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T lymphocyte trafficking: molecules and mechanisms

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1. ABSTRACT

Coordinated migratory events are required for the development of effective and regulated immunity. Naïve T lymphocytes are programmed to recirculate predominantly in secondary lymphoid tissue by non-specific stimuli. In contrast, primed T cells must identify specific sites of antigen location in non-lymphoid tissue to exert targeted effector responses. Following priming, T cells acquire the ability to establish molecular interactions mediated by tissue-selective adhesion and chemokine receptors (homing receptors) that facilitate their access to specific organs. Recent studies have shown that an additional level of homing specificity is provided by the induction of T cell migration into the tissue by recognition of antigen displayed by the endothelium. In addition, co-stimulatory signals have been recently shown not only to regulate T cell activation and differentiation, but also to orchestrate the anatomy of the ensuing T cell response. Similarly, the characterization of migratory patterns by regulatory T cells has been the subject of many recent studies. Here, we provide an overview of key concepts, which have contribute to unraveling the complex anatomy of T cell immunity.

2. INTRODUCTION - LYMPHOCYTE RECIRCULATION AND HOMING

Effective immune responses are dependent on the continuous trafficking of lymphocytes through blood, lymphoid organs and non-lymphoid tissue in a process known as recirculation (1). While other leukocytes migrate in response to non-specific inflammatory stimuli, the migratory patterns of naïve and memory T lymphocytes are well defined and vary depending on their activation, differentiation and function (2). For instance, naive T cells express L-selectin (CD62L) and chemokine receptor CCR7 and predominantly traffic to secondary lymphoid organs (SLOs) whereas antigen-experienced T cells acquire the ability to migrate to non-lymphoid sites of inflammation in the tissues where antigens are located (3, 4). By possessing a unique set of adhesion molecules and chemokine receptors - the 'homing' receptors, distinct memory T cell populations are able to interact with organ-specific endothelial cells (EC) and are recruited to distinct target tissues (5, 6). For example, lymphocyte trafficking to the intestinal *lamina propria* is mediated predominantly by the interaction between intestinal mucosal addressin cell adhesion molecule 1 (MAdCAM-1) and lymphocyte $\alpha_4\beta_7$

integrin (7). Human T cell homing to the skin requires the binding of cutaneous lymphocyte antigens (CLA, an E–selectin ligand) and the chemokine receptor CCR4 to the vascular lectin endothelial cell-leukocyte adhesion molecule 1 (ELAM-1) and the thymus and activation-regulated chemokine (TARC, CCL17) respectively (8, 9).

3. T LYMPHOCYTE EXTRAVASATION

The physiological process by which lymphocytes leave circulation, find and localize to particular tissues and to the microenvironment therein is known as extravasation (10). A wide range of chemokines, adhesion molecules and junctional molecules expressed on the EC are required to mediate and regulate this tightly controlled process. These molecules bind to their counter receptors on the migrating lymphocytes directing their entry into the tissue. Monocytes and neutrophil migration also involves a cascade-like process similar to lymphocytes (11).

In healthy tissue, the vascular endothelium is impermeable to macromolecules; it forms a non-thrombotic, non-adhesive barrier (12). Upon inflammation, the endothelial monolayer undergoes physiological and molecular changes such as the up-regulation of adhesion molecule expression. This in turn allows the exit of lymphocytes across the endothelium into the tissue without disrupting the endothelium integrity. The initial stage of lymphocyte trafficking is mostly mediated by selectins, which belong to a group of so-called C-type lectins expressed exclusively on bone marrow derived cells and ECs (13). Selectins are responsible for the initial contact between the circulating lymphocytes and the endothelium monolayer, and mediate lymphocyte tethering and rolling on the endothelium.

After this initial contact, locally produced chemokines displayed on the ECs bind to their receptors and subsequently induce integrin activation (14). Chemokine signalling induces integrin conformational changes leading to the upregulation of integrin affinity; alternatively it triggers integrin clustering on the cell surface thus increasing integrin avidity (14, 15). Activated integrins bind to their ligands on the EC leading to the establishment of firm adhesion of migrating leukocytes to the endothelial cells. This step of extravasation is thus referred to as activation (16).

Chemokines are small proteins of 8-14 kDa with chemotactic properties, which control cell trafficking. Chemokines can be categorized based on their functions; those that are homeostatic and produced constitutively and those that are induced during inflammation (17). Homeostatic chemokines are important during hematopoiesis in the bone marrow and thymus. They also control cellular traffic in the SLOs and contribute to the immune surveillance of the peripheral tissues. Inflammatory chemokines on the other hand recruit effector leukocytes as well as cells of the innate immune system to the sites of inflammation (17, 18). Chemokines may be synthesized by the endothelium itself and released on the luminal surface where they are immobilized on glycosaminoglycans (GAGs) synthesized by the vascular endothelium for binding to their receptors on the incoming lymphocytes; alternatively, they are produced by tissue parenchymal cells and transported across the endothelium (19).

Following the activation step, lymphocytes firmly adhere to and spread on the endothelial surface in a process called firm adhesion or 'arrest'. Integrins comprise a major group of adhesion molecules and consist of two non-covalently bound polypeptide chains - α and β chains. Integrins are categorized based on the type of β chain. For example, β_1 integrins include VLA1 ($\alpha_1\beta_1$), and VLA4 ($\alpha_4\beta_1$); β2 integrins include the leukocyte associated function antigen 1 (LFA-1), $\alpha_L\beta_2$, and the integrin $\alpha_4\beta_7$, which is important in T cell homing to the gut (20). During the activation step of lymphocyte extravasation, integrins bind to their ligands expressed on the endothelium such as the ICAMs, VCAM-1, and MAdCAM-1, which lead to the firm arrest of lymphocytes on the endothelium. Following firm adhesion on the EC monolayer, lymphocytes eventually transmigrate into the target tissue. Lymphocyte transendothelial migration occurs at the junction between apposing endothelial cells (paracellular route) without disrupting the EC monolayer in a complex process known as diapedesis involving the junctional adhesion molecules (21). Alternatively, leukocytes can migrate across the endothelial cell body into the tissue known as the transcellular route (22). This phenomenon was first observed in a mouse model of experimental autoimmune encephalomyelitis (23) and shown to be ICAM-1 dependent (24). It has been proposed that the contribution of either of such transmigration pathway depends on the type of blood vessel, target tissue, recruitment stimuli (25). Once across the endothelial barrier, migrating lymphocytes continue to move through the subendothelial matrix (21) and the extravascular tissue to the site of inflammation in response to chemotactic gradients (12).

