News Release

Title

A new target for the treatment of synaptic dysfunction in dementia

Key Points

○FUS, an RNA-binding protein related to frontotemporal lobar degeneration (FTLD), regulates synaptic maturation and stabilizes mRNA of SynGAP α2, a protein regulating synaptic function.

○A novel FUS knockout mouse showing abnormal synaptic maturation and behavior abnormalities that mimic those of FTLD patients has been generated. Gene therapy based on supplementation with SynGAP α2 ameliorated the symptoms of the knockout mice.

○The findings could be useful for developing a new treatment for FTLD.

Summary

A group of researchers, headed by Prof. Gen Sobue, Department of Neurology, Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, M.D., Ph.D.); principal investigator: Satoshi Yokoi), have revealed one of the mechanisms underlying the development of frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS), which are caused by depletion of the RNA-binding protein FUS. This work was published online in Cell Reports on September 26, 2017.

FTLD and ALS are devastating neurodegenerative diseases caused by mutations in genes related to RNA metabolism. One such gene is FUS, encoding an RNA-binding protein. Although extensive efforts have been made to identify the disease-developing mechanism of FUS, neither the nature of the RNA(s) responsible for the pathophysiology nor the event that actually causes the disease are currently known. To date, no treatment has been developed for these diseases.

The researchers focused on the structure of 'synapses' via which neurons communicate with each other, because synaptic dysfunction is often observed in patients with these neurodegenerative diseases. When neuronal interactions are enhanced via synapses, the shape of the synaptic structure, called the dendritic spine, adopts a mushroom shape, which is thought to be a mature form of the synapse. They found that FUS depletion reduced the number of mushroom-shaped spines in primary cultured neurons, indicating that FUS regulates synaptic maturation. Mass Spectrometry analysis of post-synaptic proteins identified SynGAP α2, one of the major factors regulating synaptic maturation. Upon FUS depletion, the SynGAP α2 protein level was significantly reduced. Moreover, they found that FUS binds directly to the mRNA encoding for SynGAP α2 and protects it from degradation. To elucidate whether SynGAP α2 is indeed responsible for synaptic dysfunction upon the loss of FUS, they generated brain-specific FUS knockout mice. These mice showed abnormal synaptic maturation and behavior deficits partially reminiscent of FTLD patients, including

disinhibition and hyperactivity, and SynGAP α2 supplementation via gene delivery using an AAV vector ameliorated these phenotypes.

These findings suggest that FTLD pathophysiology is initiated by synaptic dysfunction caused by loss of FUS function. It would be interesting to see if ALS, another devastating neurodegenerative disease caused by mutations in FUS, has a similar disease-developing mechanism. These findings have been patented, and are expected to generate new treatments for patients.

Research Background

Frontotemporal lobar degeneration (FTLD) is the second most frequent dementia after Alzheimer's disease, and is characterized by disturbances in personality and social interaction deficits. Amyotrophic lateral sclerosis (ALS) causes muscular atrophy, resulting in severe motor impairment characterized by muscle weakness. To date, no treatment has been developed for these devastating progressive neurodegenerative diseases.

While FTLD and ALS are apparently two different symptoms, RNA-binding proteins, including FUS and another RNA-binding protein TDP-43, are common causative factors in these two diseases. A number of studies have suggested that aberrant RNA metabolism of these proteins inhibits normal neuronal functions and affects disease symptoms. However, little has been known until now about which RNA(s) is crucial for the symptoms and which events initiate these diseases.

Research Results

The researchers focused on the structure of 'synapses' via which neurons communicate with each other, because synaptic dysfunction is often observed in patients with these neurodegenerative diseases. When neuronal interactions are enhanced via synapses, the shape of the synaptic structure, called the dendritic spine, adopts a mushroom shape, which is thought to be a mature form of the synapse. They found that FUS depletion reduced the number of mushroom-shaped spines in primary cultured neurons, indicating that FUS regulates synaptic maturation. Mass Spectrometry analysis of post-synaptic proteins identified SynGAP α2, one of the major factors regulating synaptic maturation. Upon FUS depletion, the SynGAP α2 protein level was significantly reduced. Moreover, they found that FUS binds directly to the mRNA encoding for SynGAP α2 and protects it from degradation. To elucidate whether SynGAP α2 is indeed responsible for synaptic dysfunction upon the loss of FUS, they generated brain-specific FUS knockout mice. These mice showed abnormal synaptic maturation and behavior deficits partially reminiscent of FTLD patients, including disinhibition and hyperactivity, and SynGAP α2 supplementation via gene delivery using an AAV vector ameliorated these phenotypes.

