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The Low Affinity Fc Receptor for IgG Functions as an Effective Cytolytic Receptor for Self-Specific CD8 T Cells

Salim Dhanji, Kathy Tse, and Hung-Sia Teh

We have recently described a population of self-Ag-specific murine CD8+ T cells with a memory phenotype that use receptors of both the adaptive and innate immune systems in the detection of transformed and infected cells. In this study we show that upon activation with IL-2 with or without Ag, between 10 and 20% of the activated self-specific CD8+ T cells express the low affinity FcR for IgG. By contrast, all IL-2-activated NK cells express high levels of this FcR. The FcR comprises the FcyRIIα and FcγR subunits. However, the FcγR subunit also associates with the CD3 complex, and this association probably contributes to the low expression of FcR in activated cells. Although the FcR is expressed at a low level on activated self-specific CD8+ T cells, it functions very efficiently as a cytolytic receptor in ADCC. FcR-dependent killing occurred in the absence of TCR stimulation, but could be augmented by concurrent stimulation of the TCR. In addition to mediating ADCC, engagement of the FcR on self-specific CD8+ T cells results in the production of both IFN-γ and TNF-α. This is the first report of an activating FcR on self-specific murine CD8+αβ TCR+ T cells and establishes the importance of innate immune system receptors in the function of these self-specific CD8+ T cells. The Journal of Immunology, 2005, 174: 1253–1258.

N atural killer cells represent a highly specialized lymphoid population characterized by potent cytolytic activity against tumor or virally infected cells. Their function is finely regulated by a series of inhibitory or activating receptors (1). The inhibitory receptors, specific for MHC class I molecules, allow NK cells to discriminate between normal cells and cells that have lost the expression of MHC class I (e.g., tumor cells). Inhibitory receptors, such as those belonging to the Ly49 family in mice and the killer Ig-like receptors in humans, contain ITIM motifs in their cytoplasmic domains (2). Engagement of these receptors results in the recruitment of inhibitory phosphatases that prevent NK cell activation. The activating receptors responsible for NK cell triggering include Nkp30, Nkp46, and NKG2D in humans and Nkp46 and NKG2D in mice (3, 4). The activating receptors, some of which belong to the same families, do not contain activation motifs, but, rather, associate with adaptor molecules or signaling partners important for signal transduction (5).

One of the first activating receptors described on NK cells is FcγRIIIa or CD16. CD16 is a low affinity FcR that binds to IgG and is involved in Ab-dependent cell-mediated cytotoxicity (ADCC),3 in which an Ab-coated target cell is destroyed by NK cells (6). Stimulation of CD16 on NK cells also results in the production of cytokines, such as IFN-γ, TNF-α, and GM-CSF (7).

FcγRIIα associates mainly with ITAM-containing homo- or heterodimers of CD3ζ and FcεRIγ (FcγR) in humans (8) or solely with FcγR homodimers in mice (9). The binding of IgG to CD16 results in the phosphorylation of ITAMs in the signaling chains, leading to the recruitment of kinases such as ZAP-70 and Syk (10). These kinases initiate a signaling cascade resulting in the lysis of Ab-coated target cells. T cells also use ITAM-containing receptors and Syk and ZAP-70 for their signal transduction (reviewed in Ref. 11). Thus, the signals transduced by the engagement of CD16 on NK cells are very similar to those transduced by the engagement of TCR on T cells.

CD16 expression is not limited to NK cells; other cell types have been described that also express this receptor. γδ T cells have been shown to express CD16, as have a population of large granular lymphocytes (mostly αβTCR+CD4-CD8- T cells) in humans (12, 13). In addition, some memory phenotype αβTCR+CD8+ T cells in humans have been shown to express CD16 (14). We have previously described a population of αβTCR+CD8αβ+ T cells in normal B6 mice that exhibit a memory phenotype characterized by the expression of high levels of CD44, IL-2Rβ, and Ly6C (15). These cells can be activated by cytokines such as IL-2 and IL-15, and upon activation they express several functional NK receptors, including 2B4, CD94, and NKG2D as well as the NK adaptor protein DAP12. Using an H-Y TCR transgenic model, we have shown that the development of CD8+CD44high T cells is driven by the high affinity interaction of the αβTCR with cognate self-Ag (16). The H-Y TCR is specific for a male Ag (H-Y) presented by H-2Db, and in H-2b H-Y female mice, the lack of male Ag results in the development of H-Y CD8 T cells with a naive phenotype (CD44low). In H-2b H-Y male mice, in contrast, the presence of the cognate (H-Y) Ag results in the development of a population of CD8+ T cells that is virtually identical in cell surface and functional phenotypes with the memory phenotype CD8+CD44high cells in normal B6 mice (16). Because memory phenotype CD8+ T cells in normal and H-Y TCR transgenic mice are specific for self-Ags, we will refer to these cells as self-specific CD8+ T cells to distinguish them from conventional memory CD8+ T cells. Self-specific CD8+ T cells from

