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Requirement for CD70 in CD4⁺ Th Cell-Dependent and Innate Receptor-Mediated CD8⁺ T Cell Priming¹

Vadim Y. Taraban,* Tania F. Rowley,* David F. Tough,† and Aymen Al-Shamkhani²*

Dendritic cell (DC) conditioning by CD4⁺ T cells, or via engagement of innate receptors, is thought to be essential for CD8⁺ T cell priming. However, the molecular features that distinguish a conditioned DC from an unconditioned DC are poorly defined. In this study, we investigate the role of CD70, a member of the TNF superfamily that is expressed on activated DC, in CD4⁺ Th-dependent and -independent CD8⁺ T cell responses. We demonstrate that CD70 is required for CD4⁺ T cell-dependent priming of CD8⁺ T cells as well as priming mediated by the viral signature, dsRNA. Accordingly, mice that were subjected to CD70 blockade during the primary response fail to generate a memory CD8⁺ T cell response. Furthermore, we find that CD70 is dispensable for CD4⁺ T cell expansion and help for B cells, thus suggesting a direct role for CD70 in CD8⁺ T cell priming. Our results show that the innate and adaptive (CD4⁺ T cells) arms of the immune system use a common signaling pathway in driving CD8⁺ T cell responses and suggest that expression of CD70 on DC represents the hallmark of conditioned DC. The Journal of Immunology, 2006, 177: 2969–2975.

The priming of CD8⁺ T cells by cell-associated Ags, such as tumor Ags, is dependent on CD4⁺ T cell help (1). In contrast, most pathogens elicit primary CD8⁺ T cell responses independent of CD4⁺ T cell help (1, 2). Despite CD4⁺ T cell help being dispensable for CD8⁺ T cell priming during many infections, it remains essential for the generation of functional memory T cells (3–5). Previous studies have demonstrated that CD4⁺ Th-cell-dependent CD8⁺ T cell priming requires cognate interactions, in which both CD4⁺ and CD8⁺ T cells recognize Ag on the same APC (6), often a DC (3, 7, 8). Furthermore, helper-dependent CD8⁺ T cell priming was shown to be critically dependent on the interaction between CD40 and its ligand CD154 (9–11). This suggested that CD154-expressing CD4⁺ T cells transmit help via APC through CD40 signaling and led to the notion that CD40 signaling leads to APC activation, or conditioning, a prerequisite for CD8⁺ T cell priming. More recently, a number of studies have indicated the existence of a CD40-independent pathway of CD4⁺ T cell help for CD8⁺ T cells (12–14). Those studies demonstrated that, although essential, CD40 signaling alone did not fully replace the requirement for CD4⁺ T cells in the generation of effector CD8⁺ T cells in vivo. Although dendritic cell (DC)² conditioning by CD4⁺ T cells is now widely accepted, the molecular features that distinguish a conditioned DC from an unconditioned DC are poorly defined. There is considerable debate about the roles of CD80 and CD86 that are up-regulated on DC by CD40 signaling, in transmitting CD4⁺ T cell help for CD8⁺ T cell priming (9, 15–18). Interpretation of the data from those studies is difficult because CD80 and CD86 are required for CD4⁺ T cell responses (19) and studies conducted in CD4⁺ T cell-depleted mice used agonistic anti-CD40 mAb, which only partially replaces the requirement for CD4⁺ T cell help (13, 14). Besides the co-stimulatory Ig superfamily members CD80 and CD86, several members of the TNF superfamily have emerged as important regulators of T cell responses (20, 21). Recently, we showed that CD70, the ligand for the TNFR superfamily member CD27, is required for the generation of a robust CD8⁺ T cell response following immunization with soluble protein and agonistic anti-CD40 mAb (22). Furthermore, we and others demonstrated that CD40 signaling induces the expression of CD70 on bone marrow (BM)-derived DC (22, 23). Taken together, these results suggested that CD70 could play a role in mediating CD4⁺ T cell help for CD8⁺ T cell priming. In this study, we examine the requirement for CD70 in CD4⁺ Th-cell-dependent CD8⁺ T responses to cell-associated OVA. This form of immunization occurs by cross-priming on host DC and is dependent on cognate help from CD4⁺ T cells (6, 7). Because many infectious agents are capable of eliciting primary CD8⁺ T cell responses through direct activation of DC (9, 24–26) and in a CD4⁺ T cell-independent manner, we also asked whether CD70 is required in this setting. To generate a CD4⁺ Th cell-independent CD8⁺ T cell response, we immunized mice with cell-associated OVA in the presence of dsRNA, an intermediate in the replication cycle of many viruses and a potent stimulus of the innate immune response (27–30). This allowed us to compare the role of CD70 in helper-dependent and -independent CD8⁺ T cell priming under conditions of identical Ag dose and persistence. Our results demonstrate a critical role for CD70 in CD8⁺ T cell priming irrespective of whether DC conditioning is mediated by CD4⁺ T cells, or via innate receptor recognition of pathogen-associated molecular patterns (PAMP).

