxis) than controls and there is a strong association between allergic disease and the A1/A3 (GT 15 repeat) heterozygote. However, no variants of the dinucleotide polymorphism are associated with elevated serum levels of IgE in the allergic patients. Further examination of the GT polymorphism alleles A1–A5 (13–17 repeats, respectively) demonstrated no association with asthma, total serum IgE levels or bronchial responsiveness to methacholine challenge. However, GT repeat A4 has a significant association with increased numbers of peripheral eosinophils. Conversely, an examination of an Indian population found an association of GT repeat A3 (GT13) with asthma but not elevated serum IgE. A later study of the GT polymorphisms identified two novel repeats GT12 and GT18 in American and British populations, respectively, although the previously identified A1 (13 repeat) and A3 (15 repeat) alleles were more common. Importantly, Gao et al. demonstrated a significant association of the A1 allele with atopic asthma and elevated serum IgE levels in American and British Caucasians and also revealed the ability of the GT repeat alleles to differentially regulate STAT6 promoter activity.

Examination of additional STAT6 SNPs in a German and Swedish sibling-pair study revealed no association with asthma or blood eosinophil count, but four SNPs (6653C/T; rs324011, 1309AG, 1507CT, and 4671AG; rs45599) are associated with increased levels of serum IgE and an additional SNP (4610AG; rs1059513) shows a strong correlation with increased bronchial responsiveness to methacholine challenge. Further studies examining STAT6 SNP rs324011 demonstrated no association with asthma but revealed a strong association with total serum
IgE levels\(^7\) and in other similar studies both rs324011 and rs1059519 were significantly associated with elevated levels of total serum IgE.\(^6,7\) Importantly, Kubesch et al. demonstrated that STAT6 SNP rs324011 in combination with IL-13 and IL-4 polymorphisms (C1112T and C589T, respectively) increase the risk of asthma and elevated serum IgE levels significantly above the maximum effect of any individual SNP or combination of only two SNPs.\(^7\) Interestingly, an examination of STAT6 SNP rs3024974 in a population of Chinese children revealed a significant association of this SNP with improved lung function assessed by forced expiratory volume.\(^6\) Lastly, in a Caucasian population, four STAT6 SNPs (rs3024975, rs841718, rs617769, rs703817) are significantly associated with atop dermatitis eczema herpeticum, a disseminated herpervirus skin infection in AD patients.\(^7\) This observation is consistent with decreased antiviral immunity in the skin of patients with AD and mice that express a constitutively active STAT6, and may be linked to a requirement for STAT6 in multiple aspects of antiviral immunity.\(^7\) Taken together, these findings provide evidence for genetic association of STAT6 with allergic disease but also identify population-specific roles of STAT6 polymorphisms in asthma and atopy.

**Mouse models.** STAT6 activation is essential for IL-4- and IL-13-induced responses and development of inflammation in several models of allergen-induced AAD. Upon induction of acute (OVA)-induced AAD, mice deficient in STAT6 display impaired Ag-induced pulmonary inflammation including reduced TH2 cytokines and eosinophil infiltration into their airways, coincident with reduced goblet cell hyperplasia, serum IgE and AHR, in comparison to WT mice.\(^10\) The degree to which eosinophil infiltration depends upon STAT6 might vary with the number of allergen challenges, with chronic challenges resulting in inflammation that is only, partially STAT6-dependent.\(^15\) Administration of IL-13 to WT mice, or transgenic mice that express a mutant IL-4R that has a glutamine to arginine substitution at position 576 (RS76), display STAT6-dependent pulmonary inflammation associated with pulmonary eosinophilia, AHR and goblet cell hyperplasia.\(^4,10\) Similarly, transgenic mice expressing IL-13 in airway epithelial cells develop STAT6-dependent pulmonary eosinophilia, goblet cell hyperplasia, fibrosis and AHR.\(^10\) STAT6 is also required for the increased OVA-induced AAD observed in T-bet-deficient mice that display enhanced pulmonary eosinophilia, goblet cell hyperplasia, and TH2 cytokines in their airways in comparison to WT mice.\(^10\) Pulmonary viral infection results in AAD similar to allergen challenge, and a similar requirement for STAT6 was observed in the AAD resulting from respiratory syncytial virus infection, or from OVA sensitization using the viral mimic poly(I:C).\(^88,89\)

In contrast to acute models of AAD that have shown a role for STAT6 in the development of allergen-induced pulmonary eosinophilia, goblet cell hyperplasia and AHR, a chronic model in which sensitized mice are challenged with OVA allergen over a 6 week period, results in the development of eosinophilia and AHR independent of STAT6, although goblet cell hyperplasia is STAT6-dependent in both models. Interestingly, mice doubly deficient in IL-4 and IL-13 do not develop pulmonary eosinophilia or AHR in OVA-induced chronic AAD, suggesting that these cytokines might have STAT6-independent function in some disease models.\(^10\) In support of this, when chronic AAD is induced after mice are exposed to Aspergillus fumigatus, mice develop AHR in an IL-13-dependent and STAT6-independent manner.\(^11\) Together, these data suggest that while IL-4 and IL-13 are critical for the development of pulmonary eosinophilia and AHR in chronic models of AAD, STAT6-independent mechanisms must occur to facilitate the development of these responses.

