

Review

IgG- and IgE-mediated antigen presentation on MHC class II

Andrew Getahun*, Birgitta Heyman

Department of Genetics and Pathology, Uppsala University, Uppsala SE-751 85, Sweden

Received 7 September 2003; accepted 25 September 2003

Abstract

IgG- and IgE-antibodies have the ability to enhance the production of antibodies directed against the antigen they are specific for. It has been suggested that the mechanism behind IgG- and IgE-mediated feedback enhancement is the ability of these isotypes to induce a more potent antigen-specific T helper cell response, increasing the chances that antigen-specific B cells receive the T cell help they require to become antibody-producing cells. With emphasis on the murine system, we will here focus on the ability of IgG and IgE to capture antigen and facilitate presentation of antigenic peptides to T helper cells. Whether this mechanism underlies feedback enhancement of antibody responses to these antigens will be discussed.

© 2003 Elsevier B.V. All rights reserved.

Keywords: Fc receptors; Immune complexes; T helper cells; CD23**1. IgG-mediated antigen presentation***1.1. Fc receptors for IgG*

Three Fc receptors (FcRs) for IgG have been described, FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16). Their structure and functions have been reviewed elsewhere [1–3]. FcγRI and FcγRIII (and the human FcγRIIA which will not be further discussed here) are activating receptors, which upon crosslinking initiate effector functions, whereas FcγRIIB is an inhibitory receptor. FcγRI is a high affinity receptor, binding monomeric IgG2a as well as complexed IgG, and is expressed on macrophages, monocytes, and dendritic cells. FcγRIII is a low affinity receptor, binding only complexed IgG and is expressed on macrophages, mast cells, dendritic cells, and NK cells. FcγRI and FcγRIII are hetero-oligomeric receptors, in which the respective ligand-binding α-chains are associated with the common γ-chain (FcRγ). FcγRIII is also associated with a β-chain. FcRγ is required for the receptor assembly and triggering of various effector functions. It contains an immunoreceptor tyrosine-based activation motif (ITAM), which upon receptor crosslinking, gets phosphorylated. Sequential acti-

vation of src and syk family tyrosine kinases results in an activating signaling cascade. FcγRIIB is a low affinity IgG receptor, composed of a single chain which exists in three isoforms: FcγRIIB1, FcγRIIB1' and FcγRIIB2. FcγRIIB is widely expressed on hematopoietic cells, absent only on erythrocytes, T cells, and NK cells. FcγRIIB1 is preferentially expressed on lymphoid cells, FcγRIIB2 on myeloid cells and FcγRIIB1' on both lineages. FcγRIIB has an immunoreceptor tyrosine-based inhibitory motif (ITIM) in its cytoplasmic tail. When, by co-crosslinking, the ITIM comes in the vicinity of an ITAM-bearing receptor-complex, the tyrosine in the ITIM will be phosphorylated, generating an SH2 recognition domain that is the binding site for the inhibitory signaling molecule SHIP, leading to downstream events interfering with ITAM-signaling.

1.2. FcγRs and MHC class II presentation in vitro

FcγRIIB2- and FcγRIII-mediated antigen presentation has been extensively studied in murine model systems using a FcγR[−] B cell line (IIA1.6) transfected with different FcγR-constructs. Efficient internalization and antigen presentation by FcγRIII was independent of the cytoplasmic domain of the ligand-binding α-chain whereas the associated FcRγ chain was essential [4]. FcγRIII was able to present a broader spectrum of epitopes than FcγRIIB2, owing to different intracellular targeting mediated by the

* Corresponding author. Tel.: +46-18-611-11-75;
fax: +46-18-55-89-31.

E-mail address: andrew.getahun@genpat.uu.se (A. Getahun).

associated Fc γ R chain [5]. The ITAM region can be mutated so that it upon crosslinking does not activate the cell but still mediates receptor internalization [6]. Downstream activation of the protein tyrosine kinase syk was important for the transport from endosomes to lysosomes [6]. Combined, these studies suggest that ITAM-mediated cell activation is responsible for intracellular targeting and presentation of certain epitopes, whereas it is not required for Fc γ R-mediated internalization. Recent studies using syk-deficient bone marrow (BM)-derived DCs, showed that, in these cells, besides being required for efficient antigen processing and presentation, syk was required for receptor internalization [7].

