

Molecular mechanisms in allergy and clinical immunology

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The role of transcription factors in allergic inflammation

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The induction of allergic inflammation and the expression of allergic disorders are dependent on the coordinated regulation of numerous genes. The products of these genes determine lymphocyte phenotype, immunologic responsiveness, eosinophil and mast cell development, activation, migration and life span, adhesion molecule expression, cytokine synthesis, cell-surface receptor display, and processes governing fibrosis and tissue repair. Although the expression of gene products involved in these processes is regulated at multiple levels (eg, transcription, mRNA processing, translation, phosphorylation, and degradation), transcription represents an essential and often the most important determinant of their contribution to cellular function. Signal-dependent and cell type-specific regulation of gene expression is generally achieved by means of combinatorial interactions between sequence-specific transcription factors that recruit chromatin remodeling machinery and general transcription factors to promoter and enhancer regions of RNA polymerase II-dependent genes. As targets of signal-transduction pathways, transcription factors integrate the response of the cell to the myriad of inputs it receives. This integration can be accomplished by the effect of signaling cascades on the activation status or subcellular locus of transcription factors or by transcription factor dimerization induced by means of ligand binding. This review will identify the major families of transcription factors important in allergic mechanisms and discuss their interactions, their mechanisms of action, and their interrelated and competitive actions, as well as implications for therapy of allergic disorders. (*J Allergy Clin Immunol* 2002;110:553-64.)

Key words: Gene transcription, transcription factors, nuclear receptors, allergic inflammation, coactivators, corepressors

Allergic diseases are an important cause of morbidity in the developed world, and their incidence has increased markedly over the past 2 decades. Various explanations for this increase have been proffered, with the most attrac-

Abbreviations used

AP-1: Activator protein 1
BCL6: B-cell lymphoma gene 6
 CBP: CAMP responsive element binding protein
 COX-2: Cyclooxygenase 2
 15d-PGJ2: 15-Deoxy- $\Delta^{12,14}$ PGJ2
 GR: Glucocorticoid receptor
 I κ B: Inhibitory κ B protein
 MIP: Macrophage inflammatory protein
 N-CoR: Nuclear receptor corepressor
 NF-AT: Nuclear factor of activated T cells
 NF- κ B: Nuclear factor κ B
 PPAR: Peroxisome proliferator-activated receptor
 SMRT: Silencing mediator for retinoic acid and thyroid hormone receptor
 STAT: Signal transducer and activator of transcription
 T_HD: T_H precursor
 TLR: Toll-like receptor

tive being the hygiene hypothesis, which postulates that a decrease in infectious stimulation permits a T_H2 bias to emerge in the developing neonatal and childhood immune responses.¹ Recent work suggests that the important stimuli to the developing immune system are transduced by the recognition of pathogen-associated molecular patterns by specialized receptors, termed toll-like receptors (TLRs), on the surface of dendritic cells. For example, endotoxin and its LPS are recognized by TLR2 and TLR4,² whereas bacterial DNA-containing CpG motifs are recognized by TLR9.³ The signals engendered by these interactions eventuate in activation of the transcription factor nuclear factor κ B (NF- κ B), resulting in the activation of gene transcription, release of IL-12, and induction of a T_H1 immune response. The mechanism whereby such an effect can be exerted suggests that regulation of gene activation, and not the genetic complement itself, is centrally important, because only such a mechanism can explain the rapid change in disease prevalence across a diverse population. It is recognized that allergic diseases, including asthma, upper airway disease, atopic dermatitis, and allergic gastroenteropathies,^{4,5} are characterized by T_H2 immune responses, which lead to inflammatory reactions mediated by IgE antibodies and orchestrated by a characteristic family of proallergic cytokines.^{6,7} These events result from the activation of

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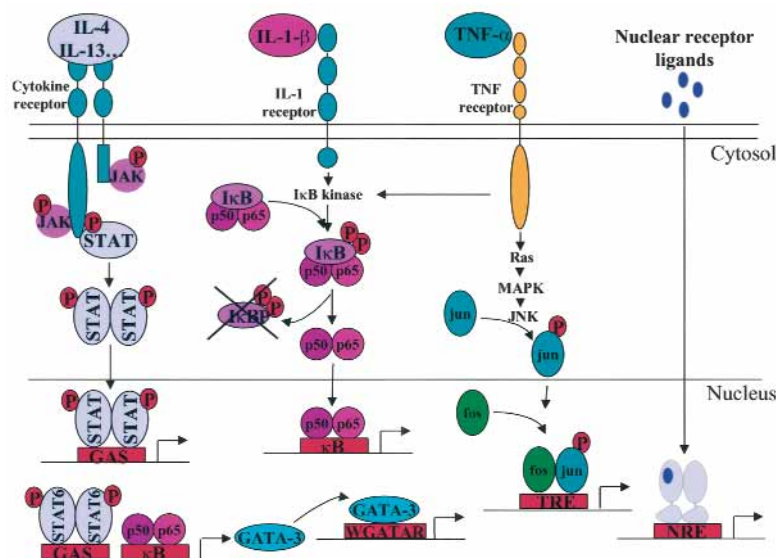


FIG 1. Signaling pathways leading to gene transcription.

