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The essential role of chemokines in the selective regulation of lymphocyte homing

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Abstract

Knowledge of lymphocyte migration has become a major issue in our understanding of acquired immunity. The selective migration of naïve, effector, memory and regulatory T-cells is a multiple step process regulated by a specific arrangement of cytokines, chemokines and adhesion receptors that guide these cells to specific locations. Recent research has outlined two major pathways of lymphocyte trafficking under homeostatic and inflammatory conditions, one concerning tropism to cutaneous tissue and a second one related to mucosal-associated sites. In this article we will outline our present understanding of the role of cytokines and chemokines as regulators of lymphocyte migration through tissues.

Keywords: Lymphocyte homing; Chemokines

1. Introduction

The initiation of an effective immune response requires that dendritic cells (DCs), located at the sites of pathogen entry recognize these microorganisms in the context of a danger signal. Thus, in response to inflammatory signals, DCs capture, process and carry antigens from the site of pathogen entry to secondary lymphoid organs where they present peptides derived from the pathogen to infrequent antigen-specific naïve T-cells [1]. These naïve, antigen-inexperienced T-cells circulate continuously through secondary lymphoid organs including spleen, peripheral lymph nodes and mucosal-associated lymphoid tissue. Although it is thought that naïve cells are excluded from non-lymphoid tissue and that only activated memory effector cells can gain access to non-lymphoid tissues, two recent reports have demonstrated that antigen-inexperienced naïve T, including the recent thymic emigrants $CD8^+$ T-cells do migrate to the lamina propria of the small intestine [2,3].

Once their cognate antigen is presented by DCs as a peptide–MHC complex, naïve T-cells differentiate into effector/memory T-cells migrating back to the site of antigen entry via efferent lymphatics where they are able to mount an immune response. Similarly, regulatory T-cells responding to self-antigens acquired by DCs under non-inflammatory conditions may migrate to tertiary tissue, although this point has not been fully resolved. If they actually have the capability of homing to tertiary tissues, Treg may provide immunoregulatory signals thus preventing tissue-targeted effector cells to accumulate in inflamed environments [4]. Alternatively, Treg may remain in secondary organs where they may block the effector activity of responding T-cells. This tropism displayed by effector/memory and regulatory T-cells is mostly determined by the expression on the cell surface of specific tissue-homing receptors and chemokines receptors and of their matching ligands in the postcapillary

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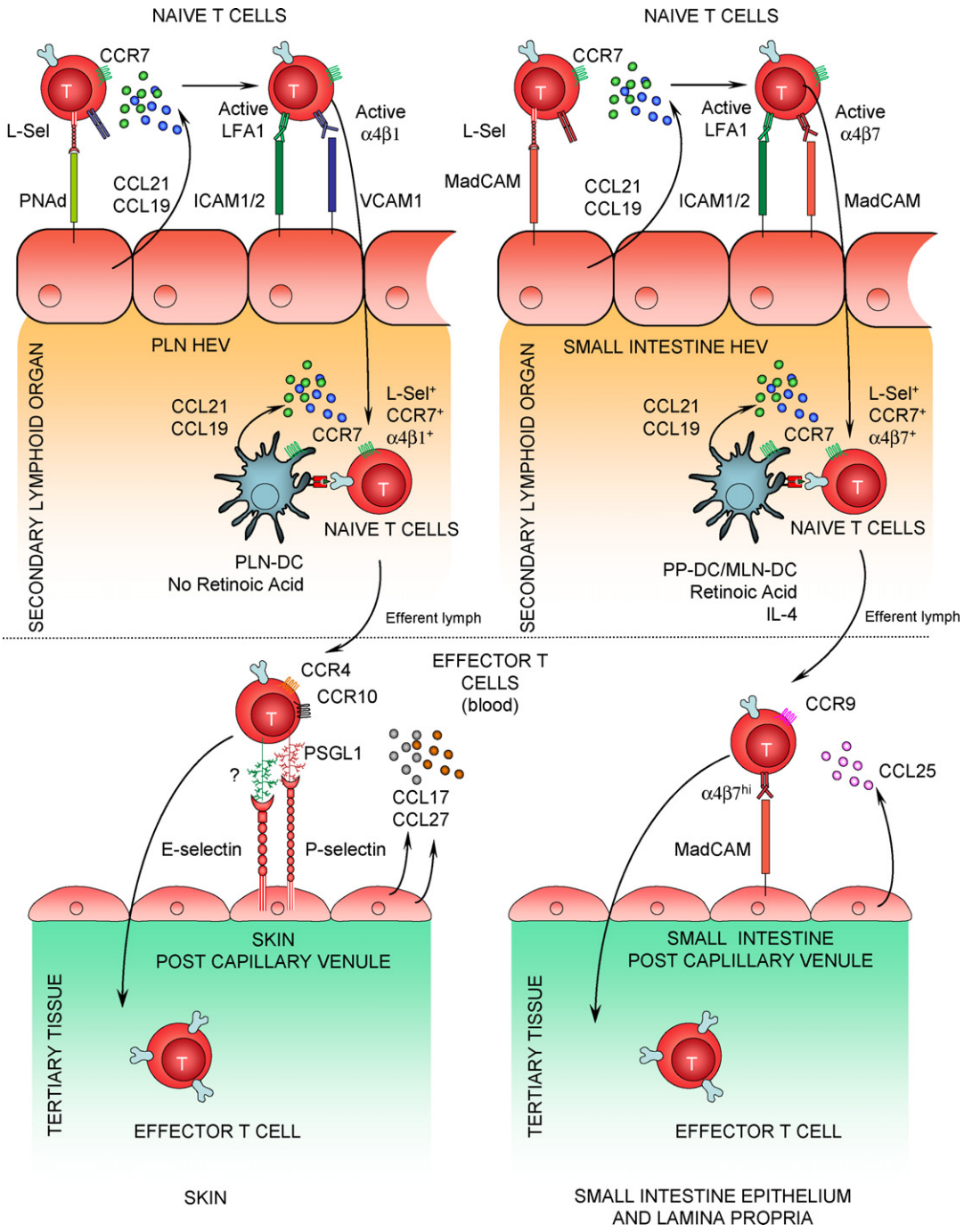

