

Therapeutic approaches for control of transcription factors in allergic disease

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

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Activity Objectives

1. To review the role of inflammatory cytokines in the promotion of various T helper phenotypes.
2. To understand the mechanisms of action of transcription factors in the development of allergic disease.
3. To review the therapeutic approaches for control of transcription factors in allergic disease.
4. To understand the mechanisms of glucocorticoid therapy in allergic disease.

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The inflammatory response observed in allergic disease involves multiple cell types but is orchestrated in part by the T_H2 cytokines IL-4, IL-5, and IL-13. In recent years, the transcription factors that control the expression and function of these cytokines have been elucidated, including signal transducer and activator of transcription 6, GATA3, nuclear factor of activated T cells, and nuclear factor κ B. These molecules are attractive targets for therapeutic intervention because they regulate the expression of numerous effector molecules and functions simultaneously. For instance, the immunosuppressive agents glucocorticoids and cyclosporin A both function by repressing the activity of transcription factors through a variety of mechanisms. In this review we examine the role of each transcription factor in allergic disease and discuss

approaches that have been taken to therapeutically interfere with transcription factor function in allergic disease. (*J Allergy Clin Immunol* 2008;121:803-9.)

Key words: Transcription factors, asthma, atopic dermatitis, signal transducer and activator of transcription 6, GATA3, T_H2, nuclear factor of activated T cells, nuclear factor κ B, glucocorticoid receptor

Allergic diseases, including asthma, are characterized by inflammation driven by CD4⁺ T_H lymphocytes of the T_H2 phenotype.¹ In allergic individuals exposure to allergen results in activation of antigen-specific T_H2 cells and secretion of a variety of cytokines and inflammatory mediators that provoke the inflammatory response. Of the numerous molecules secreted by activated T_H2 cells, the cytokines IL-4, IL-5, and IL-13 are responsible for many of the features of allergic inflammation.¹⁻³ T_H2 cell expression of IL-4 has multiple effects, including differentiation of naive T cells toward the T_H2 lineage and induction of B-cell isotype switching to produce IgE. IL-5 production is critical for the development of the eosinophilia observed in allergic disease. IL-13 is responsible for numerous features of T_H2 inflammation, especially in the asthmatic lung, such as goblet cell hyperplasia, mucus hypersecretion, and bronchial hyperresponsiveness. IL-13 can also alter the phenotype of structural cells in the airway, promoting the expression of proinflammatory mediators by airway smooth muscle.⁴

Given the central role played by T_H2 cells in allergic disease, the mechanisms that control T_H2 differentiation and activation

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Abbreviations used

AP-1:	Activator protein 1
CsA:	Cyclosporin A
GR:	Glucocorticoid receptor
IκB:	Inhibitor of NF-κB
IL-4Rα:	IL-4 receptor α
NFAT:	Nuclear factor of activated T cells
NF-κB:	Nuclear factor κB
p38:	p38 mitogen-activated protein kinase
PPAR:	Peroxisome proliferators-activated receptor
RXR:	Retinoid X receptor
SEGRA:	Selective glucocorticoid receptor agonist
siRNA:	Short interfering RNA
STAT:	Signal transducer and activator of transcription
TTP:	Tristetraprolin

have been the subject of intense scrutiny.^{5,6} This work has identified several transcription factors that perform critical functions in regulating T_H2 cell function, including signal transducer and activator of transcription (STAT) 6, GATA3, c-Maf, nuclear factor of activated T cells (NFAT), nuclear factor κB (NF-κB), glucocorticoid receptor (GR), and peroxisome proliferator-activated receptors (PPARs). Although the roles played by many of these transcription factors were elucidated in murine T_H2 cells, several studies have shown that human T_H2 cells are controlled by similar mechanisms.⁷⁻¹⁰ These transcription factors perform numerous roles in T_H2-mediated inflammation in both antigen-specific T_H2 cells and innate immune and structural cells that respond to T_H2 cytokines. Furthermore, several of these transcription factors (nuclear factor κB [NF-κB], GR, and PPARs) can regulate other genes during the chronic phases of allergic inflammation, which can be characterized by the expression of proinflammatory molecules that are not T_H2 specific. Because transcription factors can control the expression of numerous target genes and also affect cell differentiation, they have become attractive targets for therapeutic intervention.