TABLE I. Classification of the transcription factors

Class	Family	Some members
Basic domains	Leucine zipper (bZIP)	Jun, Fos, c-maf, CREB, C/EBP
Zinc fingers	Nuclear receptors (NR)	GR, PPAR, RXR (see Table III)
	Others	GATA-3
Helix-turn-helix		Ets, myc, myb
B-sheet motifs	Rel/ankyrin	NF-κB (p50, p65, c-Rel, v-Rel)
	Ankyrin	Bcl-6
	NF-ATs	NF-ATc, NF-Atp
	STATs	STAT4, STAT6

C/EBP, CCAAT/enhancer binding protein.

genes encoding cytokines, chemokines, growth factors, enzymes, receptors,^{8,9} and adhesion molecules, which are involved in the synthesis and secretion of IgE antibody^{10,11} and inflammatory mediators and the recruitment¹²⁻¹⁵ and activation of both resident tissue¹⁶ and infiltrating inflammatory cells.^{17,18} This cascade eventuates in the characteristic physiologic manifestations¹⁹⁻²¹ and histopathologic picture of allergic disease.²²⁻²⁴

Transcriptional control of genes involved in allergic inflammatory responses is mediated by several classes of signal-dependent transcription factors. These factors bind to specific response elements in target genes and can be categorized according to their structure (Table I). Signaling pathways involved in controlling inflammatory programs of gene expression include ligand-dependent activation of receptor tyrosine kinases, mitogen-activated protein kinases, and Janus-activated kinases through cell-surface receptors or, in the case of nuclear receptors, direct regulation by ligands that diffuse readily through cell membranes (Fig 1).

Because the same transcription factor can be responsible for the transcription of gene programs with diametrically opposing actions (see below), it is clear that an intricate regulatory system governing the specificity of transcription factors must exist. The mechanisms by

which sequence-specific transcription factors act to either positively or negatively regulate gene expression have recently been linked to the recruitment of intermediary factors termed coactivators and corepressors. Coactivators generally consist of large multiprotein complexes that act to remodel chromatin structure, recruit basal transcription factors to the core promoter element, or both.²⁵⁻²⁷ Several distinct coactivator complexes have been identified and are believed to function in a combinatorial manner to allow complex physiologic patterns of gene expression to evolve. The chromatin-remodeling activities of coactivator complexes are associated with distinct enzymatic functions. For example, nucleosome-remodeling activities have been associated with several coactivator complexes that contain ATP-dependent DNA helicase activities.^{28,29} Histone acetyltransferase activities have also been found to be associated with several coactivator complexes.^{30,31} Examples of important coactivators that harbor intrinsic histone acetyl transferase activity include CREB-binding protein (CBP) and the adenovirus E1A-associated protein p300, which play important roles in signal-dependent transcription mediated by the members of the activator protein 1 (AP-1), signal transducer and activator of transcription (STAT), and NF-κB families of transcription factors.^{21,32} Histone

acetylation is believed to alter the association of histones with architectural proteins that control overall chromatin structure and therefore to regulate the access of core transcriptional machinery to the promoter.^{33,34} Histone methylation has recently emerged as an additional modification associated with coactivator function.³⁵ Additional classes of coactivators, exemplified by what is referred to as the thyroid receptor-associated protein/vitamin D receptor-interacting protein/activator recruited cofactor (TRAP/DRIP/ARC) complex, appear to lack enzymatic activities but contain numerous interaction interfaces for transcription factors that appear to underlie cooperative interactions and allow direct recruitment of RNA polymerase II.^{36,37}

In general, inflammatory response genes are maintained in a repressed state in the absence of an inflammatory stimulus. The maintenance of low levels of basal gene expression has, in many cases, been found to require the recruitment of corepressor complexes by sequence-specific transcriptional repressors. These complexes often contain enzymatic activities that antagonize the functions of coactivator complexes. For example, the nuclear receptor corepressor (N-CoR) and the silencing mediator for retinoic acid and thyroid hormone receptor (SMRT) form multiprotein complexes that contain histone deacetylases.^{38,39} These enzymes reverse acetylation of histones carried out by coactivator complexes. Activation of genes in response to a signal therefore often requires both relief of repression through dismissal of corepressor complexes and subsequent recruitment of coactivators. This exchange of coactivators for corepressors can be achieved either through an exchange of transcriptional activators for repressors or by altering the activities of a single transcription factor. For example, several nuclear hormone receptors interact with N-CoR, SMRT, or both in the absence of ligand and actively repress gene transcription. On ligand binding, N-CoR, SMRT, or both are released, and coactivator complexes are recruited. Exchanges of coactivators and corepressors are likely to occur on genes regulated by members of the AP-1, NF- κ B, and STAT families of transcription factors through exchange of active members of this family for repressors, as well as through posttranslational modifications that regulate repression and activation functions.

In this review we will describe the role of the principal transcription factors involved in allergic inflammation and the regulation of the T_H2 phenotype of lymphocytes and their modulation by nuclear receptors. A better understanding of the mechanisms of action of these modulators of gene expression is helpful in elucidating the pathways involved in allergic inflammation and central to the development of new perspectives in the treatment of allergic diseases.

