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OX40 Drives Protective Vaccinia Virus-Specific CD8 T Cells\textsuperscript{1,2}

Shahram Salek-Ardakani,\textsuperscript{3*} Magdalini Moutaftsi,\textsuperscript{†} Shane Crotty,\textsuperscript{†} Alessandro Sette,\textsuperscript{†} and Michael Croft\textsuperscript{3*}

Vaccinia virus (VACV) affords long-lasting protection against variola virus, the agent of smallpox. VACV-reactive CD8 T cells contribute to protection but their molecular control is unknown. We show that the TNFR molecule OX40 (CD134) controls primary VACV-specific CD8 T cell expansion and antiviral cytokine production and dictates development of strong memory to both dominant and subdominant VACV epitopes. Using adoptive transfer of OX40-deficient CD8 TCR-transgenic T cells responding to Ag in the context of VACV infection, we found that this reflects a direct action of OX40 expressed by CD8 T cells. Furthermore, CD8 T cells that can protect against lethal VACV challenge do not develop in mice deficient in OX40. Thus, OX40, which has been found to play little if any role in the generation of CD8 T cells to several viruses, including lymphocytic choriomeningitis virus and influenza, plays a dominant role in shaping the CD8 T cell response to VACV. These data suggest that unique costimulatory pathways might control alternate antiviral CD8 responses, demonstrating the plasticity of the immune response in utilizing different mechanisms to achieve similar ultimate goals. The Journal of Immunology, 2008, 181: 7969–7976.

The CD8 T cells play an important role in controlling many viral infections and are elicited by live viral vaccines. As such, it is important to understand how CD8 cells reactive to different antigenic viral peptides become primed. Although a brief encounter (7–20 h) with Ag is sufficient to lead to proliferation of CD8 cells and a level of differentiation, increasing the duration of antigenic stimulation is necessary for strong clonal expansion, survival, and full reactivity (1–4). This suggests an important role for signals other than peptide recognition.

Two types of costimulatory signals might be considered as potentially contributing to the development of virus-specific CD8 T cells. One, the interaction of receptors on the surface of T cells with membrane-bound ligands on APCs. The other, signals from proinflammatory cytokines elicited in response to infection. The importance of membrane-bound receptor-ligand interactions to T cell priming has been strongly documented in studies of CD4 cells examining the requirement for Ig superfamily members such as CD28-B7 and TNFR/TNF superfamily members such as OX40-OX40L (5, 6). More recent studies in simple model systems have also suggested that such interactions can control aspects of the response of CD8 T cells (7–11). However, in terms of antiviral responses, an argument has been put forward that proinflammatory cytokines (12), typified by type I IFNs (IFN-I),\textsuperscript{4} might represent a dominant stimulus controlling development of virus-specific CD8 populations (13, 14). In this regard, reports have shown that IFN-\textalpha/\beta receptor-deficient CD8 T cells specific for lymphocytic choriomeningitis virus (LCMV) exhibit a severe defect in their ability to expand and generate functional memory populations after infection (13, 14). Moreover, extensive data with LCMV, as well as several other model viruses such as influenza, vesicular stomatitis virus, and mouse CMV, have revealed lesser or no roles for molecules like CD28 (15–17) and OX40 (7, 18, 19) in controlling initial priming of naive virus-specific CD8 cells. This has contributed to the conclusion that there are times where the latter more classical costimulatory molecules are not strong determinants of primary immunity and raises the issue of whether all virus-specific immune responses are controlled by similar molecular mechanisms.

