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Systemic immune derangements are shared across various CNS pathologies and reflect novel mechanisms of immune privilege

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Abstract

Background. The nervous and immune systems interact in a reciprocal manner, both under physiologic and pathologic conditions. Literature spanning various CNS pathologies including brain tumors, stroke, traumatic brain injury and de-myelinating diseases describes a number of associated systemic immunologic changes, particularly in the T-cell compartment. These immunologic changes include severe T-cell lymphopenia, lymphoid organ contraction, and T-cell sequestration within the bone marrow.

Methods. We performed an in-depth systematic review of the literature and discussed pathologies that involve brain insults and systemic immune derangements.

Conclusions. In this review, we propose that the same immunologic changes hereafter termed 'systemic immune derangements', are present across CNS pathologies and may represent a novel, systemic mechanism of immune privilege for the CNS. We further demonstrate that systemic immune derangements are transient when associated with isolated insults such as stroke and TBI but persist in the setting of chronic CNS insults such as brain tumors. Systemic immune derangements have vast implications for informed treatment modalities and outcomes of various neurologic pathologies.

Key Points

1. Acute and chronic brain injuries induce systemic immune derangements including lymphopenia.
2. Understanding underpinnings of immune derangements secondary to brain injury will advance the clinical management of all patients with acute and chronic neurological diseases.

The field of neuroimmunology has continued to uncover reciprocal communication between the nervous and immune systems. While many studies have served to highlight the impact of inflammation on central nervous system (CNS) pathologies, there has been a dearth of studies that assess how CNS pathologies, in turn, are able to affect systemic immunity.

Over the last several decades, the immunologic consequences of neurological insults have been described in

various case reports or can be found hidden among other pre-clinical or clinical datasets. However, to date, no dedicated study has truly examined the often-diminished state of peripheral immunity that can arise in the context of intracranial or other CNS pathologies.

While other groups have focused on *local* immunosuppression at the site of the tumor and how this impacts immunotherapeutic success and clinical trial design,[1–4] our groups have authored recent mechanistic studies characterizing the state of *peripheral* immunity in both patients and various mouse models with intracranial tumors. Together, we have demonstrated numerous immune deficits ranging from downregulation of major histocompatibility complex II on blood-derived monocytes and B cells[5] to memory T-cell dysfunction to potent immunosuppressive soluble factors that inhibit T-cell function and hinder cellular immunity.[5] We have demonstrated anatomical changes in both primary and secondary lymphoid organs, including atrophy of the spleen and the thymus, as well as severe T-cell lymphopenia, resulting from a decreased absolute number, not percentage, of circulating T-cells.[5,6] Our studies echo previous publications by others demonstrating that GBM patients have lower absolute counts of T-cells and are in a state of overall lowered T-cell immunity.[7–11] We have additionally discovered that T-cells accumulate in the bone marrow of mice with intracranial tumors and that this T-cell sequestration is dependent upon the loss of sphingosine-1-phosphate receptor 1 (S1P1).[6]

In this review, we will highlight the presence of similar immunologic changes, particularly T-cell changes, across multiple CNS pathologies, and term these "systemic immune derangements." Importantly, we highlight that these derangements are present not only in the setting of intracranial tumors but also in the setting of other insults (stroke, traumatic brain injury (TBI), multiple sclerosis (MS), and spinal cord injury (SCI)), provided these occur within the CNS (see Figure 1). The commonality we will reveal amidst varying CNS pathologies suggests a brain or CNS-intrinsic mechanism for limiting immune responses and secondary immune-mediated CNS damage, a mechanism that is perhaps activated by any of a number of inflammatory insults to the brain or spinal cord. Such a mechanism may be an evolutionarily adaptive response, consistent with the framework of classical definitions of CNS immune privilege. We propose here that the development of CNS pathology-driven systemic immune derangements represents a novel mechanism of immune privilege that serves to restrict the intensity of a peripheral immune response in the setting of CNS insults. We advance here a hypothesis that all brain injuries can induce some level of global immune derangement which impacts the peripheral immune organs and disrupts systemic immunity.