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3 Abbreviations used in this paper: ADCC, Ab-dependent cell-mediated cytotoxicity.
both H-Y TCR transgenic (16) and nontransgenic (15) mice preferentially kill syngeneic tumor cells. This killing of syngenic tumors involves the MHC-restricted αβ TCR as well as the activating NK receptor, NKGR2D, which results in non-MHC-restricted lysis of target cells that express the NKGR2D ligand, Rae-1 (16).

In this report we have described the expression and function of CD16 in self-specific CD8\(^+\) cells from B6 and male H-Y TCR transgenic mice. We showed that this FcR, comprising the FcγRIIIα/FcγRIγ subunits, is similar in composition to the NK FcR. Although this FcR is expressed at a low level in self-Ag-specific CD8\(^+\) T cells, it is particularly efficient at initiating the destruction of Ab-coated target cells and can induce the production of two key inflammatory cytokines, IFN-γ and TNF-α. These observations underscore the importance of innate immune system receptors in the function of these self-specific CD8\(^+\) T cells.

Materials and Methods

Mice

Breeders for C57BL/6 (B6) mice were obtained from The Jackson Laboratory. The H-Y TCR transgenic mice (17) were bred to the B6 background. Mice, 6–12 wk of age, were used for the experiments described.

Abs and flow cytometry

The following Abs were used: anti-CD4 (GK1.5), anti-CD8α (53.67), anti-CD8β (53.38), anti-NK.1.1 (PK136), anti-CD3ε (2C11), anti-CD90 (T24, Rat IgG3) (18), anti-CD16/32 (2.4G2, Rat IgG2b), anti-CD44 (PGP1), anti-FcRγ, anti-CD3γ (19), and anti-H-Y TCRα (T3.70) (17). All Abs were purchased from BD Pharmingen, except anti-FcγRγ (Upstate Biotechnology), anti-CD16/32 (American Type Culture Collection), and anti-H-Y TCRα (eBioscience). The CellQuest software program (BD Biosciences) was used for data acquisition and analysis.

Cell lines

The cell lines used were the RMA lymphoma (H-2\(^b\), Rae-1\(^-\)) and Tap-deficient RMA (H-2\(^b\), Rae-1\(^+\)). The cell lines were cultured in IMEM (Invitrogen Life Technologies) supplemented with 10% (v/v) FBS (Invitrogen Life Technologies), 5 \(\times\) 10\(^{-6}\) M 2-ME, and antibiotics (I-medium).

Cell purification and activation

CD8\(^+\)CD44\(^{high}\) T cells from B6 mice were purified and cultured in IL-2 (200 U/ml) for 5 days as previously described (15). NK cells were enriched by depletion of CD4-CD8-CD3- IgG cells using Dynabeads (Dynal Biotech) and then cultured in IL-2 for 5 days, resulting in a pure population of activated NK cells (15). Purified naïve CD8\(^+\) (CD44\(^{low}\)) cells do not respond to IL-2 alone and were activated for 5 days on plate-bound anti-CD3ε (10 μg/ml) and IL-2 (20 U/ml). Purified H-Y TCRα CD8\(^+\) T cells (1 \(\times\) 10\(^6\)) were activated by culture with 1 \(\times\) 10\(^6\) B6 splenocytes, 1 μM H-Y peptide, and 20 U/ml IL-2 for 5–6 days.

RT-PCR

RNA was extracted from activated cells and reverse transcribed as previously described (15). PCR was performed using previously described primers and reaction conditions (20).