Vaccinia virus (VACV) is a large DNA virus and is a member of the genus Orthopoxvirus, which includes variola, monkeypox, buffalopox, and cowpox. Variola, the etiological agent of smallpox, was responsible for significant morbidity and mortality in humans (20). Large-scale vaccination with live VACV proved extremely effective at protecting humans against variola and this led to the worldwide eradication of smallpox disease (20). In humans, immunization with VACV elicits a robust CD8 T cell response (21). Notably, recent analysis of cohorts of smallpox vaccine recipients demonstrated that the VACV-specific memory CD8 T cell pool is long-lived, with a half-life of 8–12 years (21–23). In mice, the Western Reserve strain of VACV (VACV-WR) results in an acute infection that also elicits strong development of CD8 T cell response (21). At the peak of the effector phase, >20% of CD8 T cells are specific for VACV (24, 25). These then contract in number, stabilize by day 30 as...
a memory population, and are maintained for >300 days postinfection (24). Thus, in many respects, VACV elicits CD8 T cells highly analogous to other viruses such as LCMV and influenza. However, there is little information on the molecules that generate protective pools of anti-VACV CD8 T cells. Furthermore, the lack of defined peptide epitopes recognized by VACV has hampered in depth studies of this virus. The recent identification of epitopes that account for nearly the entire anti-VACV CD8 pool (26, 27) has provided a unique opportunity to examine for the costimulatory requirement of anti-VACV CD8 T cells with different specificities.

In this study, we show that the TNFR family member OX40 is critical for the magnitude of primary CD8 T cell responses to both dominant and subdominant VACV epitopes, including expansion and antiviral cytokine production, and OX40 also strongly impacts the generation of memory cells. Moreover, CD8 T cells that can protect against lethal VACV challenge do not develop in mice deficient in OX40. Thus, OX40, which has been found to play little if any role in the generation of CD8 T cells to several viruses, including LCMV and influenza, plays a critical role in shaping the CD8 T cell response to VACV.

Materials and Methods

Mice

The studies reported here conform to the Animal Welfare Act and the National Institutes of Health guidelines for the care and use of animals in biomedical research. All experiments were done in compliance with the regulations of the La Jolla Institute Animal Care Committee in accordance with the guidelines by the Association for Assessment and Accreditation of Laboratory Animal Care. Eight- to 12-wk-old female and male C57BL/6 mice were purchased from The Jackson Laboratory. OT-I TCR-transgenic mice were generated in-house by crossing OT-I cells responsive to OVA-derived SIINFEKL peptide. OX40-deficient mice. Thus, OX40, which has been found to play little if any role in the generation of CD8 T cells to several viruses, including LCMV and influenza, plays a critical role in shaping the CD8 T cell response to VACV.

Peptides and tetratomers

VACV peptide epitopes used in this study were predicted and synthesized as described previously (26, 27). B8R (20–27; TSYKFESV), A3L (270–276; KSYNYMILL), A8R (189–196; ITYFYLFL), B2R (54–62; YSQVNKRYI), A23R (297–305; IGMFNLTFI). MHC/peptide tetramers for the VACV-WR epitope B8R (20–27; TSYKFESV)/H-2Kb, which were conjugated to allophycocyanin, were obtained from the National Institutes of Health Tetramer Core facility (Emory University, Atlanta, GA).

Viruses

The VACV-WR strain was purchased from the American Type Culture Collection, grown in HeLa cells, and titered on VeroE6 cells (28).

Immunization protocols

For most experiments, mice were infected i.p. with VACV-WR (2 × 10^5 PFU/mouse). For dermal scarification, mice (10 μl) was deposited at the base of the tail and the skin at the site of the droplet was scarified 25–30 times with a 25-gauge needle. After 3–4 days, pusles or scabs were observed at the scarification site, indicating a localized VACV infection. Effector responses were analyzed between days 4 and 15 postinfection, while memory responses were analyzed 30 or more days after infection, after restimulating in vitro with VACV peptides.

For adoptive transfer experiments, 1 × 10^6 naive wild-type (WT) or OX40−/− OT-I CD8 T cells were transferred into WT nontransgenic B6 or OX40−/− mice. One day later, mice were infected i.p. with recombinant VACV expressing full-length OVA protein (VACV-OVA; 2 × 10^6 PFU/mouse) or PBS as indicated. OT-I expansion and memory formation were detected by FACs staining of transgenic TCR α- and β-chains after gating on CD8 T-cell and in some cases after restimulating in vitro with OVA (SIINFEKL) peptide.

