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Regional and mucosal memory T cells

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Abstract

After infection, most antigen-specific memory T cells reside in nonlymphoid tissues. Tissue-specific programming during priming leads to directed migration of T cells to the appropriate tissue, which promotes the development of tissue-resident memory in organs such as intestinal mucosa and skin. Mechanisms that regulate the retention of tissue-resident memory T cells include transforming growth factor-β (TGF-β)-mediated induction of the E-cadherin receptor CD103 and downregulation of the chemokine receptor CCR7. These pathways enhance protection in internal organs, such as the nervous system, and in the barrier tissues—the mucosa and skin. Memory T cells that reside at these surfaces provide a first line of defense against subsequent infection, and defining the factors that regulate their development is critical to understanding organ-based immunity.

The development and functional programming of the immune system is characterized by regionalization at multiple levels. For example, the generation of mature $CD4^+$ and $CD8^+$ T cells is compartmentalized in the thymus and follows a prescribed set of selection steps geared toward achieving a functionally responsive and minimally autoreactive peripheral repertoire[1]. Although certain stochastic events designate outcomes in this process, the system is essentially closed and under normal circumstances is not heavily influenced by extrathymic events. In contrast, mature T cells responding to antigens are considerably affected by the context in which antigen presentation occurs, which often represents a continuously changing environment. Thus, the immune response to infection is subjected to a dynamic process with active changes to cell types and their locations, concentrations of inflammatory and anti-inflammatory mediators, blood and lymph flow, and antigen concentrations. In the secondary lymphoid tissues, where T cell priming occurs, the sum of these alterations dictates the type of effector T cells generated and the nature of the memory populations produced.

Memory T cells are characterized by considerable heterogeneity at the phenotypic and functional levels. Early studies identified functionally distinct subsets of human peripheral blood effector and memory $CD8^+$ T cell subsets on the basis of the expression of costimulatory and adhesion molecules[2]. Further analysis of human blood has linked the expression pattern of the lymph node-homing receptors CD62L and CCR7 to the functional status of memory $CD4^+$ and $CD8^+$ T cells[3]. That is, cells lacking these molecules have heightened constitutive effector functions (effector memory T cells (T_{EM} cells)), whereas cells expressing these receptors are apparently in a resting state (central memory T cells

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(T_{CM} cells)). These findings have led to the hypothesis that the two subsets are located in distinct tissues, with T_{CM} cells in lymph node, spleen and blood, and T_{EM} cells in spleen, blood and nonlymphoid tissues; indeed, this prediction has held true[4,5]. After immunization or infection, $CD4^+$ and $CD8^+$ memory T cells with the ability to rapidly produce cytokines, and with direct *ex vivo* cytotoxic activity in the case of $CD8^+$ T cells, are present in essentially all nonlymphoid tissues, including the lung, liver and intestine. Both localized and systemic infections can lead to the generation of memory cells that accumulate in nonlymphoid tissues[6]. However, entry of memory T cells into nonlymphoid tissues and/or their residence there can lead to tissue-specific influences that affect the phenotype and function of the memory populations[7-10]. Moreover, in some tissues there seems to be one-way traffic of effector or memory T cells into the site with no means of exit. Thus, depending on the nonlymphoid tissue, long-term, resident, regional memory is established. Here we discuss the factors that regulate the regionalization of memory, including those that regulate T cell migration, retention and exit. Additionally, we discuss the influence of tissue location on the types of effector T cell functions that develop and consider the relevance of regional memory to immunoprotection.

Inductive and effector sites of peripheral tissues

The human body is separated from the outside world by barrier surfaces that carry out many functions to promote human health. Memory T cells reside in these tissues, which consist mainly of the intestine, lungs, skin and genital surfaces. These tissues have a vast surface area and therefore contain most the body's memory T cells. Other tissues, such as the brain, bone marrow and liver, as well as essentially any tissue, may also contain memory T cells[5,6]. An appreciation of the structure and anatomy of any given tissue is essential to the understanding of T cell immunity at that site. Some of these sites, in particular the mucosal surfaces and the skin, share certain anatomical characteristics. In the case of the lungs, intestine and portions of the genitourinary tract[11], the exterior environment is separated from the internal one by a single layer of epithelial cells covered by a mucus layer. The skin is more complex, with an outer epidermal layer largely devoid of lymphatics underlaid by a dermal layer composed mainly of connective tissue. Dendritic cells (DCs) underlying the epithelium in the mucosae or within the epidermal and dermal layers of the skin are poised to capture incoming antigens and subsequently migrate to secondary lymphoid tissues for antigen presentation to T cells.