Naïve and memory T cells display different surface phenotypes, which define their functional properties and migratory patterns (26-29). Naïve T cells have little or no ability to produce cytokines (30). They recirculate from the blood, through SLOs, into the lymphatic vessels and back to the blood in search of their cognate antigen (5, 31). SLOs include peripheral lymph nodes, gut-associated lymphoid tissue (GALT, including Peyer's patches (PP), bronchus-associated lymphoid tissue (BALT), and the spleen (32). In the SLOs, naïve T lymphocytes are activated upon recognition of antigen presented by tissue-resident dendritic cells (priming), and undergo clonal expansion and differentiation into effector and memory T cells. Naive T cells enter the lymph nodes via high endothelial venules (HEVs), which are specialized postcapillary venules characterized by plump, cuboidal shapes and exclusively found in the SLOs (33, 34).

A recent study suggested that DCs sustain the entry of naive lymphocytes to lymph nodes by modulating the phenotype of HEVs during homeostasis in adult mice. HEV-mediated lymphocyte recruitment to lymph nodes is inhibited in the absence of DCs. The effect of DCs on HEV

is direct and requires lymphotoxin-β-receptor-dependent signalling (35).

Homing of naïve T cells to the peripheral lymph nodes (PLN) requires the expression of L-selectin (CD62L) and the chemokine receptor CCR7 (Table 1). L-selectin binds to peripheral lymph node addressin (PNad), which is highly expressed on the HEVs of PLNs and mesenteric lymph nodes (MLNs) (36), while CCR7 binds to the chemokines CCL19 and CCL21 expressed by HEVs of the PLNs (37, 38). CCL21 is also expressed in PPs (39). Naïve T cells have also been shown to utilize CXCR4, which is the receptor for stromal cell-derived factor1 (SDF-1, CXCL12) chemokine to circulate through secondary lymphoid tissues (40).

In humans, the majority of T cells entering the PPs are found to be naïve T cells. This process requires the interaction of integrin $\alpha_4\beta_7$ on T cells and MAdCAM-1 on the mucosal vasculature (7, 39). Consistent with this observation, human naïve T cells are found to constitutively express low levels of $\alpha_4\beta_7$ (41, 42). Studies subsequently showed that both CD62-L and integrin $\alpha_4\beta_7$ are required in a sequential and synergistic manner to mediate naïve T cell migration to the mesenteric lymph nodes (43). CD62-L binds to the PNad expressed on the MLNs, which induces the initial rolling and tethering of T cells during transendothelial migration; $\alpha_4\beta_7$ integrins subsequently bind to MAdCAM-1 and mediate firm adhesion and transmigration (43). Mice lacking β_7 integrin expression have been found to display a 90% reduction in lymphocyte migration to the PPs; and T cell migration is reduced by 55% in mice that are deficient for CD62-L (43). Collectively, this evidence highlights the importance of both CD62-L and integrin $\alpha_4\beta_7$ in naïve T cell homing to the gut secondary lymphoid tissue.

5. MEMORY T CELL HOMING TO NON-LYMPHOID TISSUE

Upon encountering antigens in SLOs, naïve T cells are sequestered and interact with antigens for 2-3 days (44). Naive T cells subsequently differentiate into short-lived effector T cells or long-lived memory T cell populations. Memory T cells leave the SLOs via the efferent lymphatics, enter the blood circulation through the thoracic duct and travel to the inflamed tissue (Figure 1). As previously mentioned, memory T cells are a heterogeneous population consisting of long-lived central memory T cells (T_{CM}), short-lived effector T cells (T_{EFF}) and long-lived effector memory T cells (T_{EM}); these cells are defined by their different phenotypes, functions and migratory patterns (45, 46).

Similar to naïve T cells, T_{CM} express CD62-L and CCR7, and share migratory patterns with naive T cells; however, unlike naïve T cells they also express inflammatory chemokine receptors which enable them to enter sites of chronic inflammation (11). T_{CM} do not have immediate effector functions but are able to proliferate rapidly during secondary immune responses (47). In contrast, both short-lived T_{EFF} and long-lived T_{EM} lack the expression of CD62L and CCR7. They use instead tissue-specific integrins and chemokine receptors to preferentially migrate to non-lymphoid tissues (46, 48). Short-lived TEFF represent mostly recently activated T cells, and are eliminated at the end of primary immune responses (29, 49). TEM have immediate effector function, and are present in the blood, peripheral tissues, spleen but not in the resting lymph nodes (50). A recent study revealed that murine TEM and TEFF can also be recruited to the reactive lymph nodes in a CCR7 independent pathway via the chemokine receptor CXCR3 in order to kill antigen-presenting dendritic cells thus preventing excessive T cell stimulation (51).

Unlike naïve T cells predominantly trafficking to the SLOs, memory T cells are endowed with the ability of infiltrating non-lymphoid tissue. Up-regulation of the integrins LFA-1 and VLA-4 facilitate this process. In addition, tissue-selective molecular interactions (homing receptor/ligand pairs) target these cells to the tissues where pathogen invasion has first occurred.

The mechanisms used by memory T cells to leave parenchymal tissue and return to the circulation have been only partially characterized. The chemokine receptor CCR7 guides T cell exit from peripheral tissues and entry into afferent lymphatics (52). Promotion of lymphocyte egress into blood and lymph is sustained by distinct sources of sphingosine-1-phosphate (53). After exit from the tissue, memory T cells may continue recirculating in the blood or localize in 'reservoir' niches: memory T cells tend to preferentially reside in the spleen in chronic inflammation with antigen persistence; alternatively they localize to the bone marrow if the infectious/inflammatory process is acute but transient (46, 54, 55) (Figure 1).

