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Fifty years later: Emerging functions of IgE antibodies in host defense, immune regulation, and allergic diseases

Hans C. Oettgen, MD, PhD *Boston, Mass*

Fifty years ago, after a long search, IgE emerged as the circulating factor responsible for triggering allergic reactions. Its extremely low concentration in plasma created significant hurdles for scientists working to reveal its identity. We now know that IgE levels are invariably increased in patients affected by atopic conditions and that IgE provides the critical link between the antigen recognition role of the adaptive immune system and the effector functions of mast cells and basophils at mucosal and cutaneous sites of environmental exposure. This review discusses the established mechanisms of action of IgE in pathologic immediate hypersensitivity, as well as its multifaceted roles in protective immunity, control of mast cell homeostasis, and its more recently revealed immunomodulatory functions. (J Allergy Clin Immunol 2016;137:1631-45.)

Key words: *IgE, mast cells, anaphylaxis*

Abbreviations used

ADAM:	A disintegrin and metalloproteinase
AID:	Activation-induced cytidine deaminase
APC:	Antigen-presenting cell
BAFF:	B cell–activating factor of the TNF family
CSR:	Class-switch recombination
DC:	Dendritic cell
DSB:	Double-stranded DNA break
HRF:	Histamine-releasing factor
IgH:	Immunoglobulin heavy chain
ITAM:	Immunoreceptor tyrosine-based activation motif
J_H:	Heavy chain joining segment
NF-κB:	Nuclear factor κB
OVA:	Ovalbumin
Sε:	ε-Switch region
STAT:	Signal transducer and activator of transcription
SYK:	Spleen tyrosine kinase
Treg:	Regulatory T
V_H:	Heavy chain variable region gene

The ability of a circulating factor to transfer allergen-specific immediate hypersensitivity was recognized early in the 20th century when Prausnitz and Küstner described a component of the γ-globulin fraction of plasma, then called reagin and now recognized as IgE, that was capable of passing skin test responsiveness from a sensitized subject to a naive host in the passive cutaneous anaphylaxis assay. As implied in the terms immediate and hypersensitivity, IgE has unique properties among immunoglobulin isotypes in its abilities both to induce extremely rapid pathologic responses, including potentially fatal anaphylaxis, and to act as a highly sensitive immunologic amplifier capable of triggering reactions after the interaction of minute quantities of antigen with just a few IgE molecules. These functions have rendered IgE an attractive target for pharmacologic intervention and IgE blockade. Many aspects of IgE immunobiology stand out as unique, including its regulation, its specific cellular receptors, the effector cell lineages mediating its functions, and its immunoregulatory properties, all of which are discussed in this review.

GENERATION OF IgE$^+$ B CELLS: IgE ISOTYPE SWITCHING

The assembly of a functional IgE gene involves a sequence of DNA recombination events within the immunoglobulin heavy chain (IgH) locus, which spans 1250 kb in human subjects.[1] In pro-B cells in the bone marrow, transcription through an assortment of genomic heavy chain variable region gene (V_H), diversity segment (D), and heavy chain joining segment (J_H) exons triggers a ***recombination-activating gene*** (RAG) 1– and 2–mediated process leading to their assembly to generate a diverse repertoire of $\boldsymbol{V_HDJ_H}$ cassettes, each encoding a V_H domain of fixed antigen specificity. Because this V_HDJ_H cassette is situated just upstream of the Cμ and Cδ exons, B cells emerging from the bone marrow produce μ and δ-heavy chain transcripts and are both IgM$^+$ and IgD$^+$. Later in B-cell life, on exposure to cytokine and T-cell stimuli, B cells can undergo immunoglobulin ***class-switch***

From the Division of Immunology, Boston Children's Hospital, and the Department of Pediatrics, Harvard Medical School.

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Corresponding author: Hans C. Oettgen, MD, PhD, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115. E-mail: hans.oettgen@childrens.harvard.edu.

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Terms in boldface and italics are defined in the glossary on page 1632.

recombination (CSR) in which a second somatic rearrangement results in the juxtaposition of V_HDJ_H cassettes with one of a series of C_H gene segments (Cγ, Cε, or Cα), each containing the C_H exons encoding constant region domains for their respective isotypes (Fig 1). Switched B cells retain the antigen specificity dictated by their original V_HDJ_H cassette but acquire the specific biological effector functions conferred by new Fc regions. Much of what we now know about CSR in general was learned from careful study of the specific process of IgE switching.

Molecular genetic mechanism of IgE isotype switching

The process of CSR involves the sequential steps of (1) transcriptional activation of one of the C_H loci, (2) chemical modification of nucleotides in the ε-switch region (Sε), (3) introduction of double-stranded DNA breaks (DSBs) in switch regions upstream of μ and the activated C_H locus, and (4) a DNA repair process leading to annealing of the VDJ and C_H regions (Fig 1).[2,3] In some situations switching can be sequential. For example, B cells initially switching from IgM to IgG can later undergo a second CSR from γ to ε or α.

Cytokine- and receptor-mediated regulation of IgE CSR

Each of the C_H gene segments (except Cδ) is an autonomous transcriptional unit 1 to 10 kb in length with its own cytokine-regulated promoter. The Iε promoter controls transcription at the ε-locus and contains binding sites for signal transducer and activator of transcription (STAT) 6, ***nuclear factor κB*** (NF-κB), Pax5, E2A, NFIL3, AP-1, C/EBP, and PU.1. The promoter is activated by IL-4 and/or IL-13 binding to receptors on B cells, leading to activation of the transcription factor

GLOSSARY

ANTIGEN-PRESENTING CELLS: Cells that take up antigens and process them into peptides for display on MHC proteins on their surfaces for presentation to T-cell receptors.

CD11c: A cell-surface molecule with a broad expression found on immune cells.

CD40: A costimulatory protein found on B cells and antigen-presenting cells (APCs) that is required for their activation. The binding of its ligand, CD40L, on helper T cells activates B cells and APCs and induces a variety of downstream effects.

CLASS-SWITCH RECOMBINATION: A mechanism that changes a B cell's production of immunoglobulin from one type to another in which the constant region of the heavy chain is changed but the variable region of the heavy chain stays the same.

FcεRI: The high-affinity receptor for the Fc region of IgE, which is constitutively expressed on mast cells, basophils, eosinophils, platelets, monocytes, dendritic cells, and Langerhans cells.

FOLLICULAR HELPER T (T_{FH}) CELLS: T cells specialized in homing to the B-cell areas of secondary lymphoid tissue through interactions mediated by the chemokine receptor CXCR5 and its ligand, CXCL13.

HAPTENS: Small molecules that elicit an immune response only when covalently bound to a large carrier, typically a protein antigen.

IL-10: A cytokine produced primarily by monocytes and, to a lesser extent, by lymphocytes, which has pleiotropic effects in immunoregulation and inflammation.

IL-12: A cytokine produced by dendritic cells, macrophages, and human B-lymphoblastoid cells in response to antigen stimulation. IL-12 is involved in the differentiation of naive T cells into T_H1 cells. It stimulates the production of IFN-γ and TNF-α from T cells and natural killer cells and reduces IL-4–mediated suppression of IFN-γ.

MHC II: A complex that presents peptides derived from extracellular antigens to T-cell receptors.

N-LINKED GLYCOSYLATION: Attachment of an oligosaccharide known as glycan to a nitrogen atom that is required for the structure and function of some eukaryotic proteins.

NUCLEAR FACTOR κB (NF-κB): A protein complex that controls transcription of DNA and plays a key role in regulating the immune response to infection. NF-κB is found in almost all animal cell types and is involved in cellular responses to a variety of stimuli.

OPSONIZE: The process by which a pathogen is labeled and made more susceptible to phagocytosis.

OVALBUMIN: The main protein found in egg white, which is a well-characterized allergen used in immunologic studies.