TRANSCRIPTION FACTORS INVOLVED IN THE T_H1/T_H2 RESPONSE

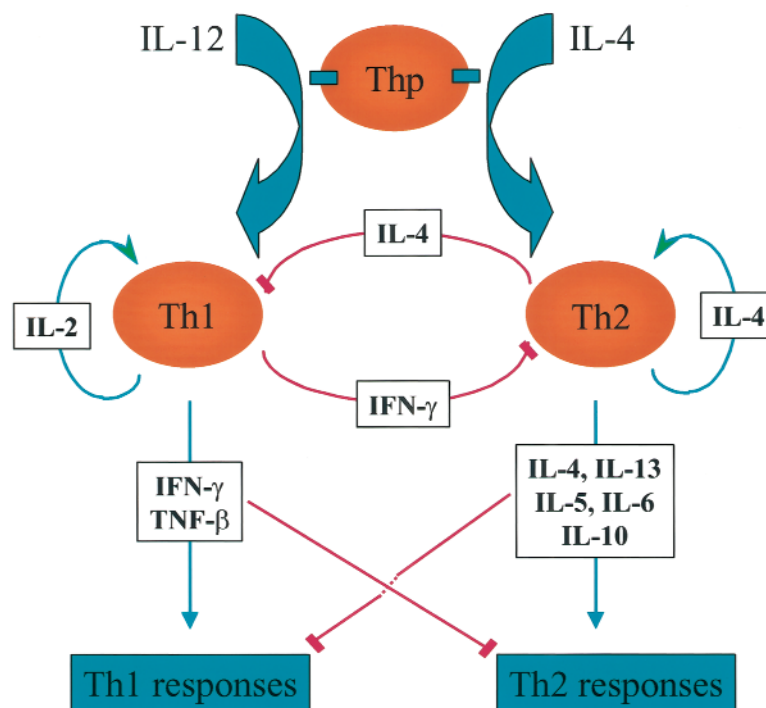
T_H lymphocytes differentiate from T_H precursor (T_{HP}) cells into 2 subsets, T_H1 and T_H2 , which have been

defined by the profile of cytokines they produce.⁴⁰ IL-4 is the critical T_H2 cytokine that mediates the differentiation of T_{HP} cells into T_H2 cells,⁴¹ whereas IL-12 is the primary inducer of the development of T_H1 responses.⁴² T_H1 cells principally produce IFN- γ , IL-2, and TNF- β and are involved in the elimination of intracellular pathogens, such as viruses and some bacteria. T_H2 cells secrete IL-4, IL-13, IL-5, IL-6, and IL-10 and are involved in the responses against parasites and in immediate hypersensitivity reactions through the production of IgE (and IgG1 in mouse) antibodies by B cells.⁴³ In vivo, once they have been established, T_H1 or T_H2 responses remain relatively stable. T_H1 and T_H2 cytokines by themselves regulate their own production and control the growth and differentiation of their subset while inhibiting the growth and differentiation of the opposite subset. Transcription factors play key roles in the tightly regulated mechanisms governing T_H1 and T_H2 cell differentiation and the on-going maintenance of the corresponding immune response (Fig 2 and Table II).

STATs

STATs are transcription factors activated by cytokines through the Janus-activated kinase pathway.⁴⁴ During differentiation of T_H cells, IL-12 induces the differentiation of T_{HP} cells into T_H1 cells through STAT4 and Jak 2/Tyk2, whereas IL-4 and IL-13 induce T_H2 cells through STAT6 and Jak 1/Jak 3.⁴⁵⁻⁴⁷ STAT4-deficient mice (STAT4^{-/-}) show a propensity toward the development of a T_H2 -biased immune response,⁴⁸ whereas in STAT6^{-/-} mice a reduced T_H2 response occurs. The development of STAT4/STAT6 double-deficient mice allowed the identification of the existence of a STAT-independent pathway in T_H differentiation, promoting exclusively T_H1 development.⁴⁹ Importantly, when STAT6 is provided to T_H1 cells, a T_H2 immune phenotype is created, further demonstrating the critical role of these transcription factors in the orientation of T_H1 and T_H2 responses^{46,50,51} and suggesting that STAT6 is critical to the expression of the T_H2 phenotype. Additionally, STAT6 is also important in the proliferative response of T_H2 lymphocytes. During the differentiation of T_H2 cells, it has been suggested that STAT6 activates the transcription of IL-4 in response to low quantities of IL-4 produced at the very beginning of T_H differentiation.^{52,53} STAT6 has been demonstrated to be required for chromatin remodeling of the *IL4/IL13* locus, which occurs in developing T_H2 cells, favoring the expression of these cytokines.³⁴

STAT6 is involved in the upregulation of IL-4-dependent genes, such as the genes encoding IL-4R, IgE, FcR, CCR4, CCR8, and MHC class II molecules, which play key roles in allergic responses. STAT6 expression in bronchial epithelium is correlated to the severity of asthma.⁵⁴ STAT6 is activated by other T_H2 cytokines, such as IL-5 and IL-13, the level of expression of which is elevated during allergic inflammation, contributing to the local amplification of the T_H2 response. The study of STAT6^{-/-} mice confirms the regulatory role of this transcription factor in allergic inflammation.^{55,56} In STAT6^{-/-} models of

FIG 2. Regulation of T_H1/T_H2 differentiation.TABLE II. Transcription factors involved in the regulation of T_H1/T_H2 responses

Transcription factors	Effects on:	
	T_H2 phenotype	T_H1 phenotype
STAT4		+
STAT6	+	
BCL-6	–	
T-bet	–	+
GATA-3	+	–
C-maf	+	
NF-ATc	+	
NF-ATp/NF-AT4	–	

allergic airway inflammation and cutaneous hypersensitivity, the production of IgE is profoundly reduced,^{57,58} and IgG2a synthesis is observed after allergen challenge. These findings are consistent with the inhibition of the expected T_H2 response and its replacement by a T_H1 response. Additionally, STAT6 has been found to play a critical role in airway hyperresponsiveness, the recruitment of eosinophils to airways and skin, the late cytokine production of mast cells in response to IgE-antigen complexes, and the production of mucus.⁵⁶⁻⁵⁹