In the tissues discussed above, the immune response is typically subdivided into events that occur at inductive sites, such as the Peyer's patches and mesenteric lymph nodes (MLNs) for the intestine, and effector sites, such as the gut lamina propria and intraepithelial lymphocyte compartment; the latter is positioned above the basement membrane (Fig. 1). In the lung, antigen presentation initially occurs in the mediastinal lymph nodes, followed by the migration of activated T cells to the lung parenchyma and the bronchoalveolar space. Pathogens that invade the host through the intestinal mucosa typically first encounter antigen-presenting cells in either the Peyer's patches or the lamina propria. Peyer's patches are unique among T cell-inductive sites, other than the spleen, because they do not acquire antigens through lymphatics but instead acquire them via specialized epithelial cells called 'M cells' that are scattered over the dome of the Peyer's patches and transfer antigen to DCs in the subepithelial dome. T cell activation can then proceed in the Peyer's patches and/or in the MLNs, because DCs continuously traffic from the mucosa to the latter site[12-14]. For example, *Shigella* subspecies[15], *Salmonella* subspecies[16], reovirus, poliovirus and other enteric viruses[17] gain access to the body mainly through the gastrointestinal tract by transit through M cells. Indeed, after oral infection with *Salmonella typhimurium*, antigen-specific $CD4^+$ T cells are activated in the Peyer's patches by local DCs[18]. M cells also provide an entry point through the lung epithelium for pathogens, including *Mycobacterium*

tuberculosis[19], and through the intestinal villous epithelium[20]. However, pathogens may also enter the body by direct transit through epithelial cells, as in humans infected with *Listeria monocytogenes* and in mice infected with recombinant *L. monocytogenes* expressing a modified internalin A protein that allows interaction with mouse E-cadherin[21] or in *L. monocytogenes*–infected mice that transgenically express human E-cadherin[22]. Continual exposure of mucosal surfaces and the skin to potentially pathogenic microorganisms requires that the immune system handle diverse and often repeated insults. Thus, pathogen encounter or vaccination can generate lifelong immunologic memory, thereby providing protection against subsequent pathogen invasion.

Memory T cell development and function

Determining how heterogeneous memory populations are generated and migrate to their appropriate locations has been a subject of much interest over the past decade. The lineage decision to generate memory occurs early after infection[23-25]. The fate of effector $CD8^+$ T cells has been identified by expression of the receptors KLRG1 (killer cell lectin-like receptor subfamily G1) and CD127 (interleukin 7 (IL-7) receptor α-chain)[26-29]. Effector $CD8^+$ T cells that express CD127 but not KLRG1 represent a true memory precursor effector cell (MPEC) population that generates long-lived $CD8^+$ T cell memory and has stem cell-like renewal qualities (Fig. 2). Although CD127 is a marker for MPECs, IL-7-mediated signaling does not seem to select for the generation of memory T cells[30-32]. Conversely, $CD8^+$ T cells expressing KLRG1 but not CD127 undergo apoptosis during contraction and are therefore called ‘short-lived effector cells’ (SLECs)[28,29,31]. Early effector $CD8^+$ T cells express neither CD127 nor KLRG1, seem to be the earliest $CD8^+$ T cell population generated after antigen encounter and give rise to both MPEC and SLEC subsets[25,33,34] (Fig. 2). Cells expressing both CD127 and KLRG1 also appear in the effector and memory $CD8^+$ T cell population, but it is unclear whether these cells represent an intermediary population or a distinct lineage of $CD8^+$ T cells. The generation of these effector $CD8^+$ T cell subsets varies greatly among different infection settings and after secondary infection; this is consistent with the regulation of their development by inflammatory mediators[28,35]. The composition of these subsets and how they might relate to memory development in nonlymphoid tissues has not yet been studied in detail, although some data are emerging. In the lung airways after influenza virus infection and in sensory ganglia after herpes simplex virus (HSV) infection, most antigen-specific effector $CD8^+$ T cells are ‘early effector cells’, whereas MPECs increase in number over time[36,37]. Further experimentation is needed to determine the effects of tissue-specific factors on effector and memory T cell development in different tertiary tissues.

