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REVIEW

Molecular mechanisms of CD8$^+$ T cell trafficking and localization

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Abstract Cytotoxic CD8$^+$ T cells are potent mediators of host protection against disease due to their ability to directly kill cells infected with intracellular pathogens and produce inflammatory cytokines at the site of infection. To fully achieve this objective, naïve CD8$^+$ T cells must be able to survey the entire body for the presence of foreign or "non-self" antigen that is delivered to draining lymph nodes following infection or tissue injury. Once activated, CD8$^+$ T cells undergo many rounds of cell division, acquire effector functions, and are no longer restricted to the circulation and lymphoid compartments like their naïve counterparts, but rather are drawn to inflamed tissues to combat infection. As CD8$^+$ T cells transition from naïve to effector to memory populations, this is accompanied by dynamic changes in the expression of adhesion molecules and chemokine receptors that ultimately dictate their localization in vivo. Thus, an understanding of the molecular mechanisms regulating CD8$^+$ T cell trafficking and localization is critical for vaccine design, control of infectious diseases, treatment of autoimmune disorders, and cancer immunotherapy.

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Introduction

Antigen-specific CD8$^+$ T cells have the ability to recognize and destroy cells infected with intracellular pathogens [1, 2]. Prior to acquiring this type of effector function, a previously naïve CD8$^+$ T cell needs to become activated through the recognition of cognate antigen presented on major histocompatibility complex-I (MHC-I) by antigen-presenting cells (APCs), which typically occurs in secondary lymphoid organs. These activated CD8$^+$ T cells must then find and successfully enter infected tissues to contribute to host protection. Because recently activated CD8$^+$ T cells will subsequently differentiate into a long-lived memory population, the mechanisms controlling CD8$^+$ T cell trafficking and localization are critically important considerations for vaccine design against a variety of pathogens [3–5]. In addition, a number of experimental models and ever growing clinical evidence have suggested that both activation and localization of CD8$^+$ T cells are critical for successful tumor immunotherapy [6]. In fact, the localization and subsequent infiltration of CD8$^+$ T cells into tumors are a key factor that predicts clinical outcome in cancer patients [7, 8]. Thus, a comprehensive understanding of the mechanisms that ultimately regulate the trafficking and localization of CD8$^+$ T cells in vivo has broad implications as it relates to human disease.

Within the human CD8$^+$ T cell repertoire, there exists a continuum of diversity ranging from antigen-naïve cells to more terminally differentiated antigen-experienced subsets [9]. This diversity is generated over time in response to a variety of environmental factors and antigens and, theoretically, functions to optimize host protection against

pathogens, while limiting severe immunopathology during tissue injury or infection. In fact, memory $CD8^+$ T cells that are specific for different viruses often exhibit diverse, virus-specific phenotypes [10–13]. This suggests that $CD8^+$ T cells that respond to any particular pathogen or environmental antigen undergo specific differentiation resulting in extensive heterogeneity within the $CD8^+$ T cell compartment. Besides exhibiting several diverse functional differences, these heterogeneous populations of $CD8^+$ T cells also likely exhibit unique trafficking patterns that ultimately contribute to their function in vivo.

In general, the trafficking and localization of all leukocyte populations are regulated through the collective integration of selectin, chemokine receptor, and integrin interactions [14]. Importantly, although both $CD4^+$ and $CD8^+$ T cells express many of the same receptors and ligands that influence trafficking and localization, it should not be always assumed that the molecular mechanisms identified that regulate trafficking and localization of one of these cell types are necessarily interchangeable with the other [15]. During homeostatic, steady-state conditions, most $CD8^+$ T cells freely distribute between the circulation and secondary lymphoid organs [16]. However, following infection or inflammatory-related injury, the trafficking patterns of $CD8^+$ T cells change dramatically, through the collective actions of antigen and inflammatory cytokines that impact the expression of homing molecules both on the T cells as well as the vasculature. In many instances, lack of expression (or artificially interfering with the binding) of a single adhesion or chemokine receptor can often result in a profound defect in the trafficking of a $CD8^+$ T cell population to a specific tissue and prevent pathogen clearance. Because of the critical role $CD8^+$ T cells play in eliminating infected or malignant cells from the body, this review focuses on the molecular mechanisms that regulate the trafficking and localization of this specific cell population.

Trafficking of naïve $CD8^+$ T cells

Following successful positive selection and exit from the thymus, mature, but antigen inexperienced $CD8^+$ T cells will enter the circulation and remain in a naïve state until efficiently stimulated by cognate antigen. Because any particular antigen-specific $CD8^+$ T cell is present at very rare frequencies in a naïve repertoire [17, 18], these cells must be able to rapidly and completely survey all areas of the body to increase the likelihood of coming in contact with their cognate antigen. To accomplish this, naïve T cells utilize the circulatory system to travel to and survey the many lymph nodes dispersed throughout the body and will also enter the white pulp of the spleen. As naïve $CD8^+$ T cells passively transit within the vasculature they will subsequently be drawn directly into lymph nodes by extravasating across high endothelial venules (HEVs) [19]. Following a phase of scanning the lymph node for antigen, the naïve $CD8^+$ T cell will exit the lymph node, enter the efferent lymphatic vessels, and then return to the blood stream via the thoracic duct or right lymphatic duct [20]. In general, naïve $CD8^+$ T cells will follow this unidirectional trafficking pattern until stimulated by mature dendritic cells presenting antigenic peptide, resulting in T cell activation.

