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Activated Primary and Memory CD8 T Cells Migrate to Nonlymphoid Tissues Regardless of Site of Activation or Tissue of Origin

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Following activation within secondary lymphoid tissue, CD8 T cells must migrate to targets, such as infected self tissue, allografts, and tumors, to mediate contact-dependent effector functions. To test whether the pattern of migration of activated CD8 T cells was dependent on the site of Ag encounter, we examined the distribution of mouse Ag-specific CD8 T cells following local challenges. Our findings indicated that activated CD8 T cells migrated pervasively to all nonlymphoid organs irrespective of the site of initial Ag engagement. Using an adoptive transfer system, migration of nonlymphoid memory cells was also examined. Although some limited preference for the tissue of origin was noted, transferred CD8 memory T cells from various nonlymphoid tissues migrated promiscuously, except to the intestinal mucosa, supporting the concept that distinct memory pools may exist. However, regardless of the tissue of origin, reactivation of transferred memory cells resulted in widespread dissemination of new effector cells. These data indicated that recently activated primary or memory CD8 T cells were transiently endowed with the ability to traffic to all nonlymphoid organs, while memory cell trafficking was more restricted. These observations will help refine our understanding of effector and memory CD8 T cell migration patterns. The Journal of Immunology, 2004, 172: 4875–4882.

It has long been appreciated that different lymphocyte populations exhibit distinct trafficking patterns. Gowans and Knight (1) observed that small (naive) lymphocytes migrate preferentially across high endothelial venules into secondary lymphoid tissue. In contrast, blasting, or activated lymphocytes, largely marginalized into peripheral tissues, such as the intestinal mucosa (1, 2). Identification and characterization of homing molecules over the ensuing decades have revealed considerable heterogeneity in homing molecule expression by lymphocytes in unique states of differentiation or isolated from distinct tissues (3–5). Naive T cells express high levels of L-selectin, low levels of CD11a/CD18 integrin, and are CCR7 positive, all of which are required for optimal extravasation at high endothelial venules to enter lymph nodes (LN)4 (6, 7), and form the basis for the multistep paradigm of leukocyte migration (8). In contrast, activated and some memory T cells down-regulate molecules used for LN entry and up-regulate molecules involved in migration to nonlymphoid tissues such as the skin and the effector sites of the intestinal mucosa, the lamina propria (LP), and the intraepithelial lymphocyte (IEL) compartment. For example, a subset of circulating memory phenotype CD4 and CD8 T cells expresses E- and P-selectin ligands, as well as the chemokine receptors, CCR4 and CCR10, which are believed to be required for their migration to skin (9–14), while gut-seeking effector and memory cells are thought to express the α4β7 integrin and CCR9 (15–18). However, while these molecules may provide a preference for migration of cells to a particular tissue, there appears to be substantial promiscuity in the use of homing molecules. For example, P- and E-selectin are used during migration of activated T cells to the inflamed peritoneal cavity (10), and a subset of CLA+ cells from skin delayed-type hypersensitivity sites coexpress the α4β7 integrin (19). Moreover, as recently demonstrated, P-selectin and P-selectin glycoprotein ligand 1 are used by CD4 T cells to migrate to the intestinal LP (20).

Tissue-specific homing to distinct nonlymphoid sites has implications for immunity to pathogens, tumors, and allografts, as well as for the development of autoimmune to sequestered self Ags. For example, the directed migration of pathogen-specific lymphocytes to sites of infection could maximize the efficiency of the response, limit competition between separate memory cell populations, and minimize immunopathological damage. In contrast, selective targeting of immune responses may be a substantial hurdle to complete clearance of pathogens that disseminate during the course of an infection, eradication of metastasizing tumors, protection against secondary infections elicited at novel sites, and the development of appropriate immunization strategies for vaccinating against peripheral infections. Thus, it is important to delineate the conditions and cell types under which tissue-specific homing occurs.

