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IgE regulation and roles in asthma pathogenesis

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Asthma and the predisposition to produce IgE are inherited as linked traits in families. In patients IgE levels correlate with asthma severity and bronchial hyperresponsiveness. The concept that IgE plays a critical role in asthma pathogenesis has driven the development of IgE blockers, which are currently being introduced into clinical use. This review focuses on the mechanisms whereby IgE participates both in immediate hypersensitivity responses in the airways and in the induction of chronic allergic bronchial inflammation. The molecular genetic events that give rise to IgE production by B cells and the cellular and cytokine factors that support IgE production in the bronchial mucosal microenvironment are discussed. It is clear that much remains to be learned regarding the roles of IgE in asthma and the genetic and environmental influences that lead to its production. Over the next few years, the emerging experience with anti-IgE in patients will provide a more complete understanding of the mechanisms whereby IgE contributes to disease, as well as the therapeutic potential of its inhibition. (J Allergy Clin Immunol 2001;107:429-40.)

Key words: *IgE, asthma, allergy, IL-4, IL-4 receptor, IL-13, CD40, CD40 ligand*

Abbreviations used

AID:	Activation-induced cytidine deaminase
APC:	Antigen-presenting cell
BHR:	Bronchial hyperresponsiveness
CD40L:	CD40 ligand
DC:	Dendritic cell
FcεRI:	High-affinity IgE receptor
JAK:	Janus family tyrosine kinase
LPR:	Late-phase response
NFκB:	Nuclear factor κB
STAT6:	Signal transducer and activator of transcription
TRAF:	TNF receptor–associated factor

ASTHMA AND THE ATOPIC TRIAD

A unifying thread that ties together the atopic conditions—asthma, allergic rhinitis, and atopic dermatitis—is their occurrence in individuals with markedly elevated levels of IgE antibodies. Bronchial hyperresponsiveness (BHR), the enhanced tendency toward bronchial smooth muscle contraction observed in asthmatic patients, also segregates together with high IgE levels in pedigree analyses.[1] In cohorts of asthmatic children, IgE levels are associated both with physician diagnosis of asthma and with physiologic evidence of BHR.[2] Elevated IgE levels have been identified as a risk factor even in nonallergic asthma.[3]

Prospective studies have shown that within atopic families, exposure to allergen and subsequent production of IgE are associated with an increased likelihood of development of asthma.[4] The same may be true in atopic dermatitis, where food allergen–triggered IgE production appears to correlate with future development of skin disease.[5] Taken together, these striking associations have suggested that IgE is a key trigger for allergic inflammation in the skin and airways. As a result, in clinical practice testing for allergen-specific IgE is used in the diagnosis of asthma and to guide therapy, including environmental modification and immunotherapy. Interfering with IgE function has also recently become a focus of pharmacologic therapy.

Observations both in animal models and in human studies suggest that some components of asthmatic pathophysiology, particularly acute reactions to antigen, can be driven by IgE but that other features of the disease arise independently of IgE antibodies. The chronic allergic inflammation of the bronchial mucosa is driven primarily by a T_H2 T-cell response to allergens. There are a number of parallels and interconnections between the regulation of IgE production and that of T_H2 responses. Here we will review the roles of IgE in asthma pathogenesis, as well as the molecular and cellular factors that ultimately regulate IgE production and T_H2 expansion.

IgE FUNCTIONS IN ASTHMA PATHOGENESIS

IgE-driven hypersensitivity in the airways

In the classic immediate hypersensitivity reaction, cross-linking of IgE bound to mast cells through the high-affinity IgE receptor (FcεRI) by means of polyva-

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lent allergen induces the release of preformed vasoactive mediators, transcription of cytokines, and de novo synthesis of prostaglandins and leukotrienes. In the airway these mediators rapidly elicit bronchial mucosa edema, mucus production, and smooth muscle constriction and eventually recruit an inflammatory infiltrate (Fig 1). In asthmatic patients subjected to allergen inhalation, these cellular and molecular events result in an acute obstruction of airflow with a drop in FEV_1.[6]

In many asthmatic individuals subjected to allergen bronchoprovocation, there is a second delayed phase of airflow obstruction, designated the late-phase response (LPR). In animal models IgE antibodies can transfer both acute and LPR sensitivity to allergen challenge.[7] Interference with mast cell activation or inhibition of the mast cell mediators blocks the onset of both acute and late-phase asthmatic responses.[8] It has been proposed that chronic obstructive symptoms in asthmatic individuals subjected to recurrent environmental allergen exposure result from persistent LPRs.[9,10]

In addition to associating with mast cells and basophils through FcεRI, IgE interacts with a number of other cell types by means of the low-affinity IgE receptor CD23. In human subjects CD23 is present on a number of cell lineages. Several investigators have now shown that the binding of allergen with specific IgE facilitates allergen uptake by CD23-bearing cells for processing and presentation to T cells (Fig 1).[11-13] Mice immunized intravenously with antigen produce stronger IgG responses when antigen-specific IgE is provided at the time of immunization.[14,15] As expected, $CD23^{-/-}$ mice cannot display augmentation of immune responses by IgE but can be reconstituted by using cells from $CD23^{+}$ donors.[14,16,17] These findings suggest a scenario in which preformed allergen-specific IgE present in the bronchial mucosa of patients with perennial allergen exposure would enhance immune responses on repeated allergen inhalation.

IgE/mast cell–mediated airway inflammation and BHR in murine models

The development of murine models of asthma over the past 5 years has facilitated investigations of the roles of IgE in asthma. Although the pathology and physiology of asthma are complex, most murine studies have focused on 2 critical features of the disease, eosinophilic infiltration of the bronchial mucosa and BHR, the enhanced tendency toward airflow obstruction in response to pharmacologic stimuli. Taken together, the data from a large number of studies suggest that IgE can contribute to some aspects of asthmatic pathophysiology but that it is not, by itself, sufficient to give rise to the characteristic allergic inflammation and BHR seen after allergen exposure; a coexisting T-cell response is absolutely required. Furthermore, studies with IgE-deficient mutants reveal that IgE responses to allergen are not necessary for the expression of allergen-induced bronchial inflammation or BHR.