Signaling cascade for entering lymph nodes

As mentioned previously, naïve $CD8^+$ T cells are restricted to the circulation, lymph nodes, lymph, and white pulp of the spleen. The molecular requirement for the entry of naive $CD8^+$ T cells into lymph nodes has been extensively studied and collectively these findings reveal a model where three critical receptor–ligand interactions are required for sufficient entry of naïve $CD8^+$ T cells across HEVs (Fig. 1). HEVs are specialized blood vessels that are decorated with the combination of adhesion molecules and chemokines that efficiently recruits naïve $CD8^+$ T cells directly into the lymph node from the circulation during homeostatic conditions. Specifically, HEVs express peripheral node addressins (PNAd), a group of mucin-like adhesion molecules that are defined by reacting with the monoclonal antibody MECA-79, which serve as ligands for L-selectin (CD62L) [21]. Specifically, MECA-79 detects expression of 6-sulfo-sialyl-Lewis X motifs on core 1 *O*-glycans and this carbohydrate motif can be found on a variety of sialomucin proteins such as CD34, glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1), endomucin, and nepmucin [22, 23]. This carbohydrate motif is not necessarily restricted to core 1 O-glycans and is also generated on both core 2 *O*-glycans and *N*-glycans [24] (Fig. 2). CD62L is expressed by all naïve $CD8^+$ T cells and mediates the initial interaction between the cell and the surface of the HEV (Fig. 1). Interestingly, activated platelets have also been shown to contribute to T cell interactions with PNAd on HEVs and can regulate lymph node homing in the absence of CD62L [25, 26]. Once selectin-mediated rolling on PNAd occurs, this brings the naïve $CD8^+$ T cell into close proximity of the HEV to allow subsequent stimulation of the chemokine receptor CCR7 with chemokines that are presented by the endothelium.

Chemokines are a family of small, structurally related proteins that bind to seven transmembrane G-protein coupled receptors and are critical regulators of leukocyte extravasation and migration [27, 28]. The binding of a chemokine to its specific chemokine receptor(s) causes GDP to GTP exchange on the Gα subunit of the associated

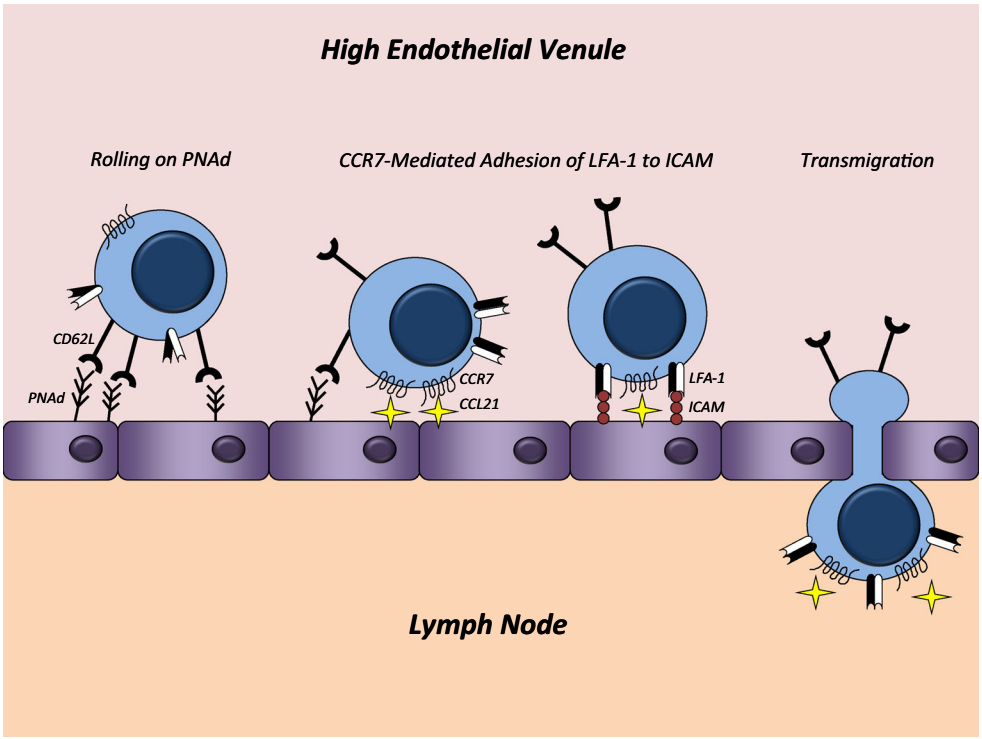

Fig. 1 Extravasation of naïve CD8$^+$ T cells across high endothelial venules. The initial interaction between a naïve CD8$^+$ T cells and HEVs occurs when L-selectin (*CD62L*) on the T cell binds to peripheral node addressins (*PNAd*) on the endothelium. The subsequent rolling that occurs due to these interactions allows the chemokine CCL21 to stimulated CCR7-mediated firm adhesion of LFA-1 to ICAM on the HEV. The naïve CD8$^+$ T cell will then scan the HEV before finally transmigrating through the endothelium and entering the lymph node

heterotrimeric (Gαβγ) complex. GDP to GTP exchange causes dissociation of the complex into the Gα and Gβγ subunits that initiate downstream signaling including the activation of Rho GTPases and mobilization of calcium, resulting in cellular polarization, reorganization of the actin cytoskeleton, activation of cell surface integrins, and ultimately, cell migration [29]. Chemokines can be broadly defined as being either 'homeostatic' or 'inflammatory' depending on whether they are present during the steady-state or following infection, respectively. Such homeostatic chemokines include those that regulate hematopoiesis, thymocyte development, and the recruitment of naïve T cells into and within lymph nodes. Both CCL19 and CCL21 are homeostatic chemokines and ligands for CCR7 [30], although CCL21 appears to be the dominant chemokine regulating naïve CD8$^+$ T cell recruitment across HEVs in mice, whereas CCL19 may also be expressed on HEVs in humans [31]. Endothelial cells of the HEV constitutively present luminal CCL21 on heparan sulfate [32] to stimulate CCR7-mediated integrin activation on circulating naïve CD8$^+$ T cells, resulting in firm adhesion of the T cell to the HEV.