Intracranial Pathologies

Brain Tumors

Patients

Many studies have focused on T-cell exhaustion,[4,12–14] including both progenitor and terminal exhaustion, within the tumor microenvironment and recent studies underscore the role of biological sex in the development of exhausted T-cells within the tumor.[15] This review, however,

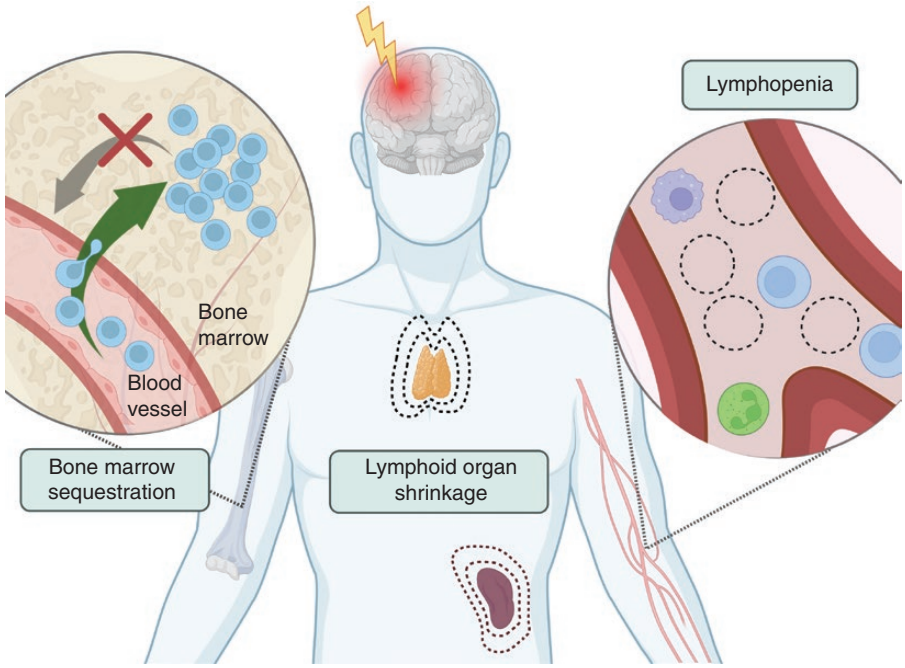

Figure 1. Systemic immune derangements include T-cell lymphopenia, lymphoid organ contraction, and sequestration of T-cells within the bone marrow.

will focus on peripheral immunosuppression. Both primary and metastatic brain tumors are difficult to treat with conventional therapies, as they display unique challenges including both intratumoral and peripheral immunosuppression. Peripheral immunosuppression includes various systemic immune derangements, which have been identified in patients,[6,16] mice,[5,6,17,18] and rats[19] with brain tumors. In patients, these immune derangements have predominantly been studied in the setting of glioblastoma (GBM), the most common primary malignant brain tumor in adults.

While many cancers are associated with vague immunosuppressive features including T-cell anergy and exhaustion, GBM-induced immunosuppression is broader, more severe, and affects all stages of T-cell development, activation, and function. Studies dating back more than 50 years have described various phenotypic and functional evidence of immunosuppression in patients with primary intracranial tumors. These studies described unique features of immunosuppression in intracranial tumors which have not been observed in other cancers. For example, it was reported that T-cells isolated from GBM patients cannot be sensitized against primary tumor antigens, and normal hypersensitivity responses on skin tests are significantly delayed in GBM patients compared to controls.[9,10] Further defects in T-cell activation, proliferation, and responses in patients with GBM were also reported.[10] Similarly, it was described that T-cells isolated from GBM patients fail to be activated properly with mitogens or typical T-cell activating protocols.[10,11,20,21] GBM patient T-cells make less IL-2, and their high affinity IL-2 receptor expression (CD25) during activation is diminished.[11,21] Finally, early T-cell activation signaling cascades and calcium mobilization have been found to be defective in GBM patients.[11,21,22] Together, these data indicated profound T-cell lymphopenia and additional functional immune defects in GBM patients and those patients with other primary brain tumors. Although lymphopenia has been observed in patients for decades, it has often been attributed to therapeutic interventions, including chemotherapy, radiation, and treatment with steroids such as dexamethasone. Importantly, however, lymphopenia and other systemic immune derangements arise in newly diagnosed, treatment-naïve patients, as demonstrated by Gustafson et al.[7] and Chongsathidkiet et al.,.[6] In the latter paper, lymphopenia was accompanied by both lymphoid organ contraction and sequestration of T-cells in the bone marrow. Additional prospective studies are needed to thoroughly characterize T-cell sequestration and lymphoid organ contraction in the setting of brain metastases.