In this review we describe the role of these transcription factors in allergic disease and report on studies aimed at therapeutic modulation of transcription factor function.

STAT6

The T_H2 cytokines IL-4 and IL-13 have overlapping but nonredundant functions caused by the shared use of a common receptor subunit, IL-4 receptor α (IL-4Rα). Binding of IL-4 or IL-13 to their receptors induces activation of the receptor tyrosine kinases Jak 1, Jak 3, and Tyk 2, which phosphorylate tyrosine residues on the IL-4Rα subunit. This phosphorylation causes recruitment of cytoplasmic STAT6 to the receptor, where it is phosphorylated at tyrosine 641. Once phosphorylated STAT6 dimerizes and translocates to the nucleus to regulate IL-4- and IL-13-dependent gene expression (Fig 1). IL-4 plays a critical role in driving T_H2 cell differentiation, and thus STAT6 is a critical transcription factor in this process. STAT6 knockout mice do not have T_H2 cells and do not induce class switching to IgE, thus demonstrating the essential role of STAT6.¹¹⁻¹³ The use of mice deficient in STAT6 in models of allergic disease has shown that it is critical for the development of T_H2-mediated inflammation. In murine models of asthma, STAT6 knockout mice do not have bronchial hyperresponsiveness, eosinophilia, or mucus overproduction.^{14,15} STAT6 deficiency also abrogates IL-4- and IL-13-dependent inflammation

in murine models of contact hypersensitivity and atopic dermatitis, with decreased eosinophilia, edema, and IgE responses in both models.^{16,17} The effects of STAT6 deficiency in these models of allergic disease depend on 2 aspects of STAT6 function. First, it is critically required for the development of T_H2 cells, and therefore STAT6 knockout mice mount a diminished T_H2 response to allergen challenge. Second, its role in IL-4 and IL-13 signaling in structural cells is also critically important. Elegant studies with mice with restricted expression of STAT6 have shown that T cell-specific expression is not sufficient for pathogenesis and that epithelial cell-specific expression is sufficient for at least some of the features of experimental asthma.¹⁸⁻²⁰

The central role of STAT6 in IL-4 and IL-13 signaling in allergic disease suggests that it would be an excellent therapeutic target, and several approaches have been taken to block STAT6 function. Antisense phosphorothioate oligodeoxynucleotides targeting STAT6 have been used *in vitro* to suppress STAT6 signaling in airway smooth muscle and epithelial cell lines.^{21,22} In each case STAT6 protein levels were efficiently downregulated, and functional blockade of signaling was observed. Double-stranded oligodeoxynucleotides containing a STAT6-binding site have been used in a model of atopic dermatitis as a decoy for STAT6 binding.¹⁷ In this study *in vivo* transfection of the STAT6 decoy into the skin by using liposomes resulted in amelioration of the IgE-mediated late-phase reaction, with reduced edema and neutrophil and eosinophil infiltration. More recently, a study by Rippmann et al²³ used a short interfering RNA (siRNA) approach to knock down STAT6 levels. The authors obtained complete knockdown of STAT6 function in the human epithelial cell line BEAS-2B and blocked the production of CCL26 by these cells.

