Immune Cell Trafficking in the Central Nervous System

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Abstract For many years, it was assumed that cells of the immune system were excluded from the central nervous system (CNS) and thus immune reactions did not occur at this site. Currently, it is widely accepted that the immune system can gain access to and function within the CNS. A growing body of work now supports that the immune system is present in the brain in the steady state. Beyond serving a role in immune surveillance, the immune cells appear to promote neurological function. Under inflammatory conditions, immune cells enter the CNS and, depending on the context, may provide protection or cause tissue pathology. For example, following several infections, the immune system is required to control pathogen replication within the CNS and prevent disease. On the other hand, autoimmune reactions in the CNS, such as multiple sclerosis, cause debilitating tissue destruction. Beyond infection and autoimmune disease, the immune system appears to be involved in many neurodegenerative disorders, such as Parkinson's disease and Alzheimer's disease. Thus, the factors that support lymphocyte entry and function in various settings of neuroinflammation are of great interest. In the following chapter, immune cell entry and behavior within the brain will be discussed, with a focus on the role of adhesion molecules and chemokines in this process.

Keywords Neuroinflammation • Lymphocyte trafficking • Chemokine • Adhesion molecules • Integrins

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1 Introduction

For nearly 100 years, the unique immunological status of the brain has been appreciated. The presence of the blood-brain barrier (BBB) and isolation of the central nervous system (CNS) from circulating immune cells and antibodies led to the classification of the CNS as an immune privileged site [1–3]. Subsequently, the detection of small numbers of leukocytes, particularly memory T cells, in the CSF suggested that immune surveillance of these unique sites occurs in the absence of inflammation [4–6]. While it is clear that the nervous system can directly impact immune function, there is also evidence that the presence of a low number of T cells within the brain promotes normal neurological function [7, 8]. Nevertheless, the recruitment of immune cells to the brain is associated with a wide variety of neurological conditions, which, depending on the context, is beneficial or pathological. For example, the immune system is required to limit the replication of a variety of viral, bacterial, and parasitic organisms within the CNS [1, 9]. While the ability to control these pathogens is critical for host survival, the accompanying inflammation can lead to life-threatening disease [10]. Similarly, the development of autoreactive T and B cells specific for antigens present in the CNS accounts for the tissue destruction and disruption of normal neurological function observed in conditions such as multiple sclerosis and limbic encephalitis [11–13]. Inflammatory processes have also been implicated in many neurodegenerative disorders, such as Parkinson's disease and Alzheimer's disease, and in response to sterile injuries that include stroke or trauma [14–18].

A common pathological feature that links many of these conditions is the influx of leukocytes into the CNS [1, 9, 11, 19]. The infiltration of immune cells also triggers changes in resident populations such as microglia and astrocytes, which can amplify the inflammatory response that causes collateral damage which impacts on neuronal survival and function [15, 20]. Thus, understanding the mechanisms that govern the trafficking of immune cells into and within the CNS and their interaction with resident glia is critical for the design of strategies to augment protective immune responses to pathogens and tumors and to prevent the deleterious effects of neuroinflammation. In this chapter, the events involved in the entry of immune cells into the CNS and how this impacts immune surveillance will be discussed, with an emphasis on recent reports that visualize the behavior of these populations in real time.

2 Licensing of Cells for Entry into the CNS

One hallmark of neuroinflammation is the infiltration of immune cells into the multiple compartments of the CNS. In the steady state, small numbers of perivascular macrophages (pericytes) and T cells are present in the meninges and perivascular spaces [21, 22]. In the context of various inflammatory stimuli, the composition of these sites can be dramatically altered to include almost every type of immune cell,

but most commonly T cells, B cells, monocytes, macrophages, and dendritic cells. Immune cells can gain access to the CNS at several sites, including the blood-brain barrier (BBB) present along the capillaries in the brain parenchyma, the choroid plexus, meningeal vessels that extend into the brain parenchyma, and postcapillary venules [1, 9, 23–26]. Local and systemic inflammation can induce changes at these sites that make them more permissive to immune cell infiltration [19, 24, 27, 28]. Consequently, understanding the mechanisms by which diverse inflammatory populations access the CNS may lead to therapeutics that can be useful to manage the inflammatory conditions that affect this site [19].