Integrins are a diverse family of heterodimeric cell surface receptors and the collective combination of an integrin α and β chain determines its specificity toward a variety of ligands. Activation of cell surface integrins occurs through a process known as "inside-out signaling", whereas signaling pathways from within the cell drive both integrin clustering and affinity maturation, resulting in an increased ability for the integrin to bind ligand [33]. In the case of naïve CD8$^+$ T cell extravasation into lymph nodes, signaling through CCR7 provides the "inside-out" signal for subsequent activation of the $\alpha_L\beta_2$ integrin (CD11a/CD18), Leukocyte Functional Antigen-1 (LFA-1) and allows it to bind to its ligands intracellular adhesion molecule-1 (ICAM-1) and ICAM-2 [34]. In fact, genetically forced high affinity status of LFA-1 results in adhesion of naïve T cells to HEVs without the need for chemokine signaling [35]. Following LFA-1-mediated firm adhesion to the HEV, naïve CD8$^+$ T cells will subsequently scan the endothelium until they find an "entry point" and complete the extravasation process (Fig. 1).

Migration within lymph nodes

Lymph nodes are specialized, compartmentalized structures that function as a crossroad between innate and adaptive immunity. It is here that professional APCs

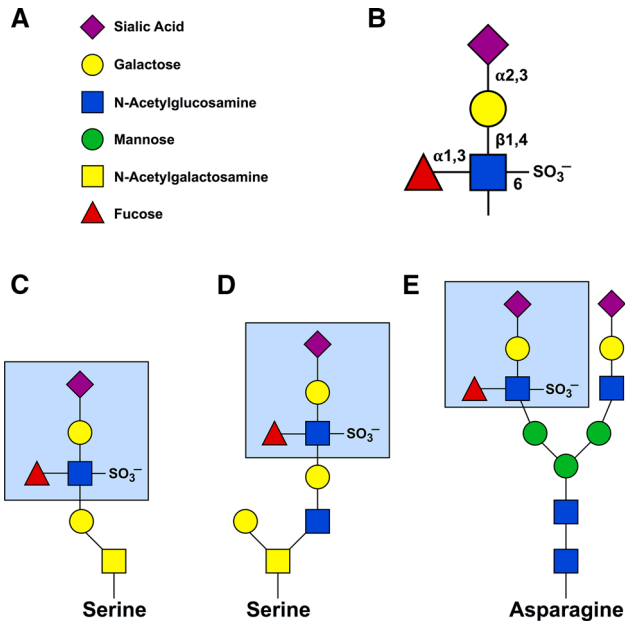

Fig. 2 Examples of 6-sulfo-sialyl-Lewis X motifs on different glycans. **a** Symbolic representation of monosaccharides found in O- and N-linked glycans. **b** Symbolic representation of the 6-sulfo-sialyl-Lewis X carbohydrate motif. **c** Core 1 *O*-glycans, **d** core 2 *O*-glycans, and **e** *N*-glycans can all bear 6-sulfo-sialyl-Lewis X. This carbohydrate motif on sialomucins such as CD34 serves as the ligand for CD62L. Expression of 6-sulfo-sialyl-Lewis X on core 1 *O*-glycans (as shown in **c**) is also used to define HEVs in vivo by reacting with the MECA-79 antibody

known as dendritic cells, which have migrated from tissues to the draining lymph node via the afferent lymph, allow naïve T cells to scan them for the presence of cognate antigen. Interestingly, the continual migration of $CD11c^+$ dendritic cells to the draining lymph node also contributes the overall integrity of HEVs [36]. Specifically, lymphotoxins (lymphotoxin α, lymphotoxin β and LIGHT) produced by these dendritic cells act directly on the HEV to maintain ligands for CD62L, which is required for the efficient recruitment of naïve $CD8^+$ T cells into the lymph node. Once a naïve $CD8^+$ T cell crosses the HEV, it will continue to migrate within the paracortex region of the lymph node, in contrast to B cells, which migrate to the follicles [37]. Recent studies using intravital microscopy have begun to characterize the mechanisms that regulate the migration patterns of naïve $CD8^+$ T cell populations within the lymph node, as well as the interactions that occur between naïve $CD8^+$ T cells and activated dendritic cells following infection.

Naïve $CD8^+$ T cells again primarily utilize CCR7 to navigate throughout the paracortex of the lymph node, although it is clear that additional G-protein-coupled receptors are also involved [38, 39]. Here, a network of fibroblastic reticular cells (FRCs) forms the navigation grid for naïve T cells to randomly scan the dendritic cells that have migrated into these T cell zones [40, 41]. Fibroblastic reticular cells produce the homeostatic chemokines CCL19 and CCL21, thus providing the ligands for CCR7-expressing naïve $CD8^+$ T cells to follow across this cellular network and retain these cells within the lymph node. Not only do these chemokines facilitate the migration pattern of naïve T cells, but it is also believed that the expression pattern of these chemokines orchestrates the compartmentalization of the lymph node into the T and B cell zones. There is also evidence that activated $CD4^+$ T cells can recruit naïve $CD8^+$ T cells toward antigen-presenting dendritic cells in the lymph node through the localized production of the chemokines CCL3 and CCL4 [42].