The lymphopenia noted in GBM patients for decades[9] has recently been correlated with decreased overall survival.[23] T-cell lymphopenia is more severe in the CD4+ compartment,[5,6,17] and there is a concomitant increase in the percentage of regulatory T-cells (Tregs).[24] Further, a retrospective study showed that nearly half of 200 newly diagnosed GBM patients exhibited decreased lymphocyte levels (<1500/μl) at baseline.[16] Lymphopenia is also observed in patients with brain metastases and is negatively correlated with survival outcomes in breast cancer patients who develop brain metastases.[25] On a related note, tumor resection surgery, which is typically performed in most GBM patients as a first line of therapy, can be considered an injury in itself further impacting peripheral lymphocyte counts. Accordingly, a recent study has shown that the number of circulating T-cells further decreases after surgical resection in a murine model of glioblastoma, though no clinical studies have examined this question to date.[26]

Animal Models

Immunocompetent mouse models of brain tumors including GBM have elegantly recapitulated major hallmarks of immune derangements observed in patients. Systemic immune derangements were initially described in patients and have been replicated in recent pre-clinical murine studies. A study by Chongsathidkiet et al. examined murine models of GBM in addition to patients and further demonstrated that T-cell sequestration in the bone marrow developed in mice when tumors were placed intracranially, but not subcutaneously, and that this trend was maintained across tumor types including GBM, melanoma, lung adenocarcinoma, and triple-negative breast cancer.[6] A study by Ayasoufi et al. supported this finding by demonstrating an increase in CD4+ T-cells in the bone marrow.[5]

In addition to T-cell sequestration in the bone marrow, T-cell lymphopenia and lymphoid organ contraction have been observed in animal models of GBM and other brain tumors. Specifically, splenic atrophy has also been observed in mice with intracranial GBM.[5,27] Thymic atrophy has been observed in mouse models of intracranial melanoma, diffuse intrinsic pontine glioma, GBM, and an RCAS-spontaneous glioma model,[5,6,18,27] and rat models of intracranial gliomas.[19] Finally, Ayasoufi et al. also demonstrated the presence of a potently immunosuppressive soluble factor in the serum of glioma-bearing mice capable of blocking T-cell function and proliferation.[5]

Stroke

Patients

Stroke patients are at risk for "stroke-induced immunodepression syndrome," severe peripheral immunosuppression that arises after ischemic stroke. A thorough review of immunosuppression in stroke by Westendorp et al. demonstrates that infection complications arise in approximately one-third of stroke patients and, strikingly, nearly 50% of patients with post-stroke infections died, as compared to only 18% of patients without infection. It is important to note that the post-stroke immunosuppression cannot be attributed to simple aspiration pneumonia due to disability. Likewise, it was not avoided by prophylactic antibiotics in a large clinical trial, thus indicating a distinct mechanism for this immunosuppression beyond simple paralysis.[28] These data suggest that brain injury-induced immunosuppression and, consequently, susceptibility to infection, plays a major role in post-stroke outcomes.[29] In line with these findings, of all CNS pathologies, systemic immune derangements have been most thoroughly characterized in stroke patients[30–38] and mouse models thereof.[38–40]

Given the feasibility of assessing lymphocyte counts in peripheral blood, lymphopenia is particularly well-described in stroke patients. Two independent retrospective studies showed that approximately one quarter of

stroke patients presented with lymphopenia on admission.[30,33] Lymphopenia on admission is independently associated with both an increased risk of infection[30,33] and mortality at 90-days post-stroke.[33] Interestingly, infarct volume is the factor that is most highly correlated with the development of lymphopenia in the first several days post-stroke.[41] This demonstrates a direct correlation between the magnitude of the brain injury and the extent of the resulting peripheral immunosuppression. Given that infection is one of the most common complications from a stroke and is significantly associated with both death[29] and larger infarct size,[42] these data suggest that more severe strokes result in lymphopenia, which in turn results in susceptibility to infection and worse patient outcomes. These conclusions are further supported by an observational study of 855 patients demonstrating that lymphopenia on admission is associated with poorer neurological status and unfavorable outcomes in patients.[35] Further, patients with sustained lymphopenia 5 days after their stroke did even worse than those who exhibited lymphopenia on admission, exhibiting increased rates of infection and poorer outcomes at 3 months of follow-up.[35] A prospective study in stroke patients demonstrated that circulating T-cells, specifically, were decreased on admission, suggesting that a decrease in T-cells drives the lymphopenia observed across studies. The same prospective study revealed that patients exhibit T-cell lymphopenia for approximately 1 week before returning to baseline,[31] while an additional study demonstrated that circulating T-cells reach their lowest levels around 12 hours post-stroke.[43]

