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Virus-Specific CD8+ T Cells Upregulate Programmed Death-1 Expression during Acute Friend Retrovirus Infection but Are Highly Cytotoxic and Control Virus Replication

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It was recently reported that inhibitory molecules such as programmed death-1 (PD-1) were upregulated on CD8+ T cells during acute Friend retrovirus infection and that the cells were prematurely exhausted and dysfunctional in vitro. The current study confirms that most activated CD8+ T cells upregulated expression of PD-1 during acute infection and revealed a dichotomy of function between PD-1hi and PD-1lo subsets. More PD-1lo cells produced antiviral cytokines such as IFN-γ and TNF-α, whereas more PD-1hi cells displayed characteristics of cytotoxic effectors such as production of granzymes and surface expression of CD107a. Importantly, CD8+ T cells mediated rapid in vivo cytotoxicity and were critical for control of acute Friend virus replication. Thus, direct ex vivo analyses and in vivo experiments revealed high CD8+ T cell functionality and indicate that PD-1 expression during acute infection is not a marker of T cell exhaustion. The Journal of Immunology, 2011, 187: 3730–3737.

CD8+ T cells, which produce cytokines and cytotoxic molecules to fight virus-infected cells, are crucial for the control of virus replication in many virus infections. However, in several chronic virus infections, like HIV or hepatitis C virus (HCV) infection in humans, virus-specific CD8+ T cells become functionally exhausted, which likely contributes to the inability of the host to eliminate the pathogen (1, 2). One mechanism leading to CD8+ T cell dysfunction is the ligation of inhibitory receptors that induce T cell exhaustion (3–5). Blocking such receptor–ligand interactions partially restores T cell function and reduces viral loads in chronically infected animals (3, 6). The inhibitory receptor that has been studied in most detail is programmed death-1 (PD-1), which is one of the prototypic inhibitory receptors described as a potent mediator of T cell exhaustion in chronic viral infection (3). It has been shown in recent studies that effector T cells already express PD-1 during acute infections. This was found in acute virus infections of humans with EBV (7), HCV (8), and hepatitis B virus (9) and monkeys with SIV (10) and SIV-HIV hybrid virus (11). The SIV study provided evidence that TCR stimulation was inducing the PD-1 expression on CD8+ T cells (10). However, the functional role of enhanced PD-1 expression on CD8+ T cells during acute infections is still poorly understood and remains controversial. Whereas some studies showed a correlation between the expression levels of PD-1 and reduced CD8+ T cell functions (11, 12), others did not find any association between PD-1 expression and CD8+ T cell responses (7). In addition, PD-1 expression by virus-specific CD8+ T cells seems to correlate with the clinical outcome of acute hepatitis B (9) but not with acute HCV infection (8). Results are also controversial when comparing studies on acute infections in which the PD-1 signaling was blocked by using programmed death ligand-1 (PD-L1) knockout mice or PD-L1–specific Abs. In these experiments, all possible outcomes, from enhanced to unchanged or even decreased CD8+ T cell responses and infection levels, were observed (7, 13–16). Not surprisingly, Brown et al. (17) wrote in their recent review that the precise role of PD-1 during acute infections remains to be defined.

A recent study (18) reported that PD-1 upregulation on virus-specific CD8+ T cells during acute Friend retrovirus (FV) infection of mice was associated with premature exhaustion, rendering the CD8+ T cell response ineffectual. Such a severe T cell dysfunction during acute virus infection was not reported in any of the studies mentioned above and is thus far unique to FV. In addition, the results contradicted previous results from the FV model (19, 20), so it was of interest to investigate this finding further. We used the same FV mouse model as Takamura et al. (18) to study the phenotypic and functional properties of effector CD8+ T cells during acute retroviral infection. Most importantly, we examined the in vivo efficacy of the antiviral CD8+ T cell response. Our results indicated that although PD-1 was indeed upregulated during acute infection, the FV-specific CD8+ T cells were not prematurely exhausted or dysfunctional. Quite to the contrary, we observed potent and rapid CD8+ T cell cytotoxicity in vivo and dependence on the CD8+ T cell response for survival from acute FV infection.

