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J Immunol 2003;170:3054-3058

This information is current as of November 20, 2011

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IgE-Mediated Activation of NK Cells Through FcγRIII¹

Noriko Arase,^{*†} Hisashi Arase,^{*} Satoshi Hirano,^{*} Tadashi Yokosuka,^{*} Daiju Sakurai,^{*} and Takashi Saito^{2*†}

NK cells express FcγRIII (CD16), which is responsible for IgG-dependent cell cytotoxicity and for production of several cytokines and chemokines. Whereas FcγRIII on NK cells is composed of both FcγRIIIα and FcRγ chains, that on mast cells is distinct from NK cells and made of FcγRIIIα, FcRβ, and FcRγ. Mast cells show degranulation and release several mediators, which cause anaphylactic responses upon cross-linking of FcγRIII as well as FcεRI with aggregated IgE. In this paper, we examined whether IgE activates NK cells through FcγRIII on their cell surface. We found that NK cells produce several cytokines and chemokines related to an allergic reaction upon IgE stimulation. Furthermore, NK cells exhibited cytotoxicity against IgE-coated target cells in an FcγRIII-dependent manner. These effects of IgE through FcγRIII were not observed in NK cells from FcRγ-deficient mice lacking FcγRIII expression. Collectively, these results demonstrate that NK cells can be activated with IgE through FcγRIII and exhibit both cytokine/chemokine production and Ab-dependent cell cytotoxicity. These data imply that not only mast cells but also NK cells may contribute to IgE-mediated allergic responses. *The Journal of Immunology*, 2003, 170: 3054–3058.

Aggregation of IgE-sensitized FcεRI induces mast cells to release various mediators and results in an anaphylactic reaction. Because FcεRI-deficient (–/–) mice were found to be resistant to cutaneous and systemic IgE-mediated anaphylaxis, a prominent role for FcεRI exclusively expressed on mast cells in classical type I hypersensitivity was established (1). By contrast, IgG was shown in the 1960s to induce passive anaphylaxis in vivo (2). The studies using FcεRIα^{–/–}, FcRγ^{–/–}, or FcγRIIB^{–/–} mice confirmed the importance of IgG in systemic and in passive cutaneous anaphylaxis. In OVA-induced systemic anaphylaxis, both IgG1 and FcγRIII are more important than IgE and FcεRI (3). Furthermore, FcγRIIB^{–/–} mice showed enhanced IgG1-mediated passive cutaneous anaphylaxis (4). These observations revealed that not only the FcεRI but also the FcγR system (3, 4) could regulate type I hypersensitivity depending on the Ag.

It was demonstrated that IgE binds to FcγRIII on a mast cell line in vitro and causes degranulation (5). Furthermore, when IgE-mediated anaphylaxis was compared between FcγRIII^{–/–} and wild-type (wt)³ mice, the anaphylaxis was more severe in wt mice than in FcγRIII^{–/–} mice (6). These studies suggested the importance of FcγRIII for not only IgG- but also IgE-mediated anaphylaxis. In contrast, it has been shown that systemic anaphylaxis occurs in mast cell-deficient W/W^v and Sl/Sl^d mice, indicating that some cells other than mast cells could induce anaphylactic responses in their absence (7–9). Moreover, Choi et al. (10) showed that sys-

temic anaphylaxis induced by penicillin occurred in mast cell-deficient mice and was correlated with the serum IgE level but not with the IgG level. Although NK cells, as well as macrophages (Mφ) and neutrophils, are known to highly express FcγRIII, its function in IgE-mediated anaphylactic responses has not been analyzed.

NK cells mediate natural cytotoxicity against a variety of tumor cells and virus-infected cells. They also produce cytokines and chemokines upon recognition of target cells, without prior sensitization (11). NK cells have also been implicated in eosinophilic airway inflammation in mice (12). In addition, a specific correlation between NK cell function and total serum IgE levels had also been observed (13). Although these analyses suggested the possible involvement of NK cells in allergic reactions, direct evidence of the functional participation of NK cells in allergic responses has not yet been reported.

Stimulation of mast cells through FcγRIII with oligomeric IgE induced serotonin secretion in vitro (5). This study provided the first evidence that IgE could bind FcγRIII and stimulates mast cells via this receptor. The composition of FcγRIII on mast cells (FcγRIIIα, FcRβ, and FcRγ chains) is different from that on other cell types, which is composed of only FcγRIIIα and FcRγ (14, 15). Therefore, it still remains unclear whether FcγRIII-expressing cells other than mast cells can be activated by IgE.