T_{CM} and T_{EM} cells arise as distinct lineages only in the MPEC population early in the immune response, and this lineage decision is influenced by T cell antigen receptor (TCR) signal strength, IL-2 and IL-15, among other factors[24,25]. The description of T_{CM} and T_{EM} cells has led to many studies attempting to delineate the factors that drive the differentiation of effector T cells and subsequent memory development. These efforts have provided insight into the physiological and anatomical differences between T cells that reside in lymphoid compartments and those that reside in nonlymphoid compartments. For example, T_{CM} cells proliferate homeostatically faster than T_{EM} cells do and gradually become the dominant memory population in lymphoid tissues[38-40]. Although some peripheral nonlymphoid tissues host a few T_{CM} cells, these cells never predominate in the lung, liver or intestinal mucosa[9,41]. These results suggest that tertiary sites contain memory cells that are not derived from the recirculating pool or that cells undergo differentiation after infiltration of the tissue[9].

The protective abilities of $CD4^+$ and $CD8^+$ T_{CM} and T_{EM} cells have also been explored in some detail[41] and, depending on the infection, both have protective abilities[42,43]. Because T_{CM} and T_{EM} cells localize to different sites, on the basis of their expression of homing molecules, direct comparison of their protective abilities is often difficult and depends on the location of pathogen replication and therefore the site of T cell priming (for example, spleen versus draining lymph nodes)[44]. A distinction between 'proliferative' recall and 'functional' reactivation should also be considered in terms of regional memory. For example, soon after secondary oral infection, a $CD8^+$ T_{EM} intestinal intraepithelial lymphocyte may kill an infected intestinal epithelial cell through constitutive lytic activity but might not undergo secondary population expansion *in situ*. In contrast, T_{CM} cells in the Peyer's patches or MLNs encounter antigen later, proliferate extensively and migrate to the infected epithelium to provide additional protection and produce a new cadre of T_{EM} cells. The particular cell type presenting antigen also influences the outcome of reactivation[45]. For example, influenza virus-specific effector $CD8^+$ T cells are triggered to kill both $CD45^+$ and $CD45^-$ target cells, whereas only costimulatory molecule-expressing $CD45^+$ antigen-presenting cells induce the production of cytokines[46]. However, HSV reactivation in the dorsal root ganglia leads to DC-mediated re-expansion of resident memory cell populations[47]. Moreover, resident memory cells seem crucial for protection against HSV reactivation, as latently infected mice cannot avoid reactivation in the absence of $CD8^+$ T cells or after a stress-induced compromise of $CD8^+$ T cell function[48]. Given that HSV-specific $CD8^+$ T cells residing in the latently infected trigeminal ganglia do not seem to be replenished by circulating cells[49], loss of protection is probably due to loss of memory surveillance in the ganglia. Similarly, memory T cells residing in the skin provide protection against HSV infection[50]. In general, it is challenging to assess the protective abilities of tissue T_{EM} cells in part because of difficulty in temporally and anatomically separating the events of memory T cell reactivation in secondary lymphoid tissue versus nonlymphoid tissue. For example, for direct testing of the protective ability of memory T cells residing in the intestinal epithelium, after challenge infection, the migration of new effectors into the intestine would need to be blocked without affecting the resident population. Thus, ongoing studies involve the development of systems to determine the intrinsic abilities of regional memory T cells.

