Published in final edited form as:

Clin Exp Allergy. 2009 March ; 39(3): 304–306. doi:10.1111/j.1365-2222.2008.03182.x.

Allergen Independent Immunomodulatory Activities Of IgE

Anthony A. Horner^{*,#} and Toshiaki Kawakami^{*,#}

^{*}Department of Medicine, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0663

[#]Department of Pediatrics, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0663

[#]La Jolla Institute for Allergy and Immunology, La Jolla, CA 92037-1387

In 1966, IgE was identified as the principal antibody responsible for mediating the type I hypersensitivity response[1]. This molecular insight ushered in a new era in our understanding of allergic diseases. More recently, it has come to light that IgE molecules also have allergen-independent immunomodulatory activities. In this month's issue of *Clinical and Experimental Allergy*, Dr Mathias and colleagues demonstrate that circulating IgE impacts on the ability of mice to become sensitized to an inhaled hapten[2]. The observation is consistent with previous studies in demonstrating that IgE has immunomodulatory activities that are not mediated by allergen cross-linking. Future studies will need to determine the mechanisms underlying IgE's allergen-independent immunomodulatory activities and their impact on human health and disease.

The level of total IgE in a subjects serum was reported to correlate with the level of high affinity IgE receptor (FcεRI) expression on their basophils[3] in the 1970s, and Furuichi et al. went on to demonstrate that incubation of RBL-2H3 rat mast cells with IgE enhances their expression of FcεRI[4] in the 1980s. Two laboratories further established that serum IgE directly regulates mast cell FcεRI expression in the mid-90s[5,6]. Functionally, IgE engagement of FcεRI has been found to prime mast cells for enhanced granule release and cytokine production upon IgE cross-linking[7]. In addition to FcεRI, serum IgE has been shown to regulate the expression of its low affinity receptor, CD23 [8,9]. For example, while all B cells express CD23, expression levels are far higher on B cells from wild-type mice than on B cells from IgE-deficient mice. Moreover, injection of IgE into IgE-deficient mice leads to increased B cell CD23 expression. Interestingly, CD23-deficient mice have higher serum IgE levels and CD23 transgenic mice have lower IgE levels than wild-type mice, suggesting that CD23 signaling helps to regulate IgE production[10,11].

It was reported in 2001 that monomeric IgE can protect growth factor-deprived mast cells from apoptotic death by inducing FcεRI aggregation[12,13]. Thus, IgE did not protect FcεRI-deficient mast cells from cell death. Furthermore, survival was found to depend on autocrine secretion of IL-3[14]. Although several laboratories have reported that FcεRI cross-linking induced with IgE plus antigen also promotes mast cell survival, other laboratories have failed to detect this anti-apoptotic effect. The discordant modulatory effects of monomeric and cross-linked IgE on mast cells are likely to be explained by the fact that only weak, but not strong FcεRI-aggregating stimuli, induce mast cell survival[14,15]. In this context, it is worth noting that comparative studies of monoclonal IgE molecules derived from different hybridomas have found that they exhibit remarkable heterogeneity in their ability to promote mast cell survival

and induce activation events, including degranulation, cytokine production, migration, and others[16]. While questions remain, studies have come a long way toward identifying the mechanisms by which monomeric and cross-linked IgE regulate the activation status and longevity of mast cells[17].

An earlier publication from Dr Oettgen's laboratory[18] established that IgE-deficient mice were unable to mount immune responses to skin contact sensitizing haptens. In these investigations, preformed IgE was found to be required for the sensitization but not the effector phase of the contact hypersensitivity response. The current issue of *Clinical and Experimental Allergy* contains an article by Drs Mathias, Oettgen and co-workers, which establishes that allergen non-specific IgE is also required for the development of airway hypersensitivity to an inhaled hapten, trinitrobenzene sulfonic acid[2].

