Review Article

Int Neurourol J 2016;20 Suppl 1:S8-14
http://dx.doi.org/10.5213/inj.1632614.307
pISSN 2093-4777 · eISSN 2093-6931

INTERNATIONAL NEUROUROLOGY JOURNAL
INJ
OPEN ACCESS

Central Nervous System-Peripheral Immune System Dialogue in Neurological Disorders: Possible Application of Neuroimmunology in Urology

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Previous concepts of immune-privileged sites obscured the role of peripheral immune cells in neurological disorders and excluded the consideration of the potential benefits of immunotherapy. Recently, however, numerous studies have demonstrated that the blood–brain barrier in the central nervous system is an educational barrier rather than an absolute barrier to peripheral immune cells. Emerging knowledge of immune-privileged sites suggests that peripheral immune cells can infiltrate these sites via educative gates and that crosstalk can occur between infiltrating immune cells and the central nervous system parenchyma. This concept can be expanded to the testis, which has long been considered an immune-privileged site, and to neurogenic bladder dysfunction. Thus, we propose that the relationship between peripheral immune cells, the brain, and the urologic system should be considered as an additional possible mechanism in urologic diseases, and that immunotherapy might be an alternative therapeutic strategy in treating neurogenic bladder dysfunction.

Keywords: Neuroimmunology; T Cell; Neurological Disorders; Immunotherapy; Neurogenic Bladder Dysfunction

- **Grant Support:** This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2015R1D1A1A02062312).
- **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

THE BLOOD–BRAIN BARRIER AND THE CENTRAL NERVOUS SYSTEM AS AN IMMUNE–PRIVILEGED SITE

Components of the immune system are widely distributed throughout the body and this system continually performs immune surveillance, the process of detecting and eliminating pathogens for maintenance of tissue homeostasis. Immune surveillance plays a critical role in individual survival. Peripheral immune cells such as leukocytes are recruited immediately by signaling from damaged sites, and subsequently, a series of fine-tuned and well-organized processes result in wound healing. However, the central nervous system (CNS) has a differentiated structure called the blood-brain barrier (BBB). The BBB is composed of endothelial basement membrane, pericytes, epithelial basement membrane, and glial basement membrane and blocks normal surveillance by peripheral immune cells. This anatomical BBB concept was confirmed by early experiments showing that foreign tissue grafted into the CNS elicits a delayed immune response [1]. These observations suggest that the CNS is an "immune-privileged site" and that the brain is free from normal immune surveillance. Indeed, in the healthy state,

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Submitted: April 30, 2016 / **Accepted after revision:** May 12, 2016

peripheral immune cells are not detected in the CNS parenchyma [2]. Instead, resident microglia, which are innate immune cells, are responsible for surveillance in the CNS, and various immune cells are found in the meningeal spaces [2]. Another reason the CNS is considered an immune-privileged site is the infiltration of peripheral immune cells in inflammatory autoimmune diseases such as multiple sclerosis (MS) [3]. For decades, peripheral immune cell infiltration into the brain's territory has been considered a pathological process resulting from BBB breakdown in which immune cells attack the CNS. Peripheral immune cell infiltration has been targeted for blockade in patients with MS. Thus, the CNS is likely protected from peripheral immune cells in its healthy state.

A NEW BLOOD–BRAIN BARRIER CONCEPT: ABSOLUTE VERSUS EDUCATIONAL BARRIER

Despite this evidence, the concept of the CNS as an immune-privileged site remains a subject of debate. Recent evidence of immune-privileged sites has been questioned in the neuroimmunology community, and compelling papers have been published on this topic indicating that the CNS may not be an immune-privileged site [4].

To understand the crosstalk between the CNS and peripheral immune cells, the anatomical structures of the BBB should be reestablished as the combination of absolute barriers and educational barriers [2,4]. The first gate is the endothelial BBB localized in CNS microvessels, capillaries, and postcapillary venules, which we have already defined as an absolute barrier in the healthy state. The highly specialized endothelial cells establish a barrier by sealing the paracellular space with complex tight junctions, forming an endothelial basement membrane with many embedded pericytes. In addition, the parenchymal basement membrane containing astrocyte endfeet establishes the glia limitans perivascularis. At the vascular segment of CNS capillaries, two segments are merged and cannot be distinguished ultrastructurally. However, in postcapillary venules, these basement membranes are separated and provide a cerebrospinal fluid (CSF)-drained perivascular space between two segments. Antigen-presenting cells can be found in the perivascular space.