OX40-OX40L: Members of the TNF superfamily expressed on a variety of cells, including activated $CD4^+$ and $CD8^+$ T cells. The OX40-OX40L complex has been shown to regulate cytokine production from T cells, antigen-presenting cells, natural killer cells, and natural killer T cells and modulate cytokine receptor signaling. This complex plays a central role in the development of multiple inflammatory and autoimmune diseases, making them ideal therapeutic candidates.

RECOMBINATION-ACTIVATING GENES (RAGs): Genes that encode enzymes that play an important role in the rearrangement and recombination of the genes of immunoglobulin and T-cell receptor molecules. RAG-1 and RAG-2 cellular expression is restricted to developing lymphocytes and generation of mature B and T lymphocytes.

RNA POLYMERASE II: An enzyme found in eukaryotic cells that catalyzes the transcription of DNA to synthesize precursors of mRNA and most small nuclear RNA and microRNA.

SOMATIC HYPERMUTATION: A cellular mechanism affecting the variable regions of immunoglobulin genes of immune cells, which diversifies and increases the affinity of antibodies.

SPLEEN TYROSINE KINASE: A nonreceptor cytoplasmic tyrosine kinase composed of a dual SH2 domain separated by a linker domain that plays a crucial role in immune receptor signaling.

Src HOMOLOGY 2 DOMAIN (SH2 DOMAIN): A sequence-specific phosphotyrosine-binding module commonly found in adapter proteins that aids in the signal transduction of receptor tyrosine kinase pathways, which allow proteins containing those domains to dock to phosphorylated tyrosine residues on other proteins.

TRANSMEMBRANE ACTIVATOR AND CAML INTERACTOR (TACI [*TNFRSF13B* GENE]): A protein found on the surfaces of B cells that is known to promote cell signaling, plays a role in B-cell survival and maturation, and is involved in class-switch recombination and antibody production.

TNF-α: Secreted by macrophages, mast cells, and many other cell types, this cytokine's primary role is the regulation of immune cells. Moreover, it is involved in the regulation of a wide spectrum of biological processes, including cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation.

TOLL-LIKE RECEPTOR LIGANDS: Ligands binding to a class of receptors expressed on macrophages and dendritic cells that recognize conserved microbial particles that can activate an immune response.

V(D)J RECOMBINATION: The somatic assembly of component gene segments that encode antigen recognition sites of receptors expressed on B and T lymphocytes.

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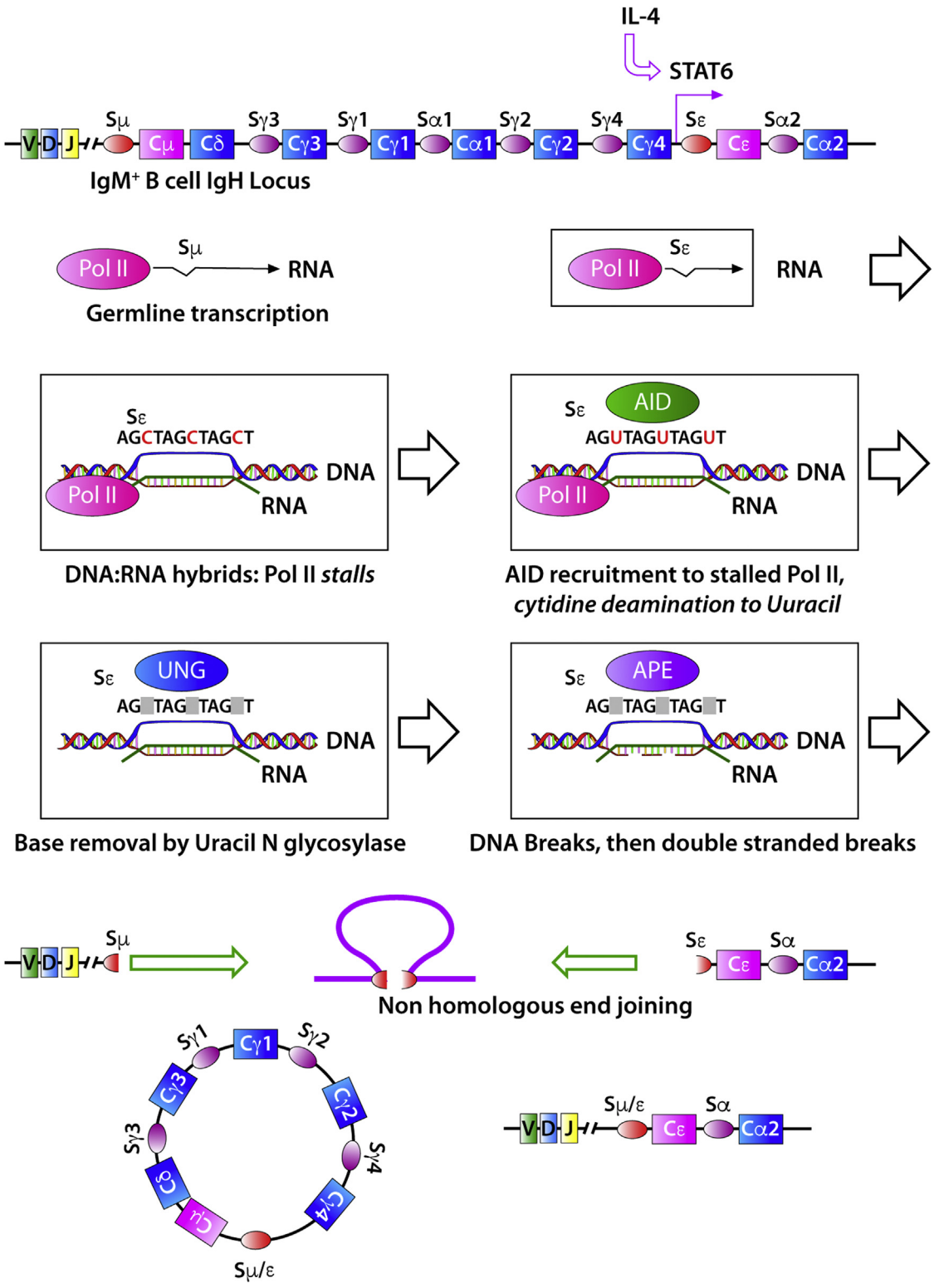

FIG 1. IgE CSR. Before switching, the IgH locus in a B cell is in its germline configuration, with exons encoding the heavy chain constant region domains distributed over 150 kb of genomic DNA. Stimulation with IL-4 initiates ε-germline transcription through the Sε region. Clustering of Gs results in a very tight interaction between the transcribed RNA and DNA template, leaving a single nontemplate DNA strand. Secondary structures arising in the single strand cause stalling of RNAse polymerase II *(Pol II)*, which results in recruitment of AID. AID catalyzes dC→dU conversions. The resultant dU nucleotides are deaminated by uracil N-glycosylase *(UNG)*, generating abasic sites, which are substrates for apurinic/apyrimidinic endonuclease 1 *(APE1)*. Single-stranded DNA breaks introduced at high density by this enzyme ultimately lead to DSBs. Breaks in Sμ and Sε are then annealed by means of classical nonhomologous end-joining *(C-NHEJ)*, a DNA repair process involving the enzymes Ku70, Ku80, and DNA-dependent protein kinase, catalytic subunit. The products of this reaction are an episomal switch excision circle along with a functional IgE gene in which the VDJ cassette encoding the heavy chain variable regions is juxtaposed to the Cε exons encoding the constant domains.

STAT6. Simultaneous engagement of ***CD40*** on B cells by its ligand, CD40L (CD154), which is transiently expressed on activated helper T cells, contributes a key second signal, activating NF-κB in a signal transduction pathway involving intracellular proteins from the TNF receptor–associated factor (TRAF) family of signaling mocecules.[4,5] STAT6 and NF-κB sites are adjacent to each other, and the 2 transcription factors act synergistically to drive transcription.[6] CD40L is encoded on the X chromosome, and boys with X-linked immunodeficiency with hyper-IgM syndrome have mutations in this gene.[7-11] Additional TNF-type receptor-ligand pairs are able to provide similar stimulatory signals to those delivered by CD40/CD40L ligation.