Fig. 1. Schematic representation of chemokine involvement in T cell homing. Chemokines contribute to naïve T cell entrance to secondary lymphoid organs through high endothelial venules (HEVs) at peripheral lymph nodes (PLN) or at mucosal sites at the small intestine (mesenteric lymph nodes, MLN; Peyer's patches, PP). Cells at HEVs within the T cell zones secrete chemokines CCL19 and CCL21 that attract naïve T-cells expressing CCR7. Also, CCR7-expressing dendritic cells are draw via afferent lymphatics to neighboring sites within secondary lymphoid organs. L-Selectin on the surface of T-cells recognizes peripheral node addressing (PNAd) on PLN and mucosal addressin cell-adhesion molecule-1 (MAdCAM-1) on small intestine HEVs. MAdCAM-1 can also interact with integrin $\alpha_4\beta_7$. Chemokines such as CCL19 and CCL21 rapidly activate integrins to promote strong adhesion of rolling lymphocytes. At PLN, lymphocyte function-associated molecule-1 (LFA-1) and integrin $\alpha_4\beta_1$ bind with high affinity to ligands ICAM-1 and 2 and VCAM-1 respectively, while at intestinal sites, activated $\alpha_4\beta_7$ binds with high affinity to MadCAM-1. These interactions result in T-cell arrest and endothelial transmigration that positions naïve T-cells at the T cell zones of the respective secondary lymphoid organs; PLN in one case and MLN or Peyer's patches in the other. T-cells that recognize their cognate antigen presented as MHC–peptide by dendritic cells differentiate into effector/memory T-cells and remodel their homing and chemokine receptors. Activation of T-cells by PLN-DCs results in a decrease in L-selectin expression and the upregulation of ligands for P- and E-selectin and of chemokine receptors 4 (CCR4) and 10 (CCR10). Secretion of chemokines 17 and 27 (CCL17 and CCL27) attract these cells to inflammed skin. T-cells activated by MLN-DCs or PP-DCs decrease L-selectin expression and upregulate integrin $\alpha_4\beta_7$, that binds to MAdCAM-1 and chemokine receptor 9 (CCR9) that responds to CCL25 produced by cells in the small intestine. These activated T-cells migrate to the epithelium and lamina propria of the small intestine. Besides chemokines, other factors such as retinoic acid (RA) and IL-4 participate in the targeting of T-cells to the small intestine. Other various arrangements of homing and chemokine receptors guide activated T-cells to tertiary organs other that skin and the gut (not depicted).

venules of the specific tertiary tissues. The induction of the ''appropriate'' homing and chemokine receptors depends at least in part on the presence in lymphoid tissue of particular DCs, the activity of which may in turn be influenced by the microenvironment existing in each secondary lymphoid organ [5].