Materials and Methods

Mice

Inbred C57BL/6 (B6) mice were maintained under pathogen-free conditions. Experiments were performed using C57BL/6 (B6), (C57BL/10 × A.BY)F1

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Y10 is H-2b/b, Fv1b/b, Fv2s/r, and Pfv3r/s genotype. The Y10.A mice are cell line 169.4 cultures. Mice were then infected with FV 2 d following the Fv2r/s, and Rfv3r/s. The B6 mice were obtained from Charles River Laboratories. All mice were females of 8–16 wk of age at the onset of the experiments.

Virus and viral infection

The FV stock used in these experiments was FV complex containing B-tropic Friend murine leukemia helper virus (F-MuLV) and polycythemia-inducing spleen focus-forming virus and was free of lactate dehydrogenase-elevating virus (21, 22). The stock was prepared as a 1% spleen cell homogenate from BALB/c mice infected 14 d previously with 3000 spleen focus-forming units of noncloned virus stock. B6 mice were infected i.v. with 0.5 ml PBS containing 20,000 spleen focus-forming units of FV. The virus was prepared from the same stock that was supplied to the Miyazawa laboratory by Kim J. Hasenkrug.

Cell-surface and intracellular staining by flow cytometry

Cell-surface staining was performed using BD Biosciences or eBioscience reagents. T cell Abs were: anti-CD4 (RM4-5), anti-CD8 (33–25.1), anti-CD44 (H12-29.1), anti-CD69 (eBioM1/69), anti-CD11b (M1/70), anti-CD43 (TCR3A), anti-CD62L (MEL-14), anti-CD107a (1D4B), dead cells (propidium iodide positive) were excluded from analyses. Intracellular granzyme A (polyclonal rabbit anti-granzyme A IgG, protein A purified) and granzyme B (monoclonal anti-human granzyme B [GB11]; Invitrogen, Darmstadt, Germany) staining was performed as described (23). For intracellular cytokine staining, spleen cells were incubated with plate-bound anti-CD3 (145-2C11) and soluble anti-CD28 (37.51) (24, 25) (polyclonal rabbit-anti-mouse CD3, protein A purified) and F-MuLV (24, 25)] were acquired on an LSR II flow cytometer (BD Biosciences) from done using FlowJo (Tree Star) and FACSDiva software (BD Biosciences).

Tetramers and tetracer staining

For detection of D5-GagL-specific CD8+ T cells, spleen cells were stained with allophycocyanin-labeled anti-CD8 (Ly-2), FITC-labeled CD43 (1B11) and PE-labeled MHC class I H2-D3 tetracer specific for FV GagL peptide (24, 25) (Beckman Coulter, Marseille, France).

In vivo cytotoxicity assay

The in vivo CTL assay described by Barber et al. (26) was modified to measure cytotoxicity in FV-infected mice. Splenocytes from naive mice were loaded with 1–5 μM D5-GagL peptide (24, 25). The loaded cells were then stained with 200 nM CFSE (Molecular Probes, Eugene, OR). As a control, spleen cells without peptide were stained with 2 nM CFSE. Splenocytes (0.5–1 × 107 cells of each population) were transferred i.v. into naive mice. Two hours after the adoptive transfer, spleens from the recipient mice were harvested, and cell suspensions were prepared. Target cells were distinguished from recipient cells and from one another based on CFSE staining. The percentage of killing was calculated as follows: 100 − ([percent peptide pulsed in infected/percent unpulsed in infected]×percent peptide pulsed in unpulsed/unpulsed in uninfected) × 100).

PD-L1 and Tim-3 blockade and CD8 depletion

Y10 mice were infected with FV by i.v. injection of 0.5 ml phosphate-buffered balanced salt solution containing 6000 spleen focus-forming units of FV complex. A total of 250 μg anti-PD-L1 (10F.9G2; Bio-Xcell), anti-Tim-3 (RM3T-23; Bio-Xcell), or control rat IgG (Bio-Xcell) was given i.p. at the time of infection and every other day for a total of five injections. For CD8+ T cell depletions, mice were given a total of three i.p. injections every other day of 0.5 ml supernatant harvested from hybridoma cell line 169.4 cultures. Mice were then infected with FV 2 d following the last treatment.