The second gate is the epithelial blood-cerebrospinal fluid barrier (BCSFB) within the choroid plexus (CP). The CP is located in four brain ventricles and is composed of fenestrated blood capillaries (endothelium of the blood vessels) and CP parenchyma (monolayer of epithelial cells interconnected by tight junctions) [5]. The CP produces the CSF, which plays a role as a neuroimmunological interface in maintaining normal brain function in both healthy and pathological states by integrating signals between the brain and blood circulation. In contrast to the BBB, the BCSFB is not an absolute barrier and peripheral immune cells can enter into the CNS (perivascular space and CSF, but not parenchyma) via the CP in the healthy state [2,4]. Thus, the migration of circulating immune cells across the BCSFB allows them to perform immunosurveillance of the CNS in the absence of neuroinflammation because of the permeability of the BCSFB to cellular elements. For example, fenestrated CP microvessels constitutively express P-selectin, allowing T cells to enter CSF-filled ventricles by breaching the BCSFB, which was confirmed by intravenously injecting fluorescently labeled T cells [6]. In addition, the observation that T cells are present in the ventricular and lumbar CSF in healthy individuals further suggests real-time immune surveillance by circulating immune cells [7]. Interestingly, the T cells found in the CSF in healthy states are mainly central memory T cells (TCM cells), which are distinct from T-cell subpopulations in the periphery or in the CNS during neuroinflammation [7,8]. Thus, this suggests that in healthy individuals, TCM cells freely enter the CSF in a regulated manner via the BCSFB for immune surveillance of the CNS.

THE EMERGING ROLE OF CIRCULATING IMMUNE CELLS IN NEUROLOGICAL DISORDERS

The prevailing dogma of the absolute impermeability of the BBB to immune cells has been increasingly challenged over the past few years. It is now apparent that the general perception of the CNS as an immune-privileged site should be revised. Circulating leukocytes have been shown to play an indispensable role in maintenance and repair of the CNS. Emerging data suggest that circulating immune cells can participate in the maintenance of homeostatic brain functions as well as the progression of neurological disorders. In this section, we review recent immunological studies of aging, neurodegenerative diseases, and psychiatric disorders.

Aging

It has not yet been established how brain senescence is influenced by aging of other body tissues. However, recently, several

studies have reported that circulating immune cells are involved in brain senescence. Aging mice and humans show increased type I interferon (IFN) response at the CP, and the neutralization of the aging-induced type I IFN response restores CP function in the brain, partially restoring cognitive function and hippocampal neurogenesis [9]. Although circulating immune cells from young blood did not directly affect brain function in aged CP (type I IFN response), this study suggests that targeting the CP, which is the major gate for circulating immune cells, might ameliorate cognitive decline in aging. In addition, a different study reported that young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice [10]. Supply of young blood using the heterochronic parabiosis model in aged mice stimulates adult neurogenic processes, oligodendrocyte activity, synaptic plasticity, and vascularization in the aged CNS [11]. Although the mechanism by which youthful blood-borne factors access the aged CNS is still unclear, it can be speculated that youth-associated leukocytes or youthful systemic factors seem to be associated with restoration of CNS functional decline with age.

Alzheimer disease

Alzheimer disease (AD) is characterized by the accumulation of amyloid beta (Aβ), and the impaired elimination of this neurotoxic peptide contributes to disease progression [12]. Cerebral amyloid angiopathy, a condition involving Aβ deposition within the cerebral vasculature, is also observed in most patients with AD. A clearance system exists within the CNS to prevent accumulation of toxic peptides, and this system is regulated by innate immune cells called microglia. Microglia modulate inflammatory reactions, phagocytize neuronal debris and foreign pathogens, and induce wound healing [13]. Thus, many studies have focused on the function of microglia in AD. Interestingly, however, it has been shown that circulating monocytes play a role in the elimination of Aβ in AD [14]. Live intravital two-photon microscopy showed that patrolling monocytes are attracted to and crawl onto the luminal walls of Aβ-positive veins, but not on Aβ-positive arteries or Aβ-free blood vessels [14]. Crawling monocytes carried Aβ in these veins and were able to circulate back into the bloodstream. These data clearly showed that enhancing the function of specific circulating monocytes by boosting the immune system constitutes a potential therapeutic target in AD.

Parkinson disease

Parkinson disease (PD) is a chronic progressive disorder that is characterized by tremor, rigidity, and bradykinesia. PD is caused by degeneration of the nigrostriatal pathway, which consists of both dopaminergic (DA) and nondopaminergic neurons [15]. The pathological hallmarks of PD are loss of nigrostriatal DA neurons and formation of Lewy bodies, which are aggregates of proteinaceous cytoplasmic inclusions [16]. Degeneration of DA neurons is accompanied by activation of microglia and infiltration of T lymphocytes into the CNS [17]. Mouse strains that lack T cells or mature T cells are relatively resistant to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced degeneration of DA neurons [18]. Notably, $CD4^+$ T cells, but not $CD8^+$ T cells, are involved in the MPTP resistance [19]. Collectively, these data indicate that the deleterious activity of MPTP is associated with infiltrating $CD4^+$ T cells. Further, passive transfer of T cells obtained from mice immunized with the immunomodulatory drug glatiramer acetate is neuroprotective against MPTP neurotoxicity, possibly by increasing anti-inflammatory cytokines such as interleukin (IL)-4, IL-10, and transforming growth factor-beta [20,21].

