Anatomy & Physiology: Current Research

Fujita et al., Anat Physiol 2017, 7:4
DOI: 10.4172/2161-0940.1000274

Commentry Open Access

Influx and Efflux of Immune Cells in the Central Nervous System

Fujita M*, **Omura S, Sato F, Park AM and Tsunoda I**

Department of Microbiology, Kindai University, Osaka, Japan

***Corresponding author:** Fujita M, Department of Microbiology, Kindai University, Osaka, Japan, Tel: +81 6-6721-2332; E-mail: mfujita47@gmail.com

Received Date: June 06, 2017; **Accepted Date:** July 18, 2017; **Published Date:** July 25, 2017

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+ T lymphocytes, CD8+ 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].

References

1. Zlotnik A, Yoshie O (2012) The chemokine superfamily revisited. Immunity 36: 705-716.
2. Proudfoot AE (2002) Chemokine receptors: multifaceted therapeutic targets. Nat Rev Immunol 2: 106-115.
3. Groom JR, Luster AD (2011) CXCR3 ligands: redundant, collaborative and antagonistic functions. Immunol Cell Biol 89: 207-215.
4. Nishimura F, Dusak JE, Eguchi J, Zhu X, Gambotto A, et al. (2006) Adoptive transfer of type 1 CTL mediates effective anti-central nervous system tumor response: critical roles of IFN-inducible protein-10. Cancer Res 66: 4478-4487.
5. Zhu X, Nishimura F, Sasaki K, Fujita M, Dusak JE, et al. (2007) Toll like receptor-3 ligand poly-ICLC promotes the efficacy of peripheral vaccinations with tumor antigen-derived peptide epitopes in murine CNS tumor models. J Transl Med 7: 5-10.
6. Fujita M, Zhu X, Ueda R, Sasaki K, Kohanbash G, et al. (2009) Effective immunotherapy against murine gliomas using type 1 polarizing dendritic cells--significant roles of CXCL10. Cancer Res 69: 1587-1595.
7. Chu HX, Arumugam TV, Gelderblom M, Magnus T, Drummond GR, et al. (2014) Role of CCR2 in inflammatory conditions of the central nervous system. J Cereb Blood Flow Metab 34: 1425-1429.
8. Zhu X, Fujita M, Snyder LA, Okada H (2011) Systemic delivery of neutralizing antibody targeting CCL2 for glioma therapy. J Neurooncol 104: 83-92.
9. Salcedo R, Ponce ML, Young HA, Wasserman K, Ward JM, et al. (2000) Human endothelial cells express CCR2 and respond to MCP-1: direct role of MCP-1 in angiogenesis and tumor progression. Blood 96: 34-40.
10. Huang B, Lei Z, Zhao J, Gong W, Liu J, et al. (2007) CCL2/CCR2 pathway mediates recruitment of myeloid suppressor cells to cancers. Cancer Lett 252: 86-92.
11. Fujita M, Scheurer ME, Decker SA, McDonald HA, Kohanbash G, et al. (2010) Role of type 1 IFNs in antiglioma immunosurveillance--using mouse studies to guide examination of novel prognostic markers in humans. Clin Cancer Res 16: 3409-3419.
12. Fujita M, Kohanbash G, Fellows-Mayle W, Hamilton RL, Komohara Y, et al. (2011) COX-2 blockade suppresses gliomagenesis by inhibiting myeloid-derived suppressor cells. Cancer Res 71: 2664-2674.
13. Peters A, Pitcher LA, Sullivan JM, Mitsdoerffer M, Acton SE, et al. (2011) Th17 cells induce ectopic lymphoid follicles in central nervous system tissue inflammation. Immunity 35: 986-996.
14. Kuerten S, Schickel A, Kerkloh C, Recks MS, Addicks K, et al. (2012) Tertiary lymphoid organ development coincides with determinant spreading of the myelin-specific T cell response. Acta Neuropathol 124: 861-873.
15. Manzo A, Bombardieri M, Humby F, Pitzalis C (2010) Secondary and ectopic lymphoid tissue responses in rheumatoid arthritis: from inflammation to autoimmunity and tissue damage/remodeling. Immunol Rev 233: 267-285.
16. Chaitanya GV, Omura S, Sato F, Martinez NE, Minagar A, et al. (2013) Inflammation induces neuro-lymphatic protein expression in multiple sclerosis brain neurovasculature. J Neuroinflammation 10: 125.
17. Adams RH, Alitalo K (2007) Molecular regulation of angiogenesis and lymphangiogenesis. Nat Rev Mol Cell Biol 8: 464-478.
18. Achen MG, Stacker SA (2012) Vascular endothelial growth factor-D: signaling mechanisms, biology, and clinical relevance. Growth Factors 30: 283-296.
19. Mauceri D, Freitag HE, Oliveira AM, Bengtson CP, Bading H (2011) Nuclear calcium-VEGFD signaling controls maintenance of dendrite arborization necessary for memory formation. Neuron 71: 117-130.
20. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, et al. (2012) A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Sci Transl Med 4: 147ra111.
21. Iliff JJ, Nedergaard M (2013) Is there a cerebral lymphatic system? Stroke 44: S93-S95.
22. Park AM, Omura S, Fujita M, Sato F, Tsunoda I (2017) Helicobacter pylori and gut microbiota in multiple sclerosis versus Alzheimer's disease: 10 pitfalls of microbiome studies. Clin Exp Neuroimmunol.