Materials and Methods

Abs, reagents, and cells

Anti-CD70 mAb (TAN 1.6, rat IgG2a), a nondepleting Ab that blocks the CD70-CD27 interaction, was described previously (22). Purified mAb against A31 lymphoma (Mc39-16, rat IgG2a) and BCL1 lymphoma (AT65, hamster IgG) Id (used as isotype-matched controls), CD4 (YTA

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3 Abbreviations used in this paper: DC, dendritic cell; BM, bone marrow; PAMP, pathogen-associated molecular pattern; poly(I:C), polyinosinic-polycytidylic acid.

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3.12, CD154 (MR1), CD80 (1610A1), CD86 (GL-1), CD40 (3/23), FcγRII/III (2.4G2), OVA (KB-4.6E, mouse IgG1), and CD11c (N418; conjugated to PE) were prepared in house and provided by M. Glennie (University of Southampton, Southampton, U.K.). The anti-CD4 mAb (YTS 191.1.2) was acquired from Cancer Research U.K. Allophycocyanin-conjugated anti-CD8α (53-6.7), anti-CD4 (RM4-5), and streptavidin; PE anti-mouse TCR Vα2 (B20.1); and FITC anti-Vβ5.1, Vβ5.2 (MR9-4) were purchased from BD Pharmingen. Biotinylation of Abs was performed using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/N-hydroxysuccinimide (Pierce). Recombinant murine IFN-α (IFN-α4) had an activity of 2 × 10^4 U/ml and was used in vivo, as described previously (31). Recombinant murine IL-4 and GM-CSF were obtained from PeproTech. Mouse cells were cultured in complete RPMI 1640, containing 10% (v/v) FCS, 2-ME, 100 U/ml penicillin, 100 μg/ml streptomycin, 2 mM L-glutamine, and 1 mM sodium pyruvate. E.G7, OVA cDNA-transfected derivative of EL4 (American Type Culture Collection), was maintained in the same medium supplemented with 0.4 mg/ml gentamicin (Invitrogen Life Technologies Cell Culture Systems).

**Mice and in vivo experiments**

C57BL/6 (B6) and OT-II (32) mice (all H-2b) were bred and maintained in a pathogen-free environment and were used at 8–10 wk of age. OVA-specific T cell responses were primed in mice by i.v. administration of OVA-loaded γ-irradiated (1500 Gy) syngeneic splenocytes (6, 11) or, in some experiments, by OVA-loaded splenocytes in combination with either poly(I:C) (100 ng per mouse) or IFN-α (31). For certain experiments, immunization (day 0) was preceded by depletion of CD4 + T cells or, conversely, adoptive transfer of CD4 + T cells (2–4 × 10^5) from sex-matched OT-II mice (day −1). In experiments with CD4 + T cell depletion (>99% efficient), mice received i.p. injections of anti-CD4 mAb (1 mg of YTA 3.1.2 and 0.5 mg of YTS 191.2) on days −3 and −1. CD4 + T cell-depleted mice also received anti-CD154 mAb (0.5 mg) on days 0 and 1. In other experimental settings, anti-CD154, anti-CD70, or an isotype-matched control Ab (Mc39-16) were given i.p. at the dose of 0.5 mg, on days −2 and −1. Animal experiments were conducted in accordance with the U.K. Home Office guidelines and approved by the University of Southampton’s Ethical Committee.