Regulation of T cell entry into nonlymphoid tissues

Tissue-specific memory populations may be generated through a process called 'imprinting.' The best-characterized imprinting events are those that occur during T cell priming in the Peyer's patches and MLNs. T cells responding to tissue-specific infection or immunization are primed in the draining lymph nodes, where they receive 'instruction' that directs their migration to the initial site of infection (Fig. 1). Imprinting for intestinal migration is mediated by specialized DC subsets that reside in the Peyer's patches or that migrate from the lamina propria to the MLNs[51,52]. Similar events occur in skin-draining lymph nodes[53,54]. Through the action of retinoic acid, the integrin $\alpha_4\beta_7$ and the chemokine receptor CCR9 are induced on intestinal mucosal T cells during priming[55,56]. The lack or blockade of either of these molecules prevents intestinal infiltration by effector T cells[57-62]. The addressin and $\alpha_4\beta_7$ ligand MAdCAM-1 is constitutively expressed by a subset of vascular endothelial cells in the intestinal lamina propria and Peyer's patches, and by high endothelial venules in the MLNs[63-65] and the sacral lymph nodes that drain the genital tract[66], whereas the ligand for CCR9 (CCL25) is constitutively expressed by intestinal epithelial cells in the small intestine[52,62]. The ability of DCs to provide gut-homing instruction to T cells is assigned to a subset of MLN- or Peyer's patch-derived DCs that express the α_E integrin (CD103) paired with the β_7 chain. $CD103^+$ DCs are also the main subset of migrating DCs that prime $CD8^+$ T cells in the draining lymph node of the lung and the skin[67-70] and 'preferentially' induce $CD4^+$ regulatory T cells in the lamina propria and MLNs through a

mechanism that depends on transforming growth factor-β (TGF-β) and retinoic acid [71,72]. CD103 expression does not seem essential for gut-homing instruction, because a monocyte-derived inflammatory DC population in the intestine and MLNs that expresses E-cadherin and preferentially primes inflammatory responses of the T_H17 subset of helper T cell responses can also home to the intestine[73]. In contrast with the response of $CD103^+$ DCs, the generation of E-cadherin-positive DCs is impaired by TGF-β, which suggests that TGF-β may negatively regulate inflammatory responses but support inhibitory responses[73] (Fig. 3).

Although mucosal lymphoid tissues preferentially prime $CD8^+$ T cells to induce a gut-homing phenotype, this requirement is not absolute, as systemic infection induced by lymphocytic choriomenin-gitis virus, vesicular stomatitis virus or *L. monocytogenes*, as well as intraperitoneal administration of soluble antigen, also leads to intestinal infiltration by antigen-specific $CD8^+$ T cells[5,74,75]. Indeed, splenic priming after intravenous infection with lymphocytic choriomeningitis virus induces a narrow window (4.5-7 days) of instruction for the intestinal migration of T cells[75]. However, although integrin $\alpha_4\beta_7$ is upregulated early in the spleen of these mice, CCR9 is induced only in the MLNs, which suggests that infiltration of the lamina propria may have contributions from splenic priming whereas localization to the epithelium requires priming in the MLNs[75]. In addition, systemic infections probably prime T cell responses in the spleen and in various lymph nodes, leading to tissue-specific migration from multiple sources. DCs that acquire antigen from the skin induce a skin-homing phenotype on responding T cells characterized by expression of E-selectin and P-selectin ligands (such as CLA) and of CCR4 and/or CCR10 (refs. 53,54,76; Fig. 2). It is unclear whether lung-draining DCs impart a particular instruction pattern for migration into the lung parenchyma or the bronchoalveolar space, or whether T cell activation alone or inflammation alone is sufficient to drive infiltration[8,77]. Leukotriene B_4, whose receptor BLT1 is expressed by activated $CD8^+$ T cells, is one factor that controls the migration of effector cells to the lung and other tissues[78,79]. In addition, the $\alpha_1\beta_1$ integrin VLA-1 is also involved in the migration or retention of effector and memory $CD8^+$ T cells in the lung[80,81]. With the increasing heterogeneity of the $CD4^+$ and $CD8^+$ T cell response now being characterized, it is important to revisit these phenomena and determine whether distinct subsets of CD8 effectors are imprinted for mucosal migration. In such a manner, divergent effector $CD8^+$ T cell populations may be imprinted differently for migration to nonlymphoid tissues.