In terms of chemokines, this family of small protein molecules was first recognized for their capacity to induce inflammation and to attract monocytes, neutrophils and activated effector T-cells [6]. Lately, it has also been established that these molecules play a central role in regulating lymphocyte traffic during normal immunological surveillance as well as during the course of an active immune response [7,8]. In addition, other lymphocyte responses, not linked to traffic or tissue positioning, are also modulated by chemokines, including T-cell maturation and effector functions [9]. For example, chemokine activity is not only related to the establishing of a chemical gradient along which cells can migrate, but they also control lymphocyte traffic by triggering activation of integrins that leads to lymphocyte adhesion and transmigration [9,10]. Finally, besides their activity in directing the appropiate physiological homing of lymphocytes, chemokines have also an active role in the localization of different subsets of lymphocytes within the different areas of lymphoid organs, a function fundamental to the generation of the immune response [10].

Chemokine activity as well as their distribution in tissues has led to the classification of these molecules as ''inflammatory'' and ''homeostatic'' chemokines [8,11]. Inflammatory chemokines, which are produced by resident and infiltrating cells in inflamed tissue after contact with pathogens act as recruiter of cells involved in innate immunity and antigen-specific effector T-cells; while homeostatic chemokines, which are constitutively produced by normal tissue operate under non inflammatory conditions, maintaining normal T cell traffic under physiological immune surveillance [12]. Chemokines and their receptors perhaps represent one of the most redundant physiological systems (more than 50 chemokines and almost 20 chemokine receptors have already been identified). The large number of these molecules identified to date clearly exceeds the combinations needed to correctly guide and position lymphocytes to their appropriate location [7,10]. This has led to the idea that there are still new migratory pathways perhaps to other tertiary tissues that remain to be defined. Also, depending on their state of differentiation, lymphocytes express on their surface a large variety of chemokine receptors, a feature that adds further complexity to the regulation of lymphocyte migration (see Fig. 1).

2. Initial migration of naïve T-cells to lymphoid tissues

In most secondary lymphoid organs, lymphocyte migration is controlled at post-capillary high endothelial venules (HEV) by specific receptor–ligand interactions that act as site recognition molecules [13]. Initial adhesion is brought about by the interaction of L-selectin present on naïve lymphocytes with its ligands on HEV. This contact is too weak to permanently arrest cells and blood flow induces cells to roll on the vessel surface. Stronger adhesion is needed to stop cells and prevent them from dislodging and re-entering the blood flow. Other secondary receptor-ligand pairs from the integrin family of adhesion receptors provide this additional, stronger binding. Activation of these additional receptors molecules occurs after chemokines – attached extracellular matrix components – bind to their own receptors present on the surface of T lymphocytes. Thus, entrance of lymphocytes to secondary lymphoid organs is a three-step process that involves an initial tethering followed by rolling and finally firm binding as a consequence of the activating stimulus of chemokines [14,15]. As a result of these multiple interactions, lymphocytes enter to secondary lymphoid organs. Once inside the lymphoid tissue, lymphocytes must encounter their cognate antigen to be activated or otherwise exit via efferent lymph. Those lymphocytes that do encounter antigen in the form of MHC–peptide on the surface of DCs remain in the lymphoid organ, are activated, differentiate into effector cells, proliferate and acquire a restricted set of new tissue homing receptors before abandoning the lymphoid organ via efferent lymphatics. These lymphocytes return to the circulation via the toraxic duct and migrate to the site of antigen entry where ligands for the newly acquired homing receptors are expressed. As we will describe later, the acquisition of new adhesion molecules and chemokines receptors, in combination with the topographical location of their ligands – addressins and chemokines, respectively – results in a combination of homing molecules that are the key to the fine-tuning of lymphocyte homing.

In regard to the homeostatic entrance of naïve T lymphocytes to secondary lymphoid tissue (lymph nodes, Peyer's patches, spleen), all evidence indicates that this process is initially guided by the presence on HEVs of addressins (L-selectin ligands) and a gradient of chemokines CCL19 (ECL), CCL21 (SLC) and CXCL13 (BCA-1) [10].

Circulating naïve T lymphocytes have the property of entering non-mucosal lymph nodes as well as mucosal sites such as Peyer's patches. This is achieved owing to the presence on these cells of L-selectin, an adhesion receptor that has the capability of binding to the peripheral node (PLN) addressin (PNAd) present on lymph nodes as well as to the mucosal addressin cell adhesion molecule-1 (MAdCAM-1) present on Peyer's patches and mesenteric lymph nodes (MLN). In addition to L-selectin, entry of naïve T lymphocytes to PLN requires the presence of β_2 integrin LFA-1 in its high affinity conformational form that interacts with ICAM-1 present on PLN endothelium. On the other hand, entry to mucosal sites requires the additional expression of integrin $\alpha_4\beta_7$ that similarly to L-selectin, also interacts with MAdCAM-1 [16–18].

