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CD8 T Cell Recall Responses Are Regulated by the Tissue Tropism of the Memory Cell and Pathogen

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Whether memory CD8 T cells can be reactivated in nonlymphoid tissues is unclear. Using mice lacking the spleen, lymph nodes, or both, we show that the secondary T cell response, but not homeostatic maintenance of memory cells, required lymphoid tissue. Whereas primary and secondary CD8 T cell responses to vesicular stomatitis virus infection were lymph node dependent, responses to Listeria monocytogenes infection were driven primarily in the spleen. Memory cell subset reactivation was also regulated by the location of the responding population and the pathogen. Thus, CD62Llow effector memory T cells (TEM) cells responded nearly as well as CD62Lhigh central memory T cells (TCM) and TCM cells after L. monocytogenes infection, and both subsets generated equivalent populations of secondary memory cells. In contrast, TCM cells, but not TEM cells, mounted a robust response to vesicular stomatitis virus infection. TCM and TEM cells also required lymphoid tissue to mount recall responses, and the bone marrow did not contribute significantly to the response of either subset. Our findings indicated that characteristics of the infectious agent and the migratory preferences of memory cells dictated the secondary lymphoid tissue requirement for the recall response to infection.

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vitro, whereas naive CD4 T cells respond solely to DCs and activated B cells (19).

Secondary lymphoid tissues, consisting of the spleen, lymph nodes (LN), and Peyer’s patches (PP), have evolved in mammals to form the epicenter for initiation of the majority of immune responses. Because both afferent lymph and the peripheral circulation drain into the LNs and spleen, respectively, these sites represent the primary inductive sites where Ag-bearing DCs migrating from distal tissues first contact naive T cells (20). Because naive T cells preferentially migrate to secondary lymphoid tissues by virtue of expression of CD62L and CCR7 (21), the rendezvous of the naive T cell with Ag-laden DCs at specialized locations represents a highly efficient mechanism whereby a very small number of Ag-specific T cells are able to encounter their cognate Ag. Additionally, in this microenvironment, CD8 T cells are juxtaposed to potential accessory cells including B cells, CD4 T cells, follicular DCs, and stromal cells. The mingling of these cell populations ensures that the appropriate costimulatory signals and growth factors are obtained to promote the activation and transition of naive cells into potent effector CD8 T cells.

Thus, although lymphoid tissue is thought to be essential for the initiation of primary T cell responses, it remains unclear whether secondary lymphoid tissue is required for reactivation of memory CD8 T cells. Experiments utilizing lymphocytic choriomeningitis virus (LCMV) infection demonstrate that TCM, which reside primarily in LNs and spleen, are superior to TEM in mediating protective immunity after secondary viral infection (22). This phenomenon was hypothesized to be due to the increased proliferative capacity of TCM vs TEM, but whether other factors are involved is unknown. Indeed, secondary challenge of mice infected with Sendai virus shows that the recall response to this lung-specific infection relies on the ability of TEM to expand robustly early after infection (23). However, long term studies of memory cells generated in this model demonstrate that at later time points, CD62Lhigh cells (TCM) dominated the secondary response, perhaps due to their increased proliferative capacity (24). Nevertheless, it remains unclear in either of these infections where reactivation occurred because memory cells with either TEM or TCM phenotypes can be found in the spleen, LNs, or nonlymphoid tissues. Because memory cells are found at high frequency in nonlymphoid tissues (2), the question remains as to whether memory cells can respond to secondary Ag challenge in situ. To address this question, we performed a comprehensive analysis of the role of secondary lymphoid tissue in the initiation of primary and secondary CD8 T cell responses to viral and bacterial infections. Additionally, the contribution of TEM and TCM to recall responses was addressed.