B-cell lymphoma gene 6 (*BCL6*) is a transcriptional repressor described to bind the STAT6 DNA-binding site on the CD23b promoter, suggesting its role in the regulation of IL-4-induced expression of this low-affinity receptor for IgE.⁶⁰ *BCL6*^{–/–} mice display an abnormal expression of T_H2 cytokines,⁶⁰ suggesting that BCL-6 plays a regulatory role during T_H2 responses through the control of STAT6-dependent genes. This repressor activity could involve the recruitment of the corepressor SMRT.⁶¹

Nuclear factors of activated T cells

The nuclear factor of activated T cells (NF-AT) transcription factors are comprised by 4 different members and are expressed in T and B lymphocytes, mast cells, and natural killer cells. NF-ATp (NF-AT1) and NF-AT4 on one hand and NF-ATc (NF-AT2) on the other play opposing roles in the development of T_H2 responses. NF-ATc^{–/–} mice have a severe T-cell defect in IL-4 production and T_H2 differentiation,⁶² whereas NF-ATp^{–/–} and NF-AT4-deficient mice show an increased T_H2 response.^{63,64} Increased numbers of eosinophils are found in the bone marrow and peripheral blood of ovalbumin-sensitized NF-ATp^{–/–} mice compared with their wild-type littermates. Upon challenge with ovalbumin, these mice display an increased eosinophilia in the pleural cavity compared with that seen in wild-type mice associated with increased levels of IL-5 and IL-13.⁶⁵ Thus NF-ATc would appear to favor T_H2 responses, whereas NF-ATp and NF-AT4 act as regulators of T_H2 responses. This regulatory pathway could be considered a potential target for new drugs modulating allergic inflammation.

C-maf

C-maf is a T_H2 -specific factor that is induced in the early events of T_H2 differentiation and transactivates the IL-4 promoter.⁶⁶ It acts in synergy with the transcription factor NF-ATp and NIP45 (NFAT interacting protein 45) to initiate the expression of IL-4 in B cells.^{66,67} Asthmatic patients display an increased expression of c-maf.⁶⁸ Mice deficient in c-maf display impaired expression of IL-4, but the expression of IL-5 and IL-13 are unaffected,⁶⁹ suggesting that the production of other T_H2

cytokines is not dependent on c-maf. Thus c-maf^{-/-} mice show a normal IgE response in models of allergic diseases, probably because of unimpaired production of IL-13.⁶⁹ C-maf has been found to be upregulated in bronchial biopsy specimens of asthmatic patients compared with that seen in normal subjects,⁶⁸ suggesting that it plays a local role in supporting the T_H2 response.

GATA-3 and T-bet

The transcription factor GATA-3 is selectively expressed in T_H2 cells and plays a critical role in T_H2 differentiation in a STAT6-independent manner.⁷⁰ GATA-3 regulates the transcription of IL-4 and IL-5.^{71,72} and, like STAT-6, has been suggested to act as a chromatin-remodeling factor, favoring the transcription of IL-4 and IL-13.⁷³

The expression of T-bet (T-box expressed in T cells), a recently discovered transcription factor, is restricted to T_H1 cells.⁷⁴ It is rapidly induced during their differentiation and has been suggested to act in T_H1 differentiation in a fashion similar to GATA-3 in T_H2 lymphocytes.⁷⁴ Although GATA-3 promotes the expression of T_H2 cytokines in developing T_H2 cells, T-bet induces the expression of IFN- γ in developing T_H1 cells.⁷⁴ Experimental overexpression of T-bet in T_H2 cells reduces their expression of IL-4 and IL-5 in an IFN- γ -independent mechanism,⁷⁴ suggesting that T-bet directly represses the expression of these genes in developing T_H1 cells. T-bet induces the expression of IL-12R β 2 in T_H1 cells, favoring the responsiveness of these cells to IL-12.⁷⁵ Overexpression of GATA-3 in developing T_H1 cells reduces the expression of the IL-12R β 2 chain,⁷⁰ suggesting that GATA-3 represses T_H1 development in developing T_H2 cells by repressing their ability to respond to IL-12.

Taken together, these studies suggest that GATA-3 and T-bet would favor the rapid dominance of T_H2 and T_H1 pathways, respectively, during T_H differentiation by transactivating the genes involved in the development of their subset and repressing the genes involved in the development of the opposite subset. The mechanisms by which GATA-3 and T-bet are able to display both transactivation and repression in a promoter-dependent manner remain to be elucidated. Finally, T-bet and GATA-3 might regulate their mutual expression, reinforcing their action in the orientation of T_H1 and T_H2 development.

Compared with that seen in normal subjects, in airways of asthmatic patients, GATA-3 is upregulated, and the number of GATA-3⁺ cells (predominantly CD3⁺ T cells) correlates directly with the expression of IL-5 mRNA and methacholine hyperresponsiveness and inversely with airways caliber.^{68,76,77} Moreover, T cell-specific expression of a dominant-negative GATA-3 attenuates IgE production, eosinophilia, and mucus production in sensitized and challenged animals,⁷⁸ reinforcing the role of GATA-3 in allergic inflammation. In mice GATA-3⁺ cells detected in the lungs of ragweed-sensitized and ragweed-challenged animals are predominantly eosinophils.⁷⁹ The facts that GATA-3 is overexpressed in eosinophils and that these cells can produce IL-5 suggest a local mechanism of amplification of eosinophilia.