Our current understanding of how immune cells enter the brain is arguably most developed for T lymphocytes. In current paradigms, naïve T cells do not readily enter the normal or inflamed CNS. Rather, T cells that enter the brain need to be highly activated, suggesting that these cells are primed in the periphery prior to gaining access to this site [9]. These observations raise many questions about the specific conditions that support T cell entry into the CNS, and a recent report has highlighted the importance of peripheral sites where T cells are "licensed" to enter the CNS [29]. In these studies, T cells specific for the CNS autoantigen myelin basic protein (MBP) were activated in vitro and transferred into mice to induce experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis. In the first days following transfer, the T cells were present in the spleen and other tissues, including the lung, but few reached the CNS. However, T cells isolated from the spleen or lung 60 h following transfer were capable of trafficking to the CNS of naïve recipient animals within hours, suggesting that these lymphocytes acquire the ability to traffic to the CNS at these peripheral sites. Microarray analysis of the different T cell populations demonstrated that the T cells that are initially transferred have an activation and replication program, whereas "licensed" T cells express a migratory program characterized by the ability to respond to inflammatory chemokines and increased expression of adhesion molecules [29]. These findings highlight that T cell activation alone is not sufficient for entry into the CNS and that additional events outside the CNS are required to make these cells responsive to the adhesion molecules and chemokine signals that facilitate access to the brain. In the remainder of this chapter, the role of some of the major adhesion molecules and chemokines that influence inflammatory processes in the CNS will be highlighted.

3 Leukocyte Extravasation and the Role of Adhesion Molecules

In many cases, local tissue damage within the CNS and perhaps even systemic insults initiate core processes similar to those employed in other tissue sites that lead to the extravasation of leukocytes across the blood-brain barrier or blood-CSF barrier [22]. However, there are some aspects of this process that appear to be unique to the CNS, and the identification of selective trafficking determinants should lead to the design of strategies to limit or promote leukocyte infiltration into the CNS. The adhesion cascade for leukocyte extravasation involves four canonical steps which