CTL assays

CTL assays against RMA and RMAS target cells were performed as previously described (15). For ADCC, the target cells were pretreated with anti-CD90 mAb (10 μg/ml) for 15 min at room temperature before use. For the FcR-blocking experiment, anti-FcR mAb (2.4G2 used at 15 μg/ml) was added to the effector cells 15 min before the addition of targets and was present throughout the assay. Spontaneous release varied from 8–15% of the maximum. All assays were performed in triplicate. The percent specific lysis was calculated as 100% \(\times\) [cpm (experimental well) – cpm (spontaneous release)]/[cpm (maximum release) – cpm (spontaneous release)].

Immunoprecipitation and immunoblot analysis

Cells were activated as described above and pelleted by sedimented in 10 mM Tris (pH 7.5), 150 mM NaCl, 1% Triton X-100, 0.1% SDS, and protease and phosphatase inhibitors. The lysates were separated on a 4–15% Tris-HCl polyacrylamide gel and transferred to a polyvinylidene difluoride membrane. Blots were developed using an ECL system (Amersham Biosciences). CD3 immunoprecipitation was performed by treating lysates with preconjugated anti-CD3e protein G-Sepharose beads for 2 h at 4°C, followed by several washes. Complexes were then removed from the beads by resuspension in 2X protein sample buffer, followed by boiling for 5 min. The samples were then run in a 4–15% Tris-HCl gel and immunoblotted as described above.

Results

Expression of FcγRIIIα/FcγRIγ on activated self-specific CD8\(^+\) cells

We have previously shown that self-specific CD8\(^+\) T cells express an activated/memory phenotype (15, 16). Initially, ex vivo self-specific CD8\(^+\) cells from B6 and male H-2\(^b\) H-Y mice did not express significant levels of CD16 (Fig. 1a and data not shown). However, upon activation with IL-2 alone (B6) or Ag and IL-2 (H-Y male) for 5–6 days, between 10 and 15% of the activated self-specific CD8\(^+\) cells from B6 (CD8\(^+\)CD44\(^{high}\)) and male H-2\(^b\) H-Y mice expressed CD16 (Fig. 1a). In contrast, all IL-2-activated NK cells expressed high levels of CD16 (Fig. 1a). Because naive (CD8\(^+\)CD44\(^{low}\)) cells from B6 and female H-Y TCR transgenic mice did not proliferate in response to stimulation with IL-2 alone, these cells were activated with anti-CD3 and IL-2 (B6) or Ag plus IL-2 (H-Y female) to induce activation and proliferation. It is clear that activated CD8\(^+\)CD44\(^{high}\) cells from B6 and female H-Y TCR transgenic mice do not express CD16 (Fig. 1a), consistent with the conclusion that conventional CD8 T cells do not express CD16 upon activation.

We have previously described the bystander expansion and activation of self-specific CD8 T cells in response to infection with the bacterial pathogen *Listeria monocytogenes* (15, 16). Therefore, we wanted to determine whether the frequency of CD16\(^+\) T cells in infected mice.

![FIGURE 1.](http://www.jimmunol.org/) Activation of CD8\(^+\)CD44\(^{high}\) cells results in the expression of CD16. a, Purified CD8\(^+\)CD44\(^{high}\) cells from B6 and CD8\(^+\) cells from male H-2\(^b\) H-Y TCR transgenic mice were used as a source of self-specific CD8 T cells. Purified CD8\(^+\)CD44\(^{low}\) cells from B6 and female H-2\(^b\) H-Y TCR transgenic mice were used as a source of naive CD8 T cells. Self-specific B6 CD8\(^+\) T cells and NK cells were activated by culture with IL-2 for 5 days. Naïve CD8 T cells from B6 mice were activated by culture with anti-CD3 and IL-2 for 5 days, and CD8 cells from male and female H-Y mice were activated with Ag and IL-2 for 6 days. The activated cells were stained for the expression of CD16/CD32. 1. CD16/CD32 profile of the indicated cell type: 2. unstained controls. b, Naive B6 mice were infected with 10,000 CFU of **L. monocytogenes**. On day 5 the mice were killed, and the spleens were removed and stained. The histograms depict the expression of CD8 and CD16 on gated CD8 T cells from infected (right) or uninfected (left) mice, and the percentages of CD16\(^+\) CD8\(^+\) T cells are indicated. Three-color analysis revealed that the CD8\(^+\)CD16\(^+\) cells also expressed high levels of CD44 (data not shown).
In uninfected B6 mice, there was a small percentage of CD8<sup>+</sup> T cells that expressed CD16, but this number increased by ∼2-fold upon infection with Listeria (Fig. 1b). In addition, all CD8<sup>+</sup> CD62L<sup>−</sup> cells in both infected and uninfected mice expressed high levels of CD44.