One TNF family member, B cell–activating factor of the TNF family (BAFF), which is expressed on monocytes and dendritic cells (DCs), binds to ***transmembrane activator and CAML interactor (TACI)*** on cytokine-stimulated B cells, inducing isotype switching, even in the absence of T cells bearing CD40L.[12,13] Although BAFF can drive IgE switching and respiratory epithelium produces BAFF, with increases in bronchoalveolar lavage fluid of segmental allergen-challenged subjects, its physiologic relevance in IgE regulation remains to be clarified.[14,15] Consistent with the existence of T cell–independent mechanisms, it has been observed that IgE CSR occurs in the airway mucosa of patients with respiratory allergy.[16] McCoy et al[17] showed that IgE can be produced, even in mice and human subjects with no T cells or ***MHC II***, and that the levels of this "natural" IgE increase with age. Such mice do not mount effective antigen-specific IgE responses, and natural IgE shows no evidence of ***somatic hypermutation*** (SHM).

Regulation of germline transcription: The Iε promoter

Transcripts arising from activation of the Iε promoter are referred to as ε-germline RNA and encompass the small Iε exon, as well as exons Cε1 to Cε4.[18,19] These RNAs are spliced, capped, and transported to the cytosol but do not give rise to proteins because multiple stop codons are present in the first exon, Iε, and have been referred to as sterile.[20] Despite this lack of a functional protein product, production of germline εRNA is indispensable to IgE switching. Targeted deletion of either the I exon or its promoter in C_H loci completely ablates switching, and insertion of a constitutively activated promoter can drive class-switching.[21-23]

The critical function of germline transcription is to induce structural changes, such as stretches of single-stranded DNA, in S-regions, which lead to recruitment of key enzymes mediating chemical DNA modification, breakage, and repair. Switch regions contain evolutionarily conserved repeats of A/T-GC-A/T sequences, the preferred substrate for the enzyme activation-induced cytidine deaminase (AID). Among heavy chain switch regions, Sε contains the fewest of these repeats, perhaps rendering it a less efficient switch target than the other isotypes.[24] RNA transcribed through switch regions contains abundant Gs. The G-rich Sε RNA transcripts bind more tightly to the C-rich template DNA than does its DNA complement. As a result, the nontemplate DNA is left free in a single-stranded form that tends to form secondary structures known as an R-loops, as well as stem loops, G quartets, and others. These structures cause stalling of ***RNA polymerase II***, which is linked to AID in complex with Spt5, a protein recruited to the stalled RNAse polymerase II (Fig 1).[25]

Induction of DNA breaks and their repair in CSR

AID catalyzes dC→dU conversions, giving rise to dU:dG mismatches.[26,27] A rare autosomal form of hyper-IgM syndrome (HIGM2), which is associated with marked lymphoid hypertrophy, is caused by mutations in AID.[28] Subsequent sequential actions on these mismatched sites by the enzymes uracil N-glycosylase and then apurinic/apyrimidinic endonuclease 1 generate single-stranded DNA breaks, which at high density give rise to DSBs. Corresponding DSBs at Sμ and Sε are annealed by the DNA repair process of classical nonhomologous end-joining, and the Cμ exons are brought together to create a functional IgE gene. Consistent with this pathway, B cells lacking Ku70, Ku80, and DNA-dependent protein kinase, catalytic subunit, all of which are involved in nonhomologous end-joining, cannot execute isotype switching normally.[29,30] For this final repair step to be directed to the correct DNA regions, the Sμ and acceptor Sε regions must be brought into physical proximity, a process mediated by chromosome looping coordinated by proteins interacting with the Eμ enhancer and the IgH 3′ regulatory region (the Cα enhancer).[31]

IgE MEMORY

In most antibody responses the processes of antigen-driven B-cell expansion, affinity maturation, isotype switch recombination, and generation of long-term B-cell memory occur in the germinal centers of secondary lymphoid tissues. For instance, high-affinity IgG-committed B cells arise in germinal centers after their IgM^+ progenitors are driven by cytokine signals and costimulatory molecules from ***follicular helper T cells*** to switch to IgG (μ-γ switch), followed by affinity maturation and generation of long-lived memory B cells. The process is different for IgE. IgE^+ B cells are short-lived in germinal centers, exhibiting both a tendency toward rapid transition to plasma cells and a susceptibility to apoptotic cell death. These properties might reflect a special fate of B cells expressing transmembrane IgE.[32]

The generation of high-affinity IgE responses and long-term memory for IgE occurs through unique mechanisms. The current understanding of IgE responses is in flux, but there is accumulating evidence that affinity maturation of IgE requires a step-wise process in which B cells sequentially undergo μ-γ and then γ-ε switches. Such a mechanism is suggested by the fact that high-affinity IgE B-cell clones tend to have hybrid switch sequences (Sμ-Sγ-Sε), which is consistent with their prior existence as IgG clones, and mice lacking the Cγ locus do not exhibit affinity maturation of their IgE responses.[33] These observations indicate that IgE memory might reside mostly in that intermediate IgG^+ B-cell stage.[34,35]

However, there is some conflicting evidence supporting the existence of IgE^+ B-cell memory. Talay et al,[36] using a transgenic mouse model in which cells expressing membrane IgE transcripts also produce a green fluorescent protein, found that IgE memory could develop through an IgE^+ germinal center intermediate and ultimately reside in IgE^+ B cells. Using a similar approach, Yang et al[37] found evidence supporting a germinal center pathway for IgE^+ cell formation but observed

that the IgE^+ cells exhibited a unique fate, rapidly upregulating the transcription factor Blimp-1 and transitioning to plasma cells. In another IgE transgenic reporter model, He et al[38] found that IgE^+ B cells do not contribute to long-lived memory. Addressing the pathways of IgE affinity maturation and memory in human subjects has been much more of a challenge. Recent very elegant work by Looney et al[39] at Stanford involving the sequencing of more than 15 million IgH regions in healthy and allergic subjects suggests that most IgE^+ cells arise from high-affinity antigen experienced (somatically hypermutated) IgG^+ precursors.

IgE STRUCTURE

IgE is the least abundant antibody isotype in plasma, present at levels (about 100 ng/mL) several logs lower than circulating IgG antibodies (5-10 mg/mL). Like other immunoglobulins, IgE antibodies are tetramers, comprised of 2 ε-heavy and 2 light chains (κ or λ) linked by numerous intrachain disulfide bonds (Fig 2). Variable (V) sequences at the N-termini of the heavy (V_H) and light (V_L) chains create unique antigen-specific binding sites. The C-terminal regions of the ε-heavy chains are made up of 4 Cε domains (compared with 3 for γ-heavy chains), each encoded by one of the Cε1 to Cε4 exons located near the 3′ end of the heavy chain locus (IgH). The IgE Cε2-4 Fc domains confer its isotype-specific functions, including binding to its receptors, ***FcεRI*** and CD23. Unlike Fcγ and Fcμ, Fcε does not activate complement.

Contact with the high-affinity IgE receptor α-chain is mediated by Cε3.[40] Cε2 is in a position comparable to the flexible "hinge" region contained in Cγ of the γ-heavy chains, and in its receptor-bound configuration, there can be a sharp turn in the molecule in the Cε2-3 region, with the pair of Cε2 domains folding back over Cε3-4.[41] In IgE^+ B cells hydrophobic sequences encoded by M1 and M2 exons present in mRNA splice variants encode a transmembrane form of IgE. IgE antibodies are more heavily glycosylated than other immunoglobulin isotypes with 7 ***N-linked glycosylation*** consensus sequences (N-X-S/T) on each ε-heavy chain, one of which (at N394 in Cε3) is required for IgE binding to its high-affinity receptor, FcεRI.[42,43] As a result of their heavy glycosylation, IgE antibodies have an affinity for galectins, lectin-type proteins that can interact with both free and cell-bound IgE.