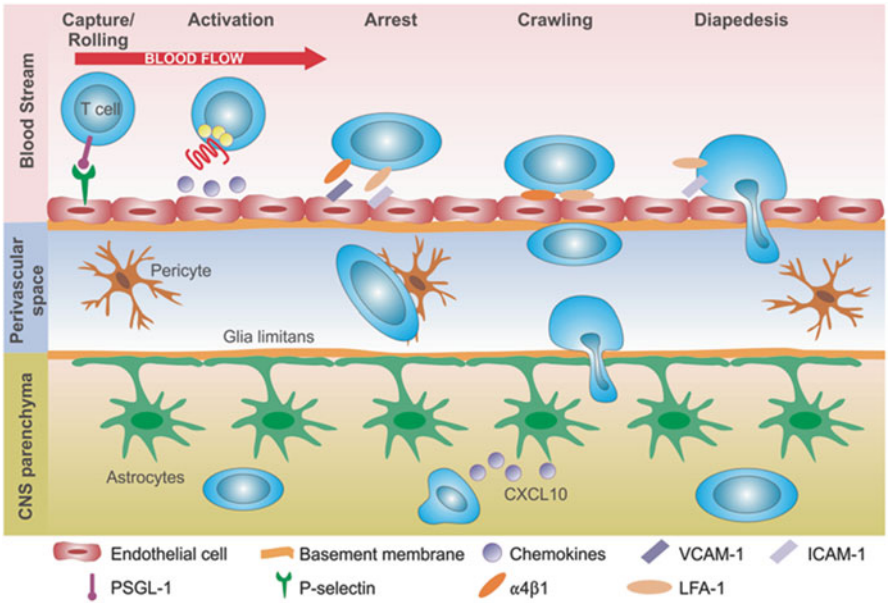

Fig. 1 T cell entry to the CNS through the blood-brain barrier. Activated T cells in the bloodstream interact with activated endothelial cells within the brain vasculature in a stepwise process. First, T cells interact with endothelial cells by binding to adhesion molecules, including PSGL-1, that induce capture or rolling. Next, chemokine signals activate integrin molecules (including $\alpha_4\beta_1$) leading to T cell arrest. Then, T cells crawl along endothelial cells before crossing the endothelium into the perivascular space in a process called diapedesis or extravasation. Within the perivascular space, T cells may interact with perivascular macrophages or pericytes. In order for T cells to gain access to the brain parenchyma, the cells must cross an additional basement membrane laid down by astrocytes, termed the glial limitans. Once T cells reach the brain parenchyma, chemokines provide signals to enhance the migration of T cells

are shared across various tissues (depicted in Fig. 1) and includes (1) capture and rolling of leukocytes regulated by selectins/mucins, (2) activation and change in conformation of integrins mediated by chemokines through Gαi receptor signaling, (3) firm arrest controlled by the integrins and their counter receptors on the endothelia, and (4) diapedesis or transmigration across the endothelial layer. After these events, the major obstacle to the entry of leukocytes is the BBB, which consists of endothelial cells with tight intercellular junctions and endothelial and glial basement membranes. The BBB limits entry from blood vessels in the parenchyma of the brain as well as the postcapillary venules in the meninges [22]. Similarly, the epithelial cells of the choroid plexus have tight junctions, which form the anatomical basis of the blood-CSF barrier. During local and systemic inflammation, endothelial cells of the BBB and epithelial cells of the choroid plexus increase expression of several adhesion molecules that support the recruitment of T cells and other immune cells [5, 19, 25, 26, 30]. Some of the important adhesion molecules required for immune cell recruitment during neuroinflammation are discussed below.

3.1 L-, P-, and E-Selectins

Selectins (L, P, and E) are surface glycoproteins involved in cell adhesion that are crucial for leukocyte rolling and capture on blood vessels. The P- and E-selectins are constitutively expressed on the cerebrovascular endothelium and are upregulated during inflammation [31]. Both P- and E-selectins can bind to PSGL-1, a mucin-type glycoprotein that is expressed on the surface of myeloid cells, activated lymphocytes, and inflamed endothelial cells. The ability of P-selectin to engage PSGL-1 leads to signaling that activates LFA-1, suggesting an indirect role for selectin-mediated signaling on integrin-mediated firm adhesion required for leukocyte recruitment [32]. This process may be relevant to normal surveillance and a model has emerged in which P-selectin expression on the choroid plexus stromal vessels promotes trafficking into this compartment and the presence of small numbers of T cells in the CSF [5, 30]. During EAE, inhibition of selectins and PSGL-1 (using blocking antibodies or mice that lack PSGL-1) has yielded mixed results. Some studies showed reduced trafficking of lymphocytes into the CNS and decreased severity of disease [31, 33], while others indicated that blockade did not impact on these processes [31, 34–36]. However, it is important to distinguish between the role of selectins in mediating leukocyte rolling at the cerebrovascular endothelium versus their function in other T cell and dendritic cell (DC) activities. For example, stimulation of DCs through PSGL-1 results in an increased ability to generate Tregs, which in turn can ameliorate disease [37, 38]. Nevertheless, the combined blockade of P-selectin and α4-integrins has shown a more profound inhibition of T cell rolling along inflamed vessels and a marked decrease in the severity and onset of EAE [32, 39]. These results suggest additive effects in the functions for P-selectin and α4-integrins in T cell rolling and illustrate the complex nature of the molecular interactions involved in these processes.