Chemokines are critical in converting the initial weak interaction between naïve lymphocytes and HEV into a strong arrest [19]. Chemokines such as CXCL12, CCL19 and CCL21 have been shown to mediate such a process [10]. Transcripts for CCL21 are strongly expressed in HEV [20]. Interestingly, mice lacking this chemokine (*plt*/*plt* mice) have a highly reduced migration of naïve T-cells to PLN and Peyer's patches [21,22]. Also, experiments have shown that this chemokine can induce the rapid integrin-dependant arrest of rolling lymphocytes *in vitro*, probably through an increase in the binding affinity of the integrin for its ligand [19,23]. Other chemokines such as CCL20 (MIP3α), CCL19 (MIP3β, ECL) and CXCL12 (SDF-1), have been also implicated in promoting stronger naïve T lymphocyte adhesion to HEV *in vitro* [10].

Evidence from a number of laboratories has validated the idea that CCL19 and CCL21, chemokines that bind to CCR7 present on naïve T-cells and a sub-population of memory T-cells and CXCL13 (BCA-1) that binds to CXCR5, are critical to the initial recruitment of lymphocytes to secondary lymphoid organs [11,24]. More recently it was described that CXCR5 has a role in the migration of naïve B cells to Peyer's patches only, while CXCR4 plays a role on naïve B cell homing to PLN and Peyer's patches [25]. The *plt*/*plt* mouse, that lacks expression of the CCL21 gene in high endothelial cells shows an almost complete absence of T-cells in lymph nodes and Peyer's patches, underscoring the importance of this chemokine in T-cell homing to secondary lymphoid tissue. The importance of CCL19 and CCL21 expression on HEV in directing naïve T-cells to secondary lymphoid tissue is further supported by data that shows a reduced homing of T-cells to lymph nodes, Peyer's patches and spleen in mutant mice with a faulty production of CCL19 and CCL21 [21,22]. On the other hand, antigen-presenting DCs also express CCR7 and thus are also competent to migrate to secondary lymphoid tissue [22,26,27] locating to the T-cell areas where they secrete additional amounts of CCL19 and CCL21 causing a co-localization with naïve T-cells [26]. The strategy employed by T lymphocytes to encounter antigen-presenting DCs has recently been revealed by confocal microscopy [28]. Subsequent to antigen capture, $CCR7^+$ DCs enter the afferent lymph, migrate to the paracortex of draining lymph nodes and locate in the vicinity of HEVs. Once there, they scan entering $CCR7^+$ naïve T-cells, retaining and activating antigen-specific T-cells. This strategy optimizes the encounter of infrequent antigen-specific T-cells and antigen-presenting DCs. Both DCs and naïve T-cells are targeted to the same region of the secondary lymphoid organ by the expression of specific chemokine and chemokine receptors as mentioned above. T-cells unable to recognize antigen leave secondary lymphoid organs and eventually enter the circulation. In this regard, it could be reasoned that additional signals may be needed to retain antigen-specific T-cells after antigen presentation. These signals could be provided by interactions with other elements of the extracellular matrix. In this regard, it was recently reported that CD69 upregulation and S1P-receptor-1, play a critical role on lymphocyte retention upon activation [29].

In humans, a small sub-population of tonsillar memory T-cells (but not naïve T-cells) expresses CXCR5, the receptor for chemokine CXCL13 (BCA-1). These cells also express L-selectin and CCR7 supporting the idea that these cells home mainly to secondary lymphoid organs. Once in this tissue these $CXCR5^+$ T-cells locate to the follicles (B-cell zone), where reticular cells in the follicular mantle and in follicular HEVs produce its ligand CXCL13 [30,31]. Interestingly, B cells also express CXCR5 and CCR7 thus migrating to the same region as this sub-population of T-cells [12]. The evidence suggests that these T-cells may play an important role in providing B-cell help and regulating humoral immune responses [30]. Thus, CXCL13 positions T-cells in a zone apart from those of CCL19 and CCL21, and may contribute to the distribution of different T-cell functions within their appropriate lymphoid tissue micro-environment.

Activation of naïve T-cells in the secondary lymphoid tissue leads to a dramatic decrease in the expression of L-selectin in these cells with a concomitant loss of their capacity to enter freely to other secondary lymphoid organs, with the exemption of the so-called central-memory T-cells [32]. Activation also brings about a reprogramming of homing molecules in such a way that the resulting memory/effect T-cells acquire an exclusive arrangement of these receptors endowing T-cells with tissue-restricted migratory properties.