Two peptide-based approaches have also been used to block STAT6 function. Stolzenberger et al²⁴ used a short peptide derived from the IL-4Rα STAT6-binding site fused to a cell-permeable peptide derived from the antennapedia homeodomain to inhibit STAT6 phosphorylation. The peptide treatment blocked STAT6 activity in a variety of cell types; however, the effect was very transient, with STAT6 phosphorylation returning to normal levels within 30 minutes. A more recent study used a dominant-negative peptide derived from the STAT6 dimerization domain coupled to the protein transduction domain 4 from the HIV-TAT protein. Using this chimeric peptide, McCusker et al²⁵ demonstrated blockade of STAT6 in murine splenocytes, resulting in decreased T_H2 cytokine production *in vitro*. Furthermore, they went on to show that intranasal administration of the STAT6 inhibitory peptide inhibited ovalbumin-induced lung inflammation and mucus production in murine models of rhinitis and asthma. They also observed reduced eosinophilia and airway hyperresponsiveness, suggesting that local administration of this peptide to the airway might have potential as a therapeutic treatment for allergic diseases.

Given the role of STAT6 in all aspects of IL-4 and IL-13 signaling, local blockade of STAT6 function remains a very promising approach for the treatment of allergic disease. Systemic treatment would likely be inappropriate because diminished T_H2 immunity would be a possible side effect.

GATA3

The zinc-finger transcription factor GATA3 is the master regulator of T_H2 cell differentiation. GATA3 expression is

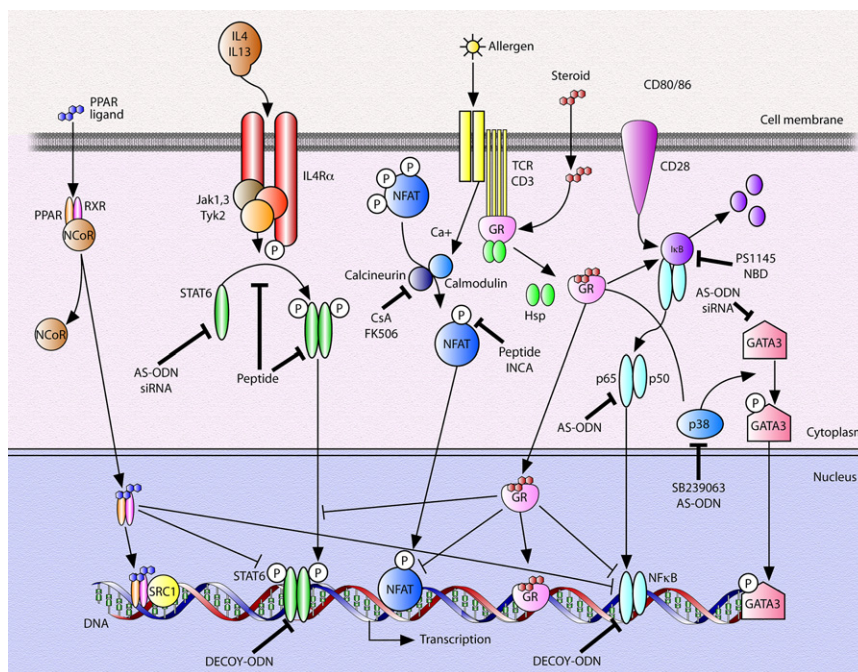


FIG 1. Transcription factor signaling pathways in allergic disease. A schematic diagram detailing the signaling pathways and the points at which therapeutic interventions have been targeted is shown. *Thin lines* represent steps in the signaling cascade. *Thick lines* represent therapeutic strategies that have been examined to date. Please refer to the text for detailed descriptions. *TCR*, T-cell receptor; *AS-ODN*, antisense oligodeoxynucleotide; *NBD*, NF- κ B essential modulator binding domain; *Hsp*, heat shock protein; *p65/p50*, subunits of NF- κ B.