VACV intranasal challenge

Mice were anesthetized by inhalation of isoflurane and inoculated by the intranasal route with 3.5 × 10^6 of VACV-WR. Mice were weighed daily for 2 wk following challenge and were euthanized when they lost 25% of their initial body weight. For protection experiments, mice were immunized s.c. at the base of the tail once with either 10 or 2 μg/mouse of CD8 VACV expressing full-length OVA protein (VACV-OVA; 2 × 10^6 PFU/mouse) or PBS as indicated. OT-I expansion and memory formation were detected by FACs staining of transgenic TCR α- and β-chains after gating on CD8 T cells and in some cases after restimulating in vitro with OVA (SIINFEKL) peptide.

FIGURE 1. Intact activation but reduced early accumulation of VACV-specific CD8 T cells in OX40-deficient mice. a, WT mice were infected i.p. with VACV-WR (2 × 10^5 PFU/mouse). On indicated days, postinfection splenocytes were harvested and stained for CD8, B8R tetramer, and OX40. Top panel, Percentage of CD44^{high} expressing B8R-specific CD8 T cells in OX40−/− mice infected i.p. with VACV-WR (2 × 10^5 PFU/mouse). On day 4, splenocytes were stained with CD8 plus CD44 and B8R tetramer. Representative plots of tetramer staining gating on CD8 cells. Percentages of activated B8R tetramer-positive CD8 T cells (CD8^+ CD44^{high} B8R^{+}) and naive cells (CD8^+ CD44^{low} ) are indicated. b, WT or OX40-deficient (OX40−/−) mice were infected i.p. with VACV-WR (2 × 10^5 PFU/mouse). On day 4, splenocytes were stained with CD8 plus CD44 and B8R tetramer. Representative plots of tetramer staining gating on CD8 cells. Percentages of activated B8R tetramer-positive CD8 T cells (CD8^+ CD44^{high} B8R^{+}) and naive cells (CD8^+ CD44^{low} ) are indicated. c, Mice were infected as above. At day 4, CD8 T-cell activation was assessed by up-regulation of CD69 and CD127, and down-regulation of CD62L and CD127 on B8R tetramer-positive cells (left panel). Naive (CD44^{low} B8R tetramer-negative) CD8 T cells were used as controls. Percentages that stained positive for each marker are indicated.
Results

OX40 controls the magnitude of expansion of CD8 T cells to VACV

Our recent data assessing reactivity to a tumor-derived Ag or a replication defective adenovirus have highlighted that OX40-OX40L interactions can play significant roles in certain CD8 responses (9, 10). Therefore, we examined the requirement for OX40 in primary expansion and effector function of VACV-specific CD8 T cells. Initially, the immunodominant VACV-reactive CD8 T cell population was tracked with a tetramer of a peptide of B8R (26, 27). OX40 was seen on a proportion of B8R tetramer-reactive CD8 T cells at day 4 postinfection with VACV-WR, and peaked at day 5 (Fig. 1a). Whereas B8R-specific CD8 T cells expanded well over 4 days in WT mice, defective accumulation was already evident in mice deficient in OX40 (Fig. 1b). This was not due to impaired activation of CD8 T cells in that CD69, CD25, and CD43 were similarly elevated in OX40−/− mice (Fig. 1c). Down-regulation of CD62L and CD127 was also not different (Fig. 1c). Both percentages and total numbers of B8R-reactive cells (CD62L high and CD62L low) were strongly reduced at the peak of the primary response at day 7 in OX40−/− mice (Fig. 2), and B8R-specific CD8 T cells that made IFN-γ or both IFN-γ and TNF, were reduced by 60–80% (Fig. 2), supporting our prior data that OX40 regulates division and survival of T cells (9–11, 19). Similar results were found for CD8 T cells responding to a range of subdominant VACV epitopes, which was not explained by delayed kinetics of expansion (Fig. 3). Impaired CD8 priming in the absence of OX40 was also observed with VACV given via dermal scarification, mimicking the route of vaccination against smallpox (data not shown). Thus, OX40 plays an important role in generating large pools of primary VACV-specific effector CD8 T cells.

Impaired generation of memory CD8 T cells in the absence of OX40

Next, we assessed the impact of OX40 deficiency on the generation of memory. Forty days postinfection, VACV-infected WT mice contained high frequencies of memory CD8 T cells specific for all epitopes examined, regardless of whether infection was i.p.
On days 4 (a), 7 (b), and 15 (c) after infection, IFN-γ-secreting CD8 cells were assessed by intracellular cytokine staining after stimulation with VACV peptides as indicated. Data are either representative plots of IFN-γ staining in gated CD8+ CD62Llow T cells, with percent positive indicated, or total numbers ± SEM of CD8+ IFN-γ+ T cells per spleen from four individual mice. *, p < 0.05 (WT vs OX40−/−). Similar results were obtained in three separate experiments.