3. Homing to mucosal tissue

Restricted migration of lymphocytes to specific organs has been known since the pioneering work of Gowans almost 40 years ago [33]. However it has been during the last 3–4 years that the regulation of these homing pathways has begun to be elucidated. Several groups have demonstrated that DCs as well as other microenvironment elements play a central role in the imprinting of the homing phenotype on T-cells [34–37]. The data demonstrates that imprinting occurs after contact of antigen-presenting DCs with naïve T-cells in secondary lymphoid organs. DCs isolated from Peyer's patches (PP-DCs) or mesenteric lymph nodes (MLN-DCs) are competent in upregulating gut homing receptors $\alpha_4\beta_7$ and CCR9 on $CD8^+$ [34,36] and $CD4^+$ T-cells [35] inducing homing of these cells to the small intestine mucosa, while DCs from PLN (PLN-DCs) do not [36,38,39].

In the small intestine, Peyer's patches assess antigens coming from the intestinal lumen, while MLN assess antigens coming from the lamina propria (LP) and from the Peyer's patches through the draining efferent lymph. On the other hand, naïve T-cells that encounter their cognate antigen at Peyer's patches or mesenteric lymph nodes (MLN) upregulate the expression of integrin $\alpha_4\beta_7$ that binds

to MAdCAM-1 and CCR9 that respond to CCL25 (thymus-expressed chemokine, TEK), a chemokine highly expressed in the epithelium from the small intestine and also present on the postcapillary venules of the lamina propria [40,41]. The interaction between naïve T-cells with Peyer's patches or MLN-DCs is critical for the acquisition of these homing receptors. Several studies in knockout mice or using anti-$\alpha_4\beta_7$ neutralizing antibodies or its receptor MAdCAM-1 have confirmed the role of this receptor pair in regulating the entry of effector T-cells to the intestinal mucosa. However, $CD8^+$ effector T-cells lacking the β_7 integrin chain do enter the epithelium of mouse small intestine and provide viral immunity, suggesting that the expression of $\alpha_4\beta_7$ is not an absolute requirement for T-cell entry to the intestinal mucosa, at least under some inflammatory settings [42,43].

Gut homing receptor CCR9 is expressed in almost all T-cells migrating to the small intestine, including intraepithelial lymphocyte expressing the γδ T-cell receptor [44,45]. This is not the case for T-cells present in the stomach or the colon. Recent reports suggest that signaling through CCR9 might be necessary for T-cell homing to the small intestine but not to the large intestine, since CCL25, the ligand for CCR9 is exclusively expressed in almost all cells of the small intestine (endothelial cells and lamina propria cells), but not in the epithelium from the colon [44,46]. Thus, restricted chemokine expression in the gut represents an important mechanism for the regionalization of the immune response operating in the small intestine versus those in the colon. Interestingly, plasma cells secreting IgA from Peyer's patches and MLN express CCR9 and migrate towards CCL25 *in vitro*, and down regulate this receptor once located in the small intestine [41,47,48]. CCR9-deficient mice show a reduced number of IgA-producing plasma cells within the lamina propria. On the other hand, IgG or IgM-secreting plasma cells do not respond to CCL25. This indicates that expression of chemokine receptors on Ig-secreting plasma cells may be correlated with the Ig isotype they will produce [49,50]. Besides the effect of CCR9 and its ligand CCL25, other chemokine/chemokine-receptor pairs have been also implicated in maintaining T-cell homing to the small intestine mucosa. Thus, there is indirect evidence supporting the participation of CCR6, and CCR10 (and their ligands CCL20 and CCL28, respectively), in the steady-state maintenance of lymphocyte traffic to this organ [50].

Cytokines such as TGF-β and IFN-γ have been also implicated in regulating T-cell homing to the small intestine, mainly through regulation of the expression of homing receptors. However, many of these *in vitro* observations have not been fully reproduced *in vivo* [51].

Chemokines and cytokines are not the only molecules regulating T-cell homing to the small intestine. In a recent report Iwata and coworkers presented compelling evidence for the role of retinoic acid (RA) in directing this process [52]. The authors showed that this molecule – a metabolite of vitamin A – induced a high expression of $\alpha_4\beta_7$ on T-cells, independent of the presence of DCs. In agreement with this observation, vitamin A-deficient animals presented lower amounts of $\alpha_4\beta_7{}^+$ T-cells and a reduced number of T-cells in the small intestine compared to wild type animals. The authors further demonstrated that DCs from Peyer's patches and MLN, but not from PLN or the spleen expressed the enzymes that participate in the synthesis of RA and that inhibitors of these enzymes abrogated the DC-induced increase in $\alpha_4\beta_7$ on T-cells [52].