Although the molecular interactions guiding T cell homing to the gut and skin are relatively well defined, mapping of T cell homing to other solid organs has revealed a great level of overlap and - perhaps with the exception of the liver (56) – other organ-specific homing receptor/ligand pairs have not yet been identified. In addition, given the size of skin and gut, further mechanism are likely to be in place which allow T cells to discriminate not only the area code for these tissues, but also the specific 'address' of antigen location.

5.1. Memory T cell homing to the skin

Human memory T cells require the expression of CLA to traffic to the skin by binding to E-selectin (CD62E, ELAM-1, endothelial cell-leukocyte adhesion molecule) which is constitutively expressed at a low level by endothelial cells in the skin and is upregulated upon cutaneous inflammation (9, 57). Human skin-infiltrating lymphocytes also express CCR4, the chemokine receptor for CCL17 (also known as the thymus and activation-regulated chemokine, TARC) displayed on the skin venules (8). Effector/memory T cell trafficking to skin depends on E-selectin, P-selectin and CCR4 (58). Further studies

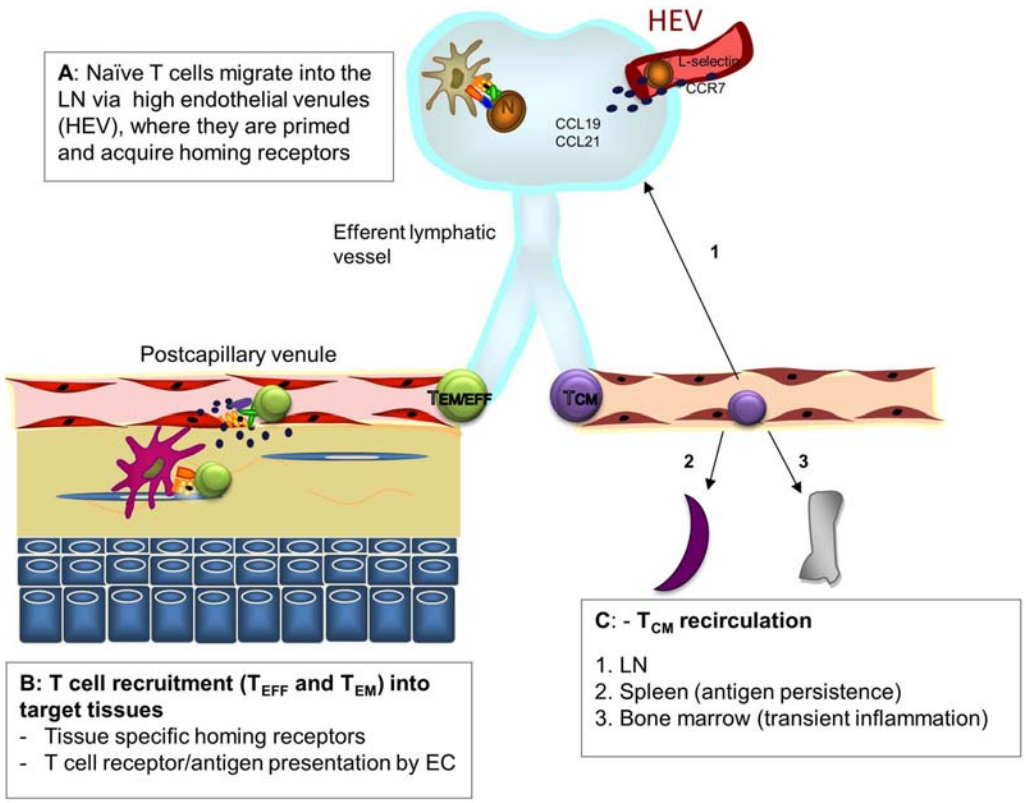

Figure 1. T-cell migration into lymphoid and non-lymphoid tissues. Naïve T cells priming and homing molecules acquisition. Naïve T cells migrate from the circulation (HEV) into lymph nodes by utilizing the lymphoid tissue homing receptors L-selectin and CCR7. DCs present antigens to naïve T cells, which subsequently differentiate into T_{EFF}, T_{EM} and T_{CM}. During priming, different homing receptors are acquired depending on the local microenvironment. T cells activated in the cutaneous secondary lymphoid tissue express skin-homing receptors CCR10 due to presence of 1,25 (OH) (2)D (3), the active form of vitamin D3. T cells activated in the mesenteric lymph nodes expressed gut-homing receptors CCR9 and α4β7 due to RA production from vitamin A by resident DCs. Primed T cells migrate to their target tissues. T-cell receptor (TCR) engagement by endothelium and tissue resident antigen presenting cells (APC) is instrumental to the selectivity of antigen-specific T cell recruitment and retention. Chemokine receptor engagement also facilitates the recruitment of specific T cells into the tissue. After exit from tissue, memory T cells may continue recirculating in the blood, or display prolonged localization into niches: memory T cells home preferentially to spleen if antigen persists after infection; alternatively, they localize to the bone marrow if the inflammation is acute but transient.

revealed that CCL27 (the cutaneous T cell-attracting chemokine, CTACK) is also crucial for attracting CLA^+ memory T cells to the skin by binding to its receptor CCR10 (59). CCR10 is important for the development of skin-specific T cells by regulating their migration and location (60). Other key molecules participating in memory T cell homing to skin include intergrin $\alpha_4\beta_1$ (VLA-1), which binds to vascular cell adhesion molecule 1 (VCAM-1) expressed by the endothelium in non-mucosal site of inflammation (42). T cells expressing high levels of $\alpha_4\beta_1$ preferentially home to the systemic non-mucosal sites including the skin, central nervous system and bone marrow (61). (Table 1).

5.2. Memory T cell homing to the small and large intestine

Effector and memory T cells and B cells require the interaction of integrin $\alpha_4\beta_7$ and MAdCAM-1 to migrate to the effector site of the gut mucosa – the *lamina propria* (7, 62). Human peripheral blood $CD4^+$, $CD8^+$ T cells and B cells have heterogeneous expression of $\alpha_4\beta_7$ (41, 63). The level of $\alpha_4\beta_7$ expression is much higher on memory cells than naïve cells (41, 42). The ability of $\alpha_4\beta_7$ expressing cells to bind to MAdCAM-1 is influenced by the level of $\alpha_4\beta_7$ expression and its functional state (41). MAdCAM-1 is constitutively expressed on the postcapillary venules of intestinal *lamina propria*, the MLNs, the HEVs of the PPs (3) and the endothelial venules of both small intestine and colon (64). Other than its crucial function in mediating lymphocyte homing to the gut, studies in mice have also revealed that $\alpha_4\beta_7$ plays a critical role in the formation of gut-associate lymphoid tissue (65). Mice lacking MAdCAM-1 have a disordered architecture in their PPs and MLNs (66).