Lymphoid organ contraction, particularly splenic atrophy, is also well-characterized in stroke patients. In a prospective study conducted by Vahidy et al. 158 healthy volunteers and an equal number of stroke patients had spleen measurements taken over the course of five consecutive days, or the first 24 hours post-stroke then daily, respectively. Splenic atrophy was seen in 40% of stroke patients.[34] Further, patients who presented with severe strokes were more likely to present with splenic atrophy on admission, or at day 3 post-stroke.[32] A prospective observational study showed that stroke patients maintained splenic atrophy until approximately four days post-stroke, then spleen size increased through day 8 post-stroke.[37] Another study showed that the onset of both lymphopenia and splenic atrophy occurs less than 24 hours post-stroke but both systemic immune derangements disappear after 7–10 days post-stroke when T-cell numbers and spleen volumes returned to normal.[38]

Animal Models

Pre-clinical models of stroke, particularly transient middle cerebral artery occlusion (tMCAO), have been used to identify the timing of systemic immune derangements. Using pre-clinical models, various studies have shown splenic[39,44,45] and thymic[46] atrophy and circulating T-cell lymphopenia.[46] In tMCAO models, thymic atrophy was observed and the number of thymocytes (developing T-cells in the thymus) was significantly lower than sham mice for the first two weeks after stroke, and only fully recovered after two months,[46] while splenic atrophy and T-cell lymphopenia was only observed for one-week post-stroke.[46]

Multiple Sclerosis

Patients

MS is a neuroinflammatory disease that is associated with brain atrophy, demyelination, debilitating disability, loss of motor function, and cognitive decline. In the 1970s, broad immunosuppressants were identified as the most effective drugs for MS.[47] MS is typically considered an inflammatory disease, hence the notion of peripheral immunosuppression in the context of MS might seem counterintuitive. However, upon close examination of the clinical and preclinical MS literature, we discovered evidence of peripheral immune derangements including T-cell lymphopenia.

Our systematic review of the literature indicated the presence of lymphopenia in MS patients. Early studies used rosetting techniques to demonstrate lymphopenia in MS patients when compared to healthy controls.[48] Similarly, CD8 T-cell deficiencies in effector and memory responses of MS patients were observed when the functional and phenotypic analysis was used to compare MS patients to healthy controls.[49] Interestingly, one study also correlated the extent of lymphopenia to active MS disease,[50] but these studies are over 20 years old and do not use modern technologies to evaluate lymphopenia. Hence, direct studies to establish the extent of lymphopenia in MS are still needed. Nevertheless, it is crucial to discuss all studies that have reported data suggestive of immunosuppression as a direct result of MS alone and those effects that can be separated from treatment-induced lymphopenia.

While immune organ involution has not been directly measured in MS patients, thymus function has been evaluated in MS patients using human T-cell excision circles (TRECs). TRECs are an excellent proxy for T-cell output and, consequently, thymic size. These studies demonstrated that MS patients had reduced TRECs numbers in general among which regulatory T-cells were further reduced.[51–54] In addition to defects seen in mature and newly generated T-cells, MS patients have reported defects in their T regs and B-cell.[52,53,55]

MS patients receive antiviral drugs, T-cell and B-cell depleting reagents, and fingolimod, which sequesters T-cells in secondary lymphoid organs.[56–58] Each of these drugs is immunomodulatory in nature and can directly induce lymphopenia. However, several studies have measured lymphocyte counts prior to treatment and determined that patients with lower baseline counts were more prone to lymphopenia after treatment. The cause of lymphopenia at baseline, however, was not determined.[59–63] Further, whether lymphopenia is due to homeostatic deficiencies downstream of these immunomodulatory drugs, or directly reflective of ongoing MS progression in the brain is unclear. Together, these studies support our hypothesis that MS activity in the brain is likely linked to lymphopenia in the blood.

