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# Immune Privilege in the Central Nervous System: Implications for Neuroinflammatory Diseases

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**ABSTRACT**

The central nervous system (CNS) has long been considered an immune-privileged site, where immune responses are tightly regulated to protect neural tissue from inflammation-induced damage. Immune privilege in the CNS is maintained through various mechanisms, including the blood-brain barrier (BBB), the absence of conventional lymphatic drainage, the specialized function of CNS-resident immune cells, and the expression of immunosuppressive molecules like TGF-β and IL-10. These protective systems are essential for preserving CNS homeostasis, as uncontrolled immune activity in the CNS can lead to irreversible damage to neurons and glial cells. However, immune privilege is not absolute. In neuroinflammatory diseases such as multiple sclerosis (MS), neuromyelitis optica (NMO), and Alzheimer's disease, immune privilege is breached, resulting in the infiltration of immune cells, chronic inflammation, and progressive neural damage. The breakdown of the BBB, immune cell activation, and dysregulated inflammation contribute to the pathophysiology of these diseases. This review examines the mechanisms that underlie immune privilege in the CNS, how these systems are compromised in neuroinflammatory conditions, and the therapeutic implications for modulating immune responses in the CNS. Targeted therapies aimed at restoring immune regulation and preserving CNS function offer promising prospects for treating neuroinflammatory diseases and maintaining CNS health.

**Keywords:** Immune Privilege, Central Nervous System, Neuroinflammatory Diseases, Blood-Brain Barrier, Multiple Sclerosis, Immunosuppressive Mechanisms

## INTRODUCTION

The central nervous system (CNS) is a highly specialized part of the body that plays an essential role in controlling sensory, motor, cognitive, and autonomic functions [1,2]. The delicate structure and organization of the CNS, which includes the brain and spinal cord, require a stable environment to ensure its proper functioning [3]. Unlike other tissues and organs in the body, the CNS has historically been considered an "immune-privileged" site, a concept first introduced by Nobel laureate Sir Peter Medawar in the 1940s [4]. Medawar's research demonstrated that foreign tissue grafts placed in the brain or eye did not elicit the same immune rejection responses seen in other parts of the body, suggesting a unique relationship between the CNS and the immune system [5]. This discovery led to the idea that the CNS is largely isolated from the rest of the immune system, shielded by barriers such as the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier [6,7]. The notion of immune privilege is vital because it reflects the CNS's need for protection from potentially harmful immune responses. Given that inflammation in the CNS can result in irreversible damage to neurons and glial cells, the immune system must strike a delicate balance between defending against pathogens and preventing collateral damage [8] Immune privilege helps ensure that the CNS is not exposed to the same degree of immune surveillance or inflammatory responses that occur in peripheral tissues. Key factors contributing to this immune privilege include the BBB, the absence of traditional lymphatic drainage, the specialized immune environment within the CNS, and the presence of immunosuppressive molecules like transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10) [9-11].

However, immune privilege in the CNS is not absolute. Recent discoveries have challenged the long-held view that the CNS is completely isolated from the immune system [12]. While it does have a more regulated immune environment, immune cells and cytokines can, under certain circumstances, infiltrate the CNS, particularly in disease states where the integrity of the BBB is compromised [13]. This regulated but not impermeable immune system is essential for maintaining CNS homeostasis, and it also becomes the source of problems in neuroinflammatory and neurodegenerative diseases [14].

Neuroinflammatory diseases such as multiple sclerosis (MS), neuromyelitis optica (NMO), and Alzheimer's disease are prime examples of how the breakdown of immune privilege can lead to devastating consequences for CNS function [15,16]. These diseases involve the infiltration of immune cells, chronic inflammation, and the loss of neurons and glial cells, often resulting in progressive neurological decline [17]. Understanding the mechanisms that govern immune privilege, and how they can become dysregulated, is key to advancing our knowledge of these conditions and developing targeted therapies [18]. This review explores the biological mechanisms underpinning immune privilege in the CNS, how these are disrupted in neuroinflammatory diseases, and the therapeutic strategies aimed at restoring immune regulation in the CNS.

## Mechanisms of Immune Privilege in the CNS

Immune privilege in the CNS is maintained through a variety of tightly regulated mechanisms that collectively protect neural tissue from inflammation and immune attack. These mechanisms include the blood-brain barrier, the absence of conventional lymphatic drainage, the role of CNS-resident immune cells, and the expression of immunosuppressive molecules [19].