The two isoforms of Fc γ RIIB, B1 and B2, are identical except for a 47 amino acid insertion in the cytoplasmic tail of Fc γ RIIB1. This insertion prevents localization in clathrin-coated pits and subsequent endocytosis via Fc γ RIIB1 [8,9]. Endocytosis of Fc γ RIIB2 is mediated by a di-leucine motif in the cytosolic domain of the receptor [10]. Expressing the two isoforms in a Fc γ R[−] B cell line showed that only Fc γ RIIB2 induced IgG-mediated antigen presentation [11]. Fc γ RIIB1 and Fc γ RIIB1' (B1' behaves like B1) are the only Fc γ Rs expressed on B cells, and since Fc γ RIIB1 was shown not to mediate endocytosis and antigen presentation, the only effect on B-cell-mediated antigen presentation by Fc γ Rs was thought to be inhibitory. Indeed, B-cell receptor- (BCR) mediated antigen presentation was inhibited upon co-crosslinking with Fc γ RIIB1 [12,13]. However, recent reports imply that B cells may after all present IgG/antigen-complexes via Fc γ Rs. A B-cell line (A20.292) only expressing Fc γ RIIB1 could efficiently induce IgG-mediated antigen presentation [14]. When using the cell line (IIA1.6) transfected with Fc γ RIIB1 or B2, originally used by Amigorena et al. [11], both isoforms induced antigen presentation although Fc γ RIIB2 was more efficient [14]. The difference between the two studies [11,14] was the use of different antigens. Supporting the idea that the antigen determines whether Fc γ RIIB1 on B cells can induce presentation, Antoniou and Watts showed that Fc γ RIIB1 induced presentation of tetanus toxin complexed to IgG, but not of the λ -repressor complexed to IgG [15] used in the original studies [11].

Although less extensively studied, available data suggest that Fc γ RI differs from Fc γ RIIB and Fc γ RIII in antigen handling. Expressing human Fc γ RI constructs in the Fc γ R[−] B cell line IIA1.6, revealed that receptor internalization is independent of the Fc γ R chain [16]. Furthermore, cells expressing only the Fc γ RI α -chain, or coexpressing a Fc γ R chain with a mutated ITAM motif, were still able to present IgG/antigen complexes on MHC class II. However, coexpression of wild-type Fc γ R chains with the α -chain, increased the efficiency of antigen presentation [16]. Murine macrophages, expressing the Fc γ RI α -chain without Fc γ R, could still endocytose but their ability to present antigen has not been tested [17].

All three Fc γ R subtypes mediate antigen presentation and the relative contribution of each type is most likely dependent on which IgG subclasses are incorporated in the immune complexes (ICs) as well as on the overall size of the complex. Bone marrow-derived macrophages present human IgG ("monovalent ICs") mainly via Fc γ RI [17] while only multivalent ICs were presented via Fc γ RIII [4].

Human and murine Fc γ R⁺ APCs present IgG-complexed antigen at concentrations over a 100-fold lower than uncomplexed antigen. This has been demonstrated for murine BM-DCs [18–20], macrophages [17,21], Langerhans cells [22], and B cells [14,15] as well as for human peripheral blood DCs [23,24], monocytes [24], macrophages [21,25], and B cells [26]. As mentioned above, Fc γ R-mediated antigen presentation by B cells is still controversial.

Crosslinking of activating Fc γ Rs by IgG/antigen complexes induce DC maturation, turning DCs into better APCs [7,18,19,27]. Both Fc γ RI and Fc γ RIII can induce DC maturation [7]. Fc γ RIIB negatively influences this IC-mediated maturation [28], suggesting that the balance in expression between activating and inhibitory Fc γ Rs can influence the ability of DCs to present IgG/antigen complexes.

1.3. IgG-mediated enhancement of antibody responses and MHC class II presentation in vivo

Our interest in IgG-mediated antigen presentation stems from our work on IgG-mediated feedback enhancement of the antibody response (reviewed in [29,30]). Antigen-specific IgG, administered together with a soluble antigen, has the ability to enhance the antibody response to this antigen. The ability of IgG3 to feedback-enhance seems to be dependent on the complement system rather than on Fc γ Rs [31] and will not be discussed further. In contrast, "classical" IgG1-, IgG2a-, and IgG2b-mediated enhancement is dependent on the presence of activating Fc γ Rs, most likely Fc γ RI, on bone marrow-derived cells [32,33].