Another ligand for E-selectin is the glycoprotein CD44, which is ubiquitously expressed by immune and nonimmune cells, and the blockade of CD44 during EAE reduces CNS inflammation and the development of clinical disease [40]. Additional explanations for this observation include the interaction between CD44 and its ligand hyaluronan (HA) and a report that CD44 expression on the inflamed CNS vessels can tether HA and promote recruitment of activated T cells [41]. Given the complex biology of CD44 that includes multiple, unrelated ligands and its ability to undergo conformational changes, there remains a major knowledge gap in our appreciation of how its interactions with the selectins contribute to various forms of CNS inflammation.

3.2 β7 Integrin and Its Role in CD49d and CD103

The pairing of the β7 integrin with α4 (Cd49d) or αE (CD103) chains leads to the formation of stable heterodimeric α4β7 and αEβ7 complexes, respectively. The α4β7-MadCAM-1 pairing has been implicated in leukocyte migration to several

sites of inflammation including the mucosa; however, their role in CNS inflammation is less clear. During EAE, blockade of α4β7 had no effect on disease course, but EAE in β7-integrin-deficient mice was reduced in severity and MAdCAM-1 blocking antibodies did inhibit EAE [42, 43]. Thus, the precise role of the α4β7 integrin and MadCAM-1 during EAE remains to be clarified [25], but these discrepancies may be related to the use of β7 as a component of CD103. DCs and T cells express β7 integrin, and in a model of vesicular stomatitis virus (VSV) infection, memory $CD8^+$ T cells that express CD103 have been detected in the parenchyma long after viral clearance [44]. Whether this population is a consequence of a postinfection surveillance mechanism or due to persistence of VSV-specific T cells within the parenchyma and if CD103 influences these cells are open questions.

3.3 VLA-4 (α4β1)/VCAM-1 Interactions

Numerous studies using EAE as a model have highlighted the importance of the VLA4 (α4β1)/VCAM-1 interactions as a major determinant in leukocyte recruitment to the CNS. VCAM-1, one of the major α4β1 integrin ligands, is upregulated on the vasculature in EAE and MS. Moreover, the adhesion of activated MBP-specific T lymphocytes to brain endothelial cells in tissue sections is mediated by α4-VCAM-1 interactions, and the severity of disease caused by different MBP-specific T cell clones correlated with levels of α4 expression [45]. Consistent with these findings, anti-α4 antibodies block the accumulation of T cells in the CNS and the development of EAE [45, 46]. α4β1 is also required for the adhesion of immature DCs to the CNS vasculature and their access to the brain during EAE; however, the accumulation of granulocytes and macrophages within the CNS is independent of this integrin [47]. VCAM-1 blockade also delayed the onset of EAE but had modest effects on the duration and severity of disease [34], suggesting a role for other α4 integrin ligands such as fibronectin in these events [48]. These proof-of-concept studies underscored the importance of the α4β1 integrins in leukocyte accumulation in the brain and led to the development of antibodies that interfere with the function of this integrin for treatment of MS. However, blockade of α4 integrins in other models has also been shown to compromise protective immunity to several pathogens within the brain, including *T. gondii*, SIV, and bornavirus [49–51]. These findings highlight that approaches that might interfere with natural immune surveillance can lead to unwanted consequences, which are discussed in more detail later.

3.4 LFA-1(αlβ2)/ICAM Interactions

LFA-1 (αlβ2) is one of the best-studied members of the β2 family of integrins, and its ligand ICAM-1 is constitutively expressed by endothelial cells within the CNS vasculature and is upregulated during inflammation [46, 52]. Several *in vitro* studies