Infectious centers assay

Dilutions of splenocytes were incubated at 37°C and 5% CO2 on Mus musculus cells for 2 d. Cells were then fixed with 95% ethanol, stained with F-MuLV envelope-specific mAb 720, and then viral foci developed with peroxidase-conjugated goat anti-mouse IgG and substrate.

Statistical Analysis

Statistics comparing two groups were done using the nonparametric t test. When more than two groups were compared, a one-way ANOVA was used with a Tukey posttest (GraphPad Prism software; GraphPad, San Diego, CA).

Results

PD-1 expression on activated virus-specific CD8+ T cells during acute FV infection

Because Takamura et al. (18) showed upregulation of the PD-1 inhibitory molecule already at 2 wk post-FV infection, we first sought to replicate this finding and determine the kinetics of PD-1 expression on activated CD8+ T cells throughout the course of FV infection. Fig. 1A shows a representative dot plot of activated (CD43+) CD8+ T cells from mice infected with FV for 10 d, which demonstrates the gating strategy for PD-1hi and PD-1lo cells. The expression of PD-1 strongly correlated with the activation status of the cells (Fig. 1B). Kinetic analysis revealed that the proportion of PD-1hi cells was already increased at 7 d postinfection (dpi) and remained elevated during both the expansion and contraction phases of the CD8+ T cell response. At the peak of the CD8+ T cell response at 10 dpi, >80% of the activated CD8+ T cells were PD-1hi (Fig. 1C). PD-1 expression on the immunodominant subset of tetramer-positive CD8+ T cells [specific for the immunodominant H-2Dd–restricted F-MuLV glycosylated gag epitope (24, 25)] was similar to the overall population of activated CD8+ T cells (Fig. 1D).

Phenotypic characteristics of PD-1hi and PD-1lo CD8+ T cells during acute FV infection

Both the PD-1hi and PD-1lo subsets were analyzed by multiparameter flow cytometry to determine if other phenotypic differences distinguished them. Splenocytes from mice at peak expansion (10 dpi) were gated on CD8+CD43PD-1hi or PD-1lo cells and analyzed for the expression of characteristic CD8+ T cell markers. Both subsets expressed similar levels of the effector cell marker CD44 (hyaluronic acid receptor) and downregulated CD62L (L-selectin). The PD-1lo subset displayed the phenotype of short-lived effector cells (27) with increased expression of CD122 (IL-2 receptor) but decreased CD127 (IL-7R) expression (Fig. 2). As expected for short-lived effectors, they also downregulated the antiapoptotic protein Bcl-2 (28) (Fig. 2). Analysis of the PD-1hi CD8+ T cells revealed a small subset with increased expression of CD127 and/or BCL-2 (Fig. 2). Dual staining showed that a proportion of the PD-1hiCD8+ T cells were double positive for CD127 and Bcl-2 (Fig. 2), characteristic of memory precursor effector cells, which are important for the development of effector and central memory cells (29). As shown by Takamura et al. (18), PD-1hiCD8+ T cells were also positive for the inhibitory receptor Lag-3 (Fig. 2). Expression of inhibitory receptors BTLA, 2B4 (6), and Tim-3 (18) was also observed. In contrast, PD-1hi were predominantly low for Lag-3, BTLA, 2B4, and Tim-3.

Functional properties of PD-1hi and PD-1lo CD8+ T cells during acute FV infection

