Published in final edited form as:

Semin Pediatr Neurol. 2017 August ; 24(3): 145–151. doi:10.1016/j.spen.2017.08.004.

A Neuroprimer: Principles of CNS Immunity

Gregory P. Owens, Ph.D.¹

¹Department of Neurology, University of Colorado Denver School of Medicine, Aurora, Colorado, 80045, USA

Abstract

Despite longstanding perceptions, robust innate and adaptive immune responses occur within the central nervous system (CNS) in response to infection and tissue damage. Although necessary to control infection, immune responses can lead to severe CNS pathology in the context of both viral infection and autoimmunity. Research into how the central nervous and immune systems communicate has accelerated over the past 20 years leading to a better understanding of pathways controlling immune activation and neuroinflammation that have guided the approval of new disease-modifying therapies to treat CNS immunopathology, particularly the inflammatory demyelinating disease multiple sclerosis. This article provides an introduction into the basic principles underlying immune responses within the CNS that developed from experimental animal models of both neurotropic virus infection and autoimmune T cell mediated CNS demyelination.

Background

Cells comprising the immune system are derived from pluripotent hematopoietic stem cells in the bone marrow that give rise to lymphoid and myeloid progenitor cells (Figure 1).¹ Lymphoid progenitors are the precursors to T- and B-lymphocytes, cells that form the basis of antigen-specific adaptive immunity. They also give rise to natural killer cells, a cytotoxic cell that is important in innate immune responses against tumor and virally infected cells. Myeloid progenitors give rise to most cells of the innate immune system. Granulocyte progenitors can differentiate into neutrophils, eosinophils and basophils whereas circulating monocytes routinely differentiate into macrophages upon tissue migration. Most dendritic cells also evolve along the myeloid pathway and like neutrophils and macrophages are phagocytic. Dendritic cells are specialized by their ability to take up antigen, process it, and present it for recognition by T lymphocytes. Within the CNS, myeloid derived macrophages and microglia are constantly surveying and responding to changes in their microenvironment. Inflammation leading to changes in the blood-brain barrier allows both

Correspondence to: Gregory P Owens, Ph.D., Department of Neurology, Mail Stop B182, RCII, 12,700 E 19th Avenue, University of Colorado Denver School of Medicine, Anschutz Medical Campus, Aurora, CO, 80045, USA. Telephone: 303-724-4314; greg.owens@ucdenver.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures

The author declares no commercial, proprietary or financial conflicts of interest.

adaptive and innate peripheral immune cells to enter into the CNS as occurs in response to infection, but also in the case of destructive autoimmune disorders. Herein, principles underlying immune surveillance and the initiation of inflammatory innate and adaptive immune responses within the CNS will be discussed. Outstanding reviews that contributed to the preparation of this chapter are cited for readers interested in a more thorough discussion of CNS immune privilege,^{2, 3} immune surveillance,⁴⁻⁸ CNS T cell responses⁹ and innate immunity.¹⁰⁻¹⁴

The CNS as a site of Immune privilege

Historically, the notion of the brain as an organ of 'immune-privilege' developed experimentally during the early to mid 20th century and was founded on the survival and/or growth of foreign tissue and tumors transplanted into the brain parenchyma, but not into peripheral sites. In 1921, Shirai demonstrated the growth of rat sarcoma transplanted into mouse brain that was destroyed when placed subcutaneously or intramuscularly.¹⁵ The survival of tumors implanted into the brain, however, was not absolute. Co-transplantation of autologous spleen or transplantation close to brain ventricles blocked tumor growth,¹⁶ indicating that the brain parenchyma was somehow detached from systemic immune surveillance. In a subsequent set of important studies, Medewar demonstrated that prior peripheral implantation of foreign skin grafts now rendered brain grafts susceptible to immune destruction.¹⁷ This informed the idea that once primed peripherally, immune cells were capable of migrating and entering into the brain parenchyma, but the brain itself could not elicit immune responses. Confirming that the afferent (immune activation within lymph nodes), but not efferent arm, was limiting immune activation within the brain, Matyszak *et al* injected mycobacterium antigen (BCG) into the brain parenchyma and allowed the blood-brain-barrier to reform. Subsequent peripheral BCG vaccination resulted in a delayed hypersensitivity inflammatory reaction within the brain parenchyma that was accompanied by demyelination and axonal damage.¹⁸

Immune surveillance of the CNS

In peripheral tissues, immune surveillance is achieved through the lymphatic system, which drains large macromolecules through lymphatic vessels or via emigration of professional antigen-presenting dendritic cells into the lymph nodes where adaptive T and B cell responses are initiated. Under normal physiologic conditions, the brain parenchyma is protected from circulating immune cells by the blood-brain barrier. Consequently, lymphocytes are uncommon and immune activation is limited by the absence of dendritic cells and sparse MHC class II expression. Within this environment, adaptive T and B cell immune responses are dependent on antigen from the neural parenchyma reaching the deep cervical lymph nodes where antigen-presentation and T cell priming can occur.¹⁹⁻²¹