**Evaluation of Ag-specific T cell responses**

For tracking of OVA-specific CD4 + T cells in vivo, blood samples were stained with PE anti-mouse TCR Vα2, FITC anti-mouse TCR Vβ5.1, Vβ5.2, and allophycocyanin anti-CD4 mAb. OVA-specific CD8 + T cells in vivo were followed in blood samples or spleens by staining with PE-H2-K b OVA 257–264 tetramer and allophycocyanin anti-CD8α mAb. Staining was conducted in the presence of FcγRII/III blocking mAb 2.4G2. Expansion of OVA-specific CD8 + T cells following in vitro restimulation was assessed on day 0 after cultivation of splenocytes with γ-irradiated E.G7 cells (360 Gy) (6). Flow cytometry was performed using BD Biosciences FACSCalibur and CellQuest software. Serum concentration of anti-OVA IgG was determined by ELISA, and bound IgG was detected by goat anti-mouse IgG (Fc-specific)-peroxidase conjugate (Sigma-Aldrich).

**Evaluation of memory CD8 + T cell responses in vivo**

B6 mice were primed by i.p. injection of OVA-loaded cells with poly(I:C) on day 0, as described previously. Primed mice were also injected with anti-CD70 or isotype control mAb (Mc39-16) on days 0 and 1 (total of 1 mg). To analyze memory responses, mice were given OVA 257–264 (30 nmol) with agonistic anti-CD40 mAb (0.5 mg) i.p. 2 mo after immunization, and Ag-specific CD8 + T cells were enumerated in peripheral blood samples.

**Analysis of CD70 expression on DC**

To obtain BM-derived DC, BM cells were cultured for 6 days with IL-4 (5 ng/ml) and GM-CSF (5 ng/ml). Twenty-four hours before FACS analysis, cells were treated with mouse soluble rCD154 (rCD154; 10 μg/ml) (28). poly(I:C) (50 μg/ml), or IFN-α (5 × 10^6 U/ml). Expression of CD80, CD86, and CD70 was determined by double labeling with anti-CD11c PE and the appropriate biotinylated mAb in the presence of 2.4G2 mAb, followed by allophycocyanin-conjugated streptavidin. To assess expression of CD70 on splenic DC, C57BL/6 Rag1 −/− mice were injected i.p. with agonistic anti-CD40 mAb (3/23; 0.5 mg), and the spleens were removed and then digested with Liberase R1 and DNase I (Roche), as described previously (33). Following digestion and RBC lysis, cells were washed and labeled with anti-CD11c PE and biotinylated anti-CD70 mAb in the presence of 2.4G2 mAb. The binding of biotinylated anti-CD70 mAbs to cells was detected by allophycocyanin-conjugated streptavidin. Samples were treated with 7-aminoactinomycin-D (2 μg/ml) 15 min before analysis so that dead and autofluorescent cells could be gated out using FL3.

**Results**

**CD70 is required for CD4 + T cell-dependent CD8 + T cell priming**

Immunization of C57BL/6 (H-2b) mice with syngeneic OVA-loaded spleen cells resulted in the priming of CD8 + T cells specific for OVA peptide 257–264 (Fig. 1). As shown previously (11), this response was dependent on the interaction between CD154 and CD40, because administration of a blocking mAb directed against CD154 resulted in complete abrogation of CD8 + T cell priming (Fig. 1). A similar defect in CD8 + T cell priming was seen when mice were injected with a blocking anti-CD70 mAb (Fig. 1). Because immunization with a noninflammatory Ag, such as cell-associated Ag, results in limited expansion of Ag-specific CD4 + T cells, we were interested in examining the role of CD70 under conditions in which help is not restricted by the low frequency of CD4 + T cells. To achieve a higher frequency of Ag-specific CD4 + T cells, we adoptively transferred OVA-specific TCR transgenic CD4 + T cells (OT-II) into C57BL/6 mice before challenging with OVA-loaded spleen cells. The transfer of OT-II T cells augmented the ability of mice to generate an OVA-specific CD8 + T cell response (Fig. 2a). As with help provided by endogenous polyclonal CD4 + T cells alone, the priming of OVA-specific CD8 + T cells in mice that received OT-II T cells remained highly dependent on the CD70-CD27 interaction (Fig. 2a). Because the number of OVA-specific CD8 + T cells detected ex vivo following blockade of CD154 or CD70 approached the sensitivity limit of the detection assay, we examined the expansion of Ag-specific CD8 + T cells following in vitro restimulation. Spleen cell cultures prepared from mice that had received anti-CD154 mAb did not yield OVA-specific CD8 + T cells and those from anti-CD70 mAb-administered mice yielded markedly reduced (>90%) numbers of Ag-specific CD8 + T cells when compared with the control group (Fig. 2b). Similar results were obtained when OVA-specific CD8 + T cells were enumerated by measurement of intracellular IFN-γ labeling.
Thus, our data clearly demonstrate that helper-dependent CD8+ T cell priming is dependent on the CD70-CD27 interaction.