Recent studies demonstrate that immunization with LPS and peptide, or systemic infection, lead to wide dissemination of activated and memory CD4 and CD8 T cells (21–24). These studies highlight the magnitude of peripheral responses, and suggest that a thorough comparison of Ag-specific immune responses within
activated and memory CD8 T cell migration in vivo

Materials and Methods

Mice

C57BL/6 (Ly-5.1) mice were purchased from The Jackson Laboratory (Bar Harbor, ME). C57BL/6-Ly-5.2 mice were purchased from Charles River Breeding Laboratories (Wilmington, MA) through the National Cancer Institute program. Transgenic mice (line 232-4) producing cytoplasmic OVA in small intestinal epithelial cells were previously described (25). The OT-I mouse line (26) was generously provided by W. Heath (WEHI, Parkville, Australia) and was maintained as a C57BL/6-Ly-5.2 line on a RAG-1-/- background. For adoptive transfer, 5 × 10^6 OT-I-RAG-1-/-/Ly-5.2 pooled LN cells were injected i.v. into line 232-4 transgenic hosts.

Infections, isolation of lymphocytes, and immunofluorescence analysis

Mice were infected i.v. with 1 × 10^6 PFU of vesicular stomatitis virus (VSV)-Indiana (27), orally with 1 × 10^6 fluorescence focus units of the epidemic diarrhea of infant mice (EDIM) strain of rotavirus, or intranasally with 200 egg ID_{50} of Sendai virus. At the indicated times later, lymphocytes from spleen, peripheral LN, mesenteric LN, mediastinal LN, lung, liver, small intestinal LP, fat-pad, peritoneal cavity, and brain were isolated, as previously described (22, 28). The following tetramers were used to detect Ag-specific CD8 T cells: for VSV-nucleoprotein, H-2Kb tetramers containing the peptide RGYVYQGL (22); for rotavirus infection, H-2Kb tetramers containing either the VP7-derived peptide, IVYRFLFV (29), or the VP6-derived peptide, VGVPFPYPGPM (30); for Sendai virus, H-2Kb tetramers containing the peptide FAPGNYPAL (31). Tetramers were generated, as previously described (32, 33). For staining, cells were incubated with 100 μl of a properly diluted mixture of tetramer and fluorochrome-labeled anti-CD8 mAb (clone 53.6.7.2; BD Biosciences, San Jose, CA) at 25°C for 1 h, as previously described (22).

Adoptive transfer of memory cells

To generate sufficient numbers of memory CD8 T cells for transfer, C57BL/6-Ly-5.1 mice that received a primary infection with 1 × 10^6 PFU VSV-New Jersey i.v. were challenged 3–6 mo later with 1 × 10^6 PFU VSV-Indiana i.v. and were rested an additional 3–6 mo. Total lymphocytes were isolated from spleen, lung, liver, or LP, and transferred i.v. into Ly-5.2 naive C57BL/6 recipients. Three days following transfer, lymphocytes were isolated from the spleen, lung, liver, and LP of recipient animals and stained with the N_{2,3,5}-K^b tetramer.

Results

Localized infections induce migration of activated CD8 T cells to many nonlymphoid tissues

To test the migratory abilities of CD8 T cells responding to a local infection, we orally infected mice with the EDIM strain of rotavirus, a natural mouse pathogen that results in an acute intestinal infection (34, 35). Although rotavirus preferentially infects intestinal epithelial cells (36), it remains possible that other cell types may be infected in vivo. Seven days following infection (at the peak of the response; data not shown), lymphocytes were isolated from spleen, LP of the small intestine, small intestinal epithelium (IEL), lung, and liver, and analyzed for tetramer binding (Fig. 1A). Interestingly, populations of activated cells (CD11a_{high}) specific for both peptides were detected not only in the LP and IEL compartments, but also in the spleen, lung, and liver. In several animals tested, there was no obvious preference for the appearance of Ag-specific cells in the intestinal mucosa (data not shown). These results indicated that despite a gut-restricted infection, activated CD8 T cells were able to migrate to nonlymphoid sites beyond intestinal tissue.

