Inflammatory monocytes and the pathogenesis of viral encephalitis

Rachael L Terry1,2,4, Daniel R Getts4, Celine Deffrasnes1,2, Caryn van Vreden1,2, Iain L Campbell2,3 and Nicholas JC King1,2*

Abstract

Monocytes are a heterogeneous population of bone marrow-derived cells that are recruited to sites of infection and inflammation in many models of human diseases, including those of the central nervous system (CNS). Ly6Chi/CCR2hi inflammatory monocytes have been identified as the circulating precursors of brain macrophages, dendritic cells and arguably microglia in experimental autoimmune encephalomyelitis; Alzheimer’s disease; stroke; and more recently in CNS infection caused by Herpes simplex virus, murine hepatitis virus, Theiler’s murine encephalomyelitis virus, Japanese encephalitis virus and West Nile virus. The precise differentiation pathways and functions of inflammatory monocyte-derived populations in the inflamed CNS remains a contentious issue, especially in regard to the existence of monocyte-derived microglia. Furthermore, the contributions of monocyte-derived subsets to viral clearance and immunopathology are not well-defined. Thus, understanding the pathways through which inflammatory monocytes migrate to the brain and their functional capacity within the CNS is critical to inform future therapeutic strategies. This review discusses some of the key aspects of inflammatory monocyte trafficking to the brain and addresses the role of these cells in viral encephalitis.

Keywords: Ly6Chi inflammatory monocytes, Viral encephalitis, Neurotrophic virus, CCL2, CCR2, VLA-4, LFA-1, Integrins

Background

Virus infection of the brain can cause severe and life-threatening disease. Despite this, few therapies beyond intensive supportive care are available to treat patients with encephalitis [1,2]. Anti-viral drugs have been developed for some viruses that can infect the brain, such as Herpes simplex virus (HSV)-1 and 2, and human immunodeficiency virus (HIV), but even with these treatments outcomes remain relatively poor [2-5]. Many patients succumb to disease, and survivors often suffer permanent neurological sequelae [6-9].

While the development and clinical implementation of novel anti-viral drugs may improve patient outcomes, it is becoming increasingly clear that therapies targeting pathogenic elements of the host immune response may be critical for successful intervention during infection [10-14]. Monocyte infiltration is a hallmark of central nervous system (CNS) inflammation, including viral infection. These cells migrate into the infected brain, where they differentiate into dendritic cell (DC), macrophage and, arguably, microglial populations. Once differentiated, these cells engage in a number of potent effector functions including antigen presentation and T cell stimulation, the production and secretion of numerous pro-inflammatory mediators as well as reactive oxygen species (ROS), all of which are focused on viral containment and clearance (Table 1). However, unbalanced and poorly controlled migration and effector functions of these cells may result in immune-mediated pathology, resulting in tissue damage and destruction during some infections (Table 1). Therefore, it is of high importance to understand the processes driving monocyte development, recruitment, differentiation and function, to aid in the development of novel therapeutics that inhibit immunopathological responses.
Monocytes are derived from hematopoietic precursors in the bone marrow

Monocytes are derived from hematopoietic stem cells (HSC) in the bone marrow (BM) (Figure 1). The earliest defined precursor is the common myeloid precursor (CMP), distinguished from HSC by the expression of CD34 but not SCA-1 [39-42] (Figure 1). These cells give rise to a pool of precursors called granulocyte/macrophage precursors (GMPs), which express CD16/32 [39]. Included within this subset is the recently defined macrophage/dendritic cell precursor (MDP), which specifically expresses high levels of the PU.1-controlled chemokine receptor CD115 (CSF-1R/M-CSFR), chemokine receptor CX3CR1 (fractalkine receptor), and Flt-3 (CD135/Flk2) [43-48] (Figure 1). The MDP gives rise to CD11b+ , CD115+ , F4/80+ , CD11c+ , Ly6G- monocytes, that can be isolated from the BM and

| Table 1 Evidence for macrophage-driven pathogenesis and control of viral encephalitis |
|--------------------------------------------------------------------------------|
| Macrophage-derived mediators | Pathogenic and anti-viral functions in the central nervous system | Pathogenic role in mouse models | Anti-viral role in mouse models |
| Pro-inflammatory cytokines | IL-1β ↑ pro-inflammatory cytokines IL-6 ↑ adhesion molecules | IL-1β−/− mice resistant to fatal neurovirulent Sindbis virus encephalitis [15] IL-6−/− mice exhibit increased mortality and virus loads in HSV-1 encephalitis [16] | |
| IL-6 | ↑ adhesion molecules | IL-6−/− mice exhibit reduced seizures in TMEV encephalitis [17] | |
| IL-12 | Reviewed in [18-22] | IL-12−/− mice show decreased clinical score during MHV encephalitis [23] Infusion of IL-12 reduces viral loads and improves survival during vesicular stomatitis virus encephalitis [24] | |
| TNF | | TNF−/− mice show improved survival in rhabies virus encephalitis [25] TNF−/− mice exhibit increased mortality and virus loads in HSV-1 encephalitis [16] | |
| Free radicals NO/reactive oxygen species | ↑ neuronal misfiring/ seizures | Inhibition of NOS2 prolonged survival in rabies virus encephalitis by delaying virus replication and inhibiting of apoptosis [26] NOS2−/− mice show increased susceptibility to CNS invasion and death in Murray Valley virus encephalitis [27] | |
| | ↑ neuronal damage/ death | Inhibition of NOS2 prolonged survival of WNV-infected animals [30] Inhibition of NOS2 reduces mortality during Junin virus encephalitis [28] and neurovirulent Sindbis virus encephalitis [29] | |
| Proteases MMP | ↑ breakdown of the BBB | MMP−/− mice show reduced viral loads and increased survival during WNV encephalitis [32] | |
| Neurotransmitters Glutamate | ↑ neuronal misfiring/ seizures | Competitive and non-competitive glutamate receptor antagonists promote survival during neurovirulent Sindbis virus encephalitis [35,36] and improved outcomes during coronavirus encephalitis [37] | |
| | ↑ neuronal damage/ death | | |
| | ↑ production of NO/ROS | | |

BBB blood brain barrier; CNS central nervous system; HSV herpes simplex virus; MDP macrophage/dendritic cell precursor; MHV murine hepatitis virus; MMP matrix metalloproteinases; NO nitric oxide; NOS2 nitric oxide synthase-2; ROS reactive oxygen species; TMEV Theiler’s murine encephalomyelitis virus; WNV West Nile virus.
blood [49-52] (Figure 1). The spleen has also been identified as an important reservoir of undifferentiated monocytes that are rapidly deployed to sites of inflammation, including the ischemic heart and brain [53-55]. Furthermore, a recent study has shown that cardiac infarction triggers a significant increase in numbers of MDPs in the spleen, which supply monocytes throughout the duration of acute inflammation [56]. Whether the spleen is a significant source of monocytes during CNS infection is yet to be determined, but presents a critical area of future investigation. It is likely that both the BM and spleen are critical for supplying monocytes to the infected CNS, particularly in cases of acute and severe infection, in which large numbers of these cells are rapidly deployed and recruited to the brain.