The mechanistic basis for an IgE requirement in the development of hapten hypersensitivity has not been adequately worked out. While basophilic cells are responsive to monomeric IgE, it has yet to be established that they mediate IgE's adjuvant influence on hapten sensitization. It is also unclear whether high-affinity FcεRI, low-affinity CD23, or both receptors mediate IgE's adjuvant activities. Finally, the signaling/inflammatory cascades that IgE renders competent, in order that mice are capable of mounting a hapten hypersensitivity response, have not been identified.

In previous studies, IgE was found to be required for adequate dendritic cell migration from the epithelial surface during hapten sensitization [18]. The influence of IgE on dendritic cell migratory behavior appears to be FcεRI and mast cell dependent, as mast cell-deficient mice also displayed resistance to contact hypersensitivity with the application of oxazolone to the skin and reduced dendritic cell migration from the epidermis. These observations suggest one potential mechanistic scenario for IgE's role in the development of hapten hypersensitivity, improving dendritic cell migration to draining lymph nodes, leading to more efficient antigen presentation to naïve T cells.

Allergen non-specific immunomodulatory activities attributed to IgE include signaling through FcεRI to promote mast cell survival and responsiveness to allergen exposure, as well as the ability to license the immune system for hapten sensitization. From a clinical perspective, it is worth noting that it is difficult to detect IgE in the blood of healthy newborns but with age, serum IgE levels increase to adult levels, which are achieved by age 16 [19]. If IgE serves to up-regulate immune responsiveness in an antigen independent manner, than one might speculate that rising serum levels could have a more global effect on immune homeostasis during childhood. For example, physiologically low IgE levels at birth may help explain why infants are particularly vulnerable to certain pathogens, including tuberculosis, which is cleared and sequestered by cells (i.e. CD8 cells) that also participate in hapten induced type IV hypersensitivities [20,21]. Likewise, IgE mediated hypersensitivities are rarely seen in the neonatal period and while the prevalence of food allergies peaks in the first years of life, peak prevalence rates for hypersensitivities to aeroallergens occur late in childhood [22]. Results presented in Dr Mathias' current paper and others suggest that the genesis of allergic diseases may require that basal IgE levels reach a threshold level before cells are adequately primed to cooperate in the development of hypersensitivities to allergens contained in foods and ambient air. While highly speculative, such theories are consistent with currently available evidence and readily testable in murine models of allergic disease. Ongoing and future investigations will no doubt lead to a far more comprehensive understanding of IgE's antigen-independent bioactivities and could lead to the development of novel therapies to manipulate FcεRI and CD23 signaling in order to prevent and/or treat allergic diseases.