One group has shown that passive sensitization of mice with allergen-specific (antiovalbumin) IgE followed by allergen inhalation confers BHR and eosinophil influx into the airways.[18] IgE-sensitized athymic BALB/c nude mice do not recruit eosinophils to the airway or mount BHR after allergen inhalation, indicating that T cells are required for the full expression of the response transferred by IgE.[19,20] Allergen-induced pathology can be reconstituted in IgE-sensitized athymic mice either by the provision of T cells or by administration of IL-5. Coyle et al[21] observed that anti-IgE treatment could block both eosinophilic inflammation and BHR in mice after active immunization with allergen.

Mast cell activation through FcεRI could certainly provide a critical initiating event in the elicitation of allergic airways symptoms by IgE. A number of groups have addressed the importance of mast cells in studies of inhaled allergen responses in the W/W^{v} (mast cell–deficient mutant) strain of mice, which is rendered deficient in mast cells by virtue of a mutation in c-kit, the receptor for stem cell factor. The results of these studies have been disparate, with some supporting a role for mast cells in driving eosinophil influx after allergen exposure[22] and others failing to confirm that mast cells are critical for the expression of either bronchial inflammation or BHR in mice.[23,24] Kobayashi et al[25] observed a requirement for mast cells in the induction of BHR but not in eosinophil recruitment to the airway. Williams and Galli[26] have provided evidence that the variability probably relates to the exact conditions of allergen sensitization and challenge. They observed that W/W^{v} mice reconstituted by means of intravenous injection of mast cells had significantly depressed inflammatory and BHR responses to inhaled antigen but only when intraperitoneal sensitization was performed in the absence of alum, an adjuvant used in most of the other published studies. Thus these observations indicate that, under some conditions, IgE-FcεRI–mediated mast cell activation and consequent mediator release drives both the recruitment of inflammatory cells and the onset of BHR.

IgE modulates expression of FcεRI and CD23, altering mast cell and B-cell function

IgE serves as a positive regulator of its receptors, FcεRI and CD23 (Fig 1). Cells cultured in the presence of IgE express higher levels of these receptors.[27-30] B cells and mast cells from $IgE^{-/-}$ mice have diminished levels of both receptors but can display normal levels after intravenous infusion of IgE.[29,31,32] In human subjects treatment with anti-IgE leads to a reversible decrease in FcεRI expression on circulating basophils.[30] The mechanism of ligand-mediated regulation has not been fully worked out for FcεRI but appears to involve alterations in protein trafficking rather than transcriptional control. In the case of CD23, IgE bound to the receptor protects it from cleavage by metalloproteases, with consequent shedding of soluble fragments (sCD23) into the medium.[28] Diminished FcεRI levels in the setting of low IgE are accompanied by a decreased sensitivity to IgE-mediated triggering, suggesting that this ligand-receptor feedback loop has functional consequences for hypersensitivity reactions.[29] The roles of B-cell CD23 in

allergic responses, and hence the consequences of ligand-mediated regulation, are not as firmly established.

Cell-bound CD23 is elevated in atopic individuals and rises with flares of disease.[33] Conversely, successful induction of remission of allergy by means of immunotherapy is accompanied by a fall in CD23 levels.[34] The emerging consensus from human and animal studies is that ligation of membrane-bound CD23 on B cells can suppress IgE production. In contrast, there is some evidence that soluble CD23 (sCD23) fragments, which are generated by means of proteolytic cleavage, may enhance IgE production, both by direct interaction with B cells (through CD21) and by binding to IgE, thereby blocking its interaction with membrane-bound CD23.

Ligation of CD23 on human B cells by means of activating antibodies suppresses IgE synthesis.[35] Mice rendered CD23 deficient by targeted gene disruption have increased and sustained specific IgE titers after parenteral or inhaled immunization, as well as increased bronchial allergic responses, which is consistent with a suppressive effect of membrane-bound CD23.[36-40]

Endogenous metalloproteases, as well as some allergens, are capable of cleaving CD23. Inhibition of proteolytic activity of Der p 1 blocks its ability to induce IgE responses in vivo.[42,43] Metalloprotease inhibitors also block sCD23 shedding and IL-4–stimulated IgE production in cultures of tonsillar B cells.[44] Although sCD23 present in B-cell culture supernatants has been reported to enhance IgE production in B cells, possibly through binding to B-cell CD21,[45] it has not been possible to reproduce this effect with recombinant sCD23.[46] Thus it is unclear whether IgE-inducing activity should be attributed to other components of sCD23-containing culture supernatants or whether the lack of activity of recombinant sCD23 is the consequence of a nonphysiologic structure.

CONSEQUENCES OF IgE DEFICIENCY OR IgE BLOCKADE IN BRONCHIAL RESPONSES TO ALLERGEN

IgE-independent pathways in asthma pathogenesis

Although the genetic and clinical associations between IgE and asthma in human subjects and the animal model data described above implicate IgE in asthma pathogenesis, it has become evident that much of the chronic inflammatory component of the disease is not IgE dependent. Equivalent degrees of eosinophilic infiltration of the bronchial mucosa and BHR are elicited by means of allergen inhalation in wild-type and IgE-deficient mice generated by gene targeting.[47,48] In addition, normal levels of eosinophil influx into the bronchial mucosa and BHR are present in allergen-challenged mice with a targeted mutation of CD40, which have a complete inability to produce IgE.[49-51] B cell–deficient mice, which cannot produce any antibody isotype, also have a robust response to inhaled allergen challenge.[52-54] Allergic rhinitis, a disease associated with striking elevations of IgE levels in human subjects, can also be induced in mice independently of the presence of IgE.[55]