Materials and Methods

Generation of mice lacking lymphoid tissue

Age- and sex-matched C57BL/6 CD45.1 and C57BL/6 CD45.2 mice were purchased from Charles River, and lymphopotent α-deficient (Ltα−/−) mice were obtained from The Jackson Laboratory. Splenectomies were performed as detailed in Current Protocols in Immunology (25). Briefly, mice were anesthetized before surgery and all hair was removed at the surgical site. A small incision was made on the left side of the mouse, and skin was loosened from the area. An additional cut was made through the peritoneal cavity, the spleen was excised from the opening, ligated off with 4-0 Dermalon nylon sutures (Henry Schein) and removed. Control mice that were mock splenectomized were obtained from The Jackson Laboratory. Splenectomies were performed in this model demonstrate that at later time points,

Analysis of CD8 memory cell turnover in vivo

Mice were given water containing 0.8 mg/ml BrdU every other day for 40 days. BrdU staining was performed after cell surface staining as previously described (32). Briefly, cells were treated with FACS Lysing Solution (BD Biosciences) for 15 min at room temperature and fixed overnight in 1% paraformaldehyde and 0.05% Nonidet P-40 in PBS at 4°C. Cellular DNA was then denatured with 50 Kunitz units of DNase 1 (Boehringer Mannheim) for 30 min at 37°C and stained with a FITC-labeled anti-BrdU mAb (BD Biosciences) diluted 1/5 in 5% FBS and 0.5% Nonidet P-40 in PBS for 45 min. The level of BrdU incorporation was determined by flow cytometry.

Results

The requirement for secondary lymphoid tissue in primary CD8 T cell responses to bacterial and viral pathogens

The preferential migratory route of naive CD8 T cells among blood, secondary lymphoid tissue, and lymph bias the location of the initial CD8 T cell priming event to either the spleen or the LNs. However, it is unclear whether the efficient priming of T cells to particular pathogens shows a preference for distinct secondary lymphoid tissues or whether the route of infection influences the priming site. To dissect the role of individual secondary lymphoid tissues in CD8 T cell priming, we used both splenectomized mice or Ltα−/− mice, which lack all LNs and PP (33). When infected with 1 × 10^8 CFU recombinant L. monocytogenes expressing OVA (LM-OVA) i.v., splenectomized mice were incapable of mounting an Ag-specific CD8 T cell response in all tissues examined as measured by MHC class I tetramer reactivity (Fig. 1a). In contrast, lymph nodes were dispensable for the primary response to the same pathogen in all tissues, except the intestinal LP (Fig. 1b), which perhaps reflected the requirement for LN and PP in imprinting an intestine-homing phenotype on these cells (34–36). In contrast to the i.v. infection, oral administration of LM-OVA generated Ag-specific CD8 T cells in asplenic mice (Fig. 1c). Additionally, infection with a higher dose (1 × 10^9 CFU) of LM-OVA i.v. also resulted in decreased splenic dependence for mounting a robust Ag-specific CD8 T cell response (data not shown), indicating that a higher bacterial burden resulted in additional priming in the LN. Together, these data indicated that the route of
infection and dose of LM-OVA dictated the site of primary CD8 T cell activation. In contrast to the response to bacterial infection, the response to i.v. infection with VSV, demonstrated an inverse requirement for secondary lymphoid tissue. That is, whereas splenectomized mice infected with VSV were capable of generating a normal CD8 T cell response, a generally poor CD8 T cell response was observed in LTα−/− mice (Fig. 1, d and e). In summary, the choice of secondary lymphoid tissue for the primary activation of CD8 T cells was dependent on the pathogen, dose, and route of infection.

Memory CD8 T cells are maintained in the absence of secondary lymphoid tissue

Because we wished to test whether lymphoid tissue was required for memory cell reactivation, it was important to determine whether memory cells were maintained normally in alymphoid mice. To test this, LTα−/− and C57BL/6 mice were infected with 1 × 10^3 CFU LM-OVA i.v. Five weeks postinfection, subsets of each group were splenectomized or mock splenectomized (mock), and 5 wk later the tissues were analyzed for the presence of memory cells. At the time of surgery, the total number of splenic OVA-specific CD8 T cells was equivalent in both the LTα−/− and C57BL/6 mice (data not shown). The absence of a spleen or LNs had no effect on the total number of OVA-specific memory cells in the reciprocal locations (Fig. 2a). More importantly, there was no significant difference in the number of memory cells found in the nonlymphoid tissues (lung, liver, and intestinal mucosa) of the splenectomized LTα−/− mice compared with all other groups. Thus, memory CD8 T cells were maintained independent of secondary lymphoid tissue.