Upon arrival in the small intestine *lamina propria*, some T cells further migrate to the gut epithelium to become intraepithelial T cells in a process dependent on

Table 1. Lymphocyte receptors associated to tissue-selective homing

Lymphocyte homing receptor	Receptor induction	Ligand	Homing tissue	Reference
CCR7		CCL19, CCL21	SLOs	(37, 38)
L-selectin		PNad	SLOs	(36)
CCR9	RA	CCL25	Intestine	(69-72)
α4β7	RA	MAdCAM-1	Intestine	(3, 41, 64)
CLA		E-selectin	Skin	(9, 57)
CCR4		CCL17	Skin	(8, 58)
CCR10		CCL27	Skin	(59)
? (Th2)		VAP-1	Liver	(79)
CD44		hyaluronate	Liver	(80)

Abbreviations: CLA, cutaneous lymphocyte antigens

the interaction of chemokine receptor CCR9 and its ligand CCL25 (also known as the thymus expressed chemokine TECK in humans and mice) (67-69) (Table 1). CCL25 is expressed in the thymus and the small intestinal glands and crypts (70). CCL25 is also expressed by gut endothelium and epithelial cells in mice (71). Within the murine small intestine, CCL25 is found at a higher concentration at the proximal segments compared to the distal segments (71). Its receptor CCR9 is expressed by thymic T cells, $\alpha_4\beta_7^+$ *lamina propria* T cells and intraepithelial lymphocytes in the small intestine as well as IgA- secreting plasma cells in the secondary lymphoid organs in humans and mice (68, 69, 72).

In mice, the CCR9-CCL25 axis has been shown to play a key role in the homing of antigen-specific $CD8^+$ T lymphocytes to the small intestine *lamina propria* (73), but less so for $CD4^+$ effector T cells (74). Other studies have also described that CCL25 plays a key role in the generation of murine small intestinal intraepithelial lymphocytes (75). In humans, CCL25 is abundantly expressed in various regions of the small intestine (jejunum and the ileum), but not in the colon or the caecum (68, 76). Consistently, CCR9 is found on all of the small intestinal *lamina propria* intraepithelial $CD4^+$ and $CD8^+$ T cells (68, 76).

In line with these observations, CCR9-CCL25 interactions are required for memory T cell homing to the small intestine, while they do not appear to be essential for T cell migration to the colon in humans or mice (68, 77). Blockade of CCL25 had no effect on murine T cell adhesion in the colon in both non-inflamed and inflamed conditions, while it significantly inhibited T cell adhesion in the small intestine (78). In humans, there is no evidence suggesting that CCL25-CCR9 interaction is required for lymphocyte homing to the healthy or inflamed colon (70). Over 90% of both $CD4^+$ and $CD8^+$ T cells isolated from the human small intestine (including intraepithelial $CD8^+$ T cells) express CCR9, in contrast only 25% of colonic $CD4^+$ and $CD8^+$T cells are CCR9 positive (68, 76). In human peripheral blood, only a small percentage of total circulating $CD4^+$ and $CD8^+$ T cells co-express $\alpha_4\beta_7^+$ and CCR9, further enforcing the concept that T cell homing to the small and large intestine may not be achieved via the same pathways (69). Instead, CCL25 may be responsible for compartmentalizing the mucosal immune responses within the gut (68, 72).

The expression of homing receptors on T cells for the skin and the gut are mutually exclusive (42). For instance, CCR4 is exclusively expressed by CLA^+ skin-homing T cells but not by intestinal memory T cells (8), and the integrin $\alpha_4\beta_1$ targets T cells to the non-mucosal sites whereas integrin $\alpha_4\beta_7$ targets memory T cells to the intestine (42).

5.3. Memory T cell homing to the liver

Besides the skin and the gut, T cell homing to the liver has received much attention in recent years, and a number of molecular mediators of T cell localization to hepatic tissue have been identified (Table 1). Studies in experimental models of liver inflammation have indicated that Th1 cells may use very late antigen-4 (VLA-4) to traffic to liver, whilst Th2 cells may use a presently uncharacterized ligand for endothelial vascular adhesion protein-1 (VAP-1), which is constitutively expressed on hepatic venules and sinusoids and locally up-regulated during inflammation (79). Other reports suggested the involvement of the hyaluronan receptor CD44 in lymphocyte homing to liver (80). Several circumstantial evidences support a role of CCR5 as a mediator of recruitment of T cells in the liver during acute inflammation as well as during numerous autoimmune diseases, including multiple sclerosis, rheumatoid arthritis and type I diabetes (81). First, T cell-mediated immune responses play a critical role in hepatocyte damage induced by autoimmunity and viral infections, and CCR5 is preferentially expressed on Th1 cells (82, 83). Second, recent clinical trials of some CCR5 antagonists were abruptly halted, due to profound hepatotoxicity (81). In addition, CCR5 deficiency in humans, as well as in experimental animal models of inflammation and infection, is associated with significant increase in tissue levels of the CCR5 ligand CCL5 (84, 85). Elevated tissue levels of CCL5 could in turn promote enhanced influx of leukocytes (including T cells) by binding to its alternative receptor, CCR1, expressed on circulating leukocytes (84, 86). The patterns of T cell migration to the intestine and the skin have been well characterized.

5.4. Mechanisms of homing receptor acquisition

The ability of local lymphoid tissue to imprint T lymphocytes with a specific set of homing receptors has long been recognized. It was first demonstrated in mice that only DCs isolated from the MLNs and the PPs preferentially up-regulated integrin α4β7 and chemokine receptor CCR9 when activating naïve T cells (73, 87, 88). In contrast, T cells activated in the cutaneous secondary lymphoid tissue expressed skin-homing receptors (88, 89). The mutually exclusive sets of skin and gut-homing receptors expressed by T cells commit them to either

destination (42, 69). These results highlighted the importance of local microenvironment in T cell acquisition of homing receptors.

