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INTEGRIN FUNCTION IN T CELL HOMING TO LYMPHOID AND NON-LYMPHOID SITES: GETTING THERE AND STAYING THERE

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Abstract

The continuous recirculation of naïve T cells and their subsequent migration to tissue following activation is crucial for maintaining protective immunity against invading pathogens. The preferential targeting of effector and memory T cells to tissue is instructed during priming and mediated by cell surface expressed adhesion receptors such as integrins. Integrins are involved in nearly all aspects of T cell life, including naïve T cell circulation, activation, and finally effector T cell trafficking and localization. Recent research has revealed that microenvironmental factors present during T cell priming result in the specific regulation of adhesion/integrin and chemokine receptor expression. Once antigen-experienced T cells enter tissue, further changes in integrin expression may occur that is critical for T cell localization, retention, effector function, and survival. This review will discuss the function of integrin expression on T cells and the multiple roles integrins play on naïve T cells and in directing effector T cell trafficking to non-lymphoid sites in order to maintain protective adaptive immunity at body barriers.

Keywords

integrin; adhesion; trafficking; retention; lymphocyte

INTRODUCTION

In contrast to the relatively static adherent cells composing the major organ systems in the body, many cells of the immune system are in a dynamic state that involves movement and directed recruitment throughout the body. This diverse set of highly specialized cells patrols the host, defending it against foreign invasion. T cells are critical not only in combating initial encounters with pathogens, but also in establishing immunological memory. In the naïve state, T cells preferentially recirculate through the secondary lymphoid organs (SLOs) of the body.¹ It is there that naïve T cells encounter cognate peptides embedded in the grooves of self-major histocompatibility proteins presented by dendritic cells (DC) and, under the appropriate conditions, differentiate into effector T cells. Both the environment and strength of this initial encounter determine the subsequent functionality of the effector population. In contrast to naïve T cells, activated effector T cells can move into peripheral non-lymphoid sites, where they enact their protection function. This non-lymphoid entry is made possible by regulated expression of adhesion molecules (integrins and selectins) and chemokine receptors, as well as site-specific endovascular expression of their ligands. Once in tissue, integrin adhesion receptors play additional, less well defined, but likely equally important roles in retention,

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localization, effector function, and survival. There is also a second level of regulation of integrin expression that is based on the tissue microenvironment. These roles have been more challenging to explore experimentally but are of great relevance to our understanding of T cell function and maintenance. This review will focus on the regulation of integrin expression and the role of integrins in targeting and retaining T cells in non-lymphoid sites.

I. INTEGRINS

Integrins are widely expressed cell surface adhesion molecules that mediate cell-extracellular matrix (ECM) and cell-cell interactions.² Integrins are composed of heterodimeric membrane spanning α and β chains.³ In the unstimulated state, T cells have little apparent adhesion to integrin ligands. However, upon activation through the T cell receptor (TCR) or chemokine receptors, a cascade of signaling events leads to enhanced integrin functionality.^{4;5} This response is referred to as “inside-out” signaling. It involves the translocation of proteins to integrin cytoplasmic domains and the assembly of multiprotein complexes. The formation of these complexes results in activation and clustering of integrins, thus enhancing both affinity and avidity of integrins for their ligands. These cytoplasmic complexes link integrins to the actin cytoskeleton, as well as intracellular signaling pathways. In this way, the well recognized adhesive function of integrins is linked to the less well understood ability of integrins to transduce signaling into the cell (“outside-in signaling”).

A. Integrin expression on naïve T cells—Naïve T cells express a fairly homogeneous array of cell surface molecules that promotes recirculation through the SLOs of the body, including the spleen, peripheral lymph nodes (pLN), mesenteric lymph node (mLN) and peyer’s patches (PP) of the small intestine. Naïve T cells express low levels of the $\alpha\text{L}\beta 2$ (LFA-1), $\alpha 4\beta 1$ (VLA-4) and $\alpha 4\beta 7$ (LPAM) integrins, which bind ICAM-1, VCAM-1, and MAdCAM-1, respectively (Fig. 1).⁶ The interaction of $\alpha\text{L}\beta 2$ with ICAM-1 is important for T cell entry into pLN and T cell interactions with antigen-presenting cells (APCs). The $\alpha 4\beta 1$ ligand VCAM-1 is expressed at low levels throughout the vasculature, but becomes upregulated on a wide array of tissue during inflammation.⁷ $\alpha 4\beta 7$ is also reported to bind with low affinity to VCAM-1 in vitro and under some circumstances may play a role in pLN entry.^{8–10} MAdCAM-1, the major ligand for $\alpha 4\beta 7$ is preferentially expressed at steady state in the mLN and PP, where it promotes entry of naïve T cells into these sites through a high affinity interaction.^{11–13}

II. LAYING THE FOUNDATION FOR CELLULAR HOMING

It has been 45 years since Gowans and Knight first demonstrated that small lymphocytes from the blood enter into SLOs and are returned to the circulation via efferent lymphatic vessels.¹⁴ They proposed that the homing of lymphocytes to lymphoid tissue was via the “special affinity” of small lymphocytes for the endothelium of the post-capillary venules. Over the ensuing years the major molecular players mediating this “special affinity” were identified as lymphocyte expressed integrins, selectins, and most recently chemokine receptors coordinated with endothelial expression of their ligands.^{1;6;13;15} Thus, the array of specific homing molecules expressed on T cells promotes re-circulation through the tissue whose vascular endothelium expresses the appropriate receptors.

A. Integrins and naïve T cell entry into lymph nodes—Naïve T cells preferentially recirculate through LNs in an integrin dependent manner. In LNs, specialized high endothelial venules (HEVs) provide the ‘landing strip’ for circulating naïve T cells. The HEVs promote both selective adhesion to and subsequent transmigration (entry) into LNs. This interaction has been extensively reviewed previously and is highly integrin dependent.^{13;16} The next section will discuss what is currently known about the role for integrins in this process.

The adhesion pathway promoting T cell movement out of the circulation into LNs has been divided into a series of at least four major steps: rolling, activation, firm adhesion, and transmigration. Integrins have been implicated in some aspect of each of these four steps. The interaction of naïve T cells with HEVs occurs under conditions of vascular shear flow and requires expression of selectins, chemokine receptors and integrins on the T cell.¹⁷ For naïve T cells, engagement of CD62L (L-selectin) with peripheral node addressin (PNAd) on HEVs results in weak tethering that promotes rolling of the T cell on the endothelial surface. This weak tethering greatly enhances the probability of encountering chemokine ligands present on the vascular lumen. The CCR7 chemokine receptor, which is expressed by all naïve T cells, interacts with CCL19 or CCL21 displayed by the HEV. Ligand binding to CCR7 results in G-protein coupled, pertussis toxin-sensitive signaling that mediates extremely rapid activation of integrins and firm adhesion to the vascular endothelium.¹⁸ CD62L-dependent signaling on T cells may also play a role in activating integrins.^{19;20} Firm integrin-mediated attachment of naïve T cells is critical to subsequent transmigration through the endothelium into the LN. In pLNs under homeostatic conditions, α L β 2 is particularly critical for firm adhesion to ICAM-1 expressed on the resting endothelium. In the PP of the small intestine, this interaction is also dependent on the activation of α 4 β 7 and firm adhesion to MAdCAM-1, which is preferentially expressed in this tissue.²¹ In addition to serving as an α 4 β 7 ligand, MAdCAM-1 also contains a mucin-like domain for binding CD62L.²² Therefore, if appropriately glycosylated, MAdCAM-1 can also participate in the initial rolling step via interaction with CD62L.