Defective priming of OX40-deficient CD8 T cells to VACV

Because OX40 is expressed on multiple cell types, we sought to show it was directly required by CD8 cells responding to VACV infection. OVA-specific OX40-deficient CD8 cells from OT-I TCR-transgenic mice were transferred into naive WT recipients subsequently infected with VACV-OVA. Strong expansion of WT OVA-specific CD8 cells was observed, similar to endogenous VACV-specific CD8 cells. In contrast, OX40-deficient CD8 cells poorly expanded to VACV-OVA (Fig. 5a).

Next, we compared the ability of WT and OX40−/− OT-I cells to divide early after VACV-OVA infection. CFSE-labeled WT or OX40−/− T cells were transferred into B6 mice and then 1 day later mice were infected with VACV-OVA or PBS as control. Without infection, similar CFSEhi Vα2Vβ5 populations of WT and OX40−/− T cells were detected (Fig. 5b). Seventy-two hours after infection, both WT and OX40−/− T cells had undergone comparable division as indicated by a reduction in CFSE staining intensity. Thus, direct OX40 signaling in CD8 T cells was not essential for induction of T cell division but was crucial for T cell survival after VACV infection. Consistent with this, in mice receiving OX40−/− T cells, significantly fewer memory cells were generated after the resolution of infection (Fig. 5c). This closely mimicked the data analyzing endogenous VACV-specific CD8 T cells in OX40−/− mice infected with VACV-WR (Figs. 3 and 4). To exclude that OX40 expression on a non-T cell population contributed to the defect observed in OX40−/− mice, we performed the reverse experiment. VACV-OVA-induced strong expansion of WT OVA-reactive IFN-γ-producing CD8 cells regardless of whether they were transferred into OX40−/− or WT mice (Fig. 5d). Thus, OX40-expressed on a CD8 T cell is required for expansion of effector cells and formation of a large population of memory cells during infection with VACV.

FIGURE 3. OX40 is required for optimal generation of effector CD8 T cells directed against dominant and subdominant VACV epitopes. WT or OX40−/− mice were infected i.p. with VACV-WR (2 × 10⁶ PFU/mouse). On days 4 (a), 7 (b), and 15 (c) after infection, IFN-γ-secreting CD8 cells were assessed by intracellular cytokine staining after stimulation with VACV peptides as indicated. Data are either representative plots of IFN-γ staining in gated CD8+ CD62Llow T cells, with percent positive indicated, or total numbers ± SEM of CD8+ IFN-γ+ T cells per spleen from four individual mice. *, p < 0.05 (WT vs OX40−/−). Similar results were obtained in three separate experiments.

FIGURE 4. Impaired generation of CD8 memory cells to both dominant and subdominant VACV epitopes in OX40-deficient mice. Groups of C57BL/6 WT or OX40-deficient (OX40−/−) mice were infected i.p. (a) or by dermal scarification (b) with VACV-WR (2 × 10⁷ PFU/mouse). At day 40, splenocytes were stimulated with VACV peptides as indicated and CD8 T cell priming was assessed by intracellular IFN-γ staining. Top, Representative plots of IFN-γ staining in gated CD8 T cells. Percent positive indicated. Bottom, Total numbers of CD8+ IFN-γ+ cells per spleen. Results are mean number ± SEM (n = 4 mice/group) from one experiment. *, p < 0.05 (WT mice vs knockout) as determined by Student’s t test. Similar results were obtained in three separate experiments.
OX40 controls development of CD8 cells that protect against lethal VACV infection