Interaction of naïve $CD8^+$ T cells with dendritic cells occurs following recognition of cognate antigen and results in stable conjugation between these two cell types. Initially, a naïve antigen-specific $CD8^+$ T cells will make brief, serial contacts with a dendritic cell before making a stable conjugate, a process that is influenced by both the affinity and quantity of antigen [43–45]. Here, stimulation of the T cell receptor (TCR) with peptide-MHC-I provides the "inside-out signal" needed for stable conjugation between the two cell types mediated by the integrin LFA-1 on the T cell and ICAM on the dendritic cell [46, 47]. Early studies suggested that these conjugations formed primarily in the T cell zone of the lymph node. However, more recent studies suggest that following a viral or parasitic infection, dendritic cell priming of T cells occurs in the subcapsular sinus region or interfollicular region of the lymph node [48, 49]. Thus, where $CD8^+$ T cell activation occurs in the lymph node appears to be regulated by the location of antigen-bearing dendritic cells and may vary based on the type of infection or vaccination.

Regulation of lymph node egress

A naïve $CD8^+$ T cell will spend approximately 12–24 h in a given lymph node before it enters the draining lymphatics and returns to the circulation [50, 51]. Egress of $CD8^+$ T cells from lymph nodes is under the control of a naturally occurring gradient of sphingosine-1 phosphate (S1P) and its receptor S1PR1 (also known as $S1P_1$) expressed on the $CD8^+$ T cell [52]. This gradient is generated through a combination of sphingosine kinases and lyases, which results in high expression of sphingosine-1 phosphate in the blood and lymph, but lower levels inside the lymph node [53]. Like chemokine receptors, S1PR1 is a G-protein-coupled receptor and its signaling causes polarization and migration of T cells toward higher concentrations of ligand. Binding of S1P to S1PR1 results in rapid internalization and degradation of the receptor, and as such, expression of S1PR1 is found on naïve $CD8^+$ T cells in the lymph node, but not in the blood or lymph. The immunosuppressive

drug FTY720 is a functional antagonist of S1PR1 and treatment results in sequestration of CD8$^+$ T cells in lymph nodes [54]. Thus, the retention time of CD8$^+$ T cells in lymph nodes during homeostatic conditions is under control of a balance of signals, CCR7 interactions with CCL19 and CCL21 on FRCs that direct migration and retention of naïve CD8$^+$ T cells throughout the lymph node compartment and S1PR1 signals that attract the cells toward the efferent lymph.

Inflammatory cytokines can also influence the retention time of naïve CD8$^+$ T cells within lymph nodes. In particular, type I interferons (IFNα and IFNβ) are produced at high levels during viral infections and will drive the expression of CD69 on naïve CD8$^+$ T cells [55]. CD69 will subsequently bind to S1PR1, causing its internalization and degradation, resulting in lymph node retention of the CD8$^+$ T cell. CD69 contains a C-type lectin-binding domain, but seems not to facilitate the interaction with S1PR1. Rather this protein–protein interaction requires the transmembrane region of CD69 and binding results in a conformational change in S1PR1 [56]. Stimulation of the TCR will also result in rapid transcriptional expression of CD69, which allows CD8$^+$ T cells to be retained in lymph nodes as they become fully activated by cognate peptide-MHC-I on dendritic cells. In fact, this suppression of S1PR1 expression dominates the retention of CD8$^+$ T cells within the lymph node during clonal expansion and does not require CCL19 and CCL21 [41]. Therefore, modulation of S1PR1 expression on naïve CD8$^+$ T cells is a critical mechanism that both increases the chance for naïve CD8$^+$ T cells to find their cognate antigen during an infection and for the retention of antigen-specific cells in the lymph node for full activation by dendritic cells presenting cognate antigen.

Trafficking of recently activated, effector CD8$^+$ T cells

When previously naïve CD8$^+$ T cells are subjected to a combination of TCR ligation, co-stimulation, and inflammatory cytokines, these recently activated 'effector' CD8$^+$ T cells lose expression of CD62L through a combination of protease-mediated cleavage and transcriptional repression [57], and thus, these cells lose the capacity to enter lymph nodes through HEVs. Instead, recently activated CD8$^+$ T cells express a cohort of new gene products that control the trafficking and localization patterns of this cell population. As a newly activated CD8$^+$ T cell begins to fully divide, its daughter cells will re-express S1PR1 and exit the lymph node. These effector cells will then re-enter the circulation and home toward inflamed tissues to combat the infection that led to their priming and generation. The cues for leukocytes to be recruited to a site of infection require changes in expression of adhesion molecules and chemokines on the vascular endothelium. Characteristics of inflamed endothelium include expression of a number of adhesion molecules including P- and E-selectin, ICAMs, vascular cell adhesion molecules (VCAMs), as well as a variety of inflammatory chemokines [58–60]. Thus, matched receptor–ligand interactions between effector CD8$^+$ T cells and vascular endothelium regulate the specific recruitment to inflamed or infected tissues.

Generation of P- and E-selectin ligands

In contrast to cells of the innate immune system such as neutrophils, which constitutively express P- and E-selectin ligands, the capacity for CD8$^+$ T cells to efficiently adhere to P- and E-selectin occurs dynamically and transiently following antigen-driven activation. P- and E-selectin expression is readily found on inflamed endothelium and facilitates the initial interaction with activated CD8$^+$ T cells that are being attracted to the site of infection or injury. Naïve CD8$^+$ T cells cannot bind to either P- or E-selectin and as a result are essentially excluded from entering inflamed tissues. However, following sufficient TCR-mediated activation, a previously naïve CD8$^+$ T cell begins expressing the enzymes required to generate O-linked glycosylation structures that bear sialyl-Lewis X motifs on cell surface proteins including P-selectin glycoprotein ligand 1 (PSGL-1), E-selectin Ligand-1, CD44, and CD43, which binds to the c-type lectin domains found on both P- and E-selectin [61, 62]. Generation of sialyl-Lewis X motifs on selectin ligands requires a number of glycotransferase enzymes. In particular, activated CD8$^+$ T cells express core 2 β1,6 *N*-acetylglucosaminyltransferase 1 (*Gcnt1*), α1,3 fucosyltransferase 7 (*Fut7*), and probably additional enzymes required to fully generate the core 2 *O*-glycans that will bind to P- and E-selectin [63, 64]. Thus, post-translational glycosylation of selectin ligands is a critical requisite for attraction of effector CD8$^+$ T cells to inflamed vascular endothelium.