The interaction of MAdCAM-1 with α 4 β 7 may also play a role in the initial tethering response that initiates naïve T cell adhesion to HEVs under shear flow.²³ α 4 β 7 is also reported to be capable of mediating T cell tethering and rolling on VCAM-1.²⁴ However, the specific contribution of α 4 integrins to initiating T cell interactions with HEVs in vivo remains unclear. Integrins also exhibit “cross-talk” whereby one integrin is thought to regulate the function of other co-expressed integrin heterodimers. Ligation of α 4 β 1 has been reported to further enhance α L β 2-mediated adhesion to ICAM-1, while another report has documented negative regulation of α 4 β 1 following α L β 2 ligation.^{25;26} This work highlights the complexity of integrin function during interactions with cells expressing multiple integrin ligands.

After firm adhesion to the vascular endothelium, the process of de-adhesion or release of integrin-integrin ligand interaction is also vital. Without this de-adhesion event, cells are unable to migrate on and subsequently transmigrate through endothelium into LNs. A membrane-proximal GFFKR sequence in the cytoplasmic tail of integrin α subunits has been proposed to form a putative salt bridge that restrains integrins in an inactive conformation. Mice expressing α L integrin with a mutation in the GFFKR sequence express constitutively active α L β 2 integrin. Lymphocytes isolated from these mice exhibit enhanced adhesion to ICAM-1, but diminished transendothelial migration.²⁷ Similar findings have been reported in mice with a salt bridge disrupting mutation in the α 4 integrin subunit, resulting in active α 4 integrins.²⁸ Another mouse with a β 7 integrin ectodomain mutation expresses constitutively active α 4 β 7.²⁹ T cells from both of these mice have enhanced firm adhesion to the vasculature of the gut, but enter inefficiently into intestinal sites.

1. Transmigration: The final and less well understood step in the homing cascade is transmigration. Though traditionally thought of as the passage of the lymphocyte between endothelial cells (paracellular), it is becoming more apparent that lymphocytes can also migrate directly through endothelial cells (transcellular).^{30–32} Both β 1 and β 2 integrins are thought to be involved in these processes via interaction with endothelial junction integrin ligands such as JAM-B and JAM-A, respectively.¹⁷ Of interest, the endothelial cell also depends on ligation of integrin ligands to form a docking structure that further strengthens the interaction of α 4 β 1 and α L β 2 with VCAM-1 and ICAM-1.³³ Signaling mediated by ICAM-1 and VCAM-1 may

then act to stimulate the vascular endothelial cell, further facilitating leukocyte transmigration.³⁴

Another possible role for integrins in promoting transmigration was recently reported. Autotaxin (ATX), a phospholipid producing enzyme, was identified as a HEV-produced soluble integrin ligand that binds chemokine activated $\alpha 4$ integrins on human T cells.³⁵ ATX's phospholipid product, lysophosphatidic acid (LPA), promotes T cell migration in vitro and injection of an enzymatically inactive ATX decreases short term homing to LNs.

B. Integrins and recirculation: leukocyte adhesion deficiencies—Genetic models in the mouse and characterization of rare human immunodeficiencies have provided striking evidence that integrins and appropriate control of integrin function are essential for proper T cell recirculation. Naïve T cells isolated from knockout mice lacking either the αL or $\beta 2$ integrin subunits have dramatically reduced numbers of naïve T cells in the pLN and migrate inefficiently to these sites.^{10;36} An array of mutations in the human $\beta 2$ integrin gene that lead to reduced or absent $\beta 2$ integrin expression is the hallmark of leukocyte adhesion deficiency-I (LAD-I).^{37;38} LAD-I patients suffer from recurrent bacterial infections secondary to a decreased ability of leukocytes to enter into inflamed tissue. More recently, several patients have been described with clinical symptoms similar to LAD-I patients. Patients with this variant of LAD-I, now classified as LAD type III (LAD-III), also exhibit a bleeding disorder. Integrin expression is normal on leukocytes and platelets from these patients, but integrin activation is impaired.³⁹ Mutations in two distinct genes have been identified, the Rap1 guanine nucleotide exchange factor CalDAG-GEFI, and kindlin-3, an integrin-binding protein that cooperates with talin to promote integrin activation.^{40–42} This group of diseases provides a striking example of how integrins and the signaling pathways regulating their function are of vital importance for appropriate leukocyte localization and immune function.

III. INTEGRIN FUNCTION IN LYMPH NODES

A. T cell movement in lymph nodes—SLOs serve as the major meeting place for lymphocytes and their potential cognate antigen. With the advent of in vivo imaging techniques such as two-photon microscopy, much knowledge has been gained regarding the factors involved in T cell movement and APC interaction within the LN environment.^{43–45} Imaging of explanted LNs and intravital inguinal LN preparations has revealed that T cells migrate rapidly in the LN with an average velocity of 11 $\mu\text{m}/\text{min}$ and peaking around 30 $\mu\text{m}/\text{min}$.⁴⁶ In comparison, fibroblasts migrate at less than 1 $\mu\text{m}/\text{min}$.⁴⁷ Thus, naïve T cells are among the most motile cells in the body. During movement, T cells take on a polarized, oblong shape while moving in a stop-and-go manner. The random-walk behavior exhibited by T cells is due primarily to CCR7-dependent migration through the fibroblastic reticular cells (FRC), the LN stromal cells that are a critical component of a structural network in the T cell-rich areas of LNs.⁴⁸ These FRCs provide “guided randomness” that promotes high probability encounters with FRC-associated DCs, which can present lymph borne antigen.⁴⁹ FRCs also form a network in the spleen that guides the entry of T cells into the T cell zone of the splenic white pulp.⁵⁰

The LN is structurally composed of a 3-dimensional scaffolding mesh with a collagen I core surrounded by microfibrils of ECM molecules.⁴⁹ Interestingly, the contiguous network of FRCs nearly completely ensheaths these ECM structural components, effectively concealing them from direct contact with T cells.⁵¹ Thus, though several potential ECM integrin ligands are highly abundant in the LN, they are generally not thought to be accessible to T cells. Following exit from the blood, T cells are known to crawl along the FRCs and quickly localize to the paracortex or T cell zone of the LN.⁴⁸ This motility and precise localization are dependent on T cell CCR7 binding to CCL19 or CCL21.^{52;53} These are both secreted by FRCs and bound to surface glycosaminoglycans, being in highest concentration in the paracortex.⁴⁸