It is possible that the mechanism behind IgG-mediated feedback enhancement of antibody responses is increased presentation of IgG/antigen complexes to T cells. A few studies provide experimental support for this. Mice transgenic for human (h)Fc γ RI, had an enhanced antibody response when immunized with hFc γ RI-specific mAbs, an antigen directly targeted to Fc γ RI. In vitro, macrophages from these mice efficiently internalized anti-hFc γ RI mAb [34]. Delayed-type hypersensitivity (DTH) reactions, mediated by CD4⁺ Th1 cells, were decreased in Fc γ R^{−/−} mice [35]. There were no defects in the function of APCs nor T cells per se, and antibody-deficient mice also had reduced DTH reactions, implying that IgG/antigen complexes prime T cells in an Fc γ R-dependent manner. Two groups have independently studied the effect on the humoral response by "immunizing" mice with BM-DC pulsed in vitro with IgG/antigen complexes or antigen alone. Production of OVA-specific IgG [18,19] as well as the size of germinal

centers [18] and ex vivo T cell proliferation were enhanced by IgG. All these effects were dependent on the presence of Fc γ Rs on the BM-DCs.

Whether IgG/antigen complexes induce a Th1- or Th2-polarized response is not clear. Ex vivo studies suggested that IC-loaded BM-DCs induce a Th1 polarized response, measured as augmented IFN γ production [18]. This was strengthened by the in vivo observations that IC-pulsed BM-DCs induced a DTH response [19]. On the other hand, no enhanced DTH was observed in mice immunized i.v. with IgG/antigen complexes [36]. Furthermore, IgG enhanced the production of both Th1- (IgG2a) and Th2- (IgG1) associated IgG isotypes [18,19,36] and antigen targeted to Fc γ Rs on macrophages induced a Th2-polarized T cell response [37].

Jenkin and coworkers have established an adoptive transfer system where expansion of antigen-specific CD4⁺ T cells can be studied. T cells from mice transgenic for a T-cell receptor (TCR) recognizing an OVA-peptide in the context of A^d [38] are transferred into syngeneic wild-type BALB/c recipients and the expansion of the OVA-specific T cells is followed using a monoclonal antibody-specific for the transgenic TCR. When such mice were passively immunized with IgG anti-OVA prior to a challenge with OVA in incomplete Freund's adjuvant, the expansion of OVA-specific T cells occurred more rapidly [39]. We have used the same adoptive transfer system and immunized mice with IgG anti-TNP/OVA-TNP complexes intravenously without adjuvants. A rapid expansion of OVA-specific T cells, peaking at day 3, preceded the enhanced OVA-specific antibody response and was dependent on the presence of activating Fc γ Rs [39b].

1.4. The biological role for IgG-mediated antigen presentation

These studies indicate that IgG in complex with specific antigen enhance antigen presentation on MHC class II, leading to T cell activation in vivo, and link this to IgG-mediated feedback enhancement of the antibody response. The identity of the responsible APC has not been unequivocally established although the DC is a likely candidate. In order for Fc γ Rs to play a role in antigen presentation, IgG must be present to capture the antigen. This requirement is fulfilled during a primary immune response against antigens that persist until an IgG response has been initiated and also during a secondary immune response when preformed IgG is present and binds to the antigen. Apart from enhancing the uptake and processing of antigen, IgG may also indirectly enhance presentation by inducing maturation of APCs [7,18,19,27].

There is a correlation between the increasing affinity of IgG during an immune response and the efficiency of antibody-mediated antigen presentation [40]. By testing different ratios between polyclonal antibodies and antigen, Manca et al. [21] found that macrophage-mediated antigen presentation was absent in extreme antibody excess, prob-

ably owing to protection of the antigen from degradation. This suggests a feedback mechanism, where excess polyclonal IgG, a result of a successful response, eventually would inhibit IgG-mediated presentation.

A qualitative effect of IgG on antigen presentation is demonstrated by studies revealing that presentation of individual epitopes can either be enhanced or suppressed [41,42]. This implies that IgG, present during an ongoing immune response, will change the repertoire of activated antigen-specific T cells.