Expression of chemokine receptors and integrins

The expression of new integrins and chemokine receptors is essential both for localizing effector CD8$^+$ T cells to inflamed endothelium as well as migration once the cells have extravasated into the tissue. Chemokine receptors expressed by effector CD8$^+$ T cells include CCR4, CCR9, CCR6, and CCR10. Ligands for these chemokine receptors belong to the "inflammatory" family of chemokines, as their expression is most often found at a site of infection. Effector CD8$^+$ T cells also strongly increase expression of CXCR3 and ligands for this chemokine receptor include CXCL9, CXCL10, and CXCL11, which collectively are known as the IFNγ-inducible chemokines [65]. In fact, it

has recently been demonstrated that antigen-specific $CD4^+$ T cell production of IFNγ can influence recruitment of effector $CD8^+$ T cells by increasing expression of CXCL9 and CXCL10 at the site of infection [66]. Effector $CD8^+$ T cells will also express a variety of integrins including $\alpha_4\beta_1$ (Very Late Antigen-4; VLA-4), $\alpha_1\beta_1$ (VLA-1) and $\alpha_4\beta_7$. In particular, $\alpha_4\beta_7$ appears to play a critical role in migration of effector $CD8^+$ T cells to the gut due to the expression pattern of its ligand mucosal addressin cell adhesion molecule (MadCAM) [67]. Expression of VLA-1 has been shown to impact trafficking and/or retention of $CD8^+$ T cells in the lung following influenza virus infection [68]. Therefore, the collective action of newly expressed chemokine receptors and integrins functions to recruit effector $CD8^+$ T cells to inflamed tissues.

Several studies have suggested that the local microenvironment or specialized dendritic cell subsets influence the expression pattern of selectin ligands, chemokine receptors, and integrins, thus allowing for homing of these newly activated T cells to a specific target tissue, a process known as "imprinting". For example, the route of infection or vaccination seems to play a significant role in the expression of tissue-specific trafficking molecules that will subsequently be expressed on $CD8^+$ T cells following activation [69–72]. Specifically, $CD8^+$ T cells primed with dendritic cells from mesenteric lymph nodes or peyer's patches have been shown to express high levels of both $\alpha_4\beta_7$ integrin and CCR9, thus establishing a "gut-homing" combination of homing molecules [73]. In contrast, $CD8^+$ T cells activated following viral infections of the skin express E-selectin ligands and CCR4, which has been described as a "skin-homing" phenotype [71, 74]. In addition, it has been suggested that acquisition of "skin-homing" molecules appears to be the default pathway following $CD8^+$ T cell activation and the "gut-homing" phenotype is generated by additional signals provided by activated dendritic cells.

Because effector $CD8^+$ T cells need to re-enter the circulation prior to trafficking to the site of infection, imprinting of specific homing receptors on these cells is an efficient mechanism to ensure that antigen-specific $CD8^+$ T cells home to the correct tissue. It should be noted, however, that a number of the studies that identify the process of imprinting were performed using either in vitro activation or on $CD4^+$ T cell populations and, thus, may not be a generalizable feature of all $CD8^+$ T cells activated in vivo. In fact, following a systemic lymphocytic choriomeningitis virus (LCMV) infection, the vast majority of recently activated effector $CD8^+$ T cells express P- and E-selectin ligands, $\alpha_4\beta_7$ integrin, and CCR9 [75, 76]. This would suggest that the effector $CD8^+$ T cells generated following systemic viral infection do not become imprinted and have the potential to localize to both the skin and gut (and possibly many other tissues). Therefore, a contrasting model of effector $CD8^+$ T cell trafficking would be that the expression of trafficking receptors on activated $CD8^+$ T cells is quite liberal (not tissue-specific) and that the changes in expression of adhesion molecules and chemokines on vascular endothelium following infection or injury is what dictates recruitment to specific tissues. Additional studies will need to be performed to fully determine the molecular and biochemical signals that ultimately regulate effector $CD8^+$ T cell trafficking in vivo and whether systemic or localized infections drive differential expression of trafficking molecules on $CD8^+$ T cells during activation.

Migration within tissues and exit via lymphatics

Although a wealth of information is known regarding the mechanisms controlling recruitment of T cells toward sites of inflammation, far less is known about how these cells migrate within and eventually leave the tissue. Migration within tissues requires $CD8^+$ T cells to interact with both a cellular and extracellular matrix network. Several integrins expressed on effector $CD8^+$ T cells function as receptors for extracellular matrix components including VLA-4 and $\alpha_v\beta_1$ which bind to fibronectin, and VLA-1 which binds to collagen. Presumably, chemokine-stimulated activation of these integrins directs migration. In fact, blocking $\alpha_v\beta_1$ inhibits the migration of activated $CD4^+$ T cells within inflamed skin [77], but whether this integrin also controls migration of $CD8^+$ T cells in tissues is currently unknown. In addition to its role in regulating recruitment from the circulation, CXCR3 and its ligands have been implicated in directing the migration of activated $CD8^+$ T cell in the brain during a chronic *Toxoplasma gondii* infection [78]. Exiting from tissues requires that $CD8^+$ T cells enter lymphatic vessels that will passively carry them to the draining lymph node and eventually back to the circulation. Like dendritic cells, $CD8^+$ T cells utilize CCR7 to efficiently enter lymphatic vessels before transiting to the draining lymph nodes [79–81]. It has also been reported that S1PR1 also guides $CD8^+$ T cells toward afferent lymphatic vessels [82]. If this is indeed the case, this would suggest that CCR7 and S1PR1 signaling act synergistically in tissues to recruit $CD8^+$ T cells to the draining lymphatics and that inflammatory chemokines might act to retain them. However, whether this model accurately predicts the migratory behavior of activated $CD8^+$ T cells in tissues has not been fully characterized.