More recent studies have shed light on the molecular mechanisms of 'local' imprinting. Skin-resident DCs have been shown to process Vitamin D3, the inactive pro-hormone naturally generated in the skin by exposure to the sun, to 1,25 (OH) (2)D (3), the active form of vitamin D3. 1,25 (OH) (2)D (3) signals T cells to express the chemokine receptor CCR10, which enables them to migrate in response to the chemokine CCL27 secreted by keratinocytes of the epidermis. In contrast, 1,25 (OH) (2)D (3) suppresses the expression of the gut-homing receptors α4β7 and CCR9. Hence, the ability of DCs to metabolize a local product underlies their ability to instruct T cell 'epidermotropism' (90).

Similar mechanisms have been identified which underlay the acquisition of gut homing receptors. A study by Iwata and colleagues highlighted the key role of the vitamin A metabolite retinoic acid (RA) produced by DCs in the imprinting of gut homing specificity on T cells (91). The small intestine has long been established as the primary site for the absorption and the processing of vitamin A and beta-carotenoids (92). Vitamin A enters the body exclusively through diet, and is mainly obtained as retinol from the liver, dairy products or as carotenoids from plants (93). Vitamin A is inactive and requires enzymatic processing to become activated (90). It is first converted to retinal catalyzed by alcohol dehydrogenases (ADH) commonly found in most cells, and then to RA catalyzed by retinal dehydrogenases (RALDH), which are only expressed by certain cell types including DCs found in the PPs, LPs and the MLNs in the small intestine (91, 94, 95). In the gut, vitamin A is metabolized locally by DCs resulting in the production of RA, which along with antigens is presented to naïve T cells during priming (91, 93). As a result, RA binds to its receptors – the retinoic acid receptor RAR and RXR expressed on naïve T cells, which up-regulate the expression of $\alpha_4\beta_7$ and CCR9 (91, 93, 96-99).

A recent study has shown that exposure to RA can redirect immune responses elicited by subcutaneous vaccination of mice from skin-draining inguinal LNs to the gut (100). When present during priming in inguinal LNs, RA induced robust upregulation of gut-homing receptors CCR9 and α4β7 by further inducing autonomous RA production in inguinal LNs DCs. Importantly, RA-supplemented subcutaneous immunization generated a potent immune response in the small intestine that protected mice from cholera toxin–induced diarrhea and diminished bacterial loads in Peyer's Patches after oral infection with Salmonella. This is supported by another study which showed that presence of exogenous RA during systemic vaccination increased numbers of effector and memory $CD8^+$ T cells in mucosa-associated tissues that provided enhanced protection against mucosal viral challenges as well as increased central memory-like T cells in systemic sites that preferentially migrate to mucosal sites upon boosting (101).

Aside from producing RA, DCs can also internalize exogenous RA produced by other cells in the gut such as LP macrophages (102), mesenteric lymph node stromal cells (103) and gut epithelial cells (104). However, the contribution of RA from sources other than DCs towards the imprinting process is not fully established (105).

Studies in murine models have also demonstrated that GALT DCs are more effective at converting Vitamin A to RA than splenic DCs and other peripheral lymph node DCs, and are therefore more effective at inducing integrin $\alpha_4\beta_7$ and CCR9 expression on T cells (91). In line with these observations, only $CD103^+$ DCs are able to induce the expression of $\alpha_4\beta_7$ and CCR9, and were found to express higher levels of enzymes required for vitamin A metabolism compared to $CD103^-$ DCs (97, 98). Moreover, among these $CD103^+$ DCs, *lamina propria* DCs are the most effective at generating $\alpha_4\beta_7^+$ $CCR9^+$ $CD8^+$ T cells compared to MLN DCs or PP DCs (98). The MLNs are believed to serve as the primary site where imprinting of gut homing specificity occurs as antigen-loaded DCs are carried into the MLNs via draining lymphatics (106-110). Further studies have shown that similar mechanisms involving vitamin A metabolism were also used to instruct regulatory T cells and B cells to become gut-tropic (99, 111-113).

5.5. Antigen-driven T cell trafficking

Although endowed with tissue-targeting homing properties that allow access to specific organs, such as the skin and gut, primed T-cells must patrol very large areas to locate antigen-rich tissue in order to exert their function. Together with the acquisition of homing receptors during activation and differentiation and non-specific inflammatory signals, additional antigen-driven mechanisms have been proposed, which orchestrate the targeted delivery of memory T cells to antigen-rich tissue. However, it is not clear to what extent the accumulation of specific T lymphocytes within parenchymal tissue is directly influenced by antigen recognition. In principle, several mechanisms could contribute to the accumulation of antigen-specific T cells at antigen-bearing sites: a), the trapping of antigen-specific T cells, for example upon TCR-triggered activation of integrin adhesion or effects on motility; b), local proliferation of antigen-specific cells; or c), a direct effect of antigen recognition on the recruitment of T cells. While trapping or local expansion may be operative during primary T cell responses, it is likely that these mechanisms 'per se' would be insufficient to achieve the efficacy and speed of specific T cell accumulation in target tissue in recall responses.

Antigen presentation by the endothelium has been repeatedly reported *in vitro* to directly contribute to the recruitment of antigen-specific T cells. Cognate recognition of ECs both in human and mice was shown to enhance T cell trans-endothelial migration. Cognate recognition of B7-deficient human and murine ECs was shown to enhance T-cell trans-endothelial migration without inducing unresponsiveness *in vitro (*114-116).