### 1. Blood-Brain Barrier (BBB):

The BBB is a highly selective barrier formed by endothelial cells, pericytes, astrocytes, and the basal lamina that separates the CNS from the circulatory system. The tight junctions between endothelial cells prevent the free movement of large molecules, immune cells, and pathogens into the CNS, helping to maintain immune privilege [20]. Under normal conditions, the BBB restricts the entry of immune cells such as T cells and B cells, thereby preventing unnecessary immune activation in the brain. However, in pathological states, the BBB can become compromised, allowing immune cells to infiltrate the CNS and contribute to neuroinflammation [21].

### 2. Absence of Conventional Lymphatic Drainage:

Unlike other organs, the CNS lacks traditional lymphatic vessels for the drainage of immune cells and antigens to nearby lymph nodes, where immune responses are typically initiated [22]. Instead, the CNS relies on alternative drainage pathways, including the recently discovered meningeal lymphatic vessels and cerebrospinal fluid (CSF) flow, which allow antigens and immune cells to be transported out of the CNS. The lack of direct lymphatic drainage contributes to the limited immune surveillance in the CNS, supporting its immune privilege [23].

### 3. CNS-Resident Immune Cells:

Microglia are the primary resident immune cells of the CNS. Unlike peripheral immune cells, microglia are specialized to maintain CNS homeostasis without inducing excessive inflammation [24]. They constantly monitor the CNS environment and can respond to injury or infection by phagocytosing debris, presenting antigens to T cells, and releasing anti-inflammatory cytokines. Microglia have a lower capacity for immune activation than peripheral macrophages, reflecting their role in minimizing damage to the sensitive neural environment [25].

### 4. Immunosuppressive Molecules:

The CNS is rich in immunosuppressive molecules that help to dampen immune responses and protect against inflammation. For example, neurons and glial cells express molecules like transforming growth factor-beta (TGF-β), interleukin-10 (IL-10), and programmed death-ligand 1 (PD-L1), which inhibit the activation of T cells and other immune cells. The low expression of major histocompatibility complex (MHC) molecules in the CNS also limits antigen presentation, further contributing to immune privilege [26,27].

## Breaching Immune Privilege: Neuroinflammatory Diseases

Despite these protective mechanisms, immune privilege in the CNS can be compromised, leading to neuroinflammatory diseases. In these conditions, the immune system either directly attacks CNS components or fails to regulate inflammatory responses, resulting in neuronal damage and disease progression [28].

### 1. Multiple Sclerosis (MS):

MS is a chronic, autoimmune disease characterized by the destruction of myelin, the protective sheath around nerve fibers, by the immune system [29]. In MS, immune privilege is breached when T cells, B cells, and macrophages cross the compromised BBB and initiate an immune attack against myelin-producing oligodendrocytes. This leads to demyelination, axonal damage, and progressive neurological disability [30]. The exact trigger for this immune response remains unclear, but genetic and environmental factors, such as viral infections, are believed to play a role. The breakdown of immune privilege in MS underscores the delicate balance between CNS protection and immune surveillance [31].

**2. Neuromyelitis Optica (NMO):**

NMO is another autoimmune disorder that primarily affects the optic nerves and spinal cord. Unlike MS, where the immune response targets myelin, NMO is characterized by the presence of autoantibodies against aquaporin-4, a water channel protein expressed on astrocytes [32]. These antibodies trigger complement-mediated destruction of astrocytes, leading to inflammation, demyelination, and neuronal damage. Similar to MS, the BBB is compromised in NMO, allowing immune cells and pathogenic antibodies to enter the CNS and exacerbate inflammation [33].

**3. Alzheimer's Disease:**

Alzheimer's disease is a neurodegenerative condition associated with the accumulation of amyloid-beta plaques and neurofibrillary tangles in the brain [35]. While Alzheimer's is not classically considered an autoimmune disease, neuroinflammation plays a key role in disease progression. Microglia, the resident immune cells of the CNS, become activated in response to amyloid-beta accumulation, leading to chronic inflammation and neuronal death. The failure of immune privilege mechanisms, such as the impaired clearance of amyloid-beta by microglia and the infiltration of peripheral immune cells, contributes to the neuroinflammatory environment in Alzheimer's disease [36].

