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

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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***

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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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