Pathways for the delivery of brain antigens and molecules to the deep cervical lymph nodes are compartmentalized within the meninges. Although historically thought to lack a conventional afferent lymphatic system, studies have recently identified structures resembling lymphatic vessels within the dura of the CNS that drain from the subarachnoid space into the deep cervical lymph nodes.^{22, 23} These structures express lineage markers of

true lymphatic endothelial cells and are associated with T cells, B cells and dendritic cells implicating meningeal lymphatic vessels as conduits of immune trafficking and surveillance.³ A second pathway is determined by the unique CNS compartmental anatomy and flow of extracellular fluid that transfers soluble CNS antigens from CSF and interstitial brain fluid to the nasal mucosa where afferent lymphatics also drain into the deep cervical lymph nodes.^{5, 24} Accordingly, both pathways indicate that brain-restricted antigens must first reach the CSF for delivery to cervical lymphoid tissue. CSF, which fills the subarachnoid space between the pia and arachnoid membranes, is generated primarily from epithelial cells lining the choroid plexus within brain ventricles, and secondarily from interstitial fluid from the brain parenchyma. CSF flows through the ventricles in a rostral to caudal direction and drains into the general circulation through arachnoid villi, which are extensions of the arachnoid membrane that extend into the cerebral venous sinuses. It is along these sinuses that meningeal lymphatic vessels are found. The free mixing of CSF with brain interstitial fluid likely occurs along unique paravascular spaces between arteries penetrating the brain and the leptomeningeal sheath (Virchow-Robin spaces). This process of waste clearance from the brain parenchyma is partially dependent on AQP4 expression in astrocytes and has been termed the “glymphatic” system.^{25, 26} In humans, the draining of soluble amyloid- β peptides from grey matter towards the surface of the brain has been followed along this pathway.^{5, 24}

Immune Sentinels of the CNS

Different cells survey the meninges and brain parenchyma for signs of infection and tissue damage. T cells, macrophages and dendritic cells routinely enter into and occupy the CSF and meninges. T cells are the predominant immune cell type and account for > 80% of cells in normal CSF. B cells are typically rare (> than 1 % of CSF lymphocytes) with the T to B cell ratio markedly reduced relative to peripheral blood. The predominant phenotype of CSF T cells is that of activated central memory CD4⁺ T helper cells, which outnumber CD8⁺ T cells about 3.5 to 1. Their most common route of entry into CSF is via transmigration across the choroid plexus.^{27, 28} Myeloid-derived MHC class II macrophages are found lining perivascular spaces and within the SAS and choroid plexus,¹² and are continuously replenished by differentiating blood monocytes. Small numbers of short-lived dendritic cells are found in the CSF and choroid plexus.^{29, 30}

Microglial cells, which are derived from migrating myeloid progenitors, occupy and patrol the brain parenchyma. They are unique in that they are both a CNS glial cell and monocytic phagocyte.^{4, 12} Microglia are positioned so that each cell occupies its own unique niche. Cell processes are in constant movement sampling their microenvironment for pathogens and signs of tissue damage. Microglia are self-renewing and respond to stimulation with distinct changes in morphology and gene expression. They are the primary innate immune cells within the brain parenchyma and have been shown to function as competent antigen-presenting cells to both CD4 and CD8 T cells in models of CNS infection,^{31, 32} Whether they truly function as potent and primary antigen-presenting cells in vivo is still being debated.⁵

Sensing danger: PAMPS, DAMPS and the inflammasome as facilitators of CNS inflammation

Cells of the innate immune system are not only the first line of responders to infection, they are critical to instructing whether or not and what type of adaptive immune response will follow.³³ Innate immune cells are capable of sensing “danger” in their microenvironment not only from microbes but also from host tissue damage resulting in a cascade of cytokine signaling events that leads to inflammation and possible adaptive immune responses. Peripheral cells capable of transmitting innate immune signals include dendritic cells, macrophages, monocytes, neutrophils, epithelial cells and cells of the adaptive immune system. Infectious agents are sensed both through recognition of evolutionarily conserved biochemical motifs termed pattern-associated molecular patterns or PAMPs and through release of host-derived signals termed danger-associated molecular patterns of cellular damage (DAMPs).

Examples of PAMPs include lipopolysaccharides (LPS) found on the membranes of gram-negative bacteria, bacterial peptidoglycans, bacterial flagellins, lipoteichoic acid from gram-positive bacteria, and modified nucleic acids associated with viral and bacterial infection including double-stranded RNA and unmethylated CpG motifs. These invariant chemical structures are recognized by sets of germ-line encoded receptors called pattern-recognition receptors (PRRs) that can be found on the cell surface, within endosomal compartments and in cytoplasm. The best studied of PRRs are the family of Toll-like receptors (TLRs), which are responsible for sensing pathogens outside the cell, within endosomal compartments and in lysosomes.³⁴ Once innate cells are stimulated through TLRs, intracellular signaling cascades lead to NF- κ B activation resulting in increased transcription of pro-inflammatory cytokines and Type 1 interferons determined by both the TLR and cell type involved.