References

1. Ishizaka K, Ishizaka T, Hornbrook MM. Physico-chemical properties of human reaginic antibody. IV. Presence of a unique immunoglobulin as a carrier of reaginic activity. *J Immunol* 1966;97:75–85. [PubMed: 4162440]
2. **Insert specific information about Mathias article.**
3. Conroy MC, Adkinson NF Jr, lichtenstein LM. Measurement of IgE on human basophils: relation to serum IgE and anti-IgE-induced histamine release. *J Immunol* 1977;118:1317–1321. [PubMed: 66288]
4. Furuichi K, Rivera J, Isersky C. The receptor for immunoglobulin E on rat basophilic leukemia cells: effect of ligand binding on receptor expression. *Proc Natl Acad Sci U S A* 1985;82:1522–1525. [PubMed: 3156380]
5. Hsu C, MacGlashan D Jr. IgE antibody up-regulates high affinity IgE binding on murine bone marrow-derived mast cells. *Immunol Lett* 1996;52:129–134. [PubMed: 8905407]
6. Yamaguchi M, Lantz CS, Oettgen HC, Katona IM, Fleming T, Miyajima I, et al. IgE enhances mouse mast cell Fc(epsilon)RI expression in vitro and in vivo: evidence for a novel amplification mechanism in IgE-dependent reactions. *J Exp Med* 1997;185:663–672. [PubMed: 9034145]
7. Yamaguchi M, Sayama K, Yano K, Lantz CS, Noben-Trauth N, Ra C, et al. IgE enhances Fc epsilon receptor I expression and IgE-dependent release of histamine and lipid mediators from human umbilical cord blood-derived mast cells: synergistic effect of IL-4 and IgE on human mast cell Fc epsilon receptor I expression and mediator release. *J Immunol* 1999;162:5455–5465. [PubMed: 10228025]
8. Kisselgof AB, Oettgen HC. The expression of murine B cell CD23, in vivo, is regulated by its ligand, IgE. *Int Immunol* 1998;10:1377–1384. [PubMed: 9786437]
9. Campbell KA, Lees A, Finkelman FD, Conrad DH. Co-crosslinking Fc epsilon RII/CD23 and B cell surface immunoglobulin modulates B cell activation. *Eur J Immunol* 1992;22:2107–2112. [PubMed: 1386315]
10. Texido G, Eibel H, Le Gros G, van der Putten H. Transgene CD23 expression on lymphoid cells modulates IgE and IgG1 responses. *J Immunol* 1994;153:3028–3042. [PubMed: 8089484]
11. Stief A, Texido G, Sansig G, Eibel H, Le Gros G, van der Putten H. Mice deficient in CD23 reveal its modulatory role in IgE production but no role in T and B cell development. *J Immunol* 1994;152:3378–3390. [PubMed: 8144922]
12. Asai K, Kitaura J, Kawakami Y, Yamagata N, Tsai M, Carbone DP, et al. Regulation of mast cell survival by IgE. *Immunity* 2001;14:791–800. [PubMed: 11420048]
13. Kalesnikoff J, Huber M, Lam V, Damen JE, Zhang J, Siraganian RP, et al. Monomeric IgE stimulates signaling pathways in mast cells that lead to cytokine production and cell survival. *Immunity* 2001;14:801–811. [PubMed: 11420049]
14. Kohno M, Yamasaki S, Tybulewicz VL, Saito T. Rapid and large amount of autocrine IL-3 production is responsible for mast cell survival by IgE in the absence of antigen. *Blood* 2005;105:2059–2065. [PubMed: 15542585]
15. Kitaura J, Xiao W, Maeda-Yamamoto M, Kawakami Y, Lowell CA, Kawakami T. Early divergence of Fc epsilon receptor I signals for receptor up-regulation and internalization from degranulation, cytokine production, and survival. *J Immunol* 2004;173:4317–4323. [PubMed: 15383560]
16. Kitaura J, Song J, Tsai M, Asai K, Maeda-Yamamoto M, Mocsai A, et al. Evidence that IgE molecules mediate a spectrum of effects on mast cell survival and activation via aggregation of the FcepsilonRI. *Proc Natl Acad Sci U S A* 2003;100:12911–12916. [PubMed: 14569021]
17. Kawakami T, Kitaura J. Mast cell survival and activation by IgE in the absence of antigen: a consideration of the biologic mechanisms and relevance. *J Immunol* 2005;175:4167–4173. [PubMed: 16177053]
18. Bryce PJ, Miller ML, Miyajima I, Tsai M, Galli SJ, Oettgen HC. Immune sensitization in the skin is enhanced by antigen-independent effects of IgE. *Immunity* 2004;20:381–392. [PubMed: 15084268]
19. Lindberg RE, Arroyave C. Levels of IgE in serum from normal children and allergic children as measured by an enzyme immunoassay. *J Allergy Clin Immunol* 1986;78:614–618. [PubMed: 3534049]

20. Smith S, Jacobs RF, Wilson CB. Immunobiology of childhood tuberculosis: a window on the ontogeny of cellular immunity. *J Pediatr* 1997;131:16–26. [PubMed: 9255187]
21. Newton SM, Brent AJ, Anderson S, Whittaker E, Kampmann B. Paediatric tuberculosis. *Lancet Infect Dis* 2008;8:498–510. [PubMed: 18652996]
22. Sigurs N, Hattevig G, Kjellman B, Kjellman NI, Nilsson L, Bjorksten B. Appearance of atopic disease in relation to serum IgE antibodies in children followed up from birth for 4 to 15 years. *J Allergy Clin Immunol* 1994;94:757–763. [PubMed: 7930310]