Because rotavirus-specific memory cells were difficult to reproducibly detect, we examined the response to Sendai virus infection that preferentially infects ciliated and secretory cells in the trachea and bronchi and type II epithelial cells in the lung, and elicits a robust CD8 T cell response focused in the lung (37) (38). Following infection, infectious virus is primarily detected in the lung and in the LN draining the lung, although early after infection low levels of virus are found in the spleen (39). Nine days following infection (the peak of the response; data not shown), Sendai virus-specific CD8 T cells in a variety of tissues were enumerated by tetramer reactivity with H-2Kb MHC tetramers. Substantial populations of activated virus-specific CD8 T cells were present in the spleen and blood as well as in the intestinal mucosa, liver, lung, fat-pad, and peritoneal cavity (Fig. 1B). Smaller populations were detected in the mediastinal LN draining the lung and the gut-draining mesenteric LN. Thus, as with primary effector populations responding to rotavirus infection, Sendai virus infection also induced CD8 T cells with broad migratory capabilities.

Sendai virus-specific memory cells are present throughout the body

Whether tissue-restricted infections resulted in widespread memory populations was also tested following Sendai virus infection. Sendai virus-specific memory cells in nonlymphoid tissues at 34 (Fig. 1C) and 64 (data not shown, except for brain and fat-pad) days after infection were quantitated. Ag-specific memory cells were detected in all nonlymphoid tissues tested, including the brain, bone marrow, LP, and peritoneal cavity (Fig. 1C). Surprisingly, in contrast to the primary phase of the response, memory cells were highly enriched in the lung-draining mediastinal LN in comparison with peripheral and mesenteric LN. Such an effect has not been previously observed in infection models and suggested that the lymph node draining the site of infection supported preferential retention or recirculation of Ag-specific memory CD8 T cells. The mechanism by which this occurs is unknown, and at present there are no known homing molecules that would preferentially mediate migration to mediastinal lymph nodes. Nevertheless, the data also suggested that this preferential localization of memory cells in mediastinal LN was not reflected among tertiary organs, as the frequency of memory cells in other tissues, such as the liver, was comparable to that found in the lung. We also noted a CD11a_{low/negative} population of Sendai virus-specific memory cells in the lung (Fig. 1C), which was not detected in any other tissue. Analysis revealed that this population was exclusive to the memory cells in the airways (obtained by bronchoalveolar lavage), while memory cells in the lung parenchyma uniformly expressed high levels of CD11a (data not shown). In a separate experiment, an analysis of the total number of Sendai virus-specific cells in the various tissues revealed that the majority of memory cells were present in the spleen and lung, while relatively small numbers were present in the liver and intestinal LP (Fig. 2). The number of tetramer^+ cells in the various LN was comparatively small, in keeping with the overall size of these tissues.

Initial activation of CD8 T cells in intestinal lymphoid tissue results in widespread migration

In all of our studies to date, infection was used to initiate T cell activation and induce migration. Although similar results were obtained whether the infection was systemic or local, it was possible that inflammation associated with the infection affected migration at distant sites. To circumvent this potential problem, we performed studies in a model system not requiring infection. A line of transgenic mice, 232-4, expresses a nonsecreted, cytoplasmic form of OVA under control of the intestinal fatty acid-binding protein promoter that directs OVA expression specifically to small intestinal mature enterocytes. Following adoptive transfer of OT-I-RAG-1-/- CD8 T cells (specific for OVA peptide presented in the
context of H-2Kb), into 232-4 mice, primary activation and division first occur within Peyer’s patches and mesenteric LN, with subsequent migration of OT-I cells to the intestinal LP and epithelium (25, 40). We used this system to determine whether local T cell activation in the absence of infection would lead to unrestricted migration of CD8 T cells. A total of 5 × 10⁵ naive B6-Ly-5.2/OT-I/RAG−/− CD8 T cells was transferred i.v. into B6-Ly-5.1 232-4 mice. Five days following transfer, lymphocytes were isolated from tissues, and the frequency of OT-I cells was determined by expression of Ly-5.2. As previously shown, the response was focused in the Peyer’s patches, LP, and IEL (Fig. 3).

The large numbers of OT-I cells in LP and epithelium are most likely the result of either retention of T cells at the site of Ag localization and/or secondary expansion upon encounter with Ag in those sites. However, all other tissues examined, including the brain, also contained substantial percentages of OT-I cells. Thus, although in this system deletion of OT-I cells throughout the body is the eventual outcome, initial T cell activation in secondary lymphoid tissues associated with the intestinal mucosa resulted in widespread migration of activated CD8 T cells.