Although FRCs express both VCAM-1 and ICAM-1,^{54;55} integrins are not essential for naïve T cell motility in LNs. Woolf et al. demonstrated that in the absence of shear flow (as in the LN environment), immobilized CCL21 promoted pertussis toxin-sensitive random T cell migration at a velocity similar to that observed in vivo using two-photon imaging.⁵⁵ Interestingly, polarization of α L β 2 to the leading edge pseudopodia and α 4 integrins to the trailing edge uropod was observed during migration. In vivo imaging revealed that loss of α L β 2 expression on T cells or ICAM-1 on FRC only reduced migration by 15%. There was no additional inhibitory effect on motility with the addition of an α 4 integrin-specific blocking antibody. Thus, interactions of T cell integrins with ligands expressed on FRCs are thought to play a minor role for basal T cell motility in the LN.⁵⁵ Intriguingly, under conditions of shear flow (as might be present when T cells are interacting with HEVs), immobilized CCL21 promoted firm integrin-mediated adhesion. Firm adhesion of integrins thus seems to be dependent on an activation event (chemokine signal) coupled to environmental force (blood flow).⁵⁶

Repeated encounters of CD4 T cells with MHC class II positive cells in the LN environment has also been shown to be vital for maintaining T cell motility.⁵⁷ In the absence of low affinity self-ligand/MHC class II-TCR interaction, T cells demonstrate a 50% reduction in motility and loss of basal activity of the Rap1 GTPase. Although Rap1 is a known activator of integrins,⁵⁸ the role of integrins in the motility promoted by tonic low level signaling induced by TCR:self-ligand interactions is currently unclear.

During the early phases of a primary immune response, T cells are retained or sequestered in the activated LN.⁵⁹ The interaction of the phospholipid sphingosine-1-phosphate (S1P) with sphingosine-1-phosphate receptor 1 (S1P₁) is critical for T cell sequestration.⁶⁰ Although integrins mediate T cell contact with APCs (see below), combined inhibition of both α L β 2 integrin and α 4 β 1 integrin does not alter T cell retention in LNs following subcutaneous antigen deposition.⁶¹

B. Integrins and T-DC interactions in the lymph node—In order for naïve T cells to achieve competent activation, they must interact with DCs presenting cognate antigen recognized by the TCR. T cells interact transiently with DCs during the first 8 hours of the T cell immune response, but then convert to a behavior characterized by prolonged contact with DCs that can last up to several hours.^{62;63} These stable contacts are dependent on ICAM-1 expression in host environment and have functional consequences for the durability of the T cell immune response. In ICAM-1-deficient mice, TCR transgenic OT-I CD8 T cells only interact transiently (less than 10 min) with mature DCs presenting cognate antigen.⁶⁴ While the loss of prolonged T-DC interactions did not affect T cell proliferation and clonal expansion, it did inhibit the survival of activated CD8 T cells and the generation of effective memory. Thus, prolonged T-DC contacts mediated by ICAM-1 (and presumably α L β 2 on the T cell) are critical for naïve T cells to receive the appropriate educational signals to differentiate into effector and memory T cells.

1. Integrins and the immunological synapse: When a T cell interacts with a DC displaying cognate antigen, a series of spatial and temporal molecular reorganization events occurs between the T cell and DC. These organizational events form a microscopically distinct structure at the contact site termed the immunological synapse (IS). The IS is a “bullseye” type structure where the TCR and other TCR signaling kinases and adapters localize to the center of the bullseye (termed central supramolecular activation clusters or cSMAC), while integrins and the integrin-associated protein talin localize to an outer ring-like structure that surrounds the cSMAC (termed pSMAC for peripheral supramolecular activation clusters).^{65–67} In vitro, the formation of the IS occurs over a time frame of 20–30 minutes, well after biochemical signaling events initiated by TCR stimulation can be detected.⁶⁸ Subsequent studies

demonstrated that T cell activation is initiated and sustained in microclusters composed of the TCR and active signaling kinases that form at the periphery of what eventually becomes the mature IS. These microclusters travel from the periphery of the T-APC contact site to the cSMAC.^{68–70} Although the cSMAC has been proposed to be a site where TCR signaling is terminated,^{69;70} recent studies have shown that the strength of antigen stimulation determines whether signaling is sustained or terminated in the cSMAC.⁷¹ This suggests that the cSMAC fine-tunes the immune response, sustaining signals from weak antigenic stimuli while terminating signals from strong antigenic stimuli.

Although integrins can clearly transduce signals that augment TCR signaling and promote specific T cell differentiation events,^{72–74} the precise function of integrins in the IS above and beyond the facilitation of adhesion between the T cell and DC remains unclear. α L β 2 integrin ligation leads to the reorganization of actin into a ring-shaped structure called an “actin cloud”. Tyrosine phosphorylated proteins accumulated with α L β 2 integrin in this novel actin structure, and formation of the actin cloud enhances TCR signaling.⁷⁵ In addition to α L β 2, the α 4 β 1 integrin has also been reported to localize to the T-APC contact site during T cell activation, even under conditions where the APC does not express VCAM-1.⁷⁶ Recent studies have shown that T cell adhesion to the α 4 β 1 integrin ligand VCAM-1 retards the actin-dependent movement of signaling microclusters containing the adapter protein SLP-76 to the cSMAC.⁷⁷ This work is consistent with the fact that TCR signaling is initiated at the periphery of the contact site, where integrins are localized, and suggests that integrins may promote efficient T cell activation by dampening the termination of TCR signaling from microclusters that move to the cSMAC.

Although integrins such as α L β 2 do not appear to be essential for T cell motility in LNs, α L β 2 is differentially expressed on the surface of a migrating T cell.⁷⁸ At the leading edge, α L β 2 is in an intermediate affinity state, while α L β 2 in the mid-cell region is associated with talin and capable of mediating firm adhesion to ICAM-1. It has recently been proposed that migrating T cells can receive TCR signals through the formation of transient contacts with APCs designated as “kinapses”.⁷⁹ The actin-regulatory protein WASp mediates conversion from kinapses to stable synapses, while the PKC θ isoform mediates conversion from stable synapses to kinapses.⁸⁰ The relationship between kinapses and the differential localization of α L β 2 integrin of differing affinities on the surface of a migrating T cell is currently unclear. However, PKC θ has recently been shown to regulate TCR-mediated activation of LFA-1 via regulation of the Rap1 GTPase.⁸¹

C. Regulation of integrin expression following T cell activation—The discovery that T cells harvested from the intestine of sheep preferentially return to the intestine laid the foundation for a model of site-directed trafficking of T cells.⁸² Subsequently, naïve and effector/memory T cells were demonstrated to possess different trafficking patterns.⁸³ Following activation, T cells upregulate molecules important for homing to non-lymphoid sites, and decrease the LN homing molecules CD62L and CCR7. It was thus postulated that differential integrin expression on effector/memory T cells imparted altered homing properties from their naïve precursors. The fact that human memory T cells displayed higher and varied integrin expression than naïve T cells led to the proposal that during T cell priming the local environment may provide a molecular “imprint” endowing cells with a selective pattern of homing molecules.⁸⁴ Additional analysis revealed that the α 4 β 1 and α 4 β 7 integrins maintained reciprocal expression on circulating human CD4 memory T cells.^{11;85} T cells with high levels of α 4 β 7 but low levels of the β 1 integrin subunit migrated preferentially into mucosal tissues such as the PP and mLN, whereas T cells with high α 4 β 1 levels but low β 7 integrin subunit expression preferentially migrated through peripheral non-mucosal tissues such as the skin.^{86;87} The factors within local lymphoid environments that control the differential expression of integrins on activated T cells are beginning to be elucidated.

