Association with FcRγ Is Essential for Activation Signal through NKR-P1 (CD161) in Natural Killer (NK) Cells and NK1.1+ T Cells

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Summary

Natural killer (NK) cells exhibit cytotoxicity against variety of tumor cells and virus-infected cells without prior sensitization and represent unique lymphocytes involved in primary host defense. NKR-P1 is thought to be one of NK receptors mediating activation signals because cross-linking of NKR-P1 activates NK cells to exhibit cytotoxicity and IFN-γ production. However, molecular mechanism of NK cell activation via NKR-P1 is not well elucidated. In this study, we analyzed the cell surface complex associated with NKR-P1 on NK cells and found that NKR-P1 associates with the FcRγ chain which is an essential component of Fc receptors for IgG and IgE. The association between FcRγ and NKR-P1 is independent of Fc receptor complexes. Furthermore, NK cells from FcRγ-deficient mice did not show cytotoxicity or IFN-γ production upon NKR-P1 cross-linking. Similarly, NK1.1+ T cells from FcRγ-deficient mice did not produce IFN-γ upon NKR-P1 crosslinking. These findings demonstrate that the FcRγ chain plays an important role in activation of NK cells via the NKR-P1 molecule.

Materials and Methods

Mice. FcRγ-deficient (γ−/−) mice with C57BL/6 background were established by gene targeting using a C57BL/6 origin ES cell

The first two authors contributed equally to this work.

The abbreviations used in this paper: γ−/−, FcRγ-deficient; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibition motif; KIR, killer inhibitory receptors.

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NK Cell Preparation. NK cells were purified as previously described (18). In brief, NK cells were purified from spleen of 6-8-wk-old C57BL/6 mice. Splenocytes were mixed with anti-CD4 mAb (GK1.5) and anti-CD8 mAb (53.6.7), and incubated with magnetic beads (Advanced Magnetics, Inc., Cambridge, MA) coupled with goat anti-mouse IgG and goat anti-rat IgG Ab (Cappel, Organon Teknika Co., West Chester, PA) to remove CD4 

The resultant cells were then stained with PE-anti-NK1.1 (PK136) mAb and FITC-anti-CD3e (145-2C11) mAb (Pharmingen, San Diego, CA) and NK1.1/CD3+ cells were sorted by FACStarplus (Becton Dickinson, Mountain View, CA). The purified NK cells were cultured in RPMI-1640 supplemented with 10% FCS, kanamycin (100 μg/ml) and 5 × 10^-5 M 2-ME in the presence of 1,000 U/ml human recombinant IL-2 (kindly provided by Dr. Junji Hamuro, Ajinomoto Co. Inc., Kawasaki, Japan) for 5 d.

Flow Cytometric Analysis of NK Cells. CD4+CD8-spleenocytes prepared as described above were cultured for 4 d in the presence of 1,000 U/ml IL-2. The cultured cells were first stained with FITC-anti-FcRII (3.2G2) mAb. Then, the cells were mixed with Biotin-anti-CD3e and PE-anti-NK1.1 mAbs followed by Quantum-red streptavidin (Sigma Chem. Co., St. Louis, MO).

Anti–NFAC (R 4-6A2) and anti–IL-4 (BVD4-1D11) mAbs was coated to capture IFN-γ and IL-4 and the captured IFN-γ and IL-4 were detected with biotinylated anti–IFN-γ (XMG1.2) and anti–IL-4 (BVD6-24G2) mAbs. These antibodies were purchased from Pharmingen. Concentrations of IFN-γ and IL-4 were determined with recombinant IFN-γ and IL-4 as a standard.

Directed Cytotoxicity of NK Cells. Cytotoxic assay was done basically as previously described (20). Briefly, freshly isolated CD4+CD8-HSA-spleenocytes from Pharmingen. Concentrations of IFN-γ and IL-4 were determined with recombinant IFN-γ and IL-4 as a standard.

Results

To elucidate signaling pathways for NK cell activation through NK-R-1, we analyzed the NK-R-1-associated complex on the cell surface using an NK1.1-expressing T cell line CTTL-2. CTTL-2 cells were surface-biotinylated and the cell lysate was immunoprecipitated with anti-NK1.1 or anti-CD3e mAbs, followed by analysis on two dimensional nonreducing and reducing SDS-PAGE.