CD70 is dispensable for CD4+ T cell activation and help for B cells.

CD27 is expressed on both CD4+ and CD8+ T cells (34), and it is possible that the abrogation of CD8+ T cell priming by anti-CD70 mAb was the consequence of a defect in CD4+ T cell activation. To address whether the CD70-CD27 interaction is important for CD4+ T cell activation, we examined the expansion kinetics of OVA-specific (OT-II) CD4+ T cells and their ability to provide help for B cells following immunization with OVA-loaded spleen cells. The number of OT-II T cells peaked 4 days postimmunization, and thereafter the number of these cells declined (Fig. 3a).

Administration of anti-CD70 mAb had no effect on the kinetics of the CD4+ T cell response (Fig. 3a). In contrast, the expansion of OT-II T cells was abolished by administration of anti-CD154 mAb.
(Fig. 3a), consistent with previous studies demonstrating a defect in CD4+ T cell priming in the absence of CD154-CD40 interaction (35). As an additional measure of CD4+ T cell function, we examined the effects of anti-CD70 mAb on the ability of CD4+ T cells to provide help for B cells. As shown in Fig. 3b, adoptive transfer of OT-II T cells augmented the OVA-specific serum IgG concentration considerably, and the anti-OVA IgG response was not significantly affected by administration of anti-CD70 mAb. In contrast, the anti-OVA Ab response was abolished following administration of anti-CD154 mAb (Fig. 3b), consistent with the role of CD154 in thymus-dependent Ab responses (36). These results demonstrate that CD70 is dispensable for CD4+ T cell responses elicited by immunization with OVA-loaded spleen cells and suggest that in helper-dependent CD8+ T cell responses CD70 exerts its effects directly on CD8+ T cells.

**Requirement for CD70 in CD4+ T cell-independent CD8+ T cell priming**

Activation of DC through engagement of innate receptors bypasses the requirement for CD4+ T cell help in CD8+ T cell priming (9, 25, 31, 37, 38). Having demonstrated a critical role for CD70 in CD4+ Th cell-dependent CD8+ T cell priming, we asked whether CD8+ T cell priming mediated by engagement of innate receptors is also dependent on CD70. To generate a CD4+ Th cell-independent CD8+ T cell response, we immunized mice with OVA-loaded cells in the presence of dsRNA (poly(I:C)). dsRNA is a ligand for TLR3 (27), and signaling via TLR3 has recently been shown to promote cross-priming of CD8+ T cells (26). Immunization with OVA-loaded cells and poly(I:C) generated a robust OVA-specific CD8+ T cell response that was independent of CD4+ T cells (Fig. 4). Furthermore, this response was significantly diminished by administration of anti-CD70 mAb (Fig. 4). Although anti-CD70 mAb clearly reduced poly(I:C)-mediated priming of OVA-specific CD8+ T cells, Ag-specific CD8+ T cells were consistently detected in these mice, suggesting that priming was not abolished (Fig. 4). These results imply that additional factors operate in promoting CD8+ T cell priming by dsRNA. One such factor could be IFN-α, known to be induced by dsRNA (31, 39). To examine the requirement for CD70 in CD8+ T cell priming mediated by IFN-α, we injected mice with OVA-loaded spleen cells and rIFN-α. As reported previously, this resulted in a CD4+ T cell-independent OVA-specific CD8+ T cell priming (31), albeit less efficiently than that mediated by injection of poly(I:C) (Fig. 4). However, unlike the priming mediated by poly(I:C), IFN-α-promoted CD8+ T cell priming was unaffected by blockade of the CD70-CD27 interaction (Fig. 4). The lack of dependency on CD70 in IFN-α-mediated CD8+ T cell priming could be due to the lack of CD70 expression on APC following administration of IFN-α. To address this possibility, we examined the expression of CD70 on BM-derived DC following treatment with IFN-α, or for comparison after activation with sCD154 or poly(I:C). Consistent with previous studies (29, 30), IFN-α induced the up-regulation of CD80 and CD86 on BM-derived DC, albeit at a lesser magnitude than sCD154 or poly(I:C) (Fig. 5). In contrast, CD70 expression was not induced by treatment with IFN-α, although its expression was detected after treatment with sCD154 or poly(I:C) (Fig. 5). These data support the notion that the lack of CD70 requirement in IFN-α-mediated CD8+ T cell priming is due to the absence of CD70 expression.