The requirement for STAT6 in the development of AAD represents function in multiple cell types. An approach that used a combination of bone marrow chimera and adoptive transfer demonstrated that STAT6 is required both in bone marrow-derived cells and tissue resident cells.\(^10\) Compared with WT recipients, STAT6-deficient mice that receive adoptively transferred WT Ag-specific TH2 cells are impaired in their ability to recruit transferred TH2 cells to their lungs which results in reduced TH2-induced pulmonary eosinophilia, goblet cell hyperplasia and AHR upon airway antigen challenge. Furthermore, expression of chemokines associated with the recruitment of TH2 cells and eosinophils are significantly reduced in the lungs of STAT6-deficient recipients in comparison to WT recipients.\(^10\) Similar conclusions were made from studies using adoptive transfer of splenic T cells from sensitized mice to STAT6-sufficient and STAT6-deficient mice followed by allergen challenge. Transfer results in an increase in AHR, although to a lesser extent in the STAT6-deficient recipients, and occurs independently of pulmonary eosinophilia. AHR does not develop in allergen challenged STAT6-deficient recipients after adoptive transfer of splenic T cells from sensitized STAT6-deficient mice.\(^10\) Moreover, while STAT6 is required for transgenic IL-13-induced AAD, reconstitution of hSTAT6 in the airway epithelial cells of STAT6-deficient IL-13 transgenic mice reconstitutes goblet cell hyperplasia and AHR, which suggests that STAT6 in individual cell types is sufficient to generate some aspects of AAD.\(^10\) AAD can also be recovered in the absence of STAT6 by administration of cytokines downstream of STAT6. Injection of recombinant mIL-5 prior to Ag-challenge can reconstitute pulmonary eosinophilia and AHR in STAT6-deficient mice.\(^10\) Similarly, intranasal administration of certain reconstitutes pulmonary eosinophilia, but not goblet cell hyperplasia and AHR in TH2 cell-transfered STAT6-deficient recipients after airway challenge.\(^11\) Together, these data suggest that STAT6 plays an obligate role in the development of many features of AAD.

**STAT6VT.** Although no coding mutations of STAT6 have been identified in patients, as reviewed above, atopy is often associated with increased expression or activation of STAT6. As a model of this phenomenon, transgenic mice were generated that express a mutant STAT6 that has a valine and threonine in the SH2 domain altered to alanines (STAT6VT) and is constitutively phosphorylated and transcriptionally active in the absence of IL-4 stimulation.\(^10\) Transgenic mice expressing STAT6VT under control of the CD2 locus have a predisposition toward the development of allergic inflammation in lungs, skin and in periocular mucosal tissues.\(^10\) Transgenic mice have...
increased production of IgE, and STAT6VT transgenic T cells have an increased ability to differentiate into Th2 cells. 101 IL-4-deficient STAT6VT mice are protected from the spontaneous development of AAD, allergic skin inflammation, and blepharialtis. 97 Allergic skin inflammation correlates with a decrease in epidermal differentiation complex (EDC) genes by IL-4, and decreased EDC gene expression, and barrier function, correlates with disease onset. 98, 99, 100 Interestingly, IL-4-deficient STAT6VT mice display an increase in EDC genes and are protected from allergic skin inflammation, demonstrating a role for IL-4 in the homeostasis of epidermal barrier function. 100 This phenotype is distinct from skin lesion-prone NC/Nga mice that develop skin lesions even in the absence of STAT6, suggesting that STAT6VT transgenic mice provide a better model for Th2-restricted inflammation. 100 STAT6VT transgenic mice are also more susceptible to vaccinia virus infection. Upon vaccinia virus skin inoculation, STAT6VT mice that are free of skin irritation at the time of exposure, display increased mortality in comparison to WT mice, correlating with enhanced viral replication in primary skin lesions and increased numbers of satellite lesions, the latter of which indicates a possible fatal systemic infection. 77 Together, these data indicate that activated STAT6 expression in T cells is sufficient to promote allergic inflammation.