In this study, we investigated the function of FcγRIII as an IgE receptor on normal NK cells and demonstrated that NK cells can be activated with IgE through their FcγRIII. NK cells exhibited secretion of several cytokines and chemokines and mediated Ab-dependent cell cytotoxicity (ADCC) against IgE-coated targets. From these data, the possible involvement of NK cells in type I hypersensitivity is discussed.

Materials and Methods

Mice

C57BL/6 mice were purchased from Japan SLC (Hamamatsu, Japan). FcRγ^{–/–} mice with C57BL/6 background were generated as previously described (16).

Preparation of NK cells

Murine NK cells were isolated as previously described (17). Briefly, splenocytes were mixed with anti-CD4 mAb (GK1.5) and anti-CD8 mAb

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Received for publication November 28, 2001. Accepted for publication January 15, 2003.

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¹ This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture (Japan). N.A. had been supported by a fellowship from the Foundation of Aging and Health (Japan).

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³ Abbreviations used in this paper: wt, wild type; ADCC, Ab-dependent cell cytotoxicity; Mφ, macrophage; BMMC, bone marrow-derived mast cell; MIP, macrophage-inflammatory protein.

(53.6.7) followed by incubation with magnetic beads coupled with goat anti-mouse and rat IgG Abs (Perceptive Biosystems, Framingham, MA). The residual cells were then stained with PE-anti-NK1.1 mAb and FITC-anti-CD3 mAb (BD PharMingen, San Diego, CA), and NK1.1⁺ CD3⁻ cells were sorted by FACStar^{plus} (BD Biosciences). The purity of the sorted cells was always >99%. Purified NK cells were cultured in RPMI 1640 containing 10% FCS, 2 mM glutamine, kanamycin (100 µg/ml), and 5×10^{-5} M 2-ME and 1000 U/ml human IL-2 (provided by Dr. J. Hamuro (Ajinomoto, Kawasaki, Japan)) for 7 days. Bone marrow-derived mast cells (BMMC) were obtained by culture of bone marrow cells for 5 wk in complete medium with 15% WIHI-3 culture supernatant as a source of IL-3. Mφ were separated by cell sorting of Mac-1⁺ cells from the peritoneal cavity from thioglycolate-injected mice.

Stimulation of NK cells

A 96-well plate was incubated overnight at 4°C with graded concentrations of either mouse IgG1 (anti-biotin; Zymed, San Francisco, CA) or IgE (anti-DNP; Sigma-Aldrich, St. Louis, MO), and then washed with PBS. Cultured NK cells (2×10^5) were stimulated in the plate immobilized with IgG1 or IgE for 2 days for ELISA. Anti-FcγRIII/III mAb (20 µg/ml; 2.4G2; BD PharMingen) was added for blocking of the FcγRIII. For real-time PCR analysis, NK cells were stimulated on the 96-well plate immobilized with 50 µg/ml IgE or IgG mAb. After 6- or 12-h stimulation, the cells were harvested and lysed.