Results from our laboratory suggest that IL-4 is also involved in instructing naïve T-cells to express the gut-associated homing receptor CCR9 (M. Rosemblatt and R Elgueta, unpublished observations). Thus, effector T-cells generated after co-culture with MLN-DC show a higher expression of CCR9 when exposed to the presence of IL-4. On the other hand, IL-4 had no effect on CCR9 expression when naïve T-cells were polyclonally activated in the absence of MLN-DCs, suggesting that the effect of IL-4 on CCR9 expression passed through the DC. This was confirmed by information indicating that effector T-cells generated by MLN-DC from *Il-4ra*$^{-/-}$ mice showed much lower CCR9 expression and a greatly reduced migration to the small intestine compared to T-cells activated by wild type MLN-DCs. Following the observations that RA affects gut-homing molecules on T-cells [52], we further demonstrated that IL-4 induces an increased expression of RALDH2 mRNA, one of the critical enzyme involved in the synthesis of RA and that citral (a RALDH inhibitor) partially blocked the increased expression of CCR9 induced by IL-4-treated MLN-DC. These results provides additional points of control for the expression of gut-homing receptors and T-cell migration to the small intestine and links the direct reported effect of retinoic acid on T cell gut tropism with IL-4, a cytokine present in gut tissue.

On the other hand, migration of T-cells to the colon is partially regulated by mechanisms different from those reported for the small intestine [53]. Although integrin $\alpha_4\beta_7$ has been implicated in T lymphocyte migration to the colon, $\alpha_4\beta_1$ has also been described to participate in this phenomenon [54]. Furthermore, the CCL25/CCR9 pair has apparently no participation in T-cell tropism to the large intestine. Recent data showed that CCL25 (TECK) is not expressed in the large intestine and that this organ is deficient in $CCR9^+$ T lymphocytes, although this may not be so conclusive in humans [44,46]. Experiments designed to block CCL25 activity or desensitization of CCR9 led to the inhibition of T-cell adhesion to the small intestine, with no effect on T cell adhesion to the colon, indicating the participation of other chemokines in migration of T-cells to the large intestine [55].

4. Homing to cutaneous tissue

The skin, together with the gut and the respiratory mucosa, represents the largest epithelium in contact with the external environment and is therefore considered one of the

main doors for pathogen entry. Skin-homing effector T lymphocytes express ligands for P and E-selectin as well as chemokine receptor CCR4 and/or CCR10 [38,56–58]. A homing receptor highly expressed on skin-homing T-cells is the cutaneous lymphocyte antigen (CLA), a glycoprotein containing a modified form of carbohydrate that can interact with both P and E-selectins, the latter highly expressed on endothelial cells of inflamed skin (although it is also found constitutively in the skin, albeit at much lower levels), the female genital tract and oral mucosa [59]. Regulation of the expression of CLA is poorly understood, but the expression of α1,3-fucosyltransferase-VII (FucT-VII) in T-cells is crucial for the generation of E-selectin ligands [60,61]. Expression of FucT-VII seems to be regulated by several cytokines, including TGF-β, IL-12, and by chemokine CXCL8 (IL-8) [62–65]. Additionally, skin-homing T-cells do not express the gut-homing integrin $\alpha_4\beta_7$ and instead express high levels of $\alpha_4\beta_1$, a VCAM-1-binding molecule. Also, RA blocks the expression of P and E-selectin ligands on these cells [53]. VCAM-1, which is not expressed in uninflamed endothelium, is induced by pro-inflammatory cytokines such as IL-1, TNF-α and by the chemokine CXCL8 [14].

Recent data demonstrate that chemokines (and their receptors) also participate in directing effector and memory $CD8^+$ T-cells to the skin. Accordingly, CCL17 (TARK) a known ligand for CCR4 is expressed by uninflamed skin endothelial cells under normal homeostatic conditions while CCL27 (CTAKC) a CCR10 ligand is secreted by skin keratinocytes [40,66]. In a delayed-type hypersensitivity (DTH) model situation CCR4 and CCR10 have shown overlapping and redundant activities since inhibition of lymphocyte skin homing requires blocking of both receptors [58]. However, although chemokine receptors CCR4 and CCR10 are highly expressed on CLA^+ T-cells and absent in gut-homing lymphocytes, these cells migrate poorly into non-inflamed skin, indicating that homeostatic expression of these ligands is not sufficient to induce migration [67]. However, the extent of T cell homing to the skin may vary depending on the type of antigen that causes inflammation, and both CCR4 or CCR10 appear as necessary for T-cell entry at sited of DTH [58,68]. It should be noted that E- and P-selectins are expressed on endothelial cells lining the vasculature of several tissues beside the skin; therefore expression of these molecules alone cannot be considered as strict indicators of skin homing. Similarly, CCR4 cannot be regarded as an exclusive skin-homing receptor, since its expression has also been detected on lymphocytes in the lungs and other tissues [69–71].