strongly upregulated during T_H2 differentiation.²⁶ Overexpression of GATA3 in T cells induces T_H2 cytokine expression in both naive cells and committed T_H1 cells in both mice and human subjects.^{27,28} GATA3 is believed to function by causing chromatin remodeling of the T_H2 cytokine locus by binding at multiple sites and thus allowing T_H2 cells to express IL-4, IL-5, and IL-13.^{5,10} Mice deficient in GATA3 are embryonically lethal because it plays an important role in vertebrate development; however, T cell-specific deletion of GATA3 demonstrated the essential function of this factor in T_H2 differentiation.^{29,30} Human subjects who have only one functional GATA3 allele also have diminished T_H2 responses.³¹ Transgenic mice that overexpress GATA3 spontaneously have both atopic dermatitis and asthma-like symptoms.³² The number of GATA3-positive cells is increased in the asthmatic lung and in allergic rhinitis and is further increased after allergen challenge.^{33,34} In murine asthma models transgenic mice overexpressing GATA3 in T cells show enhanced airway hyperresponsiveness, increased subepithelial fibrosis, and smooth muscle hyperplasia.^{35,36}

Collectively, these studies indicate that GATA3 would be a suitable target for therapeutic downregulation of T_H2 cell function. Finotto et al³⁷ used antisense phosphorothioate oligonucleotides directed at GATA3 to suppress IL-4-producing T cells *in vitro* and *in vivo*. Local intranasal administration of the antisense oligonucleotides in a murine asthma model resulted in a reduction of lung inflammation, including eosinophil infiltration and T_H2 cytokine production. A reduction in airway hyperresponsiveness was also observed on antisense GATA3 treatment. A recent study has examined the use of lentivirus-mediated GATA3 RNAi in a murine model of allergic asthma.³⁸ Intratracheal instillation of lentiviral particles expressing GATA3 siRNA alleviated

airway eosinophilia, T_H2 cytokine production, and airway hyperresponsiveness. siRNA targeting GATA3 in human T cells has also been shown to downregulate T_H2 cytokine production, suggesting that this might be a potential therapeutic approach.³¹ Recent studies have also shown that GATA3 is serine phosphorylated through p38 mitogen-activated protein kinase (p38).³⁹ GATA3 phosphorylation is required for nuclear translocation and T_H2 cytokine induction. Therefore inhibition of p38 function could be a further avenue through which to explore GATA3 modulation for therapeutic purposes (Fig 1). Indeed, the selective p38 inhibitor SB239063 reduces eosinophilia and cytokine production in murine asthma models, and inhaled antisense oligonucleotides targeting p38 also ameliorate asthma-like symptoms.^{40,41}

NFAT

The NFAT family of transcription factors consists of 5 members (NFAT1-5), 4 of which are regulated by calcium signaling (NFAT1-4).^{42,43} NFAT was initially identified as an inducible nuclear transcription factor that bound to the IL-2 promoter on T-cell activation. The NFAT family members were subsequently identified and shown to have highly conserved DNA-binding domains. Three of these transcription factors are regulated by calcium signaling in T cells: NFAT1, NFAT2, and NFAT4. In resting T cells NFAT molecules are cytoplasmic and phosphorylated at numerous serine residues in the NFAT homology region (Fig 1). On T-cell activation, calcium binds calmodulin, which then activates the phosphatase calcineurin. Activated calcineurin dephosphorylates NFAT in the NFAT homology region, which causes nuclear translocation and activation of NFAT-responsive genes, including cytokines (Fig 1). Numerous studies have demonstrated

a critical role for NFAT in transcription of the T_H2 cytokine genes during T-cell activation in partnership with other transcription factors, such as activator protein 1 (AP-1), GATA3, and c-Maf.⁴⁴ Deficiency of NFAT1 and NFAT2 in mice causes profound defects in T-cell cytokine production, including IL-4 and IL-5 production.⁴⁵

The immunosuppressive drugs cyclosporin A (CsA), FK506 (tacrolimus), and pimecrolimus block calcineurin-dependent dephosphorylation of NFAT through their cellular receptors cyclophilin and FK506-binding protein, respectively.⁴³ These drugs have been used extensively systemically to improve graft survival during transplantation and in autoimmune disease.⁴⁶ Topical administration of CsA, tacrolimus, or pimecrolimus has proved very effective in the treatment of atopic dermatitis and eczema.⁴⁷ In recent years, there has been some concern regarding a possible association of topical calcineurin inhibitor treatment and skin cancer or lymphoma; however, current evidence suggests that these adverse events are unrelated to the calcineurin inhibitor treatment.⁴⁷ Systemic administration of CsA to patients with severe asthma has provided some improvement in lung function but often has unacceptable side effects.^{48,49} A locally active derivative of these drugs (MLD987) has recently been developed for inhalation treatment in asthma.⁵⁰ Studies in animal models suggest that this molecule might suppress T_H2 -mediated inflammation without the negative systemic side effects seen with CsA, such as nephrotoxicity and hepatotoxicity. It will be interesting to see how this molecule performs in clinical trials.