RT-PCR

Total cellular RNA was extracted with an RNeasy mini kit (Qiagen, Tokyo, Japan) and was reverse transcribed using Superscript II (Invitrogen, Tokyo, Japan) and random hexamers (Invitrogen) as primer. Real-time PCR was conducted by iCycler thermocycler (Bio-Rad, Hercules, CA) using SYBR green PCR master mix (Qiagen) and 300 pmol/ml each primer pair. Amplification condition was as follows: 95°C for 5 min, 50 cycles of 95°C for 30 s, 57°C for 30 s, and 72°C for 30 s. For the analysis of the FcR expression in NK cells, RNA was extracted by guanidinium-isothiocyanate method, and cDNA was prepared by RT-PCR. cDNA was amplified by PCR under the following conditions: 94°C for 15 s, 57°C for 30 s, and 72°C for 1 min with 22–24 cycles for β-actin or 30–34 cycles for other primers. The following primers were used: FcγRI, 5'-CTGCTACTTTGGGTTCCAG and 3'-CCGAATCTGAAGAACTGA; FcγRIIB, 5'-CCCAAGTCCAGCAGGTCTTTA and 3'-CTGTTTCTATCCAGGGC TT; FcγRIIIα, 5'-GTTTAAGGCCACAGTCAATG and 3'-GGTTGGCTTTTGGGATAG; FcεRIα, 5'-TGAGTGCCACCGTTCAAGA and 3'-CA AACAATCGCCACCAAC; FcεRβ, 5'-CAGACATGGCGGACATT and 3'-GTTGTTTCATATAAGCGAAGTT; FcγR, 5'-AAGAATTCAGCGCCG CAGCCCCAGCG and 3'-GGAATTCGCTGCCTTTCGGACCTGGAT; and β-actin, 5'-ACCCACACTGTGCCCATCTA and 3'-TCATGGATGCC ACAGGATTC. To detect several cytokines and chemokines, the following primers were used: IFN-γ, 5'-CCTCAGACTCTTGAAGTCT and 3'-CAGCGACTCCTTTTCGCTT; TNF-α, 5'-ATGAGCACAGAAAGCAT GATCCGCGAC and 3'-TCACAGAGCAATGACTCCAAAGTAGACCTG; GM-CSF, 5'-CCGCTCACCCATCACTGTAC and 3'-AGGCTGTCTATG AAATCCGCA; and macrophage-inflammatory protein (MIP)-1α, 5'-CAA GTCTTCTAGCGCCATA and 3'-TCTTTGGAGTCAGCGCAGAT.

Measurement of IFN-γ production

The amount of IFN-γ produced was measured by ELISA (16) using anti-IFN-γ mAbs (R4-6A2 and XMGI.2; BD PharMingen).

Analysis of ADCC activity

ADCC activity was analyzed as previously described except for the target cell preparation (17). For preparing hapten-coupled streptavidin, 0.5 mg of streptavidin (1 mg/ml; Sigma-Aldrich) dialyzed with 0.1 M NaHCO₃ overnight was reacted with 25 µg of DNP-X succinimidyl ester or 25 µg of dansyl-X succinimidyl ester (Molecular Probes, Eugene, OR) for 2 h at room temperature, and dialyzed with PBS. P815 cells were surface biotinylated (EZ-Link Sulfo-NHS-Biotin; Pierce, Rockford, IL), followed by incubation with ⁵¹Cr-labeled sodium citrate (Amersham Bioscience, Tokyo, Japan). The cells were labeled with DNP-streptavidin or dansyl-streptavidin, then incubated with 5 µg/ml anti-DNP IgE mAb (Sigma-Aldrich) and anti-DNP IgG1 mAb (F1E2; kindly provided by Dr. S. Taki (Shinshu University, Matsumoto, Japan)), or with 5 µg/ml anti-dansyl IgE and anti-dansyl IgG2b mAbs (BD PharMingen). A standard short-term ⁵¹Cr release assay was performed by mixing 1×10^4 IL-2-activated NK cells with graded numbers of the ⁵¹Cr-labeled target cells in the presence of 5 µg/ml each Ab in a U-bottom 96-well plate (BD Biosciences) for 4 h and then measuring the released ⁵¹Cr in the supernatant. Specific cytotoxicity was cal-

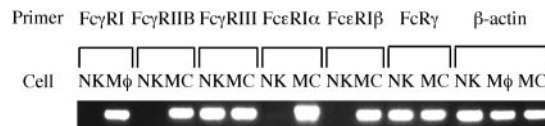


FIGURE 1. RT-PCR analysis for mRNA expression of various FcRs in NK cells. mRNA expressions of FcγRI, FcγRIIB, FcγRIIIα, FcεRIα, FcεRβ, FcγR, and β-actin in cultured NK cells (NK), BMMC (MC), and Mφ were analyzed by RT-PCR using each specific primer.

culated as follows: $((E - C)/(M - C)) \times 100$ (E , ⁵¹Cr release by effector cells plus target cells; C , target cells alone; and M , the maximum release).