The second class of cytoplasmic PRRs recognizing host-derived danger-associated molecular patterns (DAMPs) can be activated by infection, autoimmunity and in response to sterile injury. Activation of DAMP receptors leads to their assembly into cytosolic oligomeric protein complexes called the “inflammasome”. The inflammasome serves as a platform for the activation of caspase-1, that further promotes the proteolytic processing and secretion of master pro-inflammatory cytokines such as IL-1 β and IL-18.^{13, 35, 36} Assembly of the inflammasome often follows a prior priming event (e.g TLR activation) of the NF- κ B pathway that together enhance pro-inflammatory IL-1 β cytokine expression and secretion. PRR families in humans that are components of the inflammasome complex include both NOD-like (NLRs) and AIM-like receptors. Defining the diverse set of DAMPS, their PRRs and pathways leading to inflammasome activation are topics of immense interest in inflammatory processes; some known DAMPS include heat shock proteins, S100 protein, HMGB1 complex, ds DNA, extracellular ATP, reactive oxygen species and ion flux. Detailed molecular descriptions of the receptor families, their molecular domains and adapter proteins, and assembly into inflammasomes can be found in the following excellent reviews.^{10, 13, 14, 34, 35}

Classic innate immune cells of the periphery are absent within the brain under normal conditions. Microglia are the primary innate immune cells within the neural parenchyma,

whereas macrophages sample the choroid plexus, meninges and perivascular spaces. Microglia respond vigorously to PRR signaling following infection, stroke, neurodegeneration, and trauma with marked changes in morphology, enhanced respiratory metabolism and release of cytokines, chemokines and reactive oxygen species that together serve as signals for the recruitment of both peripheral inflammatory cells (dendritic cells, macrophages & neutrophils) and adaptive immune cells into the CNS further amplifying the inflammatory response.⁴

The NLR receptors NLRC4, NLRP1 and NLRP3 are activated within the CNS.¹⁴ The NLRC4 inflammasome senses bacterial flagellin and is critical for innate immune response to CNS infection of macrophages and microglia including *Legionella pneumophila* and *Listeria monocytogenes*, which can lead to encephalitis or meningitis.^{37, 38} Innate immune microglial responses are not necessarily beneficial as neuroinflammation has a likely deleterious effect in human autoimmune and neurodegenerative diseases.^{11, 39} CNS cells are particularly sensitive to IL-1 β and IL-18 signaling. Astrocytes express IL-1 signaling receptor and proliferate (astrogliosis) and release neurotoxic chemicals in response to stimulation.⁴⁰ Similarly, caspase-1 activation appears to be a mediator of neuronal death following hypoxia and ischemic stroke.⁴¹ NLRP3 is the most extensively investigated inflammasome and can be activated by a wide array of viral, fungal, and bacterial components as well as host DAMPs including extracellular ATP, uric acid crystals, and amyloid-B.¹⁴ NLRP3 caspase-1 activation promotes disease in animal models of CNS demyelination,⁴² and has been associated with neurodegenerative processes in Parkinson's disease, Alzheimer's disease,⁴³ prion disease and ALS.⁴⁴ During CNS infections, the NLRP3 inflammasome has been shown to promote pathology in *S pneumoniae* meningitis,⁴⁵ and to be protective in West Nile virus encephalitis.⁴⁶

T and B cell responses in the CNS

Adaptive T and B cell responses are necessary to control or eliminate CNS infections, but come with the risk of bystander immune-mediated damage, particularly within the brain parenchyma. Adaptive immune responses against self-antigens are now understood or suspected to underlie multiple human neurologic diseases including multiple sclerosis, neuromyelitis optica, acute disseminated encephalomyelitis and paraneoplastic disorders of the CNS. A wealth of knowledge regarding CNS T cell responses has been gained from animal models of CNS infection and autoimmune CNS spinal cord demyelination.^{5, 9} Experimental allergic encephalomyelitis (EAE) is induced by immunization with myelin proteins or peptides in the presence of Freund's adjuvant and pertussis toxin, and has been adopted in multiple variations, different genetic strains and host species to study mechanisms underlying T cell mediated neuroinflammation. Immunization induces expansion of antigen-specific T cells that can be recovered from peripheral lymphoid tissue and cultured in the presence of cytokines to program helper CD4⁺ T cells into distinct phenotypes, Th1 and Th17. Inoculation of programmed T cells into naïve animals produces T cell infiltration into the CNS, macrophage recruitment and demyelination. Th1 cells are defined by the production of pro-inflammatory cytokines, particularly IFN- γ , and are typically important for the clearance of intracellular parasites.⁴⁷ Encephalitogenic Th17

cells, which secrete IL-17A, IL-21 and IL-22, initiate immunity against fungi and some bacteria. In EAE, Th17 cells produce a severe CNS immunopathology.⁹