Monocytes are classified into two phenotypically and functionally distinct subsets

The MDPs give rise to two phenotypically and functionally distinct subsets of monocytes [50,57]. Ly6C\textsuperscript{hi} monocytes are characterized by high expression of the chemokine receptor CCR2, adhesion molecule CD62L and low expression of the fractalkine receptor CX3CR1 [48,51,58]. These cells have been termed ‘inflammatory’ because they are selectively recruited to sites of inflammation and infection in many models of disease, including atherosclerosis [59-62]; rheumatoid arthritis [63]; experimental colitis [64]; cardiac infarction [65]; and CNS infections including experimental autoimmune encephalomyelitis (EAE) [66,67], amyotrophic lateral sclerosis [68], and stroke [53]. Recent studies have shown that these cells are also recruited to the virus-infected brain in animal models of HSV, HIV, murine hepatitis virus (MHV), Theiler’s murine encephalomyelitis virus (TMEV) and a number of flaviviral encephalitides, where they give rise to macrophage, DC and, arguably, to microglial populations [11,13,14,69].

Conversely, Ly6C\textsuperscript{lo/-} monocytes are smaller in size than their Ly6C\textsuperscript{hi} counterparts and express low levels of CCR2 and CD62L and high levels of CX3CR1 [48,51,58] (Figure 1).
Several studies have shown that Ly6C<sup>hi</sup> monocytes can give rise to circulating Ly6C<sup>lo/-</sup> monocytes [58,70-72]. Interest in this subset has increased substantially in the past few years [72,73]. Recent studies have described the patrolling behavior of these cells in the vasculature [73], and have shown that in some models of disease they rapidly enter inflamed tissue and can contribute to early inflammatory responses before domination by Ly6C<sup>hi</sup> monocytes [73]. In the resolution phase of some diseases, Ly6C<sup>lo/-</sup> monocytes are critical for wound healing and angiogenesis [50]. While apparently important in the periphery, the role of Ly6C<sup>lo/-</sup> monocytes during CNS infection remains poorly defined, with little evidence supporting their migration into the brain during inflammation [74].

**Monocyte egress from the bone marrow is controlled by chemokine/chemokine receptor interactions**

The importance of monocyte-derived cells in the pathogenesis of brain infection highlights the importance of understanding the pathway(s) through which monocytes migrate from the periphery into the brain. It is apparent that this process is regulated by cytokine/chemokine and integrin/cellular adhesion molecule interactions that facilitate emigration from the BM into the blood and entry into the CNS. For example, the chemokine receptor CXCR4 and one of its ligands CXCL12 (SDF-1) directly enhance VLA-4-dependent adhesion and thereby aid in retaining immature cells in the BM. Deficiency in either molecule results in impaired myelopoiesis [75-80]. In addition to CXCR4, CCR2 and its ligands, CCL2 and CCL7 (MCP-3), are a critical requirement for Ly6C<sup>hi</sup> monocyte egress from the BM into the blood. CCL2/CCR2 deficiency or blockade with antibody results in monocyte accumulation in the BM in multiple disease models, including EAE, WNV and HSV encephalitides [11,61,67,81-87].

**Monocyte recruitment into the infected brain is dependent on integrin/adhesion molecule interactions**

A number of chemokines and their receptors have been implicated in the recruitment of Ly6C<sup>hi</sup> monocytes from the blood and into the brain. CCR5 is expressed by Ly6C<sup>hi</sup> monocytes and is important for trafficking to sites of inflammation in some models of disease. In the brain, its ligand CCL5 (RANTES) expression is highly upregulated during infection/inflammation, including WNV, MHV, HSV and tick-borne encephalitis virus encephalitides [88-92]. Another chemokine of interest that controls the trafficking of monocytes into the brain parenchyma is SDF-1/CXCL12, in conjunction with its receptor CXCR4, expressed by monocytes [93]. In animal models of CNS inflammation including EAE [94], HIV [95] and WNV [96], there is significant upregulation of CXCL12. In EAE and WNV, CXCL12 has been shown to play an important role in retaining leukocytes in the perivascular space, thereby inhibiting infiltration into the parenchyma. Loss of this interaction resulted in the loss of perivascular cuffs and uncontrolled infiltration of CXCR4<sup>+</sup> leukocytes, including monocytes, into the parenchyma. [94,96].

While it is clear that there are a multitude of soluble mediators that represent potential targets for future therapies aimed at blocking monocyte migration, the CCR2/CCL2 axis remains the most potent pathway based on the available literature. Ly6C<sup>hi</sup>/CCR2<sup>hi</sup> monocyte recruitment into the CNS in models of stroke [53], peripheral inflammation [97], Alzheimer’s disease (AD) [98,99] and EAE encephalitis [103]. No matter the source of CCL2, the inhibition of CCL2 can significantly reduce the infiltration of inflammatory monocyte-derived macrophages and microglia into the infected brain [11,13,69,88,102,104-108].

The focus in the last decade has been heavily on the chemokines involved in monocyte trafficking, however, cellular adhesion molecules and their integrin ligands are obviously also important. In most models of viral infection, very late antigen-4 (VLA-4) and leukocyte function-associated antigen-1 (LFA-1) are expressed by Ly6C<sup>hi</sup> monocytes. In addition, their respective binding partner’s vascular cell adhesion molecule-1 (VCAM-1) and inter-cellular adhesion molecule-1 (ICAM-1) are usually upregulated on endothelium and other cell types in the inflamed brain [109-115].