have shown that LFA-1-ICAM-1 interactions are required for the adhesion of T cells to the CNS vascular endothelium and for their optimal migration across this barrier. There are also reports that entry of Th17 cells into the brain parenchyma during EAE occurs in the absence of α4 integrins but is dependent on LFA-1 [53]. However, blockade of LFA-1/ICAM-1 and the use of ICAM-1-deficient and LFA-1-deficient mice (*Cd11a*$^{-/-}$) during EAE have resulted in responses ranging from prevention of EAE to exacerbation of disease [54–57]. Since LFA-1 is a component of the immunological synapse and has a prominent role in T cell activation, it is possible that the broader effects of LFA-1 blockade during EAE also influence the generation of the pathological T cells. Nevertheless, LFA-1 has also been implicated in the migration of adoptively transferred dendritic cells to the brain during toxoplasmic encephalitis [58] and so appears to be part of a core adhesive program that is relevant to many immune populations. Whether this influences other facets of immune function such as migration within the brain is unknown, and some of the disparate findings in EAE indicate that the biology is more complex than currently appreciated.

3.5 Therapeutic Significance of Targeting VLA-4 and LFA-1

With the need to develop more effective treatments to manage the clinical manifestations of MS, one approach has been the development of strategies that would limit the migration of pathogenic T cells into the CNS. The identification of α4β1 as a key molecule required for immune cell access to the CNS provided the rationale for the development of a monoclonal antibody (natalizumab) directed against integrin α4, as a treatment for MS. Clinical trials with this therapy demonstrated significant benefits including fewer inflammatory CNS lesions and reduced numbers of relapses in MS patients. However, the drug was temporarily withdrawn due to reports that, in a limited number of patients, this treatment was associated with the development of progressive multifocal leukoencephalopathy (PML), a potentially fatal disease caused by reactivation of JC polyomavirus [59]. Not surprisingly the use of another antibody (efalizumab) that blocks LFA-1 also results in PML (and was withdrawn from the market in 2009) [60]. Latent JC virus can persist in multiple tissues including the kidney, bone marrow, and brain. Whether the CNS disease caused by this virus is a consequence of reduced local immunosurveillance or whether it reflects the reactivation of the virus in the peripheral compartments and spread to the CNS is uncertain. Nevertheless, natalizumab continues to be used primarily as a monotherapy for treatment of MS, with careful consideration of prior JCV antibody titers in patients and close monitoring for development of PML. The challenge in this field is to determine whether the knowledge gained from basic and clinical studies can be used to design improved or more selective approaches that allow normal surveillance while targeting pathological processes.

4 Role of Chemokines in Homeostasis and Inflammation

In humans, there are approximately 50 chemokines and 19 chemokine receptors whose expression varies among immune cells [61, 62]. Several chemokines are expressed constitutively in the steady state and control homeostatic processes such as the natural circulation and homing of different immune cells [63, 64]. For example, the chemokine, CCL25, is expressed in the gut, and T cells and dendritic cells expressing CCR9 (the receptor for CCL25) home specifically to this tissue site during the steady state. Similarly, CCR4 and CCR10 mediate normal trafficking of T cells to the skin. The impact of chemokines and their receptors on tissue-specific homing patterns has been likened to an address code for immune cells [65, 66]. Specific chemokine receptor expression has also been associated with distinct classes of T helper cell subsets: Th1 cells express CXCR3 and CCR5, whereas Th17 cells express CCR6 [65, 67, 68]. To date, no brain-specific "address code" has been identified, but numerous studies have implicated chemokines in various aspects of neuroinflammation and elements of this literature are reviewed below.

4.1 CCR7/CCL19, CCL21

Several homeostatic chemokines are expressed during the steady state and contribute to the localization and behavior of lymphocyte populations within secondary lymphoid organs [69]. Two of these chemokines, CCL19 and CCL21, are constitutively expressed in the spleen and lymph nodes where they influence the migration of CCR7-expressing naïve and memory T cells as part of normal recirculation events [70]. Within the brain, CCL19 expression has been detected in venules and it has been proposed that it promotes immune surveillance by CCR7-expressing T cells [71]. Moreover, in a model of T cell acute lymphocytic leukemia (T-ALL), CCR7 is critical for the entry of tumor cells into the CNS where they can evade chemotherapy and act as a source of relapses [72]. Thus, blocking CCR7 may prevent metastasis to the CNS and reduce the need for aggressive treatment of T-ALL.