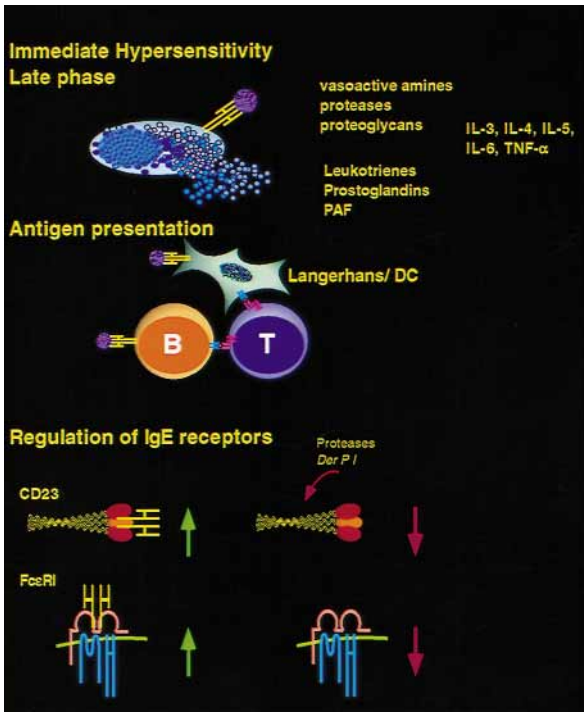

FIG 1. IgE functions in asthma pathogenesis. Levels of IgE specific for environmental aeroallergens are elevated in many individuals with asthma. In the bronchial mucosa IgE associates with FcεRI on the surface of mast cells and with CD23, which is present on B cells and a number of other cell types. Aggregation of FcεRI-bound IgE by means of polyvalent allergens leads to receptor cross-linking, resulting in mast cell activation with degranulation and release of preformed vasoactive amines, proteases, and proteoglycans. Activated mast cells also produce arachidonic acid metabolites and a number of cytokines. In the airways mast cell mediators drive an immediate hypersensitivity response characterized by contraction of bronchial smooth muscle, mucosal edema, and mucus hypersecretion, all accompanied by a drop in airflow (FEV_1). These mast cell mediators also give rise to an LPR that occurs a number of hours later and leads to a second wave of declining FEV_1. Allergen-specific IgE also supports antigen presentation by facilitating antigen uptake by B cells (mediated by CD23) and DCs. Cutaneous DCs (ie, Langerhans' cells) express FcεRI, and allergen sensitization through the skin has been shown to induce bronchial sensitivity and inflammatory responses on challenge. In a positive feedback loop, IgE directly regulates the expression of both its receptors, FcεRI and CD23. CD23 levels are enhanced in the presence of IgE because the ligand blocks receptor proteolysis and shedding from the cell surface.

The airways of patients with asthma are infiltrated with $CD4^+$ T_H2 cells.[56-58] A number of murine studies have now established T cells and their cytokine products as both necessary and sufficient for the generation of eosinophilic inflammation of the airways and BHR after allergen inhalation. Adoptive transfer of ovalbumin-specific $CD4^+$ cells polarized to T_H2 cytokine production to immunologically naive mice confers both eosinophilic inflammatory responses and BHR to inhaled antigen challenge.[59,60] These responses can be detected 1 day after transfer, a time frame far too short for the active production of IgE in the recipients. Active responses to allergen cannot be generated in mice defi-

cient in the recombinase-activating gene *(RAG)*, which have neither B nor T cells. Reconstitution of *RAG*$^{-/-}$ animals with CD4^{+} T cells alone, without transferring B cells, restores their capacity for both allergen-induced inflammation and BHR.[61] T cells are not only necessary during the sensitization phase of the immune response but are critical effectors at the time of challenge. The acute depletion of T cells with anti-CD3 antibodies immediately before allergen inhalation inhibits the inflammatory response.[62]

Taken together, the vigorous bronchial responses to allergen of IgE-deficient mice and the established necessity and sufficiency of T cells in these responses in murine models reveal that chronic allergic airway inflammation and BHR may be driven primarily by allergen-specific T cells. The multifaceted clinical expression of asthma in human subjects, though, suggests a process significantly more complex than that recreated in the murine asthma models. Although asthmatic patients clearly mount T cell–driven responses to environmental aeroallergens with resultant BHR, mucus oversecretion, and sometimes fixed airflow obstruction, they also experience acute flares of disease, with bronchoconstriction, mucosal edema, and decreased FEV_1 immediately after contact with allergen. The rapid onset of such responses suggests an IgE/mast cell–driven immediate hypersensitivity pathophysiology. It has been difficult to date to detect such acute bronchoconstrictive responses to allergen inhalation in murine models, although they can be observed after intravenous challenge.[47,63] This may relate to differences in murine airway anatomy and mast cell distribution, as well as limitations in physiologic monitoring techniques. In view of such limitations of the animal model, it is likely that human studies now underway with IgE blockers may provide better direct evidence on the role of IgE in some features of pathogenesis.

Effects of anti-IgE on asthma: Experience with recombinant humanized mAb-E25

Recombinant humanized (rhu) antibodies to IgE have recently been introduced. Studies of one of these, rhumAb-E25, in several cohorts of asthma patients have provided some insights into the role of IgE in asthma, as well as the potential utility of blockers as therapeutic agents.[64-66] These antibodies have the important property that they inhibit IgE binding to mast cells but do not cross-link FcεRI-bound IgE and provoke mast cell degranulation. They also block the interaction of IgE with CD23. Treatment with rhumAb-E25 induces a significant drop in serum-free IgE, whereas total IgE concentrations are elevated, presumably because of persistence of IgE/rhumAb-E25 immune complexes. The decrease in free IgE correlates with a reversible downregulation in basophil FcεRI density.[30]

After administration of rhumAb-E25, asthmatic subjects have significantly less airflow obstruction induced by inhalation of nebulized allergen. The maximal drop in FEV_1 is about 18% in treated patients compared with 30% in control subjects. Early and late-phase bronchoconstrictive responses are both affected, with significant differences in FEV_1 between treated and untreated groups as prolonged as 7 hours after allergen challenge. The fraction of eosinophils in induced sputum samples is about 4-fold less in the rhumAb-E25 group than in control groups. Surprisingly, rhumAb-E25 therapy appears to have minimal, if any, effect on airway responsiveness to methacholine.[64]

Clearly, these observations support the concept that IgE incites immediate responses to inhaled allergen, but they do not address the role of IgE in chronic allergic inflammation and persistent asthma. A large multicenter trial evaluating rhumAb-E25 in patients with moderate-to-severe asthma (most on inhaled glucocorticoids) has recently been completed and shows a modest decrease in symptom scores, as well as a small but significant reduction in glucocorticoid use.[66] As in many other asthma studies, symptom scores fall about 30%, even in the placebo group, but the rhumAb-E25–treated patients' scores decreased a bit more, about 40%.