The importance of VLA-4 and VCAM-1 and LFA-1 and ICAM-1 in the recruitment of Ly6C<sup>hi</sup> monocytes to sites of inflammation is evident in experiments using gene knockout animals or specific blockade of these molecules. VLA-4 and VCAM-1 interactions are critical for monocyte migration to the heart in models of atherosclerosis and arterial injury [116-118] and the inflamed peritoneum [119]. VLA-4 is also critical for Ly6C<sup>hi</sup> monocyte infiltration of the CNS in several models of inflammation, including EAE and spinal cord injury [97,109,120]. During viral infection of the brain, we have found that recruitment of monocytes to the CNS is also VLA-4-dependent. VLA-4 antibody neutralization significantly impairs the recruitment of Ly6C<sup>hi</sup> monocytes to the infected brain, in both WNV and JEV infection ([30], CvV et al., unpublished observations). LFA-1 and ICAM-1 interactions are also important for
monocyte recruitment to atherosclerotic plaques [121,122] and to the CNS during EAE [110]. We have shown that LFA-1 is also important for recruitment of monocytes to the WNV-infected brain, however blockade resulted in a smaller reduction in monocytes infiltration compared to VLA-4 neutralization, which suggests the differential use of adhesion molecules by Ly6C hi monocyte subsets which enter the WNV-infected brain [30].

Monocytes differentiate into macrophages and dendritic cells in the infected brain

In models of CNS diseases, such as EAE and stroke, Ly6C hi monocytes have been shown to primarily differentiate into macrophage and DC populations exhibiting a M1 pro-inflammatory phenotype, which in-vitro effectively stimulates Th1 and Th17 responses in T cells [53,66,67,74]. Similarly, in models of viral encephalitis, Ly6C hi monocytes have been shown to give rise to M1 pro-inflammatory CD45 hi macrophages and CD11c+ DC populations, which express high levels of nitric oxide (NO) and TNF during HSV, WNV, MHV, TMEV and JEV ([11-14,30,69], CvV et al., unpublished observations). We have shown that these CD45 hi macrophages are highly effective at processing and presenting antigen and effectively stimulate T cell proliferation [30].

Resident microglia originate from a myeloid lineage distinct to that of infiltrating monocytes

Microglia are the resident macrophage population of the brain. Similar to other tissue resident cells such as Kupffer cells of the liver and Langerhans cells of the epidermis, microglia originate from the yolk sac during embryogenesis, from a myeloid lineage that is independent of BM HSC and therefore distinct from that of BM-derived monocytes [123-125]. Microglia can be distinguished from infiltrating monocyte-derived macrophages and DC by their low to intermediate expression of CD45 and lack of Ly6C expression [11,126]. In most infections, resident microglia play functionally distinct roles from that of monocyte-derived cells. For example, during acute WNV encephalitis, resident microglia express lower levels of pro-inflammatory mediators such as NO, express lower levels of MHC-II, and show a significantly reduced capacity to process antigen and stimulate T cell proliferation compared to the highly activated infiltrating macrophages [30]. In comparison, in acute TMEV infection, resident microglia and infiltrating macrophages express similar levels of pro-inflammatory cytokines and show similar antigen processing and presentation capacity; however, in chronic stages of disease, macrophages are more efficient at stimulating T cell responses [127].

Monocytes may serve as microglial precursors during brain infection

There is evidence to suggest that infiltrating monocytes have the capacity to give rise to microglial cells in some models of CNS inflammation, including AD, Parkinson’s disease, EAE, as well as in infectious models such as scrapie and bacterial meningitis [128-134]. These immigrant microglial cells appear to play distinct functional roles compared to their resident counterparts during disease. For example, immigrant microglia are more efficient at clearing amyloid plaques than resident microglia during AD [128,135]. However, a caveat of these studies has been in the use of irradiation to generate BM chimeras to distinguish resident microglial from BM-derived cells. There are currently no immunophenotypic markers that can definitively separate these two populations. As a result, the generation of chimeras can be used distinguish tissue resident and BM-derived populations. However, irradiation can disrupt the blood–brain barrier (BBB) and promote CCL2 production, resulting in the recruitment of monocytes to the CNS [136]. Therefore, it is difficult to conclude whether monocyte engraftment is a normal feature of disease in unper- turbated animals or whether it is primarily the result of brain preconditioning by irradiation. A recent study using the parabiosis model in place of irradiated BM chimeras has shown that engraftment of monocyte-derived microglia during EAE is only a transient response [137]. The parabiosis models have also been employed to show that there is no significant engraftment of monocyte-derived microglia in facial nerve axonomy or amyotrophic lateral sclerosis [138]. Also, another recent study has compared the recruitment of monocyte-derived microglia into brain during AD, using chimeric mice generated with or without head protection during irradiation. They found that these cells do not engraft the brain of protected animals [99]. However, one major caveat of the head-protection model is the existence of BM in the skull that may be capable of reconstituting the animal. Further studies are required to definitively determine whether monocyte-derived cells can give rise to microglia and if these cells truly engraft the parenchyma and remain there if/when disease is resolved.

There are few studies that examine the recruitment of monocyte-derived microglia during viral infection of the CNS. We have shown that in WNV encephalitis, inflammatory monocytes not only give rise to CD45 hi macrophages in the brain, but also to a CD45 int subset, which is phenotypically analogous to activated resident microglia, apart from the expression of Ly6C [11,30]. Although chimeras were initially utilized to investigate this phenomenon, we further confirmed that the recruitment of these monocyte-derived cells was not the result of BBB breakdown, using methods that do not use any irradiation...
including bone marrow adoptive transfer studies and microparticle-based systems which track these cells with minimal perturbation of the disease system [11]. Furthermore, these cells were found to contribute to the immunopathogenesis of WNV encephalitis, as CCL2 blockade significantly reduced recruitment into the CNS and prolonged survival of lethally-infected animals [11]. Current studies in our laboratory aim to determine whether monocyte-derived microglia truly engraft the brain parenchyma during WNV encephalitis, the functional role of these cells throughout infection, and whether these cells remain in the CNS after disease is resolved.

**Monocytes contribute to viral clearance or viral burden in different models of infection**

Ly6C^hi^ monocytes appear to play a paradoxical role in many disease models. For example, higher mortality rates and increased pathogen loads are seen in Toxoplasma [139,140], Listeria [83,141], Cryptococcus [142,143], Yersinia infections [144], HSV-2, [145] and coronavirus [146], as well as MHV [88] when these cells are depleted. On the other hand, Ly6C^hi^ monocytes are direct targets for pathogens such as HIV, TMEV, Listeria and Toxoplasma [12,69,147-152]. Infected monocytes can be directly responsible for the dissemination of infection in a "Trojan horse" fashion into the CNS thereby potentiating disease and increasing potential mortality [153-156].