Results

Exclusive expression of FcγRIII on NK cells

The expression of various FcR chains in our NK cell population was examined by RT-PCR analysis to exclude the possibility of a low expression of other FcR in our NK cell preparation (Fig. 1). cDNAs prepared from IL-2-cultured murine NK cells, peritoneal Mφ, and BMMC were amplified with specific primers for each FcR chain. Consequently, the NK cell preparation expressed only FcγRIIIα and FcγR, but not FcεRIα, FcεRβ, FcγRIα, or FcγRIIB. These results demonstrate that NK cells expressed FcγRIII, but not FcεRI. FcγRIII on NK cells associates only with FcγR, but not with FcεRβ (18). Thus, FcγRIII on NK cells was composed of FcγRIIIα and FcγR, while FcγRIII on mast cells was composed of FcγRIIIα, FcεRβ, and FcγR as described (14, 15).

IFN-γ production upon stimulation of NK cells with IgE

To analyze the possible stimulation of NK cells with IgE, murine NK cells were stimulated with immobilized IgG or IgE mAb for 2 days, because we determined that the maximum response for IFN-γ production by NK cells upon stimulation with immobilized IgG was 2 days (data not shown). IFN-γ secretion in the culture supernatants was analyzed by ELISA (Fig. 2A). Immobilized IgG induced a high level of IFN-γ from NK cells in a dose-dependent manner. To our surprise, a considerable amount of IFN-γ was

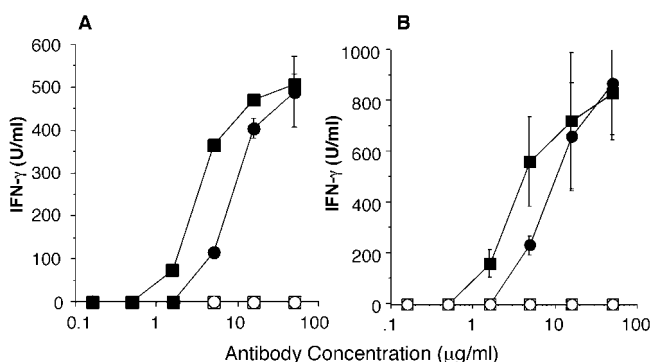


FIGURE 2. IFN-γ production by NK cells stimulated with IgE through FcγRIII. **A**, NK cells from C57BL/6 mice were stimulated with graded concentrations of immobilized IgG (□ and ■) or IgE (○ and ●) in the presence (○ and □) or absence (● and ■) of 20 µg/ml 2.4G2 mAb. The concentrations of Abs used for coating plates are indicated on the x-axis. The amount of IFN-γ produced in the culture supernatants was determined by ELISA. IFN-γ production by NK cells upon stimulation with IgE through FcγRIII was confirmed in three independent experiments. **B**, NK cells from wt (● and ■) and FcγR^{-/-} (○ and □) C57BL/6 mice were stimulated with graded concentrations of immobilized IgG (□ and ■) or IgE (○ and ●) for 2 days. The absence of IFN-γ production by NK cells from FcγR^{-/-} mice was confirmed in two independent experiments.

detected in the supernatant of NK cells stimulated with immobilized IgE, also in a dose-dependent fashion. The efficiency of NK cell stimulation by IgE was less than that by IgG and the difference in the dose-response curve was 3- to 10-fold. This result shows that NK cells can be activated to produce IFN- γ upon stimulation with immobilized IgE.

IgE-mediated activation of NK cells through Fc γ RIII

Next, we investigated the possibility that NK cell activation was mediated through Fc γ RIII, because Fc γ RIII has been reported to be a low affinity receptor for IgE on mast cells (5). When we added an anti-Fc γ RIII mAb 2.4G2 (20 μ g/ml) to the culture of IgG- and IgE-stimulated NK cells, IFN- γ production upon stimulation with either IgG or IgE was totally abrogated by 2.4G2 mAb, suggesting that Fc γ RIII mediates the stimulation with IgE as well as IgG (Fig. 2A). Furthermore, IFN- γ production upon stimulation with either IgG or IgE was completely abrogated when NK cells from Fc γ -deficient mice were used (Fig. 2B). Together with the previous findings that NK cells from Fc γ -deficient mice did not induce IgG-mediated ADCC through Fc γ RIII due to the lack of the cell surface Fc γ RIII expression (16, 18), these data indicate that IgE-induced NK cell activation is also mediated through Fc γ RIII and Fc γ . These results clearly demonstrate that NK cells were activated with IgE through the Fc γ RIII complex composed of Fc γ RIII α and the Fc γ .