Analysis of VACV-WR titers in the ovaries and spleen did not reveal any significant difference in the kinetics of primary clearance in WT vs OX40−/− mice (Fig. 6). Together with results indicating that depletion of CD8 T cells has no major effect on initial viral titers (25), this suggested that enhanced development of VACV-reactive CD8 T cell populations controlled by OX40 might be relevant for protection against subsequent exposure to virus. Because Ab can protect against VACV, we chose a model where CD8 T cell activity can be separated from Ab-mediated protection. After intranasal infection with VACV-WR, naive mice exhibited weight loss and death within 6–9 days (31, 32), and memory CD8 T cells induced by peptide vaccination can afford protection in this model (26, 33). Mice were therefore immunized with a high dose of the immunodominant peptide B8R20–27, given in IFA, and challenged 3 wk later with a lethal intranasal dose of VACV-WR (Fig. 7). An average of 90% of immunized WT mice survived the infection (Fig. 7b). Weight loss (15–20%) was seen in these mice, suggesting that they were not fully immune (Fig. 7b), but protection was dependent on CD8 T cells since their depletion before challenge resulted in 100% mortality (Fig. 7c). Most significantly, when OX40−/− mice were immunized, no protection was evident and all succumbed to the infection (Fig. 7b). Far fewer B8R-specific memory CD8 T cells were present in the lungs of OX40−/− mice after immunization (Fig. 7, d and e; day 0) and far fewer accumulated after VACV infection (Fig. 7, d and e; day 5), suggesting the extent of protection was directly related to the number of VACV-specific CD8 T cells. In WT mice, immunization with a low dose of B8R20–27 (2 μg) peptide resulted in significantly fewer memory CD8 T cells (0.061 × 10^5 cells/lung) that were generated in the lungs compared with immunization with 10 μg (0.168 × 10^5 cells/lung; Table I), but comparable to

**FIGURE 5.** OX40 is required directly by CD8 T cells responding to VACV infection. CFSE-labeled naive WT or OX40−/− OT-I CD8 T cells were adoptively transferred into WT B6 (a–c) or OX40−/− (d) mice. One day later, mice were infected i.p. with recombinant VACV expressing full-length OVA (VACV-OVA; 2 × 10^6 PFU/mouse) or PBS as indicated. After 8 (a and d), 3 (b), or 30 (c) days, CD8 T cell expansion (a and d), division as measured by CFSE dilution (b), and memory formation (c) were analyzed by tracking the transgenic TCR. Dot plots, Representative costaining for Vα2 and Vβ5 after gating on CD8 cells. Percent positive indicated. Bottom, Total numbers of CD8+Vα2+Vβ5+ cells (a–d) or CD8+Vα2−Vβ5− IFN-γ+ cells (d) per spleen. Histograms, Cell division of WT and OX40−/− CD8 T cells was analyzed on gated CD8+Vα2+Vβ5+ cells 72 h after infection with VACV-OVA. Results are mean number ± SEM (n = 4 mice/group) from one experiment. *, p < 0.05 (WT mice vs knockout) as determined by Student’s t test. Similar results were obtained in one additional experiment.

**FIGURE 6.** OX40-deficient mice clear primary vaccinia infection with similar kinetics compared with WT mice. WT or OX40−/− mice were infected i.p. with VACV-WR (2 × 10^6 PFU/mouse). On the indicated days postinfection, ovaries were removed and VACV-titers were determined as described in Materials and Methods.
that seen when OX40−/− mice (0.016 × 10^5) were immunized with 10 μg of B8R peptide (Table I). Again, the extent of protection (20% vs 90%) directly correlated with the number of IFN-γ-producing B8R-specific memory CD8 cells that were generated before challenge (Table I). Thus, the use of OX40 by naive VACV-specific CD8 T cells dictates the frequency of protective VACV-specific memory CD8 T cells that are elicited.

