The who, where, and when of IgE in allergic airway disease

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Allergic asthma and allergic rhinitis/conjunctivitis are characterized by a T_H2-dominated immune response associated with increased serum IgE levels in response to inhaled allergens. Because IgE is a key player in the induction and maintenance of allergic inflammation, it represents a prime target for therapeutic intervention. However, our understanding of IgE biology remains fragmentary. This article puts together our current knowledge on IgE in allergic airway diseases with a special focus on the identity of IgE-secreting cells ("who"), their location ("where"), and the circumstances in which they are induced ("when"). We further consider the therapeutic implications of the insights gained. (J Allergy Clin Immunol 2012;129:635-45.)

Key words: *IgE, atopic asthma, allergic rhinitis, memory B cells, plasma cells*

Abbreviations used

Bcl-6:	B-cell lymphoma 6
BCR:	B-cell receptor
Blimp-1:	B-lymphocyte maturation protein 1
CD40L:	CD40 ligand
Cε:	Constant domain of IgE
CSR:	Class-switch recombination
DC:	Dendritic cell
GC:	Germinal center
GLT:	Germline transcript
mIg:	Transmembrane immunoglobulin
NGF:	Nerve growth factor
PC:	Plasma cell
SHM:	Somatic hypermutation
STAT:	Signal transducer and activator of transcription
T_{FH}:	Follicular helper T

IgE, the fifth and least abundant class of immunoglobulins, is thought to have evolved in mammals from a first line of defense mechanism against parasites, particularly helminths and protozoa. However, today it is best known as a mediator of allergic reactions ranging from allergic rhinitis and asthma (Box 1) to life-threatening anaphylactic shock. IgE is composed of a pair of light chains and a pair of heavy chains (Fig 1). Like IgM, IgE has 4 heavy chain domains (Cε1-Cε4) and lacks a hinge region. IgE differs from other antibody isotypes in being located predominantly in tissues, where it is tightly bound to mast cells and basophils through its high-affinity receptor. In this cell-bound state IgE can persist for extended periods of time.[1] Most IgE is retained in tissues, and free serum IgE levels are the lowest of all immunoglobulin classes (50-200 ng/mL in healthy subjects compared with 10 mg/mL for IgG_1 and 3 mg/mL for IgA_1, Table I). In addition, its serum half-life is short: 2 days compared with 21 days for IgG_1 and 6 days for IgA_1. IgE does not activate complement and exerts its functions mostly through its receptors (Fig 2 and Box 2). The high-affinity receptor FcεRI is expressed on basophils and mast cells as an $\alpha\beta\gamma_2$ tetramer and on Langerhans cells, myeloid dendritic cells (DCs), plasmacytoid DCs, monocytes and eosinophils as an $\alpha\gamma_2$ trimer.[2-5] The low-affinity receptor FcεRII (CD23) is a C-type lectin and can be induced on a broad range of immune cells, such as activated B cells, macrophages, eosinophils, natural killer T cells, T cells, and follicular dendritic cells, but also on structural cells, such as airway epithelial cells and smooth muscle cells.[6]

STATE OF THE ART ON IgE$^+$ B-CELL DEVELOPMENT

Typically, mature naive B cells encounter antigen in peripheral lymphoid organs, where it is presented by DCs. T-dependent antibody responses are initiated when rare B and T cells specific for an incoming antigen cluster at the boundary between B-cell follicles and T-cell zones and engage in cognate interactions. Activated B cells then can adopt one of 2 fates: movement into extrafollicular areas followed by proliferation and terminal differentiation into short-lived plasma cells (PCs) or movement into B-cell follicles followed by proliferation and establishment of germinal centers (GCs).[7]

Cognate T_H cells interact with B cells and provide them with the necessary helper signals. The ligation of CD40, which is constitutively expressed on B cells, by CD40 ligand (CD40L), which is upregulated on activated $CD4^+$ T_H cells, is known to play an essential role in differentiation, class-switch recombination (CSR), and GC formation.[8,9] Specialized follicular helper T (T_{FH}) cells, characterized by CXCR5, B-cell lymphoma 6 (Bcl-6), programmed death-1, and inducible costimulator expression, provide specialized B-cell help with a plethora of cytokines, such as IL-2, IL-4, IL-21, and TGF-β1.[10,11] Of these cytokines, IL-21 plays a particularly crucial role in GC formation by providing growth and differentiation signals and sustaining the expression of Bcl-6, a transcription factor necessary for GC B-cell development.[12,13] Among the different subtypes of T_{FH} cells,

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Disclosure of potential conflict of interest: H. J. Gould has received research support from the Wellcome Trust, the Medical Research Council, and the Biotechnology and Biological Sciences Research Council. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication September 28, 2011; revised October 18, 2011; accepted for publication October 19, 2011.

Available online December 9, 2011.

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0091-6749/$36.00

doi:10.1016/j.jaci.2011.10.029

Box 1. IgE in patients with atopic asthma and atopic rhinitis

Allergic asthma and allergic rhinitis/conjunctivitis are characterized by a T_H2-dominated immune response associated with increased serum IgE levels in response to inhaled allergens. Symptoms of atopic asthma are intermittent attacks of breathlessness, wheezing, and cough after exposure to inhaled allergens. These are caused by chronic inflammation and remodeling of the conducting airways. Atopic rhinitis/conjunctivitis is an inflammation of the nasal passages, usually associated with swelling, watery nasal discharge, and itching of the nose and eyes. The association between allergen-specific serum IgE levels and asthma was established through epidemiologic studies. Burrows et al[85] found a close correlation between serum IgE levels, skin test reactivity, and asthma. Involved antigens are mostly indoor aeroallergens derived from, for example, house dust mite, animal dander, cockroach, and molds. In patients with allergic rhinitis, seasonal allergens from pollens and grasses play an equally important role as aeroallergens.