Promiscuous migration of CD8 memory T cells following transfer

To test the migration patterns of bona fide memory CD8 T cells from distinct anatomic compartments, B6-Ly-5.1 CD8 lymphocytes isolated from the spleen and various nonlymphoid tissues of previously infected mice were transferred to naive B6-Ly-5.2 recipients. The flow cytometric analysis is shown in Fig. 4, and the quantitation of the transferred and recovered populations is shown in Table I. Splenic memory cells showed some preference for migration back to the spleen, with a 2- and 6-fold preference over migration to the lung and liver, respectively. Lung-derived memory cells migrated equally to the lung and spleen, but were less effective at trafficking to the liver. However, liver memory cells showed the most efficient migration back to the liver (e.g., a 5-fold preference over splenic memory cells migrating to the liver), but

FIGURE 1. Ag-specific primary and memory CD8 T cells disseminate widely in response to tissue-specific infections. A, C57BL/6J mice were infected by gavage with 1 × 10⁵ fluorescence focus units of the EDIM strain of rotavirus, and 7 days later lymphocytes were isolated from spleen, LP, IEL, lung, or liver. These data are derived from four independent experiments with four to six mice per group. B, C57BL/6 mice were infected intranasally with 200 egg ID₅₀ Sendai virus and 9 days, or C, 34 days (+ or 64 days) later lymphocytes were isolated from spleen, peripheral (P) LN, mesenteric (mes) LN, mediastinal (med) LN, LP, IEL, blood (PBL), peritoneum (Perit), lung, liver, fat-pad, bone marrow (BM), and brain. Tissues were perfused before cell isolations. The values are derived from analysis of four to six mice per group. Day 9 fat-pad data are the mean of three samples, each pooled from two mice. Day 34 LP data are from one sample pooled from six mice. The percentage of Ag-specific CD8 T cells was assessed by reactivity with the indicated tetramers, anti-CD8 mAb, and anti-CD11a mAb, and analysis was performed by fluorescence flow cytometry. Plots shown are gated on CD8⁺ lymphocytes, and values are mean percentages ± SEM of tetramer⁺ cells.
also migrated equally to the lung and the spleen. Thus, although strict migration to the tissue of origin was not evident, the results suggested that subsets of memory cells may exist in each tissue with bias toward homing to their original site. In contrast to these results, transferred memory cells from all tissues migrated poorly, if at all, to the intestinal LP. Even when LP-derived lymphocytes were transferred, H-2K^b/N\textsubscript{52–59} specific memory CD8 T cells were below the levels of detection within LP, but could be consistently detected in the liver and the lung. Interestingly, only a minor population of LP-derived memory cells was found in the spleen, suggesting that memory cells from the intestinal mucosa migrated more poorly to secondary lymphoid tissue than did memory cells from the lung and liver. These data suggested that a substantial portion of memory cells in spleen, lung, and liver may comprise a common recirculating pool, while smaller subsets of tissue-specific populations may exist. In contrast, LP-homing memory cells were either very rare, or once memory cells were established in the LP, little recirculation occurred in or out of the effector sites of the intestinal mucosa.

**CD8 memory cells in the intestinal mucosa are phenotypically distinct**

The adoptive transfer data suggested the possibility that once memory cells entered the intestinal LP, they became fixed in tissue or were only slowly replaced from the recirculating pool. If true,
then long-term residence in the mucosa might exert detectable effects on these memory cells. To test this possibility, we compared the expression of a variety of cell surface ligands on LP and other lymphoid and nonlymphoid memory cells. CCR7 (as assessed by binding of CCL19-Ig) and CD62L were not expressed by most memory cells in nonlymphoid tissues, while ~20% of splenic and LN memory cells expressed low levels of CCR7, ~10-fold less than naive T cell levels, and a subset of these expressed CD62L (data not shown). Two molecules that were differentially expressed by intestinal LP and epithelial memory cells were the $\beta_7$ integrins and CD69 (Fig. 5). Although memory cells in the spleen, liver, and lung lacked CD69 expression, nearly all VSV-specific memory cells from other tissues lacked or expressed only low levels of CD69, while peripheral memory cells in the LP expressed lower levels of the $\beta_7$ integrin (41, 42). This data imply that intestinal memory cells modify their phenotype while resident in the mucosa, suggesting that these memory populations may not be part of the recirculating CD8 memory pool. What the functional consequences of these and other changes might be, and whether Ag-specific CD4 memory cells undergo similar modifications remain to be determined.