1. Gut homing and the $\alpha 4\beta 7$ integrin: The $\alpha 4\beta 7$ integrin ligand MAdCAM-1 is expressed by the HEVs of the mLN, PP, and the venules of the small and large intestine^{12;88} and promotes the entry of $\alpha 4\beta 7$ -expressing cells into intestinal sites.⁸⁹ Mice lacking $\beta 7$ integrin have decreased numbers of PP and intestinal T cells, and reduced migration to the gut.^{90;91} Inflammation results in enhanced expression of MAdCAM-1 on venules in the intestine, resulting in increased entry of $\alpha 4\beta 7$ -positive cells into the gut. Patients with inflammatory bowel disease have both enhanced expression of MAdCAM-1 and an increased number of infiltrating T cells.⁸⁸ Furthermore, blocking antibodies against $\alpha 4\beta 7$ attenuate some mouse models of intestinal inflammation and are clinically effective in the treatment of human ulcerative colitis.^{92;93} In addition to $\alpha 4\beta 7$, a role for $\alpha 4\beta 1$ and $\alpha L\beta 2$ in mediating T cell entry into the intestine during inflammation has also been reported.^{94–96}

The restricted expression of MAdCAM-1 in the gut suggests that it is critical to understand the factors that control the expression of $\alpha 4\beta 7$ during T cell activation responses. Adoptive transfer approaches using OT-II TCR transgenic T cells demonstrated that priming in differential SLOs resulted in differential upregulation of adhesion molecules.⁹⁷ In pLNs, T cells downregulated $\alpha 4\beta 7$ and expressed high levels of a P-selectin ligand following antigen challenge. In contrast, T cells activated in mLNs expressed high levels of $\alpha 4\beta 7$ and became responsive to CCL25, a chemokine expressed in the small intestine that promotes firm adhesion of $\alpha 4\beta 7$ to MAdCAM-1.⁹⁸ These results suggest that the mLN environment is conducive to the generation of $\alpha 4\beta 7$ + effector T cells.

Similar results were observed in in vitro experiments utilizing DCs isolated from different LNs. When compared to DCs isolated from pLNs, the addition of DCs isolated from mLNs to anti-CD3 stimulated T cell cultures resulted in a higher proportion of T cells expressing high levels of $\alpha 4\beta 7$ integrin.⁹⁹ Similar results were reported using DCs isolated from PPs.¹⁰⁰ In these studies, the expression of other integrins such as $\beta 1$ and αL was not altered. T cells activated in vitro by DCs isolated from PPs also had enhanced homing to intestinal lymphoid sites when compared to T cells isolated by pLN-derived DCs. T cells activated by PP DCs showed particularly enhanced trafficking to the non-lymphoid small intestine. In contrast, T cells activated by pLN DCs exhibited preferential trafficking to pLNs.

2. All-trans retinoic acid and the regulation of $\alpha 4\beta 7$: The soluble mediator inducing gut-homing molecules was subsequently identified as the vitamin A metabolite, all-trans retinoic acid (ATRA). Iwata et al. demonstrated that the addition of ATRA enhanced the expression of $\alpha 4\beta 7$ and the CCR9 chemokine receptor on CD4 T cells following activation with anti-CD3 and anti-CD28 antibodies.¹⁰¹ DCs isolated from mLN or PP express several isoforms of the ATRA-producing enzymes, retinal dehydrogenase (RALDH). Inhibition of these enzymes reduced the ability of intestinal DCs to induce $\alpha 4\beta 7$ expression in vitro. This further supports a role for these DCs in the production of ATRA and induction of $\alpha 4\beta 7$ integrin and other gut-homing molecules on T cells (Fig. 2A).

ATRA likely regulates T cell integrin expression at the transcriptional level, as a retinoic acid receptor (RAR) antagonist inhibited the ability of PP DCs to induce $\alpha 4\beta 7$ expression.¹⁰¹ RARs primarily form heterodimers with retinoid X receptors (RXR).¹⁰² ATRA binds RAR with high affinity and this complex translocates to the nucleus, where it binds to RA response elements (RARE). Although the $\beta 7$ integrin gene is reported to have a RARE half site,¹⁰¹ $\alpha 4$ integrin mRNA was the only integrin message consistently elevated following activation by PP DCs.¹⁰³ In contrast, transcripts for $\beta 7$, $\beta 1$, or αE integrin were not altered significantly. This suggests that ATRA-mediated changes in $\alpha 4\beta 7$ expression are likely to be controlled at the level of $\alpha 4$ integrin. The possibility of further post-transcriptional, translational, or protein level regulation is still an area of active investigation.

Several groups have had similar findings concerning the role of ATRA in inducing $\alpha 4\beta 7$ integrin expression.¹⁰⁴ DCs derived from the small intestine that express the αE (CD103) integrin subunit are believed to be a source of ATRA, as they enhance RAR signaling and induce both $\alpha 4\beta 7$ and CCR9 expression on responding CD4 and CD8 T cells.^{105–109} The conditioning of αE integrin positive DCs to produce ATRA is thought to be mediated by intestinal epithelial cells prior to DC migration to the mLN or PP.^{110;111} mLN stromal cells are also reported to participate in the imprinting of gut-homing T cells through further production of ATRA, as they express high levels of RALDH1/RALDH3.^{112;113}

3. Other factors regulating $\alpha 4\beta 7$ expression: The OX40-OX40L costimulatory pathway has also been implicated in regulating $\alpha 4\beta 7$ integrin expression following T cell activation (Fig. 2A).⁸⁹ An anti-OX40L antibody inhibited the ability of mLN-derived DCs to promote $\alpha 4\beta 7$ integrin expression on T cells both in vitro and in vivo.^{105;114} This suggests that OX40-OX40L signaling synergizes with ATRA to promote the upregulation of $\alpha 4\beta 7$ on activated T cells.

Antigen concentration has also been shown to vary the ability of cultured mLN DCs to induce $\alpha 4\beta 7$ expression on CD8 T cells (Fig. 2A).¹⁰⁹ In a reciprocal fashion, higher antigen doses resulted in less $\alpha 4\beta 7$ expression. The mechanism underlying antigen dose-dependent inhibition of $\alpha 4\beta 7$ expression is unknown, but it seems to be independent of RAR mediated signaling. This suggests the possibility that additional undefined soluble factors are capable of mediating the inhibition of $\alpha 4\beta 7$ expression at high antigen dose.