The initial anti-IgE studies have shed some light on the function of IgE in asthma and provide some basis for optimism that, eventually, higher-affinity IgE blockers may prove effective in therapy. They clearly implicate IgE in both the immediate and late-phase physiologic responses of aeroallergen-sensitive patients. The suppression of these responses by rhumAb-E25 in patients studied to date is clearly not complete, however, as documented by significant residual bronchoconstrictive responses to allergen and persistence of cutaneous hypersensitivity. It is likely that some of this response may be accounted for by residual IgE (about 10 IU/L after treatment). Mast cells are exquisitely sensitive to activation by FcεRI; only about 10^3 receptors of the 10^4 to 10^6 present on the mast cell surface must be ligated to achieve activation. Thus the elimination of IgE-mediated mast cell activation will require complete depletion of circulating IgE. The importance of residual IgE has also been clear from the initial studies with allergic rhinitis, in which symptom scores in rhumAb-E25–treated patients were related to residual ragweed-specific IgE.[67,68] As higher affinity anti-IgE reagents are engineered, it may be possible to study individuals with more dramatically elevated IgE levels and to further extend the protocols to patients with atopic dermatitis or severe food allergy. Parallel approaches to interfering with IgE function might effectively complement the effect of IgE blockers. Inhibition of IgE synthesis itself, by interfering with the molecular signals and intracellular genetic events that lead to its production, might provide a potent second angle of attack on IgE-mediated airway allergy. The application of such a strategy requires a clear delineation of the mechanisms regulating IgE isotype switching, an area that has seen impressive progress in the past few years.

MOLECULAR GENETIC CONTROL OF IgE SYNTHESIS

The production of IgE antibodies by B cells is triggered by a complex series of secreted signals and cell sur-

face interactions, followed by molecular genetic rearrangements at the immunoglobulin heavy chain locus, IgH. Initially, all B cells produce IgM antibodies. At this point, a $V_H(D)J_H$ cassette of sequences encoding the variable domain is immediately adjacent to the Cμ exons, which encode the IgM constant regions at the 5′ end of the IgH locus. Further downstream in IgH are several widely spaced clusters of exons, Cγ, Cε, and Cα, encoding the constant region domains of the IgG, IgE, and IgA heavy chain isotypes. On stimulation by cytokines, along with critical cell-cell interactions with $CD4^+$ T-cell surface accessory molecules, B cells can change the isotype of the antibodies they produce while retaining their original antigenic specificity. This process requires that genomic DNA be spliced and rejoined to move the VDJ elements from their location proximal to Cμ to a position many kilobases downstream next to the C-region exons encoding the heavy chains of other isotypes.[69] A large amount of intervening DNA is excised and discarded in this irreversible process, and therefore the mechanism is referred to as deletional switch recombination.

Before the initiation of these genomic rearrangements, IL-4/IL-13–stimulated B cells destined to switch from IgM to IgE must first activate RNA transcription at the unrearranged or germline ε-heavy chain locus. The RNA produced is referred to as ε-germline transcript and is driven from a promoter 5′ of the Iε exon located just upstream of the 4 Cε exons. Mature ε-germline RNA includes a 140-bp Iε exon and exons Cε1 to Cε4.[70,71] Iε contains several stop codons, and therefore these transcripts do not encode a functional protein and are referred to as sterile.[72] Germline transcription must occur before deletional switch recombination can proceed. B cells in which the I exon or its promoter have been mutated are unable to undergo isotype switching.[73-76] Conversely, the introduction of an active promoter upstream of the I exon not only promotes germline transcription but also isotype switching.

IL-4, IL-13, their receptors, and signal transduction

The cytokines IL-4 and IL-13 alone are sufficient to drive ε-germline transcription in cultured B cells.[70,77,78] IL-4 and IL-13 receptors are multimeric and share the IL-4Rα chain. The IL-4 receptor consists of ligand-binding IL-4Rα and the signal-transducing common cytokine receptor γ chain, γc. The IL-13 receptor is composed of the IL-4Rα chain, along with an IL-13–binding chain (IL-13Rα1 or IL-13Rα2). Signaling by means of the IL-4 receptor is initiated by the activation of Janus family tyrosine kinase (JAK) 1 and JAK3, kinases associated with the IL-4Rα and γc chains, respectively.[79,80] There is evidence that the IL-13Rα chain associates with JAK2[81] and TYK2 (another JAK family tyrosine kinase).[82] These JAKs then phosphorylate tyrosine residues in the intracellular domains of the receptor chains, which serve as binding sites for the signal transducer and activator of transcription (STAT) molecule STAT6, which is in turn phosphorylated and then dimerizes and translocates to the nucleus.[83,84]

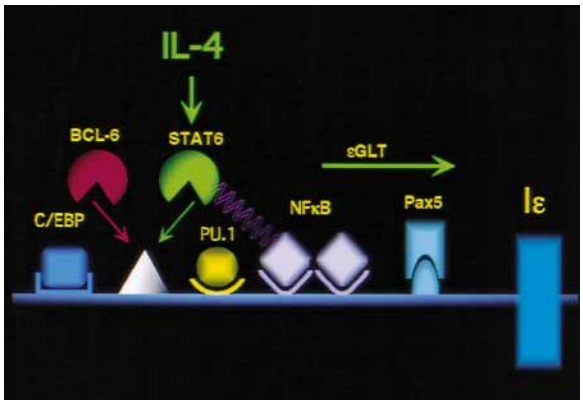

FIG 2. IL-4/IL-13–driven activation of the Iε promoter. Before deletional isotype switching and commitment to IgE production, B cells stimulated by IL-4, IL-13, or both produce germline ε-transcripts originating at a promoter 5′ of Iε. Although the critical regulatory transcription factor in activation of the promoter by these cytokines is STAT6, the promoter contains target sequences for several other transcription factors, including C/EBP, PU.1, NFκB, and Pax 5 (BSAP), and these must be intact for normal induction of germline transcription. STAT6 and NFκB, which bind to proximal promoter elements, interact physically and affect transcription synergistically. BCL-6 acts as a repressor, competing with STAT6 for promoter binding, and can attenuate Iε transcription.