Regulatory T cells (T_{reg} cells), a specialized T-cell subtype, can be neuroprotective [21]. *In vitro*, T_{reg} cells suppress the inflammatory microglial phenotype, whereas $CD4^+CD25^-$ effector T cells (T_{eff} cells) exacerbate the inflammatory microglial phenotype [22]. In an *in vivo* PD model, adoptive transfer of activated T_{reg} cells, but not T_{eff} cells provided neuroprotective effects in MPTP-induced DA cell loss [23]. These studies demonstrate that T cells are important participants in mediating cytotoxicity and neuroprotection in models of PD, depending on their subtype and microenvironment. Therefore, novel therapeutic approaches are needed to clarify the role of innate and adaptive immune responses in patients with PD.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig disease, is a neurodegenerative disorder characterized by fatal progressive motor neuron death, consequently resulting in death within 3–5 years [24]. There is no effective therapeutic regimen, and several clinical trials using various types of stem cells as well as new chemical drugs are ongoing [25,26]. Neuroinflammation similar to other neurodegenerative diseases is one of the most striking hallmarks of ALS [27], a heterogeneous disease with various genetic backgrounds [28,29]. Recent studies have demonstrated that innate and adaptive immune cells

play interdependent roles in regulating the rate of disease progression in ALS [30]. T lymphocytes, a type of adaptive immune cell, are able to infiltrate into the spinal cord in patients with ALS, and in an ALS mouse model, $CD4^+$ T lymphocytes slowed disease progression, shaped microglial phenotypes, and extended survival [31,32]. ALS patients with elevated peripheral T_{reg} cell levels exhibited slow disease progression in a prospective cohort study, suggesting that T_{reg} cells may be associated with the slowing of ALS progression [30,33]. Because neuroinflammation is a prominent pathological feature in ALS, up-regulating T_{reg} cell activity or increasing the T_{reg} cell ratio in the immune system of patients with ALS may represent a potential therapeutic strategy.

Depression

Major depression exhibits various disease courses with inconsistent response to antidepressant treatments [34]. Despite the availability of both pharmacological and psychotherapeutic treatments to a large number of patients, major depression has high rates of relapse and recurrence. A long course of treatment is required for complete recovery from symptoms and prevention of relapse, which is considered the major obstacle in the treatment of major depressive disorder [35].

Most antidepressants were developed based on the "monoamine theory," which postulates that persistent reduction in the levels of serotonin, norepinephrine, and dopamine in the synaptic cleft induces neuroplastic changes, inhibits neurogenesis, and affects cognitive function, finally leading to depression. Thus, current antidepressants are designed to elevate monoamines in CNS. However, more than 50%–70% of patients who recover from a first episode of depression are vulnerable to stress and are at risk of chronic depression [35,36]. In addition, more than 50% of patients are resistant to antidepressant treatment [35,36]. Thus, new approaches beyond the monoamine theory are needed to better treat depression.

Systemic inflammation is associated with the lack of clinical therapeutic benefit of antidepressants in patients resistant to treatment [37,38]. In addition, recent studies have demonstrated that the peripheral immune system is involved in susceptibility or resilience to social stress [39]. In an animal study, mice receiving IL-6 knockout bone marrow transplantation after irradiation were resilient to social stress, suggesting that the peripheral immune system interacts actively with the CNS to shape synaptic circuits [39]. Nude mice, which are T cell depleted, exhibit stress vulnerability, showing depressive-like behaviors in a single foot shock session [40]. Peripheral IL-4/10, an anti-inflammatory cytokine, prevents stress vulnerability in depressed mice via restoration of alternatively activated microglia phenotype [40]. The kynurenine pathway has been demonstrated as a factor linking "cytokine theory" and "monoamine theory" in depression, since pro-inflammatory cytokines lead to tryptophan degradation by indoleamine 2,3-dioxygenase and its metabolites with downstream enzymes inducing neurotoxicity, eventually resulting in depression [41]. Regarding the role of the innate immune system in the CNS, recent studies have demonstrated the role of microglia in depression [42]. Several data suggest that microglia are involved in brain homeostasis processes, such as synaptic transmission and neural plasticity, as well as in pathological brain processes [43]. Microglia interact closely with the peripheral immune system in healthy and diseased states [44]. Peripheral immune cells such as T_{reg} and Th2 cells and their releasing factors restore microglia functional phenotype in depressed mice, leading to reduced stress vulnerability [40]. Thus, targeting the circulating immune system could be an alternative therapeutic strategy, especially in recurrent and refractory forms of depression.