Contrary to GATA-3, T-bet is downregulated in airways of asthmatic patients compared with that seen in control subjects, which is consistent with the characteristic T_H2 phenotype observed in this asthmatic disorder.⁸⁰ Szabo et al⁸¹ have developed T-bet-deficient mice in which CD4⁺ T lymphocytes produce less IFN- γ and more IL-4 and IL-5 than wild-type mice. Importantly, in the absence of any sensitization or allergen challenge, these T-bet-deficient mice have airway hyperresponsiveness to methacholine, show recruitment of eosinophils and lymphocytes to the airway, and display characteristic histopathologic features of airway remodeling, and their expression of IL-5 is increased.⁸⁰ The development of these characteristic features of human asthma in T-bet-deficient mice suggest that this transcription factor is involved in the control of T_H2 responses and is an enticing target for new drug development in asthma.

TRANSCRIPTION FACTORS INVOLVED IN THE ALLERGIC INFLAMMATORY RESPONSE NF- κ B

NF- κ B belongs to the Rel family of proteins. This family consists of 5 members, termed NF- κ B1 (p105/p50), NF- κ B2 (p100/p52), p65 (RelA), RelB, and c-Rel. NF- κ B is a heterodimer usually consisting of the 2 subunits p65 and p50, although other forms exist. In resting cells NF- κ B is cytoplasmic and bound to the regulatory subunit inhibitory κ B protein (I κ B), which covers its nuclear localization signals.

Upon cell activation, I κ B is phosphorylated by inhibitory κ B protein kinase and degraded after ubiquitination, a process that allows freed NF- κ B to rapidly enter the nucleus, where its subunits can bind to κ B motifs (5'-GGGACTTTCCC-3') located on promoters of genes. NF- κ B plays an important role in the regulation of genes involved in allergic inflammation, such as those encoding inflammatory cytokines, regulatory chemokines, adhesion receptors, enzymes (eg, markers of airway inflammation cyclooxygenase 2 [COX-2] and inducible nitric oxide synthase)⁸²⁻⁸⁴ and the remodeling enzyme matrix metalloproteinase 9.⁸⁵ Nuclear p65 has been found to be upregulated in epithelial cells and macrophages from asthmatic patients compared with levels seen in normal subjects, and this upregulation is associated with an increased number of eosinophils and macrophages in the submucosa.⁸⁶ In a murine model of allergic airway inflammation, Poynter et al⁸⁷ showed a rapid nuclear translocation of p65 in the airway epithelium occurring within 15 minutes after allergen challenge and persisting for 24 hours. The induction of NF- κ B-dependent genes in lung tissue has been confirmed by using transgenic mice expressing an NF- κ B-luciferase reporter gene. The rapid activation of NF- κ B is associated with the rapid upregulation of macrophage inflammatory protein (MIP) 2 (a rodent analog of human IL-8) and the early recruitment of neutrophils in the airway after allergen challenge,⁸⁷ suggesting that NF- κ B is involved in the early events in the development of allergic inflammation. NF- κ B is also

involved in the recruitment of T lymphocytes to the airways during allergic challenge, probably by upregulating RANTES and IL-16 synthesis,⁸⁸ as well as by inducing the expression of MIP-1 α and MIP-1 β in the lung.⁸⁹ By using c-Rel-deficient mice and a model of allergen sensitization and challenge, Donovan et al⁹⁰ showed that this transcription factor is required for eosinophilia and airway hyperresponsiveness and participates in the serum IgE response. Mice deficient in p50 can not produce either IL-5 or eotaxin and are unable to mount airway eosinophilic inflammation after allergen challenge.⁸⁹ Their inability to develop eosinophilia has been recently related to their inability to produce IL-4 and IL-13.⁹¹ Indeed, CD4⁺ T cells from p50-deficient mice were found to be incapable of inducing GATA-3 expression under T_H2-differentiating conditions, demonstrating a role of NF- κ B in the development of T_H2 cells. In addition, a direct action in eosinophilia has been attributed to NF- κ B by upregulating the expression of the eotaxin receptor in dermal fibroblasts, suggesting its involvement in the pathogenesis of atopic dermatitis.⁹² NF- κ B also is important in mediating the survival of eosinophils. It is important in the expression of GM-CSF⁹³ and involved in the GM-CSF-mediated antiapoptotic effect of IL-15⁹⁴ and in inhibiting the PGD₂-mediated caspase-dependent apoptotic death of eosinophils.⁹⁵ All these effects would prolong eosinophil survival at sites of allergic inflammation. Finally, NF- κ B upregulates the expression of the proinflammatory cytokines IL-1 β and TNF- α , which in turn activate the NF- κ B pathway, amplifying and extending the persistence of local inflammatory responses.⁹⁶ In addition to the transcriptional promoter activity of NF- κ B, p50 homodimers have been found to act as repressors.⁹⁷ Thus it is possible that genes that bind p50 homodimers in normal conditions are derepressed after allergen challenge and could participate in allergic inflammation. Target genes for such a p50/p50 effect remain to be identified.