**Monocytes significantly contribute to immunopathology during brain infection**

An arguable role of monocytes during brain infection is their potential contribution to immune-mediated pathology. In several models of CNS disease, Ly6C^hi^ inflammatory monocytes cause significant damage and destruction in the brain, directly contributing to morbidity and mortality. Ly6C^hi^ monocytes contribute significantly to the pathogenesis of disease during stroke [53]. Mice with CCL2^{−/−} and CCR2^{−/−} deficiency show smaller infarcts and enhanced functional outcomes relative to wild-type controls following transient cerebral ischemia [157,158]. Similarly, in models of traumatic brain injury, CCL2^{−/−} mice showed reductions in macrophage infiltration and lesion volume compared to wild-type mice, corresponding with improved functional recovery after injury [159]. In addition, CCR2^{−/−} and CCL2^{−/−} mice exhibit milder symptoms and, in some models, are completely resistant to the development of EAE [100,136,160,161]. Furthermore, a recent study has shown that Ly6C^hi^ monocyte recruitment to the CNS is detrimental in amyotrophic lateral sclerosis [68]. In the case of encephalitic disease, studies in our laboratory using WNV as well as others using TMEV have shown that Ly6C^hi^ monocytes are recruited into the infected brain where they contribute significantly to the immunopathogenesis of disease. Inhibition of inflammatory monocyte migration into the WNV or TMEV-infected brain can significantly reduce morbidity and mortality [11,12,69,108]. Furthermore, abrogation of monocyte migration into the CNS during MHV encephalitis results in the delayed onset of demyelinating disease [105]. The precise pathways through which inflammatory monocytes contribute to pathology are still under intense investigation. However, it is clear that differentiation into effector cells such as macrophages and DC plays a substantial role. Once differentiated, these cells are significant producers of NO, matrix metalloproteinases (MMP) and other factors known to culminate in tissue destruction, breakdown of the BBB, as well as neuronal damage (Table 1). While in many organs such toxicity is not a major concern due to regenerative capabilities, the brain is largely comprised of many irreplaceable cellular subsets. As such not only is mortality a concern, in patients that survive serious CNS inflammatory insults will often suffer long-term sequelae and neurological imbalance [6-9].

**Conclusions**

Although Ly6C^hi^ monocyte infiltration is a hallmark of viral encephalitis, the role of these cells in viral clearance and immunopathology is not well defined. While it is clear that these cells are critical for the control and clearance of some viruses, they are directly responsible for recruiting others into CNS, or cause significant immunopathology. Future studies which target monocyte development and migration to the CNS in a therapeutic manner will not only provide significant insight into pathways by which monocytes are recruited to the CNS, but will identify new targets for intervention during viral encephalitis.

**Abbreviations**

AD: Alzheimer's disease; BBB: Blood–brain barrier; BM: Bone marrow; CNS: Central nervous system; CMP: Common myeloid precursor; DC: Dendritic cells; EAE: Experimental autoimmune encephalomyelitis; GMP: Granulocyte/macrophage precursor; HIV: Human immunodeficiency virus; HSC: Hematopoietic stem cells; HSV: Herpes simplex virus; ICAM-1: Inter-cellular adhesion molecule-1; JEV: Japanese encephalitis virus; LFA-1: Leukocyte function-associated antigen-1; MDP: Macrophage/DC precursor; MHV: Murine hepatitis virus; MMP: Matrix metalloproteinases; NO: Nitric oxide; NOS2: Nitric oxide synthase-2; ROS: Reactive oxygen species; TMEV: Theiler's murine encephalomyelitis virus; VCAM-1: Vascular cell adhesion molecule-1; VLA-4: Very late antigen-4; WNV: West Nile virus.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

RLT drafted the manuscript. DRG, CD, CVV, ILC and NJCK contributed to the interpretation and critical evaluation of content and revision of the manuscript. All authors read and approved the final manuscript.

**Acknowledgements**

The authors cited in this review were supported by the National Health and Medical Research Council grants 512413 and 1007757 to NJCK and ILC. RLT
was supported by an Australian Postgraduate Award and a Wenkart Foundation Scholarship.

Author details
1 Department of Pathology, School of Medical Sciences, Blackburn Circuit, The University of Sydney, Sydney 2006, Australia.
2 Bosch Institute, The University of Sydney, Sydney 2006, Australia.
3 School of Molecular and Microbial Biosciences, Burton Avenue, The University of Sydney, Sydney 2006, Australia.
4 Department of Microbiology-Immunology, Feinberg School of Medicine, Chicago Avenue, Northwestern University, Chicago 60611, USA.

