【Grant-in-Aid for Specially Promoted Research】

Biological Sciences

Title of Project： Regulation of synaptic and non-synaptic functions by extracellular scaffolding proteins

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【Purpose and Background of the Research】

Neurons are interconnected by synapses, which are cell-cell adhesions formed by various synaptic organizers, to achieve fast neurotransmission. Since a broad range of neuropsychiatric and neurological disorders are caused by abnormal synaptic functions, understanding how synapses are formed, maintained and eliminated by synaptic organizers is one of the most important goals of basic and clinical neuroscience.

We have recently proposed a new class of synaptic organizers, termed extracellular scaffolding proteins (ESPs), which are secreted and serve as a scaffold at the synaptic cleft. In addition to fast neurotransmission, neurons communicate with each other and with peripheral tissues by “volume transmission,” in which modulatory neurotransmitters diffuse and reach their receptors located at distant targets. Interestingly, non-synaptic cell-adhesion structures mediated by certain ESPs are often found in neurons that achieve volume transmission.

The goal of this research is to clarify when, how, and why various ESPs regulate synaptic and non-synaptic cell adhesion. Guided by structural information, we also aim to develop synthetic connector molecules that will expand the range and affinity of trans-synaptic and non-synaptic interactions.

【Research Methods】

Complement family proteins (C1q, Cbln1-4, C1ql1-4) and neuronal pentraxins (NPs) belong to the ESP-type synaptic organizer. In this project, we will focus on C1q, Cbln2, Cbln4 and NPs, which are ESPs reported to play important roles in key neuronal circuits. We aim to identify their receptors and downstream signaling pathways.

We also aim to identify molecules that mediate non-synaptic cell-adhesion structures in three model brain regions (extended amygdala, striatum and cerebellum).

We have recently developed a synthetic synaptic connector, CPTX, combining structural elements from Cbln1 and NP1 (Figure 1). Application of CPTX to mouse models of cerebellar ataxia, Alzheimer's disease and spinal cord injury could successfully restore synapses and improve motor coordination, spatial and contextual memories, and locomotion associated with these disease models, respectively. We aim to develop new synthetic synaptic connectors that contain combinations of ESPs found in synaptic and non-synaptic cell adhesion structures.

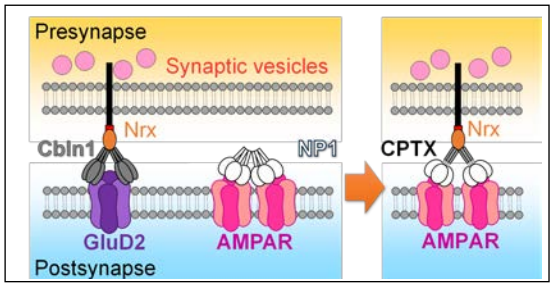

Figure 1 A synthetic synapse connector CPTX

【Expected Research Achievements and Scientific Significance】

Although the catalog of ESPs continues to grow, mechanisms by which ESPs regulate synaptic functions remain largely unclear. Identification of missing receptors and downstream signaling pathways for key ESPs will greatly advance our understanding of physiological and pathological synapse dynamics.

Modulatory transmitters, such as acetylcholine, dopamine and serotonin, achieve slow and diffuse volume transmission. In addition, autonomic nervous systems that regulate various target organs, such as heart and bowels, send signals by volume transmission. Identification of molecules that mediate non-synaptic cell-adhesion structures and volume transmission will be a major breakthrough in the field of modulatory neurotransmitters.

Structure-based design of new synthetic synaptic connectors is expected to pave the way for new treatments in neuropsychiatric or neurological disorders caused by synaptic abnormalities.

【Publications Relevant to the Project】

・ Suzuki K, Elegheert J, Song I, Sasakura H, (18 others), Yuzaki M. A synthetic synaptic organizer protein restores glutamatergic neuronal circuits. Science 369, eabb4853, 2020.
・ Yuzaki M. Two Classes of Secreted Synaptic Organizers in the Central Nervous System. Annu Rev Physiol 80:243-262, 2018.

【Term of Project】 FY2020-2024

【Budget Allocation】 463,200 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.yuzaki-lab.org