The Ab used to detect CD16 expression also bound to CD32, and it was important to determine which FcR subunits were actually expressed by the self-specific CD8<sup>+</sup> cells. RT-PCR with primers specific for various FcR subunits was used to determine the composition of the expressed FcR. It is clear from this analysis that activated self-specific CD8<sup>+</sup> cells from B6 and male H-2<sup>b</sup> H-Y mice as well as NK cells from B6 mice expressed the mRNA for only FcyRIIa (CD16) and FcγR<sub>y</sub>, not FcyRI or FcyRIIB (Fig. 2a). A macrophage cell line was used as a positive control for the expression of FcyRI and FcγRIIB (Fig. 2a).

In murine NK cells, CD16 can only pair with FcγR homodimers (9). Furthermore, atopic expression of CD3ζ in murine NK cells actually interfered with the surface expression and function of CD16 through the formation of CD3ζ/FcγR<sub>y</sub> heterodimers, which cannot associate with CD16 (21). This finding suggests that the low cell surface expression of CD16 on self-specific CD8<sup>+</sup> cells may be due to the high expression of CD3ζ in these cells. To address this possibility, we compared the total amount of CD3ζ and FcγRIIy in activated NK and self-specific CD8<sup>+</sup> cells by Western blot. Fig. 2b shows that activated NK cells express an undetectable level of CD3ζ and the most FcγR<sub>y</sub> compared with self-specific CD8<sup>+</sup> cells from B6 (CD8<sup>+</sup>CD44<sup>high</sup>) and H-Y male mice. By contrast, self-specific CD8<sup>+</sup> cells from B6 and H-Y male mice express both CD3ζ and FcγR<sub>y</sub> (Fig. 2b). As expected, activated conventional CD8 (CD8<sup>+</sup>CD44<sup>low</sup>) cells only express CD3ζ. These findings suggest that the low levels of CD16 surface expression in self-specific CD8<sup>+</sup> cells are probably due to the inhibition of binding of FcγR<sub>y</sub> homodimers to CD16 by CD3ζ/FcγR<sub>y</sub> heterodimers in these cells.

In conventional T cells, the αβ TCR family with the CD3 complex of signaling chains, including CD3ε and CD3ζ (22). Because FcγR<sub>y</sub> is expressed in self-specific CD8<sup>+</sup> cells, we determined whether this signaling molecule could associate with the TCR/CD3 complex in these cells. To determine whether FcγR<sub>y</sub> associates with the CD3 complex, we immunoprecipitated the CD3 complex from IL-2-activated self-specific CD8<sup>+</sup> cells from B6 and H-Y mice using an anti-CD3ε Ab and immunoblotted with either an anti-CD3ζ or anti-FcγR<sub>y</sub> Ab. Fig. 2c clearly shows that anti-CD3ζ precipitates both CD3ζ and FcγR<sub>y</sub> in self-specific CD8<sup>+</sup> cells from B6 and male H-Y mice. As expected, anti-CD3ε precipitates only CD3ζ in conventional CD8<sup>+</sup> CD44<sup>low</sup> cells. This association of FcγR<sub>y</sub> with the CD3 complex in self-specific CD8<sup>+</sup> cells probably interferes with the association of CD16 with FcγR<sub>y</sub>, resulting in low expression of CD16 in these cells.

