Allergy 1995: 50: 193–199
Printed in Belgium – all rights reserved

Copyright © Munksgaard 1995
ALLERGY
ISSN 0105-4538

Review article

IgE-mediated antigen presentation

Mudde GC, Bheekha R, Bruijnzeel-Koomen CAFM. IgE-mediated antigen presentation.
Allergy 1995: 50: 193–199. © Munksgaard 1995.

G. C. Mudde [1], R. Bheekha [1], C. A. F. M. Bruijnzeel-Koomen [2]

[1] Department of Immune Regulation, Sandoz Research Institute, Vienna, Austria;
[2] Department of Dermatology, Dermato-Allergology Unit, University Hospital Utrecht, Utrecht, The Netherlands

Dr G. C. Mudde
Sandoz Research Institute
Department of Immune Regulation
Brunnerstrasse 59
1235 Vienna
Austria

Accepted for publication 18 May 1994

Atopic allergy afflicts at least 20% of the population in developed countries. It comprises a wide range of IgE-mediated disorders, such as hay fever, asthma, atopic dermatitis (AD), and food allergies. Higher serum IgE concentrations correlate with hyperreactive diseases in which larger parts of skin, mucosa, or both are involved (Fig. 1) (66). Clearly, there is a direct connection between IgE titers and the distribution of effector cells which bear high-affinity receptors for IgE ($Fc_\varepsilon RI$), such as mast cells and basophils. However, the view that these cells are unique in expressing $Fc_\varepsilon RI$ cannot be sustained since the recent discovery of $Fc_\varepsilon RI$ on normal Langerhans' cells (6, 65), on monocytes from atopic patients (36), and on eosinophils in parasitic infections (54). The finding of $Fc_\varepsilon RI$ in human skin (44) and blood, on cells different from effector cells such as mast cells and basophils, suggests an additional role for IgE in immune responses (38). Moreover, not only can $Fc_\varepsilon RI$ be found on antigen-presenting cells (APCs), but also the low-affinity receptor for IgE ($Fc_\varepsilon RII$ or CD23) can be found and induced on many different cell types including APCs (60). Therefore, the data pointing to a role of IgE in antigen focusing are accumulating. In addition, we propose that IgE has a role in allergy expansion by generating allergies to new allergens.

IgE levels in allergic disease

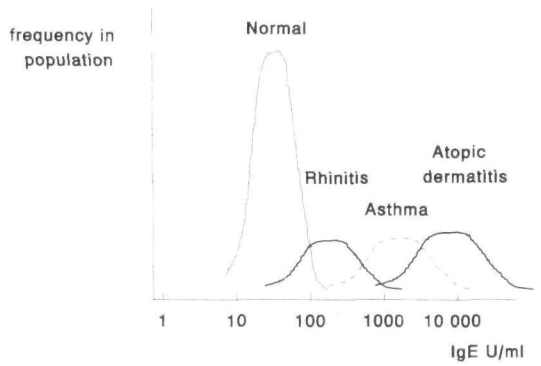

Fig. 1. Relation between serum IgE titers and allergic disease. Patients with higher IgE titers tend to have larger parts of their body involved in allergic disease.

CD23: a multifunctional receptor

The low-affinity receptor for IgE has been the subject of debate since its discovery. It is different from all other Fc receptors, because it is a single-chain, type II membrane molecule, with its carboxyl group outside. Interestingly, CD23 molecules tend to coil around each other, forming dimers (16) or even trimers (23, 57), and that explains why monomeric IgE can bind stably to this receptor for a relatively long time (51). In addition, this may explain why IgE binding to CD23 does not inhibit, but rather enhances, interaction between CD23 and its newly discovered ligand CD21 (3, 7). It is thus clear that CD23 can bind to at least two molecules, which are completely different in structure: IgE and CD21. The binding of IgE of CD23 inhibits the autocleavage of CD23 into its soluble products, some of which have

special functions by themselves. Soluble CD23 has been reported to be a growth factor for B cells and a cofactor for IgE synthesis (55), as well as a germinal-center B-cell survival factor (22). The stabilizing effect of IgE binding to CD23 may be a negative signal for IgE production (45, 52). Bonnefoy and coworkers have shown that the interaction between CD23 on T cells and CD21 on B cells is also important for IgE production, and that Fab fragments of anti-CD23 antibodies *in vivo* inhibit IgE synthesis by more than 90% (21). The influence of IgE binding to CD23 on T cells or B cells has not been evaluated in this system.

$Fc_\varepsilon RI$ expression on antigen-presenting cells

In 1986, Bruijnzeel-Koomen et al. showed that, in AD, Langerhans' cells may express IgE (12), which was later shown to be bound to a CD23-negative Fc receptor (11). Only when antibodies against the human $Fc_\varepsilon RI$ became available was the real nature of this IgE receptor clarified. Two groups independently found $Fc_\varepsilon RI$ expression on normal Langerhans' cells (6, 65), which were confirmed as the IgE-binding structure in AD (24). In a more recent study, $Fc_\varepsilon RI$-bearing cells in normal skin have been found not only in the epidermis (Langerhans' cells) but also in the dermis, and all of these cells were CD45 positive, human lymphocyte antigen (HLA) class II positive, and mainly RFD7 positive (a marker for macrophages (47)). Only a subpopulation of these cells showed CD1a expression (44). The same group simultaneously showed increased expression of $Fc_\varepsilon RI$ on monocytes from atopic donors (36).