Animal Models

Leading animal models of MS include the experimental autoimmune encephalitis (EAE) model, demyelination in certain strains of mice caused by Theiler's murine encephalomyelitis virus (TMEV), and the cuprizone-mediated model of demyelination. Most MS lesions in patients are infiltrated by CD8+ T-cells[64,65] while EAE pathology is CD4+

T-cell-mediated. Both CD4 and CD8 T-cells likely play crucial roles in MS pathogenesis yet the role of each T-cell type across mouse models of MS remains controversial. While addressing this controversy is beyond the scope of the review at hand, all models of MS are unanimously considered to induce severe neuroinflammation. The TMEV model is a direct model of virus-induced damage and brain injury that is due to both damage directly caused by the virus and damage caused by the immune system to the neurons.[66–69] This model demonstrates the involvement of CD8 T-cells in the brain but ensues picornavirus viral infection which may not then directly model human MS. Finally, the cuprizone model is a chemically induced model of damage to the CNS that leads to eventual demyelination.[70] While none of these models solely recapitulate the complexity and heterogeneity of all MS pathologies, they all contain significant levels of neuroinflammation. Interestingly, peripheral immune derangements, including T-cell lymphopenia, thymic, and splenic involution, have been documented in each of the preclinical models discussed above. Specifically, thymic and splenic involution was reported transiently in EAE, acutely post-intracranial TMEV infection, and during cuprizone-induced demyelination.[5,71–74] While one paper reported reduced B and T-cell counts in the spleen within 6 days post EAE induction,[75] another study reported that spleen involution in the EAE model is heterogenous and dependent on mouse strain, pathology, and time points measured.[76]

Additional Demyelinating Diseases

Current data establish Epstein-Barr Virus as a strong causative link to MS development.[77–79] Therefore, we have also included studies that investigated systemic immune derangements in demyelinating viral infections below.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare, but severe complication of long-term immunosuppression.[80] PML is caused by viral infections in the brain that induce encephalitis. Nearly all case reports on PML patients directly mention or show lymphopenia (lymphocyte counts < 1000), suggesting that active PML induces severe lymphopenia.

Krabbe Disease

Researchers have also described progressive peripheral lymphopenia in the context of other demyelinating diseases including Krabbe disease, a lysosomal beta-galactosylceramidase deficiency that results in severe demyelination. In a mouse model of this disease, the severity of neurological symptoms directly correlated with the extent of lymphopenia.[81]

Canine Distemper Virus

Lymphopenia following brain infection has also been reported after canine distemper virus (CDV) infection.[82] Although CDV infection alone is known to directly lyse lymphocytes, strong evidence of severe lymphopenia and thymic involution only occurred with intracranial, not extracranial, CDV infections.[83,84] Therefore, it is the intracranial locale of the infection that directly determined the extent of lymphopenia in these studies.

Traumatic Brain Injury

Patients

Each year, ~70 million people worldwide will suffer from a TBI. Similar to other brain pathologies, systemic immune derangements are present in patients,[85] mice,[86] and rats[87,88] after TBI. Whereas approximately one quarter of stroke patients presented with lymphopenia, a 10-year retrospective study of over 2500 TBI patients determined that more than one-third of TBI patients presented with lymphopenia on admission.[85] Further, lymphopenia on admission was associated with worse outcomes including longer length of hospital stay, a higher level of care required upon discharge, and an increased risk of mortality.[85] Lymphopenia was also more prevalent in patients with more severe TBI[85] and did not resolve until 1 week after the injury.[89]

Animal Models

There are a number of accepted animal models of TBI, including models of fluid percussion injury, controlled cortical impact injury, weight-drop impact acceleration injury, and blast injury (reviewed by Xiong et al.).[90]

In terms of lymphoid organ contraction, thymic atrophy is most well-described in the context of TBI. A study in mice demonstrated a 60% loss in thymus weight one-day post-injury when compared to sham controls[86] and studies in rats have recapitulated thymic atrophy after TBI.[87,88] Another study described a bimodal pattern of thymic T-cell loss and thymic atrophy, immune cell loss from the spleen, and depressed hematopoiesis in the bone marrow following the induction of TBI in mice.[91]

Other CNS Pathologies

Spinal Cord Injury

Although most frequently noted in the setting of intracranial pathologies, systemic immune derangements occur after spinal cord injury (SCI) as well, indicating the impact of a CNS-specific injury on systemic immune function. A cross-sectional study in individuals younger than 60 years demonstrated that patients with SCI had significantly lower lymphocyte concentrations in the blood compared with healthy individuals.[92] The same study suggested that these decreased lymphocyte counts, contributing to general "immune frailty" were implicated in infection complications and decreased longevity.[92] Further clinical studies have shown significant decreases in circulating lymphocytes in the first week after injury and have shown that lymphopenia at admission was correlated with higher level injuries.[93,94] Murine studies of T3 SCI noted both lymphopenia[95,96] and splenic atrophy.[96–98]