Antigen-specific T cell infiltration of the CNS usually follows a well-choreographed sequence of events. Step 1 requires priming of autoreactive or virus-specific T cells in peripheral lymph nodes by activated antigen-presenting cells. Only under conditions of severe inflammation has activation of naïve T cells within the CNS been demonstrated.⁴⁸ Following intracerebral injection of neurotropic mouse hepatitis virus, antigen-specific CD8⁺ T cells are first observed in draining cervical lymph nodes supporting the view that this is the initial site of antigen-presentation and T cell priming for CNS-specific infections.^{49, 50} Recent studies in EAE indicate that the commensal gut microbiota may have a critical impact on the peripheral programming and specificity of CNS autoreactive T cell responses and have spurred investigations into the gut microbiome and its relationship to human CNS autoimmunity.^{51–53}

Efferent pathways for the migration of leukocytes into the CNS typically occur through fenestrated endothelium and epithelial cells of the choroid plexus or across leptomeningeal vessels.⁶ In step 2, virus and autoimmune effector T cells must be re-stimulated once reaching the CNS. This likely occurs within the ventricles, SAS and perivascular spaces where T cells encounter resident myeloid antigen-presenting cells.^{27, 54} Following reactivation, T cells secrete cytokines according to their programmed phenotypes and cross into the brain parenchyma to execute their function. This process of T cell extravasation from vessels, re-stimulation within the subarachnoid space and invasion of the brain parenchyma has been beautifully visualized using two-photon microscopy in the EAE model.⁵⁵ Importantly, investigations of acute viral meningitis using lymphocytic choriomeningitis virus, also demonstrate the reactivation of virus-specific cytotoxic CD8⁺ T cells within the subarachnoid space leading to the subsequent infiltration of monocytes and neutrophils that are the cause of fatal vascular injury.⁵⁶

In 1942, Erwin Kabat described increased production of CSF IgG as a clinical feature of patients with neurosyphilis and the CNS demyelinating disease multiple sclerosis.⁵⁷ Electrophoretic techniques devised to resolve increased CSF IgG by isoelectric focusing revealed an oligoclonal banding (OCBs) pattern in > 90 % of MS patients as opposed to the heterogeneous distribution of polyclonal Ig observed in normal CSF that became part of the diagnostic criteria for MS and intrathecal IgG synthesis.⁵⁸ Intrathecal synthesis of oligoclonal IgG was not unique to MS and OCBs were found to be antibodies against the causative agent in many CNS infectious diseases including neurosyphilis, subacute sclerosing panencephalitis (SSPE) and other viral encephalitides, as well as in cryptococcal meningitis and neuroborreliosis.^{59–63}

B cells are infrequent in CSF under normal physiologic conditions. Concomitant with intrathecal IgG synthesis and presence of CSF OGBs, there is a recruitment and expansion of B cells within the CNS of autoimmune and infectious disorders that can be recovered and analyzed. The phenotype of B cells recovered from CSF of patients with multiple sclerosis, CNS infections and paraneoplastic disease reveal significant enrichment of class-switched memory (CD19⁺CD27⁺) and antibody-secreting B cells.^{64–69} B cells expressing surface

markers consistent with a phenotype of short-lived plasma blasts (CD19, CD27^{high}, CD38^{high}, CD138, HLA-DR^{high}) represent the primary antibody-secreting cell recovered from MS and SSPE CSF.^{70, 71} As discussed for T cell immunity, there is no evidence for activation of naïve B cells within the CNS compartment and stimulation likely occurs within B cell follicles of cervical lymph nodes along typical B cell maturation pathways (Figure 2). Experimentally, the intracerebral injection of T cell-dependent antigen into sensitized animals with an intact blood brain barrier elicits antigen-specific antibody responses within the CNS in which cervical lymph nodes play an important role. Responses are characterized by a measurable increase in the CSF antibody index, intrathecal synthesis of oligoclonal IgG, and CD4⁺ T cell and antigen-specific plasma cell infiltration to the site of antigen deposition.⁷²

Intrathecal B cell responses likely require the retention of target antigen within the CNS, although the requirements and locales of B cell stimulation and differentiation are not as well understood, but also presumably occur within the meninges and perivascular spaces. Studies of B cell trafficking in multiple sclerosis reveal that cervical lymph nodes are the likely site for the maturation of CSF B cell clones.⁷³ Whether migratory plasma blasts or activated memory B cells from the periphery re-enter a T cell dependent germinal center-like reaction within the CNS before undergoing clonal expansion, additional somatic hypermutation and terminal differentiation is intriguing but unknown. It is fascinating that enrichment of B cell subsets normally associated with germinal center reactions (GC) in secondary lymphoid follicles are present in MS CSF including those of proliferating germinal center centroblasts and centrocytes.⁶⁶ Lymphoid-like structures resembling ectopic germinal centers have been detected in the meninges of MS patients with secondary progressive disease and are associated with subpial demyelination and neuronal loss.^{74–76} Ectopic follicles contain proliferating B cells, T cells and a network of reticular cells expressing markers for follicular dendritic cells and the B cell chemokine CXCL13. CD138⁺ antibody-secreting cells can be found adjacent to these follicles and within demyelinated brain parenchyma, suggesting that ectopic follicles can sustain local B cell differentiation within the CNS. Whether these structures are unique to a disease with chronic B cell infiltration such as MS or represent a structure sustaining B cell differentiation in other human CNS inflammatory disease is unknown. Following the resolution of CNS infections, intrathecal IgG synthesis and OCBs eventually dissipate.⁷⁰

Acknowledgments

Funding

Supported by research grant NS072141 from NINDS.