Received: 29 August 2012 Accepted: 19 November 2012
Published: 17 December 2012

References
1. Chaudhuri A, Kennedy P: Diagnosis and treatment of viral encephalitis. Postgrad Med J 2002, 78:575–583.
2. Whitley R, Gnann J: Viral encephalitis: familiar infections and emerging pathogens. Lancet 2002, 359:507–513.
3. Rischilas F, Wolff M, Delatoru F, Chaffaut F, De Broucker T, Chevret S, Lemon P, Cantor P, Rozenberg F: Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. Clin Infect Dis 2003, 35:254–260.
4. Lawrence DM, Major EO: HIV-1 and the brain: connections between HIV-1-associated dementia, neuropathology and neuroimmunology. Microbes Infect 2002, 4:301–308.
5. Domingues RB: Treatment of viral encephalitis. Cent Nerv Syst Agents Med Chem 2003, 5:95–62.
6. Ulley TF, Opden AAR IA, Gibb A, McGrath N, Anderson NE: The long-term neuropsychological outcome of herpes simplex encephalitis in a series of unselected survivors. Neuropsychiatry Neuropsychol Behav Neurol 1997, 10:180–189.
7. McGrath N, Anderson NE, Croxon MC, Powell KW: Herpes simplex encephalitis treated with acyclovir: diagnosis and long term outcome. J Neurol Neurosurg Psychiatry 1997, 61:321–326.
8. McArthur JC: HIV dementia: an evolving disease. J Neuroimmun 2004, 157:3–10.
9. Ito Y, Kimura H, Yabuta Y, Ando Y, Murakami T, Shiomi M, Morishima T: Chronic interleukin-1beta expression in mouse brain leads to leukocyte infiltration and neutrophil-independent blood brain barrier permeability without overt neurodegeneration. J Neurosci 2007, 27:9301–9309.
10. Allan SM, Tyrell PJ, Rothwell NJ: Interleukin-1 and neuronal injury. Nat Rev Immunol 2005, 5:629–640.
11. Spooner A, Kolmunos A, Laurens G, Clincer J, Keyser J, Haegeman G, Gerro S: Interleukin-6, a mental cytokine. Brain Res Rev 2011, 71:157–183.
12. Park KM, Bowers WJ: Tumor necrosis factor-alpha mediated signaling in neuronal homeostasis and dysfunction. Cell Signal 2010, 22:977–983.
13. McCloy MK, Tansey MG: TNF signaling inhibition in the CNS: implications for normal brain function and neurodegenerative disease. J Neuroinflammation 2008, 5:45.
14. Kapil P, Atkinson R, Ramakrishna C, Cua DJ, Bergmann CC, Stohlman SA: Interleukin-12 (IL-12), but not IL-23, deficiency ameliorates viral encephalitis without affecting viral control. J Virol 2009, 83:5978–5986.
15. Komatsu T, Banna M, Reiss CS: Interleukin-12 promotes recovery from viral encephalitis. Viral Immunol 1997, 10:25–47.
16. Camelo S, Lafage M, Lafon M: Absence of the p55 KD TNF-alpha receptor promotes survival in rabbies virus acute encephalitis. J Neurovirol 2000, 6:507–518.
17. Uboh S, Sukwattanapan C, Maneerat Y: Inducible nitric oxide synthase inhibition delays death of rabbies virus-infected mice. J Med Microbiol 2001, 50:38–42.
18. Lobigs M, Mullbacher A, Wang Y, Pasy M, Lee E: Role of type I and type II interferon responses in recovery from infection with an encephalitic flavivirus. J Gen Virol 2003, 84:567–572.
19. Gomez RM, Yed A, Schattner M, Berria MJ: Junin virus-induced astrocytosis is impaired by INOS inhibition. J Med Virol 2003, 69:145–149.
20. Tudor C, Griffin DE, Chou S, Bui N, Weiselsingh S: Inhibition of nitric oxide synthase increases mortality in Sindbis virus encephalitis. J Virol 1996, 70:3972–3977.
21. gets DR, Terry RL, Gets MT, Muller MA, Radford J, Rana S, Ashhurst T, Deffrennes C, Hofer M, Thomas S, Campbell IL, King NJ: Targeted blockade in lethal West Nile virus encephalitis shows a critical role for VLA-4-dependent recruitment of nitric oxide-producing macrophages. J Neuroinflammation 2012, 9:246.
22. Calabrese V, Mancuso C, Calvani M, Rizzelli E, Baldo BA, Stella AM: Nitric oxide in the central nervous system: neuroprotection versus neurotoxicity. Nat Rev Neurosci 2007, 8:766–775.
23. Wang P, Dai J, Bai F, Kong SY, Weng SJ, Montgomery RR, Madri JA, Fikrig E: Matrix metalloproteinase 9 facilitates West Nile virus entry into the brain. J Virol 2008, 82:1978–1985.
24. Yong WW: Metalloproteinases: mediators of patholgy and regeneration in the CNS. Nat Rev Neurosci 2005, 6:931–944.
25. Yong WW, Power C, Forsyth P, Edwards DR: Metalloproteinases in biology and pathology of the nervous system. Nat Rev Neurosci 2001, 2:502–511.
26. Greene JP, Lee LY, Prow N, Ngwab G, Griffin DE: Protection from fatal viral encephalomyelitis: AMPA receptor antagonists have a direct effect on the inflammatory response to infection. Proc Natl Acad Sci USA 2008, 105:3575–3580.
27. Nargi-Aizenman JL, Havert MB, Zhang M, Irani DN, Rothstein JD, Griffin DE: Glutamate receptor antagonists protect from virus-induced neural degeneration. Ann Neurol 2004, 55:541–549.
28. Brison E, Jacomy H, Desforges M, Taltot PJ: Glutamate excitotoxicity is involved in the induction of paralysis in mice after infection by a human coronavirus with a single point mutation in its spike protein. J Virol 2011, 85:12464–12473.
29. Hendriks JJ, Teunissen CE, de Vries HE, Dijkstra CD: Macrophages and neurodegeneration. Brain Res Brain Res Rev 2005, 48:185–195.
30. Akashi K, Traver D, Miyamoto T, Weissman IL: A clonogenic common myeloid progenitor that gives rise to all myeloid lineages. Nature 2000, 404:193–197.
31. Spangrude GJ, Heimfeld S, Weissman IL: Purification and characterization of mouse hematopoietic stem cells. Science 1988, 241:58–62.
32. Kondo M, Weissman IL, Akashi K: Identification of clonogenic common lymphoid progenitors in mouse bone marrow. Cell 1997, 91:661–672.
33. Reddy MA, Yang BS, Yue X, Barnett CJ, Ross IL, Sweet MJ, Hume DA, Ostrowski MC: Opposing actions of c-ets/PU.1 and c-myc protooncogene products in regulating the macrophage-specific promoters of the human and mouse colony-stimulating factor-1 receptor (c-fms) genes. J Exp Med 1994, 180:2309–2319.
44. Krysinska H, Hoogenkamp M, Ingram R, Wilson N, Tagoh H, Laslo P, Singh H, Bonifer C: A two-step, PU.1-dependent mechanism for developmentally regulated chemotax remodeling and transcription of the c-fms gene. Mol Cell Biol 2007, 27:878–887.

45. Dekter RP, Walsh JC, Singh H: PU.1 regulates both cytokine-dependent proliferation and differentiation of granulocyte/macrophage progenitors. EMBO J 1998, 17:4450–4458.

46. Tagoh H, Himes R, Clarke D, Leenen PJ, Riggs AD, Hume D, Bonifer C: Transcription factor complex formation and chemotaxis fine structure alterations at the murine c-fms (CSF-1 receptor) locus during maturation of myeloid precursor cells. Genes Dev 2002, 16:1721–1737.

47. Fogg DK, Sibon C, Miled C, Jung S, Aucouturier P, Littman DR, Cumano A, Geissmann F: A clonogenic bone marrow progenitor specific for macrophages and dendritic cells. Science 2006, 311:83–87.

48. Auffray C, Fogg D, Nanni-Mancinelli E, Senechal B, Trouillet C, Saederup N, Leemput J, Bigot K, Campisi L, Abitbol M, Molina T, Charo I, Hume DA, Cumano A, Lauvau G, Geissmann F: CX3CR1+ CD115+ CD145+ common macrophage/DC precursor and the role of CX3CR1 in their response to inflammation. J Exp Med 2009, 206:695–706.

49. Fogg D, Sibon C, Miled C, Jung S, Aucouturier P, Littman D, Cumano A, Geissmann F: A clonogenic bone marrow progenitor specific for macrophages and dendritic cells. Science 2006, 311:83–87.

50. Auffray C, Siewelke MH, Geissmann F: Blood monocytes: development, heterogeneity, and relationship with dendritic cells. Annu Rev Immunol 2009, 27:669–692.