STAT6 binds to specific sequences (TTCNNN[N]GAA) in the promoters of a number of genes, including the gene encoding Iε (Fig 2).

IL-4– or IL-13–induced STAT6 activation triggers RNA transcription at the Cε locus. Target sites for several transcription factors have been identified in the Iε promoter, including STAT6, nuclear factor κB (NFκB), PU.1, BSAP (Pax 5), and C/EBP. IL-4/IL-13–induced activation of STAT6 is clearly the critical regulator in ε-germline transcription. Germline transcription and IgE class switching are markedly impaired in mice deficient in STAT6.[85] Although STAT6 may be the key factor controlling the Iε promoter, NFκB and BSAP (Pax 5) elements must be present and functional.[86-88] STAT6 and NFκB interact physically and synergize in activating the promoter.[89] The ligation of CD40, a TNF-receptor superfamily member and required trigger for IgE isotype switching, leads to activation of NFκB and may thereby augment ε-germline transcription. NFκB $p50^{-/-}$ mice have impaired isotype switching,[90] and B cells from mice deficient in the NFκB inhibitor, IκBα, have enhanced IgE production.[91] Recently, a PU.1 element overlapping the distal NFκB site has been identified.[92] Like NFκB, PU.1 can synergize with STAT6 in activating the promoter.

Activation of the Iε promoter and generation of germline RNA are subject to negative regulation as well. BCL-6, a POZ/zinc-finger transcription factor expressed in B cells, binds to the same DNA target site as STAT6 and can repress ε-germline transcription induced by IL-4.[93] BCL-6–deficient mice have increased IgE isotype switching. The role of BCL-6 in this system could prove

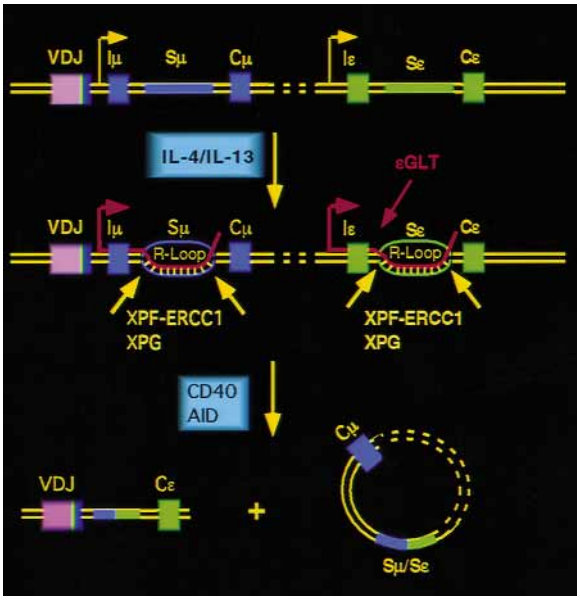

FIG 3. Mechanisms in germline transcript-mediated class-switch recombination. In naive resting B cells, the VDJ sequences encoding the immunoglobulin heavy chain variable region are positioned in the 5′ end of the IgH locus, near the Cμ exons, which encode the IgM heavy chain constant region domains. After stimulation by IL-4 (or IL-13), RNA is transcribed at the germline ε heavy chain locus originating at the Iε promoter to produce ε-germline transcripts (ε-germline transcript is indicated in red). Sε RNA remains hybridized to one of the strands of Sε DNA, forming an R-loop structure, which is a substrate for endogenous nucleases, which introduce double-stranded DNA breaks. Analogous processes result in the introduction of DNA breaks at the Sμ locus. Joining of the DNA breaks upstream of the Cε cluster of exons and downstream of the VDJ exons then generates a complete IgE heavy chain gene containing VDJ sequences encoding the antigen-binding site and Cε exons encoding the constant region domains. The intervening DNA forms an episomal excision circle, which is eventually lost during cell division.

to be clinically relevant if structural or regulatory polymorphisms in BCL-6 were associated with enhanced or diminished repression at the Iε promoter. In support of this possibility, a restriction fragment length polymorphism of BCL-6 has been identified, which is significantly associated with atopy (high IgE levels and multiple strongly positive RAST results) but not with IgE levels alone.[94] Although the restriction fragment length polymorphism resides in the first intron of the *BCL6* gene, it could be linked to mutations that affect BCL-6 expression or its physical interaction with STAT6.

ε-Germline transcripts target nucleases to the IgE locus in switch recombination

Because ε-germline transcripts do not encode a functional protein, their role in the mechanism of isotype switching has long been mysterious. A number of recently published observations have shed new light on this matter. It appears that germline transcripts participate in the assembly of complex DNA-RNA hybrid structures, which then target nucleases to the ε locus for the initial DNA cleavage in the cut-and-paste reaction of deletional switch recombination (Fig 3). In deletional switch recombination at the ε locus, DNA cleavage and ligation are carried out within the Sε cassette, which contains repeats of GAGCT and GGGGT and is located between the Iε and Cε exons. ε-Germline transcripts, originating at the Iε promoter, pass through the Sε region and then on into the Cε exons. Cell-free in vitro transcription experiments have shown that the S region containing RNA does not separate from its genomic template but rather remains associated to form a DNA-RNA hybrid.[95-97] Tian and Alt[98] have found that these hybrids create *R loops*, in which the S transcript hybridizes to the template DNA, leaving the opposite strand as single-stranded DNA. Two endogenous excision repair nucleases, XPF-ERCC1 and XPG, previously known to target duplex-single strand junctions, have been shown by the same group to be capable of cleaving these R loops. These observations have given rise to a model in which R loops formed by the association of Sε RNA with its Sε genomic template serve as substrates for nucleases that generate double-strand DNA breaks in the first step of deletional switching. In subsequent steps of the process, these breaks can be annealed by DNA end joining to analogous breaks in Sμ, located between $V_H(D)J_H$ and the Cμ exons. This ligation juxtaposes the $V_H(D)J_H$ and Cε sequences, thereby creating a functional IgE gene. Although these reports establish the existence of R loops and demonstrate that XPF-ERCC1 and XPG can cleave these structures, they do not show that these enzymes are the nucleases relevant to the deletional isotype switch mechanism. The DNA repair enzymes normally used by B cells for this process still need to be identified. It is likely that many of the proteins involved in isotype switching are constitutively expressed in B cells. Recent findings, however, indicate that some components of the deletional recombination apparatus are induced by switch stimuli. Although IL-4 and IL-13 are excellent inducers of ε-germline transcription in cultured B cells, a second signal, provided in the form of T-cell surface CD40 ligand (CD40L), is required to drive the IgE switch to completion and lead to measurable IgE production.