Similar mechanisms have been shown to sustain the recruitment of specific T cells to antigenic sites *in vivo*. Islet-specific homing by insulin-specific $CD8^+$ T cells was abrogated in mice lacking MHC class I expression, or in mice displaying impaired insulin peptide presentation by local endothelium due to lack of insulin secretion, suggesting that EC can cross-present tissue antigens to $CD8^+$ T cells (117). Similarly, homing of insulin-specific $CD8^+$ T cells to the islets of Langerhans during the onset of autoimmune diabetes in non-obese diabetic (NOD) mice *in vivo* was impaired in IFN-γ-deficient NOD mice (118). In particular, T cell diapedesis was significantly diminished. This effect was reversible by treatment of the animals with recombinant IFN-γ. Moreover, major histocompatibility complex (MHC) class II molecule expression by microvascular endothelium in the central nervous system precedes and is required for the formation of T cell infiltrates in EAE in guinea pigs (119). Finally, up-regulation of H2 molecules and HY antigen presentation by local vessels led to peritoneal recruitment of HY (male)-specific H2-D^b–restricted $CD8^+$ lymphocytes T cells in male, but not female mice (120). Intravital microscopy analysis revealed that antigen presentation by the endothelium selectively enhanced T cell diapedesis into the tissue, without affecting rolling and adhesion.

Crosstalk between TCR- and chemokine receptor-mediated signalling has recently been shown to be essential for T cell migration. CXCR4 signal transduction in human T cells requires the zeta-associated protein 70 (ZAP-70), a key element in TCR signalling (121). In addition, chemokine receptor expression is regulated by T cell activation (122). Chemokines contribute to antigen-specific T cells homing following cognate recognition of the endothelium *in vivo* (117, 123).

The relative contribution of antigen-specific and non-antigen-specific signals to memory T-cell recruitment is likely to be determined by the intensity of the inflammatory response. It is possible that TCR-mediated primed T-cell localization to antigenic sites may be essential to ensure efficient, rapid memory responses in the event of limited inflammatory signals. For example, insulin-specific H2-K^d-restricted T cells are efficiently recruited to pancreatic islets of various H2-K^d-positive mouse strains that are free of pre-existent inflammation (117). In contrast, severe inflammation or a pre-existing large antigen-specific T-cell repertoire (for example during direct alloresponses) may override the requirement for selective antigen-dependent T-cell recruitment (124).

5.6. Co-stimulatory molecules regulate T cell migration

Co-stimulatory signals such as those mediated by CD28 delivered to T cells in conjunction with TCR engagement are required to sustain T cell division, differentiation and survival (125). Negative co-stimulators (such as CTLA-4) counteract these effects thus promoting homeostatic mechanisms and preventing autoimmunity. These co-stimulators have been shown to regulate adhesion molecules activity and cytoskeletal rearrangement *in vitro* (126-129). *In vivo*, CD28-mediated signals promote the localization of T cells to target tissue following priming. A prominent feature of CD28-deficient immune responses is the inefficient localization of primed T cells to non-lymphoid antigenic site (130-132) and intact CD28 signalling is required for primed T cells to leave lymphoid tissue and migrate to antigenic sites following priming (133). TCR-transgenic T cells carrying a mutation in the cytoplasmic tail of CD28 ($CD28^{Y170F}$) that abrogates phosphatidylinositol-3'-kinase (PI3K) recruitment without leading to defects in clonal expansion (134) failed to localize to target tissue following priming.

The mechanism by which CD28 facilitates migration of primed T cells to non-lymphoid tissue is unclear. CD28 does not appear to directly mediate adhesion (135), but may favor primed T cell migration to non-lymphoid tissue by inducing integrin mediated-adhesion (133). The long-term effect of CD28-mediated signals on T cell migration (133) suggests that additional mechanisms, such as transcriptional regulation of chemokine receptor expression (136), are likely to be involved.

Despite sharing adhesion-inducing and pro-migratory properties *in vitro* (137), CTLA-4-mediated signals lead to effects antagonistic to those induced by CD28 on T cell migration *in vivo*. CTLA-4 ligation reduced conjugate formation with cognate DCs and their retention in lymph nodes in response to antigen (138), suggesting that CTLA-4 engagement may limit the expansion of specific T cells by reducing their cumulative interactions with cognate DCs. In addition, tissue infiltration by a murine HY-specific H2-K^k-restricted T cell clone was abrogated by CTLA-4 ligation (133), suggesting that CTLA-4 engagement can antagonize recruitment of primed T cells to target tissue mediated by antigen-induced signals.

In addition to CD28 and CTLA-4, a number of other costimulatory molecules have been implicated in the regulation of T-cell migration. For example, OX40/OX40 ligand interaction has been shown to be required for T-cell migration to germinal centres (139), and the inducible costimulatory molecule (ICOS) regulates human memory T-cell migration through tumor necrosis factor (TNF)-α-treated endothelial cells (140).

5.7. PI3K—mediated control of T cell migration

PI3K signaling mediates not only events downstream of TCR and CD28 (141, 142) leading to T cell division and differentiation, but also T cells responses to chemokines (143). It has recently been shown that both TCR- and CD28-driven T cell migration rely upon PI3K p110δ activity (144, 145). Studies using T cells from mice expressing a catalytically inactive p110δ isoform or treated with the p110δ selective inhibitor, IC87114, revealed an essential role for this molecule in TCR-dependent localization of both $CD4^+$ and $CD8^+$ T cells in a male antigen-specific transplantation model (144). Interestingly, and in support of previous findings (146), there was no defect in the p110δ mutant mice of either normal constitutive trafficking or migratory response to chemokines.

Recent evidence also strongly correlates CD28-induced migration with PI3K (likely p110δ) signaling. TCR-transgenic mice carrying an ovalbumin-specific T cell receptor (OT-II) and a mutation in the cytoplasmic tail of CD28 that abrogates class I PI3K recruitment without leading to defects in clonal expansion ($CD28^{Y170F}$) (134) were generated to allow discrimination of conventional co-stimulation-driven clonal-expansion from their ability to infiltrate antigenic tissue (OT-II/$CD28^{Y170F}$). OT-II and OT-II/$CD28^{Y170F}$ naïve T cells proliferated equivalently following immunization with $OVA_{323-339}$ peptide. However, OT-II/$CD28^{Y170F}$ $CD8^+$ memory T cells failed to localize to target tissue upon antigen challenge. It has to be borne in mind that the PI3K binding motif in CD28 is also required for binding of the adaptors Grb2 and Gads and the involvement of PI3K is implied but not proven.