51. Geissmann F, Jung S, Littman D: Blood monocytes consist of two principal subsets with distinct migratory properties. Immunity 2003, 19:71–82.

52. Strauss-Ayali A, Conrad SM, Mosser D: Monocyte subsets differentially employ CCR2, CCR5, and CX3CR1 to accumulate within atherosclerotic plaques. J Clin Invest 2010, 122:2381–2396.

53. Butovsky O, Siddiqui S, Gabriely G, Lanser AJ, Dake B, Murugaiyan G, Doykan CE, Wu PM, Gali RR, Iyer UK, Lawson R, Berry J, Kitchevsky AM, Cudkowicz ME, Weiner HL: Modulating inflammatory monocytes with a unique microRNA gene signature ameliorates murine ALS. J Clin Invest 2012, 122:3063–3087.

54. Christoph G, Hudson CA, Panos M, Gruber RC, Massa PT: Modulation of macrophage infiltration and inflammation activity by the phosphatase SHP-1 in virus-induced demyelinating disease. J Virol 2009, 83:522–539.

55. Tacke F, Randolph G: Migratory fate and differentiation of blood monocyte subsets. Immunology 2008, 124:669–681.

56. Vanl J, Lansdam L, Fogg D, Greenshein L, Gildor B, Margalit R, Kelchen V, Geissmann F, Jung S: Monocytes give rise to mucosal, but not splenic, conventional dendritic cells. J Exp Med 2007, 204:171–180.

57. Davison AM, King NJ: Accelerated dendritic cell differentiation from migrating Ly6C(lo) bone marrow monocytes in early dermal West Nile virus infection. J Immunol 2011, 186:2382–2396.

58. Lapp J, Leenen PJM: Additive roles for MCP-1 and MCP-3 in CCR2-mediated recruitment of monocyte/macrophage infiltration and adhesion to CS-1/fibronectin and VCAM-1. J Immunol 2007, 178:2382–2396.

59. Tacke F, Randolf G: Monocyte emigration from bone marrow during bacterial infection requires signals mediated by chemokine receptor CCR5. J Exp Med 2004, 200:1101–1112.

60. Saederup N, Cardona A, Croft K, Mizutani M, Cotleur A, Tsou C, Ransohoff R, Charo I: Selective chemokine receptor usage by central nervous system myeloid cells in CCR2-red fluorescent protein knock-in mice. PLoS One 2010, 5:e13693.

61. Nogawa T, Hirota S, Tachibana K, Takakura N, Nishikawa S, Kitamura Y, Yoshida N, Kikutani H, Kishimoto T: Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBF5/SDF-1, Nature 1996, 382:635–638.

62. Zar Y, Kottmann AH, Kuroda M, Tanouchi I, Littman DR: Function of the chemokine receptor CXCR4 in hematopoiesis and in cerebellar development. Nature 1998, 398:595–599.

63. Hidalgo A, Sanz-Rodriguez F, Rodriguez-Fernandez JL, Albella B, Baya C, Wright N, Cabanas C, Prosper F, Gutierrez-Ramos JC, Teixido J: Chemokine stromal cell-derived factor-1alpha modulates VLA-4 integrin-dependent adhesion to fibronectin and VCAM-1 on bone marrow hematopoietic progenitor cells. Exp Hematol 2001, 29:345–355.

64. Beri CC, Fulhavigge RC, Casasnovas JM, Ittui A, Springer TA: A highly efficacious lymphocyte chemattractant, stromal cell-derived factor 1 (SDF-1), J Exp Med 1996, 184:1101–1109.

65. Katayama Y, Hidalgo A, Peire A, Frenette PS: Integrin alpha4beta7 and its counterreceptor MadCAM-1 contribute to hematopoietic progenitor recruitment into bone marrow following transplantation. Blood 2004, 104:2020–2026.

66. Sanz-Rodriguez F, Hidalgo A, Teixido J: Chemokine stromal cell-derived factor-1alpha mediates VLA-4 integrin-mediated multiple myeloma cell adhesion to CS-1/fibronectin and VCAM-1. Blood 2001, 97:346–351.

67. Serbina N, Palmer E: Monocyte emigration from bone marrow during bacterial infection requires signals mediated by chemokine receptor CCR2. Nat Immunol 2006, 7:311–317.

68. Shi C, Velazquez P, Hohl T, Leier I, Dustin M, Palmer E: Monocyte trafficking to hepatic sites of bacterial infection is chemokine independent and directed by focal intercellular adhesion molecule-1 expression. J Immunol 2010, 184:6266–6274.

69. Jia T, Serbina NV, Brandl K, Zhong MX, Leiner IM, Charo IF, Palmer EG: Additive roles for MCP-1 and MCP-3 in CCR2-mediated recruitment of
inflammatory monocytes during Listeria monocytogenes infection.  
J Immunol. 2008, 180:6846–6853.

84. Engel D, Maurer J, Tittel A, Weisheit C, Caviar T, Schumak B, Limmer A, van Rooijen N, Trautwein C, Tacke F, Kruts C. CCR2 mediates homeostatic and inflammatory release of Gr(1) monocytes from the bone marrow, but is dispensable for bladder inflammation in bacterial urinary tract infection.  
J Immunol 2008, 181:5579–5586.

85. Tsou CL, Peters W, Si Y, Slaymaker S, Aslanian AM, Weisberg SP, Mack M, Charo IF: Critical roles for CCR2 and MCP-3 in monocyte mobilization from bone marrow and recruitment to inflammatory sites.  
J Clin Invest 2007, 117:902–909.

86. Wang Y, Cui L, Gonsiorek W, Min SH, Antilkumar G, Rosenblum S, Kozlokov J, Lundell D, Fine JS, Grant EP. CCR2 and CXCR4 regulate peripheral blood monocyte pharmacodynamics and link to efficacy in experimental autoimmune encephalomyelitis.  
J Immunol (Lond) 2009, 6:32.

87. Bovin N, Menarisa R, Gosselin D, Rivest S, Bovin G: Impact of deficiency in CCR2 and CX3CR1 receptors on monocytes trafficking in herpes simplex virus encephalitis.  
J Gen Virol 2012, 93:1294–1304.

88. Chen BP, Kuzel WA, Lane TE: Lack of CCR2 results in increased mortality and impaired leukocyte activation and trafficking following infection of the central nervous system with a neurotropic coronavirus.  
J Immunol 2001, 167:4585–4592.

89. Ruzek D, Salat J, Singh SK, Kopeczy J: Breakdown of the blood–brain barrier during tick-borne encephalitis in mice is not dependent on CD8+ T-cells.  
PloS One 2011, 6:e20472.