Although resting memory cells were present at an equivalent frequency in mice devoid of a spleen, LNs, or both, it was possible that the loss of secondary lymphoid tissue resulted in differences in the homeostatic proliferation of memory cells. Thus, we examined the proliferative ability of memory cells through incorporation of BrdU (Fig. 2b). The loss of a spleen or LNs alone failed to impact memory cell division in the alternate lymphoid tissue. Analysis of lung and liver memory cells, however, revealed subtle differences in the rates of cell division. For example, the removal of either a spleen (B6 splenectomized) or LNs (LTα−/−) resulted in increased memory cell division in the liver and lung (Fig. 2b). Interestingly, the division of memory CD8 T cells was substantially increased in the absence of all lymphoid tissue, with memory cells in the lung and liver of alymphoid mice incorporating 30–50% more BrdU than those in normal mice. The ratios of CD62Lhigh and CD62Llow Ag-specific cells in the lung and liver of alymphoid mice were similar to those found in lymphoid mice.
in control mice (data not shown), suggesting that the increased memory cell proliferation observed in LTA−/− splenectomized mice was not due to a greater frequency of TCM, which proliferate more rapidly than TEM. However, one possible explanation for the observed differences, particularly with asplenic mice, was that increased memory cell proliferation was a result of relative lymphopenia.
Secondary lymphoid tissues are required for generation of CD8 recall responses

Although many Ag-specific memory cells are localized in nonlymphoid tissues after infection (2, 37), it is unclear whether nonlymphoid memory cells are able to mount a productive recall response. To analyze the requirement for lymphoid tissues in the recall response of CD8 memory T cells, C57BL/6 and LTα−/− mice were infected with 1 × 10^3 CFU LM-OVA i.v. After 4 wk, the mice were either splenectomized or mock splenectomized and subsequently infected with LM-OVA; the recall response was measured by tetramer reactivity. With the exception of the response in the LP, when mice were challenged with LM-OVA i.v., the recall response was largely independent of LNs but required the spleen (Fig. 3a). In the absence of secondary lymphoid tissue, the OVA-specific response was further dampened in the lung and liver, suggesting that in the absence of a spleen a low level response could be mounted in the LN. Oral LM-OVA infection generated equivalent recall responses in the lung and liver of all mice except the LTα−/− splenectomized mice (Fig. 3b), suggesting that following oral challenge, the response could be initiated in either the spleen or LNs. Interestingly, the recall response in the intestinal LP to both the i.v. and oral LM-OVA rechallenge was distinct from that observed in the lung and liver. Only the removal of both the spleen and the LNs affected the CD8 recall response after i.v. infection and this decrease was not as evident as that observed in other nonlymphoid sites. Further, the LP recall response against oral LM-OVA infection was partially dependent on the spleen and fully dependent on the presence of both secondary lymphoid tissues. Thus, the route of infection, as with the primary CD8 T cell response, dictated the requirement for secondary lymphoid tissue for mounting a recall response. Also, infection of LTα−/− mice with or without a spleen did not lead to differences in clearance of bacteria. This conclusion was based on bacterial colony counts performed after infection, which were no different between groups of animals and bacteria were cleared by day 10 or earlier in all experiments. In addition, CFSE-labeled OT-1 cells transferred to LM-OVA infected LTα−/− or control mice ~1 mo after splenectomy did not proliferate (data not shown).

The requirement for lymphoid tissue in generating a recall response to VSV infection was also examined. When mice were challenged with VSV-OVA i.v., the response was essentially abolished in LTα−/− mice with or without a spleen (Fig. 4). Unlike the primary response to VSV, the recall response in splenectomized C57BL/6 mice was reduced by approximately one-half. Splenectomy removed a substantial number of memory cells present in the spleen at the time of surgery, which may affect the magnitude of the recall response. However, the dual observations that a higher frequency of OVA-specific memory CD8 T cells was found in the PLN of splenectomized mice and the splenic CD8 T cell response to VSV was impaired suggests that LN-resident memory cells, perhaps TCM, predominated in the recall response to VSV.