General mechanisms for antigen uptake

The immune response to foreign proteins is strongly dependent on the efficiency and selectivity of antigen uptake by APCs. Internalized antigen is then processed and presented to T cells in an HLA class II restricted way (reviewed in Ref. 9). Until now, three mechanisms of antigen trapping by APCs have been generally accepted.

Phagocytosis of particles is the means by which cells of the mononuclear phagocyte system take up antigens, allowing both primary and recall antigens to be internalized and processed. Phagocytosis is enhanced by opsonization of particles with IgG, which interacts with IgG Fc receptors ($Fc_\gamma R$) or with complement receptors on these mononuclear cells (15). Dendritic cells and B cells cannot use phagocytosis, but may utilize the more general process of *pinocytosis* (53). B cells may additionally use an *antigen-specific surface immunoglobulin* for antigen capture (35, 49). This process is more efficient, because the required antigen concentrations are 1000 times less than for pinocytosis (35). However, despite the efficient binding by B cells, this process may be limited by the relatively small number of specific B cells and B cells which produce rheumatoid factor (49).

Recently, several groups have reported a fourth possible mechanism of antigen trapping, both *in vivo* (29, 40) and *in vitro* (33, 46, 63). The APC may bind monomeric *antigen-specific IgE* by an $Fc_\varepsilon R$ which will then capture antigen and increase the efficiency of antigen presentation. Furthermore, IgE/antigen complexes may also be used by the APC for antigen focusing (46, 63). This mechanism, which is like antigen-specific binding by B cells, may be of general importance (38), but it is clearly important in allergy.

IgE-mediated antigen capture

Mast cells

The concept of IgE as an antigen-capturing antibody was first described for mast cells. Allergen may bind to "empty" IgE bound to the $Fc_\varepsilon RI$ on the surface of the mast cell. Cross-linking of the receptors will then cause release of inflammatory mediators which are involved in immediate-type hypersensitivity reactions.

Langerhans' cells

The first evidence that IgE may play a role in antigen capture by APC was found in AD patients (10). In 1986, Bruijnzeel-Koomen et al. (12) showed that, in AD, IgE may be found on epidermal Langerhans' cells, a finding which has been confirmed and extended to other skin diseases by other researchers (5). Recently, we have shown (10, 40) that the Langerhans' cells from AD patients depend on surface IgE to mount specific T-cell responses to house-dust allergen (HDA), both *in vivo* and *in vitro* (40). *In vitro*, only IgE-bearing Langerhans' cells could present HDA to autologous T cells from blood, whereas the presentation of HDA by monocytes was IgE independent. Furthermore, *Candida albicans* antigens could be presented by monocytes as well as Langerhans' cells, regardless of the presence of IgE on the surface of the APC (40). *In vivo*, IgE on Langerhans' cells was strongly correlated with the outcome of epicutaneous application of aeroallergens to the skin of AD patients (40). This patch test reaction, which is specific for AD patients, has recently been shown to induce an allergen-specific T-cell infiltration into the skin (50, 64).

Thus, it appears that, as in the case of the mast cell, IgE, bound to the $Fc_\varepsilon RI$ on the Langerhans' cell functions *in vivo* to capture antigens before antigen processing and presentation. In this connection, we

reanalyzed part of our data from the published experiments (40). Originally, we showed that preincubation with antilight chains or anti-IgE antibodies before incubation with allergen reduced antigen-specific proliferation of T cells to 70%. Non-T-cell-mediated antigen presentation from the same donors was not significantly affected by this treatment. However, we now realize that this was only partly true (Fig. 2). Six donors could be reanalyzed, and in three of the six, anti-IgE antibodies inhibited HDA-specific proliferation, but anti-light-chain antibodies had no significant influence. This indicates that, in these three donors, IgE might have been involved in antigen trapping by non–T cells, whereas, in the other three donors, IgE was not involved. Langerhans' cells have either IgE on their surface or no Ig at all; therefore, anti-light-chain and anti-IgE antibodies are expected to have the same effect. However, in non–T cells, which are about 70% monocytes (39), anti-light-chain antibodies would also detect monomeric IgG bound to $Fc_{\gamma}RI$ (CD64). Therefore anti-IgE antibodies might inhibit antigen trapping, whereas anti-light-chain antibodies, by binding to IgG, would activate rather than inhibit the non–T cells, leading to extra production of interleukin (IL)-1 and IL-6 (34, 62). The enhanced production of IL-1 and IL-6 may explain the slight increase in T-cell proliferation over the untreated cells (30).