AP-1

AP-1 is a transcription factor composed of either homodimers or heterodimers within the Jun family (c-Jun, JunB, and JunD) or among the members of the Jun and Fos families (c-Fos, FosB, Fra1, and Fra2).⁹⁸ The Fos-Jun complex binds DNA with the highest affinity and is the predominant form in most cells. The increased synthesis of Fos and the phosphorylation of c-Jun leads to the activation of AP-1, which can be counteracted by phosphatase-mediated dephosphorylation of Jun. Interactions between AP-1 and NF- κ B have been reported to lead to the synergistic activation of target genes.⁹⁹ It is therefore not surprising to note that AP-1, like NF- κ B, regulates many of the genes upregulated during allergic inflammation. Increased expression of c-Fos has been found in epithelial cells from asthmatic patients.¹⁰⁰ In ovalbumin-sensitized and ovalbumin-challenged Brown Norway rats, the phosphorylated form of Jun is detected in the lung,¹⁰¹ suggesting its involvement in the activation of inflammatory genes. An increase in AP-1 activation has also been found in keratinocytes of patients with

atopic dermatitis associated with the upregulation of the expression of GM-CSF.¹⁰² Recently, AP-1, composed of JunB, has been described to be overactivated in response to IL-4 in PBMCs from patients with atopic dermatitis.¹⁰³ Finally, increased expression of c-Fos in PBMCs has been suggested to play a role in corticoid resistance,¹⁰⁴ perhaps by sequestering the glucocorticoid receptor (GR α) to interact with other proteins.

Thus NF- κ B and AP-1 appear to play a critical role in mediating the inflammatory response in allergy, and the novel approaches to the treatment of allergic inflammation could well involve inhibition of their transcriptional activity.

ROLE OF NUCLEAR RECEPTORS IN THE MODULATION OF ALLERGIC INFLAMMATION

Nuclear receptors are transcription factors whose effect on gene transcription is directly modulated by the binding of small lipophilic molecules. Such transcription factors include receptors for endocrine hormones, adopted orphan receptors, and orphan receptors (Table III). In this review we will focus on those most relevant to allergic inflammation: the glucocorticoid receptor GR α known to mediate the anti-inflammatory effects of corticosteroids in asthma and peroxisome proliferator-activated receptors (PPARs), which appear to share some anti-inflammatory mechanisms with GR α and represent a potential new pathway of modulation of allergic inflammation.

The inactive form of GR α is in the cytosol bound to a protein complex, including 2 subunits of the heat shock protein hsp90. In this form its nuclear localization is prevented. When GR α binds glucocorticoids, hsp90 dissociates, and the activated receptor enters the nucleus, where it binds, as a homodimer, to specific DNA sequences termed glucocorticoid response elements and/or interacts with coactivators or corepressors.¹⁰⁵ Another isoform, termed GR β , is generated by means of alternative splicing in human subjects and has been suggested to act as a dominant negative form of GR because it is unable to transactivate the glucocorticoid response element-dependent promoter.^{106,107} The relative abundance of GR α and GR β in cells determines the action of GR β as a dominant negative. Increased expression of GR β has been associated with fluticasone propionate-insensitive nasal polyposis and fatal asthma^{108,109} and a low ratio of GR α /GR β with steroid-resistant asthma.¹¹⁰ These studies show the importance of the GR α /GR β balance for the expression of steroid action in allergic inflammation. Thus one form of glucocorticoid resistance in allergy is believed to be due to a T_H2 cytokine-mediated decrease of the GR α /GR β ratio.

Although GR α can mediate the inhibitory effects of glucocorticoids in inflammation by increasing the synthesis of anti-inflammatory genes, the predominant mechanism by which GR α exerts its anti-inflammatory effects is by inhibiting the expression of proallergic inflammatory genes. In blood monocytes the GR α ligand dexamethasone inhibits IL-4-induced expression of

TABLE III. Classification of nuclear receptors

Family		Name	Ligands
Endocrine receptors	Steroid receptors	GR	Glucocorticoids
		ER α , β	Estrogen
		PR	Progesterone
		AR	Androgen
	Nonsteroid receptors	MR	Mineral corticoid
		RAR α , β	Retinoic acid
		TR α , β , γ	Thyroid hormone
		VDR	Vitamin D
		RXR α , β , γ	9-cis retinoid acid
		PPAR α , β , γ	Thiazolidinediones, lipid-lowering fibrates, 15d-PGJ2, 15-HETE, 12-HETE
Adopted orphan receptors		LXR α , β	Oxysterols
		FXR	Bile acids
		PXR, SXR, CAR	Xenobiotics
		ROR, ERR, HFN-4...	?
Orphan receptors			

HETE, Hydroxyeicosatetraenoic acid.

Fc ϵ RI in vitro and in vivo.¹¹¹ GR α also inhibits the expression of the cytokines involved in airway inflammation, such as IL-1 β , TNF- α , GM-CSF, IL-4, IL-5, and IL-8, and reduces the production of eotaxin and the eosinophil survival by antagonizing the transcriptional activity of NF- κ B, AP-1, and CCAAT/enhancer binding protein β . The mechanism of GR α -mediated gene repression will be discussed below.

PPARs were first described in adipocytes,¹¹² but their role has since been extended to other cells, including macrophages and mast cells.^{113,114} Three subtypes of PPARs have been described: PPAR- α , PPAR- β (- δ), and PPAR- γ . PPARs transactivate genes by forming heterodimers with the retinoid X receptor and by binding promoters that contain PPAR response elements.¹¹⁵ Among the different PPAR ligands, 15-deoxy- $\Delta^{12,14}$ -PGJ2 (15d-PGJ2),¹¹⁶ 13-hydroxyoctadecadienoic acid, and 15-hydroxyeicosatetraenoic acid¹¹⁷ represent endogenous PPAR- γ ligands that are generated from arachidonic acid and linoleic acid metabolism, respectively.