4. Opposing roles for vitamin A and vitamin D metabolites: In addition to causing the upregulation of gut-homing molecules, ATRA has been shown to suppress expression of molecules that promote T cell trafficking to the skin.¹⁰¹ More recently, the vitamin D metabolite, 1,25 dihydroxy-VitD3 (1,25VitD3) was shown to mediate a reciprocal expression pattern of homing molecules. When present during T cell activation, 1,25VitD3 induced the skin-homing chemokine receptor CCR10 on human T cells and suppressed expression of $\alpha 4\beta 7$ and CCR9 in the presence of ATRA (Fig. 2B).¹¹⁵ These findings point to opposing roles for ATRA and 1,25VitD3 in the regulation of gut versus skin-homing T cells. Expression of other skin homing molecules, such as P- and E- selectin ligands and CCR4, is upregulated in a 1,25VitD3 independent manner and their upregulation may involve other unidentified factors.¹¹⁶ There also seem to be some species differences in these effects, as 1,25VitD3 failed to inhibit the induction of $\alpha 4\beta 7$ integrin on mouse T cells by ATRA or mLN DCs.¹⁰⁹

The molecular mechanism whereby 1,25VitD3 suppresses $\alpha 4\beta 7$ expression may involve cytoplasmic receptor competition.^{115;117} Both the RAR and the vitamin D receptor bind to the RXR prior to translocation to the nucleus. Thus, when 1,25VitD3 is present along with ATRA, there may be competition for RXR that inhibits downstream activation of RAREs by ATRA-bound retinoic acid receptor.¹¹⁸

5. Integrins and T cell trafficking to bone marrow: The bone marrow vasculature, as well as stromal cells, express the $\alpha 4\beta 1$ integrin ligand VCAM-1.¹¹⁹ Intravital microscopy has revealed that $\alpha 4\beta 1$ mediates firm adhesion to the bone marrow.¹²⁰ Inhibition of $\alpha L\beta 2$ integrin function has little effect. However, in the absence of VCAM-1, firm adhesion was not completely abolished so other adhesion molecules are likely involved. Conditional VCAM-1 knockout mice have also demonstrated the importance of VCAM-1 expression for entry of T cells into the bone marrow.¹¹⁹ Thus, T cell entry into the bone marrow is thought to be highly dependent on the $\alpha 4\beta 1$ -VCAM-1 interaction. There is some evidence that $\alpha 4\beta 7$ integrin may also be involved in homing to the inflamed bone marrow following irradiation through interaction with induced MAdCAM-1.^{121;122} As bone marrow stromal cells express VCAM-1, there may be a role for $\alpha 4\beta 1$ integrin in enhancing both the retention of T cells and the delivery of survival cytokines (IL-7, IL-15) that are reported to be present in the bone marrow.^{123;124}

Recent studies have highlighted an important role for the bone marrow as a reservoir for memory CD8 T cells,¹²⁰ but the specific role of $\alpha 4 \beta 1$ integrin in maintenance/retention of memory T cells in the bone marrow remains undefined.

6. Integrins and T cell trafficking to the brain: Both VCAM-1 and ICAM-1 are expressed on the vasculature of the inflamed brain. In particular, VCAM-1 is known to promote T cell entry through its interaction with $\alpha 4 \beta 1$ expressed on activated T cells.¹²⁵ In accordance with these findings, the ability of brain autoreactive T cells to cause disease has been correlated with their expression of $\alpha 4$ integrin.¹²⁶ Anti- $\alpha 4$ integrin antibodies have also been successful in the treatment of human multiple sclerosis (MS) in humans^{127–129} and inhibiting or reversing a CD4 T cell-mediated brain disease, experimental autoimmune encephalomyelitis (EAE), in mice.^{130–132}

The site of priming of encephalogenic T cells is thought to be deep cervical LNs (cLN).¹³³ As the brain has no anatomical lymphatic drainage, the mechanism by which antigen is delivered to the cLN is unknown. Migration of DCs, parenchymal APCs, or the direct drainage of antigen have all been hypothesized.¹³⁴ Priming of CD8 T cells in the cLNs following intracranial tumor implantation results in high expression of $\alpha 4 \beta 1$ and low expression of $\alpha 4 \beta 7$ (Fig. 2C).¹³⁵ These cells also migrated better to the brain than cells primed in the inguinal LN. The specific factors involved in the ‘imprinting’ of brain-tropic $\alpha 4 \beta 1$ -high $\alpha 4 \beta 7$ -low T cells are unknown. These results are consistent with APC programming at the site of antigen capture and subsequent migration to the draining LN, where naïve T cells are activated and educated with specific homing preference. It is not known if CD4 T cells primed in a similar manner also develop similar integrin expression and brain tropism, as would be predicted based on EAE studies.

D. INFLAMMATION, INTEGRINS AND T CELL TRAFFICKING—Pathogen infection is often accompanied by an inflammatory response. Inflammation promotes the influx of both naïve and memory T cells into reactive LN.¹³⁶ Global hyperthermia (fever) is a programmed physiological response driven by endogenous or exogenous pathogen-associated pyrogens during an infection. The acute phase reactant IL-6, which is produced during inflammation, can mediate this fever response and has been more recently shown to increase the expression of ICAM-1 on reactive LN HEVs, thereby promoting the influx of naïve and memory T cells.¹³⁷ CCL21 expression was also increased, further promoting enhanced firm adhesion mediated by LFA-1 to ICAM-1.

It has been proposed that the presence of inflammation may additionally promote T cell homing promiscuity to non-lymphoid sites.^{89;138} This idea is supported by the known alterations of vascular endothelial expression of integrin ligands that occurs during acute/chronic inflammation or disease. LPS or TNF α treatment results in a global increase in VCAM-1 and ICAM-1 expression on vascular endothelial cells.⁷ VCAM-1 upregulation was particularly pronounced in the small intestine. This is consistent with other work demonstrating that inhibition of VCAM-1 function in some models of colitis is more effective than inhibition of MAdCAM-1 function.¹³⁹ MAdCAM-1 expression in the gut is also enhanced following TNF α treatment.¹⁴⁰ In chronic disease states such as inflammatory bowel disease and diabetes, MAdCAM-1 is additionally upregulated on the inflamed venules of non-intestinal sites, such as the liver, joints, eyes, skin, and pancreas.^{141;142} It has therefore been proposed that the “aberrant” homing of mucosal T cells expressing high levels of $\alpha 4 \beta 7$ to the liver may underlie the hepatic complications observed in inflammatory bowel disease.¹⁴¹ Thus, during inflammation the site specific expression of endovascular integrin ligands may be altered, potentially allowing the entry of T cells expressing a less specific set of integrin molecules.

E. INTEGRIN FUNCTION IN NON-LYMPHOID TISSUE—Effector and memory T cells that access non-lymphoid tissue encounter a microenvironment that is quite distinct from that found in SLOs. While SLOs are densely packed with cells, the intercellular spaces in non-lymphoid tissue contain collagen fibrils and other ECM proteins.¹⁴³ Thus, T cells in non-lymphoid tissue are much more likely to encounter and interact with ECM molecules. This suggests a more prominent role for ECM-binding integrins in controlling T cell function in non-lymphoid tissue.

1. Integrins and T cell movement in non-lymphoid tissue: Very little is known about the movement of T cells in non-lymphoid sites. Collagen matrices have been utilized in vitro to demonstrate that T cells exhibit a high rate of motility and form short-lived interactions with DCs.¹⁴⁴ This pattern of motility is strikingly similar to the behavior of naïve T cells in LNs, as observed with two-photon imaging^{46;62}. This suggests that T cells in non-lymphoid tissue may also exhibit high rates of basal motility. In addition, the presence of collagen may promote migratory behavior, as exposure of lymphoid cells to collagen in vitro stimulates cell migration.¹⁴⁵ In vitro studies have provided conflicting results on the role of integrins in T cell motility through collagen matrices.^{146;147} In one study, antibodies specific for $\beta 1$, $\beta 2$, $\beta 3$ and αV integrins did not alter T cell movement in collagen gels.¹⁴⁸

Genetic ablation of all integrins expressed on wild-type mouse DCs has recently been shown to have no effect on DC migration in a three-dimensional matrix in vitro and in the ear dermis in vivo.¹⁴⁹ The dispensability of integrins for DC movement was explained by a “flowing and squeezing” model, where the protrusive flow of the actin cytoskeleton drives the cell forward and a myosin-II contractile module propels the trailing nucleus through confined ECM spaces. These findings support the view of integrins as immobilizers rather than locomotive molecules on leukocytes. This predicts a role for integrins in tissue retention instead of migration. The phenotype or function of T cells from these global integrin-deficient mice was not reported.

