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

Broad Section I

Title of Project： Multilevel mechanisms of the neural network restoration under the neurological disorders

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【Purpose and Background of the Research】

Peripheral and central nervous system (CNS) disorders (e.g., cerebrovascular disorders, brain, and spinal cord trauma, neurodegenerative diseases, and higher brain dysfunction) lead to spatial and temporal changes in the nervous system, immune system, vascular system, biological systems composed of various organs, and pathological conditions. The purpose of this study is to investigate disorders of neural networks in the CNS and the subsequent repair process from the viewpoint of the functional network of biological systems, and comprehensively elucidate the control mechanism underlying a series of processes in the spatiotemporal dynamics of biological systems. The final goal of this research is to elucidate the control mechanism linking neural circuits and organs. Specifically, this study aims to: (1) clarify the mechanism of neural networks in the CNS by analyzing disorders of neural networks in the CNS and the functional recovery process, as seen in the dynamics of the whole biological system; (2) promote simultaneous studies in three species (i.e., rodents, monkeys, and humans) to gain insights for developing new drugs; and (3) develop a scheme of systematic research that seamlessly transitions from basic nervous system research to applied research.

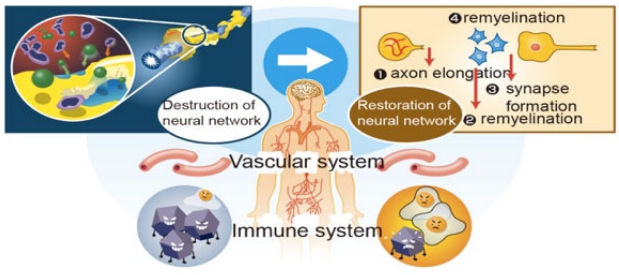

Figure 1 Biological systems that regulate rewiring of neural network after CNS injury

【Research Methods】

The corticospinal tract is a major CNS pathway that is involved in voluntary movement and is of significant clinical importance. We plan to explore potential connections between this pathway, which is already well-characterized in terms of anatomy and physiology, and other biological systems, which warrants the use of experimental mouse models for spinal cord injury, autoimmune encephalomyelitis (EAE), and amyotrophic lateral sclerosis (ALS). This will then ultimately lead to a greater understanding of the mechanisms involved. Higher-order dysfunction, in contrast, tends to originate in the cerebral cortex and hippocampus, which warrants the use of experimental mouse models for attention-deficit/hyperactivity disorder (ADHD). Using these pathological models, we will explore spatial and temporal changes in the cellular dynamics and gene expression of specific cell populations around both the site(s) of neural injury/deficits and other organs (*Aim 1*). We also intend to determine the mechanisms by which neural circuit dysfunction and repair are regulated by immune system cells (*Aim 2*), vascular cells, organs, and other factors (*Aim 3*). In addition, we will explore the human relevance of these mechanisms by comparing a primate models (*Macaca mulatta*) with human samples from patients with spinal cord injury, ALS and multiple sclerosis (*Aim 4*). With this acquired knowledge, we will determine how neural circuitry is repaired via the differential activation of various cell populations, shed light on the principles governing the biological responses at work, and use this information to propose new seed compounds suitable for the development of novel therapies (*Aim 5*).

【Expected Research Achievements and Scientific Significance】

Studies focusing on neural circuits are important because they can lead to the development of new treatments for the repair of damaged neural circuits. In fact, the antibody therapeutic targeting molecule found by the applicant is currently undergoing clinical trials in Japan and the United States. The applicant's research is leading the world and we would like to build a framework for basic research at the earliest to obtain further insight for developing new drugs.

【Publications Relevant to the Project】

・ Ito, M., Muramatsu, R., Kato, Y., Sharma, B., Uyeda, A., Tanabe, S., Fujimura, H., Kidoya, H., Takakura, N., Kawahara, Y., Takao, M., Mochizuki, H., Fukamizu, A. and Yamashita, T. (2021) Age-dependent decline in myelination capacity is mediated by apelin-APJ signaling. Nat. Aging 1, 284-294.
・ Tanabe, S. and Yamashita, T. (2018) B-1a lymphocytes promote oligodendrogenesis during brain development. Nat. Neurosci. 21, 506-516.

【Homepage Address and Other Contact Information】

http://www.med.osaka-u.ac.jp/pub/molneu/index.htm