CCR7 also appears to have a role in lymphocyte entry into the CNS during inflammation. CCR7 blockade reduced the adhesion of activated T cells to sections of inflamed brain ex vivo [71]. In the context of infectious disease, CCL21 expression increases in the brain during chronic toxoplasmosis, and $CD4^+$ T cells that infiltrate the CNS in response to infection co-localize with CCL21 [51, 73]. Indeed, in $plt^{-/-}$ mice, which lack CCL19 and CCL21, $CD4^+$ cells were not able to access the brain parenchyma during toxoplasmic encephalitis. However, in mice that constitutively express CCL21 in astrocytes, lymphocytes did not enter the brain in the absence of infection. Thus, CCL21 alone is not sufficient to promote the entry of lymphocytes into the uninflamed CNS, but this chemokine has a key role during infection.

4.2 CXCR4/CXCL12

In contrast to many chemokines that are expressed in response to inflammatory signals, CXCL12 is expressed constitutively by the endothelium at the BBB and in the choroid plexus. Interestingly, instead of promoting inflammation, it has been proposed that CXCL12 limits the entry of $CXCR4^{+}$ immune cells into the brain. During MS and EAE, the localization of CXCL12 changes from the basal to the luminal side of the endothelium, which may promote T cell entry into the CNS [74–77]. These studies emphasize how altered expression patterns of chemokines at the BBB or BCSFB can influence the entry of immune cells to the CNS.

4.3 CCR6/CCL20

The receptor CCR6 is expressed by multiple cell types, including IL-17 producing T cells, which are associated with pathological T cell responses in many sites, including the CNS. Several recent studies have explored the role of CCR6 during EAE. Reboldi and colleagues reported that CCR6-deficient mice were resistant to EAE, and this phenotype was ascribed to a critical role for CCR6 in the initial recruitment of activated T cells to the CNS. The observation that CCR6-expressing Th17 T cells were associated with the choroid plexus which constitutively expresses CCL20 led to the hypothesis that entry of IL-17 producing cells occurs at this portal [78]. In contrast, two other reports have found that EAE is exacerbated in CCR6-deficient mice [79, 80]. Since regulatory T cells (Tregs) also express CCR6, an increase in pathology in CCR6-deficient mice may be a result of Treg dysfunction. Indeed, Treg recruitment to the CNS is reduced in the absence of CCR6 [79, 80]. Because this receptor is expressed on multiple cell types that influence many facets of the immune responses during neuroinflammation, these apparently contradictory studies illustrate the complexities of interpreting studies that involve total chemokine receptor knockout mice.

4.4 CXCR3/CXCL9,10,11

CXCR3 and its multiple ligands have been associated with various forms of neuroinflammation and surveillance of the CNS. In the absence of inflammation, T cells present in the CSF of patients express CXCR3 [81]. During EAE, as well infections that impact the CNS, CXCR3 is highly expressed by infiltrating T cells [82–89]. In some instances, CXCR3 is required for optimal trafficking of T cells to the CNS [86, 88]. In addition, $CXCR3^{-/-}$ mice develop less severe inflammation in models of viral encephalitis and cerebral malaria [82, 83, 86, 87]. While neurons and infiltrating myeloid cells are capable of producing CXCR3 ligands, astrocytes are a predominant source of CXCL10 and microglia of CXCL9 during EAE [90–93].