Naïve T cells express the adhesion molecule CD62L and the chemokine receptors CCR7 and sphingosine-1-phosphate receptor 1 (S1P1), which facilitate their trafficking to SLOs. Upon TCR engagement, the PI3K-AKT-mTOR axis promotes the transcriptional downregulation of CD62L, CCR7 and S1P1 via the inhibition of the transcription factor KLF2 (147, 148). Rapamycin-mediated inhibition of mTOR causes effector T cells to re-express KLF2, CD62L and CCR7 and home to SLOs where they are retained preventing elimination of target cells in the periphery (147, 148). In addition to the involvement in expression of CD62-L and CCR7, AKT, has also been implicated in F-actin polymerization and myosin assembly (149-152). Accordingly, PI3K (s) contribute to several aspects of the migratory machinery, including gradient sensing, signal amplification, actin reorganization and hence cell motility (153-155).

6. REGULATORY T CELL TRAFFICKING

Regulatory T cells (T_{regs}) exert their function by suppressing T cell functional responses, thus preventing the development of autoimmunity (156, 157). T_{regs} are characterized by the constitutive expression of the transcription factor FoxP3, which confers them potent suppressive activity (158, 159). Humans with mutations affecting the FoxP3 gene suffer from fatal autoimmune diseases (IPEX: immune polyendocrine enteropathy X-linked syndrome) (159). Similarly, mice with a spontaneous mutation in the FoxP3 gene – known as 'scurfy' mice - develop fatal autoimmune diseases affecting multiple organs (158). In IPEX patients and scurfy mice, chronically activated and self-reactive $CD4^+$ T cells are found to be responsible for the symptoms developed (160). These studies thus demonstrated the importance of T_{regs} in homeostasis in both animals and humans.

6.1. Naturally occurring regulatory T cells

Regulatory T cells were first described in mice by Sakaguchi and coworkers in 1995 as a subset of $CD4^+$ T cells with a constitutive expression of IL-2 receptor alpha-chain CD25 (161). These naturally occurring cells develop in the thymus and constitute approximately 5-10% of all peripheral $CD4^+$ T cells in mice (162). They are anergic in nature and exhibit potent suppressive function both *in vivo* and *in vitro* (162-164). Treg cells require activation signals via the T cell receptor; however, once activated their suppressor function is antigen non-specific (165).

$CD4^+CD25^+$ regulatory T cells were isolated from human peripheral blood in 2001 (166, 167). Unlike mice, in which both $CD25^{high}$ and $CD25^{low}$ of the $CD4^+CD25^+$ population exhibit suppressor functions, in humans only $CD4^+CD25^{high}$ T cells are suppressive (166). Human $CD4^+CD25^{high}$ regulatory T cells account for 1-2% of the total peripheral $CD4^+$ T cell population (166).

It must also be considered that high levels of CD25 and FoxP3 are transiently expressed by recently activated human T cells, which do not display suppressor functions (168, 169). Thus, a Treg-specific marker has yet to be identified. Despite this, markers important for the survival and the suppressive functions of T_{regs} have been identified such as the cytotoxic T lymphocytes antigen 4 (CTLA-4) and glucocorticoid-induced TNF-receptor-related protein (GITR) (170, 171).

6.2. Induced regulatory T cells

Aside from naturally occurring regulatory T cells, T_{regs} can be induced from naïve $CD4^+$ $CD25^-$ T cells *in vitro* and *in vivo (*172-174). Thus far, the differentiation of naïve T cells into induced T_{regs} (iT_{regs}) *in vivo* has been documented in the murine intestine (96), inflamed lung (175), tumors (176) and transplanted tissues (177).

The possible underlying mechanisms of iTreg generation have also been explored in both humans and mice. *In vitro* generation of iTregs has been shown to be dependent on TGF-β and IL-2 (172, 178). The Vitamin A metabolite RA also facilitates the generation of regulatory T cells mediated by TGF-β following priming by DCs in the secondary lymphoid tissue (96, 99). In addition, studies have shown that only $CD103^+$ DCs in the small intestinal LPs and the MLNs are capable of generating $FoxP3^+$ T_{regs} in the presence of TGF-β and retinoic acid (96, 99). Regulatory T cells generated in the presence of retinoic acid also express fully functional gut-homing receptors $\alpha_4\beta_7$ and CCR9 (113). Naturally occurring T_{regs} and induced T_{regs} have both been shown be anergic and able to suppress effector T cell responses *in vitro* and *in vivo* (179).

6.3. Treg homing to secondary lymphoid organs

T_{regs} play a key role in tolerance induction and maintenance. Evidence suggests that Tregs-mediated immune suppression operates in both SLOs (180) and non-lymphoid tissue (181, 182). Appropriate trafficking and retention are therefore indispensable for T_{regs} to efficiently modulate immune response *in vivo*. Distinct chemokine and adhesion receptors may contribute to trafficking and retention of T_{regs} at sites where regulation is required (183-185). Naturally occurring T_{regs} express the adhesion molecule CD62L and the chemokine receptor CCR7, which facilitate their homing to the T-cell area in lymph nodes (180, 186, 187).

Migration to tissue-associated lymph nodes is required for their regulatory function. $CD62L^+$ T_{regs}, rather

than CD62L$^-$ T_{regs}, efficiently delay diabetes in prediabetic nonobese diabetic (NOD) mice (188) and protect from acute graft-versus-host disease (GVHD) (189). Similarly, CD62L-dependent T_{reg} homing to lymph nodes is necessary for the induction of transplantation tolerance (190). In addition T_{regs} from CCR7 knockout mice were inefficient in homing to lymph nodes and did not suppress antigen-induced activation of T cells (191).

To exert their regulatory function, T_{regs} need close physical contact with effector cells (192). Thus, effective suppression can only occur when migration and homing of T_{regs} run in parallel with those by effector cells. Evidence suggests that T_{regs} and effector T cells home to similar areas of the lymph nodes (193).

At the T-cell zone, naïve T_{regs} may recognize antigens and become activated (194). Upon activation, T_{regs} lose CCR7 expression and reduce CD62L expression (195, 196) and gain the expression of CXCR5, a chemokine receptor that promotes T_{regs} migration into germinal centres in response to CXCL13, where they regulate the magnitude and characteristics of antibody responses (197, 198). T_{regs} homing to lymph nodes therefore controls the induction phase of immune response (180, 193).