CsA and FK506 inhibit calcineurin function rather than NFAT activity, and it is thus likely that these drugs alter the function of all calcineurin targets, which might explain some of the adverse side effects observed.^{51,52} Recently, attempts have been made to generate more specific NFAT antagonists, with some success.⁵³⁻⁵⁵ Noguchi et al⁵³ used a cell-permeable fusion peptide containing the VIVIT sequence fused to polyarginine to facilitate peptide uptake. The VIVIT peptide is an NFAT inhibitor sequence based on the calcineurin docking site of the NFAT family.⁵⁶ The authors showed that the peptide could block calcium-dependent nuclear translocation and IL-2 transcription *in vitro*. Furthermore, they demonstrated that treatment of mice with the peptide allowed allogeneic islet transplantation without the hyperglycemia associated with CsA or FK506.⁵³ Roehrl et al⁵⁴ screened a library of small organic molecules for inhibition of VIVIT peptide binding to calcineurin. They identified a series of molecules with similar structures termed inhibitors of NFAT-calcineurin association (INCA). Treatment of Cl.7W2 T cells with INCA-6 resulted in blockade of NFAT dephosphorylation, nuclear translocation, and transcription of target cytokine genes.⁵⁴ Future studies with these novel NFAT inhibitors in models of allergic disease will be of great interest considering the potency of the calcineurin inhibitors already in use in the clinic. Because the novel inhibitors are NFAT selective, it would be expected that some of the adverse side effects observed with calcineurin inhibition would be avoided.

NF- κ B

NF- κ B is a central transcription factor in a variety of proinflammatory responses in both innate and adaptive immunity. It is made up of p50 and p65 (RelA) subunits in a dimer that is retained in the cytoplasm bound to the inhibitor of NF- κ B (I κ B) under unstimulated conditions (Fig 1).⁵⁷ On activation, the I κ B complex is degraded, and the NF- κ B dimer translocates to the

nucleus, where it regulates transcription of NF- κ B-responsive genes through binding to DNA. NF- κ B signaling has been implicated in the pathogenesis of allergic diseases in a number of studies. High levels of NF- κ B signaling are observed in bronchial biopsy specimens from asthmatic subjects and in animal models of asthma.⁵⁸⁻⁶¹ Mice deficient in NF- κ B p50 or p65 do not have eosinophilia and airway inflammation in murine asthma models.^{62,63} This is due to the NF- κ B knockout mice being unable to mount T_H2 responses because the T cells cannot induce GATA3 expression, even under T_H2 -inducing conditions.⁶⁴ Mice deficient in the NF- κ B family member RelB spontaneously have widespread dermatitis with features resembling those of human atopic dermatitis.^{65,66} Targeted disruption of I κ B δ also causes an atopic dermatitis-like disease in mice, indicating that NF- κ B signaling is likely involved in atopic skin diseases.^{67,68}