In contrast to IgG antibodies, which have a half-life of about 3 weeks, IgE is very short-lived in plasma (half-life, <1 day), but receptor-bound IgE can remain fixed to mast cells in tissues for weeks or months. This long tissue half-life has significant clinical implications. For example, solid organ transplant recipients can exhibit peanut reactions mediated by mast cell–fixed donor IgE in the organ.[44,45]

IgE RECEPTORS

The biological functions of IgE antibodies are mediated by their dual interactions with specific antigens and 2 structurally very different receptors, FcεRI and CD23, each present on a broad range of effector cells.

FcεRI structure

The high-affinity IgE receptor FcεRI is a multimeric protein expressed in 2 isoforms, a tetrameric αβγ2 receptor present on mast cells and basophils and a trimeric αγ2 receptor expressed by eosinophils, platelets, monocytes, DCs, and Langerhans cells, although at 10- to 100-fold lower levels (Fig 3).[46] The α-chain contains 2 extracellular immunoglobulin-like domains and mediates binding to the Cε3 domain of the ε-heavy chain of IgE. The β-subunit has 4 transmembrane-spanning domains with both N- and C-termini on the cytosolic side of the plasma membrane. The γ-chains are transmembrane dimeric disulfide-linked proteins. The β- and γ-chains have intracellular immunoreceptor tyrosine-based activation motifs (ITAMs), 18 amino acid tyrosine-containing sequences that provide docking sites for ***Src homology 2 (SH2) domain***-containing proteins when phosphorylated, including the proximal signaling protein tyrosine kinase of FcεRI signaling, ***spleen tyrosine kinase*** (SYK). IgE antibodies play an important role in regulating the density of their own high-affinity receptor, stabilizing FcεRI at the cell surface.[47-52]

Dehlink et al[53] have described a circulating soluble form of FcεRI-α. In cultured cells crosslinking of surface FcεRI triggers generation of the soluble α-chain. The physiologic functions of the soluble form of FcεRI-α are under investigation, but the observation that recombinant soluble FcεRI-α can block mast cell and basophil activation, as well as passive cutaneous anaphylaxis, suggests functions in downregulation of allergic responses.

FcεRI activation on mast cells and basophils: Immediate hypersensitivity

FcεRI has high affinity for IgE (dissociation constant [Kd] 10^{-9} mol/L), and therefore mast cell and basophil FcεRI are fully occupied under physiologic conditions, and once bound, IgE remains permanently attached until internalized.[54] In the classic immediate hypersensitivity reaction, allergen-induced cross-linking of IgE bound through FcεRI triggers a cascade of signaling events, leading to mediator release and gene transcription.[55] Cross-linking of neighboring FcεRI receptors leads to aggregation and transphosphorylation of cytosolic ITAMs on the FcεRI β- and γ-chains by constitutively receptor-associated Lyn tyrosine kinase. These ITAM phosphotyrosines provide docking sites for the SH2-containing SYK protein tyrosine kinase. Activated SYK phosphorylates tyrosines in a number of adapter molecules, including LAT1/2, SLP-76, and Grb2, leading to the assembly of a supramolecular plasma membrane-localized signaling complex. The coordinate initiation of downstream signaling pathways from this complex ultimately leads to increases in cytosolic calcium, activation of gene transcription (IL-4, TNF, and IL-6), induction of synthesis of prostaglandins and cysteinyl leukotrienes and granule fusion with the plasma membrane, leading to release of preformed mediators of hypersensitivity, including histamine, proteoglycans, and proteases. These mediators rapidly induce vasodilation, plasma extravasation, tissue edema, mucus production, and smooth muscle constriction. In many subjects immediate responses are followed by delayed "late-phase" reactions. These manifest as repeated onset of airflow obstruction, gastrointestinal symptoms, skin inflammation, or anaphylaxis 8 to 24 hours after allergen challenge and after the initial response has completely subsided. Passively transferred IgE antibodies confer both acute and late-phase sensitivity to allergen challenge, and interference with IgE signaling, mast cell activation, or inhibition of the mast cell mediators blocks both responses.[56,57]

The nanomolar affinity of FcεRI for IgE together with the potency of the vasoactive mediators produced by mast cells and