In summary, these data indicate a role for IgE in antigen trapping by non–T cells. Of course, we cannot distinguish among monocytes, B cells, or even dendritic cells in the non-T-cell population, but, since the recent finding of $Fc_{\varepsilon}RI$ on monocytes from atopic donors (36), it is tempting to speculate that the IgE-mediated antigen presentation by the non–T cells was through $Fc_{\varepsilon}RI$ on the monocytic population. Preliminary data from our laboratory indicate that, as expected, the $Fc_{\varepsilon}RI$ on monocytes from atopic donors may be involved in IgE-mediated antigen presentation.

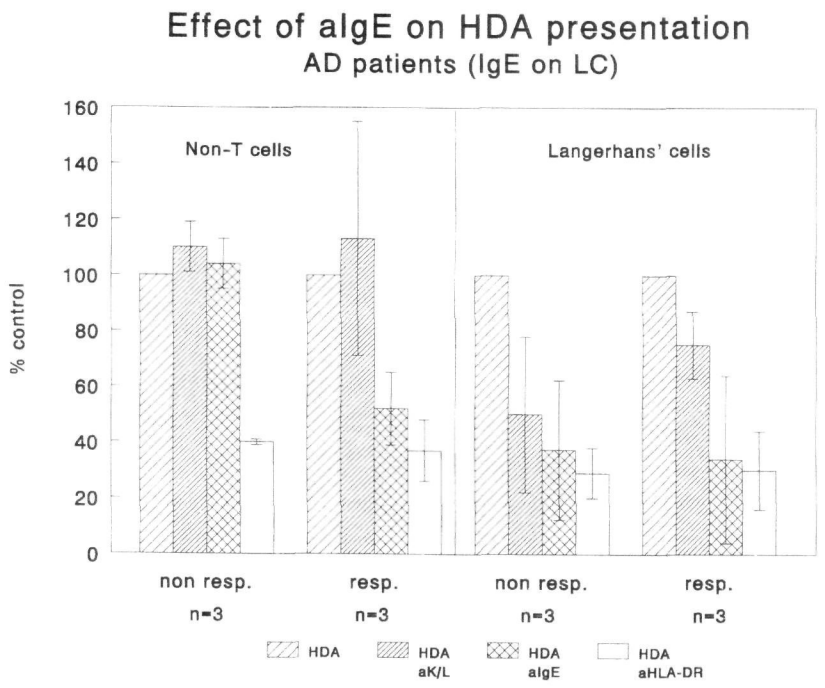

Fig. 2. Effect of anti-IgE antibodies and anti-light-chain antibodies on HDA-induced proliferation of peripheral-blood T cells. Preincubation with both anti-IgE and anti-light-chain antibodies inhibited HDA responses induced by Langerhans' cells. With non–T cells, only 50% of patients responded to anti-IgE treatment, whereas anti-light-chain antibodies tended to increase responses. Anti-HLA DR inhibited all responses equally well.

In vivo *IgE-mediated antigen presentation*

Heyman *et al.* (29) were the first to show *in vivo* IgE-mediated antigen presentation by CD23 in mice. They showed that trinitrophenyl (TNP)-specific IgE, injected (i.v.) before bovine serum albumin (BSA)-TNP enhanced antigen capture and presentation, and led to strong IgG anti-BSA production in the absence of adjuvants. As in our *in vitro* model, the IgE antibodies had to recognize the antigen to mediate antigen presentation, because TNP-specific IgE did not potentiate the response against BSA. Antibodies against CD23 completely inhibited the IgG anti-BSA response in these animals. Interestingly, these data indicate that, in mice, high-affinity receptors for IgE on APCs are not involved. Indeed, as yet, such cells have not been described in mice. On the other hand, the route by which the antigen was administered (i.v.) in this *in vivo* model might bypass APCs with $Fc_{\varepsilon}RI$ expression.

B cells

Further evidence of a possible role of IgE in antigen capture by APCs comes from *in vitro* studies using CD23 expressing B cell-lines, and monoclonal antigen-specific IgE (33, 46). Kehry & Yamashita (33) showed in mice that IgE bound to CD23, unlike IgG1 bound to $Fc_{\gamma}R$, allows nonspecific B cells to bind antigen specifically, and present very low amounts of antigen to antigen-specific T cells. More recently, these data have been confirmed in man by Pirron et al. (46), who have shown that, as in mice, human Epstein-Barr virus (EBV) B cells, by means of CD23, can internalize and present IgE/antigen complexes. Roosnek & Lanzavecchia (49) confirmed the observation by Kehry & Yamashita (33) in mice and Pirron et al. in man (46) that IgG/antigen complexes are not internalized and presented by human EBV B cells, probably because of a mutation in the CD32 receptor (37). Both groups (33, 46) used IgE complexed with antigen in their studies. However, *in vivo*, the existence of antibody/antigen complexes consisting purely of IgE are not very likely; therefore, we first studied the role of monomeric IgE bound to CD23 on APCs (51). Indeed, we were able to show that monomeric IgE binds to EBV B cells and, ad-

ditionally, that it can be used to capture allergens very efficiently.