In a murine CD4 T cell line, septins have recently been revealed to provide cortical rigidity and the absence of septin 7 results in defective motility.¹⁵⁰ Septins are hypothesized to promote a stable platform from which actomyosin filaments can apply force, resulting in forward protrusion of the leading edge. The role of integrins in this process remains unclear, although motility speed on ICAM-1 coated coverslips under shear flow was found to be septin-dependent.

2. Regulation of integrin expression and function by the non-lymphoid tissue

microenvironment: Tissue resident effector/memory T cell exhibit distinct functions, such as the ability to rapidly produce cytokine, that are not seen in their lymphoid resident counterparts. The expression of specific integrins is also known to be altered following entrance into non-lymphoid sites. These phenotypic changes following T cell entry are dependent on factors in the non-lymphoid tissue microenvironment.¹⁵¹ The first place these phenotypic changes can be imparted upon T cells is during the transmigration process through the endothelium. $\alpha L\beta 2$ integrin-dependent interactions between CD4 T cells and endothelial cells in vitro result in activation of the transcription factor AP-1 without sustained NF- κB activation.¹⁵² Transmigrated T cells also upregulate αL and $\alpha 4$ integrin, are more migratory and are hyperresponsive to antigenic stimulation. Several other reports have also demonstrated enhanced T cell sensitivity to antigen following transmigration through endothelium.^{153;154}

Once in non-lymphoid sites, the microenvironmental milieu may further alter the function and phenotype of the tissue resident T cell. Following LCMV infection, splenic and intraepithelial lymphocyte (IEL) memory CD8 T cells demonstrate different function and phenotype. For example, the IELs express dramatically higher granzyme B, a marker of cytolytic function, and higher $\alpha E\beta 7$ integrin expression. However, in vivo restimulation of $\alpha E\beta 7$ high IELs

following adoptive transfer into secondary recipient mice resulted in tissue-specific development of function and phenotype. Restimulated T cells harvested from the spleen were $\alpha\text{E}\beta 7$ integrin low, while restimulated T cells harvested from the intestine were $\alpha\text{E}\beta 7$ integrin high.¹⁵⁵ Reversible alterations in memory T cell expression of $\alpha 4$ integrin in the peritoneum and αL integrin in the lung have also been described.^{156;157} This suggests that T cell function and integrin expression is dependent upon tonic/continuous environmental factors present in the particular tissue.

Integrins likely also transduce signals to T cells upon engagement with ligands in the microenvironment. In non-lymphoid tissue, T cell interactions with ECM proteins such as fibronectin, laminin and collagen may provide signals that facilitate T cell activation responses. This hypothesis is supported by many studies demonstrating that $\beta 1$ integrin-mediated interactions of T cells with ECM proteins can enhance TCR signaling.¹⁵⁸

3. Integrin-mediated retention of T cells in non-lymphoid tissue: The gastrointestinal tract, skin, and lungs are in constant interaction with the environment. Therefore, the maintenance of T cells in a non-lymphoid site is of great importance for sustaining protective immunity as body barriers. The epithelium of these tissues provides the first layer of defense against pathogen invasion. Situated within and underneath the epithelial layers of these organs reside immune cells poised to recognize and destroy foreign organisms. To maintain such surveillance functions, cells need to be retained and positioned properly within each of these sites. Integrins implicated in retaining T cells in non-lymphoid tissue include the $\alpha\text{E}\beta 7$ integrin, which binds to E-cadherin, and the collagen-binding integrins $\alpha 1\beta 1$ (VLA-1) and $\alpha 2\beta 1$ (VLA-2).

$\alpha\text{E}\beta 7$ integrin was originally identified to be expressed by the vast majority of IELs and nearly 50% of T cells in the lamina propria of the small intestine.^{159–161} Notably, $\alpha\text{E}\beta 7$ integrin is also expressed on subsets of both murine and human CD4 regulatory T cells.^{162;163} Unlike the other member of the $\beta 7$ integrin subfamily, $\alpha 4\beta 7$, $\alpha\text{E}\beta 7$ integrin is not thought to be involved in the homing of T cells to the intestine and it does not interact with MAdCAM-1.^{164;165} E-cadherin is the only known ligand for $\alpha\text{E}\beta 7$ integrin and it is expressed on the lateral and basolateral surfaces of epithelial cells.¹⁶⁶ Naïve murine CD8 T cells also express $\alpha\text{E}\beta 7$ integrin but this expression is quickly lost after activation.¹⁵⁵ Interestingly, high level expression of $\alpha\text{E}\beta 7$ integrin is subsequently induced upon entry into the small intestine in a TGF- β dependent fashion.^{167;168} The entry of $\alpha 4\beta 7$ -high T cells into the TGF- β rich environment of the intestine is reported to result in a switch from $\alpha 4\beta 7$ expression to $\alpha\text{E}\beta 7$ expression (Fig. 3A). The exact mechanism for this switch is currently unknown, but Smad7 transgenic mice, which have impaired TGF- β signaling, are unable to induce $\alpha\text{E}\beta 7$ expression.¹⁶⁹ These mice have reduced IELs similar to the αE integrin-deficient mice.¹⁷⁰ Signaling from the CCR9 chemokine receptor upon engagement with CCL25 may be critical to enhancing $\alpha\text{E}\beta 7$ expression and promoting adhesion to E-cadherin as well.^{171;172}

The mechanism by which IELs are maintained in the intestine is still unclear. Almost all IELs express $\alpha\text{E}\beta 7$ and αE integrin knockout mice have a reduced number of IELs.¹⁷⁰ However, the severity of this phenotype does have some mouse strain dependence. IELs also express the $\alpha 1\beta 1$ and $\alpha 4\beta 1$ integrins, which have been proposed to mediate IEL binding to type IV collagen¹⁷³ and intestinal mesenchymal cells,¹⁷⁴ respectively. Although there is a 50% reduction in IELs in $\alpha 1$ integrin knockout mice,¹⁷⁵ no reduction in IEL numbers was reported in $\beta 1$ integrin-deficient bone marrow chimeric mice.¹⁷⁶ The reason for this discrepancy may be due to mouse strain differences and/or compensation by other integrins or adhesion molecules.