CD40 signaling is required for isotype switching

CD40/CD40L interaction is critical in the activation of immunoglobulin isotype switching. CD40L is transiently induced on T cells after stimulation of the T-cell receptor by antigen/MHC complexes.[99] After interaction with CD40L, CD40 aggregation triggers signal transduction through 4 intracellular proteins, which belong to the family of TNF-receptor associated factors (TRAFs).[100-104] TRAF-2, TRAF-5, and TRAF-6 promote the dissociation of NFκB from its inhibitor, IκB.[101,102,104,105] Active NFκB can then synergize with STAT6 induced by IL-4/IL-13 signaling to activate the Iε promoter, as described above.[106,107] In addition to promoting TRAF associations, aggregation of CD40 activates protein tyrosine kinases, including JAK3,[108,109] which plays an important role in immunoglobulin class switching.

CD40L is encoded on the X chromosome, and patients with the X-linked hyper-IgM syndrome are deficient in CD40L. Their B cells are unable to produce IgG, IgA, or IgE.[110-114] Mice with a targeted disruption of the *CD40L*[115] or *CD40*[116,117] genes have the same defect in antibody production.

The execution of switching in response to the combined signals of cytokines and CD40L requires the synthesis of new proteins. Recently, Muramatsu et al[118] have identified one of these proteins as activation-induced cytidine deaminase (AID). AID is expressed in activated splenic B cells and in the germinal centers of lymph nodes. Mice with a targeted mutation of AID have a major defect in isotype switching, with elevated IgM levels and low or absent IgG, IgE, and IgA. The gene encoding human AID is on chromosome 12, and a rare autosomal form of hyper-IgM syndrome (HIGM2) has now been attributed to mutations in this gene.[120] An unexpected finding in both mice and human subjects with AID mutations is a decrease in somatic V-region hypermutation during active antibody responses. Human subjects with HIGM2 also exhibit a striking lymphoid hypertrophy.

Although it is clearly critical in isotype switching, the mechanisms whereby AID participates in switch recombination remain obscure at present. AID has homology to the RNA editing enzyme, APOBEC, which modifies specific sites in ApoB precursor RNA to give rise to a transcript encoding the functional apoB48 protein. Within the immune system, AID might execute a similar RNA-editing function, processing pre-RNA–encoding proteins (eg, nucleases) involved in the mechanisms of switch recombination and hypermutation. Alternatively, AID might mediate the construction of ribozymes, complex RNA structures with nuclease activity, or it could act directly on DNA substrates in the heavy chain locus.

The recent elucidation of possible roles of ε-germline transcripts in targeting switch recombination along with the identification of proteins such as AID have constituted major advances in our understanding of how cytokine and CD40 signals drive isotype switching in B cells. Having reviewed these molecular events that regulate IgE production at the level of the B cell, it is now important to step back and consider the major sources of the molecular activators (IL-4 and CD40L) of IgE production, the T_H2 lineage of $CD4^+$ T helper cells. Of course, T_H2 cells are critical not only in supporting IgE production by B cells, but their cytokine products provide many other signals in allergic pathogenesis, promotion of eosinophil development and recruitment, mucus production, IgE receptor expression, and adhesion molecules.

CELLULAR REGULATION OF ALLERGIC RESPONSES AND IgE PRODUCTION

$CD4^+$ T_H2 cells provide the signals for IgE production

$CD4^+$ T_H2 cells are present in respiratory mucosa and regional lymphoid tissues of individuals with asthma. For many years, they have been identified solely on the basis of a characteristic constellation of cytokine production, which includes IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, and GM-CSF.[121] There is now evidence that these cells can also be distinguished on the basis of their expression of certain cell surface molecules that may regulate their trafficking to allergic sites and activation in settings of allergic inflammation. These include several chemokine receptors, CCR3 (eotaxin/CCL11 receptor), CCR4 (a receptor for TARC/CCL17 and MDC/CCL22), CRTH2, and CCR8 (I309/CCL1 receptor), and an orphan receptor of the IL-1 receptor family, T1/ST2.[122-125]

When naive T cells are first activated by antigen, they produce abundant quantities of IL-2 but relatively insignificant amounts of the T_H1- and T_H2-specific cytokines IFN-γ and IL-4. Recently, a number of elegant analyses of chromatin remodeling (changes in DNase I hypersensitivity), gene methylation, and transcriptional activity have established that this initial antigenic contact also triggers a phase of differentiation, in which genes encoding T_H1- or T_H2-specific cytokines become accessible for transcription (Fig 4).[126] Three stages of cytokine expression then follow, which ultimately drive T_H cells to the fully committed antigen-specific T_H1 or T_H2 phenotype. In the case of T_H2 development, the first phase (initiation phase) is highly dependent on antigen, IL-4, and signaling by means of STAT6. Initiation is associated with changes in chromatin structure.[127-129] A commitment phase follows, in which transcription of the T_H2 constellation of cytokines is fixed by the action of T_H2-specific transcription factors, including GATA3 and cMaf. These factors may bind to regulatory sequences, recruit chromatin remodeling enzymes, and lead to stable inherited changes, as also occurs in other developmental pathways, including erythroid development.[130] Subsequent activation of the committed T_H2 cells by antigen triggers acute gene transcription driven by the transcription factor nuclear factor of activated T cells, which selectively interacts with the cytokine promoters relevant to the lineage.