An explanation for the monomeric binding of IgE to a low-affinity receptor lies in the characteristic of CD23 to form dimers or even trimers (23, 57), thus increasing the avidity for IgE. For the antigen-presentation assay, we used a system in which T-cell clones specific for *Der p* I (a major allergen of house-dust mite) (64) were stimulated to produce significant amounts of granulocyte/macrophage-colony stimulating factor (GM-CSF) after antigen presentation by EBV B cells. The EBV B cells were preincubated with or without monoclonal NIP-specific IgE antibodies (42), and subsequently the B cells were preincubated with *Der p* I or *Der p* I to which we had coupled the hapten NIP (*Der p* I-NIP). Specific T-cell responses were seen with as little as 10 ng/ml of *Der p* I-NIP, but only when NIP-specific IgE was present on the B-cell membrane. NIP-specific IgE-bearing B cells were not able to focus *Der p* I. However, *Der p* I (as well as *Der p* I-NIP) could stimulate the T cells in the absence of IgE, but even a 5000 times higher antigen concentration, incubated for 12 h (12 times longer), did not result in the same level of T-cell stimulation (51). In fact, the concentration of *Der p* I(-NIP) necessary to mimic the response after IgE-mediated antigen focusing in a 1-h incubation is toxic for B cells. On the other hand, the IgE concentration sufficient for significant T-cell stimulation could be as low as 10 ng/ml, a concentration not detectable by fluorescence-activated cell sorter. These data show the potency of IgE in antigen presentation, and also the potential danger of the high (allergen-specific) IgE titers found in atopic donors.

In a later set of experiments (R. Bheekha, P. Kidd, A. Pearce, G. C. Mudde, paper in preparation), we tried to mediate antigen presentation by IgG antibodies, using the same system of NIP-specific IgG antibodies of all four isotypes (13), NIP coupled *Der p* I and *Der p* I-specific T-cell clones. No monomeric binding of IgG1, 2, 3, or 4 could be detected and no IgG-mediated antigen presentation was found. Therefore, we adopted the method previously used by Pirron *et al.* (46) and compared the ability of IgE/*Der p* I and IgG/*Der p* I complexes to induce a *Der* p I-specific immune response in the T-cell clones. We used three NIP molecules per *Der p* I molecule; to our surprise, we found binding only of IgE complexes to the B cells (CD23 specific), but detected no binding with the IgG complexes. Only when we increased the number of NIP molecules per *Der p* I molecule to around 10 did we find binding of IgG complexes to CD32 on B cells. This confirms previous findings by Valim & Lachmann (61). In addition, *Der p* I-$NIP_{(3)}$ did precipitate IgE molecules in an Ouchterlony assay, but not IgG molecules, whereas *Der p* I-$NIP_{(10)}$ formed large complexes with all isotypes (R. Bheekha, P. Kidd, A. Pearce, G. C. Mudde, paper in preparation).

The absolute number of epitopes on *Der p* I for IgE or IgG antibodies within one donor is difficult to determine, but, in general, it is believed that in one patient fewer than five epitopes are recognized by IgE and IgG antibodies (4, 14, 25, 26, 31, 32). Consequently, *in vivo*, the chances of IgG forming complexes with *Der p* I big enough to bind to CD32 are very low. Therefore, IgG/CD32-mediated antigen presentation is not probable. This is confirmed by van der Heijden et al. (63), who used sera from AD donors to form complexes with *Der p* II. They found that only preincubation of the sera with polyclonal anti-IgE antibodies (not polyclonal anti-IgG antibodies) could inhibit antigen presentation to *Der p* II-specific T-cell clones. This confirms that IgG, although present in the sera of the patients, is not involved in antigen focusing on EBV B cells. Moreover, it is unlikely that IgG complexes, even if they could bind to CD32, would allow antigen presentation, because it has previously been shown by Roosnek & Lanzavecchia (49) that CD32 on human EBV B cells does not internalize after cross-linking. On the other hand, monocytes which express CD64 are highly capable of binding IgG (complexes) and of antigen presentation through this mechanism.

IgE responses are tightly controlled

IgE responses are highly controlled, perhaps because of their role in modulating immune responses, and because high levels of IgE are associated with immune-mediated disease. At least four different mechanisms are involved in regulation of IgE responses.

First, although IgE bound to mast cells can be detected over a period of weeks, serum IgE has a half-life of 2–3 days. This short half-life favors a rapid return to normal IgE levels when the antigen is cleared.

Second, IgE may be more susceptible to anti-idiotype regulation than other immunoglobulin classes, as has been shown in mice for the antibody response to phosphorylcholine epitope T15 (8).

Third, IgE responses are closely regulated by T-cell-derived cytokines. In mice, there are two types of helper T cells, Th1 and Th2, which produce lymphokines with different effects on IgE production. Th1 cells produce IL-2 and interferon-gamma (IFN-γ) while Th2 cells produce IL-4, IL-5, and IL-10 (reviewed in Ref. 56). Separate, clear-cut Th1 and Th2 populations have also been described in man (41, 64). It has been shown that IL-4 and IL-13 (18, 48) increase, while IFN-γ decreases, IgE production (45). This is true of noncognate interactions,

but in an antigen-specific stimulation, IFN-γ can no longer influence Th2-mediated IgE induction (43). Moreover, superantigen-induced IgE production by normal B cells and Th2 cells is not under the control of exogenous IFN-γ (2).