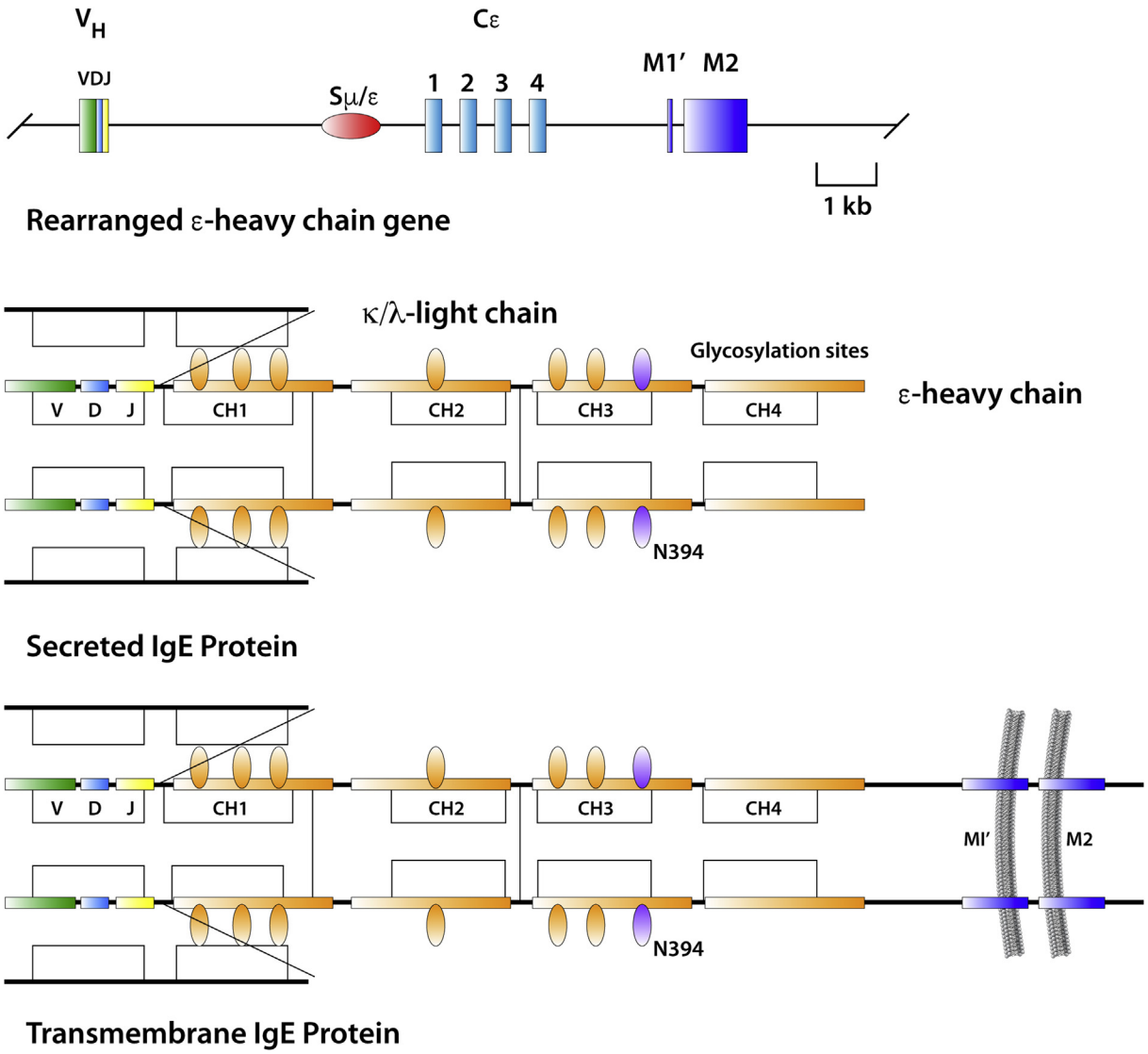

FIG 2. Structures of the mature ε-heavy chain gene and IgE protein. The ε-heavy chain gene generated in the IgH locus through deletional CSR (Fig 1) contains a VDJ cassette encoding the heavy chain variable regions juxtaposed to the Cε exons encoding the constant domains. A hybrid Sμ/Sε sequence remains between the V_H and Cε exons, a byproduct of the isotype-switching process. The secreted IgE protein has 4 constant regions, 1 more of these domains than IgG. Intrachain disulfide bonds are contained within each of the immunoglobulin domains. IgE molecules are heavily glycosylated (7 N-linked sites as indicated by *ovals*). The N394 oligosaccharide is essential for IgE-FcεRI binding. The transmembrane form of IgE, which contains M1 and M2 exons encoded by ε-mRNA splice isoforms, is expressed at the surface of IgE^+ B cells.

basophils make a highly bioamplified response system to allergens, the sensitivity of which is subject to regulation. Modulation of the cell-surface density of FcεRI by ambient IgE levels is a strong determinant of signaling threshold, and the effects of omalizumab in downregulating FcεRI likely account for much of the clinical benefit of IgE blockade. The sensitivity of FcεRI signaling is also diminished after repeated activation events, a phenomenon that might be the result of SYK downregulation.[58] Concurrent signaling by IgG antibodies interacting with the same allergens as FcεRI can also attenuate the strength of the IgE signal. These antibodies interact with the inhibitory IgG receptor FcγRIIb, setting off negative signaling pathways originating from receptor-associated protein tyrosine phosphatases and inositol phosphatases. The reduction in allergen sensitivity occurring after subcutaneous immunotherapy in aeroallergen-sensitive patients and also in subjects with food allergy completing oral immunotherapy (both of which retain significant IgE levels) might be mediated in part by the strong inhibitory IgG responses induced by these therapies.[59,60]

Blocking immediate hypersensitivity: Inhibition of FcεRI/IgE interaction

Effective pharmacologic blockade of the binding of IgE to FcεRI was achieved with the introduction of omalizumab, a humanized mAb recognizing the Cε3 domain of free but not receptor-bound IgE antibodies.[61] Omalizumab effectively blocks both acute IgE-mediated responses to inhaled and ingested

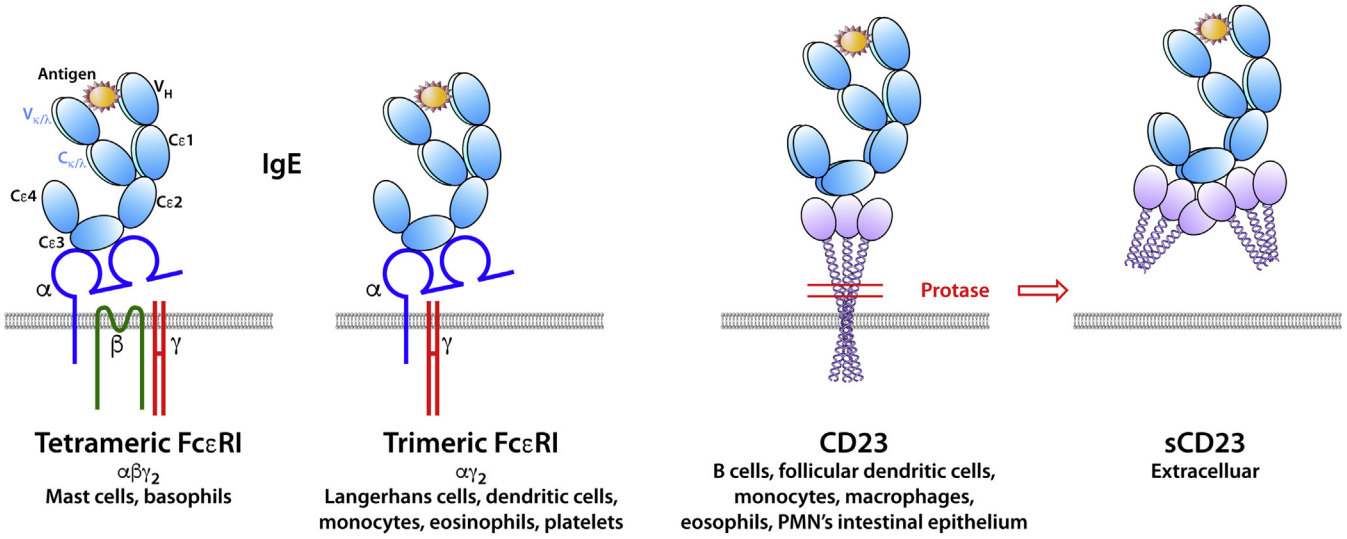

FIG 3. IgE receptors. The high-affinity IgE receptor FcεRI is expressed in its tetrameric form ($\alpha\beta\gamma_2$) on mast cells and basophils. In human subjects a trimeric form ($\alpha\gamma_2$) is found on a number of lineages, including various types of professional APCs. CD23, the low-affinity IgE receptor, is broadly distributed and is a type II transmembrane protein (N-terminus intracellular) assembled as a multimer with α-helical coiled-coil stalks terminating in IgE-binding C-type lectin heads. Protease-sensitive sites in the stalks can be cleaved by endogenous proteases (including ADAM10) or exogenous proteases (including the Der p 1 protease of dust mites).

allergens, as well as late-phase responses to inhaled allergens.[62,63] In seminal clinical trials led by Solèr in Europe[64] and Busse in the United States,[65] IgE blockade by omalizumab was shown to decrease the frequency of flares in steroid-requiring asthmatic patients but did not lead to substantial improvement in lung function or day-to-day symptoms. This suggests that although immediate hypersensitivity reactions are blunted by IgE inhibition, T_H2 cell–driven eosinophil influx, mucus metaplasia, and airway remodeling, aspects of asthma previously shown to arise independently of IgE in animal models, are less affected.[66] The beneficial effect of omalizumab in preventing acute responses to allergen inhalation might be mediated in large part by the downregulation of IgE receptors in the setting of low ambient IgE levels, with a consequent decrease in responsiveness of allergen-challenged mast cells and basophils.[67-69] The effects of omalizumab on FcεRI are complex, however, as evidenced by the findings of Zaidi et al[70] that β-chain levels decrease while SYK levels and the efficiency of signaling by individual FcεRI molecules are increased after omalizumab treatment.