As shown in Fig. 1A, immunoprecipitation with anti-NK1.1 mAb revealed that a 9-kD homodimer was coprecipitated with NK1.1 molecule. In contrast, when the TCR complex was precipitated with anti-CD3e mAb, CD3ζ homodimers, CD3ζ-FcRγ heterodimers and a small amount of FcRγ homodimers were observed as previously reported (21). Interestingly, the 9-kD homodimers coprecipitated with NK1.1 appeared to be identical to FcRγ within the TCR complex. Indeed, the homodimers coprecipitated with NK1.1 were blotted with anti-FcRγ Ab similarly to FcRγ observed in the CD3e-immunoprecipitates (Fig. 1B). The association of the FcRγ chain with the NK-R-1 molecule was also observed in a rat NK cell line, RNK-16 (data not shown). We next analyzed normal NK cells to generalize the physical association between FcRγ and NK-R-1 in normal NK cell population. Similar to CTTL-2, when NK1.1 was immunoprecipitated from IL-2 activated NK cells, the FcRγ homodimer was coprecipitated with NK1.1 (Fig. 2). Collectively, these data indicate that the association of FcRγ with NK-R-1 is generally observed for NK cells in vivo.

To elucidate the physiological role of the association between FcRγ and NK-R-1 particularly on signal transduction in NK cells, NK cells were prepared from γ−/− mice and analyzed for NK-R-1 expression and NK-R-1-mediated NK cell activation. When CD4+CD8-spleenocytes from γ−/− mice were stained with anti-NK1.1 and anti-CD3e mAbs, normal development of NK cells (NK1.1/CD3−) was observed (data not shown). When expression of FcγRIII on IL-2-expanded NK cells was analyzed, NK cells from γ−/− mice did not express FcγRIII (Fig. 3). In addition, the expression level of NK1.1 on the cell surface of IL-2-expanded NK cells from γ−/− mice was decreased (Fig. 3), suggesting that the expression of NK1.1 might be regulated by FcγRIII transduction of γ−/− mice.
was significantly lower than that of NK cells from $\gamma^+/+$ and $\gamma^+/-$ mice. However, the difference of NK1.1 expression between $\gamma^-/-$ and $\gamma^+/-$ mice was marginal when freshly isolated NK cells were analyzed (data not shown). This suggested that FcR $\gamma$ is not absolutely required for but affects the surface expression of the NKR-P1 molecule.

Recently, we have shown that cross-linking of NKR-P1 on NK cells with anti-NK1.1 mAb induced not only cytotoxicity but also IFN-$\gamma$ production (10). Thus, we stimulated purified NK cells from $\gamma^-/-$ mice with immobilized F(ab)$_2$ fragment of anti-NK1.1 mAb in order to avoid the binding of the Ab to Fc receptors, and measured the amount of IFN-$\gamma$ produced in the culture supernatant. Surprisingly, NK cells from $\gamma^-/-$ mice did not produce IFN-$\gamma$ at all upon NKR-P1 cross-linking, whereas NK cells from $\gamma^+/-$ mice produced a large amount (Fig. 4). In contrast, NK cells from both $\gamma^-/-$ and $\gamma^+/-$ mice produced almost equal amount of IFN-$\gamma$ upon IL-12 stimulation. This suggests that the defect of IFN-$\gamma$ production upon NKR-P1 cross-linking by NK cells from $\gamma^-/-$ mice is not due to the inability of IFN-$\gamma$ production but the signaling defect via NKR-P1.

Because NK1.1$^+$ T cells also produce IFN-$\gamma$ but not IL-4 upon NKR-P1 cross-linking (10), we also analyzed the function of NK1.1$^+$ T cells in $\gamma^+/-$ mice. As we have pre-
viously reported (22), NK1.1+ T cells develop normally in γ−/− mice. NK1.1+ T cells were prepared from γ+/+ and γ−/− mice and stimulated with immobilized anti-NK1.1 mAb (Fig. 5). Similar to NK cells, NK1.1+ T cells from γ−/− mice did not produce IFN-γ upon NK-R-P1 cross-linking whereas these cells from γ+/+ mice produced a significant amount of IFN-γ. In contrast to the stimulation through NK-R-P1, NK1.1+ T cells from both γ+/+ and γ−/− mice showed increased cytotoxicity against P815 and IFN-γ and IL-4 upon TCR cross-linking. These observations demonstrate that the FcγR chain is required for IFN-γ production via NK-R-P1 cross-linking both in NK cells and NK1.1+ T cells.