Fourth, IgE production may be downregulated by the binding of IgE to B-cell CD23. IgE binding stabilizes the CD23 molecule and inhibits the formation of soluble CD23 (sCD23) (20). It has been claimed that soluble CD23, which is an enzyme cleavage product of the low-affinity IgE receptor, potentiates ongoing IgE synthesis (reviewed in Ref. 19). This remains controversial, because it has been found in the mouse that soluble CD23 has no effect on IgE synthesis (17). Furthermore, the absence of a negative signal for IgE switching when IgE binds to CD23 implies that IgE binding at suboptimal concentrations still allows production of sCD23 and subsequent IgE switching.

IgE-mediated antigen presentation in allergy: out of the frying pan into the fire

The presence of both Th2 cells specific for an allergen (call it allergen 1) and high titers of allergen 1-specific IgE may lead to CD23-mediated allergen 1 presentation by *in vivo* activated bystander (naive) B cells. These B cells, which express CD23 after recognition of their specific antigen (call it AgX1), present AgX1 as well as allergen 1 to specific T cells. The allergen 1-specific T cells, being Th2, induce a switch to IgE in these previously innocuous B cells. Consequently, the B cell produces new IgE antibodies, and the patient, originally allergic to allergen 1, now also produces IgE against a previously innocuous AgX1. The newly formed IgE causes degranulation of mast cells when cross-linked by AgX1 (Fig. 3).

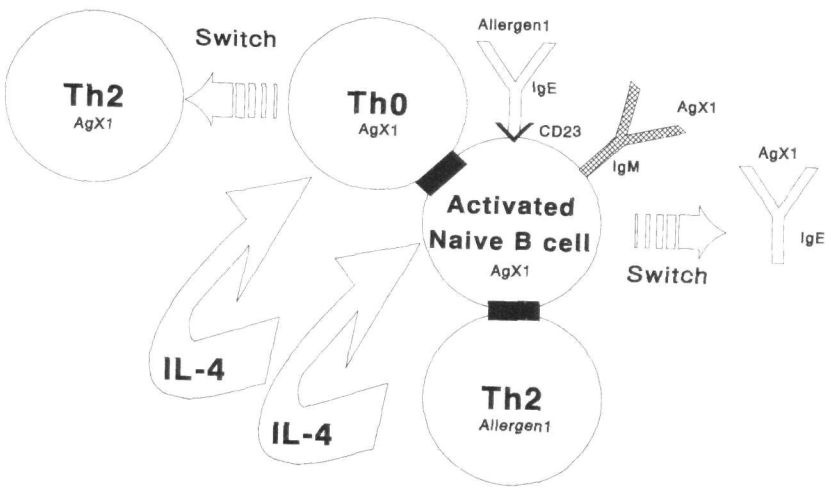

Fig. 3. IgE-mediated antigen presentation through CD23 on activated B cells. B cells which express CD23 after recognition of their specific antigen (AgX1) present AgX1, as well as allergen 1, to specific T cells. Allergen 1-specific T cells, being Th2, induce switch to IgE in these B cells. Consequently, B cells produce new IgE antibodies. In addition, IL-4 produced by allergen 1-specific Th2 cells may also influence phenotype of naive AgX1-specific T cells, by changing these T cells into Th2 cells (1, 27, 58, 59).

In addition to this effect of Th2 cells on the antigen-presenting B cell, the IL-4 produced by the allergen 1-specific Th2 cells may also influence the phenotype of naive AgX1-specific T cells, by changing these T cells into Th2 cells (1, 27, 58, 59). Thus, even if IgE binding to CD23 inhibits direct switching of the AgX1-specific B cells, IgE-mediated antigen presentation may indirectly, by inducing Th2 cells specific for AgX1, cause IgE switching later, leading to progression of the allergic state.

Conclusion

IgE-antibodies specific for allergens are known to directly cause immediate-type hypersensitivity reactions, when cross-linked by antigen recognition on the surface of effector cells such as mast cells and basophils. In addition, IgE may be involved in another (indirect) mechanism fundamental to the pathogenesis of allergic diseases. This may arise by the enhancement of the antigen-capturing capacity of APCs such as monocytes, Langerhans' cells, and activated B cells. IgE-mediated antigen presentation may lead to a continuous activation of the immune system by very low concentrations of allergen. As a result, Th2 cell populations may expand and induce more B cells to switch to IgE production. Subsequently, the overproduction of IgE and Th2 cells in one patient may lead to a change from allergy to a single allergen into allergy to many allergens. Clinically, this was seen in a group of young children (under 2 years old) with mild AD who were sensitive to food allergens, but not to aeroallergens. Within 3 years, these children (27/29 cases) developed more severe AD with sensitivity to aeroallergens; in addition, 23 of these children developed respiratory symptoms (28). Therefore, control of IgE production is not only important for symptom treatment in allergy, but may also prevent deterioration of allergy through the mechanism of CD23/IgE-mediated allergen presentation by B cells.