A number of additional strategies for IgE inhibition have been explored or are under development. IgE synthesis is not affected by omalizumab, a limitation that led to the development of quilizumab, a humanized mAb that targets the M1-prime segment of membrane-expressed IgE present on IgE-switched B cells. Unfortunately, although quilizumab reduced circulating IgE levels to greater than 40%, it did not significantly affect asthma flares, lung function, or quality of life in adults with poorly controlled asthma.[71] This result is consistent with the past observations of Casale et al[72] that the effectiveness of IgE blockade in reducing clinical symptoms correlates with reduction of IgE to very low levels. Because omalizumab does not displace IgE bound to FcεRI at current treatment doses, the onset of clinical benefit is delayed for weeks or months until preexisting cell-associated IgE is internalized. This limitation has prodded the development of disruptive agents that dislodge IgE from its receptor. Among these is a designed ankyrin repeat protein, DARPin E2_79, which efficiently dissociates FcεRI-IgE complexes and blocks IgE-mediated mast cell activation in culture and *in vivo*, as developed by Jardetzky et al.[73,74] Low-molecular-weight compounds, including DNA aptamers and peptides, have also been studied as potential blockers of IgE binding to FcεRI, but a range of issues, including their susceptibility to hydrolysis, bioavailability, and pharmacodynamics, have prevented their translation to clinical use.[75-79]

Antigen-independent signaling through FcεRI: Cytokinergic IgEs and histamine-releasing factor

Although classical dogma has held that signaling through FcεRI is dependent on antigen/IgE-mediated receptor aggregation, evidence accumulating over the past 15 years has demonstrated that the binding of IgE to FcεRI can deliver activating signals, even in the absence of allergen. Experiments with cultured bone marrow mast cells revealed that IgE acts through FcεRI in the absence of antigen to exert a survival-enhancing effect, protecting these cells from apoptosis after growth factor withdrawal.[80,81] Indeed, there is *in vivo* evidence that mast cell survival is regulated by IgE. Tissue mast cell expansion in parasitized mice and in animals exposed to allergens depends on the presence of IgE antibodies.[82-84] Thus in addition to their role in allergen-triggered mast cell activation, IgE antibodies are key regulators of mast cell homeostasis.

Since the initial observation that IgE antibodies control mast cell survival, a number of additional responses have been found to be induced in cultured mast cells by IgE in the absence of antigen, including cytokine production, histamine release, leukotriene synthesis, and calcium flux.[85-87] There is indirect evidence that the baseline cytokine profile

of cutaneous mast cells is influenced by IgE levels, even in the absence of antigen.[88] Not all IgE antibodies are equally capable of inducing antigen-dependent mast cell activation. Those with the greatest activity have been referred to as "cytokinergic."[89] Detailed analyses of the structure of one of the most cytokinergic IgE antibodies, SPE-7, which is specific for the ***hapten*** dinitrophenyl, have revealed possible mechanisms underlying antigen-independent IgE/FcεRI aggregation. Bax et al[90] provided evidence for homotypic interactions between the variable domains (Fv) of free SPE-7 and their counterparts on FcεRI-bound SPE-7.[90] Previously, James et al[91] reported that SPE-7 exists in conformational isomers, some of which bind to autoantigens, including the protein thioredoxin. Taken together, these observations suggest that FcεRI activation by IgE in the absence of nominal antigen can be mediated by a tendency to self-associate, as well as to recognize autoantigens, interactions that, even at low affinity, lead to sufficient FcεRI crosslinking to initiate detectable signaling in this very highly amplified pathway. It is possible that such nonspecific IgE interactions with autologous proteins drive the mast cell activation underlying idiopathic urticaria. Patients affected by this disorder do not have allergen-specific IgE antibodies but exhibit dramatic and often rapid improvement after treatment with omalizumab.[92]

An additional mechanism for antigen-independent activation of IgE signaling might involve histamine-releasing factors (HRFs), which have been studied for more than 30 years. In 1995, MacDonald et al[93] reported the molecular structure of HRF, which turned out to be a secreted protein variously known as translationally controlled tumor protein, fortilin, and other names. In addition to playing key roles in cell-cycle progression and proliferation as an intracellular protein, the secreted form of HRF is found in bronchoalveolar and nasal lavage fluids and binds to a subset of IgE and IgG molecules.[94,95] The physiologic contributions of HRF to IgE-driven FcεRI signaling *in vivo* are currently under investigation.

CD23, the low-affinity IgE receptor: Structure

Commonly referred to as the low-affinity IgE receptor, CD23 actually binds IgE tightly with an association constant (K_A) of 10^8 mol^{-1}. [96] RNA splice variants encode 2 isoforms of the protein, CD23a, which is present predominantly on B cells, and CD23b, which is expressed on a wide range of cells, including monocytes, DCs, Langerhans cells, eosinophils, and gastrointestinal and respiratory epithelial cells. Unlike FcεRI or any of the Fcγ receptors, CD23 is a type II transmembrane protein (N-terminus intracellular) with an IgE-binding C-type lectin domain, making it the only immunoglobulin receptor that is not a member of the immunoglobulin superfamily.[97] The IgE-binding domains of CD23 are connected to its transmembrane segments through α-helical coiled-coil stalks (Fig 3). These mediate multimerization, and only oligomeric CD23 binds IgE.[98] In addition to serving as a receptor for IgE, CD23 in humans binds to a second ligand, the B-cell surface molecule CD21 (also known as CR2 and the EBV receptor).[99] Like FcεRI, surface levels of CD23 are regulated by IgE itself.[100] Occupancy by IgE protects sensitive sites proximal to its C-type lectin heads from cleavage by a variety of proteases, including allergens (like the Der p 1 protease of dust mites) and the endogenous a disintegrin and metalloproteinase (ADAM) proteases, especially ADAM10. Released oligomeric CD23 heads, referred to as soluble CD23 (sCD23), retain their IgE-binding capacity.

CD23 functions: Transepithelial allergen transport, facilitated antigen presentation, and regulation of IgE synthesis

CD23 on intestinal epithelial cells mediates the transport of food allergen–IgE complexes from the gut lumen into the mucosa.[101] CD23 on ***antigen-presenting cells*** (APCs) has been shown to mediate "facilitated antigen presentation," enhancing the uptake of antigen-IgE complexes for processing and presentation to T cells.[102-104] Gustavsson et al[105] and Martin et al[106] have described a mechanism whereby circulating B cells can transport IgE-antigen complexes to the spleen, where B-cell exosomes, generated in an ADAM10- and CD23-mediated process, transfer antigen to DCs for uptake, processing, and presentation. Ligation of CD23 on B cells by activating antibodies inhibits IgE synthesis,[107] and transgenic mice overexpressing CD23 have suppressed IgE responses.[108,109] Conversely, CD23-deficient mice have higher and more sustained specific IgE titers after immunization.[110-112] As predicted by these observations, anti-CD23 therapy (lumilixi-mab) results in decreased IgE levels.[113,114] Unlike transmembrane CD23, soluble CD23 (sCD23) fragments, which are generated by means of proteolytic cleavage of the IgE-binding heads, can have an opposing effect, enhancing IgE production.[115]

IgE IN HOST DEFENSE

The evolutionary persistence of the IgE isotype, along with a committed network of receptors and effector cell lineages, points to an important adaptive advantage. A clue regarding the forces driving the selection of this system is provided by the presence of high IgE levels in subjects residing in helminth-endemic regions, an association that has long suggested that IgE might be important in controlling host-parasite interactions. In areas with a high prevalence of *Schistosoma mansoni*, total IgE levels correlate with subjects' resistance to reinfection, and studies done more than 30 years ago by Joseph et al[116] showed that IgE can ***opsonize*** *S mansoni* for killing by eosinophils, providing direct evidence for a protective function. Animal models have provided additional support for a protective function of IgE. IgE enhances granuloma formation in the liver and promotes clearance of adult worms during primary infection with *S mansoni* in mice.[117] IgE antibodies also enhance production of parasite-specific IgG_1 antibodies, which have been implicated in anti-schistosomal immunity. IgE facilitates the elimination of another helminth, *Trichinella spiralis*, from the intestine and drives the destruction of tissue cysts, which are heavily coated with IgE antibodies.[82]

One might predict that the high IgE levels present in parasite-endemic regions would be associated with increased rates of atopic disease. However, the data on this point are complicated. A number of studies have pointed to the opposite effect, namely a decrease in allergic conditions in parasitized subjects.[118,119] In the setting of chronic filarial infestation, this has been associated mechanistically with an ***IL-10***–driven state of T_H1 and T_H2 suppression. In contrast, investigations in *Ascaris* or *Toxocara* species–infected subjects point to a parasite-induced increase in allergen-specific T_H2 responses and allergic symptoms, including

wheezing.[120-122] Cross-reactivity between parasitic antigens and allergens might play a significant role, as has been suggested by the observation that IgE formed in response to the tropomyosin of *Ascaris lumbricoides* recognizes the homologous proteins from the dust mite or cockroach.[123]