The host and environmental factors that promote a T_H2 shift in allergic individuals have become the subjects of intense scrutiny. Genetics clearly play a role. Among inbred mouse strains, some have a propensity for T_H2-dominated responses to particular antigens, and others are characterized by T_H1-dominant responses. Selective pressures exerted by particular patterns of pathogen exposure through evolution may account for this; strains of mice with a dominant T_H1 response are well equipped to mount effective attacks against intracellular pathogens, such as *Leishmania* species,[131,132] whereas T_H2 responsiveness may provide an advantage for the elimination of parasites.[133] Similarly, in human subjects it is clear that the tendency toward development of allergic responses to antigens varies greatly among individuals raised within nearly identical environmental conditions and that this allergic tendency is familial.

These genetic predispositions toward T_H1 or T_H2 are related in part to T cell–autonomous tendencies to transcribe T_H1 or T_H2 cytokines but are also the result of myriad other influences surrounding the initial encounter

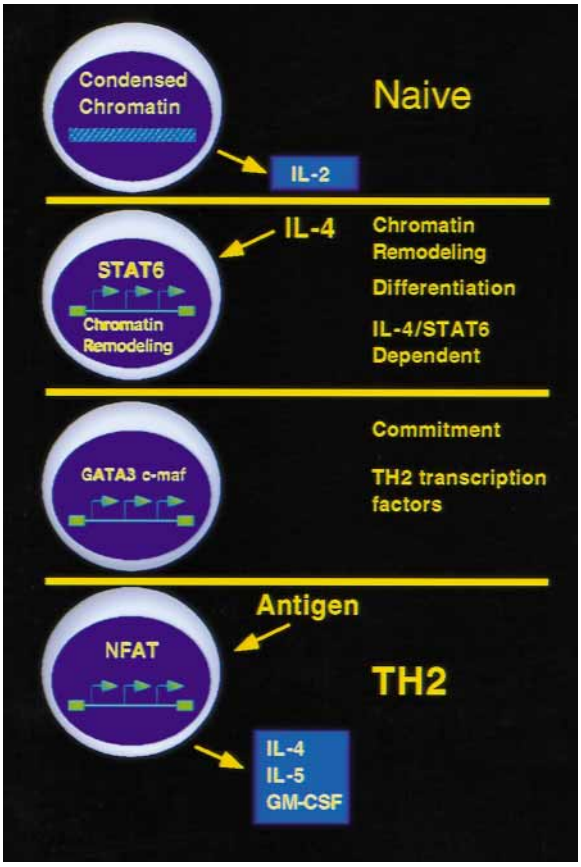

FIG 4. Differentiation of naive CD4+ T helper cells to the T_H2 phenotype. Naive T_H cells are good IL-2 producers but do not make significant quantities of IL-4 or IL-5, even after activation by means of the T-cell receptor. Under the influence of IL-4, in a process that requires IL-4R/STAT6 signaling, these cells undergo a process that renders the T_H2 cytokines competent for transcription. This requires chromatin decondensation and changes in DNA methylation, which make these loci accessible for transcription. The T_H cells are then committed to the T_H2 phenotype under the control of lineage-specific transcription factors, including cMaf and GATA3. Fully differentiated T_H2 cells then respond to antigenic stimulation by means of production of the characteristic constellation of cytokines.

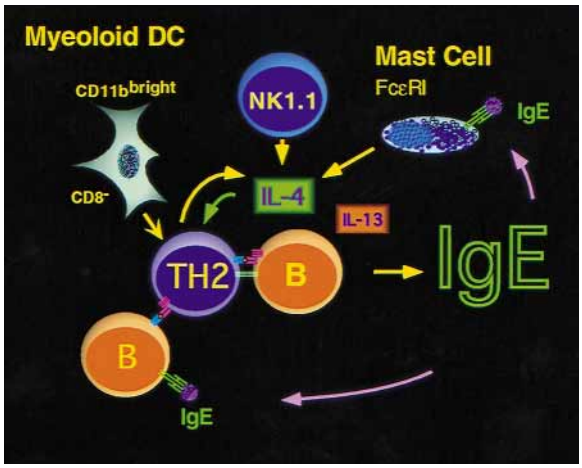

FIG 5. Cellular control of IgE production in the respiratory mucosa. A confluence of cellular and molecular stimuli supports IgE synthesis in the bronchial mucosa of asthmatic patients. DCs of the myeloid phenotype ($CD8^-$, $CD11b^{bright}$) translocate to bronchial associated lymphoid tissue after allergen encounter, during which they attain competence as APCs and drive the generation of T_H2 expansion. B cells can also serve as APCs. This function is augmented when preformed IgE (generated during previous allergen encounter) is present and can facilitate B-cell antigen uptake by means of CD23 for subsequent processing and presentation. IL-4 and IL-13 are derived from numerous cellular sources in the bronchial mucosa. In the setting of recurrent allergen challenge, preexisting allergen-specific T_H2 T cells are likely to provide a major source of IL-4. Additional producers of IL-4 include $NK1.1^+$ cells (both T and non-T) and mast cells. Mast cell IL-4 synthesis can be triggered by means of FcεRI in the presence of preformed IgE. IL-4 and IL-13, along with cognate T-B interactions involving antigen presentation and CD40 signaling, then support IgE isotype switching in B cells.

between T_H0 cells and antigen-presenting cells (APCs), some of which are genetic and some of which are environmentally defined.[134] Perhaps the most potent effect is exerted by the cytokine milieu, particularly local levels of IL-4, IL-12, and IFN-γ. IL-4 drives T_H2 responses and suppresses T_H1 development. IL-12 promotes and maintains T_H1 differentiation (an effect that is greatly potentiated by the presence of IFN-γ) and can inhibit or even reverse T_H2 development. In chronic established immune responses, these cytokines can be provided by T cells previously committed to a particular T_H phenotype. In de novo allergen encounters, cytokines produced by cells of the innate immune response may tip the balance.

