

## Influx and Efflux of Immune Cells in the Central Nervous System

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### Abstract

The influx and efflux of immune cells in the central nervous system (CNS) have long remained to be unclear. In this regard, we have addressed this issue using animal models of CNS tumors and experimental autoimmune encephalitis (EAE) that is relevant to multiple sclerosis (MS) in human. For immune cells to migrate into brain parenchyma, chemokines play central roles. In contrast, when immune cells exit the brain parenchyma, lymphatic system plays central roles. Most recently, the relationship between the CNS immunology and gut microbiome is being addressed using the same systems.

### Immune Responses in the Central Nervous System (CNS)

We have extensively investigated the immune responses in the central nervous system (CNS) using animal models of CNS tumors and experimental autoimmune encephalitis (EAE) that is relevant to multiple sclerosis (MS) in human. More specifically, we have addressed the influx and efflux of immune cells in the CNS. For immune cells to migrate into brain parenchyma, chemokines play central roles. In contrast, when immune cells exit the brain parenchyma, lymphatic system plays central roles. In this short commentary, we would like to introduce our achievements as well as our perspectives briefly.

### Chemokine-mediated immune cell influx shown by CNS tumors

Regarding the immune cell influx into the CNS, chemokines are the most important. Chemokines are a family of cytokines and classified into four main subfamilies: CXC, CC, CX3C and XC [1] and act as a chemoattractant to guide the migration of leukocytes [2]. Some chemokines are involved in immune surveillance; they direct lymphocytes to the lymph nodes, and the lymphocytes interact with antigen-presenting cells to screen for pathogens. Some chemokines are involved in development; they promote angiogenesis or guide cells to the tissues that provide specific signals critical for cellular maturation. Other chemokines are involved in chronic inflammation; they are continuously released from a wide variety of cells during the inflammation and keep recruiting other leukocytes.

For instance, CXCR3 is a chemokine receptor that is rapidly induced on naïve T lymphocyte following the activation and preferentially remains highly expressed on type-1 helper (Th1)-type CD4<sup>+</sup> T lymphocytes, CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs), and innate-type lymphocytes such as natural killer (NK) [3]. CXCR3 interacts with the following chemokines: CXCL9, CXCL10, and CXCL11. In particular, the CXCR3-CCL10 axis is associated with the influx of type-1 CTLs (Tc1; the most potent effector T cells against CNS tumors) into the CNS tumor sites [4-6]. In other words, CXCR3 is preferentially upregulated on Tc1, which is critical for efficient CNS tumor-homing of Tc1.

CCR2 is another chemokine receptor, which regulates the mobilization of monocytes from bone marrow to the CNS inflammatory sites [7]. CCR2 is activated by several chemokines such as CCL2, CCL7, CCL8, CCL12, CCL13, and CCL16. Among them, CCL2 is the most potent activator of CCR2 signaling. In the CNS tumor setting, CCL2 is secreted by tumor cells [8] and directly promotes angiogenesis through the recruitment of tumor-associated macrophages [9]. In addition, CCL2 is critical for cell proliferation, invasion, and metastasis of the CNS tumors [10]. Based on these findings, CCL2 is considered to be an immunosuppressive chemokine and a potent therapeutic target for anti-CNS tumor immunotherapy [8,11,12].

### Lymphatic vessel-mediated immune cell efflux shown by CNS autoimmune diseases

Recently, tertiary lymphoid organs (TLOs) with ectopic lymphoid follicles have been observed in the CNS inflammation sites such as EAE and MS [13,14]. The characteristic features of TLOs include compartmentalization of T and B cells, presence of lymphatic vessels, and high endothelial venules [14,15]. Th17 cells and B cells are suggested to be the main contributors in the formation of these structures. In addition, regarding the immune cell efflux from the CNS, we have identified altered expressions of lymphatic molecules such as LYVE-1, VEGF-D, etc. [16]. Here, LYVE-1 is suggested to be involved in lymph angiogenesis [17]. VEGF-D is also one of the most potent lymphangiogenic factors [18] and plays an important role in neuronal synaptic activity, dendritic length, and dendrite arborization [19]. We observed the alteration of VEGF-D expression levels in EAE/MS settings [16]. These observations indicate that CNS neuroinflammatory diseases alter neuro-lymphatic protein expressions that are involved in the clearance of fluids from the CNS diseases [20,21]. The detailed mechanism of these proteins in the etiology, development and progression of MS remains an important area of investigation.

### The impact of gut microbiome on CNS immunology

We recently directed our focus on the relationship between the CNS immunology and gut microbiome. Although a variety of factors can affect the CNS immunopathology, two essential systems maintaining

whole-body homeostasis might be involved: the lymphatic system and microbiota. Although the lymphatic system and microbiota have been independently described in most medical textbooks of anatomy, immunology, and microbiology, their roles in CNS immunopathology had long been unclear. To elucidate this question, we are currently focusing on the involvement of the CNS lymphatics and gut microbiota [22].

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