Epilepsy

Although there are relatively few papers detailing the extent of systemic immune derangements in seizure disorders, these have been noted in both epileptic patients and murine models of epilepsy. In particular, patients with convulsive status epilepticus, a seizure lasting longer than 5 minutes or more than one seizure in 5 minutes, exhibited lymphopenia in the first-hour post-seizure compared to a healthy control group.[99,100] Further, patients exhibited decreased lymphocyte counts in the acute phase of status epilepticus (at the time of seizure) compared to the subacute phase (72 hours post-seizure).[99] These same findings were noted in patients with generalized tonic-clonic ("Grand mal") epileptic seizures.[100] These data suggest a reversal of lymphopenia upon resolution of neurological insult. Notably, lymphopenia, splenic and thymic contraction, and decreased thymic cellularity have been described in murine models of epilepsy.[5,101]

Parkinson's Disease

Attempts to understand the role of immunity in the pathogenesis of Parkinson's disease (PD) have uncovered systemic immune derangements in patients. As early as 2001, studies demonstrated lymphopenia in the peripheral blood of PD patients.[102,103] Notably, even studies that have not identified an absolute decrease in lymphocyte numbers have noted a lower CD4+:CD8+ T-cell ratio in PD patients compared to controls.[104] One particularly compelling study from 2018 examined the peripheral blood of 60 PD patients compared to 30 healthy controls.[105] In addition to observing a decreased mean T-cell count in the overall PD group, they found that advanced PD was associated with lower CD4+ and CD8+ T-cell counts than earlier-stage disease. This relationship between disease severity and the number of circulating T-cells was replicated by Bhatia et al. in 2021, showing that, for their cohort, reductions in CD8+ T-cells drove lymphopenia and were correlated with disease severity.[106]

Cardiac arrest and cardiopulmonary resuscitation

Just as the local ischemia and reperfusion within the CNS induced by stroke can cause systemic immune derangements, occlusion of CNS blood supply from other causes may have similar effects.[107–109] As a pathology that indirectly impacts the CNS, decreased circulating lymphocytes have been identified in patients within the first days following CA/CPR.[110,111] Consistent with findings in the single-insult pathologies described above, peripheral lymphocytes in CA/CPR patients hit their nadir approximately 90 minutes following the reperfusion event then begin to return to baseline.[112]

Many of the observations drawn from human patients following cardiac arrest are mirrored in mouse models. Both chemical and asphyxial murine models of CA/CPR have demonstrated peripheral blood lymphopenia, as well as splenic and thymic contraction within three days of mouse resuscitation.[108,113] Together, these data indicate that immune derangements are associated with brain injuries even in instances where brain injury was an indirect result of cardiac insufficiency and resulting hypoxia.

Blood–brain barrier disruption

BBB disruption is a severe neuroinflammatory event that can be considered a form of brain injury. We demonstrated in a model of blood–brain barrier disruption where the damage is mediated by virus-specific resident memory CD8 T-cells, that BBB disruption is directly associated with peripheral lymphopenia in the blood.[114] Importantly, BBB disruption and brain atrophy are two major brain pathologies confirmed in numerous COVID patients.[115–119] In fact, the reported lymphopenia in COVID patients with severe brain involvement directly supports our interpretation that brain insults induced by BBB disruption or endothelial cell damage was linked to peripheral lymphopenia.[108]

Concluding Remarks

As described in the preceding sections, systemic immune derangements have been described across various CNS pathologies (Figure 2). Most of these systemic immune derangements have been noted in clinical, rather than pre-clinical, settings, indicating a lack of recognition of the connections between these phenomena and the need for further mechanistic studies to uncover their etiologies. However, several seminal mouse studies have paved the way for mechanistic studies into the origins of immunosuppression following brain injuries by recapitulating hallmark features of immune derangements in patients with acute and chronic neurological diseases (Table 1).