More recently it was reported that when in the presence of both – gut homing and skin homing signals – (provided by the respective DCs), activated T-cells acquire a gut-homing phenotype, denoting that chemokines and/or cytokines providing gut-homing signals take precedence over skin-homing signals and indicating that when present, gut-homing instructions can suppress the induction of skin tropism [61]. This report suggested that the up-regulated expression of selectin ligands, i.e. skin tropism, may represent a ''default'' pathway, and that this predetermined response may be overturned to a gut homing phenotype by gut-homing signals [61]. In this regard, it is interesting to remark a report showing that IL-4, a cytokine that contributes to the homing of $CD4^+$ T-cells to the gut, down regulates expression of the (opposing) skin homing CLA ligand [72]. The authors also showed that another cytokine, IL-12 had an antagonistic effect, inducing the up-regulation of CLA, but that the presence of IL-4 exerted a (negative) overriding effect on CLA expression, frequently resulting in the complete loss of expression of this skin-homing receptor [72].

Interestingly, skin-attracting chemokines CCL17 and CCL27 are molecules closely related to the recently identified chemokine CCL28 (MEC) [73,74]. The known ligand for this chemokine is CCR10 the same ligand identified for CCL27. In spite of these similarities, CCL28 does not appear to directly operate as skin-homing chemokine, but it appears to function as an attractant of antibody-secreting cells to mucosal tissues [59] (see below).

5. Homing to other tertiary tissues

In contrast to the available knowledge defining the acquisition of gut- versus skin-specific tropism, very little is known on the mechanisms regulating lymphocyte homing to other non-inflamed tissues. Information on the origin of T-cells migrating to other tertiary tissues and the site where they may acquire their own codes of entry is controversial. A recent report showed that entry of effector T-cells to non-inflamed lung depends on the expression on lymphocytes of the β_2 integrin LFA-1 and the presence of CCL5 in this organ [75], while another article showed that $CCR9^+$ $\alpha_4\beta_7{}^+$ effector $CD8^+$ T-cells generated in gut-draining lymph nodes migrated to the lung and liver, suggesting that effector T-cells do not need to be activated in draining lymph nodes to enter the lung [34]. These same gut-derived T-cells were found in other extra-gut tissue such as liver, brain and kidneys [76]. These results are consistent with data showing that in primary sclerosis cholangitis, lamina propria $\alpha_4\beta_7$ lymphocytes bind to liver endothelium through vascular adhesion protein 1 (VAP-1) and an ectopic expression of MAdCAM-1 [77]. Functional recruitment and transmigration of lymphocytes require the activation of integrins through chemokine signaling. In studies of liver-infiltrating lymphocytes in primary sclerosis cholangitis it was established that T-cells were recruited to the liver due to the abnormal expression of CCL25, a chemokine that is normally expressed in the gut. The authors argued that CCL25 induced the activation of integrin $\alpha_4\beta_7$ and recruitment of $CCR9^+$ $\alpha_4\beta_7{}^+$ T-cells to the inflamed liver [77].

In another study the migratory properties of $CD8^+$ T-cells responding to antigens originated from different tumors have been assessed [78]. Implantation of a model tumor in mice showed that in s.c. established tumors activation occurred in a single local draining lymph node; that i.p. implantation recruited many lymph nodes and the spleen while intracranial implantation engaged a limited array of superficial and deep cervical lymph nodes [78]. The latter results support the idea that activation of $CD8^+$ T-cells to tumor-specific antigens occurs at local secondary lymphoid organs even in immunological privileged sites. Furthermore, depending on the site of tumor implantation, $CD8^+$ T-cells expressed individual but overlapping homing molecules indicating that even within a single secondary lymphoid organ several homing ligands could be induced, presumably depending on the origin of the antigen-presenting cells. T-cells found in intracerebral implanted tumors expressed high levels of the homing integrin $\alpha_4\beta_1$, low levels of $\alpha_4\beta_7$ and the up-regulation of E- and P-selectin ligands [78]. Overall these data suggest that imprinting of a homing phenotype on T-cells may be determined by cross-presenting DCs that transport antigens they have captured in the periphery to the local lymph nodes. Although at present the factors regulating this type of phenomenon are unknown, experimental evidence indicates the existence of homing phenotypes clearly different from those described for gut and skin homing T-cells.

As mentioned above, CCL28 is a chemokine recently described as closely related to skin tropic chemokines. This chemokine is heavily expressed in bronchial epithelia, colon, salivary gland and mammary glands but absent from the skin [59]. CCL28 has also been described as a chemoattractant for IgA-secreting plasma cells to mucosal tissues including exocrine glands, trachea and colon. Interestingly, this chemokine that binds to CCR10 and CCR3, appears to have a dual role, acting as a broad-spectrum antimicrobial peptide and a plasma cell chemoattractant [79].