The abundance of mast cells in the skin along with the itch response elicited by arthropods, such as ticks, has suggested a role for IgE in protection from these ectoparasites. Such a defense mechanism might also indirectly protect against the numerous pathogens for which ticks serve as vectors. Brown et al[124] first demonstrated that antibodies to the tick conferred a basophil-mediated protective response in guinea pigs. Subsequent studies with genetically manipulated mice confirmed that both mast cells and basophils contribute to tick immunity in an IgE-dependent mechanism.[125-127]

Even a single exposure to the lone star tick, *Amblyomma americanum*, can induce a strong IgE response to tick antigens including a carbohydrate determinant, galactose-α-1,3-galatose, which is also present in certain meats. This response is responsible for a unique form of delayed food-induced anaphylaxis first described by Commins et al,[128] which is most common in the southern and eastern United States and occurs 3 to 6 hours after ingestion of mammalian food products, including beef and pork. IgE antibodies with the same galactose-α-1,3-galatose specificity are also responsible for more classical systemic anaphylaxis induced by oligosaccharides on the Fab portion of cetuximab, a chimeric mouse/human mAb against the epidermal growth factor receptor used for the treatment of various metastatic cancers.[129]

Proteases from IgE-activated mast cells inactivate reptile and hymenoptera venoms

In some subjects exposure to Hymenoptera venoms elicits strong IgE responses that can even provoke life-threatening anaphylactic reactions on re-exposure. Emerging data suggest that this might represent a pathological overreaction of a defense mechanism originally evolved to inactivate toxic venom constituents and thereby protect the host. A beneficial function for mast cell activation in the neutralization of venoms was first suggested by the observations of Higginbotham[130] in 1965 that mast cells prevented the formation of local skin lesions in mice injected with snake venom. An elegant series of experiments performed over the past decade by the group of Stephen Galli has given rise to an entirely new paradigm in which IgE antibodies might mediate resistance to both reptile and arthropod venoms.[131-134] These studies showed that exposure of mice to snake or bee venoms induces the production of IgE antibodies that mediate resistance to challenge with normally lethal doses. The failure of mast cell–deficient $Kit^{W\text{-}sh}/Kit^{W\text{-}sh}$ or IgE-deficient ($Igh7^{-/-}$) mice to acquire such protection implicates the IgE–mast cell pathway in this adaptive response. Independent studies by Palm et al[135] at Yale showed that acquired resistance to bee venom phospholipase A_2 was also mediated by an IgE mechanism. Although these findings are currently restricted to mouse models, they prod us to rethink the dogma that IgE responses to venom are invariably pathologic in human subjects.

IMMUNE REGULATION BY IgE

Both FcεRI and CD23 are expressed on APCs and can facilitate the uptake of allergen bound to IgE.[104] The trimeric form ($\alpha\gamma_2$) of FcεRI is expressed by monocytes, as well as conventional and plasmacytoid DCs, in many tissues of human subjects (but not mice) and can mediate antigen uptake for presentation.[136,137] FcεRI on dermal DCs and Langerhans cells in the skin of patients with atopic dermatitis is markedly upregulated during allergic flares.[138] FcεRI signaling in cultured monocytes and DCs leads to activation of the NF-κB pathway and production of proinflammatory mediators, including ***TNF-α***, IL-6, and CCL-28.[139-142] FcεRI crosslinking has also been observed to elicit the production of anti-inflammatory factors, including IL-10 and indoleamine 2,3-dioxygenase, and to suppress T-cell proliferation *in vitro*.[143-145] An immunosuppressive effect of IgE signaling in the setting of viral infections is suggested by the FcεRI-mediated attenuation of type I interferon production in response to the exposure of plasmacytoid DCs to influenza virus, rhinovirus, or ***Toll-like receptor*** ligands.[146,147] Asthmatic patients have been reported to have impaired rhinovirus-induced IFN-α and IFN-β responses in bronchoalveolar lavage cells,[148] and it has been speculated that the decrease in asthma flares during respiratory virus seasons observed after omalizumab treatment[149] might relate to the inhibition of IgE-mediated suppression of innate viral immunity through this type I interferon pathway.

The absence of FcεRI on rodent APCs has made it a challenge to assess the physiologic role of IgE/FcεRI on APCs with the usual mouse models of allergic diseases and T_H2 induction. Significant advances have been made in this regard by the generation of transgenic mice constitutively expressing FcεRI under control of the ***CD11c*** promoter active in DCs.[150] Sallmann et al[150] found that these mice have an enhanced pulmonary late-phase response (lung infiltration with inflammatory cells and antigen-specific T cells) to ovalbumin (OVA) inhalation after intraperitoneal or epicutaneous OVA sensitization. In contrast, a study by Platzer et al[151] using the same animals revealed a less severe phenotype with decreased inflammation, airway responsiveness, and mast cell progenitor recruitment and attenuated T_H2 responses. These investigators also observed blunted responses in an OVA food allergy model and decreased total IgE levels, the latter observation consistent with prior findings of Greer et al[152] showing that FcεRI on DCs promotes IgE clearance by internalization and transport to an endolysosomal compartment. The conflicting findings in these reports reveal the need for additional investigation on the functions of DC FcεRI.

B cells, Langerhans cells, follicular DCs, T cells, and eosinophils express CD23.[153] The binding of allergen by specific IgE bound to CD23 on cultured APCs facilitates its uptake.[154,155] The relevance of CD23-mediated antigen uptake to immune responses *in vivo* has been shown in mouse models in which wild-type but not $CD23^{-/-}$ animals immunized intravenously produce stronger IgG responses when specific IgE is provided along with antigen at the time of immunization.[102,103] In this system $CD23^{-/-}$ mice acquire responsiveness to IgE after reconstitution with B cells from $CD23^{+}$ donors.[105,156] Observations by Gustavsson et al[105] suggest a process whereby allergen-specific IgE-allergen complexes bound to B cells in the periphery through CD23 are transported to B-cell follicles in the spleen, where they are made available to splenic DCs.

Adjuvant effects of IgE-activated mast cells and basophils on allergic inflammation and T_H2 responses

Mast cells activated by IgE-FcεRI produce an array of cytokines that exert proinflammatory and immunomodulatory effects (Fig 4).[157] Mast cell development and survival are