The brain microenvironment has also been demonstrated to induce $\alpha\text{E}\beta 7$ expression on tumor-reactive CD8 T cells, potentially enhancing their retention in the brain (Fig. 3B).¹⁷⁷ Expression

of $\alpha\text{E}\beta 7$ integrin on CD8 T cells may play a more general role in promoting CD8 T cell function. CD8 T cells expressing $\alpha\text{E}\beta 7$ integrin can kill E-cadherin positive cells and this killing is inhibited by an anti- αE integrin antibody.¹⁷⁸ In addition, $\alpha\text{E}\beta 7$ integrin expressed on cytotoxic CD8 T cells is recruited to the IS during interaction with E-cadherin positive tumor cells and is required for cytotoxic granule polarization and release.¹⁷⁹ TGF- β in the tumor microenvironment may play an important role in regulating $\alpha 4\beta 7$ expression on tumor-resident CD8 T cells.

The $\alpha 1\beta 1$ (VLA-1) and $\alpha 2\beta 1$ (VLA-2) integrins were initially discovered as antigens that were induced after long-term in vitro activation of human T cells.^{180–182} Both $\alpha 1\beta 1$ and $\alpha 2\beta 1$ mediate cell adhesion to collagen. $\alpha 1\beta 1$ mediates adhesion to type IV collagen, while $\alpha 2\beta 1$ mediates adhesion to type I collagen. As naïve T cells do not bind to collagen, even after acute stimulation signals that promote integrin-dependent adhesion to ICAM-1, VCAM-1 and fibronectin,¹⁸³ the regulated expression of $\alpha 1\beta 1$ and $\alpha 2\beta 1$ on effector/memory T cells may be critical to promoting effective T cell adhesion to collagen found in non-lymphoid tissue. Initial studies using integrin blocking antibodies and $\alpha 1$ integrin-deficient mice clearly highlighted a role for collagen-binding integrins in various inflammatory models, as well as in a mouse model of arthritis.¹⁸⁴ Subsequent studies in a variety of model systems have suggested multiple functions in non-lymphoid tissue for $\alpha 1\beta 1$ and $\alpha 2\beta 1$ expressed on activated T cells.

In the lung, $\alpha 1\beta 1$ integrin enables both retention and survival of influenza specific CD8 T cells.¹⁸⁵ Although $\alpha 1\beta 1$ integrin is not required for T cell entry into the lung, many more T cells in the lung are $\alpha 1\beta 1$ integrin-positive compared to activated T cells in the spleen. This suggests that $\alpha 1\beta 1$ integrin expression may be specifically induced on CD8 T cells after their entry into the lung. $\alpha 1\beta 1$ integrin-positive cells had reduced levels of apoptosis compared to the $\alpha 1\beta 1$ integrin-negative population in the lung. Other work has supported this role for $\alpha 1\beta 1$ integrin in promoting the survival of lung-resident CD8 T cells, potentially via signaling mechanisms that synergize with TNF Receptor II.¹⁸⁶ Antibody-mediated inhibition of $\alpha 1\beta 1$ integrin resulted in both a loss of cells from the lungs and reduced ability to protect against a secondary challenge.¹⁸⁵ Mice deficient in $\alpha 1$ integrin expression also exhibit enhanced susceptibility to secondary virus challenge. $\alpha 1\beta 1$ integrin-positive CD8 T cells isolated from the lung produce effector cytokines, such as IFN- γ and TNF α . CD4 T cells in the lung express higher levels of $\alpha 2\beta 1$ integrin than CD8 T cells, and this is associated with CD4 T cell localization to interstitial spaces in the lung that express type I collagen. In vitro analysis of these CD4 T cells suggest a role for $\alpha 2\beta 1$ in enhancing IFN- γ production.¹⁸⁷ Thus, these studies suggest that collagen-binding integrins promote T cell survival, retention, and effector function in the lung parenchyma, thus enhancing protective immunity.

$\alpha 1\beta 1$ has also been shown to retain pathogenic type 1 effector T cells in the epidermis in a xenograft model of psoriasis.¹⁸⁸ In this model, $\alpha 1$ integrin-specific blocking antibodies prevented the development of psoriasis by preventing the accumulation of these cells in the epidermis. These intraepidermal $\alpha 1\beta 1$ integrin-positive T cells were also shown to co-express $\alpha\text{E}\beta 7$ integrin. The lack of expression of $\alpha 1\beta 1$ on dermal T cells suggests that $\alpha 1\beta 1$ integrin may be upregulated during passage through the collagen IV rich dermo-epidermal basement membrane. Entry into the E-cadherin rich epidermis might also promote upregulation of $\alpha\text{E}\beta 7$, which would facilitate epidermal localization of CD8 T cells in the skin. In addition, the $\alpha\text{E}\beta 7$ integrin inducing molecule, TGF- β , is found in high concentration in areas underlying psoriatic lesions.¹⁸⁹

Overall, there is emerging evidence that the microenvironment in non-lymphoid tissue can both modulate integrin expression on T cells and provide adhesive ligands that promote T cell retention, survival and effector function. Integrins such as $\alpha\text{E}\beta 7$, $\alpha 1\beta 1$ and $\alpha 2\beta 1$ have been proposed to play unique roles in promoting T cell retention in non-lymphoid tissue. However,

it is known that the presence of antigen is important for the retention of effector/memory T cells in non-lymphoid sites.¹⁹⁰ In addition, MHC class II-positive DCs have recently been reported to migrate to non-lymphoid tissue and interact with memory CD4 T cells.¹⁹¹ Thus, TCR-mediated signals that activate integrins may allow multiple integrins expressed on effector T cells to promote retention in tissue via adhesion to APCs or ECM proteins.

4. Integrins and exit from non-lymphoid tissue: The factors that control the movement of T cells out of non-lymphoid tissue into afferent lymphatics remain incompletely characterized. Expression of the CCR7 chemokine receptor is critical for migration of both DCs^{192;193} and T cells^{194;195} out of non-lymphoid tissue and into draining LNs. Studies with integrin-null DCs indicate that integrins are not required for DCs trafficking out of non-lymphoid tissue.¹⁴⁹ However, recent work has revealed a role for S1P₁ in retaining T cells in peripheral tissue via modulation of integrin function.¹⁹⁶ Treatment of T cells with the S1P₁ agonist FTY720 inhibited migration into the afferent lymphatic vessel by promoting firm adhesion of T cells to the basal (tissue) side of afferent lymph vessels mediated by both α L β 2 and α 4 β 1 integrins. This suggests a regulatory interplay between the S1P₁ system and integrins, and that changes in S1P levels may control T cell egress out of non-lymphoid tissue via effects on integrin function.

F. INTEGRINS AND THERAPEUTICS—Based on the homing preference of specific subsets of T cells and other leukocytes, therapies targeting integrins have made their way into the modern medical armamentarium. Natalizumab is a humanized anti- α 4 integrin antibody that is approved for treatment of both multiple sclerosis and Crohn's disease. Although preclinical studies and clinical trials showed efficacy,¹⁹⁷ a few patients taking natalizumab developed a rare and often fatal demyelinating disorder called progressive multifocal leukoencephalopathy (PML).¹⁹⁸ The development of PML in these patients may be due to the high level of immunosuppression induced by bi-therapy with natalizumab and interferon. Currently, natalizumab is approved as a monotherapy and no further cases of PML have been reported.¹⁹⁹ As natalizumab targets both α 4 β 1 and α 4 β 7, there is interest in developing therapies that more specifically target certain integrins. An α 4 β 7 specific antibody (MLN-02) has been shown to be effective in inducing clinical remission in the treatment of ulcerative colitis and active Crohn's disease.^{93;200} Although the mechanism of action of these antibodies is presumed to be primarily at the level of modulating integrin-dependent functions that control T cell migration and localization, it is important to consider other potential effects of these antibodies on T cell function.²⁰¹ Recent studies in the mouse suggest that antibodies against α 4 integrin or α 4 integrin deficiency can alter T cell activation and differentiation.^{76;202–206} Thus, additional research is clearly needed to more fully define the mechanism by which these therapies ameliorate disease.