Not only the ability to help B cells, but also other CD4⁺ T cell effector functions such as DTH could be positively influenced by IgG [19,35]. A role for IgG-mediated antigen presentation in a mouse model for multiple sclerosis was suggested by the observation that FcR $\gamma^{-/-}$ mice did not show myelin destruction (a process involving myelin reactive T cells), despite the initiation of a peripheral autoimmune response [43].

A recent development in IgG-mediated antigen presentation is the discovery that IgG/antigen complexes, besides inducing MHC class II presentation, also induce antigen presentation on MHC class I, so called cross-presentation [18,19,27,28,44]. The ability of IgG to activate both CD4⁺ and CD8⁺ T cells could play a role in anti-viral and anti-tumor responses, as both cell types are of importance. Indeed, tumor rejection studies showed that the ability of IgG/antigen-loaded BM-DC to provide tumor immunity required both functional MHC class I and II presentation [19]. Work by Villinger et al. [45] suggests a role for virus-specific antibodies in the cytotoxic T lymphocyte (CTL) response to Simian immunodeficiency virus (SIV) in rhesus macaques. Restimulation of peripheral blood mononuclear cells isolated from SIV-infected monkeys with SIV Gag antigen complexed with antigen-specific IgG (isolated from infected monkeys) induced higher frequencies of antigen-specific precursor CTLs. The ability to enhance was dependent on the availability of Fc γ Rs and on the presence of CD4⁺ T cells. These findings suggest that IgG acts not only by inducing ADCC or neutralizing virus, but that tumor- or virus-specific antibodies could directly influence the anti-tumor or anti-viral T-cell responses.

2. IgE-mediated antigen presentation

2.1. Fc receptors for IgE

There are two FcRs for IgE, the high affinity Fc ϵ RI and the low affinity Fc ϵ R2 (CD23) (reviewed in [46,47]). In addition, murine Fc γ R2 and Fc γ R3 have been reported to bind IgE [48] although the biological significance of this is unknown. In mice, only one isoform of Fc ϵ RI has been described. This is a tetramer consisting of one α -chain, one β -chain and two disulfide-linked FcR γ chains. In humans, an additional isoform consisting of one α -chain and two FcR γ chains has been found. Mice express Fc ϵ RI in non-B

non-T cells including mast cells and basophils. Human mast cells, basophils, eosinophils, and platelets express Fc ϵ RI as an $\alpha\beta\gamma_2$ tetramer, whereas human monocytes, Langerhans cells and DCs express the $\alpha\gamma_2$ trimer [46]. Unlike other Fc receptors, CD23 does not belong to the immunoglobulin superfamily, but is instead a C-type lectin [49]. The receptor is present on the cell surface both as monomers and trimers, the latter having a higher affinity for IgE [50]. In humans, CD23 is expressed in two isoforms, CD23a and CD23b [51]. CD23a is constitutively expressed on B cells; CD23b is expressed on some T cells, monocytes, eosinophils, and platelets. Upon IL-4-stimulation, CD23b is upregulated on B cells and Langerhans cells ([51,52] and references therein). Mice constitutively express a homologue of CD23a on B cells [53] and follicular dendritic cells (FDCs) [54]. Upon stimulation with IL-4 and lipopolysaccharide, mRNA for the CD23b isoform can be detected in murine B cells and other haematopoietic cells [55] and under certain culture conditions, murine Langerhans cells express CD23 [56].

2.2. Fc ϵ Rs and MHC class II presentation in vitro

A series of in vitro studies revealed that APCs expressing Fc ϵ RI can take up and process IgE/antigen complexes and present antigenic peptides on MHC class II molecules. Isolated human monocytes [57] and peripheral blood DCs [58] presented antigen on MHC class II over a 100-fold more effectively when antigen was targeted to Fc ϵ RI via antigen-specific IgE. Further studies on BM-DCs revealed that Fc ϵ RI efficiently channels antigen into MHC class II compartment-like organelles [59]. As only professional APCs express the $\alpha\gamma_2$ -isoform of Fc ϵ RI, it has been suggested that this isoform facilitates antigen presentation whereas the $\alpha\beta\gamma_2$ isoform facilitates hypersensitivity reactions [46,58]. The expression of Fc ϵ RI is more restricted in the mouse and in this species only bone marrow-derived mast cells have been shown to present antigen taken up via this receptor [60].

