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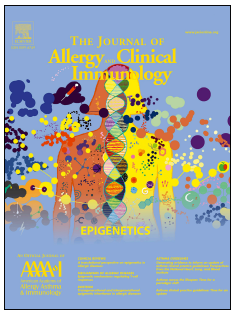

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Anaphylactic or tolerant outcomes with IgE

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Text

Immunoglobulin (Ig) E protects the host against parasites and venoms; however, IgE also plays a central role in the pathogenesis of allergic diseases. The high-affinity receptor for IgE, FcεRI, expressed on the cell surface of mast cells and basophils is a heterotetrameric structure ($\alpha\beta\gamma_2$) composed of an IgE-binding α subunit, a signal-amplifying β subunit, and two disulfide-linked signal-triggering γ subunits [1]. Multivalent allergen exposure induces the cross-linking of FcεRI, initiating activation events which lead to degranulation and the release of preformed histamine and proteases, as well as de novo production and secretion of cysteinyl leukotrienes, prostaglandins, cytokines and chemokines (**Table I**). These chemical, lipid, and protein mediators induce allergic reactions, including potentially lethal anaphylaxis. FcεRI devoid of the β subunit ($\alpha\gamma_2$) is expressed in several cell types, such as dendritic cells (DCs), and facilitates antigen presentation by capturing low-concentration antigens via receptor-bound IgE, leading to T cell responses.

IgE has another low-affinity IgE receptor CD23 (or FcεRII) [2]. CD23 is a type II transmembrane protein composed of a short N-terminal intracellular domain, a transmembrane sequence, a coiled-coil stalk and an IgE-binding, C-type lectin head domain. This molecule commonly exists as a homo-trimer, and the IgE binding domains are connected to the membrane via a triple stalk region. In addition to this membrane bound form (mCD23), there is a soluble fragment (sCD23) released by cleavage in the stalk region by proteases termed sheddases such as ADAM10. A mite allergen Der p 1 can also work as a sheddase. There are two isoforms, CD23a and CD23b, generated by differential splicing that contrast in their first seven (CD23a) or six (CS23b) N-terminal amino acids. CD23a is expressed predominantly by B cells, and CD23b is inducible by IL-4 in a range of cells including B cells and epithelial cells (**Table I**). Binding of mCD23 by IgE immune complexes (IgE-ICs) downregulates IgE synthesis, whereas monomeric or trimeric sCD23 molecules impose downregulating or upregulating effects, respectively, on membrane IgE expressing B cells. CD23a internalizes IgE-ICs by endocytosis, while CD23b uptakes IgE-coated particles by phagocytosis. Internalized IgE-ICs via CD23 are degraded in human monocyte-derived DCs, but CD23 is recycled in B cells. Antigens captured by CD23 on B cells are transferred to DCs for antigen presentation to T cells [3].

IgE-mediated immune responses are elaborately regulated at multiple levels. High turnover rate (half-life 2-3 days), low efficiency of class-switch recombination to IgE, lower surface expression of membrane IgE on germinal centers (GCs) and increased apoptosis of IgE^+ GC B cells all contribute to low IgE levels. IgE is also the scarcest among Ig isotypes in

the serum; however, once bound to FcεRI, the half-life of IgE extends by weeks to months. The main function of IgE as an antigen sensor does not require a high amount of antibody; this is in sharp contrast with IgM, IgG or IgA, whose function is to neutralize their targets. Although the scarcity of the IgE-positive B cells in vivo has hindered attempts to track their ontogeny and fate, recent studies have revealed that IgE^+ B cells are predisposed to swiftly exiting GCs and differentiating into plasma cells, and IgE-producing GC B cells die by apoptosis. The specificity of IgE comes from that of IgGs as sequential class switch recombination from IgM to IgG (IgG1 only in mice; IgG1, IgG3 and IgG4 reported in humans) to IgE is the predominant route for the production of affinity-matured IgE [4]. IgE cells also develop directly from IgM cells, but the resultant IgE has a lower affinity. Therefore, affinity maturation occurs during the development of IgG^+ cells, and IgE succeeds their antigen specificity and affinity. Indeed, mouse $IgG1^+$ memory B cells can give rise to IgE-producing cells in secondary response [5]. IL-4 derived from T follicular helper (Tfh) cells is necessary for IgE production, but it is not sufficient. A recent study identified a rare population of IL-13-producing Tfh13 cells that are required for the production of high-affinity anaphylactogenic IgE [6]. Therefore, Th2-type inflammatory context is one of the key commands to convert neutralizing antibodies into IgE and distributing it to the peripheral FcεRI-positive mast cells and basophils.