The site of priming determines the contribution of TEM and TCM CD8 T cells to the recall response

To compare the effect of different priming sites on the ability of both CD8 memory subsets to generate potent recall responses, sorted TCM (CD62Lhigh) and TEM (CD62Llow) cells were adoptively transferred into naive recipients which were then infected with VSV-OVA. Before the infection, both TCM and TEM were present in the spleen, whereas TCM, but not TEM, were present in the LN (data not shown). Seven days postinfection, ~4–7 times more tetramer+ cells were recovered from the spleen, lung, and liver of those animals that had received TCM vs TEM (Fig. 5a). The dominant response of TCM over TEM early in the recall response would be in keeping with a TCM response.
also resulted in an increased frequency of TCM-derived memory cells 34 days postinfection (Fig. 5b). Given that the input number of memory cells in each group was equivalent, these data indicated that TCM cells were more efficient than TEM cells at mediating recall responses to VSV. Thus, the observed increase in the frequency of reactivated CD8 T cells in the PLN of splenectomized mice (Fig. 4) can be directly attributed to the contribution of TCM, which predominate in the LN.

We also examined the overall kinetics of the response of TEM and TCM cells in the blood of B6 mice after infection with LM-OVA. When either TCM or TEM were transferred, a rapid increase in the percentage of OVA-tetramer+ donor cells was observed in the blood, with TCM cells having a slight advantage over TEM cells before and at the peak of the recall response. However, by days 12 and 20 postinfection, the response was similar in both groups, indicating that both TCM and TEM could be effectively reactivated (Fig. 6a). To determine to what extent the two memory CD8 T cell subsets contributed to the establishment of memory populations, the same cohort of mice was sacrificed at day 35 postinfection. At this time point, the number of memory cells derived from TEM and TCM donor populations was similar, with equivalent numbers of donor tetramer+ CD8 T cells recovered from the spleen, lung, and liver (Fig. 6b).

To test the ability of TEM and TCM CD8 T cells to mount a recall response in the absence of LN, spleen or both, sorted memory cells were transferred to groups of mice as indicated in Fig. 6, c–f, and the mice were then infected i.v. with LM-OVA. In C57BL/6 mice, both TEM and TCM cells mounted a recall response and increased substantially in the spleen, lung and liver but underwent only minimal expansion in the bone marrow. In the absence of a spleen, the recall response was substantially blunted, and primarily TCM responded in keeping with the presence of these, but not TEM cells in LN. In the LTα−/− mice, the response was decreased by approximately one-half as compared with the response in B6 mice but both TEM and TCM cells responded, with TCM outpacing TEM in the spleen but not in the lung and liver (Fig. 6c). These results are in agreement with our previous results showing that both LN and spleen contribute to the anti-LM recall response (Fig. 3). In alymphoid mice, the recall response was minimal, indicating that a substantial proliferative recall response was not mounted in nonlymphoid tissues, including the bone marrow (Fig. 6d).

Discussion

The results presented here indicated that different infectious agents prime T cells in distinct lymphoid tissues. The priming or reactivation event was also dependent on the route of infection and additionally on the dose of the pathogen administered. Thus, VSV...
or *L. monocytogenes* infection primed naive T cells in the LN or spleen, respectively. A previous study using CTL activity as a measure of the CD8 T cell response also shows that LN but not the spleen are important in mounting an anti-VSV primary CTL response (38). In contrast to these results, influenza or gammaherpes virus infections prime CD8 T cell responses, albeit delayed, in the absence of the spleen or LN (39–41) Nevertheless, at least for influenza virus infection, lymphoid tissue appears to be essential because T cell activation in this situation is thought to occur in inducible bronchus associated lymphoid tissue (42). The route of infection in our models also directly shaped the initial site of pathogen detection. Thus, the CD8 T cell response to oral *LM*-infection in our models also directly shaped the initial site of response (38). In contrast to these results, influenza or gammaherpes virus infections prime CD8 T cell responses, albeit delayed, in the absence of the spleen or LN (39–41) Nevertheless, at least for influenza virus infection, lymphoid tissue appears to be essential because T cell activation in this situation is thought to occur in inducible bronchus associated lymphoid tissue (42). The route of infection in our models also directly shaped the initial site of pathogen detection. Thus, the CD8 T cell response to oral *LM*-infection was less dependent on the spleen than the response after l.v. infection (Fig. 1). Secondary responses to oral infection were largely independent of the spleen (Fig. 3b), but again the LP response was diminished in splenectomized mice. In the absence of secondary lymphoid tissue, the response to oral immunization was nearly abrogated indicating that both the spleen and LN participated in the response (Fig. 3b). These results also suggested that there was not an absolute requirement for activation to occur in a mucosal tissue such as the mesenteric LNs or PP to impart mucosal homing properties to the CD8 T cells (43, 44).