Mechanisms of T cell retention in tertiary tissues

Once priming and imprinting has occurred, effector T cells enter the efferent lymphatics and subsequently return to the bloodstream through the thoracic duct (Fig. 1). The circulating cells may then interact with the appropriate adhesion ligands expressed by specialized endothelial cells to facilitate extravasation into the tissue. Recently emigrated cells may be further influenced by the local microenvironment of the tissue. For example, effector and memory $CD8^+$ T cells migrating into the lamina propria and intraepithelial lymphocyte compartment upregulate CD103 and the activation marker CD69 (refs. 7,82,83). Indeed, although $\alpha_4\beta_7$ expression is required for lymphocyte entry into the intestinal lamina propria and epithelium, once there, most effector and memory $CD8^+$ T cells down-regulate $\alpha_4\beta_7$ and upregulate CD103 (refs. 7,84). Thus, most intestinal $CD8^+$ T cells have high expression of CD103, whereas most lymphoid $CD8^+$ T cells lack or have low expression of CD103, which suggests a prominent role for this integrin in the mucosa. Because the ligand for CD103 is E-cadherin expressed by intestinal epithelial cells, researchers have hypothesized that CD103 is involved in retention of $CD8^+$ T cells in the epithelium[85]. Parabiosis and tissue-grafting studies also suggest that most gut memory T cells do not emigrate from the gut and are only minimally replenished by circulating lymphocytes[7,75,86]. That idea is further

supported by studies describing resident memory T cells (T_{RM} cells) in other tissues[47,50,87]. T_{RM} cells seem to be maintained long-term with less homeostatic turnover and at present are restricted to intestinal tissues[7,75] and nervous tissues[87-89] and the skin epidermal layer[47,50]. The idea that this strict compartmentalization of residence in the nervous tissue is complete in humans may be called into question by the finding that reactivation of JC polyo-mavirus occurs in some people treated with antibody to integrin α_4; whether this is due to inhibition of T cell responses remains speculative[90-92]. In contrast, in the lung and liver parenchyma, memory $CD8^+$ T cells seem to be repopulated with cells from the circulation[7]. However, although perfusion has been used for cell isolation in these studies, the extensive circulatory systems of these tissues could promote contamination by blood-borne lymphocytes. Further study is needed to test this possibility. As for the lung airways, after influenza virus infection, antigen-specific memory $CD8^+$ T cells migrate to the airways only when residual cognate antigen is present[8]. Moreover, antigen-specific memory $CD8^+$ T cells are preferentially retained in the mediastinal lymph nodes, whereas they freely migrate through other lymph nodes because of the presence of residual antigen in the mediastinal lymph nodes[8]. In contrast, Sendai virus-specific airway memory $CD8^+$ T cells are continuously replenished from circulating cells[77], although it is not known whether antigen is retained long term after this infection. Residual antigen is also involved in the induction and maintenance of CD103 and CD69 expression by influenza virus-specific $CD8^+$ T cells[93]; these processes are involved in the migration and retention of these cells in the lung tissue[10], thereby promoting protection.

The main similarity between memory $CD8^+$ T cells resident in the gut, lung, skin and brain is their expression of CD103 and CD69 (refs. 7,50,82,87). CD103 binds E-cadherin, which is expressed mainly by epithelial cells and through homotypic interactions is essential for development and maintenance of tissue integrity[94]. KLRG1 also binds E-cadherin as well as N-cadherin, and the CD103-binding site is distinct from that of KLRG1 (ref. 95). Whether similar mechanisms exist for $CD4^+$ T cells is not yet clear, although most $CD4^+$ intestinal intraepithelial lymphocyte s and~20% of $CD4^+$ lamina propria T cells also express CD103 (ref. 96). CD103 induction depends on TGF-β, which is produced by epithelial cells as well as by DC subsets (Fig. 3). In the absence of signaling through the TGF-β receptor, effector $CD8^+$ T cells infiltrating the intestinal epithelium during graft-versus-host disease do not upregulate CD103 (ref. 83) and are less pathogenic. In the lungs, CD103-deficient $CD8^+$ T cells are inefficiently retained after influenza viral infection[10]. CD103 may have other important roles in immune responses, such as facilitating movement through epithelial cell layers, as interaction with E-cadherin influences cellular shape and motility of lymphocytes within the skin epidermal layer[97].

In addition, signal transduction via CD103 can augment T cell functions, including lytic activity and lytic granule polarization in tumor-infiltrating lymphocytes; these processes facilitate tumor clearance[98]. These abilities suggest that CD103 ligation provides critical signals for T cell function in tertiary tissues.