Existing clinical studies have highlighted that an insult to the CNS, regardless of the nature of the insult, leads to several distinct and predictable phenotypes, namely, systemic immune derangements. Importantly, depending on the nature of the insult, systemic immune derangements are either chronic, as in the setting of brain tumors, or transient, in the setting of TBI, infections, and stroke. Although we propose that systemic immune derangements develop in response to acute or chronic injury, the transient nature of systemic immune derangements after acute injury supports the idea that this is an evolutionarily adaptive mechanism to protect the CNS from inflammation, and as such, represents a novel mechanism of immune privilege. The potential benefit vs. harm of mitigating immune derangement must be evaluated per intracranial pathology. In brain tumors, we argue, this mitigation results in benefits while in MS it might not. In parallel, profound immunosuppression in MS can cause further harm due to a lack of protective immunity. Hence, extensive discussions and specific targets will be required to specifically mitigate immune derangements while protecting the CNS. It is important for future studies, in brain tumors, to design ways to overcome these systemic immune derangements, as they likely limit immunotherapeutic efficacy, regardless of the protection against damaging inflammation this mechanism may provide the CNS. Should novel therapeutics overcome these systemic immune derangements, patients could be

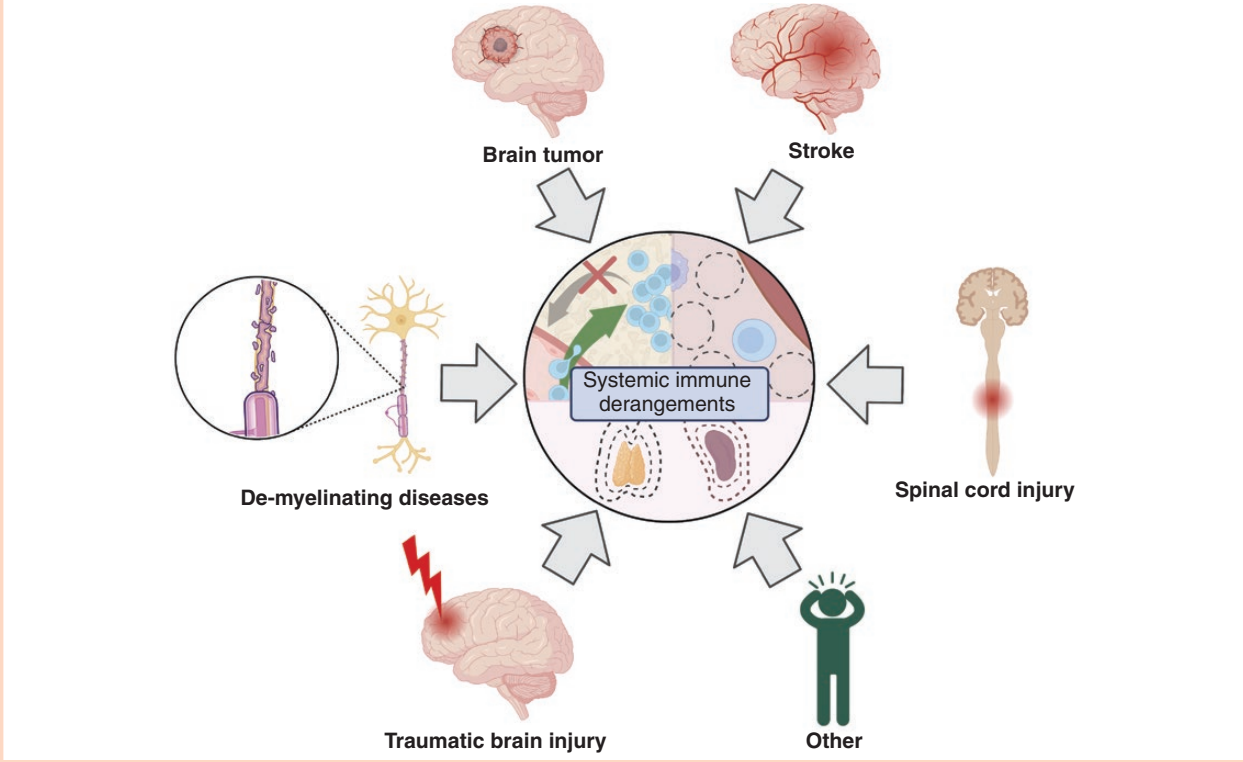

Figure 2. Various CNS pathologies including brain tumors, stroke, SCI, traumatic brain injury, and de-myelinating diseases result in systemic immune derangements.

medically managed with steroids for life-threatening CNS inflammation but initiating sufficient anti-tumor responses in the CNS and initiating such inflammation remain the current challenge. Further mechanistic insights are needed in order to mitigate immune derangements in a pathology and cell type-specific manner in order to maximize patient outcomes.