CD23 is involved in antigen presentation both in human and murine systems. In vitro experiments with human EBV-transformed B cells [61–63], a murine B-cell hybridoma [64], and murine spleen cells [65] all demonstrate that B cells present IgE-complexed antigen at concentrations 100- to 1000-fold lower than they present uncomplexed antigen. Blocking experiments with anti-CD23 mAbs revealed that the enhanced antigen presentation was dependent on CD23. Functional studies using the human CD23 isoforms showed that only CD23a facilitates IgE-mediated endocytosis [66], implying an important role for B cells.

2.3. IgE-mediated enhancement of antibody responses and MHC class II presentation in vivo

Antigen-specific IgE has the ability to feedback enhance antibody responses to soluble protein antigens (reviewed in [29,67]). IgE administered together with its specific anti-

gen upregulates the primary IgM-, IgG-, and IgE-responses against this antigen, often by several 100-fold [68–71]. The number of specific IgG-producing B cells peaks 6 days after primary immunization and the titers of specific IgG and IgE remain high for weeks [71]. Priming with IgE immune complexes induces a more efficient immunological memory [70].

Enhancement is completely dependent on CD23, as IgE cannot upregulate antibody responses in mice treated with anti-CD23 mAbs [68,70] or lacking CD23, owing to gene targeting [69,72]. In support of an exclusive role for CD23, Fc γ -deficient mice (lacking Fc ϵ RI) responded normally to immunization with IgE/antigen [32]. CD23 is constitutively expressed in the mouse only on B cells and FDCs, and FDCs play a role in the trapping and retaining of IgE ICs [54]. Antigen captured by FDCs is presented to B cells in the form of iccosomes [73], but since FDCs cannot endocytose antigen they cannot present peptides on MHC class II to T cells. Using an adoptive transfer system, we have demonstrated that the ability of IgE to enhance antibody responses is dependent on the presence of CD23 on bone marrow-derived cells (presumably B cells), whereas FDCs played a marginal role [72]. This finding, together with the in vitro studies mentioned above, suggest that the mechanism behind IgE-mediated enhancement of antibody responses is increased presentation of antigen to T cells via CD23⁺ B cells. The fact that IgE requires the presence of T cells in order to enhance antibody responses supports this idea [70]. The first in vivo data linking CD23-mediated antigen presentation to enhancement of antibody responses came from Daniel Conrad's laboratory [74]. Antigen covalently coupled to an anti-CD23 mAb was presented by B cells in vitro at concentrations over a 1000-fold lower than unconjugated antigen. Mice immunized with these anti-CD23/antigen conjugates produced higher levels of specific IgG and IgE than mice immunized with unconjugated antigen.

We have investigated the effects of immunization with IgE/antigen complexes on specific T cell proliferation in vivo. By using the adoptive transfer system mentioned above, where transgenic OVA-specific T cells are transferred into syngeneic recipients, we found that immunization with IgE anti-TNP/OVA-TNP complexes induced a rapid expansion of OVA-specific CD4⁺ cells, peaking day 3 [74b]. The number of specific T cells was 5–10-fold higher than in mice immunized with antigen alone. The T cell expansion was followed by an enhanced antibody response in the groups given IgE/antigen. In analogy with IgE-mediated enhancement of antibody responses, IgE-mediated T-cell activation was absent when CD23 was blocked with mAbs or in mice lacking CD23 but normal in Fc ϵ RI-deficient Fc γ ^{−/−} mice.

2.4. The biological role for IgE-mediated antigen presentation

A number of in vivo and in vitro observations thus point to a role for CD23⁺ B cells in presentation of IgE-complexed

antigen and imply that this is the mechanism behind the dramatic ability of IgE to upregulate antibody responses. The majority of mature B cells express CD23 and, regardless of specificity, bind IgE/antigen complexes *ex vivo* [75]. This is presumably also the case *in vivo* and therefore, all CD23⁺ B cells can be assumed to present IgE/antigen to specific T cells even if they do not recognize the antigen with their BCR. Since IgE enhances antibody responses only to the antigen with which it forms a complex [68,70,72], these unspecific CD23⁺ B cells would not be activated to produce antibodies.