In addition to active retention mechanisms, the loss of molecules involved in signaling pathways that promote exit from tissues may also enhance tissue localization. For example, sphingosine 1-phosphate receptor type 1 ($S1P_1$) is involved in thymocyte emigration and the exit of naive T cells from the lymph node, whereas CD69 may suppress $S1P_1$ function through an intracellular interaction with this receptor[99-101]. In this way, CD69 expression decreases $S1P_1$ function and prolongs the retention of activated T cells in the lymph node. CD69 promotes the migration or retention of $CD8^+$ T cells in influenza virus-infected lungs[10] and thus may have a general role in the tissue retention of effector and memory T cells. CCR7 is also involved in the exit of effector and memory $CD8^+$ T cells from the lung and skin to the afferent lymphatics[102,103] and may also operate in other tertiary tissues.

Because most effector T cells downregulate CCR7 and T_{EM} cells lack CCR7, this downregulation may be an additional mechanism by which exit from the tissues is regulated (Fig. 2). Thus, the theme of induction of specialized retention molecules and down-regulation of exit signals in several tissues suggests a fundamental mechanism by which effector and memory $CD8^+$ T cells carry out surveillance functions in critical organ systems.

Implications and significance

Defining the processes that control the tissue-specific migration and retention of effector and memory T cells has major implications for disease pathogenesis and for the design of therapeutic interventions. Effective vaccination in humans induces long-lived antibody responses as well as T cell memory[104]. $CD8^+$ T cell responses could be exploited for protection against infection with human immunodeficiency virus, whose major portals of entry are the genital and intestinal mucosa[105,106]. Similarly, influenza virus enters via the respiratory mucosa, and induction of memory $CD8^+$ T cells specific for conserved viral epitopes could provide broad-based protection against multiple serotypes. Thus, designing vaccines that induce the proper homing and retention molecules on the responding T cells would probably substantially increase protective efficacy at the entry point of these and other pathogens. In contrast, tissue-specific effector and memory T cells may be involved in disease pathogenesis, such as in inflammatory bowel disease and multiple sclerosis. In these cases, inhibition, rather than promotion, of homing and retention might provide disease amelioration. Thus, treatment with antibodies to $\alpha_4\beta_7$ and α_4 is being tested to combat inflammatory bowel disease and multiple sclerosis, respectively, although such treatments have risks[107,108]. Defining the molecular and cellular events that surround the induction and maintenance of tissue-specific memory T cells may provide the foundation for the future development of new therapies.

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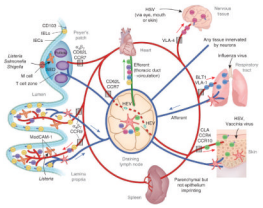

Figure 1.

The migration of effector and memory T cells to sites of localized infection. DC acquisition of antigen occurs at peripheral sites such as the lung, skin or gut after a breach in the epithelial layer or local infection. After capturing antigen, DCs access initial afferent lymphatics mediated by signals from integrins, chemokines and semaphorins to migrate to draining lymph nodes to activate naive or memory cells. For example, breach of the intestinal mucosa leads to T cell priming in the MLNs and/or Peyer's patches. The spleen is poised to generate a substantial T cell response if pathogens are not compartmentally contained and gain access to the bloodstream. In either scenario, a robust T cell population expansion program follows with DC-mediated instruction for migration to the site of initial infection. Activated T cells and circulating memory cells exit the lymph node via the efferent lymphatics and return to circulation through the thoracic duct (colors indicate T cells instructed to home to specific tissues). As T cells migrate through the circulation, integrin and chemokine signals direct their emigration into tissues. In this manner, imprinted T cells have a specific key that allows access to restricted tissues (gates) under normal homeostatic conditions. IEL, intraepithelial lymphocyte; IEC, intestinal epithelial cell; VLA-4, integrin $\alpha_4\beta_1$.

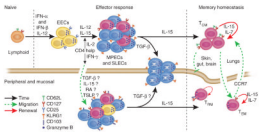

Figure 2.