Trafficking and localization of antigen-experienced memory $CD8^+$ T cell populations

Following resolution of the contraction phase of the $CD8^+$ T cell response to antigen, the surviving cells differentiate

into long-lived 'memory' populations. Although these populations of cells closely resemble naïve CD8$^+$ T cells when comparing overall gene expression profiles [83], many important functional differences clearly distinguish a naïve CD8$^+$ T cell from an antigen-experienced, memory CD8$^+$ T cell. Specifically, these cells are now able to produce cytokines such as IFNγ [84], rapidly kill cells with perforin and granzyme following antigenic stimulation [85], and undergo substantial homeostatic proliferation [86], which may contribute to the longevity of the population. Furthermore, in contrast to naïve CD8$^+$ T cells which are restricted to entering lymph nodes and effector CD8$^+$ T cells which are attracted primarily to inflamed tissues, memory CD8$^+$ T cells exhibit a diverse trafficking pattern that encompasses features of both naïve and effector CD8$^+$ T cells. This results in populations of memory CD8$^+$ T cells to be distributed throughout the body, both in tissues and secondary lymphoid organs [87, 88].

The 'Central' and 'Effector' memory T cell paradigm

Shortly after the discovery that T cells utilized the selectin CD62L and the chemokine receptor CCR7 to directly enter lymph nodes by crossing HEVs, it was identified that in humans, some antigen-experienced memory CD8$^+$ T cells (and CD4$^+$ T cells) expressed the combination of these receptors, while others did not [89, 90]. This resulted in categorizing memory T cell populations into one of two broad categories based on this trafficking ability. Memory CD8$^+$ T cells that expressed CD62L and CCR7 were labeled "Central Memory" (T_{CM}), due to their capacity to directly enter lymph nodes and undergo robust expansion following re-stimulation. In contrast, memory CD8$^+$ T cells that lacked expression of these receptors were termed "Effector Memory" (T_{EM}), as they are largely absent from lymph nodes, localize more preferentially to peripheral tissues and exhibit enhanced killing capacity. This paradigm has been also verified using mouse models of infection, as CD62L$^{-/-}$ memory CD8$^+$ T cells are almost entirely excluded from lymph nodes, but readily localize to the spleen and other tissues [91]. Therefore, the expression of CD62L and CCR7 is critical for localizing memory CD8$^+$ T cells into secondary lymphoid organs where they can undergo secondary expansion following stimulation by antigen on mature dendritic cells.

Conceivably, the generation of both T_{CM} and T_{EM} CD8$^+$ T cells occurs to optimize host protection against re-infection, where T_{EM} can provide a first line of defense in tissues and T_{CM} can undergo re-expansion in draining lymph nodes. In fact, numerous studies have examined the protective capacity these two memory subsets provide and the results suggest that protection is largely pathogen specific. For example, T_{EM} CD8$^+$ T cells are potent mediators of host protection following infection with *Listeria monocytogenes*, a Gram-positive bacteria that infects the spleen and liver and also against both a systemic and local Vaccinia virus infection [91–93]. In contrast, T_{CM} CD8$^+$ T cells are superior in preventing a chronic LCMV infection due to both their lymph node localization and their potent recall potential [91, 94]. T_{CM} CD8$^+$ T cells have also been shown to be more potent contributors to anti-tumor immunity than T_{EM} due to their lymph node homing capacity [95]. Thus, these studies suggest that the differential localization of memory CD8$^+$ T cell subsets plays a critical role in providing protective immunity against a variety of pathogens and disease conditions.

The ratio of T_{CM} to T_{EM} populations that exist following a primary infection or vaccination is heavily influenced by the presence (or absence) of inflammatory cytokines. High levels of inflammatory cytokines such as type I interferons or IL-12 during CD8$^+$ T cell priming and expansion will drive not only more extensive proliferation, but also the formation of more T_{EM} in the subsequent memory population [96]. Conversely, CD8$^+$ T cells primed in a low inflammatory environment expand less, but predominantly form T_{CM}. In addition, priming of naïve CD8$^+$ T cells in a low inflammatory environment allows for rapid boosting following secondary vaccination or infection [97]. Therefore, exposure to inflammatory cytokines following infection or vaccination not only impacts the immediate proliferative response to antigen, but also subsequently affects the overall distribution, localization, and boosting capacity of memory CD8$^+$ T cells following contraction.

Recruitment of memory CD8$^+$ T cells to inflamed tissues

Following an injury or infection, memory CD8$^+$ T cells rapidly localize to the inflamed tissue in an antigen-independent manner. This biological process was first observed when memory CD8$^+$ T cells specific for one respiratory virus were recruited to the site of infection following subsequent challenge with a different respiratory virus [98]. Thus, antigen-experienced memory CD8$^+$ T cells acquire the capacity to rapidly localize to an inflamed environment, regardless of whether they will be able to subsequently recognize the antigens expressed by the pathogen. Therefore, following re-infection, antigen-specific memory CD8$^+$ T will be recruited to the site of infection in two phases. Initially, memory CD8$^+$ T cells will traffic to the inflamed environment regardless of antigen specificity and provide immediate protection if cognate antigen is present. The second phase occurs as previously T_{CM} CD8$^+$ T cells in the draining lymph node undergo antigen-driven expansion and subsequently

localize to the site of infection [99]. The overall set of mechanisms that control the antigen-independent recruitment of memory CD8$^+$ T cells to sites of infection is mostly still unknown, although the chemokine receptors CCR5 and CXCR3 have been shown to impact recruitment of memory CD8$^+$ T cells to the lung airways in this manner [100, 101].