**IL-2-activated self-specific CD8<sup>+</sup> cells can mediate ADCC**

After observing the expression of CD16 on IL-2-activated self-specific CD8<sup>+</sup> cells, we determined whether this receptor could mediate ADCC. To this end, we activated self-specific CD8<sup>+</sup> cells and NK cells from B6 mice with IL-2, then tested their ability to kill Ab-coated RMAS targets cells. Anti-CD3- and IL-2-activated naive CD8 (CD8<sup>+</sup>CD44<sup>low</sup>) cells were included as a negative control. TAP-deficient RMAS cells were used as target cells to rule out contribution by MHC class I molecules in the killing reaction. The RMAS cells were left untreated or were pretreated with anti-CD90 (clone T24; 10 μg/ml) mAb before use as target cells. Fig. 3a clearly shows that IL-2-activated self-specific CD8<sup>+</sup> and NK cells can efficiently kill Ab-coated RMAS cells, whereas anti-CD3- and IL-2-activated conventional CD8 (CD8<sup>+</sup>CD44<sup>low</sup>) cells show absolutely no activity. We noted that anti-CD90 was more efficient in promoting the killing of RMAS targets by self-specific CD8<sup>+</sup> cells compared with NK cells. This finding is remarkable considering that only a small fraction of the self-specific CD8<sup>+</sup> cells express CD16, and the level of CD16 expressed per cell is significantly lower than that for NK cells (Fig. 1a). Because RMAS cells are killed efficiently by activated NK cells, the lack of killing of untreated RMAS cells by activated self-specific CD8<sup>+</sup> cells also indicates the lack of contaminating NK cells in the killing assay.

After observing that self-specific CD8<sup>+</sup> cells from B6 mice could efficiently lyse RMAS targets, we determined whether the presence of MHC class I had any effect on lysis by using TAP-sufficient RMAS targets. In addition, we determined whether blocking the CD16 receptor with an anti-CD16 mAb on the activated self-specific CD8<sup>+</sup> cells could block killing of Ab-coated target cells. Fig. 3b demonstrates that self-specific CD8<sup>+</sup> cells efficiently killed Ab-coated RMAS cells. Furthermore, the killing of Ab-coated target cells was greatly reduced by blocking the CD16 receptor on self-specific CD8<sup>+</sup> cells before culture with Ab-coated RMA targets. For NK cells, the lysis of Ab-coated RMA cells was only partially inhibited by blocking CD16 on NK cells. This was probably due to the high expression of CD16 on NK cells, which could not be blocked completely by the anti-CD16 Ab treatment. An alternative explanation for the inefficient blocking of killing of Ab-coated target cells by NK cells is that the anti-CD16 mAb

**FIGURE 2.** Activated self-specific CD8<sup>+</sup> T cells express a low affinity FcR similar to NK cells. Cells were activated as described in Fig. 1. a, RT-PCR analysis of FcyRIIa, FcγR<sub>y</sub>, FcyRI, and FcyRIIB transcripts present in activated cells. RNA from the J774 macrophage cell line was used as a positive control for FcγRI and FcγRIIB. b, Whole cell lysates of the activated cells were subjected to immunoblot analysis for the detection of FcγR<sub>y</sub> and CD3ζ protein. Blots were stripped and reprobed with anti-ERK2 as a loading control. c, Activated cells were lysed, and the lysates were immunoprecipitated (IP) with anti-CD3c Ab. The immunoprecipitates were then immunoblotted (IB) with anti-CD3ζ or anti-FcγR<sub>y</sub> mAbs. N.D., not determined.
killing reaction. It is clear from the data presented in Fig. 4 that the FcR in the killing reaction. Inclusion of the H-Y peptide in the assay allows an estimation of the contribution of H-Y TCR in the killing reaction. In the assay against MHC-sufficient RMA target cells that had been treated with anti-CD16 mAb (10 μg/ml) or left untreated. The assay was performed at a constant 10:1 E:T cell ratio with addition of the indicated concentrations of H-Y peptide. Error bars represent the SD of triplicate cultures.

The killing of anti-CD90-coated target cells in the absence of exogenous H-Y peptide was used as a measure for the contribution of the H-Y TCR in the killing reaction. Inclusion of the H-Y peptide in the assay allows an estimation of the contribution of H-Y TCR in the killing reaction. It is clear from the data presented in Fig. 4 that the expression of MHC class I molecules on the target cells does not affect FcR-mediated killing.