6.4. T_{reg} homing to nonlymphoid tissue

The effector phase of immune response involves migration to and infiltration of antigen-rich non-lymphoid tissue by effector T cells. By migrating to non-lymphoid sites of inflammation T_{regs} control effector immune responses (195, 199, 200). T cell trafficking to different tissues is determined by the combined expression of chemokine receptors and adhesion molecules on the cell surface (201). T_{regs} activated in the lymph nodes draining a tissue acquire homing receptors that allow them to migrate back to the inflamed tissue drained by the lymph nodes. Like conventional T cells, the migratory properties of T_{regs} are shaped by the tissue microenvironment and organ-resident dendritic cells during priming (111). For example, T_{regs} activated in MLNs and PPs acquire α4β7 and CCR9, which direct their trafficking to the gut. By contrast, T_{regs} activated in peripheral lymph nodes express CCR8, but not α4β7 and CCR9 (202). Interestingly, it has been shown that increased CLA or α4β7 expression by circulating human T_{regs} is associated with reduced risk of skin or gut acute GVHD, respectively (203). Expression of tissue specific homing receptors depends on microenvironment-specific cues, such as retinoic acid produced by dendritic cells of gut tissue (91, 93).

In humans, expression of trafficking markers on circulating regulatory T cells is less well characterized. Recent studies have shown that a high frequency of the peripheral blood T_{regs} express the skin-homing receptors, CCR4, CLA. In contrast, CD103 and the gut-homing receptors $\alpha_4\beta_7$ and CCR9 are found on a small number of circulating T_{regs} (204, 205). This observation raises the question of how regulatory T cells execute their suppressor functions in the gut (170). A possible explanation is that MAdCAM-1, the ligand of $\alpha_4\beta_7$, is also capable of binding to CD62L found on regulatory T cells in humans and mice (6, 199, 206). CD62L therefore may target T_{regs} to the MLNs and the PPs where they carry out suppressor functions (204).

Activated T_{regs} express αEβ7, which binds its ligand E-cadherin and allows efficient migration to- and retention within inflamed tissue to suppress the effector phase of immune response (195, 207). αEβ7$^+$ T_{regs} display a heterogeneous pattern of tissue-specific homing receptors. A subset of activated T_{regs} up-regulates CXCR4 expression and become responsive to SDF-1 (stromal-derived facor-1), enabling them to migrate to the bone marrow (208), where T_{regs} can suppress immune responses (209-211). It has been described that more than 25% of CD4$^+$ T cells are T_{regs} in bone marrow – as compared to 5-10% of CD4$^+$ T cells in the peripheral blood - of human and mice. T_{regs} exit from the bone marrow is achieved through granulocyte colony-stimulating factor (G-CSF) and reduced expression of CXCL12, the ligand for CXCR4 (208). The bone marrow is a critical site of immunity as studies have shown that long-lived, antibody-secreting plasma cells (211) and functional memory T cells (210, 212) reside in this organ. Thus, it appears that T_{regs} are actively, rather than passively, recruited and retained in the bone marrow to regulate immune responses during homeostasis.

T_{regs} must migrate to transplanted organs to effectively suppress intragraft anti-donor immune response. It has been shown that T effector cells with high avidity for donor antigens home to transplanted heart to mediate transplant rejection (213). Intragraft T_{regs} have been associated with tolerance induction. T_{regs} with unique chemokine profile have been shown to migrate to different tissue grafts. The recruitment of Tregs in heart allograft of tolerant mice is associated with CCR4 expression (182). Tregs migration into isl*et al*lografts is dependent on the chemokine receptors CCR2, CCR4, CCR5 and P- and E-selectin ligands expression (214). Wysocki and colleagues have shown that CCR5 plays an important role in T_{regs} recruitment to both lymphoid tissues and graft versus host disease (GVHD) target organs (215).

It is thought that T_{regs} share many homing receptors with conventional T cells. However, T_{regs} express more receptors associated with homing to non-lymphoid tissue, such as CXCR6, CCR5, CCR6 and CCR8 emphasizing the requirement for their migration to control inflammation at the effector site (202).

A study by Tomura *et al.* showed that in steady-state T_{regs} constitutively migrated from the skin to draining LNs in mice. Furthermore, they demonstrated that not only does skin inflammation exacerbate LN-directed T_{reg} homing, but it also triggered reverse circulation of T_{regs} from LNs to skin, whereby these cells contribute to regulation of the immune response (216).

Emerging evidence suggests that T_{regs} trafficking and compartmentalization can be modulated allowing efficient tissue targeting after *ex vivo* expansion. Siewert and colleagues have shown that T_{regs} can be configured both *in vitro* and *in vivo* with organ-selective homing

properties allowing efficient migration into target tissue. This suggests that modulation of T_{regs} designed to serve for therapeutic purposes with specific homing properties is feasible for adoptive T cell therapy (111). Moreover, α4β7+ regulatory T cells generated *in vitro* are also able to effectively clear acute inflammation in the small intestine when transferred into the diseased animals (217).

7. CONCLUDING REMARKS

The immune system is unique in representing a network of interacting cells of enormous complexity and yet being based on single cells travelling around the body. Every decade of immunological research appears to reveal novel functional subsets of T cells. How this expanding universe of specialists becomes co-ordinated and appropriately targeted to the hot-spots of immunoreactivity would have remained a mystery if, at the same time, our knowledge of the mechanisms of cell trafficking had not greatly improved. Co-operating adhesion molecules and chemokine receptors equip the migrating cells with an almost unlimited combinatorial diversity which allows them to recognize the signatures defining tissues and compartments, to distinguish different inflammatory processes depending on the kind of triggers, site of inflammation, or involved cell populations and so on. Monitoring of the migration of T-cell subsets associated with immune-mediated diseases may prove to be essential in allowing us to understand pathogenic mechanisms, to design prognostic and therapeutic tools and to predict therapeutic responses. If these goals are to be achieved, we must address the many unanswered questions.

Keywords: homing receptors; T lymphocytes; T-cell homing, T cell migration

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