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

Biological Sciences (Biological Sciences)

Title of Project : How are Synapses Formed, Fine-tuned and Eliminated in vivo?—Novel Mechanisms by the Complement Family Proteins

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【Purpose and Background of the Research】

Neuronal synapses are generated, fine-tuned and eliminated from early development all the way to adulthood, in an activity-dependent manner. These processes are thought to play crucial roles in cognitive functions and certain neurodevelopmental and neuropsychiatric disorders.

A complement C1q belongs to the innate immune system and recognizes various non-self targets to be eliminated. Recently, proteins related to C1q (C1q family) are shown to regulate glucose and lipid metabolism. Furthermore, we found that Cbln1 and C1ql1, which belong to the C1q family, are crucial for synapse formation, maintenance and synaptic plasticity.

In this project, focusing on major neuronal circuits in the hippocampus and cerebellum, we aim to clarify how C1q family proteins regulate synapse morphology and its functions. In addition, we will clarify how C1q family proteins play new roles in coordinating multiple systems involving energy metabolism and brain functions.

【Research Methods】

The cerebellum is essential for motor coordination and motor memory. Its major input fibers (parallel and climbing fibers) require Cbln1 and C1ql1, respectively, for synapse integrity. On the other hand, Cbln1, Cbln4, C1ql2 and C1ql3 exert crucial functions in specific hippocampal synapses to mediate episodic memory. We will clarify molecular mechanisms by which these C1q proteins regulate specific synapses.

C1q proteins are upregulated by increased neuronal activities, inflammation and metabolic needs. We aim to clarify how C1q proteins are produced, secreted and bind to specific receptors to coordinate multiple systems (Fig. 1).

Finally, we will develop molecular tools that could regulate C1q signaling to modify synaptic functions *in vivo*.

【Expected Research Achievements and Scientific Significance】

By clarifying signaling mechanisms mediated by C1q proteins, we expect to obtain better understanding about how synapses are generated, fine-tuned and eliminated *in vivo*. The results of these studies are also expected to pave the way for new and better treatment of certain neuropsychiatric disorders.

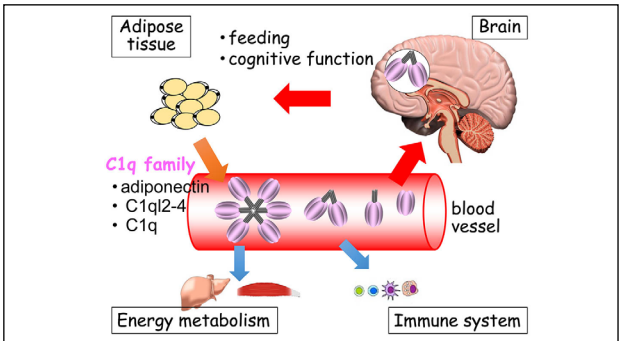

Fig. 1 C1q family integrate immune, metabolic and neural systems

【Publications Relevant to the Project】

・Kakegawa W, Mitakidis N, Miura E, Abe M, Matsuda K, Takeo YH, Kohda K, Motohashi J, Takahashi A, Nagao S, Muramatsu SI, Watanabe M, Sakimura K, Aricescu AR, Yuzaki M. Anterograde C1ql1 signaling is required in order to determine and maintain a single-winner climbing fiber in the mouse cerebellum. Neuron, 85:316-329, 2015.
・Matsuda K, Miura E, Miyazaki T, Kakegawa W, Emi K, Narumi S, Fukazawa Y, Ito-Ishida A, Kondo T, Shigemoto R, Watanabe M, Yuzaki M. Cbln1 is a ligand for an orphan glutamate receptor δ2, a bidirectional synapse organizer. Science, 328: 363-368, 2010.

【Term of Project】 FY2015-2019

【Budget Allocation】 135,800 Thousand Yen

【Homepage Address and Other Contact Information】

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