**4. Viral Encephalitis and Meningitis:**

Viral infections can also breach immune privilege in the CNS. In viral encephalitis and meningitis, pathogens such as herpes simplex virus, West Nile virus, or enteroviruses infect the CNS, leading to a robust immune response [37]. The entry of peripheral immune cells into the CNS through a compromised BBB can result in inflammation, swelling, and neuronal damage. Although the immune response is necessary to clear the infection, excessive inflammation can cause long-term neurological sequelae [38].

**Therapeutic Implications**

Understanding immune privilege in the CNS has significant therapeutic implications for neuroinflammatory diseases. Therapies aimed at modulating the immune response in the CNS must balance the need to prevent excessive inflammation while preserving immune function to protect against infections and other insults [39].

**1. Immunomodulatory Therapies:**

In diseases like MS and NMO, immunomodulatory drugs, such as interferon-beta, fingolimod, and natalizumab, have been developed to reduce the activation and migration of immune cells into the CNS. These therapies aim to restore immune privilege by preventing the infiltration of pathogenic immune cells and reducing inflammation. However, they carry the risk of increasing susceptibility to infections due to their broad immunosuppressive effects [22].

**2. Targeted Therapies:**

Advances in immunotherapy have led to the development of more targeted treatments that specifically inhibit the immune components driving neuroinflammation. For example, monoclonal antibodies that block specific cytokines, such as anti-IL-6 therapy in NMO, or inhibit complement activation, offer the potential to reduce CNS inflammation with fewer systemic side effects [14].

**3. Restoring BBB Integrity:**

Therapies that aim to restore the integrity of the BBB are also being explored as a way to prevent immune cells from infiltrating the CNS [28]. By strengthening the BBB and preventing its disruption, it may be possible to maintain immune privilege and reduce neuroinflammation.

**4. Neuroprotective Strategies:**

In neurodegenerative diseases like Alzheimer's, where immune privilege is breached by chronic inflammation, neuroprotective strategies that target microglial activation and amyloid-beta clearance are under investigation [39,40]. By modulating the immune response to prevent excessive inflammation, these therapies aim to slow disease progression and preserve cognitive function.

**CONCLUSION**

Immune privilege in the CNS is a critical mechanism that protects the brain and spinal cord from immune-mediated damage while allowing for limited immune surveillance. However, when this privilege is breached, as seen in neuroinflammatory diseases like MS, NMO, and Alzheimer's, the consequences can be devastating. Understanding the balance between immune protection and the risk of neuroinflammation is essential for developing effective therapies that preserve CNS function while preventing immune-mediated damage. Advances in immunotherapy, BBB-targeted treatments, and neuroprotective strategies offer promising avenues for managing neuroinflammatory diseases and maintaining immune privilege in the CNS.

**REFERENCES**

1. Rouleau, N., Murugan, N.J. & Kaplan, D.L. Functional bioengineered models of the central nervous system. *Nat Rev Bioeng* **1**, 252–270 (2023). https://doi.org/10.1038/s44222-023-00027-7