The killing of anti-CD90-coated target cells was slightly enhanced by the addition of H-Y peptide (Fig. 4). The activated self-specific CD8+ T cells from male H-Y mice required almost 10 nM exogenous H-Y peptide to attain the same level of killing as that seen with anti-CD90-coated target cells in the absence of H-Y peptide. This is remarkable because the entire population of H-Y male cells expressed the H-Y TCR, whereas at most 20% of the cells expressed CD16. By contrast, activated conventional CD8+ T cells from female H-Y mice could only kill peptide-loaded target cells, and the presence of Ab on the targets had no effect on this killing. These results suggest that CD16 functions independently of the TCR as an effective cytolytic receptor on self-specific CD8+ cells. Furthermore, the FcR and the TCR can act in an additive manner in the killing reaction.

Engagement of CD16 on self-specific CD8+ cells induces cytokine production

CD16 engagement on NK cells has been shown to induce the expression of several cytokines in addition to being able to induce ADCC (7). To test whether CD16 engagement on self-specific CD8 T cells could also mediate the production of cytokines, we cultured Ag-activated H-Y male CD8 cells with RMA targets that had been pretreated with anti-CD90 or left untreated. We found that these cells showed a significant increase in IFN-γ production in response to anti-CD90-coated RMA cells (7.2% IFN-γ) over untreated RMA cells (1.3%). Furthermore, this increase in IFN-γ production was reduced to near basal levels by the inclusion of soluble anti-CD16 mAb in this assay (Fig. 5a). This result suggests that the Fc portion of the bound anti-CD90 mAb on RMA cells induces the production of IFN-γ by H-Y male CD8 cells.

To obtain more direct evidence for FcR-mediated cytokine production by H-Y male CD8 cells, we used Ab cross-linking to stimulate CD16 directly. We cultured day 6 Ag-activated H-Y male CD8 T cells in wells coated with no Ab (Fig. 5b, upper row), anti-CD16 (middle row), or anti-CD3ε (bottom row). After a 5-h
CD8+ T cells to detect infected or transformed target cells, which might not be detected by NK cells.

It is interesting to note that even though the H-Y male cells represent a clonal population in which all cells should have been activated equivalently, only a fraction of the activated cells express CD16. The low cell surface expression of CD16 on self-specific CD8+ cells is probably due to the high expression of CD3ζ in these cells. In murine NK cells, CD16 can only pair with FcRγ dimers (9). Furthermore, the atopic expression of CD3ζ in murine NK cells interfers with the surface expression and function of CD16 through the formation of CD3ζ/FcRγ heterodimers, which cannot associate with CD16 (21). We found that the FcRγ-chain in self-specific CD8+ T cells is coprecipitated with CD3ζ by the anti-CD3ε mAb. It is likely that the resulting CD3ζ/FcRγ heterodimers interfere with the expression of the FcR on IL-2-activated self-specific CD8+ T cells. The association of the FcRγ-chain with CD3ζ is not unique to self-specific CD8+ T cells, because in large granular lymphocytes and in T cells from tumor-bearing mice, the CD3 complex has been shown to associate with FcRγ (23, 24). The association of CD3ζ with the FcRγ-chain also provides a potential explanation for the high efficiency of lytic activity of the FcR in these cells. We speculate that engagement of the FcR causes conformational changes in CD3ζ, resulting in activation of signaling pathways associated with the αβ TCR. A second, nonmutually exclusive explanation is that the differences in the lytic activity of CD16 in these two cell types may be cell intrinsic, which reflects differences in their physiology and/or developmental pathway.

We have previously shown that self-specific CD8+ cells undergo bystander expansion in vivo in response to Listeria infection, probably as a consequence of the high expression of IL-2Rβ by these cells, which enabled these cells to proliferate in response to IL-2 or IL-15 (16). Furthermore, self-specific CD8+ T cells that proliferate in response to bacterial infection exhibit a heightened ability to produce IFN-γ (16). These properties of self-specific CD8+ T cells would enable them to detect infected cells and provide an early source of IFN-γ. The expression of a self-specific TCR and NKG2D on these cells would allow them to focus on host targets as well as in the production of inflammatory cytokines. The possession of activating receptors of the innate as well as the adaptive immune system distinguished these cells from NK cells and suggests that this interesting cell type may be particularly adept in providing an early response to infected and transformed cells. These cells will also provide an early source of cytokines, such as IFN-γ and TNF-α, which would prime the adaptive immune system for the elimination of infected and transformed cells.

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References