90. Glass WG, Lim JK, Cheleza R, Pleinve AG, Gan JL, Murphy PM. Chemokine receptor CCR5 promotes leukocyte trafficking to the brain and survival in West Nile virus infection.  
J Exp Med 2005, 202:1087–1098.

91. Glass WG, Liu MT, Kuzel WA, Lane TE: Reduced macrophage infiltration and demyelination in mice lacking the chemokine receptor CCR5 following infection with a neurotropic coronavirus.  
Virology 2001, 288:6–17.

92. Wilea MC, Mansur DS, Lacendera-Queiroz N, Rodrigues DH, Lima GK, Arantes RM, Kroon EG, Da Silva Campos MA, Teixeira MM, Teixeira AL. The chemokine CCL5 is essential for leukocyte recruitment in a model of severe Herpes simplex encephalitis.  
Ann N Y Acad Sci 2009, 1153:236–250.

93. Malik M, Chen YY, Kienzle MF, Tomkowicz BE, Crollman KG, Paznokz A: Monocyte migration and LFA-1-mediated attachment to brain microvascular endothelia is regulated by SDF-1 alpha through Lyn kinase.  
J Immunol 2008, 181:4632–4637.

94. McCandless EE, Wang Q, Woerner BM, Harper JM, Klein RS: CXCL12 limits inflammation by localizing mononuclear infiltrates to the perivascular space during experimental autoimmune encephalomyelitis.  
J Immunol 2006, 177:8053–8064.

95. Peng H, Erdmann N, Whitney N, Dou H, Garanta S, Gendelman HE, Ghosepanda A, Zhou J. HIV-1-infected and/or immune activated macrophages regulate astrocyte SDF-1 production through IL-1beta.  
Glia 2006, 54:619–629.

96. McCandless EE, Zhang B, Diamond MS, Klein RS: CXCR4 antagonism increases T cell trafficking in the central nervous system and improves survival from West Nile virus encephalitis.  
Proc Natl Acad Sci USA 2008, 105:11270–11275.

97. D’Mello C, Le T, Swain M. Monocyte migration and LFA-1-mediated attachment to brain microvascular endothelia is regulated by SDF-1 alpha through Lyn kinase.  
J Immunol 2008, 181:4632–4637.

98. D’Mello C, Le T, Swain M. Monocyte migration and LFA-1-mediated attachment to brain microvascular endothelia is regulated by SDF-1 alpha through Lyn kinase.  
J Immunol 2008, 181:4632–4637.

99. D’Mello C, Le T, Swain M. Monocyte migration and LFA-1-mediated attachment to brain microvascular endothelia is regulated by SDF-1 alpha through Lyn kinase.  
J Immunol 2008, 181:4632–4637.

100. D’Mello C, Le T, Swain M. Monocyte migration and LFA-1-mediated attachment to brain microvascular endothelia is regulated by SDF-1 alpha through Lyn kinase.  
J Immunol 2008, 181:4632–4637.

101. D’Mello C, Le T, Swain M. Monocyte migration and LFA-1-mediated attachment to brain microvascular endothelia is regulated by SDF-1 alpha through Lyn kinase.  
J Immunol 2008, 181:4632–4637.

102. D’Mello C, Le T, Swain M. Monocyte migration and LFA-1-mediated attachment to brain microvascular endothelia is regulated by SDF-1 alpha through Lyn kinase.  
J Immunol 2008, 181:4632–4637.

103. D’Mello C, Le T, Swain M. Monocyte migration and LFA-1-mediated attachment to brain microvascular endothelia is regulated by SDF-1 alpha through Lyn kinase.  
J Immunol 2008, 181:4632–4637.

104. D’Mello C, Le T, Swain M. Monocyte migration and LFA-1-mediated attachment to brain microvascular endothelia is regulated by SDF-1 alpha through Lyn kinase.  
J Immunol 2008, 181:4632–4637.