IgE-induced production of cytokines and a chemokine

NK cells are known to promptly produce a large amount of cytokines, such as IFN- γ , TNF- α , and GM-CSF upon stimulation through Fc γ RIII with IgG (19, 20). Therefore, we analyzed whether NK cells produce these cytokines or chemokines after stimulation with IgE by using real-time quantitative RT-PCR. In addition to IFN- γ production, NK cells produced significant levels of TNF- α and GM-CSF upon stimulation with IgE or IgG, particularly at the early stage of the stimulation (Fig. 3). The secretion of a chemokine MIP-1 α was also induced after stimulation with IgE or IgG. Because the maximum concentration of IgG and IgE (50 μ g/ml, Fig. 2) was used to stimulate NK cells in this experiment, the amounts of these cytokines/chemokines by IgE stimulation were comparable to those by IgG stimulation. Because TNF- α , GM-CSF, and MIP-1 α are important to anaphylaxis, NK cells seem to play a role in anaphylaxis by producing these factors and chemokines with IgE stimulation.

Induction of ADCC upon IgE-mediated NK cell activation

Finally, we addressed the question of whether the IgE-mediated NK cell activation induces cytotoxicity against IgE-coated target cells. To compare the ADCC activity induced by IgG and that by IgE, we used two pairs of IgG and IgE mAbs that share the same Ag specificity: anti-DNP IgG and IgE mAbs or anti-dansyl IgG and IgE mAbs. P815 cells, an NK-resistant cell line, were coated with these haptens (DNP or dansyl) by surface biotinylation followed by addition of DNP-streptavidin or dansyl-streptavidin. These targets were mixed with NK cells in the presence of anti-hapten IgG or IgE mAb (anti-DNP IgG/IgE for Fig. 4 or anti-dansyl IgG/IgE for Fig. 5). NK cells induced strong ADCC with IgG and also showed significant cytotoxicity against IgE-coated target cells. In both cases with anti-DNP Abs (Fig. 4) and anti-dansyl Abs (Fig. 5), IgE induced significant ADCC, although with less efficiency than IgG. In contrast, NK cells from Fc γ ^{-/-} mice, which lack the expression of the cell surface Fc γ RIII, completely failed to exhibit ADCC against either IgE- or IgG-coated target cells (Fig. 5). These results suggest that the enhancement of IgE-mediated ADCC is specifically mediated through Fc γ RIII. IgE-

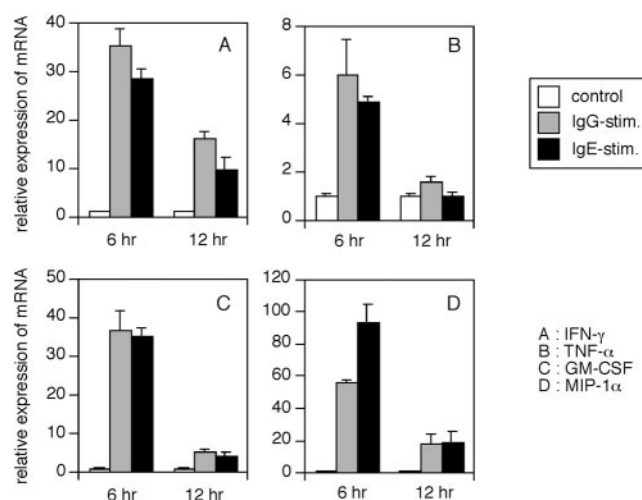


FIGURE 3. Production of cytokines and a chemokine from NK cells with IgE stimulation. RNA was prepared from NK cells after stimulation with immobilized IgE and IgG for 6 or 12 h, and cDNA was prepared by reverse transcription. Real time-PCR analysis was performed in triplicate for each primer. The amount of cDNA of each stimulation was analyzed by iCycler iQ software. The value of the amount of each stimulation was first divided by the amount of β -actin of each stimulation, and then the value was normalized with the value of the control (no stimulation) as fold increase. $\square$ and $\blacksquare$, Relative expressions upon stimulation with IgG and IgE, respectively. The data are representative of three independent experiments.

mediated ADCC of NK cells was also observed using other target cells including T cell hybridoma cells (data not shown). These results revealed that ADCC was induced upon activation of NK cells through binding of IgE to Fc γ RIII. It is noteworthy that IgE-mediated but not IgG-mediated ADCC requires continuous presence of Ab during the killing assay for 4 h (data not shown), suggesting that IgE has lower affinity-binding to Fc γ RIII (5) and requires a higher dose of Ab for ADCC as compared with IgG.