To analyze whether PD-1hi and PD-1lo effector T cells had different functional properties during acute FV infection, the production of cytokines, cytotoxic molecules, and surface expression of the degranulation marker CD107a (30, 31) were analyzed. At 10 dpi, the mean percentage of PD-1hiCD43+CD8+ T cells that produced the cytokines IFN-γ, TNF-α, or IL-2 was significantly higher than that of PD-1hi cells (Fig. 3A). Because CD8+ T cells producing multiple cytokines have been uniquely associated with
nonprogression in HIV infection (32), we measured the number of cytokines produced by individual T cells of the PD-1hi versus PD-1lo T cell population. Fig. 3B shows that PD-1hi cells were more effective in producing multiple cytokines than PD-1lo cells. To analyze the cytokotoxic potential of the subpopulations, intracellular expression of the granzymes A and B and surface expression of the degranulation marker CD107a was measured. Although most of the PD-1lo cells produced cytokines, only a small percentage of them expressed granzymes or CD107a (Fig. 3C). In contrast, approximately half of the PD-1hi cells were positive for markers associated with cytotoxicity. Analysis of CD107a expression in the PD-1hi and PD-1lo subsets of tetramer+ virus-specific CD8+ T cells produced similar results as the general population of activated CD8+ T cells (Fig. 3D). In absolute numbers per spleen, these percentages calculated to \( \sim 3 \times 10^6 \) tetramer+ cells of the PD-1hi subset expressing CD107a compared with \(<10^5\) cells of the PD-1lo subset (data not shown). Thus, the direct ex vivo analysis of CD8+ T cells from acutely infected mice showed no evidence of exhaustion or dysfunction.

**Rapid in vivo killing during acute FV infection**

As the elimination of virus-infected cells is one of the most critical functions of CD8+ T cells, in vivo CTL assays were next performed at 10 dpi both in resistant C57BL/6 (H-2b/b) mice and more susceptible Y10.A mice. Splenocytes loaded with the same viral peptide recognized by tetramer+CD8+ T cells were injected i.v. into FV-infected or noninfected mice. In infected C57BL/6 mice, an average of 63% of peptide-loaded target cells were eliminated within 2 h, with equivalent killing in Y10.A mice (Fig. 3E). This rapid killing demonstrated the high cytotoxic activity of CD8+ T cells during acute FV infection. These data indicate potent antiviral effector functions of CD8+ T cells inconsistent with premature exhaustion and dysfunction.

**Blocking the PD-1/PD-L1 and Tim-3 pathways during acute FV infection**

Although several studies have shown that blockade of PD-1 signaling by treatment with anti–PD-L1 Abs during chronic infections can reactivate exhausted CD8+ T cells to reduce chronic viral loads, studies on acute infections are limited and somewhat contradictory (17). To determine the effects of PD-1/PD-L1 signaling blockade during acute FV infection, Y10 mice were treated with anti–PD-L1 blocking Ab during the first 10 d of infection. No significant increase of the mean percentage of virus-specific (tetramer+) CD8+ T cells was found compared with acutely infected mice that were treated with an irrelevant isotype control Ab (Fig. 4A). Functional analysis of the tetramer+CD8+ T cells also revealed no effects on either granzyme B expression (Fig. 4B) or CD107a expression (Fig. 4C). Finally, in two independent in vivo CTL experiments, mice treated with control Ab showed >90% killing and anti–PD-L1 blockade produced no significant enhancement of killing (Fig. 4D). Furthermore, anti–PD-L1 blockade produced no reduction in spleen virus levels (black bar, Fig. 4E). Thus, blocking the PD-1–PD-L1 pathway during acute FV infection...
produced no significant enhancement of CD8 responses. Because no effect on CTL killing or infection levels was observed from PD-L1 blockade, we wanted to analyze the effect of a combined blockage of two inhibitory receptors during acute FV infection. Takamura et al. (18) found that PD-1 signaling blockade combined with blockade of Tim-3 produced a pronounced effect on virus levels. We also observed a significant reduction in spleen virus titers when PD-L1 blockade was combined with Tim-3 blockade (light gray bar, Fig. 4E), but it was not as dramatic as reported by Takamura et al. (18). Dual blockade did not significantly increase in vivo CTL killing (data not shown), but again, that is likely because killing was already 90% without therapeutic intervention. Interestingly, Tim-3 blockade by itself resulted in paradoxically increased spleen virus titers, suggesting that it might play a positive role in anti-FV immunity in the presence of intact PD-1 signaling. Contrasting roles for Tim-3 in regulating immune responses have previously been reported, predominantly affecting type 1 Th responses (33). These results suggest that some negative signaling of immune responses occurs during acute FV infection, but that it requires more than one signal and does not induce premature exhaustion of CD8+ T cells.