![FIGURE 5. Expression of CD70 on in vitro-generated DC is induced by CD154 and dsRNA, but not IFN-α. In vitro-generated DC were cultured with rsCD154, poly(I:C), or IFN-α for 24 h, or left untreated in culture medium. Expression of CD80, CD86, or CD70 (open histograms) on CD11c+ cells was determined by flow cytometry. Staining observed with isotype-matched control mAb (AT65 as a control for CD80, and Mc39-16 as a control for CD86 and CD70) is represented by a filled histogram. The data shown are representative of two independent experiments.](http://www.jimmunol.org/Downloaded from http://www.jimmunol.org/)

**CD80**

**CD86**

**CD70**

**media**

**sCD154**

**poly I:C**

**IFN-α**
Expression of CD70 on in vivo-activated DC

We and others (22, 23) have shown that activation of DC through CD40 signaling is highly efficient in triggering CD70 expression on BM-derived DC (Fig. 5). However, in vivo expression of CD70 on DC is not well documented. To address this question, we administered agonistic anti-CD40 mAb, an established procedure for triggering DC maturation in vivo (10, 11, 40), and examined the expression of CD70 on splenic DC. Although CD70 expression was very low, or absent on CD11c+ DC obtained from control mice, it was up-regulated following administration of anti-CD40 mAb (Fig. 6). These results demonstrate that CD70 is expressed upon in vivo maturation of DC.

CD70 blockade during priming results in defective CD8+ T cell memory

To assess whether CD70 signals during priming affect CD8+ T cell memory, we compared memory responses in mice that had been immunized with OVA-loaded cells and poly(I:C) with those that were immunized and subjected to CD70 blockade during the primary response. We chose to immunize with OVA-loaded cells and poly(I:C) because with this immunization protocol CD8+ T cell priming is only partly inhibited after CD70 blockade (Fig. 4). Fig. 7 shows that the magnitude of the secondary response in mice that had received the blocking anti-CD70 mAb was dramatically reduced when compared with that of mice that received an irrelevant control mAb. Thus, CD70 blockade during priming severely impairs the generation of functional memory CD8+ T cells.

Discussion

There is compelling evidence for DC conditioning as the mechanism of CD4+ T cell help for priming of CD8+ T cell responses (6, 8–11). However, the molecular features of conditioned DC and the nature of the T cell signals that lead to CD8+ T cell proliferation and development of memory are not well understood. Using an immunization protocol that depends on cognate CD4+ T cell help to generate a CD8+ T cell response (6, 11), we show that blockade of CD70 inhibits CD8+ T cell priming, without affecting CD4+ T cell activation and help for B cells. Thus, we have identified the CD70-CD27 interaction as an important pathway in transmitting CD4+ T cell help to CD8+ T cells. Our data suggest that expression of CD70 on DC represents the hallmark of conditioned DC.

CD70 is expressed upon activation of DC, B cells, and T cells (34), and constitutively on a population of nonhemopoietic cells in the gut lamina propria (41). Several lines of evidence support the notion that CD70 expression on DC is required for CD8+ T cell priming. Thus, CD8+ T cell priming by cell-associated Ag was shown to be intact in B cell-deficient mice (10), but abolished following depletion of CD11c+ DC (7). Furthermore, using an agonistic anti-CD40 mAb to mimic CD4+ T cell help, we have demonstrated a requirement for CD70 in CD8+ T cell priming in the absence of CD4+ T cells and B cells (22) (data not shown). A role for CD70 expression on DC in transmitting CD4+ T cell help for CD8+ T cells is also consistent with the cognitive nature of CD4+ T cell help for CD8+ T cell priming in which both T cell subsets recognize Ag on the same APC (6). Theoretically, CD70 expression on activated CD8+ T cells could contribute to the expansion of Ag-specific CD8+ T cells through CD8-CD8+ T cell interaction. However, this is unlikely because in vivo priming of OVA-specific OT-I TCR transgenic T cells with Ag in the absence of adjuvant is unaffected by CD70 blockade (data not shown), while administration of soluble CD70 enhances the response (42). It is noteworthy that at high precursor frequency OT-I T cells are...
less dependent on CD4+ T cell help (43); however, they remain responsive to CD70 stimulation (42). Taken together, these data argue against a role for CD70 expression on activated CD8+ T cells in T cell priming.