Schizophrenia

Schizophrenia is disabling neuropsychiatric disorder, characterized by positive symptoms (hallucinations and delusions), depression-like negative symptoms, cognitive dysfunction, and neurodegeneration [45,46]. Epidemiological and genetic studies strongly implicate neuroinflammation and peripheral immunity in the pathogenesis of schizophrenia [46-48]. Crosstalk between the peripheral immune system and the brain has been investigated extensively in the context of schizophrenia pathophysiology [49]. Recent population-based longitudinal studies and meta-analysis show an association between elevated levels of pro-inflammatory cytokines and the risk of psychosis [46-48]. In addition, malfunctions of both the innate and adaptive immune systems are observed in schizophrenia. As mentioned above, it is now well established that adaptive immunity in conjunction with innate immunity plays an active role in brain development and homeostasis. Recently, neurodegeneration has been demonstrated to be one of the predominant underlying mechanisms in schizophrenia progression, in which immunemodulatory processes play a crucial role [50]. For example, T-cell-related molecular changes in immune dysfunction have been demonstrated in patients with first-onset schizophrenia [51], and activated lymphocytes in the CSF and hippocampus

of patients have been reported, suggesting BBB impairment [52]. Altogether, these studies indicate that T-cell-mediated immunity is involved in schizophrenia pathogenesis [53].

LESSONS FROM NEUROIMMUNOLOGY: THE ROLE OF THE CIRCULATING IMMUNE SYSTEM IN UROLOGY

The peripheral immune system appears to be actively involved in the development of neurologic disorders. The central concept of involvement of the circulating immune system in neurological disorders is a new insight concerning immune-privileged sites. Similarly, in urology, the testis is no longer considered an immune-privileged site. A layer of epithelial sertoli cells, which are interconnected by tight junctions, encloses the testis germinal compartment, and though leukocytes are strictly blocked from the lumen of the seminiferous tubules in normal tissue, they occasionally penetrate the blood-testis barrier (BTB) of tubuli recti [54,55]. In addition, the testis has a BTB gating system at the seminiferous tubule [2]. The interstitial space, like the perivascular space in the CNS, is a place where immunomodulatory mechanisms are evoked by circulating immune cells. In addition, testicular autoimmunity is primarily observed in "normal" tubuli recti and rete testes, indicating that these structures may be a site of lymphocyte entry.

From a neurourology viewpoint, circulating immune cells may play various roles. Neurogenic lower urinary tract dysfunction can occur in patients with various neurological disorders. For example, PD is one of the most common neurological disorders causing lower urinary tract dysfunction, and DA brain lesions induced by 6-hydroxydopamine injections into the medial forebrain bundle cause bladder dysfunction [56]. Stroke may also cause voiding dysfunction. In an animal model, intracerebral hemorrhage (ICH) induced lower urinary tract dysfunction, showing that ICH significantly enhanced bladder contraction pressure and time, while simultaneously reducing voiding pressure and time [57]. The crosstalk between the CNS and circulating immune cells suggests that the immune system may affect urologic function indirectly via the CNS in patients with neurological disorders. In regard to drug treatment, immune-regulating drugs might be repositioned in neurogenic bladder dysfunction via both immune and brain system. Thus, the relationship between peripheral immune cells, the brain, and the urologic system can be considered an additional possible mechanism in urologic diseases, and immunotherapy might be an alternative therapeutic strategy in neurourological disorders.

CONCLUSION

Modulating peripheral immune cells to treat neurological disorder is no longer an "if" but a "how." Over the past two decades, numerous studies have investigated the pivotal role of peripheral immune cells in the progression of neurological diseases. Proper balance between the CNS and circulating immune cells maintains homeostatic brain functions, but the breakdown of this balance may cause or aggravate aging, neurodegenerative disease, and psychiatric disorders. Peripheral immune cells show varying kinetics in terms of the molecular and cellular immune response in neurological diseases, acting as aggravating or resolving factors depending on the microenvironment and immune state. Thus, a deeper understanding of the crosstalk between the CNS and the immune system will shed light on the pathologies of aging, neurodegenerative diseases, and psychiatric disorders. In addition, effective immunotherapies for timely and beneficial modulation of the immune response might present alternatives for treatment of various intractable diseases.

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