STAT6 in mast cells. Although STAT6 is not required for mast cell development, 101 Th2 cytokines can limit mast cell function and inflammatory responses. STAT6-dependent IL-4 signals downregulate FceRI expression in mouse bone marrow-derived mast cells (BMMC), which reduces the inflammatory response associated with IgE stimulation. 102 In addition, STAT6-deficient BMMC transduced with a retrovirus expressing constitutively active STAT6 (STAT6VT) display significantly decreased FceRI expression in comparison to control cells. 103 Furthermore, IL-4 induces STAT6-dependent apoptosis in WT mouse bone marrow cultures through the mitochondrial pathway. Overexpression of STAT6VT in mouse bone marrow cells cultured in the absence of IL-4 results in decreased cell survival. 104 Together, these data indicate that IL-4 induced STAT6 activation inhibits mouse bone marrow mast cell development and effector function, suggesting a homeostatic role for IL-4 and STAT6 in attenuating immune responses which are associated with mast cell function, such as allergic inflammation.

Allergic intestinal inflammation. In a mouse model of intestinal allergic inflammation, sensitized mice that receive oral administration of OVA develop severe diarrhea associated with increased serum IgE levels as well infiltration of eosinophils, mast cells and Th2 cells in the large intestine but not the small intestine. Mice deficient in STAT6 are protected from OVA-induced diarrhea and display undetected eosinophilia in the large intestine along with decreased serum IgE levels in comparison to WT mice. 105 In another study, it was shown that transgenic mice that have mIL-9 overexpressed in the enterocytes of the small intestine develop both spontaneous and oral-Ag-induced IL-4R-β and STAT6-dependent intestinal anaphylaxis, which is associated with intestinal mastocytosis, permeability and intravascular leakage. 106 Similarly, STAT6 is required for cytokine-induced eosinophilic esophagitis. 107 Thus, IL-9-mediated mast cell responses and Th2 cytokine responses in the intestine elicit inflammation in a STAT6-dependent manner.

Inhibitors. As STAT6 is central to the development of allergic inflammation, targeting it might be an effective therapy. A cell penetrating peptide that binds to STAT6 has been shown to effectively inhibit several aspects of OVA-induced AAD. When administered to the airway prior to each allergen challenge, the STAT6 inhibitor localizes to airway epithelial cells and impairs Ag-induced pulmonary eosinophilia, goblet cell hyperplasia, IL-13 production in the airways, AHR induction of mast cell, and mucus genes in the lung. 108 Similar effects on AAD have been shown with small molecule inhibitors of STAT6. 109 Moreover, a topical STAT6 oligonucleotide ointment reduced the severity of the inflammatory skin lesions present in patients with atopic dermatitis. 109 Although specificity and targeting continue to be challenges, STAT6 remains an attractive target for treatment of allergic inflammation.

Direct targets of STAT6 in inflamed tissue. STAT6 functions as a regulator of gene expression. 109 Although much of the published work on direct effects of STAT6 has focused on T and

Table 2. STAT target genes in airway and skin cells

| STAT protein | Target gene | Cell type | Stimulation | References |
|--------------|-------------|-----------|-------------|------------|
| STAT3        | Eotaxin-1/CCL11 | HASMC     | IL-9        | 24         |
| STAT3        | Eotaxin-1/CCL11 | HASMC     | IL-17A      | 25         |
| STAT3        | Eotaxin-1/CCL11 | HASMC     | Oncostatin M| 26         |
| STAT3        | IL-4         | HASMC     | PDGF        | 29         |
| STAT3        | IL-6/CCL8     | HASMC     | PDGF        | 29         |
| STAT3        | VEGF         | HASMC     | Oncostatin M| 27         |
| STAT6        | Eotaxin-1/CCL11 | BEAS-2B   | IL-4 and IL-13 | 113, 114 |
| STAT6        | IL-19        | NHBE      | IL-13       | 116        |
| STAT6        | Eotaxin-1/CCL11 | Human dermal fibroblasts | IL-4 | 115 |
| STAT6        | Eotaxin-1/CCL11 | Human dermal fibroblasts, Esophagal epithelial cells | IL-4 and IL-13 | 118, 119 |
| STAT6        | P-selectin   | Human dermal microvascular endothelial cells | IL-4 | 120 |
| STAT6        | 12/15-lipoxygenase | BEAS-2B   | IL-4       | 121         |
**Conclusions**

As required factors for cytokine responses, STATs provide a critical link between the pro-allergic microenvironment and both immune and target-organ cells. A number of the STAT proteins impact the development of T helper subsets that are important factors in allergic inflammation and suggest specific genotypes will define how each STAT functions at the molecular level to promote the allergic phenotype. The association of STAT gene SNPs with atopic phenotypes further supports a role for these factors in allergic inflammation and suggests specific genotypes or haplotypes that may be useful in identifying children at risk for the development of atopic disease. Targeting STATs with small molecules or biological inhibitors remains a potentially useful approach to treating allergic disease.

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