Given that the preponderance of evidence for systemic immune derangements is clinical, it is important to note that sample availability impacts the frequency at which certain systemic immune derangements are observed. Importantly, this does not necessarily reflect isolated etiologies for specific immune derangements, but rather, limitations of retrospective human studies. For example, there are several retrospective studies that highlight lymphopenia, but none that assess T-cell sequestration in the bone marrow. This reflects the fact that patients regularly have blood drawn but do not routinely undergo invasive procedures, such as bone marrow aspiration, which is necessary to assess T-cell numbers in the bone marrow. Furthermore, retrospective studies often highlight lymphopenia but are unable to assess T-cell lymphopenia specifically, as many of the studies described in this review include patient data from the United States in a healthcare system that does not routinely collect complete blood counts with differentials. Therefore, pre-clinical data is needed to fill in the gaps.

Although there is a dearth of mechanistic studies to assess the etiology of systemic immune derangements following brain insults, there are three main mechanisms through which the CNS "communicates" with the rest of the body. The first is the Hypothalamic–Pituitary–Adrenal (HPA) axis, with hormonal outputs such as cortisol released from the adrenal cortex. The second is through the autonomic nervous system via the release of signaling molecules, catecholamines, and acetylcholine, as well as direct end-organ innervation. The third is through the release of non-steroidal soluble factors by the injured brain into the blood circulation that can affect functions of immune cells and immune organs at distant target organs. Both the HPA axis and autonomic nervous system mediate stress responses in the body and should be studied prospectively in the setting of various CNS pathologies to evaluate their contributions and potentially novel areas of intervention.

In conclusion, we present data characterizing a group of immune deficits common to various CNS pathologies that we have collectively termed 'systemic immune derangements. These derangements represent a novel mechanism of immune privilege that includes T-cell lymphopenia, lymphoid organ contraction, and T-cell sequestration in the bone marrow. To the best of our knowledge, this is the first body of work to highlight these derangements as a collective and demonstrate their conserved presence across pathologies. We further demonstrate that the persistence of these pathologies is dependent upon whether the CNS insult is acute or chronic. These systemic immune derangements have important implications for disease pathology and outcomes, particularly in chronic pathologies such as brain tumors. As a mechanism of persistent immunosuppression, systemic immune derangements in brain tumor

Table 1. Summary of data on systemic immune derangements in human or animal models among the pathologies discussed in this review

	Lymphopenia	T cell sequestration to the bone marrow	Splenic contraction	Thymic contraction	T cell dysfunction/ other (see notes)
Brain tumors	Patients Mouse models	Patients, Mouse models	Patients, Mouse Models	Mouse models	Delayed hypersensitivity, defects in activation, proliferation
Stroke	Patients Mouse models	*Not reported*	Patients Mouse models	Mouse models	*Not reported*
Multiple Sclerosis/EAE	Patients Mouse models (strain and time point dependant)	*Not reported*	*Not reported in patients/ Splenic T cell contraction reported in EAE, overall spleen atrophy depends on pathology, strain, and model*	Patients (reduced TRECs =proxy) Mouse models (transient thymic involution in EAE)	Defects in CD8+ effector and memory responses Defects in Trges
TMEV/cuprizone-induced demyelination	Mouse models (time point dependent)	*Not reported*	*Not reported in TMEV/spleen atrophy in cuprizone models*	Mouse models—TMEV and cuprizone	*Not reported*
Additional demyelinating diseases	Patients: PML, Krabbe disease, Dogs: canine distemper virus	*Not reported*	*Not reported*	Dogs: canine distemper virus	*Not reported*
Traumatic Brain Injury	Patients	*Not reported*	*Mouse models have immune cell loss from spleen*	Mouse and rat models	*Depressed homeostasis in the bone marrow*
Spinal Cord Injury	Patients Mouse models	*Not reported*	Mouse models	*Not reported*	*Not reported*
Epilepsy	Patients Mouse models	*Not reported*	Mouse models	Mouse models	*Not reported*
Parkinson's disease	Patients	*Not reported*	*Not reported*	*Not reported*	*Not reported*
CA/CPR	Patients Mouse models	*Not reported*	Mouse models	Mouse models	*Not reported*
BBB disruption	Patients Mouse models	*Not reported*	*Not reported*	*Not reported*	*Not reported*

patients present a unique challenge to immunotherapeutic success. Therefore, mechanistic insights are critical for licensing immunotherapies in this patient population. Understanding the etiology and mechanistic underpinnings of immune derangements secondary to brain injury will advance the clinical management of all patients with acute and chronic neurological diseases.

Keywords

brain injury | glioblastoma | immunosuppression | lymphopenia |T-cells

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Conflicts of Interests

None.
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