References

1. Janeway, CA., Jr, Travers, P., Walport, M., Schlomchik, MG. *Immuno Biology*. 6. New York: Garland Science Publishing; 2005.
2. Galea I, Bechmann I, Perry VH. What is immune privilege (not)? *Trends Immunol*. 2007; 28:12–8. [PubMed: 17129764]
3. Louveau A, Harris TH, Kipnis J. Revisiting the Mechanisms of CNS Immune Privilege. *Trends Immunol*. 2015; 36:569–77. [PubMed: 26431936]

4. Ousman SS, Kubes P. Immune surveillance in the central nervous system. *Nat Neurosci.* 2012; 15:1096–101. [PubMed: 22837040]
5. Ransohoff RM, Engelhardt B. The anatomical and cellular basis of immune surveillance in the central nervous system. *Nat Rev Immunol.* 2012; 12:623–35. [PubMed: 22903150]
6. Ransohoff RM, Kivisakk P, Kidd G. Three or more routes for leukocyte migration into the central nervous system. *Nat Rev Immunol.* 2003; 3:569–81. [PubMed: 12876559]
7. Russo MV, McGavern DB. Immune Surveillance of the CNS following Infection and Injury. *Trends Immunol.* 2015; 36:637–50. [PubMed: 26431941]
8. Shechter R, London A, Schwartz M. Orchestrated leukocyte recruitment to immune-privileged sites: absolute barriers versus educational gates. *Nat Rev Immunol.* 2013; 13:206–18. [PubMed: 23435332]
9. Korn T, Kallies A. T cell responses in the central nervous system. *Nat Rev Immunol.* 2017; 17:179–194. [PubMed: 28138136]
10. Martinon F, Tschopp J. Inflammatory caspases: linking an intracellular innate immune system to autoinflammatory diseases. *Cell.* 2004; 117:561–74. [PubMed: 15163405]
11. Ransohoff RM, Brown MA. Innate immunity in the central nervous system. *J Clin Invest.* 2012; 122:1164–71. [PubMed: 22466658]
12. Ransohoff RM, Cardona AE. The myeloid cells of the central nervous system parenchyma. *Nature.* 2010; 468:253–62. [PubMed: 21068834]
13. Schroder K, Tschopp J. The inflammasomes. *Cell.* 2010; 140:821–32. [PubMed: 20303873]
14. Walsh JG, Muruve DA, Power C. Inflammasomes in the CNS. *Nat Rev Neurosci.* 2014; 15:84–97. [PubMed: 24399084]
15. Shirai Y. On the transplantation of the rat sarcoma in adult heterogeneous animals. *Japan Med. World.* 1921; 1:14–15.
16. Murphy JB, Sturm E. Conditions Determining the Transplantability of Tissues in the Brain. *J Exp Med.* 1923; 38:183–97. [PubMed: 19868782]
17. Medewar PB. Immunity to homologous grafted skin. *Brit. J. Exp. Path.* 1948; 29:58–69. [PubMed: 18865105]
18. Matyszak MK, Perry VH. Demyelination in the central nervous system following a delayed-type hypersensitivity response to bacillus Calmette-Guerin. *Neuroscience.* 1995; 64:967–77. [PubMed: 7753389]
19. Cserr HF, Knopf PM. Cervical lymphatics, the blood-brain barrier and the immunoreactivity of the brain: a new view. *Immunol Today.* 1992; 13:507–12. [PubMed: 1463583]
20. Harling-Berg CJ, Park TJ, Knopf PM. Role of the cervical lymphatics in the Th2-type hierarchy of CNS immune regulation. *J Neuroimmunol.* 1999; 101:111–27. [PubMed: 10580795]
21. Traka M, Podojil JR, McCarthy DP, et al. Oligodendrocyte death results in immune-mediated CNS demyelination. *Nat Neurosci.* 2016; 19:65–74. [PubMed: 26656646]
22. Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature.* 2015; 523:337–41. [PubMed: 26030524]
23. Aspelund A, Antila S, Proulx ST, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med.* 2015; 212:991–9. [PubMed: 26077718]
24. Weller RO, Djuanda E, Yow HY, Carare RO. Lymphatic drainage of the brain and the pathophysiology of neurological disease. *Acta Neuropathol.* 2009; 117:1–14. [PubMed: 19002474]
25. Iliff JJ, Wang M, Zeppenfeld DM, et al. Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain. *J Neurosci.* 2013; 33:18190–9. [PubMed: 24227727]
26. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science.* 2013; 342:373–7. [PubMed: 24136970]
27. Kivisakk P, Mahad DJ, Callahan MK, et al. Human cerebrospinal fluid central memory CD4+ T cells: evidence for trafficking through choroid plexus and meninges via P-selectin. *Proc Natl Acad Sci U S A.* 2003; 100:8389–94. [PubMed: 12829791]
28. Stuve O, Marra CM, Jerome KR, et al. Immune surveillance in multiple sclerosis patients treated with natalizumab. *Ann Neurol.* 2006; 59:743–7. [PubMed: 16634029]