Many studies suggest that PPARs favor T_H2 immune responses. In dendritic cells PPAR- γ induces the expression of CD86, which has been described to induce cytokine expression in T_H2 cells and IgE production in B cells, while in contrast reducing the secretion of chemokines involved in T_H1 cell recruitment.¹¹⁸ The production of IL-12 has been described to be increased in PPAR- α ^{-/-} mice¹¹⁹ and inhibited by PPAR- γ ligands in vitro in dendritic cells and macrophages and in vivo^{118,120} in a model of allergic encephalomyelitis.¹²¹ Finally, PPAR- γ has been described to be upregulated by IL-4¹²² and downregulated by IFN- γ .¹²³ Taken together, these data suggest a new pathway in which PPARs participate in the orchestration of T_H2 immune responses.

PPAR- γ has been described as a marker of airway remodeling in asthma. In asthmatic subjects, in contrast with normal patients, this transcription factor is expressed in eosinophils and macrophages of bronchial submucosa, airway epithelium, and smooth muscle.¹²⁴ It is also associated with the thickness of the subepithelial

basement membrane and the magnitude of collagen deposition, all of which are characteristic alterations of the airway in asthmatic individuals.

PPAR- γ regulates arachidonic acid metabolism, the products of which, prostanoids and leukotrienes, are important mediators of the allergic inflammatory response. It appears that PPAR ligands can exert proinflammatory or anti-inflammatory effects on the production of arachidonic acid metabolites according to the activation status of cells. In unstimulated cells PPAR- γ has been described to induce the expression of COX-2, enzyme involved in the production of prostanoids.^{125,126} In contrast, the production of leukotrienes is inhibited in A23187-stimulated rat peritoneal neutrophils and in dinitrophenol-specific IgE-sensitized RBL-2H3 mast cells by the synthetic PPAR- γ ligand troglitazone.¹²⁷ In vivo 15d-PGJ2 reduces cytokine production and the expression of COX-2 in models of acute and chronic inflammation,¹²⁸ as well as the expression of inducible nitric oxide synthase and the recruitment of neutrophils.¹²⁸ Taken together, these data suggest that PPAR- γ would, by inducing the expression of COX-2, initially promote the inflammatory response, but later, the COX-2-dependent generation of 15d-PGJ2 would be involved in a feedback mechanism regulating PPAR- γ activity, reducing the production of prostanoids and thereby contributing to the resolution of inflammation.

Indeed, in a model of acute inflammation, the late production of 15d-PGJ2 has been suggested to regulate resolution of inflammation.¹²⁹ The interpretation of these data are complicated, however, by the finding that in some model systems, 15d-PGJ2 acts in a PPAR- γ independent manner.

Additional evidence supports the anti-inflammatory action of PPARs. PPAR ligands inhibit the production of the proallergic cytokines GM-CSF, TNF- α , IL-5, and MIP-1 α in anti-IgE-stimulated cultured human mast cells¹¹⁴ and IL-8 in airway epithelial cells.¹³⁰ Compared with wild-type littermates, heterozygous PPAR- γ mutant (PPAR- $\gamma^{+/-}$) mice exhibit a more severe antigen-induced arthritis associated with a greater number of inflammatory

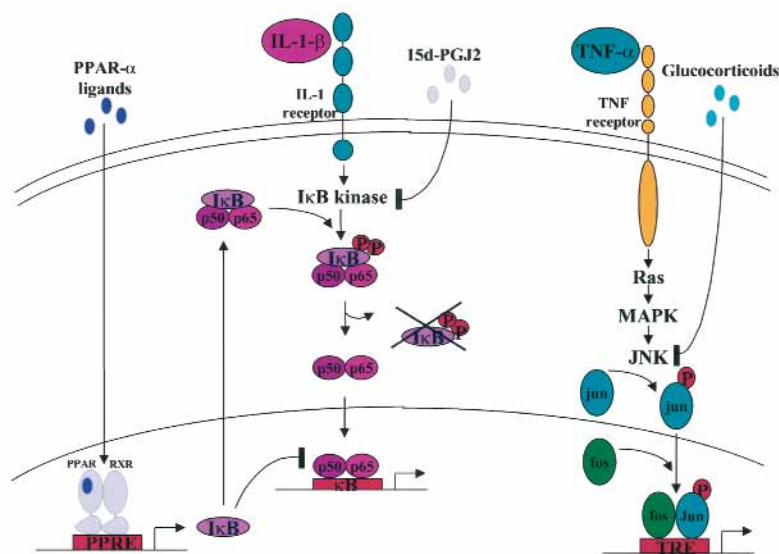


FIG 3. Modulation of gene transcription by nuclear receptor ligands through signaling pathway inhibition. *RXR*, Retinoid X receptor.