105. D’Mello C, Le T, Swain M. Monocyte migration and LFA-1-mediated attachment to brain microvascular endothelia is regulated by SDF-1 alpha through Lyn kinase.  
J Immunol 2008, 181:4632–4637.
124. Takahashi K, Naito M, Takeya M: Development and heterogeneity of macrophages and their related cells through their differentiation pathways. Pathol Int 1996, 46:473–485.
125. Gnhoud F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, Mehler MF, Conway SJ, Ng LG, Stanley ER, Samokhvalov IM, Menad M: Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science 2010, 330:841–845.
126. Sedgwick JD, Schwender S, Imlich H, Dorries R, Butcher GW, ter Meulen V: Isolation and direct characterization of resident microglial cells from the normal and inflamed central nervous system. Proc Natl Acad Sci USA 1991, 88:7438–7442.
127. Mack CL, Vanderlugt-Castaneda CL, Neville KL, Miller SD: Microglia are activated to become competent antigen presenting and effectors cells in the inflammatory environment of the Th1-Th2 model of multiple sclerosis. J Neuroimmunol 2003, 144:68–79.
128. Simard AR, Soulet D, Gowing G, Julien JP, Rivest S: Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer’s disease. Neuroen 2006, 4:489–502.
129. Malm TM, Kostinaho M, Parepalo M, Vatanen T, Ooka A, Karlsson S, Kokovay E, Cunningham LA: Bone marrow-derived microglia contribute to the recruitment of monocytes in early and rapid engraftment of bone marrow-derived microglia in scrapie. Proc Natl Acad Sci USA 2005, 103:2540–2545.
130. Heppner FL, Greter M, Marino D, Falsig J, Raivich G, Hovelmeyer N, Waisman A, Simard AR, Soulet D, Gowing G, Julien JP, Rivest S: Bone-marrow-derived cells contribute to the recruitment of microglial cells in response to beta-amyloid deposition in APP/PS1 double transgenic Alzheimer mice. Neurobiol Dis 2005, 18:134–142.
131. El Khoury J, Toft M, Hickman SE, Means TK, Terada K, Geula C, Luster AD: Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer’s disease. J Neurosci 2004, 24:4383–4391.
132. Serbina NV, Salazar-Mather TP, Biron CA, Kuziel WA, Pamer EG: Bone marrow-derived microglia contribute to the pathology following meningitis in mice. J Exp Med 2008, 204:2394–2403.
133. Drevets DA, Dillon MJ, Schwang J, Van Rooijen N, Enchrjen J, Sunderkotter C, Leenen PJ: The Ly-6C(high) monocyte subpopulation transports Listeria monocytogenes into the brain during systemic infection of mice. J Immunol 2004, 172:4418–4424.
134. Serbina NV, Salazar-Mather TP, Biron CA, Kuziel WA, Pamer EG: Bone marrow-derived monocytes contribute to the pathogenesis of viral encephalitis. J Virol 2010, 84:2891–2899.
135. Charlier C, Nielsen K, Daou S, Brigitte M, Chretien F, Dromer F: Evidence of a role for monocytes in dissemination and brain invasion by Cryptococcus neoformans. Infect Immun 2009, 77:1120–127.
136. Charlier C, Nielsen K, Daou S, Brigitte M, Chretien F, Dromer F: Evidence of a role for monocytes in dissemination and brain invasion by Cryptococcus neoformans. Infect Immun 2009, 77:1120–127.
137. Serbina NV, Salazar-Mather TP, Biron CA, Kuziel WA, Pamer EG: Bone marrow-derived microglia mediate conventional dendritic cell recruitment and the formation of bronchovascular mononuclear cell infiltrates in the lungs of mice infected with Cryptococcus neoformans. J Immunol 2008, 181:610–620.
138. Dunay JR, Fuchs A, Sibley LD: Inflammatory macrophages but not neutrophils are necessary to control infection with Toxoplasma gondii in mice. Infect Immun 2010, 78:1546–1550.
139. Serbina NV, Salazar-Mather TP, Biron CA, Kuziel WA, Parner EG: TNF/iNOS-producing dendritic cells mediate innate immune defense against bacterial infection. Immunity 2003, 19:59–70.
140. Osterholzer JJ, Curtis JL, Polak T, Arnett T, Chen GH, McDonald R, Huffnagle GB, Toews GB: CCR2 mediates conventional dendritic cell recruitment and the formation of bronchovascular mononuclear cell infiltrates in the lungs of mice infected with Cryptococcus neoformans. J Immunol 2008, 181:610–620.
141. Scuttoro AM, Kaise WA, Toews GB, Huffnagle GB: CCR2 expression determines T1 versus T2 polarization during pulmonary Cryptococcus neoformans infection. J Immunol 2000, 164:2011–2027.
142. Ye Z, Uttenhoogard AM, Cohen DA, Kaplan AM, Ambati J, Strailey SC: Differential CCR2(+)/Gr1(+) cells control growth of the Yersinia pestis DeltaTayloyM mutant in liver and spleen during systemic plague. Infect Immun 2011, 79:674–687.
143. Tijima N, Mattei LM, Iwasaki A: Recruited inflammatory monocytes stimulate antiviral Th1 immunity in infected tissue. Proc Natl Acad Sci USA 2011, 108:284–289.
144. Sheahan T, Morrison TE, Funkhouser W, Uematsu S, Akira S, Baric RS, Heise MT: MyD88 is required for protection from lethal infection with a mouse-adapted SARS-CoV. PLoS Pathog 2008, 4:e1000240.
145. Martini C, Menia I, Bricchi M: Thleiler’s virus infection of primary cultures of bone marrow-derived monocytes/macrophages. J Virol 2002, 76:12823–12833.
146. Lipton HL, Twaddle G, Jelachich ML: The predominant virus antigen burden is present in macrophages in Thleiler’s murine encephalomyelitis virus-induced demyelinating disease. J Virol 1995, 69:2525–2533.
147. Clatci RH, Miller SD, Metzner R, Dalt CMC, Lipton HL: Monocytes/macrophages isolated from the mouse central nervous system contain infectious Thleiler’s murine encephalomyelitis virus (TMEV). Virology 1990, 176:244–254.
148. Blakemore WF, Welsh CJ, Tonks P, Nash AA: Observations on demyelinating lesions induced by Thleiler’s virus in CBA mice. Acta Neuropathol 1988, 76:381–389.
149. El Khoury J, Toft M, Hickman SE, Means TK, Terada K, Geula C, Luster AD: Ccr2 deficiency impairs conventional dendritic cell recruitment and blood-borne cell extravasation and migration. J Immunol 2003, 171:1146–1152.
150. Ajami B, Bennett JL, Krieger C, McNagny KM, Rossi FM: Infiltrating monocytes trigger EAE progression, but do not contribute to the resident microglia pool. Nat Neurosci 2011, 14:1142–1149.
151. Scuttoro AM, Kaise WA, Toews GB, Huffnagle GB: Recruit inflammatory monocytes and the microglia contribute to the pathology following meningitis in mice. Brain 2006, 129:2394–2403.
152. Krause T, Ermini F, Bondolfi L, Krenger W, Burbach GJ, Deller T: Circulating monocytes engraft in the brain, differentiate into microglia and contribute to the pathology following meningitis in mice. Brain 2006, 129:2394–2403.
153. Mack CL, Vanderlugt-Castaneda CL, Neville KL, Miller SD: Microglia are activated to become competent antigen presenting and effectors cells in the inflammatory environment of the Th1-Th2 model of multiple sclerosis. J Neuroimmunol 2003, 144:68–79.
154. Simard AR, Soulet D, Gowing G, Julien JP, Rivest S: Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer’s disease. Neuroen 2006, 4:489–502.
155. Malm TM, Kostinaho M, Parepalo M, Vatanen T, Ooka A, Karlsson S, Kokovay E, Cunningham LA: Bone marrow-derived microglia contribute to the recruitment of monocytes in early and rapid engraftment of bone marrow-derived microglia in scrapie. Proc Natl Acad Sci USA 2005, 103:2540–2545.
156. El Khoury J, Toft M, Hickman SE, Means TK, Terada K, Geula C, Luster AD: Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer’s disease. J Neurosci 2004, 24:4383–4391.
157. Serbina NV, Salazar-Mather TP, Biron CA, Kuziel WA, Pamer EG: Bone marrow-derived monocytes contribute to the pathogenesis of viral encephalitis. J Virol 2010, 84:2394–2403.
158. Serbina NV, Salazar-Mather TP, Biron CA, Kuziel WA, Pamer EG: Bone marrow-derived microglia mediate conventional dendritic cell recruitment and the formation of bronchovascular mononuclear cell infiltrates in the lungs of mice infected with Cryptococcus neoformans. J Immunol 2008, 181:610–620.
159. Scuttoro AM, Kaise WA, Toews GB, Huffnagle GB: CCR2 expression determines T1 versus T2 polarization during pulmonary Cryptococcus neoformans infection. J Immunol 2000, 164:2011–2027.

[Terry et al. Journal of Neuroinflammation 2012, 9:270](http://www.jneuroinflammation.com/content/9/1/270)