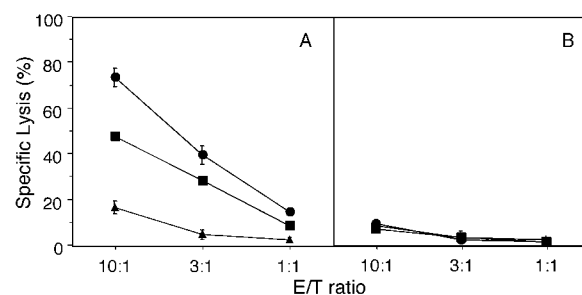


FIGURE 4. IgE-mediated ADCC by NK cells. A, IgE ($\blacksquare$)- and IgG ($\bullet$)-mediated ADCC activity of NK cells was measured. P815 target cells were surface-biotinylated and labeled with ^{51} Cr. Then the cells were labeled with DNP-coupled streptavidin, followed by incubation with either 5 μ g/ml anti-DNP IgE mAb or 5 μ g/ml anti-DNP IgG mAb. NK cells were cultured with the DNP-modified P815 target cells at the indicated E:T ratio for 4 h in the presence of 5 μ g/ml IgG and IgE, and the released ^{51} Cr was measured. Specific lysis was calculated as described in *Materials and Methods*. $\blacktriangle$, Spontaneous cytotoxicity of target cells in the presence of NK cells without Ab against the DNP-coated same target cells. B, IgE ($\blacksquare$)- and IgG ($\bullet$)-mediated spontaneous cytotoxicity of the target cells biotinylated without streptavidin-DNP. $\blacktriangle$, Spontaneous cytotoxicity of target cells without Abs in the presence of NK cells. IgE-mediated ADCC by NK cells was confirmed in five independent experiments.

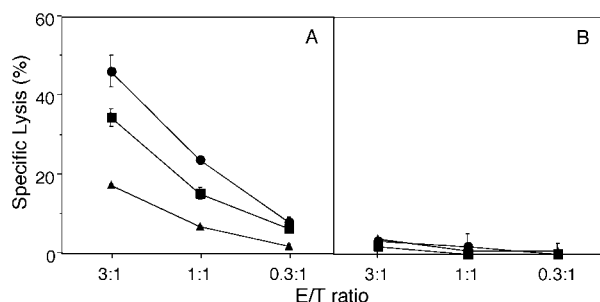


FIGURE 5. IgE-mediated ADCC by NK cells from normal mice and FcγR^{-/-} mice. IgE (■)- and IgG (●)-mediated ADCC activity of NK cells from C57BL/6 mice (A) and FcγR^{-/-} mice (B) was measured. P815 target cells were surface-biotinylated, labeled with ⁵¹Cr, and incubated with 10 μg/ml dansyl-coupled streptavidin, followed by incubation with either 5 μg/ml anti-dansyl IgE mAb or anti-dansyl IgG mAb. NK cytotoxicity was measured as described in Fig. 4. ⁵¹Cr was measured in the presence of anti-dansyl IgE (■) or anti-dansyl IgG (●), similarly in Fig. 4. ▲, Spontaneous cytotoxicity of target cell in the presence of NK cells without Ab. Similar results were obtained from six independent experiments.

Discussion

FcεRI is expressed mainly on mast cells, basophils, and eosinophils. It has been thought to be necessary and sufficient for IgE-mediated anaphylaxis, based on the analysis of FcεRIα-deficient mice (1). However, further analyses using genetic mutant or gene-targeted mice have revealed that FcεRI and IgE are not the only initiators of anaphylactic reactions. Indeed, in the late 1960s, Vaz and Ovary (2) showed that IgG induced cutaneous anaphylaxis. Recent studies using both FcγR^{-/-} and FcεRIα^{-/-} mice confirmed that OVA-induced systemic anaphylaxis largely depends on IgG1 binding to FcγRIII (3). Furthermore, Ujike et al. (6) showed that IgE-mediated systemic anaphylaxis was reduced in FcγRIII-deficient mice, suggesting a contribution of FcγRIII not only to IgG- but also to IgE-mediated passive anaphylactic response.