CD8+ T cell depletion abrogates acute virus control

Ultimately, the functionality of the CD8+ T cell response during acute FV infection is measured by its ability to control virus replication in vivo. Y10 mice were depleted of CD8+ T cells, infected with FV, and spleen virus titers were measured at 7 and 14 dpi. At 7 dpi, CD8-depleted mice had an approximately half log_{10} increase in spleen virus titers (Fig. 5A). By 14 dpi, when most CD8-depleted mice were recovering from acute infection, virus titers remained very high in the CD8-depleted mice (Fig. 5B). Thus, CD8+ T cells not only displayed numerous hallmarks of functionality directly ex vivo and mediated rapid killing of CTL targets but also were absolutely critical for recovery from acute FV infection.

Discussion

The current studies provide convincing evidence that the CD8+ T cell response to FV infection is not only vigorous and effective, but is also critical for virus control. As in the Takamura et al. (18) study, we found that expression of PD-1 was increased in a large proportion of effector CD8+ T cells during acute FV infection. However, in contrast to their results from in vitro restimulation experiments, which they interpreted as premature exhaustion of the PD-1^{hi} CD8+ T cells, our in vivo and direct ex vivo studies showed high cytolytic potential of PD-1–expressing CD8+ T cells and rapid in vivo killing of viral peptide-loaded targets. Interestingly, the function of the activated CD8+ T cells in terms of cytokine production versus cytotoxic potential corresponded to relative PD-1 expression levels. For example, Fig. 3 shows that approximately half of the activated PD-1^{lo} CD8+ T cells expressed granzymes and the degranulation marker CD107a. These results and the phenotypic analysis shown in Fig. 2 strongly suggest that the minor PD-1^{lo} subset was a potent producer of cytokines and contained a significant proportion of effector memory precursors, whereas the PD-1^{hi}CD8+ T cells were terminally differentiated effector cells that were the main mediators of cytotoxic activity during acute FV infection. This lytic activity was clearly demonstrated in in vivo CTL assays using target cells...
labeled with the same FV epitope peptide that we and Takamura et al. (18) used to detect virus-specific CD8+ T cells. Rapid and efficient FV-specific killing was detected in both FV-resistant C57BL/6 and FV-susceptible Y10.A mice, indicating that CD8+ T cell cytotoxicity was not influenced by the Fv-2 genetic background of mice, as had been discussed in two letters to the Journal of Immunology (34). The results from the in vivo CTL assays also indicate that high expression of granzyme B is not, as suggested by Takamura et al. (18), an indicator of excessive T cell activation and exhaustion, but an indicator of cytolytic potential. In fact, it is the loss of granzyme expression that has been defined as a hallmark of CD8+ T cell exhaustion (reviewed in Refs. 3, 35).

Although PD-1 has been defined as a major inhibitory molecule on exhausted CD8+ T cells during chronic infections, and blockade of the PD-1 signaling pathway can revitalize exhausted cells, the mere upregulation of PD-1 and other inhibitory receptors on CD8+ T cells did not correlate with an exhausted phenotype during acute infection. This finding is consistent with recent studies supporting the notion that the effect of PD-1 signaling varies between acute immunological responses and situations of chronic Ag exposure (36). Although PD-1 signaling may indeed provide an inhibitory signal, the biological effect is dependent on the overall strength of that signal in the context of other signals in the cell, both positive and negative. A comparable system of activating and inhibitory receptors controls the function of NK cells (37). During acute infections, the combination of strong TCR signaling, costimulation, and cytokine signaling may outweigh the inhibitory effects of PD-1 on CD8+ T cells. As the infection is brought under control, the signaling milieu changes from overall positive to negative, such that the response contracts to prevent overwhelming cytotoxic CD8+ T cell activity that could cause severe immunopathology. This is in line with our current results showing that blockade of either PD-1 and Tim-3 alone did not improve CD8+ T cell function, but blocking both at the same time resulted in a significant reduction in acute FV viral loads (Fig. 4). Similar findings have been made by other groups (6), suggesting a requirement for an orchestrated inhibitory signaling machinery composed of multiple receptors to suppress T cell responses. Such a system should ensure that effector CD8+ T cells have enough time to control pathogens before they are shut down in their activity.
However, our PD-1 and Tim-3 blocking experiments indicate that although CD8+ T cells expressing these receptors mediate vigorous virus-specific cytotoxic responses during acute FV infection, some degree of inhibition is already initiated during this phase. For some viruses, the immune system is not able to completely clear the infection and transition to chronic infection occurs. After chronic infection has been established, signaling through inhibitory receptors sustains and contributes to the progressive functional exhaustion of the remaining effector CD8+ T cells (38). Thus, inhibitory receptors, like PD-1, are excellent markers for the identification and tracking of exhausted T cells during the course of many chronic infections (3, 12, 39) but do not identify dysfunctional T cells during acute infections (7, 8, 14, 15). In addition, in healthy adult humans, most PD-1hiCD8+ T cells are effector memory cells rather than exhausted cells (40). During chronic FV infection, virus-specific CD8+ T cells do develop functional exhaustion, which is associated with loss of granzymes, CD107a surface expression, and undetectable target cell killing in the in vivo CTL assay (41). We previously showed that this exhaustion is in large part mediated by regulatory T cells, which suppress the proliferation and function of virus-specific CD8+ T cells.