The generation of a diverse and dynamic memory T cell population is a highly orchestrated process. Naive $CD8^+$ T cells rapidly downregulate CD62L and CD127 after exposure to their cognate antigen in the proper contextual environment. IL-12, type I interferons (IFN-α and IFN-β) and IL-2 regulate the initial development of a heterogeneous effector T cell population in lymphoid tissues. $CD4^+$ T cells are thought to be crucial to distinct aspects of this process. After certain infections, such as with *l. monocytogenes*, $CD4^+$ T cell help is essential for the generation of a robust SLEC population and may also regulate the generation of T_{CM} cells through IL-2 production[25,34]. However, IFN-γ produced by $CD4^+$ T cells regulates recruitment of $CD8^+$ T cells to the site of peripheral infection, such after infection of the genital tract with HSV[109]. Once T cells enter peripheral tissues, various molecules from the tissue microenvironment may further influence effector heterogeneity. For example, the cytokines TGF-β and TSLP can have tissue-specific effects on the differentiation of T cells in the intestinal mucosa[71,83,110,111]. Contraction of the T cell response is regulated in part by TGF-β and IL-15, which mediate opposing fates of the effector pool[33,112]. At least in lymphoid tissues, TGF-β seems to induce apoptosis of SLECs, whereas IL-15 promotes T cell survival and entry into the memory pool[33,112]. T_{CM} cells reside mainly in lymphoid tissues and downregulate expression of granzyme B, whereas T_{EM} and T_{RM} cells reside in peripheral nonlymphoid tissues and maintain granzyme B expression and direct lytic activity. The migration of memory T cells into the skin, gut and brain seems to be restricted, whereas replenishment of liver and lung parenchyma (but not airway) memory T cells occurs through the circulation. Memory T cells located in peripheral tissues may also be regulated by CCR7-mediated emigration signals, which allows the potential for further modification of the T_{EM} cell population[102,103]. EEC, early effector cell.

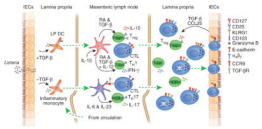

Figure 3.

Multifaceted roles of TGF-β in generating mucosal effector and memory T cell populations. TGF-β seems to regulate many aspects of CD8 memory T cell formation in mucosal and potentially other peripheral tissues. Initially, TGF-β derived from intestinal epithelial cells influences the antigen-presenting cells, which migrate to the draining lymph nodes to prime local T cell responses. The presence or absence of TGF-β regulates the expression of CD103 or E-cadherin on antigen-presenting cell subsets in the lamina propria (LP). $CD103^+$ DCs, which also produce TGF-β, mediate imprinting of gut-homing T cells by a mechanism that depends on TGF-β and retinoic acid (RA) and are also responsible for the generation of regulatory T cells (T_{reg})[71]. In conjunction with IL-15, T helper type 1 (T_H1) and T_H17 cells are 'preferentially' generated, which skews the T cell response to a proinflammatory nature[113]. However, TGF-β also suppresses the generation of E-cadherin-positive DCs, which 'preferentially' drive a T_H17 response in a colitis model[73]. It is unknown whether $CD8^+$ T cells of the SLEC type, which express KLRG1, or other $CD103^+$ $CD8^+$ T cells can interact with E-cadherin expressed by these inflammatory DCs. Whatever holds true, $CD4^+$ T cells primed by these DCs are fully able to migrate to the lamina propria. Once T cells emigrate into the lamina propria, $\alpha_4\beta_7$ is rapidly downregulated and CD103 expression is upregulated in a TGF-β-dependent manner in a subset of lamina propria $CD8^+$ T cells. CCL25 expression by intestinal epithelial cells mediates a chemotactic gradient to recruit effector $CD8^+$ T cells into the epithelium. TGF-β signals also drive the apoptosis of $CD8^+$ T cells of the SLEC type, at least in lymphoid tissues, but may also mediate distinct outcomes on the basis of the presence of other inflammatory or anti-inflammatory mediators[33,113]. In this system, TGF-β is probably produced by both the epithelium and lamina propria DCs, but the relative contributions of each source remain unclear. Foxp3, T-bet and RORγt are transcription factors; CTL, cytotoxic T lymphocyte; TGF-βR, TGF-β receptor.