2. Kilinc, M., Calderon, D.P., Tabansky, I., Martin, E.M., Pfaff, D.W. (2016). Elementary Central Nervous System Arousal. In: Pfaff, D., Volkow, N. (eds) Neuroscience in the 21st Century. Springer, New York, NY. https://doi.org/10.1007/978-1-4614-6434-1_79-4
3. Thau L, Reddy V, Singh P. Anatomy, Central Nervous System. [Updated 2022 Oct 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542179/
4. InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. In brief: How does the nervous system work? [Updated 2023 May 4]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279390/
5. Simpson E. Medawar's legacy to cellular immunology and clinical transplantation: a commentary on Billingham, Brent and Medawar (1956) 'Quantitative studies on tissue transplantation immunity. III. Actively acquired tolerance'. Philos Trans R Soc Lond B Biol Sci. 2015 Apr 19;370(1666):20140382. doi: 10.1098/rstb.2014.0382. PMID: 25750245; PMCID: PMC4360130.
6. J.Y. Niederkorn, Dynamic Immunoregulatory Processes that Sustain Immune Privilege in the Eye, Editor(s): Darlene A. Dartt, Encyclopedia of the Eye, Academic Press, 2010, Pages 63-68, https://doi.org/10.1016/B978-0-12-374203-2.00005-1.
7. Park HW. Managing failure: Sir Peter Brian Medawar's transplantation research. Notes Rec R Soc Lond. 2018 Mar 20;72(1):75-100. doi: 10.1098/rsnr.2017.0020. Epub 2017 Nov 22. PMID: 31390421; PMCID: PMC5906423.
8. Engelhardt, B., Carare, R.O., Bechmann, I. *et al.* Vascular, glial, and lymphatic immune gateways of the central nervous system. *Acta Neuropathol* **132**, 317–338 (2016). https://doi.org/10.1007/s00401-016-1606-5
9. Louveau A, Harris TH, Kipnis J. Revisiting the Mechanisms of CNS Immune Privilege. Trends Immunol. 2015 Oct;36(10):569-577. doi: 10.1016/j.it.2015.08.006. PMID: 26431936; PMCID: PMC4593064.
10. Hong S, Van Kaer L. Immune privilege: keeping an eye on natural killer T cells. J Exp Med. 1999 Nov 1;190(9):1197-200. doi: 10.1084/jem.190.9.1197. PMID: 10544192; PMCID: PMC2195673.
11. Antoine Lampron, Ayman ElAli, Serge Rivest, Innate Immunity in the CNS: Redefining the Relationship between the CNS and Its Environment, Neuron, 2013; 78(2): 214-232: https://doi.org/10.1016/j.neuron.2013.04.005.
12. Michal Schwartz, Kuti Baruch, Breaking peripheral immune tolerance to CNS antigens in neurodegenerative diseases: Boosting autoimmunity to fight-off chronic neuroinflammation, Journal of Autoimmunity, 2014; 54, 8-14. https://doi.org/10.1016/j.jaut.2014.08.002.
13. Buckley MW, McGavern DB. Immune dynamics in the CNS and its barriers during homeostasis and disease. Immunol Rev. 2022 Mar;306(1):58-75. doi: 10.1111/imr.13066. Epub 2022 Jan 23. PMID: 35067941; PMCID: PMC8852772.
14. Robyn S. Klein, Christopher A. Hunter, Protective and Pathological Immunity during Central Nervous System Infections, Immunity, 2017; 46(6): 891-909. https://doi.org/10.1016/j.immuni.2017.06.012.
15. Dantzer R. Neuroimmune Interactions: From the Brain to the Immune System and Vice Versa. Physiol Rev. 2018 Jan 1;98(1):477-504. doi: 10.1152/physrev.00039.2016. PMID: 29351513; PMCID: PMC5866360.
16. Su, Y., Zheng, H., Shi, C. *et al.* Meningeal immunity and neurological diseases: new approaches, new insights. *J Neuroinflammation* **20**, 125 (2023). https://doi.org/10.1186/s12974-023-02803-z
17. Salam, A., Borsini, A. & Zunszain, P. Trained innate immunity: a salient factor in the pathogenesis of neuroimmune psychiatric disorders. *Mol Psychiatry* **23**, 170–176 (2018). https://doi.org/10.1038/mp.2017.186
18. Lucille C. Rankin, David Artis, Beyond Host Defense: Emerging Functions of the Immune System in Regulating Complex Tissue Physiology, Cell, 2018; 173(3): 554-567, https://doi.org/10.1016/j.cell.2018.03.013.
19. Louveau A, Harris TH, Kipnis J. Revisiting the Mechanisms of CNS Immune Privilege. Trends Immunol. 2015 Oct;36(10):569-577. doi: 10.1016/j.it.2015.08.006. PMID: 26431936; PMCID: PMC4593064.
20. Carson MJ, Doose JM, Melchior B, Schmid CD, Ploix CC. CNS immune privilege: hiding in plain sight. Immunol Rev. 2006 Oct;213:48-65. doi: 10.1111/j.1600-065X.2006.00441.x. PMID: 16972896; PMCID: PMC2633103.
21. Leonel Ampie, Dorian B. McGavern, Immunological defense of CNS barriers against infections, Immunity, 2022; 55(5):781-799. https://doi.org/10.1016/j.immuni.2022.04.012.