If this scenario is correct, CD23⁺ B cells, capturing IgE/antigen complexes, act as non-specific APCs and activate T cells in a similar manner as macrophages and DCs, increasing the number of specific T cells and the probability that such cells find specific B cells which they can provide with cognate T cell help. Given the debate of whether or not B cells can activate naive T cells *in vivo*, this is an interesting possibility [76–79]. The biological significance of such a pathway for antigen presentation is unknown. Obviously it would enable rapid expansion of T cells when specific IgE is present, i.e. in situations when a pathogen or an allergen has already elicited an IgE-response. This would result in a positive feedback loop, strengthening the specific T- and B-cell responses for good or for bad. *In vitro* studies suggest that B cell-mediated T-cell activation favors the induction of Th2 cells [80,81], thought to be important in the development of allergic disease. The implications of IgE-mediated antigen presentation in the human immune system are hard to predict as mice and humans differ in the expression of FcεRs on APCs. However, using an autologous system where B and T cells were derived from the same atopic dermatitis patient, van der Heijden et al. showed that patient serum containing IgE anti-Der p II (major house dust mite) facilitated EBV-B cell-mediated antigen presentation to T helper cells *in vitro* [63].

Acknowledgements

The work in the authors' laboratory described herein was supported by Agnes and Mac Rudberg's Foundation; Ellen, Walter and Lennart Hesselman's Foundation; Hans von Kantzow's Foundation; King Gustaf V's 80 Years Foundation; Lilly and Ragnar Åkerhams's Foundation; The Swedish Foundation for Health Care Science and Allergy Research; The Swedish Medical Research Council; The Swedish Association against Rheumatism; Ollie and Elof Ericsson's Foundation; the "Network for Inflammation research" funded by the Swedish Foundation for Strategic Research, and the Swedish Society for Medical Research.

