【Grant-in-Aid for Scientific Research (S)】

Broad Section H

Title of Project : Brain inflammation and repair mechanism by adaptive immunity

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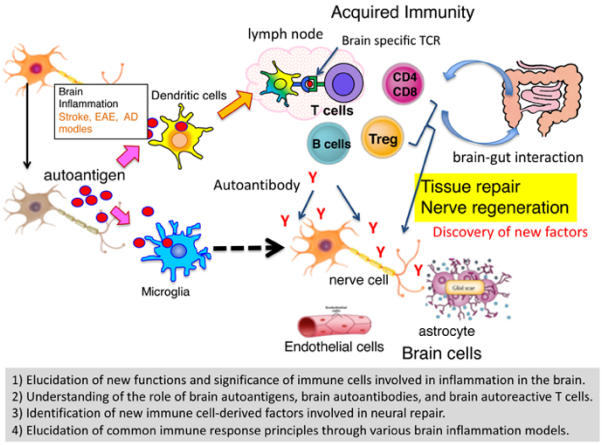
Research Project Number : 21H05044 Researcher Number : 90182815
Term of Project : FY2021-2025 Budget Allocation : 145,600 Thousand Yen
Keyword : Immunoregulation, T cells, Neuroinflammation, Microglia, Astrocytes

【Purpose and Background of the Research】

Although microglia have been analyzed as immune cells in the brain, the importance of lymphocytes such as T cells and B cells, which are responsible for acquired immunity, is finally being recognized. The brain inflammatory response caused by immune cells is harmful to neurons in the early phase of the diseases, it is thought to be essential for the restoration and maintenance of brain functions after the resolution of inflammation. However, significance of lymphocytes in the brain at the molecular and cellular level has not been well elucidated. Using a mouse model of cerebral infarction, our group has shown that inflammation and immune cells after brain injury are involved in the exacerbation of infarction and neurological symptoms in the early stage of the disease, however, promote nerve repair in the chronic stage. In this study, we will clarify the roles of the acquired immune system in neurological injury and repair process in brain injury such as cerebral infarction and neurodegenerative diseases including Alzheimer's disease. By analyzing the interactions between various immune cells and brain cells, we aim to elucidate the mechanisms of neural repair in central nervous system by immune cells and to understand the pathogenesis of



diseases caused by abnormalities in the immune system.

【Research Methods】

We aim to elucidate the molecular basis of neural disorders and repair by immune-neuronal cell interactions. To this end, we aim to understand the cell-cell interactions spatially and temporally by using single-cell RNA sequencing (scRNAseq) and to identify novel molecules and cells involved in immune-neuronal cell interactions. We will use stroke model and neurodegenerative disease models including Alzheimer's disease. We will also establish *in vitro* cell-cell interaction assay systems such as two- and three-dimensional co-culture systems of immune cells with glial and neuronal cells to identify factors that are important for immune and brain cells interaction.

【Expected Research Achievements and Scientific Significance】

This study will lead to the discovery of common principles for differentiation and activation of acquired immune system cells in both acute or chronic brain inflammation. We will obtain a better understanding of the molecular mechanisms of brain function and neural repair by immune cells which promote neurological repair and healthy life span. For example, this study will discover intracerebral lymphocytes which are involved not only in acute brain damage such as cerebral infarction but also in neurodegenerative diseases and psychiatric disorders. This study may lead to the development of antibodies that selectively induce intracerebral lymphocytes to treat psychiatric disorders in which brain inflammation has been implicated.

【Publications Relevant to the Project】

・Ito M, Komai K, Mise-Omata S, Iizuka-Koga M, Noguchi Y, Kondo T, Sakai R, Matsuo K, Nakayama T, Yoshie O, Nakatsukasa H, Chikuma S, Shichita T, Yoshimura A. 2019. Brain regulatory T cells suppress astrogliosis and potentiate neurological recovery. ***Nature*** 565: 246-50
・Shichita T, Ito M, Morita R, Komai K, Noguchi Y, Ooboshi H, Koshida R, Takahashi S, Kodama T, Yoshimura A. 2017. MAFB prevents excess inflammation after ischemic stroke by accelerating clearance of damage signals through MSR1. ***Nature Med*** 23: 723-32
・Ito M, Shichita T, Okada M, Komine R, Noguchi Y, Yoshimura A, Morita R. Bruton's tyrosine kinase is essential for NLRP3 inflammasome activation and contributes to ischaemic brain injury. ***Nature Commun*** 2015; 6: 7360.

【Homepage Address and Other Contact Information】

http://kompas.hosp.keio.ac.jp/contents/medical_info/science/201903_02.html
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