The role of CD80 and CD86 in transmitting CD4+ T cell priming has been difficult to assess accurately because of their essential role in promoting CD4+ T cell responses (19). Thus, studies that have attempted to examine the contribution of this pathway used agonistic anti-CD40 mAb to mimic CD4+ T cell help. Those studies provided conflicting evidence for the requirement of the CD80/CD86-CD28 pathway in CD8+ T cell responses (9, 15–17). The discrepancies between these findings may lie in the very different model systems used. Due to the overlap in the proximal signaling pathways between the TCR and CD28 (44), it is possible that in some models an increase in the potency of signaling via the TCR bypasses the requirement for CD82 (45). Our own studies comparing the role of CD27 and CD28 signaling in CD8+ T cell priming following immunization with soluble OVA and agonistic anti-CD40 mAb indicate that both pathways are required in this model (data not shown). This therefore suggests that at least in this model the CD27 and CD28 pathways act synergistically. Our results also provide an explanation for the paradoxical observations that DC that express high levels of CD80 and CD86 fail to stimulate CD8+ T cells against the male Ag H-Y, yet blockade of CD80 and CD86 inhibits priming by conditioned DC (9).

The role of CD70-CD27 pathway in CD4+ T cell responses is not fully established. Our data demonstrating that CD4+ T cell responses following immunization with OVA-loaded cells are independent of CD70-CD27 contrast with the role of this pathway in CD8+ T cell responses. These results are in agreement with recent findings showing that the expansion of alloreactive TCR transgenic CD4+ T cells is not significantly affected by CD70 blockade (46). It is plausible that other TNFR superfamily members, such as OX40, which is expressed on activated CD4+ T cells, compensate for the lack of CD27 signaling (20, 21).

DC conditioning through the interaction of PAMP with innate receptors such as TLR promotes CD8+ T cell priming against pathogens and bypasses the need for CD4+ T cell help (3–5, 9, 24, 25, 37, 38). In this study, we show that CD70 is required for optimal expansion of CD8+ T cells during the primary response and generation of functional memory when dsRNA is used as the innate stimulus. Because the effects of CD70 were observed in the absence of CD4+ T cells, these results demonstrate unequivocally an important role for CD70 in DC conditioning by pathogen-derived signals that are recognized by innate receptors. Our results also provide an explanation for the reduced CD8+ T cell response to influenza virus in CD27-deficient mice (47, 48), an infection that triggers diminished, but still potent CD8+ T cell responses in the absence of CD4+ T cell help (49, 50).

The interaction of PAMP with innate receptors results in the up-regulation of costimulatory molecules, including CD80, CD86, and CD70 (23, 51). Additionally, recognition of PAMP triggers the release of IFN-γ (29, 30, 51), which can promote CD8+ T cell priming independent of CD4+ T cell help (31). IFN-γ augment the expression of CD80 and CD86 on APC (29, 30) and also provide a direct signal to CD8+ T cells to promote their survival during immune responses (39). We found no significant up-regulation of CD70 on DC following exposure to IFN-γ, and, furthermore, CD70 blockade had little, if any, effect on IFN-γ-mediated priming of CD8+ T cells. Thus, the direct effects of IFN-γ on CD8+ T cell survival may account for the residual CD8+ T cell priming by dsRNA observed in our study during CD70 blockade. These results suggest that the requirement for costimulation in CD8+ T cell responses elicited by pathogens could differ depending on the amount of IFN-γ induced by the infection, which varies among different pathogens (31). Accordingly, IFN-γ may promote CD8+ T cell responses against Ags that are presented by nonprofessional APC that lack costimulatory ligands.

In this study, we have shown that CD70 is critical for CD4+ T cell as well as innate receptor-mediated CD8+ T cell priming. How does CD70 promote CD8+ T cell priming? Studies using either mouse or human CD8+ T cells have demonstrated that CD27 signaling promotes proliferation, IL-2 production, and cell survival (42, 48, 52), and these effects are likely to be mediated by activation of the NF-κB and JNK pathways (34). Exactly how these and other potential CD27 signaling pathways contribute to CD8+ T cell expansion awaits further investigation. Nonetheless, our findings point out a critical pathway for CD8+ T cell priming, and thus potentially a new approach for developing vaccines that elicit CD8+ T cell responses without the inflammation associated with infection.

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Disclosures
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