References

- [1] Hulett MD, Hogarth PM. *Adv Immunol* 1994;57:1–127.
- [2] Daëron M. *Annu Rev Immunol* 1997;15:203–34.
- [3] Ravetch JV, Bolland S. *Annu Rev Immunol* 2001;19:275–90.
- [4] Amigorena S, Salamero J, Davoust J, Fridman WH, Bonnerot C. *Nature* 1992;358:337–41.
- [5] Amigorena S, Lankar D, Briken V, Gapin L, Viguier M, Bonnerot C. *J Exp Med* 1998;187:505–15.
- [6] Bonnerot C, Briken V, Brachet V, Lankar D, Cassard S, Jabri B, et al. *EMBO J* 1998;17:4606–16.
- [7] Sedlik C, Orbach D, Veron P, Schweighoffer E, Colucci F, Gamberale R, et al. *J Immunol* 2003;170:846–52.
- [8] Miettinen HM, Rose JK, Mellman I. *Cell* 1989;58:317–27.
- [9] Miettinen HM, Matter K, Hunziker W, Rose JK, Mellman I. *J Cell Biol* 1992;116:875–88.
- [10] Hunziker W, Fumey C. *EMBO J* 1994;13:2963–7.
- [11] Amigorena S, Bonnerot C, Drake JR, Choquet D, Hunziker W, Guillet JG, et al. *Science* 1992;256:1808–12.
- [12] Wagle NM, Faassen AE, Kim JH, Pierce SK. *J Immunol* 1999;162:2732–40.
- [13] Minskoff SA, Matter K, Mellman I. *J Immunol* 1998;161:2079–83.
- [14] Berg M, Uellner R, Langhorne J. *Eur J Immunol* 1997;27:1022–8.
- [15] Antoniou AN, Watts C. *Eur J Immunol* 2002;32:530–40.
- [16] van Vugt MJ, Kleijmeer MJ, Keler T, Zeelenberg I, van Dijk MA, Leusen JH, et al. *Blood* 1999;94:808–17.
- [17] Barnes N, Gavin AL, Tan PS, Mottram P, Koentgen F, Hogarth PM. *Immunity* 2002;16:379–89.
- [18] Akiyama K, Ebihara S, Yada A, Matsumura K, Aiba S, Nukiwa T, et al. *J Immunol* 2003;170:1641–8.
- [19] Rafiq K, Bergtold A, Clynes R. *J Clin Invest* 2002;110:71–9.
- [20] Serre K, Machy P, Grivel JC, Jolly G, Brun N, Barbet J, et al. *J Immunol* 1998;161:6059–67.
- [21] Manca F, Fenoglio D, Li Pira G, Kunkl A, Celada F. *J Exp Med* 1991;173:37–48.
- [22] Esposito-Farese ME, Sautes C, de la Salle H, Latour S, Bieber T, de la Salle C, et al. *J Immunol* 1995;155:1725–36.
- [23] Sallusto F, Lanzavecchia A. *J Exp Med* 1994;179:1109–18.
- [24] Fanger NA, Voigtlaender D, Liu C, Swink S, Wardwell K, Fisher J, et al. *J Immunol* 1997;158:3090–8.
- [25] Gosselin EJ, Wardwell K, Gosselin DR, Alter N, Fisher JL, Guyre PM. *J Immunol* 1992;149:3477–81.
- [26] Liu C, Gosselin EJ, Guyre PM. *Cell Immunol* 1996;167:188–94.
- [27] Regnault A, Lankar D, Lacabanne V, Rodriguez A, Thery C, Rescigno M, et al. *J Exp Med* 1999;189:371–80.
- [28] Kalergis AM, Ravetch JV. *J Exp Med* 2002;195:1653–9.
- [29] Heyman B. *Annu Rev Immunol* 2000;18:709–37.
- [30] Heyman B. *Immunol Lett* 2003;88:157–61.
- [31] Diaz de Ståhl T, Dahlström J, Carroll MC, Heyman B. *J Exp Med* 2003;197:1183–90.
- [32] Wernersson S, Karlsson MC, Dahlström J, Mattsson R, Verbeek JS, Heyman B. *J Immunol* 1999;163:618–22.
- [33] Diaz de Ståhl TD, Heyman B. *Scand J Immunol* 2001;54:495–500.
- [34] Heijnen IA, van Vugt MJ, Fanger NA, Graziano RF, de Wit TP, Hofhuis FM, et al. *J Clin Invest* 1996;97:331–8.
- [35] Hamano Y, Arase H, Saisho H, Saito T. *J Immunol* 2000;164:6113–9.
- [36] Wernersson S, Kleinau S, Heyman B. *Scand J Immunol* 2000;52:563–9.
- [37] Anderson CF, Mosser DM. *J Immunol* 2002;168:3697–701.
- [38] Kearney ER, Pape KA, Loh DY, Jenkins MK. *Immunity* 1994;1:327–39.
- [39] (a) Merica R, Khoruts A, Pape KA, Reinhardt RL, Jenkins MK. *J Immunol* 2000;164:4551–7;
(b) Getahun A, Dahlström J, Wernersson S, Heyman B. IgG2a-mediated enhancement of Ab- and T-cells responses and its relation to inhibitory and activating FcγRs, submitted for publication.
- [40] Guermontprez P, England P, Bedouelle H, Leclerc C. *J Immunol* 1998;161:4542–8.
- [41] Watts C, Lanzavecchia A. *J Exp Med* 1993;178:1459–63.
- [42] Dai Y, Carayanniotis KA, Eliades P, Lymberi P, Shepherd P, Kong Y, et al. *J Immunol* 1999;162:6987–92.