Several approaches have been used to block NF- κ B signaling in allergic disease settings. In a murine model of asthma, antisense phosphorothioate oligonucleotides directed at NF- κ B p65 can inhibit established allergic inflammation, including decreased airway hyperresponsiveness and reduced T_H2 cytokine production.⁶⁹ Administration of NF- κ B decoy oligonucleotides into sensitized mice resulted in a strong attenuation of allergic lung inflammation.⁷⁰ Desmet et al⁷⁰ used double-stranded phosphorothioate oligodeoxynucleotides containing the consensus binding site for NF- κ B as decoys and administered them intratracheally to ovalbumin-sensitized mice. The mice had diminished NF- κ B function in the airways and reduced airway hyperresponsiveness and T_H2 cytokine production.⁷⁰ Small-molecule inhibitors of NF- κ B and AP-1 have also been used in experimental models of asthma with some success; however, it is unclear whether the amelioration of allergic inflammation is through NF- κ B or AP-1.^{71,72} A recent study has implicated NF- κ B activation as a downstream effect of IL-13 signaling in structural cells of the airway.⁷³ Chapoval et al⁷³ used 2 different approaches to block NF- κ B signaling in a murine asthma model: a small-molecule inhibitor of I κ B α kinase (PS1145) and a peptide containing the NF- κ B essential modulator-binding domain. Both methods resulted in attenuation of IL-13-mediated lung inflammation and a reduction in airway remodeling in a murine model of asthma. These studies suggest that blockade of NF- κ B signaling with these approaches might be a good therapeutic target for future studies in human subjects.

GRs

Glucocorticoids are one of the most effective classes of drugs for the treatment of allergic disease. They function through interaction with the GR, a member of the nuclear hormone receptor family, to activate and repress a variety of genes. On ligand binding, GR dissociates from heat shock proteins and translocates to the nucleus, where it can either activate or repress gene expression, depending on the genomic context (Fig 1). The mode of action of glucocorticoids and their role in allergic diseases have been extensively studied and reviewed in depth recently.⁷⁴⁻⁷⁶ Activation of gene expression by the GR occurs through binding of the GR to glucocorticoid response elements and transcriptional activation. This mechanism results in the induction of a variety of anti-inflammatory genes, such as annexin-1 and mitogen-activated protein kinase phosphatase 1.⁷⁷⁻⁷⁹ Direct binding of the GR to DNA can also result in transcriptional repression through binding to negative glucocorticoid response

elements; however, the majority of the repressive functions of the GR appear to occur through interaction with other proinflammatory transcription factor pathways. The GR can directly bind to and interfere with the function of AP-1, STAT6, and NF- κ B transcription factors.⁸⁰⁻⁸² The GR can also suppress NF- κ B signaling by inducing I κ B expression.⁸³ Another mechanism of GR repression of cytokine expression is through binding to NFAT- and GATA3-binding sites that control the expression of IL-5, IL-13, and GM-CSF.^{84,85} The GR repression of NFAT and GATA3 function appears to involve GR-mediated recruitment of transcriptional repressors and histone deacetylases.^{84,86}

Two recent studies that do not involve classical mechanisms of GR action are of particular interest in relation to GR function in allergic disease. Glucocorticoids are known to induce rapid nongenomic effects, although the mechanism by which this occurs has remained unclear. A recent study by Lowenberg et al⁸⁷ has shown that in resting human T cells the GR is found in a T-cell receptor protein complex along with heat shock protein 90 and the signaling molecules Lck and Fyn. They show that this complex is essential for T cell receptor-mediated activation of LCK and FYN. Short-term treatment with either glucocorticoids or GR siRNA show that the GR is an essential component of this signaling complex.⁸⁷ The authors suggest that this is a novel mechanism of nongenomic glucocorticoid-mediated immunosuppression. This has implications for steroid function in allergic disease because it is believed that one of the principal targets of steroid action is the T_H2 cell. Therefore this mechanism needs to be considered in the design of improved or dissociated steroids.

A recent study by Smoak and Cidlowski⁸⁸ has shed light on another mechanism of glucocorticoid-mediated repression. They demonstrate that glucocorticoid treatment induces expression of tristetruprolin (TTP) in A549 epithelial cells and various rat tissues. TTP is an RNA-binding protein that cooperates with the miR-16 microRNA to induce destabilization of mRNAs containing AU repeats.⁸⁹ They go on to show that mRNA for TNF- α is destabilized by the steroid-induced TTP through AU repeats.⁸⁸ Many other cytokine genes, including GM-CSF, IL-4, IL-5, and IL-13, contain these AU repeats, and thus this could represent another mechanism by which steroids mediate their suppressive effects in allergic disease.