22. Ilena Vincenti, Doron Merkler, New advances in immune components mediating viral control in the CNS, Current Opinion in Virology,2021; 47, 68-78. https://doi.org/10.1016/j.coviro.2021.02.001.
23. Tian, L., Ma, L., Kaarela, T. *et al.* Neuroimmune crosstalk in the central nervous system and its significance for neurological diseases. *J Neuroinflammation* **9**, 155 (2012). https://doi.org/10.1186/1742-2094-9-155
24. Wekerle, H., Sun, Dm. Fragile privileges: autoimmunity in brain and eye. *Acta Pharmacol Sin* **31**, 1141–1148 (2010). https://doi.org/10.1038/aps.2010.149
25. Casali BT, Reed-Geaghan EG. Microglial Function and Regulation during Development, Homeostasis and Alzheimer's Disease. Cells. 2021 Apr 20;10(4):957. doi: 10.3390/cells10040957. PMID: 33924200; PMCID: PMC8074610.
26. Prinz M, Masuda T, Wheeler MA, Quintana FJ. Microglia and Central Nervous System-Associated Macrophages-From Origin to Disease Modulation. Annu Rev Immunol. 2021 Apr 26;39:251-277. doi: 10.1146/annurev-immunol-093019-110159. Epub 2021 Feb 8. PMID: 33556248; PMCID: PMC8085109.
27. Katharina Borst, Anaelle Aurelie Dumas, Marco Prinz, Microglia: Immune and non-immune functions, Immunity, 2021; 54(10): 2194-2208. https://doi.org/10.1016/j.immuni.2021.09.014.
28. Woodburn, S.C., Bollinger, J.L. & Wohleb, E.S. The semantics of microglia activation: neuroinflammation, homeostasis, and stress. *J Neuroinflammation* **18**, 258 (2021). https://doi.org/10.1186/s12974-021-02309-6
29. Gao, C., Jiang, J., Tan, Y. *et al.* Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. *Sig Transduct Target Ther* **8**, 359 (2023). https://doi.org/10.1038/s41392-023-01588-0
30. Muzio L, Perego J. CNS Resident Innate Immune Cells: Guardians of CNS Homeostasis. *International Journal of Molecular Sciences.* 2024; 25(9):4865. https://doi.org/10.3390/ijms25094865
31. Sochocka, M., Diniz, B.S. & Leszek, J. Inflammatory Response in the CNS: Friend or Foe?. *Mol Neurobiol* **54**, 8071–8089 (2017). https://doi.org/10.1007/s12035-016-0297-1
32. Shumway CL, Patel BC, Tripathy K, et al. Neuromyelitis Optica Spectrum Disorder (NMOSD) [Updated 2024 Jan 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK572108/
33. Thangaleela S, Sivamaruthi BS, Radha A, Kesika P, Chaiyasut C. Neuromyelitis Optica Spectrum Disorders: Clinical Perspectives, Molecular Mechanisms, and Treatments. *Applied Sciences.* 2023; 13(8):5029. https://doi.org/10.3390/app13085029
34. DeTure, M.A., Dickson, D.W. The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegeneration* **14**, 32 (2019). https://doi.org/10.1186/s13024-019-0333-5
35. Leslie Crews, Eliezer Masliah, Molecular mechanisms of neurodegeneration in Alzheimer's disease, *Human Molecular Genetics*, Volume 19, Issue R1, 15 April 2010, Pages R12–R20. https://doi.org/10.1093/hmg/ddq160
36. Manglani M, McGavern DB. New advances in CNS immunity against viral infection. Curr Opin Virol. 2018 Feb; 28:116-126. doi: 10.1016/j.coviro.2017.12.003. Epub 2017 Dec 29. PMID: 29289900; PMCID: PMC5990251.
37. McGavern DB, Kang SS. Illuminating viral infections in the nervous system. Nat Rev Immunol. 2011 May;11(5):318-29. doi: 10.1038/nri2971. PMID: 21508982; PMCID: PMC5001841.
38. Antoine Louveau, Tajie H. Harris, Jonathan Kipnis, Revisiting the Mechanisms of CNS Immune Privilege, Trends in Immunology, 2015; 36(10): 569-577. https://doi.org/10.1016/j.it.2015.08.006.
39. Onyango IG, Jauregui GV, Čarná M, Bennett JP Jr, Stokin GB. Neuroinflammation in Alzheimer's Disease. Biomedicines. 2021 May 7;9(5):524. doi: 10.3390/biomedicines9050524. PMID: 34067173; PMCID: PMC8150909.
40. Wareham, L.K., Liddelow, S.A., Temple, S. *et al.* Solving neurodegeneration: common mechanisms and strategies for new treatments. *Mol Neurodegeneration* **17**, 23 (2022). https://doi.org/10.1186/s13024-022-00524-0


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