**Reactivation of central or effector memory cells induces rapid expansion, $\beta_7$ integrin up-regulation, and widespread migration**

Whether CD8 effector memory T cells residing in nonlymphoid tissues can respond to antigenic challenge by clonal expansion has not been tested. To do so, we transferred different populations of memory cells into naive mice that were then infected with VSV-Indiana. $\beta_7$ integrin expression was also examined before transfer and 4 and 6 days after infection. Before transfer, tetramer$^+$ memory cells in spleen, lung, and liver lacked or expressed low levels of $\beta_7$ integrin (Fig. 6). In contrast, as shown above, a subset (~30%) of memory LP cells expressed high levels of $\beta_7$ integrin. Rechallenge of transferred memory cells resulted in robust expansion by day 4 after infection (Fig. 6, recipients). Reactivated memory cells derived from all tissues were capable of homing to the intestinal mucosa, as well as to other nonlymphoid tissues and the spleen. VSV-specific donor CD8 T cells isolated from lung, liver, or spleen of recipients had significantly up-regulated the $\beta_7$ integrin at 4 days after infection (Fig. 6). This was true regardless of the origin of the donor population, indicating de novo $\beta_7$ integrin up-regulation, as memory CD8 T cells from nonmucosal tissues uniformly expressed low $\beta_7$ integrin levels (Fig. 6). In contrast to donor cells in other tissues, tetramer$^+$ cells that had trafficked to the LP expressed lower levels of the $\beta_7$ integrin, perhaps due to receptor down-regulation upon extravasation into the mucosa. Interestingly, by 6 days after infection, $\beta_7$ integrin levels had decreased on donor tetramer$^+$ cells in all tissues, including the LP. Indeed, at this time point, Ag-specific LP CD8 T cells expressed the lowest levels of $\beta_7$ integrin, compared with tetramer$^+$ cells in all other tissues tested.

**Discussion**

In this study, we demonstrated that local challenges were adequate to elicit widespread dissemination of activated CD8 T cells (Figs. 1 and 2). Furthermore, Sendai virus infection generated long-term memory within all tissues examined, including the brain (Fig. 1C). It should be noted that local infection with rotavirus and Sendai virus may result in Ag presentation outside of the initial infection site, which could result in T cell activation in secondary lymphoid tissues other than the draining LN, such as the spleen. This possibility could potentially be extended to any tissue-specific infection, and thus would represent a physiologically relevant event. Irrespective of this caveat, our results show that activated CD8 T cells can readily migrate to uninfected tissues. These data raise

<table>
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<th>Transferred Cells</th>
<th>No. of Cells Transferred</th>
<th>Spleen</th>
<th>Lung</th>
<th>Liver</th>
<th>LP</th>
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<td>2,786 ± 589</td>
<td>103 ± 30</td>
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<tr>
<td>Lung</td>
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<td>64,769 ± 8,481</td>
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<tr>
<td>Liver</td>
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<tr>
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<td>1.9%</td>
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*Values indicate the total number of tetramer$^+$ donor cells isolated and the percentage of recovery of the total transferred population from each tissue. Values of total tetramer$^+$ cells from recipient tissues are the average ± SD derived from two or three mice from all tissues, except the liver cell transfer, which represents a single recipient.*
important teleological questions. Why do activated and memory CD8 T cells patrol all tissues after infection? This action may be essential to ensure complete elimination of the pathogen in many cases. For instance, some pathogens may initially induce confined acute local infections, yet distant sites may harbor pathogens capable of recrudescence following attrition of the immune response. Likewise, while bacteria and viruses may initiate infection in an isolated tissue, hematogenous spread may ensue. Indeed, many viruses are directly injected into the bloodstream by arthropod vectors (e.g., yellow fever virus), or, after mucosal infection, spread to other organs (e.g., measles and polio viruses). The pervasive migration of Ag-specific memory CD8 T cells would also be expected to have important consequences for protection from secondary infection, in which they may act as sentinels in all tertiary tissues regardless of the initial site of infection. Thus, it would appear advantageous for primary and memory CD8 T cells to undergo widespread dissemination.