29. Anandasabapathy N, Vitorica GD, Meredith M, et al. Flt3L controls the development of radiosensitive dendritic cells in the meninges and choroid plexus of the steady-state mouse brain. *J Exp Med*. 2011; 208:1695–705. [PubMed: 21788405]
30. Kivisakk P, Mahad DJ, Callahan MK, et al. Expression of CCR7 in multiple sclerosis: implications for CNS immunity. *Ann Neurol*. 2004; 55:627–38. [PubMed: 15122702]
31. Mack CL, Vanderlugt-Castaneda CL, Neville KL, Miller SD. Microglia are activated to become competent antigen presenting and effector cells in the inflammatory environment of the Theiler's virus model of multiple sclerosis. *J Neuroimmunol*. 2003; 144:68–79. [PubMed: 14597100]
32. Malone KE, Stohlman SA, Ramakrishna C, et al. Induction of class I antigen processing components in oligodendroglia and microglia during viral encephalomyelitis. *Glia*. 2008; 56:426–35. [PubMed: 18205173]
33. Medzhitov R, Janeway CA Jr. Innate immunity: impact on the adaptive immune response. *Curr Opin Immunol*. 1997; 9:4–9. [PubMed: 9039775]
34. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell*. 2010; 140:805–20. [PubMed: 20303872]
35. Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. *Nat Med*. 2015; 21:677–87. [PubMed: 26121197]
36. Mills KH, Dunne A. Immune modulation: IL-1, master mediator or initiator of inflammation. *Nat Med*. 2009; 15:1363–4. [PubMed: 19966773]
37. Jamilloux Y, Pierini R, Querenet M, et al. Inflammasome activation restricts *Legionella pneumophila* replication in primary microglial cells through flagellin detection. *Glia*. 2013; 61:539–49. [PubMed: 23355222]
38. Wu J, Fernandes-Alnemri T, Alnemri ES. Involvement of the AIM2, NLRC4, and NLRP3 inflammasomes in caspase-1 activation by *Listeria monocytogenes*. *J Clin Immunol*. 2010; 30:693–702. [PubMed: 20490635]
39. Glass CK, Saijo K, Winner B, et al. Mechanisms Underlying Inflammation in Neurodegeneration. *Cell*. 2010; 140:918–934. [PubMed: 20303880]
40. Allan SM, Tyrrell PJ, Rothwell NJ. Interleukin-1 and neuronal injury. *Nat Rev Immunol*. 2005; 5:629–40. [PubMed: 16034365]
41. Zhang WH, Wang X, Narayanan M, et al. Fundamental role of the Rip2/caspase-1 pathway in hypoxia and ischemia-induced neuronal cell death. *Proc Natl Acad Sci U S A*. 2003; 100:16012–7. [PubMed: 14663141]
42. Gris D, Ye Z, Iocca HA, et al. NLRP3 plays a critical role in the development of experimental autoimmune encephalomyelitis by mediating Th1 and Th17 responses. *J Immunol*. 2010; 185:974–81. [PubMed: 20574004]
43. Halle A, Hornung V, Petzold GC, et al. The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. *Nat Immunol*. 2008; 9:857–65. [PubMed: 18604209]
44. Meissner F, Molawi K, Zychlinsky A. Mutant superoxide dismutase 1-induced IL-1 β accelerates ALS pathogenesis. *Proc Natl Acad Sci U S A*. 2010; 107:13046–50. [PubMed: 20616033]
45. Hoegen T, Tremel N, Klein M, et al. The NLRP3 inflammasome contributes to brain injury in pneumococcal meningitis and is activated through ATP-dependent lysosomal cathepsin B release. *J Immunol*. 2011; 187:5440–51. [PubMed: 22003197]
46. Ramos HJ, Lanteri MC, Blahnik G, et al. IL-1 β signaling promotes CNS-intrinsic immune control of West Nile virus infection. *PLoS Pathog*. 2012; 8:e1003039. [PubMed: 23209411]
47. Reiner SL, Locksley RM. The regulation of immunity to *Leishmania major*. *Annu Rev Immunol*. 1995; 13:151–77. [PubMed: 7612219]
48. McMahon EJ, Bailey SL, Castaneda CV, et al. Epitope spreading initiates in the CNS in two mouse models of multiple sclerosis. *Nat Med*. 2005; 11:335–9. [PubMed: 15735651]
49. Marten NW, Stohlman SA, Zhou J, Bergmann CC. Kinetics of virus-specific CD8 $^{+}$ T-cell expansion and trafficking following central nervous system infection. *J Virol*. 2003; 77:2775–8. [PubMed: 12552021]
50. MacNamara KC, Bender SJ, Chua MM, et al. Priming of CD8 $^{+}$ T cells during central nervous system infection with a murine coronavirus is strain dependent. *J Virol*. 2008; 82:6150–60. [PubMed: 18417581]