Taken together, our current results from ex vivo and in vivo experiments preclude premature exhaustion of CD8+ T cells during acute FV infection. This is also strongly supported by several CD8+ T cell-depletion studies, which show that CD8+ T cells are absolutely critical to control initial FV replication and disease progression in FV-resistant as well as FV-susceptible mouse strains (Fig. 5) (42).

FIGURE 4. Inhibitory signal blockade during acute FV infection. Y10 mice were treated with blocking Abs at the time of infection and every other day for a total of five injections. A, CD8+ splenocytes from naive mice (gray bar) or mice treated with anti–PD-L1 (black bars) or isotype-matched control IgG (white bars) at 10 dpi were analyzed by flow cytometry for FVgagL tetramer binding. Gated CD8+ tetramer+ T cells were analyzed for intracellular expression of granzyme B (B) and surface expression of CD107a (C). Bars depict the mean fluorescence intensity (MFI). D, An in vivo cytotoxicity assay was performed using adoptive transfer of CellTrace Violet-labeled control splenocytes and CFSE-labeled FVgagL peptide-loaded targets into the anti–PD-L1 or control IgG-treated mice at 10 dpi. Two hours after transfer, the spleens were analyzed by flow cytometry for the percentage of target cell killing. Data are combined from two independent experiments with similar results, and mean values with SD are shown (n = 8 mice/group). E, Spleen infectious centers at 10 dpi from mice treated as indicated. All columns of data were compared with the Ig control using a one-way ANOVA with Tukey’s posttest. All columns were significantly different (p < 0.0001) except the control versus anti–PD-L1 (n = 8 for the control and anti–PD-L1 groups and n = 4 for anti–Tim-3 and dual treatment groups).

FIGURE 5. CD8+ T cell depletion during acute FV infection. Y10 mice were depleted of CD8+ T cells as described in the Materials and Methods section and remained depleted to <1% of splenocytes through 14 dpi. Data on viral loads are combined from two separate experiments. The dotted line represents the detection limit of the assay. A, Infectious centers at 7 dpi. Differences between the groups were statistically significant (p = 0.0192). B, Infectious centers at 14 dpi. Differences between the groups were statistically significant (p < 0.0001).
receptors, indicating that this suppressive pathway does not seem to play a major role in their control. Hence, inhibitory receptors may be predominantly associated with the control of the cytotoxic function of effector CD8+ T cells. Also of import, a significant proportion of the activated CD154+ CD8+ T cells did not have the phenotype of short-lived terminally differentiated effector cells, but had phenotypic markers indicative of effector memory precursor cells, a population of long-lived effector cells that develop into central or effector memory T cells (29). This finding implies that memory precursor T cells do not upregulate inhibitory receptors during acute infections, most likely because their effector functions are not associated with severe immunopathology, and their survival is critical for the establishment of immunological memory. This is in line with a recent report showing that defects in PD-1 signaling result in enhanced central memory CD8+ T cell responses after an acute vaccinia virus infection (44). Thus, blocking the PD-1/PD-L1 pathway during vaccination against virus infections as well as new treatments for acute infections.

Disclosures
The authors have no financial conflicts of interest.

References

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