References

1. Abehsira-Amar O, Gibert M, Joliy M, Thèze J, Jankovic DL. IL-4 plays a dominant role in the differential development of Th0 into Th1 and Th2 cells. J Immunol 1992: 148: 3820–9.
2. Armerding D, van Reijsen FC, Hren A, Mudde GC. Induction of IgE and IgG1 in human B cell cultures with staphylococcal superantigens: role of helper T cell interaction, resistance to interferon-gamma. Immunobiology 1993: 188: 259–73.
3. Aubry J-P, Pochon S, Graber P, Jansen KU, Bonnefoy J-Y. CD21 is a ligand for CD23 and regulates IgE production. Nature 1992: 358: 505–7.
4. Beavil AJ, Sutton BJ, Hart DT, Hill MR, Hart BJ.

A preliminary molecular structure of the major house dust mite allergen *Der p* I [Abstract]. Clin Exp Allergy 1990: 20 (Suppl. 1): 46.
5. Bieber T, Braun-Falco O. IgE-bearing Langerhans' cells are not specific to atopic eczema but are found in inflammatory skin diseases. J Am Acad Dermatol 1991: 24: 658–9.
6. Bieber T, De la Salle H, Wollenberg A, et al. Human epidermal Langerhans' cells express the high affinity receptor for immunoglobulin E ($Fc_{\varepsilon}RI$). J Exp Med 1992: 175: 1285–90.
7. Björck P, Elenström-Magnusson C, Rosén A, Severinson E, Paulie S. CD23 and CD21 function as adhesion molecules in homotypic aggregation of human B lymphocytes. Eur J Immunol 1993: 23: 1771–5.
8. Blaser K, Perrig N, Lötscher M, Held W, Rieben R, Heusser CH. Idiotypic regulation of the IgE antibody response. Allergologie 1989: 12 (Suppl.): 44–9.
9. Brodsky FM, Guagliardi LE. The cell biology of antigen processing and presentation. Annu Rev Immunol 1991: 9: 707–44.
10. Bruijnzeel-Koomen CAFM, Boland GJ, Mudde GC. IgE-mediated antigen presentation by epidermal Langerhans' cells from patients with atopic dermatitis. In: Thivolet J, Schmitt D, eds. The Langerhans' cell. Montrouge: Colloque INSERM/John Libbey, 1988: 335–41.
11. Bruijnzeel-Koomen CAFM, van der Donk EMM, Bruijnzeel PLB, Capron M, de Gast GC, Mudde GC. Associated expression of CD1 antigen and the Fc receptor for IgE on epidermal Langerhans' cells from patients with atopic dermatitis. Clin Exp Immunol 1988: 74: 137–42.
12. Bruijnzeel-Koomen CAFM, van Wichen DF, Toonstra J, Berrens L, Bruijnzeel PLB. The presence of IgE molecules on epidermal Langerhans' cells from patients with atopic dermatitis. Arch Dermatol Res 1986: 278: 199–205.
13. Brüggeman M, Williams GT, Bindon CI, et al. Comparison of the effector functions of human immunoglobulins using a matched set of chimeric antibodies. J Exp Med 1987: 166: 1351–61.
14. Cardot E, Pestel J, Callebaut I, et al. Specific activation of platelets from patients allergic to *Dermatophagoides pteronyssinus* by synthetic peptides derived from the allergen *Der p* I. Int Arch Allergy Immunol 1992: 98: 127–34.
15. Cohen BE, Rosenthal AS, Paul WE. Antigen macrophage interaction. II. Relative roles of cytophilic antibodies and other membrane sites. J Immunol 1973: 111: 820–6.
16. Conrad DH. Murine CD23/Fc_{ε} RII. Structure and function and comparison with the human counterpart. Monogr Allergy 1991: 29: 9–27.
17. Conrad DH, Keegan AD, Kalli KR, van Dusen R, Rao M, Levine AD. Superinduction of low affinity IgE receptors on murine B lymphocytes by lipopolysaccharide and IL-4. J Immunol 1988: 141: 1091–7.
18. Defrance T, Carayon P, Billian G, et al. Interleukin 13 is a B cell stimulating factor. J Exp Med 1994: 179: 135–43.
19. Delespesse G, Sarfati M. IgE-binding factors (soluble CD23) and IgE regulation. Res Immunol 1990: 141: 75–7.
20. Delespesse G, Sarfati M, Hofstetter H. Human IgE binding factors. Immunol Today 1989: 10: 159–64.
21. Flores-Romo L, Shields J, Humbert Y, et al. Inhibition of an *in vivo* antigen-specific IgE response by antibodies to CD23. Science 1993: 261: 1038–41.