51. Berer K, Mues M, Koutrolos M, et al. Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. *Nature*. 2011; 479:538–41. [PubMed: 22031325]
52. Haghikia A, Jorg S, Duscha A, et al. Dietary Fatty Acids Directly Impact Central Nervous System Autoimmunity via the Small Intestine. *Immunity*. 2015; 43:817–29. [PubMed: 26488817]
53. Jangi S, Gandhi R, Cox LM, et al. Alterations of the human gut microbiome in multiple sclerosis. *Nat Commun*. 2016; 7:12015. [PubMed: 27352007]
54. Kivisakk P, Imitola J, Rasmussen S, et al. Localizing central nervous system immune surveillance: meningeal antigen-presenting cells activate T cells during experimental autoimmune encephalomyelitis. *Ann Neurol*. 2009; 65:457–69. [PubMed: 18496841]
55. Bartholomaeus I, Kawakami N, Odoardi F, et al. Effector T cell interactions with meningeal vascular structures in nascent autoimmune CNS lesions. *Nature*. 2009; 462:94–8. [PubMed: 19829296]
56. Kim JV, Kang SS, Dustin ML, McGavern DB. Myelomonocytic cell recruitment causes fatal CNS vascular injury during acute viral meningitis. *Nature*. 2009; 457:191–5. [PubMed: 19011611]
57. Kabat EA, Moore DH, Landow H. An Electrophoretic Study of the Protein Components in Cerebrospinal Fluid and Their Relationship to the Serum Proteins. *J Clin Invest*. 1942; 21:571–7. [PubMed: 16694947]
58. Mattson DH, Roos RP, Arnason BG. Comparison of agar gel electrophoresis and isoelectric focusing in multiple sclerosis and subacute sclerosing panencephalitis. *Ann Neurol*. 1981; 9:34–41. [PubMed: 6163394]
59. Burgoon MP, Hammack BN, Owens GP, et al. Oligoclonal immunoglobulins in cerebrospinal fluid during varicella zoster virus (VZV) vasculopathy are directed against VZV. *Ann Neurol*. 2003; 54:459–63. [PubMed: 14520657]
60. Grimaldi LM, Castagna A, Lazzarin A, et al. Oligoclonal IgG bands in cerebrospinal fluid and serum during asymptomatic human immunodeficiency virus infection. *Ann Neurol*. 1988; 24:277–9. [PubMed: 3140714]
61. Grimaldi LM, Roos RP, Devare SG, et al. HTLV-I-associated myelopathy: oligoclonal immunoglobulin G bands contain anti-HTLV-I p24 antibody. *Ann Neurol*. 1988; 24:727–31. [PubMed: 3207356]
62. Mehta PD, Patrick BA, Thormar H. Measles-specific IgG in CSF and serum from patients with subacute sclerosing panencephalitis. *Immunology*. 1982; 46:423–8. [PubMed: 7084997]
63. Porter KG, Sinnamon DG, Gillies RR. *Cryptococcus neoformans*-specific oligoclonal immunoglobulins in cerebrospinal fluid in cryptococcal meningitis. *Lancet*. 1977; 1:1262.
64. Cepok S, Jacobsen M, Schock S, et al. Patterns of cerebrospinal fluid pathology correlate with disease progression in multiple sclerosis. *Brain*. 2001; 124:2169–76. [PubMed: 11673319]
65. Cepok S, von Geldern G, Grummel V, et al. Accumulation of class switched IgD-IgM- memory B cells in the cerebrospinal fluid during neuroinflammation. *J Neuroimmunol*. 2006; 180:33–9. [PubMed: 16952404]
66. Corcione A, Casazza S, Ferretti E, et al. Recapitulation of B cell differentiation in the central nervous system of patients with multiple sclerosis. *Proc Natl Acad Sci U S A*. 2004; 101:11064–9. [PubMed: 15263096]
67. Haubold K, Owens GP, Kaur P, et al. B-lymphocyte and plasma cell clonal expansion in monosymptomatic optic neuritis cerebrospinal fluid. *Ann Neurol*. 2004; 56:97–107. [PubMed: 15236406]
68. Pranzatelli MR, Travelstead AL, Tate ED, et al. B- and T-cell markers in opsoclonus-myoclonus syndrome: immunophenotyping of CSF lymphocytes. *Neurology*. 2004; 62:1526–32. [PubMed: 15136676]
69. Pranzatelli MR, Travelstead AL, Tate ED, et al. CSF B-cell expansion in opsoclonus-myoclonus syndrome: a biomarker of disease activity. *Mov Disord*. 2004; 19:770–7. [PubMed: 15254934]
70. Cepok S, Rosche B, Grummel V, et al. Short-lived plasma blasts are the main B cell effector subset during the course of multiple sclerosis. *Brain*. 2005; 128:1667–76. [PubMed: 15800022]
71. Wings KM, Gilden DH, Bennett JL, et al. Analysis of multiple sclerosis cerebrospinal fluid reveals a continuum of clonally related antibody-secreting cells that are predominantly plasma blasts. *J Neuroimmunol*. 2007; 192:226–34. [PubMed: 17997491]