Interestingly, alloreactive T cell responses may be an exception to the requirement for lymphoid tissues in mounting a primary or recall response. Adoptively transferred TCR transgenic naive CD8 T cells can be activated in the liver (45), and transferred memory CD8 T cells can reject cardiac allografts in the absence of secondary lymphoid tissue (46). Also, the T cell response to a tumor-derived Ag, although dependent on cross-priming, is not lymphoid tissue dependent (47). The site(s) of priming in these instances is not known, although the bone marrow can apparently act as a site for initiation of T cell responses (48–50). Also, in each of these cases, the frequency of Ag-specific T cells is artificially very high as a result of transfer of large numbers of TCR transgenic T cells. Thus, whether T cells at the normally low endogenous frequency would respond similarly in the absence of secondary lymphoid tissue is unknown. Overall, the results indicated that the nature and the mechanism of delivery of the Ag are critical to determining the requirement for and the type of secondary lymphoid tissue involved in T cell response initiation.

Perhaps surprisingly, our findings demonstrated that, similar to naive CD8 T cells, memory CD8 T cells required secondary lymphoid tissue for optimal reactivation following secondary infections with VSV or *L. monocytogenes*. Indeed, the requirements mirrored those for the primary response in that the spleen or LNs were critical for recall of memory cells by infection with *L. monocytogenes* or VSV, respectively, despite the fact that Ag-specific memory cells are found in multiple nonlymphoid tissues and that both agents were introduced directly into the bloodstream. These results were further bolstered by the demonstration that in the absence of lymphoid tissue, transferred TCM and TEM cells did not expand in nonlymphoid tissues or the bone marrow after *L. monocytogenes* infection (Fig. 6). The lack of a response in the bone marrow also suggested that T cell activation in this tissue is not a hallmark of all responses. Coupled with our previous results showing that DC are required for a maximal proliferative recall to these pathogens (51), we conclude that DCs bearing Ag in the spleen or LN are responsible for CD8 memory T cell reactivation. In

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**FIGURE 6.** TEM and TCM CD8 T cell recall responses to *L. monocytogenes* infection require lymphoid tissue. Splenic memory cells from LM-OVA-infected CD45.1 C57BL/6 mice were purified by sorting, and $5 \times 10^{3}$ TEM or TCM were adoptively transferred to the naive mice indicated above each panel. One day later, the mice were infected with $1 \times 10^{6}$ CFU LM-OVA and 10 (c–f); or 35 days later, (b) the total number of donor (as determined by CD45.1,2 expression) tetramer $^+$ CD8 T cells in the spleen (SP), lung (LG), bone marrow (BM), or liver (LV) was determined by fluorescence flow cytometry. The percentage of tetramer $^+$ CD8 T cells was also assessed in the blood at the times indicated (a). Data are mean ± SE of two to four mice per group in two experiments.
the CD11c-DTR system used for the latter studies, however, some subsets of macrophages are depleted (52, 53) leaving open the question of whether this cell type is also involved in recall responses. The reasons that VSV and LM infections induce memory CD8 T cell reactivation at distinct locations are not entirely clear. Both infectious agents have been shown to infect cell types in the spleen, particularly macrophages (54, 55). Thus, why VSV specific CD8 T cells appear to be preferentially activated in the LN is not obvious but activation of LM-specific CD8 T cells in the spleen is perhaps not surprising given the predilection for LM to replicate in this tissue. VSV is neurotropic but is believed to have a promiscuous pattern of infectivity (56) although little in vivo analysis of infectious foci outside of the nervous system has been performed. Further analysis following infection via different routes and doses of these pathogens will be needed to address the detailed properties of Ag handling resulting in primary and memory T cell activation.