The β 7 integrin has also been used as target for the delivery of siRNA to gut-homing phenotype cells.²⁰⁷ In these experiments, siRNA targeting cyclin D1 was delivered in vivo via stabilized nanoparticles that had been coated with anti- β 7 integrin antibody. Cyclin D1 knockdown in cells expressing β 7 integrin resulted in a reversal of the development of experimental colitis in mice. The HIV cell surface glycoprotein, gp120, was recently shown to directly bind α 4 β 7 potentially facilitating HIV entrance into CD4 T cells.²⁰⁸ Supporting this hypothesis, several but not all integrin blocking antibodies reduced viral replication in CD4 T cell cultures. This suggests the possibility that previously developed and clinically available therapies designed at blocking α 4 β 7 may decrease the ability of HIV to spread by infecting new CD4 T cells. However, one recent study has shown that natalizumab does not inhibit HIV replication in CD4 T cell cultures.²⁰⁹

CONCLUSIONS

The involvement of integrins in all phases of the T cell life cycle calls for their regulated expression depending upon the current need of the cell. On naïve T cells, integrins promote efficient T cell entry into peripheral LNs. Although integrins are not required for motility in LNs, they provide adhesive forces that promote T cell interactions with APCs that are critical for effective T cell priming. The microenvironment within the LN is critical to determining the specific changes in integrin expression that occur as naïve T cells clonally expand and differentiate into effector T cells. While factors such as ATRA have been identified that promote expression of specific integrins such as $\alpha 4\beta 7$, our understanding of these environmental signals that regulate integrin expression on activated T cells is still in its infancy. These environmental signals play a central role in defining the ability of effector T cells to access various non-lymphoid tissue sites. The environment within non-lymphoid tissue differs dramatically from the LN environment. Although there is now strong evidence suggesting that the non-lymphoid tissue environment can induce expression of certain integrins on T cells after their entry from the blood, the factors that control this induction of integrin expression remain unclear. This will be an important area of future investigation, as it is clear that integrins play an important role in the retention, survival and function of T cells in non-lymphoid tissue.

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FIGURE 1. T cell integrin expression and their ligands

Naïve CD4 and CD8 T cells express low levels of the $\alpha L\beta 2$ (LFA-1), $\alpha 4\beta 1$ (VLA-4) and $\alpha 4\beta 7$ (LPAM) integrins. In the extended, high affinity state, these integrins bind to ICAM-1, VCAM-1, and MAdCAM-1 expressed on antigen presenting cells (APC) or the vascular endothelium. These integrin ligands are members of the Immunoglobulin (Ig) superfamily and are composed of several Ig domains represented by the circular repeats composing their structure. Of note, MAdCAM-1 also contains a mucin-like domain that is capable of binding CD62L.

FIGURE 2. Specific LN microenvironments lead to the acquisition of preferential homing of T cells to the small intestine, the skin, and the brain

Naïve T cells enter into lymph nodes (LN) via their well characterized interaction with the vascular high endothelial venules. In the mesenteric LN (mLN) or Peyer's patch (PP) of the small intestine (SI), naïve T cells bind to MAdCAM-1 and ICAM-1 via CCR7-activated $\alpha 4 \beta 7$ and $\alpha L \beta 2$ integrins. (A). Antigen-laden αE (CD103) integrin-positive dendritic cells (DCs) migrate from the SI parenchyma into the mLN (A1). During T cell priming, these αE integrin-positive DCs produce an active metabolite of vitamin A, all-trans retinoic acid (ATRA), that induces expression of molecules involved in homing to the SI, $\alpha 4 \beta 7$ integrin and CCR9 (A2). These 'gut' homing T cells then exit the mLN and preferentially circulate to the SI via interaction between $\alpha 4 \beta 7$ /MAdCAM-1 and CCR9/CCL25 (A3). (B). Skin derived DCs transport antigen to the local skin draining lymph node (B1). Skin draining DCs are believed to produce 1,25 dihydroxy-VitD3 (1,25VitD3) from Vitamin D present in the skin. The presence of 1,25VitD3 during T cell priming results in the upregulation of skin homing molecules (CCR10) and suppression of the induction of gut homing molecules such as $\alpha 4 \beta 7$ and CCR9 (B2). Other skin homing molecules are also induced by other unknown factors. These 'skin' homing T cells then exit the pLN and preferentially circulate to the skin via interactions between $\alpha L \beta 2$ /ICAM-1, CCR10/CCL27, and P-selectin ligand (P-lig)/P-selectin (B3). (C). The mechanism by which antigen reaches the cervical LNs (cLNs) is poorly defined, but may involve migration of brain derived DCs, other antigen presenting cells (APCs), or direct drainage (C1). T cells responding to brain-derived antigens upregulate $\alpha 4 \beta 1$ and become $\alpha 4 \beta 7$ low (C2). The factors involved in this process are entirely unidentified. These 'brain' homing T cells then exit the cLN and preferentially enter the brain via interactions between $\alpha 4 \beta 1$ /VCAM-1 (C3).

FIGURE 3. Integrin expression induction and function in non-lymphoid tissue

Following entry into non-lymphoid sites such as the small intestine (A) or the brain (B), T cell integrin expression is altered by microenvironmental factors of the tissue. (A). $\alpha 4 \beta 7$ integrin high cells enter through venules of the small intestine expressing MAdCAM-1. Upon entry into the small intestine, CCR9 positive CD8 T cells migrate through the lamina propria to reach the collagen IV-rich basement membrane of the epithelium. Here, in a TGF- β dependent fashion, T cells downregulate $\alpha 4 \beta 7$ integrin and upregulate $\alpha E \beta 7$ integrin (A1). CCR9 binds CCL25 present on the small intestinal epithelial cells, triggering $\alpha 4 \beta 7$ integrin-dependent adhesion to E-cadherin expressed on the epithelial cells (A2). $\alpha 1 \beta 1$ integrin is believed to interact with collagen IV, further promoting retention/survival of the intraepithelial lymphocytes (IELs) (A3). (B.) $\alpha 4 \beta 1$ integrin high CD8 T cells gain entry into the brain parenchyma through a high affinity interaction with VCAM-1 expressed on inflamed venules. Brain tumor infiltrating T cells are hypothesized to encounter TGF- β which is abundant in the tumor microenvironment. This results in the upregulation of $\alpha 4 \beta 7$ integrin (B1). Cognate interactions between the TCR and peptide/MHC class I on E-cadherin positive tumor cells is believed to result in $\alpha 4 \beta 7$ integrin binding to E-cadherin in the immune synapse (B2). This interaction results in the polarization and release of cytotoxic granules containing perforin and granzyme B (cytotoxins) and the killing of tumor cells (B3).