72. Knopf PM, Harling-Berg CJ, Cserr HF, et al. Antigen-dependent intrathecal antibody synthesis in the normal rat brain: tissue entry and local retention of antigen-specific B cells. *J Immunol.* 1998; 161:692–701. [PubMed: 9670944]
73. Stern JN, Yaari G, Vander Heiden JA, et al. B cells populating the multiple sclerosis brain mature in the draining cervical lymph nodes. *Sci Transl Med.* 2014; 6:248ra107.
74. Lucchinetti CF, Popescu BF, Bunyan RF, et al. Inflammatory cortical demyelination in early multiple sclerosis. *N Engl J Med.* 2011; 365:2188–97. [PubMed: 22150037]
75. Choi SR, Howell OW, Carassiti D, et al. Meningeal inflammation plays a role in the pathology of primary progressive multiple sclerosis. *Brain.* 2012; 135:2925–37. [PubMed: 22907116]
76. Serafini B, Rosicarelli B, Magliozzi R, et al. Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. *Brain Pathol.* 2004; 14:164–74. [PubMed: 15193029]
77. Obermeier B, Mentele R, Malotka J, et al. Matching of oligoclonal immunoglobulin transcriptomes and proteomes of cerebrospinal fluid in multiple sclerosis. *Nat Med.* 2008; 14:688–93. [PubMed: 18488038]
78. Bennett JL, Lam C, Kalluri SR, et al. Intrathecal pathogenic anti-aquaporin-4 antibodies in early neuromyelitis optica. *Annals of Neurology.* 2009; 66:617–629. [PubMed: 19938104]
79. Bradl M, Misu T, Takahashi T, et al. Neuromyelitis optica: pathogenicity of patient immunoglobulin in vivo. *Ann Neurol.* 2009; 66:630–43. [PubMed: 19937948]

Clinical Implications

Under normal homeostatic conditions, the brain and spinal cord are protected from external immune cells via the protective blood-brain barrier. We now understand that disruption of this barrier during CNS inflammation as occurs in response to infection, stroke and autoimmunity can lead to severe CNS damage. This review summarizes the basics of innate and adaptive immune processes that underlie CNS surveillance, T and B cell activation, and entry of peripheral immune cells into the CNS. Importantly, our understanding of immune mechanisms developed from the study of animal models has led to a wide array of new disease-modifying therapies with the purpose of reducing CNS inflammation. Drugs and monoclonal antibodies that target egress from secondary lymphoid follicles, migration of T-lymphocytes across the blood-brain barrier, and specific immune cell subsets are now being used to treat multiple sclerosis and other CNS inflammatory diseases. CNS immune processes are also regulated by a wide array of cytokines, chemokines and immune receptors that were not addressed in this review and have also become the target of potential disease interventions. As improved genomic and bioinformatics tools reveal secrets underlying the causes of human disease, novel and disease-specific treatments are likely to emerge.

Figure 1. Cells comprising the immune system arise from pluripotent hematopoietic stem cells in bone marrow

Bone marrow pluripotent stem cells divide to yield lymphoid and myeloid progenitor cells. Lymphoid stem cells give rise to T- and B-lymphocytes and to natural killer (NK cells). T and B cells are the basis of adaptive immunity and upon antigen stimulation can differentiate into T effector cells, which include helper (Th) and cytotoxic (Tc) effector subsets, or into antibody-secreting plasma cells. Myeloid stem cells are precursors to white blood cells that include granulocytes (neutrophil, eosinophils and basophils) and monocytes, which differentiate into phagocytic macrophages within tissues. Dendritic cells are predominately derived from the myeloid lineage but can also arise from lymphoid progenitors. Mast cells important in allergic reactions differentiate from an unknown myeloid intermediate.

Figure 2. B cell responses in the CNS

B cells mature within the bone marrow and are released as naïve B cells to circulate between blood and peripheral lymphoid tissue. Antigenic stimulation in lymph nodes and with the help of Th cells leads to a germinal center reaction that results in clonal expansion, B cell class switching, somatic mutation and release of long-lived memory B cells and antibody-secreting plasma blasts back into circulation. Cells returning into bone marrow can become long-lived plasma cells that are the source of most peripheral blood antibodies. In infectious and inflammatory CNS disease, CNS resident plasma blasts are the likely source of increased intrathecal IgG and CSF oligoclonal bands.⁷⁷ It is postulated that activated memory cells crossing into the CNS are re-stimulated and locally differentiate into antibody-secreting plasma blasts. Whether this requires T cell help or occurs within ectopic germinal-like clusters of B and T cells is an intriguing possibility. Alternatively, peripherally generated migratory plasma blasts could enter the CNS directly. In neuromyelitis optica, antibodies directed against the AQP4 water channel expressed on astrocytes are the cause of a severe CNS immunopathology.⁷⁸ In the absence of oligoclonal bands in CNS, it is believed that circulating anti-AQP4 antibodies crossing a damaged blood-barrier may be the initial cause of pathology.⁷⁹