Asthmatic patients who do not respond to common allergens on a skin prick test are defined as nonatopic. About a third of adult asthmatic patients are nonatopic by this definition. Nonatopic asthmatic patients usually have more severe and difficult-to-control disease. They also have increased total IgE serum levels compared with those seen in healthy control subjects.

Experimental asthma can be induced in animals in the absence of B cells or IgE,[86,87] suggesting that other immunologic effector pathways can induce allergen-driven airway inflammation.

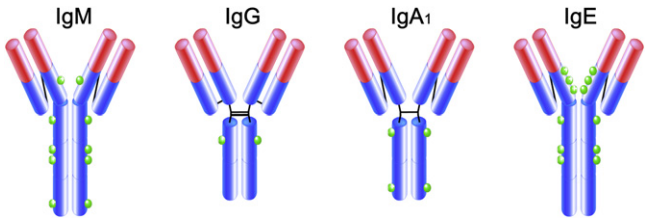

FIG 1. Protein structure of soluble IgE in comparison with IgM, IgG, and IgA. Schematic representation of the protein and domain structure showing the variable regions in *red* and the constant heavy chain regions in *blue*. Interdomain disulfide bridges are represented by *black lines*, and sites of N-linked glycosylation are represented by *green spheres*.

TABLE I. Human serum immunoglobulin levels and their main function

Isotype	Serum concentration (mg/mL)	Serum half-life (d)	Main effector functions
IgD	0.03	3	Binding to mast cells and basophils Neutralizing airway microbes
IgM	1.5	10	Classical pathway of complement activation Neonatal immunity
IgG			
IgG_1	9.0	21	Classical pathway of complement activation
IgG_2	3.0	20	
IgG_3	1.0	7	Fc receptor–dependent phagocytosis
IgG_4	0.5	21	Neonatal immunity
IgA			
IgA_1	3.0	6	Mucosal immunity: secreted into lumens of respiratory and gastrointestinal tracts Alternative pathway of complement activation
IgA_2	0.5		
IgE	5×10^{-5}	2	High-affinity binding to mast cells and basophils (immediate hypersensitivity reactions)

T_H2-like T_{FH} cells are the only subset capable of inducing IgE class-switching in naive B cells.[14]

Once B cells have entered the GC reaction, they undergo clonal expansion and selection, antibody affinity maturation through somatic hypermutation (SHM), and CSR (Fig 3). Two signals are required for class-switching to IgE: IL-4/IL-13 and CD40 ligation.[15] This is illustrated by decreased IgE levels in mice deficient for CD40 or IL-4.[16,17] The T_H2 cytokines IL-4 and IL-13 are strong inducers of IgE switch through signal transducer and activator of transcription (STAT) 6, whereas CD40 ligation signals through nuclear factor κB. Both signaling molecules can bind the Iε promoter (STAT6 with a higher affinity) to initiate the production of "sterile" ε germline transcripts (εGLT).[18,19] Production of εGLTs from the Iε promoter precedes IgE class-switching and makes the ε switch region available for recombination. Nuclear factor κB and, to a lesser extent, STAT6,[20] induce expression of activation-induced cytidine deaminase, which initiates a series of reactions leading to recombination of the heavy chain between the Sμ and Sε regions.[21] This results in rearranged mature ε chain mRNA and a circular piece of DNA that is looped out, referred to as a switch circle. Both direct μ to ε CSR, as well as sequential switch through γ intermediates have been observed in human subjects,[22,23] as well as mice.[24]

An isotype-switched affinity-matured B cell exiting the GC reaction will become either a memory B cell or a long-lived PC. How this decision is made is not yet known. Memory B cells are long-lived, dividing B cells that carry their B-cell receptor (BCR) at high levels on the surface and secrete little immunoglobulin.[7] On antigen recall, they react rapidly and give rise to antigen-specific antibody-secreting PCs. PC precursors or plasmablasts that emerge from GC reactions are highly proliferative cells and migrate primarily to the bone marrow, where they terminally differentiate into PCs. They downregulate several B-cell lineage–specific markers and upregulate the PC marker CD138 (syndecan-1). The transcription factors B-lymphocyte maturation protein 1 (Blimp-1) and X-box protein 1 are necessary for PC development because they regulate secretory processes and endoplasmic reticulum stress, allowing the endoplasmic reticulum machinery to adapt to high-level antibody production. Long-lived PCs provide long-term antibody titers; they do not self-renew and express very low to undetectable levels of membrane immunoglobulin.[25] Together, memory B cells and long-lived PCs ensure humoral memory. In the case of IgE, it is not clear whether both long-lived PCs and memory B cells exist. Fig 4 provides an overview of immunoglobulin expression, membrane markers, and transcription factors in the different stadia of B-cell differentiation.

OUTSTANDING QUESTIONS/GAPS IN OUR KNOWLEDGE OF IgE BIOLOGY

"Who": Is IgE memory ensured by PCs and memory B cells?

"Where": Where do IgE-secreting cells reside?

"**When**": Does IgE CSR take place during GC formation? Can it happen independently of T-cell help?