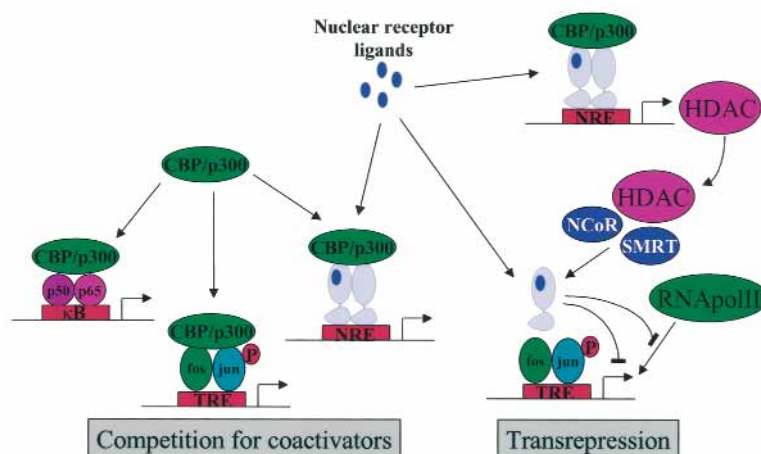


FIG 4. Hypothetical mechanisms of repression of gene transcription by nuclear receptors. *HDAC*, Histone deacetylase; *NRE*, Nuclear hormone response element; *TRE*, TPA-response element.

cells in periarticular tissues.¹³¹ PPAR- α ligands decrease the expression of vascular cell adhesion molecule 1 in endothelial cells.¹³² Taken together, these studies suggest that PPARs could downregulate the recruitment of inflammatory cells in sites of allergic inflammation.

PPARs, such as GR α , inhibit the expression of proinflammatory genes by antagonizing the effects of other classes of transcription factors, such as NF- κ B, AP-1, and STATs.^{113,120,133} Their anti-inflammatory mechanisms can be exerted through different mechanisms. First, they can alter the signaling pathways leading to transcription factor activation (Fig 3). GR α can inhibit Jun kinase activity, leading to the abolition of c-Jun phosphorylation and subsequent AP-1 activation.^{134,135} 15d-PGJ2 represses NF- κ B transcriptional activity by inhibiting I κ B kinase activity and consequently preventing I κ B α degradation, but does so in a PPAR- γ -independent manner.^{136,137}

PPAR- α ligands also induce the expression of nuclear I κ B α NF- κ B inhibitor, in primary smooth muscle leading to a decrease in NF- κ B DNA-binding activity¹³⁸ and a reduction of the duration of inflammatory responses.¹³⁹

The inhibitory effect of GR α and PPARs on AP-1-, NF- κ B-, and STAT-dependent genes also might be due to a competition of the recruitment of their coactivators (Fig 4). CBP/p300, the concentration of which is functionally limiting, is a common coactivator of these transcription factors.²¹ The nuclear presence of these receptors could deprive AP-1, NF- κ B, and STAT of CBP/p300 and thereby inhibit their transcriptional activity.¹⁴⁰ In support of this concept, overexpression of CBP/p300 has been shown to partially relieve the suppressive effect of ciglitazone (a PPAR ligand) on COX-2 expression.¹⁴¹

GR α and PPARs can also inhibit gene transcription by directly interacting with AP-1,¹⁴²⁻¹⁴⁴ NF- κ B,^{120,143,145}

and STATs¹⁴⁶⁻¹⁴⁸ by a mechanism of ligand-dependent transrepression, which does not require DNA binding by the nuclear receptor (Fig 4). Mutant mice for GR α , termed GR^{dim}, express a mutant GR α protein unable to bind DNA and thereby transactivate genes, but it retains transrepressional activity, demonstrating that GR α -mediated transrepression does not require a direct interaction between GR α and DNA.¹⁴⁹

An additional mechanism whereby GR and PPARs can alter gene expression is by modifying the acetylation of histones. Glucocorticoids repress histone acetylation by directly inhibiting CBP-associated histone acetyl transferase activity and by recruiting histone deacetylases.¹⁵⁰ As noted above, the deacetylation of histones reduces access of the transcription factors, such as AP-1 and NF- κ B, to their response elements on DNA. Nuclear receptors could also bind corepressor molecules, such as N-CoR and SMRT, to exert their anti-inflammatory activity.¹⁵¹ All 3 PPARs and GR α can bind N-CoR,^{152,153} and microinjection of antiserum to SMRT blocks PPAR- γ -mediated repression.¹⁵⁴

Finally, on the IL-8 promoter, GR α has been described to inhibit NF- κ B-induced gene expression by interfering with the phosphorylation of RNA polymerase II.¹⁵⁵

In conclusion, the action of transcription factors is central to the expression of allergic disease and allergic inflammation. The recent increase in the incidence of allergic disorders, especially in the developed world, requires the collaborative interaction of transcription factors and proinflammatory genes and a concerted use of coactivator and corepressor molecules. The sum effect of this process in allergy is the development of a T_H2-committed lymphocyte population, the generation of allergen-specific IgE, the sensitization of mast cells, and the upregulation of eosinophil production, activation, recruitment, and survival. In addition, a dysregulation of collagen production and persistent inflammatory cell infiltration into the airway epithelium, submucosa, and smooth muscle characterize asthma and allergic rhinitis. Similar changes in skin and gastrointestinal tissue are central to the expression of allergic disease in these sites. Some of these effects are due to enhanced gene transcription by means of the direct action of transcription factors, some to the generation of proinflammatory molecules by the use of transcriptional coactivators and others to the inhibition of protective pathways, perhaps by use of corepressor mechanisms. As the various pathways of transcriptional activation are clarified and the specific DNA-binding sites and coactivator-corepressor binding sites on transcription factors are identified, new targets of drug action are uncovered. The promise of modified glucocorticoids with an action analogous to that of tamoxifen in relation to estrogen is an example of how our understanding of transcriptional regulation might benefit the treatment of allergic disease. Additionally, the role of specific and unique transcription factors in the regulation of T_H1/T_H2 development and the potential to target-specific genes for transcriptional activation, repression, or both can be appreciated for the possibilities uncovered for the

development of new therapeutics in allergic diseases. The next decade will surely bring this promise to fruition.

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