Table I. Frequency of B8R-specific CD8 T cells in the lung before challenge correlates with degree of protection against lethal VACV infection

<table>
<thead>
<tr>
<th>Mice</th>
<th>B8R peptide (μg/mouse)</th>
<th>No. of CD8⁺ IFN-γ⁺ (×10^5 cells/lung)</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT (n = 30)</td>
<td>10</td>
<td>0.168 ± 0.006</td>
<td>2.61 ± 0.06</td>
</tr>
<tr>
<td>WT</td>
<td>2</td>
<td>0.061 ± 0.005</td>
<td>0.88 ± 0.03</td>
</tr>
<tr>
<td>OX40−/−</td>
<td>10</td>
<td>0.016 ± 0.002</td>
<td>1.184 ± 0.08</td>
</tr>
</tbody>
</table>

*WT or OX40−/− mice were immunized s.c. at the base of the tail with 10 μg of B8R peptide in IFA. Control groups received adjuvant but no peptide (PBS). Three weeks after vaccination, mice were infected intranasally with a lethal dose of VACV-WR (3.5 × 10^6 PFU/mouse). Animals were weighed daily and euthanized if weight loss was ≥25% body weight. %, Mean percent survival and percentage of initial body weight from the indicated numbers of mice. Mean weight data in some cases were not plotted beyond the point at which mice died and beyond day 7 reflected only mice that survived infection. As indicated, groups of WT mice were depleted of CD4 (anti-CD4) or CD8 (anti-CD8) T cells before intranasal VACV challenge (day 0) and after challenge (day 5). Results are mean number ± SEM (n = 4 mice/group) from one experiment.

Discussion

Numerous spatially and temporally regulated interactions might exist between receptors on the surface of CD8 cells and their soluble or membrane-bound ligands. Defining the precise nature of these molecular interactions during different viral infections is of great interest and may allow us to understand how to augment antiviral immunity. In this study, we provide evidence of the importance of OX40-OX40L interactions to the generation of protective CD8 T cells reactive with VACV. Data from OX40−/− and OX40 ligand (OX40L)−/− mice have shown that these molecules play little to no role in primary CD8 T cell responses to LCMV, vesicular stomatitis virus, influenza, and mouse CMV (7, 18, 19, 34). With VACV, our results highlight a previously unappreciated role for OX40 in initial antiviral immunity. We show that OX40 can strongly influence the response of VACV-specific CD8 T cells and dictates the absolute numbers of effector T cells that accumulate. Furthermore, OX40 is necessary for the generation of large populations of memory cells to dominant and subdominant VACV MHC class I epitopes. Thus, the capacity of naive CD8 T cells to bypass a requirement for OX40 signaling is not a property of all viruses, and OX40 dependence likely reflects differences related to the rate of viral replication, antigenic load, cell tropism, and perhaps the specific cytokine milieu induced in response to each virus.

Targets of OX40 are the antiapoptotic proteins of the Bcl-2 family, such as Bcl-xL, Bfl-1, and Bcl-2, which are increased after...
OX40 ligation and correspondingly decreased in T cells that cannot express OX40 (6, 9, 35, 36). Additionally, OX40 might simultaneously exert suppressive effects on expression or activity of proapoptotic proteins such as Bad and Bim (36). More recently, survivin (an inhibitor of apoptosis family protein) was shown to be weakly expressed in the absence of OX40 and to control cell cycle progression and coincident apoptosis (37). Therefore, the simplest model, which is supported by our results, is that OX40 signals are required for late proliferation and survival of CD8 T cells when VACV Ag is encountered. Without these signals many of the responding T cells will die, rather than expand and survive to form the high frequency pools of effector and memory cells. Interestingly, this exact function was also proposed for IFN-I during LCMV responses (13, 14), further substantiating the idea of molecular plasticity in using alternate receptors for similar functions in different situations. Like OX40 (36), IFN-I has been reported to promote cell survival by activating PI3K and Akt (38). In contrast, IFN-I-induced survival in T cells was suggested to be independent of Bcl-2 and Bcl-xL, antiapoptotic proteins (39), raising the intriguing idea that similar functional outcomes in CD8 T cells could be mediated through alternate signaling pathways.

An important observation is that OX40 is strongly active in the development of CD8 T cells that protect against lethal VACV challenge. Extensive studies in the intranasal model of vaccinia infection have shown that passive immunotherapy with immune serum or mAbs are protective (28, 40–42). However, a role for infection have shown that passive immunotherapy with immune cells promoting cell survival by activating PI3K and Akt (38). In contrast, IFN-I-induced survival in T cells was suggested to be independent of Bcl-2 and Bcl-xL, antiapoptotic proteins (39), raising the intriguing idea that similar functional outcomes in CD8 T cells could be mediated through alternate signaling pathways.

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