We also investigated the involvement of FcγR in the NK-R-P1-mediated cytotoxicity of NK cells. Since NK-R-P1 is known to induce redirected cytotoxicity against FcγR-expressing cells, we analyzed cytotoxicity of NK cells against FcγR-expressing P815 cells in the presence of anti-NK1.1 mAb (Fig. 6). NK cells from γ+/+ and γ−/− mice showed increased cytotoxicity against P815 cells in the presence of anti-NK1.1 mAb, whereas NK cells from γ−/− mice failed to enhance cytotoxicity. These results demonstrate that FcγR is involved in both IFN-γ production and cytotoxicity upon stimulation through the NK-R-P1 molecule.

The failure of NK cell activation through NK-R-P1 in γ−/− mice is likely due to a defect in signaling pathway of the NK-R-P1 molecule. However, since the NK1.1 expression on the cell surface of NK cells from γ−/− mice is slightly lower than that of γ+/+ and γ+/− mice, it might be attributed to the low expression of the cell surface NK-R-P1.

To clarify these possibilities, we prepared two populations of NK cells from normal mice expressing low or high level of NK-R-P1 (NK-R-P1lo and NK-R-P1hi, respectively) by cell sorting. The expression level of NK-R-P1 on the NK-R-P1hi population was almost identical to that of γ−/− mice. Then, we stimulated these NK cell populations with immobilized anti-NK1.1 mAb. NK-R-P1hi NK cells from γ+/+ mice produced significant amount of IFN-γ upon NK-R-P1 cross-linking, although the amount of IFN-γ was lower than that by NK-R-P1lo NK cells (Fig. 7 C). In contrast, NK cells from γ−/− mice did not produce any detectable level of IFN-γ upon NK-R-P1 cross-linking. These observations confirm the crucial role of FcγR in signaling pathway through NK-R-P1 for NK activation and also demonstrate that FcγR is partly involved in the expression of the cell surface NK-R-P1.

Discussion

FcγR was originally identified in the FcγRI complex and found to play an essential role in the expression and signaling of FcγRI (23). FcγR was also found to be required for the expression and function of FcγRI, FcγRII and FcγRIII (24, 25). On the other hand, we found that FcγR also associates with the TCR complexes in two types of T cells. One is T cells in epithelia such as CD8α− TCR-γ/δ+ intestinal intraepithelial lymphocytes and TCR γ/δ+ dendritic epidermal cells and the association with FcγR in these cells was shown in vivo from the analysis of

![Figure 5](image-url) Defect of IFN-γ production by NK1.1+ T cells from γ−/− mice upon stimulation with NK1.1 cross-linking. NK1.1+ T cells from γ+/+ (closed bar) and γ−/− (open bar) mice were stimulated with immobilized anti-NK1.1 mAb or anti-TCRβ mAb and IFN-γ and IL-4 produced in the culture supernatant was measured. Data are presented as mean ± SD of triplicate assay.

![Figure 6](image-url) Defect of NK1.1 mediated cytotoxicity by NK cells from γ−/− mice. Cytotoxicity of NK cells from γ+/+, γ+/−, and γ−/− mice against P815 cell line was analyzed in the presence (open circles) or absence (closed circles) of anti-NK1.1 mAb. Data are presented as mean ± SD of triplicate assay.
CD3ε-deficient mice (26). The second population is NK1.1+ TCR-α/β+ T cells (22). However, these T cells obtained from γ−/− mice showed no clear defect in function upon TCR activation, although the expression level of the TCR complex was slightly decreased (27). Accordingly, it is striking that NK cells and NK1.1+ T cells from γ−/− mice show no response upon NK-R-P1 cross-linking in spite of normal development. This finding suggests that CD3ε expressed in NK cells and NK1.1+ T cells can not be replaced for FcRγ in signaling through NK-R-P1, because NK-R-P1 bind to FcRγ dimers but not to CD3ε homodimers or CD3ε-FcRγ heterodimers. In contrast, T cells show no functional defect in γ−/− mice probably because the TCR complexes can utilize both CD3ε and FcRγ and CD3ε can replace for FcRγ in the TCR complexes of γ−/− mice.