In contrast, W/W mutant mice bearing a *c-kit* gene mutation and mast cell deficiency were shown to induce active anaphylactic responses associated with physiological changes and mortality rates that are similar to those observed in the Ag-sensitized normal mice (7–9). From these studies, some cells other than mast cells might be involved in allergic responses to certain Ags. In fact, mast cells may not be involved in systemic anaphylaxis induced by penicillin V, although the anaphylaxis is well correlated with serum IgE level (10). Collectively, all these data suggest the involvement of cells other than mast cells at the cellular level and FcγRIII at the molecular level in IgE-mediated systemic anaphylaxis in vivo, although the cells responsible for these IgE-mediated FcγRIII-dependent responses remained to be identified.

We have demonstrated in the present study that IgE-stimulated NK cells produce cytokines and chemokines that are related to anaphylaxis, and they exhibit IgE-mediated ADCC through FcγRIII. Takizawa et al. (5) previously reported that IgE binds to FcγRIII on FcγRIII-transfected COS cells, as well as to Mφ and mast cell lines. These authors also showed serotonin release upon stimulation of mast cells with aggregated IgE through FcγRIII. FcγRIII on NK cells is composed of only FcγRIIIα and the FcRγ dimer, while that on mast cells is made up of FcγRIIIα, FcRβ, and the FcRγ dimer. Therefore, our study demonstrated for the first time that IgE binding to the FcγRIIIαγ₂ complex induces activation and effector function of NK cells.

The affinity constant of monomeric IgE toward FcγRIII was calculated to be $4.8 \times 10^5 \text{ M}^{-1}$, whereas that of IgG to FcγRIII was $6.7 \times 10^6 \text{ M}^{-1}$ (5). In our study, stimulation of FcγRIII with

IgE was always weaker than with IgG for both cytokine production and ADCC. The cytokine production by NK cells upon IgE stimulation despite very low affinity of IgE binding to FcγRIII may be mediated by cooperation of specific adhesion molecules because adhesion molecules have been shown to be involved in cytokine production and cytotoxicity by NK cells (21, 22). An obvious question may occur whether IgE-mediated NK activation takes place under physiological conditions with such low affinity of IgE to FcγRIII and requirement of higher concentration of IgE than IgG. It is noteworthy that the concentration of IgE in the plasma of some atopic patients reaches 10 μg/ml (23), and the serum IgE level of NC/Nga mice, a recently established mouse model for allergic dermatitis is ~80 μg/ml (24). We observed significant ADCC of NK cells upon stimulation with 5 μg/ml IgE. Thus, it is possible to activate NK cells with IgE under physiological conditions in vivo including some pathological situation. Considering that the tissue distribution of NK cells and mast cells is quite different, it is possible that NK cells may be involved in allergic responses at different sites from mast cells.

Recently, several reports have described the involvement of NK cells in allergy. In particular, NK cells were shown to regulate the development of allergen-induced eosinophilic airway inflammation in mice (12), although how NK cells contribute to the process was not defined. NK cells produced a large amount of cytokines and chemokines, including IFN-γ, TNF-α, GM-CSF, and TGF-β, upon stimulation through FcγRIII (19, 20). Furthermore, we have observed that NK cells also produced the chemokines MIP-1α and MIP-1γ after activation (our unpublished observation). Our present study showed that NK cells induced the production of IFN-γ, TNF-α, GM-CSF, and MIP-1α upon IgE stimulation. TNF-α and TGF-β contribute to anaphylaxis in either induction or promotion of the response (25). MIP-1α and MIP-1γ induce chemotaxis of T cells and eosinophils (26, 27). Through the production of these cytokines and chemokines during an anaphylactic response, NK cells may play an important role in allergy. Indeed, it is possible that the NK cell may be one of the cells responsible for the FcεRI-independent allergic reactions by the production of a large amount of cytokines and chemokines.

Type II hypersensitivity is believed to be mediated solely by IgG-induced ADCC against autoantigens. However, several reports indicated that idiopathic thrombocytopenic purpura correlates with IgE levels (28). If IgE-mediated ADCC through FcγRIII on NK cells functions in vivo, IgE might also be involved in type II hypersensitivity.

Acknowledgments

We thank Dr. L. L. Lanier for discussion and reading the manuscript, Dr. S. Taki for reagents and discussion, Ms. R. Shiina and Ms. M. Sakuma for technical assistance, and Ms. H. Yamaguchi for secretarial assistance.

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