Induction of T_H2 expansion in the atopic bronchial mucosa

In atopic individuals T_H2 responses to allergen and subsequent IgE production are supported by a number of unique features of the bronchial microenvironment (Fig 5). The conditions of antigen processing and presentation in the mucosa and bronchial-associated lymphoid tissue favor T_H2 deviation of T-cell responses. In addition, the presence of numerous IL-4–producing cell types, including mast cells, NK 1.1^+ T cells, and $NK1.1^+$ non-T cells, creates a cytokine milieu favorable to T_H2 development.

As in other T-cell responses to protein antigens, the induction of an allergen-specific immune response requires uptake and processing by APCs, followed by the presentation of peptides. The most potent APCs in the lung are dendritic cells (DCs), and recent studies have revealed phenotypic variability in this population, which can strongly polarize the developing T_H response. DCs reside in the bronchial mucosa, where they sample inhaled aeroallergens and then migrate to regional lymphoid tissues. On arrival in the lymph nodes, DCs have increased surface expression of MHC II antigens and B7-1/B7-2 accompanied by a markedly enhanced capacity to trigger responses in T cells of appropriate specificity.[135-137] Interference with the function of these APCs, either by conditional lineage-specific ablation or by blockade of TNF-α (which is required for their efficient translocation), blocks pulmonary allergic inflammation in murine models.[138]

Although all DCs have phenotypic markers in common, including MHC class II, B7, HSA, and CD40, analyses of both cultured and in vivo DCs have identified subsets with differential expression of certain other surface molecules. These subsets are also characterized by significant differences in the polarity of the T_H responses that they elicit. In mice the administration of the cytokine Flt-3 ligand in vivo expands 2 DC subsets. $CD8^+CD11b^{dull}$ lymphoid DCs, abundant in thymus and spleen, are effective T_H1 inducers, whereas DCs with a $CD8^-CD11b^{bright}$ myeloid phenotype, which can also be expanded with GM-CSF and are present in the spleen, are better T_H2 inducers.[139] Myeloid DCs can be derived in vitro as well, by culture of murine bone marrow with Flt-3 ligand and GM-CSF. When pulsed with ovalbumin and introduced into the airway, these cells rapidly migrate to the regional lymph nodes.[140] Subsequent inhaled ovalbumin challenge of these animals induces a T_H2 response.

Although human airway DCs have not been as well characterized, there is evidence to suggest a variability in quantity and phenotype analogous to that seen in mice. The bronchoalveolar lavage fluid of asthmatic patients contains increased numbers of DCs compared with control individuals, and these DCs have higher levels of MHC class II antigens. This activated phenotype correlates with an enhanced capacity to present Der p 1 allergen to T cells and elicit the production of IL-4 and IL-5.[141,142]

A relative abundance of cellular IL-4 sources in the bronchial mucosa in atopic individuals (with a concomitant deficiency of IFN-γ production) may also contribute to their T_H2-dominant allergen responses. In settings of established allergic responses and repetitive allergen inhalation, existing T_H2 cells may constitute the major source of IL-4. However, other resident cells have the capacity to contribute IL-4 to the bronchial cellular microenvironment. Mast cells, which are abundant in the respiratory mucosa, are excellent producers of both IL-4 and IL-13.[143,144] Mast cells bearing preformed specific IgE bound to FcεRI, are triggered by allergen to transcribe these cytokines.[145-148]

$NK1.1^+$ $CD4^+$ T cells represent another potential IL-4 reservoir. $NK1.1^+$ cells express T-cell receptors of a very restricted αβ repertoire, which interact with the nonclassical MHC class I molecule CD1.[149] The intravenous injection of anti-CD3 in mice induces large amounts of IL-4, which is derived primarily from these $NK1.1^+$ T cells. They are not required for the generation of T_H2 responses, as evidenced by the observation that animals with a targeted mutation of β_2-microglobulin (and hence deficient in CD1) do not have $NK1.1^+$ T cells but can mount T_H2 responses.[150] Nevertheless, these $NK1.1^+$ T cells may modulate T_H2 responses. Mice with abundant $NK1.1^+$ cells have enhanced IL-4 production and IgE synthesis, whereas those depleted of the same population show suppressed T_H2 responses.[151]

In addition to $NK1.1^+$ T cells, NK cells themselves may also provide IL-4 in developing responses to allergen. As is observed in $NK1.1^+$ T cell–deficient $\beta_2m^{-/-}$ mice (see above), CD1d1-deficient mice, which also lack $NK1.1^+$ T cells, are able to develop allergic responses, but such reactions are suppressed by pretreatment with anti-NK1.1 antibodies.[152] This suggests that a non-T-cell $NK1.1^+$ population, presumably NK cells, provides an important source of IL-4. There is evidence for NK polarity in human subjects as well. Cultured human NK cells can be differentiated to produce either IL-10 and IFN-γ (NK1) or IL-5 and IL-13 (NK2), a polarity analogous to that observed in the T_H1/T_H2 paradigm. This skewing has been observed in human NK cells in vivo as well.[153,154] These are intriguing findings in light of the strong association between asthma flares and viral respiratory infections and raise the possibility that NK cell–derived cytokines, provided early during immune responses to viruses, might create a bronchial cytokine milieu favorable to T_H2 responses. Polarity of cytokine production has recently been reported for B cells as well. Harris et al[155] have identified cytokine-secreting effector B cells of 2 phenotypes, Be1 and Be2, in vivo. These B cells have the ability to regulate the differentiation of naive $CD4^+$ T_H cells toward either T_H1 or T_H2 cytokine production.[155]

CONCLUSION

Years of clinical experience, as well as genetic analyses and prospective studies of cohorts of individuals at risk for asthma, have taught us that there is a strong connection between the production of aeroallergen-specific IgE and the development and severity of asthma. In addition to triggering mast cell–mediated acute and late-phase airflow obstruction, IgE probably participates in the regulation of chronic allergic responses by facilitating antigen uptake and processing, as well as modulating IgE receptor expression. Therefore targeting IgE actions with new anti-IgE therapeutics offers the potential to interfere with asthma pathogenesis at several levels. The last couple of years have witnessed significant strides in understanding both the molecular genetic events involved in IgE isotype switching within B cells and the environmental influences and transcriptional controls that govern the development of T_H2 lineage T cells, the critical inducers of IgE. It is possible that future strategies against IgE will be directed toward these mechanisms, regulating its production.

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