The ability to modulate binding to P- and E-selectin has also been shown to contribute to localization of memory CD8$^+$ T cells in vivo [76]. Most memory CD8$^+$ T cells do not bind to P- or E-selectin during homeostatic conditions. However, it has been recently demonstrated that memory CD8$^+$ T cells modulate their ability to generate P- and E-selectin ligands during an infection or inflammatory episode, and this also occurs in an antigen-independent manner. Specifically, memory CD8$^+$ T cells exhibit an open chromatin conformation at the *Gcnt1* gene locus, the enzyme responsible for core 2 *O*-glycan synthesis in T cells. In response to inflammatory IL-15, memory CD8$^+$ T cells will express *Gcnt1*, resulting in the generation of core 2 *O*-glycans that serve as P- and E-selectin ligands (Fig. 3). These antigen-experienced CD8$^+$ T cells are then drawn specifically toward inflamed tissues and, if cognate antigen is present, provide host protection against infection [76]. Importantly, naïve CD8$^+$ T cells do not express core 2 *O*-glycans in response to IL-15 stimulation due to epigenetic differences at the *Gcnt1* gene locus, and thus, are not able to localize to inflamed tissues using this mechanism. Overall, these studies collectively suggest that the protection mediated by circulating memory CD8$^+$ T cells requires an antigen-independent recruitment phase, followed by antigen-dependent elimination of infected cells.

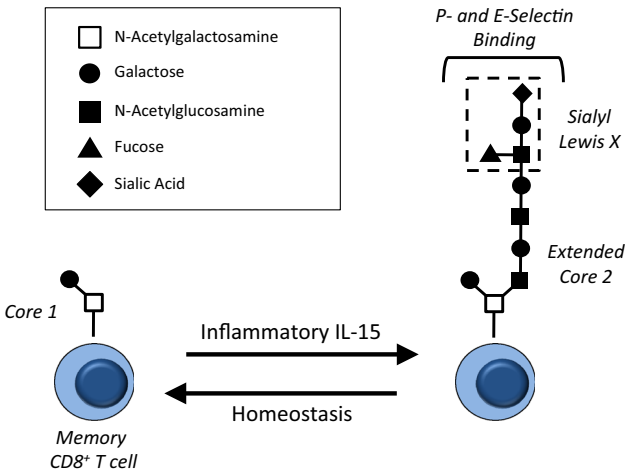

Fig. 3 Memory CD8$^+$ T cells express P- and E-selectin ligands in response to inflammation. Most memory CD8$^+$ T cells do not express core 2 *O*-glycans or bind to P- or E-selectin during homeostatic, steady-state conditions (*left*). However, in response to inflammatory IL-15, memory CD8$^+$ T cells will synthesize core 2 *O*-glycans in a TCR-independent manner. The newly synthesized core 2 *O*-glycans on proteins such as PSGL-1 serve as ligands for P- and E-selectin and will subsequently attract these memory CD8$^+$ T cells to inflamed tissues

Trafficking of memory CD8$^+$ T cells following multiple antigen stimulations

Recent experimental studies have demonstrated that CD8$^+$ T cells that are exposed to multiple antigenic challenges (like what would occur during recurring exposure to infections or booster immunizations) exhibit a transcriptional gene profile and phenotype that resembles a "terminally differentiated T_{EM}" population of memory cells [92, 102, 103]. Similar types of memory CD8$^+$ T cell populations are readily found following chronic or latent viral infections, such as those specific for certain epitopes of murine cytomegalovirus (MCMV) [104]. As suggested by the T_{EM} phenotype, these cells strongly reduce their expression of CD62L and CCR7, greatly diminishing their lymph node homing potential and undergo limited proliferation following antigen re-challenge. However, these cell populations express higher levels of chemokine receptors and integrins that would regulate recruitment to inflamed tissues, such as CCR5 and VLA-1. Accordingly, these repeatedly stimulated CD8$^+$ T cells are now enriched in peripheral tissues such as the lung. Collectively, these studies suggest that populations of CD8$^+$ T cells that are continually stimulated by antigen are excluded from secondary lymphoid organs and are enriched in peripheral tissues, where they can serve as a first line of defense against re-infection.

Tissue-resident memory CD8$^+$ T cells

In the past few years, the major advance in our overall understanding of CD8$^+$ T cell trafficking has actually focused much more on the "lack thereof". As discussed previously, memory CD8$^+$ T cells are often defined based on their expression of lymph node homing receptors and the cells that lack those receptors are typically labeled T_{EM}. However, recent experimental studies provide compelling evidence that there is a specialized subset of CD8$^+$ T_{EM} that do not re-enter the circulation following the resolution of an infection and are retained in tissues such as the skin, lung, and gut, and have been named "resident memory" CD8$^+$ T cells (T_{RM}) [105–108]. Besides exhibiting a unique gene expression profile [109], these cells provide potent protection against a number of pathogens following re-infection [110–112]. Because of the superior protective capacity of these cell populations compared to circulating memory CD8$^+$ T cells, there has been considerable interest in studying the molecular and biological mechanisms that

regulate the formation of T_{RM}, especially with regard to vaccine design.