In this issue of the Journal, Engeroff et al. report a simple but elegant dichotomy of IgE effects on FcεRI and CD23 [7]. FcεRI on mast cells and basophils preferentially binds monomeric IgE while CD23 on B cells preferentially binds IgE-ICs (**Table I**). These differential binding properties translate to biological functions: as has been known for many years, mast cells and basophils, when sensitized first with monomeric IgE, then incubated with antigen, are activated to initiate allergic inflammation. However, these cells, exposed to IgE-ICs without prior sensitization with monomeric IgE, showed reduced amounts of IgE bound to FcεRI and were much less activated in in vitro cultures and in vivo passive systemic anaphylaxis. By contrast, IgE binding to CD23 on B cells was much higher when incubated with IgE-ICs than with monomeric IgE, and IgE-ICs did not show in vivo anaphylactic responses. Another aspect of this study was a confirmation of the role of CD23 in clearing IgE-ICs from the serum. They showed that the IgE-IC clearance was drastically delayed in CD23 KO mice. Although it is not determined whether this function of CD23 might be conducted by mCD23 and/or sCD23, the authors interpret that CD23 is part of the negative regulation of IgE: in addition to an earlier study that CD23 is a negative regulator of IgE synthesis [8], when more IgE is bound by CD23 on B cells, the less FcεRI on basophils and mast cells are sensitized by IgE.

Can our current knowledge of IgE and IgE receptors sufficiently explain the above phenomenon of dichotomy? Of concern is whether or not free IgE in the serum forms significant levels of ICs with allergens. The vast majority of IgE is tissue bound, but not circulating in free form in the way that IgG or IgM is found. Allergens encountered at mucosal surfaces may bind IgE on mast cells in respiratory, gastrointestinal, and cutaneous tissues before going into the circulation. Compared to IgG and IgM that form ICs, concentrations of circulating IgE are extremely low to favor IC formation. Under some high IgE situations such as allergen-specific immunotherapy and helminth infections, however, substantial serum levels of IgE-ICs may be found. Structurally, IgE-Fc binds FcεRI with an open conformation of Cε3-Cε4 domains while it binds CD23 with a closed conformation of the Cε3-Cε4 domains [9]. Although IgE-Fc binds to FcεRI and CD23 mainly by interacting via opposite ends of the Cε3 domain, allosteric changes in IgE-Fc caused by binding to FcεRI do not allow IgE to bind to CD23 at the same time, and vice versa. Similar conformational changes may occur in IgE when bound to allergens that do not allow IgE to bind both receptors. However, no information of three-dimensional structures has been obtained on allergen-bound IgE that also is bound to either receptor. Another point of discussion with regard to this study is its relevance to therapeutic approaches. As implied above, desensitization by allergen-specific immunotherapy may potentially be due to increased serum IgE levels and resulting increases in IgE-ICs, which reduce sensitization of mast cells and basophils. Efficacy of anti-IgE omalizumab is not only due to lowering IgE levels [10], but also to formation of IgE-anti-IgE immune complexes and inhibition of IgE binding to CD23. Further studies are required to address these issues.

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Table I

receptor	type or isoform	expressing cells	Function and IgE preference
FcεRI	$\alpha\beta\gamma_2$	Mast cells, Basophils	Degranulation, de novo production and secretion of allergenic mediators; preferred receptor over CD23 by monomeric IgE that leads to allergic sensitization
	$\alpha\gamma_2$	DCs, Langerhans cells, Monocytes, Macrophages, Neutrophils, Eosinophils, Platelets, and others	Facilitated antigen presentation
CD23	CD23a	B cells	Negative regulation of IgE synthesis, Ag capture; preferred receptor over FcεRI by IgE-ICs that lead to noninflammatory outcomes
	CD23b	Monocytes, Macrophages, Eosinophils, Langerhans cells, Platelets, Follicular DCs, B cells, T cells	Ag presentation
	sCD23	Soluble products cleaved by sheddase like ADAM10, Der p 1	Monomeric and trimeric sCD23 molecules impose downregulating and upregulating effects, respectively, on IgE synthesis