The secondary response to infection was also dependent on the homing molecule expression of the responding CD8 memory T cells. That is, CD62L<sub>high</sub>T<sub>CM</sub> cells responded to VSV infection to a much greater magnitude than did CD62L<sub>low</sub>T<sub>EM</sub> cells (Fig. 5). Since CD62L is essential for lymphocyte entry into the LN from the blood, this result is in keeping with the demonstration that CD8 T cell priming to VSV-derived Ags occurred primarily in the LN. Conversely, since priming to low dose LM infection occurred primarily in the spleen, both T<sub>CM</sub> and T<sub>EM</sub> responded to LM Ags since both subsets were present in that tissue (Fig. 6). Similarly, intranasal infection with Sendai virus elicits both T<sub>CM</sub> and T<sub>EM</sub> reactivation in the lung (23). More recent data demonstrates that the relative contributions of these subsets to the anti-Sendai virus response changes over time, such that while T<sub>EM</sub> dominate the secondary response relatively early after primary infection, T<sub>CM</sub> cells dominate the response at later time-points (24). These changes likely reflect the accumulation of T<sub>CM</sub> over time (57–59), which proliferate at a higher rate than T<sub>EM</sub> (60). A previous study in which the T<sub>EM</sub> and T<sub>CM</sub> recall responses to LCMV infection were analyzed shows that T<sub>CM</sub> respond preferentially over T<sub>EM</sub> (22). This finding was suggested to indicate that T<sub>CM</sub> are the prime responders in a secondary infection and that T<sub>EM</sub> do not significantly contribute to the establishment of the next generation of memory cells. However, our data indicated that responding T<sub>CM</sub> and T<sub>EM</sub> contributed equally to the resulting memory pool when reactivated following LM infection. Therefore, our results suggest that the recall response to LCMV infection, as for the primary CTL response (38), occurs preferentially in the LN where T<sub>CM</sub>, but few T<sub>EM</sub> reside, particularly after i.v. transfer of purified memory subsets.

The presence of distinct lymphoid tissues also impacted the basal level of homeostatic proliferation of memory cells in nonlymphoid tissues. Memory cells in either the lung or liver had increased incorporation of BrdU when all secondary lymphoid tissues were removed (Fig. 2b). As both the total number of memory cells in these tissues (Fig. 2a) and the ratios of T<sub>CM</sub> and T<sub>EM</sub> was equivalent in normal and allogeneic mice, the displacement of LN-residing T<sub>CM</sub> to these sites was not responsible for this difference. Thus, the nonlymphoid environment may be superior in supporting memory cell proliferation through localized concentrations of cytokines and growth factors, such as IL-15, a cytokine known to be important for memory cell turnover (61–63). Alternatively, while the nonlymphoid tissues promoted memory cell proliferation, secondary lymphoid tissues may partially suppress division. As T<sub>CM</sub> appear to divide more rapidly when compared with T<sub>EM</sub>, perhaps compensatory homeostatic mechanisms exist in lymphoid tissues, particularly the LN, to maintain the appropriate balance of T<sub>CM</sub> and T<sub>EM</sub>. However, these hypotheses remain untested.

The overall results presented in this work highlight the differential need for both secondary lymphoid tissues in generation of the primary and secondary responses to distinct pathogens. Additionally, the site of reactivation directly influences the resultant responding memory cell population. While current vaccine regimens have focused on boosting the number of responding memory cells, the results presented herein imply that biasing the type of memory cell (T<sub>CM</sub> vs T<sub>EM</sub>) and influencing the location of reactivation may be equally important for vaccine development.

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Disclosures
The authors have no financial conflict of interest.

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