- [43] Abdul-Majid KB, Stefferl A, Bourquin C, Lassmann H, Linington C, Olsson T, et al. *Scand J Immunol* 2002;55:70–81.
- [44] Schuurhuis DH, Ioan-Facsinay A, Nagelkerken B, van Schip JJ, Sedlik C, Melief CJ, et al. *J Immunol* 2002;168:2240–6.
- [45] Villinger F, Mayne AE, Bostik P, Mori K, Jensen PE, Ahmed R, et al. *J Virol* 2003;77:10–24.
- [46] Kinet JP. *Annu Rev Immunol* 1999;17:931–72.
- [47] Gould HJ, Suttan BJ, Beavi AJ, Beavil RL, McCloskey N, Coker HA, et al. *Annu Rev Immunol* 2003;21:579–628.
- [48] Takizawa F, Adamczewski M, Kinet J-P. *J Exp Med* 1992;176:469–76.
- [49] Kikutani H, Inui S, Sato R, Barsumian EL, Owaki H, Yamasaki K, et al. *Cell* 1986;47:657–65.
- [50] Dierks SE, Bartlett WC, Edmeades RL, Gould HJ, Rao M, Conrad DH. *J Immunol* 1993;150:2372–82.
- [51] Yokota A, Kikutani H, Tanaka T, Sato R, Barsumian EL, Suemura M, et al. *Cell* 1988;55:611–8.
- [52] Conrad DH. *Annu Rev Immunol* 1990;8:623–45.
- [53] Rao M, Lee WT, Conrad DH. *J Immunol* 1987;138:1845–51.
- [54] Maeda K, Burton GF, Padgett DA, Conrad DH, Huff TF, Masuda A, et al. *J Immunol* 1992;148:2340–7.
- [55] Kondo H, Ichikawa Y, Nakamura K, Tsuchiya S. *Int Arch Allergy Immunol* 1994;105:38–48.
- [56] Nagaoka Y, Nakamura K, Yasaka N, Watanabe T, Asahina A, Tamaki K. *J Invest Dermatol* 2002;119:130–6.
- [57] Maurer D, Ebner C, Reininger B, Fiebiger E, Kraft D, Kinet JP, et al. *J Immunol* 1995;154:6285–90.
- [58] Maurer D, Fiebiger S, Ebner C, Reininger B, Fischer GF, Wichlas S, et al. *J Immunol* 1996;157:607–16.
- [59] Maurer D, Fiebiger E, Reininger B, Ebner C, Petzelbauer P, Shi GP, et al. *J Immunol* 1998;161:2731–9.
- [60] Tkaczyk C, Viguier M, Boutin Y, Frandji P, David B, Hébert J, et al. *Immunology* 1998;94:318–24.
- [61] Bheekha Escura R, Wasserbauer E, Hammerschmid F, Pearce A, Kidd P, Mudde GC. *Immunology* 1995;86:343–50.
- [62] Pirron U, Schlunck T, Prinz JC, Rieber EP. *Eur J Immunol* 1990;20:1547–51.
- [63] van der Heijden FL, Joost van Neerven RJ, van Katwijk M, Bos JD, Kapsenberg ML. *J Immunol* 1993;150:3643–50.
- [64] Schmaltz R, Wang YY, Kung QX, Liu FT, Petro T, Chen SS. *Immunol Invest* 1996;25:481–93.
- [65] Kehry MR, Yamashita LC. *Proc Natl Acad Sci USA* 1989;86:7556–60.
- [66] Yokota A, Yukawa K, Yamamoto A, Sugiyama K, Suemura M, Tashiro Y, et al. *Proc Natl Acad Sci USA* 1992;89:5030–4.
- [67] Heyman B. *Allergy* 2002;57:577–85.
- [68] Heyman B, Tianmin L, Gustavsson S. *Eur J Immunol* 1993;23:1739–42.
- [69] Fujiwara H, Kikutani H, Suematsu S, Naka T, Yoshida K, Tanaka T, et al. *Proc Natl Acad Sci USA* 1994;91:6835–9.
- [70] Gustavsson S, Hjultstrom S, Heyman B. *J Immunol* 1994;152:4793–800.
- [71] Westman S, Gustavsson S, Heyman B. *Scand J Immunol* 1997;46:10–5.
- [72] Gustavsson S, Wernersson S, Heyman B. *J Immunol* 2000;164:3990–5.
- [73] Tew JG, Wu J, Qin D, Helm S, Burton GF, Szakal AK. *Immunol Rev* 1997;156:39–52.
- [74] (a) Squire CM, Studer EJ, Lees A, Finkelman FD, Conrad DH. *J Immunol* 1994;152:4388–96;
(b) Getahun A, Hjelm E, Carlsson F, Heyman B. IgE/Ag complexes induce rapid Ab- and T-cell responses in vivo, in preparation.
- [75] Gustavsson S, Chomez S, Heyman B. *Scand J Immunol* 1999;50:45–51.
- [76] Jenkins MK, Khoruts A, Ingulli E, Mueller DL, McSorley SJ, Reinhardt RL, et al. *Annu Rev Immunol* 2001;19:23–45.
- [77] Ho WY, Cooke MP, Goodnow CC, Davis MM. *J Exp Med* 1994;179:1539–49.
- [78] Constant S, Schweitzer N, West J, Ranney P, Bottomly K. *J Immunol* 1995;155:3734–41.
- [79] Milich DR, Chen M, Schodel F, Peterson DL, Jones JE, Hughes JL. *Proc Natl Acad Sci USA* 1997;94:14648–53.
- [80] Gajewski TF, Pinnas M, Wong T, Fitch FW. *J Immunol* 1991;146:1750–8.
- [81] Stockinger B, Zal T, Za A, Gray D. *J Exp Med* 1996;183:891–9.