Consistent with the evolving view of chemokine biology, CXCR3 and its ligands are not simply involved in the recruitment of T cells to the CNS. Recently, the influence of CXCL10 on T cell behavior in the tissue parenchyma has been visualized using multiphoton microscopy of $CD8^+$ T cells responding to infection with *T. gondii*. Surprisingly, blockade of CXCL10 decreased the velocity of $CD8^+$ T cell migration, but did not influence the directionality of movement or the walk behavior of the cells. This alteration in migration was predicted to decrease the ability of cytotoxic T cells to find infected target cells and limit parasite replication [88]. Thus, a model is emerging in which chemokines within the inflamed CNS promote the movement of T cells through tissues, which may support pathogen control but presumably would also contribute to the development of autoimmune lesions in the CNS. Interestingly, $CXCR3^{-/-}$ mice exhibit exacerbated EAE [85, 94] and one study found that the localization of Tregs in the CNS is altered in these mice [85]. In light of recent studies that Tregs acquire similar phenotypes to the effector cell populations that they regulate [95–98], this change in Treg localization may lead to a reduced ability to limit the autoimmune effector T cell responses leading to more severe disease. Taken together, studies examining the role of CXCR3 in neuroinflammation highlight the complex nature of chemokine biology, with multiple cell types expressing a common receptor, single cells expressing multiple receptors, and differential ligand expression within a tissue.

4.5 CCR2/CCL2

The receptor CCR2 and its ligand CCL2 (monocyte chemoattractant protein 1) play a major role in the mobilization of inflammatory monocytes and neutrophils. The infiltration of CCR2-expressing $Ly6C^{hi}$ monocytes has been observed in a variety of neurological conditions. In the context of EAE, blockade of CCR2 suppressed disease [99, 100] and mice lacking CCL2 developed less severe EAE associated with reduced infiltration of monocytes [27, 101]. Similarly, during certain viral infections, CCR2-dependent accumulation of monocytes is associated with development of pathology characterized by demyelination [102] or vascular injury and the onset of seizures [103]. During other infections, including *T. gondii* and MHV, the lack of CCR2 resulted in decreased leukocyte trafficking and activation of immune cells within the CNS, leading to a reduced ability to control these pathogens [104, 105]. Together, these reports on diverse experimental models highlight the contribution of CCR2 to the recruitment of myelomonocytic cells to destructive and protective immune responses.

5 Future Directions

The studies highlighted in the previous section illustrate the key role of integrins and chemokines in the orchestration of neuroinflammation. Given that chemokines utilize G-protein-coupled receptors to signal, these receptors are attractive targets for

small-molecule inhibitors that may lead to the development of selective antagonists [106–108]. However, successful treatments that target chemokines may ultimately require that specific ligands or combinations of receptors be targeted for the most efficacious result. For example, many studies that have examined the involvement of α4β1/VCAM-1 in T cell entry into the brain support a direct inhibition of T cell adhesion to CNS vessels as the possible mechanism. Similarly, while it is clear that chemokines have a central role in neuroinflammation, how initial entry of cells into the brain or subsequent events are most critically influenced by these factors is still unclear. In many instances, interfering with these pathways results in differences in the number of inflammatory cells within the CNS, which may be due to defective priming, reduced recruitment across barriers into the CNS, or an inability to retain these cells within the tissue. The development of intravital imaging of individual cells combined with the generation of fluorescent reporter mice specific for different cell types (such as DCs, neutrophils, antigen-specific $CD4^+$ and $CD8^+$ T cells, microglia, astrocytes) and cytokines has made it possible to study the interaction between infiltrating immune cells with CNS-resident cells [1, 51, 109–111]. The application of this technology has the potential to fundamentally advance our appreciation for how immune cells enter and behave in the CNS and may lead to the refinement or discovery of therapeutic strategies to better manage neuroinflammation. This information will also be relevant to the development of complex therapies that use stem cells to repair tissue damage in the brain or chimeric antigen receptor (CAR) T cells to treat tumors that affect the CNS [112–114]. In particular, for CAR T cells, an understanding of the environmental cues provided by integrins and chemokines that influence T cell functions in the brain should inform the strategies used to engineer optimal tumor-specific effector T cells that can access and operate within the CNS.

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