22. Gordon J, Cairns JA, Liu Y-J, et al. Role of membrane and soluble CD23 in lymphocyte physiology. Monogr Allergy 1991: 29: 156–68.
23. Gould H, Sutton BJ, Edmeades R, Beavil A. CD23(Fc_{ε}RII: C-type lectin membrane protein with a split personality. Monogr Allergy 1991: 29: 28–49.
24. Grabbe J, Haas N, Hamann K, Kolde G, Hakimi J, Czarnetzki BM. Demonstration of the high-affinity IgE receptor on human Langerhans' cells in normal and diseased skin. Br J Dermatol 1993: 129: 120–3.
25. Greene WK, Cyster JG, Chua KY, O'Brien RM, Thomas WR. IgE and IgG binding of peptides expressed from fragments of cDNA encoding the major house dust mite allergen *Der p* I. J Immunol 1991: 147: 3768–73.
26. Greene WK, Thomas WR. IgE binding structures of the major house dust mite allergen *Der p* I. Mol Immunol 1992: 29: 257–62.
27. Gross A, Ben-Sasson SZ, Paul WE. Anti-IL-4 diminished *in vivo* priming for antigen-specific IL-4 production by T cells. J Immunol 1993: 150: 2112–20.
28. Guillet G, Guillet MH. Natural history of sensitizations in atopic dermatitis. A 3-year follow-up in 250 children: food allergy and high risk of respiratory symptoms. Arch Dermatol 1992: 128: 187–92.
29. Heyman B, Tianmin L, Gustavsson S. *In vivo* enhancement of the specific antibody response via the low-affinity receptor for IgE. Eur J Immunol 1993: 23: 1739–42.
30. Holsti MA, Raulet DH. IL-6 and IL-1 synergize to stimulate IL-2 production and proliferation of peripheral T cells. J Immunol 1989: 143: 2514–19.
31. Jeannin P, Didierlaurent A, Gras Masse H, et al. Specific histamine release capacity of peptides selected from the modelized *Der p* I protein, a major allergen of *Dermatophagoides pteronyssinus*. Mol Immunol 1992: 29: 739–49.
32. Jeannin P, Pestel J, Bossus M, Lassalle P, Tartar A, Tonnel AB. Comparative analysis of biological activities of *Der p* I-derived peptides on Fc epsilon receptor-bearing cells from *Dermatophagoides pteronyssinus*-sensitive patients. Clin Exp Immunol 1993: 92: 133–8.
33. Kehry MR, Yamashita LC. Low-affinity IgE receptor (CD23) function on mouse B cells: role in IgE-dependent antigen focusing. Proc Natl Acad Sci U S A 1989: 86: 7556–60.
34. Krutmann J, Kirnbauer R, Köck A, et al. Cross-linking Fc receptors on monocytes trigger IL-6 production: role in anti-CD3-induced T cell activation. J Immunol 1990: 145: 1337–42.
35. Lanzavecchia A. Antigen uptake and accumulation in antigen-specific B cells. Immunol Rev 1987: 99: 39–51.
36. Maurer D, Fiebiger E, Reininger B, et al. Expression of functional high affinity immunoglobulin E receptors ($Fc_{\varepsilon}RI$) on monocytes of atopic individuals. J Exp Med 1994: 179: 745–50.
37. Miettinen HM, Rose JK, Mellman I. Fc receptor isoforms exhibit distinct abilities for coated pit localization as a result of cytoplasmic domain heterogeneity. Cell 1989: 58: 317–27.
38. Mudde GC, Hansel TT, van Reijsen FC, Osterhoff BF, Bruijnzeel-Koomen CAFM. IgE: an immunoglobulin specialized in antigen capture. Immunol Today 1990: 11: 440–3.
39. Mudde GC, van Dam D, de Gast GC. Human peripheral blood B cell subpopulations: surface IgD positive cells respond to pokeweed mitogen with plasma cell differentiation. Clin Exp Immunol 1986: 64: 150–7.
40. Mudde GC, van Reijsen FC, Boland GJ, de Gast GC, Bruijnzeel PLB, Bruijnzeel-Koomen CAFM. Allergen presentation by epidermal Langerhans' cells from patients with atopic dermatitis is mediated by IgE. Immunology 1990: 69: 335–41.
41. Mudde GC, van Reijsen FC, Bruijnzeel-Koomen CAFM. Percutaneous sensitization to aeroallergens in atopic dermatitis. In: Wüthrich B, ed. Highlights in allergy and clinical immunology. Göttingen: Hogrefe and Huber, 1992: 247–52.
42. Neuberger MS, Williams GT, Mitchell EB, Jouhal