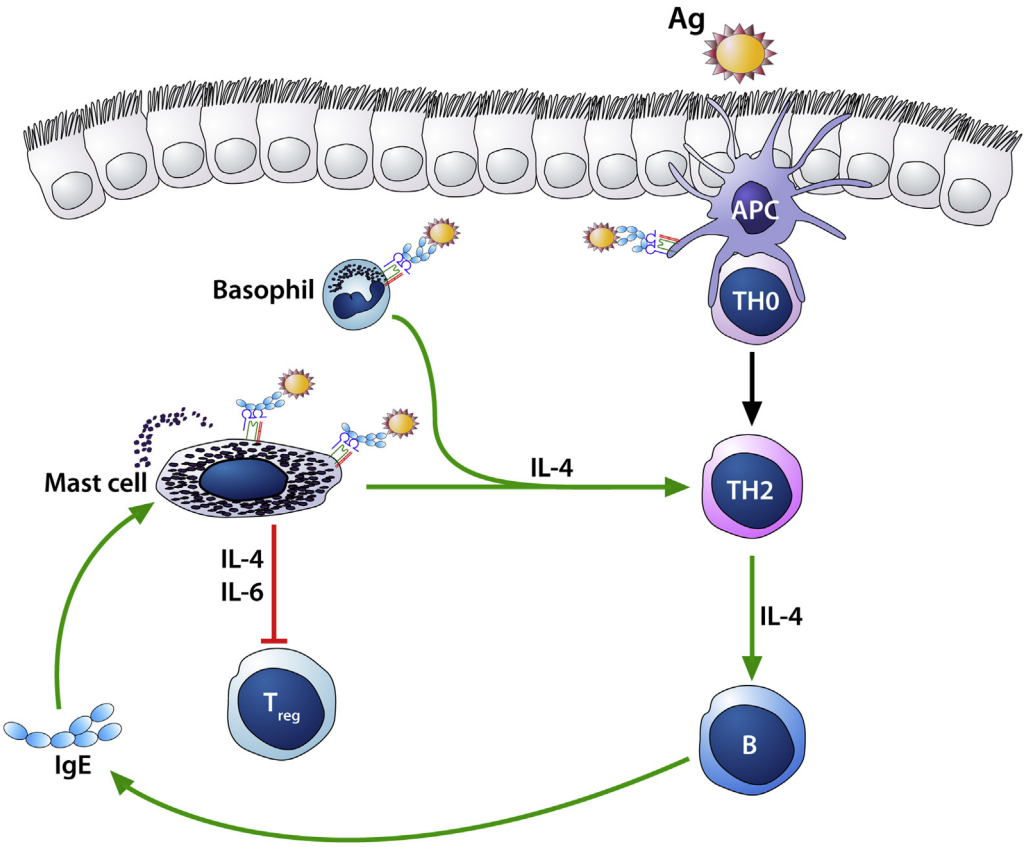

FIG 4. Proposed adjuvant and immunoregulatory functions of IgE and FcεRI. Mast cells and basophils residing in mucosal and skin sites produce IL-4 in response to antigen-induced IgE-FcεRI signaling. IL-4 promotes the induction of T_H2 cells and sustains their local survival. These provide the IL-4 and cognate T-B interactions critical for driving IgE class-switching in mucosal B cells. Mast cells suppress Treg cell expansion and function, possibly through cytokines, including IL-4 and IL-6. Trimeric FcεRI present on APCs facilitates antigen uptake for presentation to local T cells.

dependent on the cell-surface receptor protein tyrosine kinase c-Kit. Kit-mutant mice, which lack mast cells, have provided an excellent tool for analysis of the immunomodulatory effects of mast cells *in vivo*. Studies by Stephen Galli's group comparing the responses of c-Kit–deficient $Kit^{W\text{-}sh/W\text{-}sh}$ and/or $Kit^{W/W\text{-}v}$ mice that lack mast cells with those of control animals and mutant mice reconstituted with normal or cytokine-deficient mast cells first showed that mast cell–derived TNF-α can amplify the development of allergic airway and skin inflammation in adjuvant-free systems of allergen senstization.[157-159] These observations ran counter to those of some prior investigations that did not show a mast cell role in the induction of allergic inflammation but in which sensitization was achieved by using artificial adjuvants, such as alum, a discrepancy that suggested that mast cells themselves act to stimulate emerging immune responses, substituting for artificial adjuvants.[160]

We have observed a similar adjuvant function of IgE-activated mast cells in a mouse model of peanut allergy, showing that the efficient induction of peanut-specific T_H2 cells and IgE production in atopy-prone *IL4raF709* mice is dependent on the presence of IL-4–producing mast cells and IgE antibodies.[84] Analyses of IL-4–producing lineages using 4get reporter mice have revealed that mast cells are a major source of IL-4 in the intestine,[161] and Finkelman et al[162] have shown that enteral challenge of food-sensitized mice leads to a rapid IgE-dependent increase in plasma IL-4 levels. Mast cells, although not professional APCs, express MHC II and ***OX40L*** on activation, and mouse and human mast cells are able to present antigen *in vitro*.[163,164] IgE-activated mast cells have also been shown to reduce ***IL-12*** production by DCs, conferring a T_H2-inducing phenotype.[165,166]

In addition to promoting T_H2 responses, there is evidence that IgE-activated mast cells suppress the generation of regulatory T (Treg) cells and might divert them toward a T_H2 or T_H17 phenotype. Among the cytokines produced by IgE-activated mast cells, IL-1, IL-4, IL-6, and TNF-α are known to inhibit Treg cell development and function.[167,168] In the *IL4raF709* murine model of peanut allergy mentioned above, IgE-mediated mast cell activation has been shown to favor a reprogramming of the Treg phenotype with induction of GATA3 expression and production of IL-4.[169] Mast cell–derived IL-6 destabilizes Treg cell expression of Foxp3, resulting in a shift to IL-17 production.[170] The interaction of mast cell OX40L with ***OX40*** on Treg cells inhibits Treg cell suppressive functions.[170,171]

Basophils have also been implicated as IgE-triggered inducers of allergic inflammation and T_H2 responses. Twenty-five years ago, Seder et al[172] identified $FcεRI^+$ cells with ultrastructural features characteristic of basophils in the bone marrow and circulation as the major nonlymphocytic source of IL-4 in parasitized mice, a finding subsequently confirmed by the same group and others in IL-4 reporter mice.[173,174] Skin inflammation

elicited by means of passive immunization with hapten-specific IgE, followed by intradermal challenge, was used by Karasuyama et al[175] to implicate basophils in the induction of IgE-mediated allergic inflammation. Subsequent investigations using a genetic strategy to deplete basophils (transgenic expression of the diphtheria toxin receptor under control of the basophil-specific *mcpt8* promoter) also blocked the induction of IgE-driven skin inflammation.[176] We and others[177-179] have found that the same basophil depletion strategies attenuate T_H2 sensitization and allergic airway inflammation induced by allergen inhalation, and Noti et al[180] have reported that the induction of food allergy by means of epicutaneous antigen application is dependent on IgE antibodies and basophils.

Limitations inherent in the approaches used to deplete mast cells or basophils have occasionally given rise to controversy.[161] Some of the strategies used to remove mast cells either do not completely eliminate all mast cell subsets or have unwanted off-target effects on basophils and other lineages.[181-183] Conversely, the common approaches applied for basophil depletion, MAR-1 treatment (anti-FcεRI antibody), and $Mcpt8^{cre}$ transgenes might have off-target effects on mast cells.[184,185] In the most convincing studies complementation of a lost phenotype in mast cell– or basophil-deficient recipients by means of transfer of the corresponding highly purified cell population has been used to confirm the physiologic relevance of the targeted lineage. The aggregate findings to date obtained by using a range of model systems support key roles for both IgE-activated mast cells and basophils in induction of T_H2 responses, and it is likely that they have complementary and synergistic functions.

IgE and asthma: Epidemiologic evidence for a role in driving allergic inflammation

A function for IgE antibodies in the induction of allergic inflammation in human subjects is strongly suggested by epidemiologic data. There is a close correlation between "allergic sensitization," the production of aeroallergen-specific IgE antibodies detected by prick skin testing or direct IgE measurement, and development of asthma.[186,187] In wheezing toddlers greater levels of allergen-specific IgE are associated with persistence of wheezing to school age.[188] The German Multicenter Allergy Birth Cohort Study of 1314 children revealed the importance of IgE-mediated sensitivity in disease progression.[189] During the preschool years, wheeze symptoms were similar between allergic and nonallergic children. However, by adolescence, 90% of the nonallergic children had no wheezing and normal lung function, whereas more than half of allergic wheezers had active asthma with impaired lung function.

CONCLUSION

In addition to bringing to a close the quest for the elusive reagin, the discovery of IgE 50 years ago ushered in a fruitful era of investigation into its genetics, structure, and functions. In many cases research on IgE has had a truly far-reaching effect on our understanding of fundamental immunologic processes, including the mechanisms of immunoglobulin class-switching and the functions and interactions of immunoglobulin receptors. The coming decades will likely witness further advances in our understanding of IgE biology along with the introduction of next-generation anti-IgE therapies and innovative strategies to manipulate the IgE axis to modulate allergic disease.

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