FcγRIII which is associated with FcRγ is known to activate NK cells upon cross-linking. Therefore, there is a possibility that NKR-P1 associates with FcγRIII on the cell surface and delivers activating signal through FcRγ which is coupled with FcγRIII. However, this is unlikely because of two reasons. One is that FcγRIII was not expressed on the cell surface of CTLL-2 (data not shown), whereas the association between FcRγ and NKR-P1 was readily detected in the CTLL-2 (Fig. 1). Second, we used the (Fab)2 fragment of anti-NK1.1 mAb for cross-linking of NKR-P1 and thus it is unlikely that immobilized anti-NK1.1 mAb activated FcγRIII. Taken together, the association of FcRγ with NKR-P1 is essentially independent of FcγRIII.

Recent analysis revealed that activation of NK cells is negatively regulated by several killer inhibitory receptors (KIR) possessing immunoreceptor tyrosine-based inhibition motif (ITIM) (28, 29). These receptors such as p58, NKG2, and Ly49 recognize specific MHC class I molecule and deliver inhibitory signal for the cytotoxicity by NK cells (30–32). Furthermore, association of SHP-1 phosphatase with ITIM is important for the inhibition of NK cell activation (28, 29). Although the coprecipitation of CD3ζ or FcRγ with p58 was suggested, functional significance remained unclear (33). On the other hand, only a few receptors which deliver positive signal for NK cell activation have been identified such as NKR-P1 and CD94/NKG2-C (34) and the molecular mechanism of NK cell activation through these receptors remains unclear. Under these circumstances, it is noteworthy that FcRγ, a signal transducing chain possessing immunoreceptor tyrosine-based activation motif (ITAM), is involved in signal transduction through NK-R-P1. Because Syk tyrosine kinase interacts with the phosphorylated ITAM of FcRγ and is involved in NK cell activation through FcR (35, 36), it is likely that Syk also mediates the activating signal through NKR-R-P1 in NK cells. Furthermore, it has been shown that Lck directly associates with NKR-P1 (14). Taken together, both Syk and Lck seem to play an important role in mediating activation signals through NKR-P1 in NK cells.

Although the NKR-P1 molecule belongs to the C-type lectin superfamily and has been shown to have affinity to specific carbohydrates (12), the exact function of NKR-P1 has remained unclear. This is partly because antibodies against mouse or rat NKR-P1 do not block cytotoxicity of NK cells against YAC-1, a NK-sensitive target cell line. In addition, NK cells from γ−/− mice showed normal cytotoxicity against representative NK targets (data not shown). However, the failure of blocking with anti-NKR-P1 mAb can be explained by the possible redundancy of NKR-P1 family molecules on NK cells. Indeed, recent observation that introduction of NKR-P1 into a NKR-P1-deficient NK cell line restored cytotoxicity against specific tumor cell targets and the restored cytotoxicity was blocked by anti-NKR-P1 mAb (11) strongly suggested that NKR-P1 is involved in the recognition of specific target molecules on NK cells. A couple of reports demonstrating that anti-NK1.1 mAb blocked cytotoxicity of NK cells against specific targets also support this idea (37, 38). Further analysis of NK cells in γ−/− mice may elucidate novel function of NKR-P1 molecule in the host defence.

Figure 7. Activation defect of NK cells from FcRγ-deficient mice upon NKR-P1 crosslinking is not due to the low level of NKR-P1 expression. (A) NK11 expression on NK cells from γ+/+ and γ−/− mice. NK cells from γ+/+ or γ−/− mice were stained with anti-NK1.1 mAb (solid line) or control Ab (dotted line). (B) Preparation of NK cell population expressing high (hi) and low (lo) level of NKR-P1 from wild-type mice. (C) Production of IFN-γ by NK cell population expressing low NKR-P1 upon stimulation with immobilized anti-NK1.1 mAb. Two NK cell populations expressing high (NK1.1hi) and low (NK1.1lo) level of NK11 as shown in B from γ−/− mice and NK cells from γ−/− mice were stimulated with immobilized (Fab)2 fragment anti-NK1.1 mAb and IFN-γ production was measured.

1961 Arase et al.
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