SS, FLANAGAN JG, RABBITTS TH. A hapten-specific chimaeric IgE antibody with human physiological function. Nature 1985: 314: 268–70.
43. OHMORI H, HIKIDA M, HARUNA K, KISHIMOTO T. *In vitro* antigen-specific IgE response is refractory to suppression by interferon-gamma. Immunol Lett 1992: 34: 99–104.
44. OSTERHOFF BF, RAPPERSBERGER K, WANG B, et al. Immunomorphologic characterization of $Fc_{\varepsilon}RI$-bearing cells within the human dermis. J Invest Dermatol 1994: 102: 315–20.
45. PÈNE J, ROUSSET F, BRIÈRE F, et al. IgE production by normal human lymphocytes is induced by interleukin 4 and suppressed by interferons gamma and alpha and prostaglandin E_2. Proc Natl Acad Sci U S A 1988: 85: 6880–4.
46. PIRRON U, SCHLUNCK T, PRINZ JC, RIEBER EP. IgE-dependent antigen focussing by human B lymphocytes is mediated by the low-affinity receptor for IgE. Eur J Immunol 1990: 20: 1547–51.
47. POULTER LW, CAMPBELL DA, MUNRO CS, JANOSSY G. Discrimination of human macrophages and dendritic cells using monoclonal antibodies. Scand J Immunol 1986: 24: 351–7.
48. PUNNONEN J, AVERSA G, COCKS BG, et al. Interleukin 13 induces interleukin 4-independent IgG4 and IgE synthesis and CD23 expression by human B cells. Proc Natl Acad Sci U S A 1993: 90: 3730–4.
49. ROOSNEK E, LANZAVECCHIA A. Efficient and selective presentation of antigen-antibody complexes by rheumatoid factor B cells. J Exp Med 1991: 173: 487–9.
50. SAGER N, FELDMANN A, SCHILLING G, KREITSCH P, NEUMANN C. House dust mite-specific T cells in the skin of subjects with atopic dermatitis: frequency and lymphokine profile in the allergen patch test. J Allergy Clin Immunol 1992: 89: 801–10.
51. SANTAMARIA LF, BHEEKHA R, VAN REIJSEN FC, et al. Antigen focusing by specific monomeric immunoglobulin E bound to CD23 on Epstein-Barr virus-transformed B cells. Hum Immunol 1993: 37: 23–30.
52. SARFATI M, BETTLER B, LETELLIER M, et al. Native and recombinant soluble CD23 fragments with IgE suppressive activity. Immunology 1992: 76: 662–7.
53. SCHULER G, STEINMAN RM. Murine Langerhans' cells mature into potent immunostimulatory dendritic cells *in vitro*. J Exp Med 1985: 161: 526–46.
54. SOUSSI GOUNNI A, LAMKHIOUED B, OCHIAI K, et al. High-affinity IgE receptor on eosinophils is involved in defence against parasites. Nature 1994: 367: 183–6.
55. STEVENS RH, BRIEVA JA, MARTIN RA, SAXON A. Regulation of specific antibody production via CD23. Monogr Allergy 1991: 29: 169–77.
56. STREET NE, MOSMANN TR. Functional diversity of T lymphocytes due to secretion of different cytokine patterns. FASEB J 1991: 5: 171–7.
57. SUTTON BJ, GOULD HJ. The human IgE network. Nature 1993: 366: 421–8.
58. SWAIN SL, WEINBERG AD, ENGLISH M, HUSTON G. IL-4 directs the development of Th2-like helper effectors. J Immunol 1990: 145: 3796–3806.
59. TANAKA T, HU-LI J, SEDER RA, FAZEKAS DE ST GROTH B, PAUL WE. Interleukin 4 suppresses interleukin 2 and interferon gamma production by naive T cells stimulated by accessory cell-dependent receptor engagement. Proc Natl Acad Sci U S A 1993: 90: 5914–18.
60. TAUSSIG MT, SIMS MJ, KRAWINKEL U. Regulation of immunoglobulin gene rearrangement and expression. Immunol Today 1989: 10: 143–6.
61. VALIM YML, LACHMANN PJ. The effect of antibody isotype and antigenic epitope density on the complement-fixing activity of immune complexes: a systematic study using chimaeric anti-NIP antibodies with human Fc regions. Clin Exp Immunol 1991: 84: 1–8.
62. VAN DE WINKEL JGJ, CAPEL PJA. Human IgG Fc receptor heterogeneity: molecular aspects and clinical implications. Immunol Today 1993: 14: 215–21.
63. VAN DER HEIJDEN FL, VAN NEERVEN RJJ, VAN KATWIJK M, BOS JD, KAPSENBERG ML. Serum-IgE-facilitated allergen presentation in atopic disease. J Immunol 1993: 150: 3643–50.
64. VAN REIJSEN FC, BRUIJNZEEL-KOOMEN CAFM, KALTHOFF FS, et al. Skin-derived aeroallergen-specific T-cell clones of Th2 phenotype in patients with atopic dermatitis. J Allergy Clin Immunol 1992: 90: 184–93.
65. WANG B, RIEGER A, KILGUS O, et al. Epidermal Langerhans' cells from normal human skin bind monomeric IgE via $Fc_{\varepsilon}RI$. J Exp Med 1992: 175: 1353–65.
66. WEEKE B, POULSEN LK. Diagnostic test for allergy. In: HOLGATE ST, CHURCH MK, eds. Allergy. London: Gower 1993: 111–14.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.