Like typical T_{EM}, T_{RM} do not express CD62L, but rather have been identified by the expression of the α_E integrin (CD103) chain of $\alpha_E\beta_7$ and CD69. The ligand for $\alpha_E\beta_7$ is E-cadherin [113] and it is believed that expression of this integrin–ligand interaction helps to retain T_{RM} specifically in tissues, as CD103$^{-/-}$ CD8$^+$ T cells fail to generate T_{RM} following herpes simplex virus (HSV) infection [109]. As mentioned previously, CD69 targets S1PR1 for degradation and S1PR1 has been implicated in guiding CD8$^+$ T cells out of tissues. In fact, transcriptional downregulation of S1PR1 also contributes to the generation of T_{RM} in the skin [114]. This finding also supports the mechanism that CD8$^+$ T cells utilize S1PR1 for exiting tissues. Therefore, these studies demonstrate that expression of CD103 and CD69 not only can be used as "markers" for the identification of T_{RM} CD8$^+$ T cells populations, but also contribute to their overall retention and differentiation.

The mechanisms controlling both the establishment and maintenance of T_{RM} CD8$^+$ T cells have begun to be elucidated. Interestingly, the presence of cognate antigen does not appear to be necessary for the generation of T_{RM} as transfer of in vitro activated CD8$^+$ T cells also become T_{RM} after localizing to inflamed tissues [115]. Rather, several cytokines have been implicated in driving T_{RM} generation. In particular, Transforming Growth Factor (TGF)-β seems to be potent driver of T_{RM} differentiation, although IL-33 and tumor necrosis factor alpha (TNFα) may also contribute [106, 109, 114, 116]. Like conventional, circulating memory CD8$^+$ T cells, IL-15 stimulates the survival of these cells in the tissues, even though they express low levels of IL-2Rβ (the receptor for IL-15) and do not undergo significant homeostatic proliferation [105, 109]. Collectively, these studies suggest a model where naïve CD8$^+$ T cells are initially activated in the draining lymph node and subsequently re-enter the circulation. These recently activated effector CD8$^+$ T cells will now home to tissue and upon exposure to TGF-β (and possibly TNFα and IL-33) will subsequently differentiate into a T_{RM} (Fig. 4).

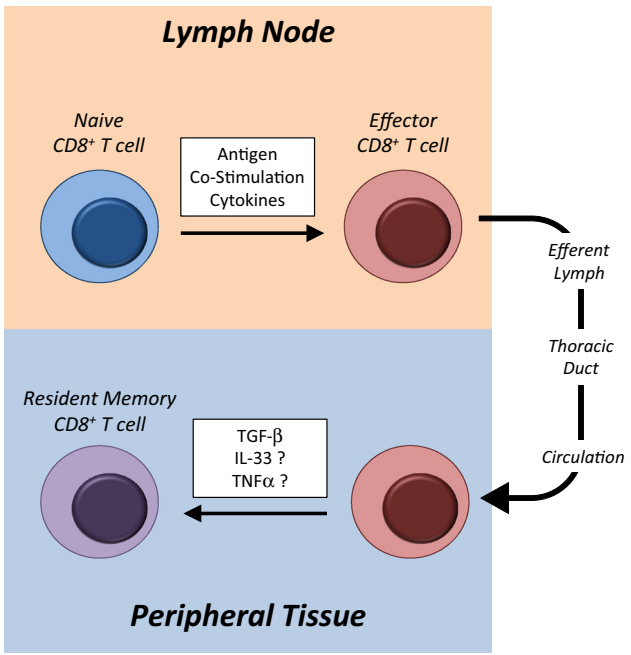

Fig. 4 Differentiation of tissue-resident memory CD8$^+$ T cells. Following infection, naïve CD8$^+$ T cells become activated in draining lymph nodes by antigen, co-stimulation, and inflammatory cytokines, which drive their conversion into effector CD8$^+$ T cells. These activated CD8$^+$ T cells will then enter the efferent lymph and return to the circulation via the thoracic duct. After homing into tissues, effector CD8$^+$ T cells will subsequently differentiate into resident memory CD8$^+$ T cells in response to TGF-β. IL-33 and TNFα may also contribute to the establishment of tissue-resident memory CD8$^+$ T cell populations

Concluding remarks

As described in this review, the trafficking and localization of different CD8$^+$ T cells will vary considerably based on a number of factors that ultimately influences the expression of selectin and selectin ligands, chemokine receptors, and integrins. The specific molecular and biochemical signals that influence the expression of various homing receptors during CD8$^+$ cell activation and memory differentiation still remain mostly undefined and it is also unclear whether "imprinting" is a generalizable mechanism or if it only occurs during certain biological settings. In addition, our overall understanding of how antigen-experienced memory CD8$^+$ T cells traffic is still rather limited, which is significant because as we age, most CD8$^+$ T cells in humans exhibit an antigen-experienced, memory phenotype. The recent identification and characterization of the T_{RM} subset of memory CD8$^+$ T cells have generated considerable interest in the field and suggest there are probably additional, specialized memory CD8$^+$ T cells beyond the broadly defined T_{CM} and T_{EM} subsets. In fact, recent evidence suggests that memory CD4$^+$ T cells do not use CCR7 for homing to lymph nodes and CCR7 deficiency only has minimal effect on memory CD8$^+$ T cell lymph node homing [117]. Therefore, even the most fundamental principles of memory CD8$^+$ T cell trafficking are still being disputed in the literature. Overall, by fully characterizing certain memory CD8$^+$ T cells subsets, we will be able to make more sophisticated predictions of the ability for these cells to traffic to different tissues and how to influence this process therapeutically. These fundamental principles will be critical for vaccine design, optimizing cancer immunotherapy strategies, and treating autoimmune disorders.

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