Our data derived from adoptive transfer studies provided interesting insights into the migratory patterns of memory CD8 T cells. A substantial pool of memory cells appeared to be comprised of blood-borne migrants with the capability to enter into at least the lung, the liver, and the spleen. Thus, transfer of memory cells from any of these tissues resulted in migration to all three sites. However, some partial preference was noted for memory cells from the tissue of origin to return to that tissue upon transfer. These results suggested that small independent subsets may exist, each with the capacity to migrate only to a particular tissue. Indeed, the intestinal and the lung mucosa each contained a phenotypically distinct subpopulation of memory cells. In the case of the lung, memory cells in the airways expressed low levels of CD11a, while memory cells in all other tissues expressed high levels of this integrin. The functional significance of this finding is not yet known, but may help explain the low constitutive lytic activity of BAL-derived memory T cells (38). With regard to the gut, a subset of CD8 memory cells in the intestinal LP expressed high levels of β7 integrin, largely due to expression of the αEβ7 integrin, which may be involved in retention of cells in the LP or the epithelium (43–45). This integrin appears to be up-regulated following entry of activated CD8 T cells.
cells into the LP and epithelium (41). More surprising was the unexpected expression of CD69 on nearly all Ag-specific CD8 memory cells in the intestinal LP and epithelium. Although CD69 is thought to be an early activation marker, memory cells in lung and liver as well as LP are not blasting, but exert immediate lytic activity (22), despite the fact that the former do not express CD69. CD69 expression is also preferentially expressed on memory cells obtained by bronchoalveolar lavage following respiratory virus infections (24, 38), although intestinal LP memory cells were not analyzed in those studies. In our system, VSV is cleared rapidly after infection, but it remains possible, although unlikely, that Ag is sequestered only in the LP, and mRNA-encoding VSV proteins could not be detected in any tissue several months after infection (D. Masopust and K. S. Schluns, unpublished data). Coupled with our data showing that memory CD8 T cells derived from LP, or elsewhere, were not capable of homing back to LP following i.v. transfer (Fig. 3), the results suggested that, unlike memory cells in lung and liver, LP and intraepithelial memory cells may not exit the intestinal mucosa and recirculate. Furthermore, these findings implied that the vascular beds of some tissues, such as LP, do not constitute memory CD8 T cells. It should be noted, however, that in these short-term transfer studies, it is possible that a small subset of LP-seeking memory cells would not be detectable.

Our studies in which transferred memory cells were challenged with virus infection demonstrated that both central and effector memory CD8 T cells were capable of potent recall responses. Whether central and effector memory cells develop as separate lineages or are interrelated remains unclear (23). A recent study using lymphoctic choriomeningitis virus-specific TCR transgenic memory cells suggested that central memory cells could be derived from effector memory cells (46). However, this conclusion was based on the gradual acquisition of CD62L by effector memory CD8 T cells. It should be noted, however, that in these short-term transfer studies, it is possible that a small subset of LP-seeking memory cells would not be detectable.

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17. Kunkel, E. J., J. J. Campbell, G. Haraldsen, J. Pan, J. Boisvert, A. I. Roberts, H. O. Lee, G. S. Kansas, and T. A. Barrett. 2003. P-selectin and P-selectin glycoprotein ligand 1 are major determinants for Th1 cell recruitment to non-lymphoid sites of challenge. Perhaps microenvironmental factors within a tissue, including Ag, inflammation, cytokines, and matrix components, play an important role in regulating CD8 T cell frequency and phenotype subsequent to extravasation. These observations may have important implications for the development of autoimmunity due to molecular mimicry, vaccine development, and current approaches for disease treatment by selectively blocking lymphocyte migration into particular tissues.

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