The numerous mechanisms of GR function explain the potency of glucocorticoids in the treatment of allergic disease; however, there are notable side effects that include osteoporosis.⁷⁶ Several groups have attempted to address this problem by generating improved steroid molecules that dissociate the immunosuppressive functions from the adverse effects.^{90,91} These novel GR ligands, termed selective glucocorticoid receptor agonists (SEGRAs), were originally based on steroidal structures and showed good dissociation of the transactivation and transrepression functions *in vitro*; however, the dissociation was not observed *in vivo*.⁹² More recently, a variety of unrelated nonsteroidal compounds have been shown to function as SEGRAs, and the dissociated activity has been maintained in *in vivo* settings.⁹³ It will be of great interest to determine the effectiveness of these SEGRAs in a clinical setting in allergic disease.

PPARs

PPARs compose a family of ligand-activated transcription factors that consists of 3 members: PPAR α , PPAR β , and

PPAR γ .^{94,95} They belong to the nuclear hormone receptor superfamily with similarity to the retinoid, glucocorticoid, and thyroid hormone receptors. PPARs form heterodimers with the retinoid X receptors (RXRs) RXR α , RXR β , and RXR γ . In the absence of ligand, the PPAR/RXR heterodimer is bound to corepressor complexes, such as nuclear receptor corepressor, that stop interaction with PPAR response elements (Fig 1). On ligand binding, the corepressor complexes disassociate, and the PPAR/RXR dimer binds to coactivator complexes, such as steroid receptor coactivator 1. Similar to the GR, PPAR-dependant gene regulation can involve direct transcriptional activation or repression through PPAR response elements or alternatively by interfering with other transcription factor pathways, such as NF- κ B or STATs.⁹⁶ A wide range of endogenous and synthetic lipid PPAR ligands have been identified, and although PPARs bind ligand promiscuously, some selective ligands are available, such as rosiglitazone.⁹⁷

Evidence for PPAR involvement in allergic diseases has come from some elegant studies in gene-targeted mice. PPAR α -deficient mice exhibit increased airway hyperresponsiveness and eosinophilia in an ovalbumin challenge model of asthma.⁹⁸ Woerly et al⁹⁸ also demonstrated that the PPAR γ -selective ligand ciglitazone reduces airway hyperresponsiveness and eosinophilia in the same mouse model, strongly implicating PPARs in the modulation of asthma. A very recent study has also shown that PPAR α -deficient mice display increased inflammation and epidermal thickening in a model of atopic dermatitis.⁹⁹ Furthermore, topical administration of the selective PPAR α agonist WY14643 decreased antigen-induced inflammation in the atopic dermatitis model.

The recent mechanistic studies in animal models suggest that PPAR agonists might represent a very effective novel treatment for allergic diseases, especially given their extensive use and relative safety in diabetes. It will be interesting to see how the PPAR agonists perform in clinical trials of asthma and atopic dermatitis.

CONCLUDING REMARKS

The identification of the transcription factors involved in the development of atopic diseases has provided considerable insight into the disease processes. Elucidation of the signaling pathways that regulate these transcription factors has provided numerous points at which therapeutic intervention can be targeted (Fig 1). Small-molecule inhibitors of several signaling pathways have been identified and might play an important role in therapy for allergic disease once clinical studies have been completed. In addition, the advent of antisense RNA and siRNA approaches provides an exciting new avenue for therapeutic intervention, especially given the highly specific nature of the technology. One major challenge that needs to be addressed by the field is the method of delivery of such molecules. Viral delivery has proved problematic to date; however, antisense and siRNA approaches might be particularly applicable in asthma because small respirable RNA molecules are easily taken up by the cells of the lung as a result of interaction with cationic surfactant.^{100,101} The next few years hold the prospect of several exciting new therapeutic tools in the management of allergic disease.

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