6. Migration of regulatory T-cells

Recently, a new set of immunoregulatory T lymphocytes has been described capable of suppressing T-cell activation and maintaining immune tolerance [80–83]. These $CD4^+$/$CD25^+$ regulatory T (Treg) cells play an essential role in the maintenance of immunological homeostasis through the suppression of effector T lymphocytes. These specialized T-cells have been described in several lymphoid tissues such as thymus, lymph nodes, spleen and peripheral blood as well as in other peripheral sites including tumors, transplanted organs, and other sites experiencing an active immune response [84–87]. Although several studies have demonstrated that Treg can act locally by downregulating already established immune responses, few studies have addressed the question regarding the mechanisms guiding Treg to the proper site. More recently, a model of DTH and FucT-VII-deficient mice whose T-cells cannot migrate into inflamed sites due to their lack of E and P-selectin ligands was used to study the role of Treg in the local suppression of an inflammatory response [88]. Treg cells deficient in ligands for E and P-selectins were unable to resolve the DTH inflammatory reaction, suggesting that appropiate localization of Treg to the site of the immune response is essential for the *in vivo* immunoregulatory activity of these cells. These authors reported that these Treg shared the same chemokine receptors with effector T-cells. This may preclude the use of anti-chemokines as therapeutic agents since the same treatment would prevent infiltration of advantageous Treg cells. Interestingly, blockade of CCR2 in a model of collagen-induced arthritis led to an aggravation of the histological symptoms of the disease [89], suggesting an interference with the localization of $CCR2^+$ Treg cells.

In an apparently conflicting report, co-transfer of $CD4^+$/$CD25^+$ Treg prevented effector T cell-induced colitis in SCID or $RAG^{-/-}$ mice models [90]. In the $RAG^{-/-}$ model, Treg from $\beta_7{}^{-/-}$ mice prevented the effector T cell-induced colitis in spite of the fact that the number of Treg present in the intestine of protected $RAG^{-/-}$ mice was substantially lower that those present in normal wild type mice. Thus, although initiation of intestinal inflammation was dependant on β_7 integrin expression on effector inflammatory T-cells, regulation by Treg was not. The same report showed that $\beta_7{}^{-/-}$ as well as $\beta_7{}^{+/+}$ accumulated and expanded in the spleen and lymph nodes. Although it is possible that a very low number of Treg in the intestine could contribute to prevent colitis, these results suggest that Treg need not to be present at the site of inflammation to suppress the immune response. These results are in apparent contradiction with the data discussed above and from another report showing that $CD4^+$/$CD25^+$ Treg can be used to treat an already established colitis and that this occurred due to the migration of Treg to the site of inflammation [91]. However, these reports are not necessarily in disagreement since they refer to different situations. While in one case [90] the experiments were designed to demonstrate the prevention of the onset of colitis by Treg—which probably occurs in the MLN, the other report demonstrated that Treg treatment could ''cure'' an already established colitis, which probably takes place in the lamina propria [91].

More recently, the presence of $CCR10^+$ Treg in inflamed human liver has been reported. These cells accumulated around the bile ducts that expressed important levels of CCL28, strongly suggesting that Treg do migrate to tertiary tissues [92].

7. Future directions

In spite of the significant recent advances in our understanding of the role of chemokine and cytokines in the regulation of lymphocyte traffic, many questions remain

to be addressed. Finding answers to some key outstanding issues will help in defining some new immunotherapeutic strategies in clinical situations. Most of the present knowledge in this area comes from studies done on T-cells in experimental mouse models on that need to be corroborated in humans, especially if one considers that some of the subsets of lymphocytes and their receptors may vary within species. Additionally, more work is needed in defining the tropic preferences of B lymphocytes and their precursors. Also, new research is needed to define the strategies used by lymphocytes for their migration to tissues different from skin and the small intestine and how chemokines and cytokines regulate tropism to other organs. In this regard, a number of questions remain to be addressed: are new molecules involved in defining the tropism to other tissues or do different combinations of the same receptors operate to direct the traffic of immune cells to these tissues? What are the mechanisms that operate in defining the migratory behavior of effector and regulatory T lymphocytes to tumors? In the future, finding answers to these and other questions may help to target lymphocytes for intervention with the purpose of fine-tuning immune responses for therapeutic use in situations such as tumors, autoimmune diseases or immunosuppressive drug treatment.

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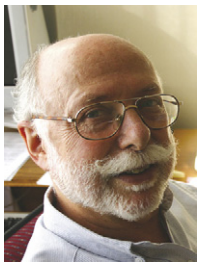

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