Research Summary and Future Perspective

This study provides new insights that could lead researchers engaged in the study of synaptic dysfunction to develop novel targets for the treatment of neurodegenerative diseases. The results may also be applicable to ALS, another devastating neurodegenerative disease caused by FUS mutations.

These findings could be useful for the future development of new treatments for these neurodegenerative diseases.

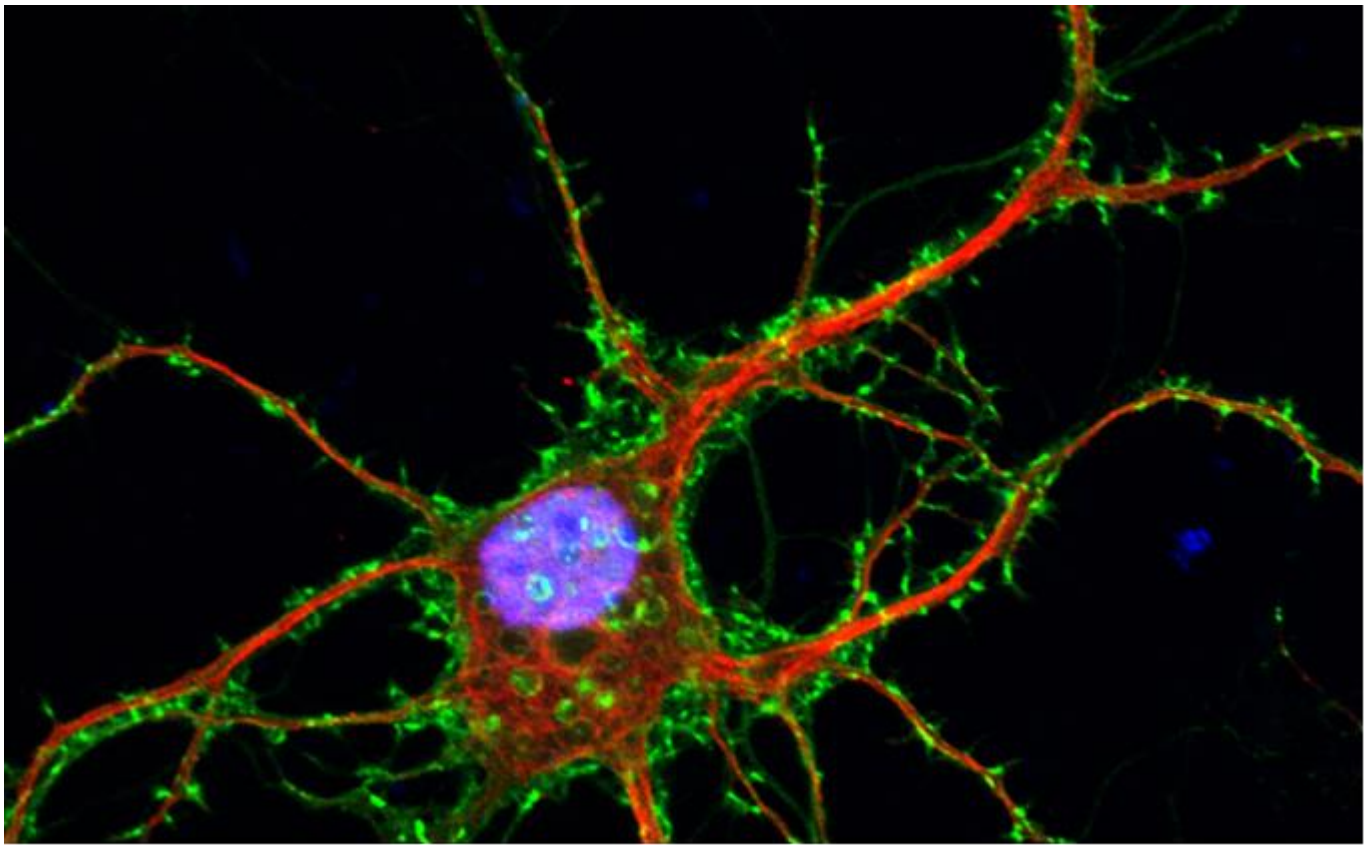

Figure 1: Immunocytochemistry of mouse primary cultured neuron (blue; nucleus, red; dendrite, green; post-synapse/spine). Researchers analyzed the morphology of spines which were stained with green.

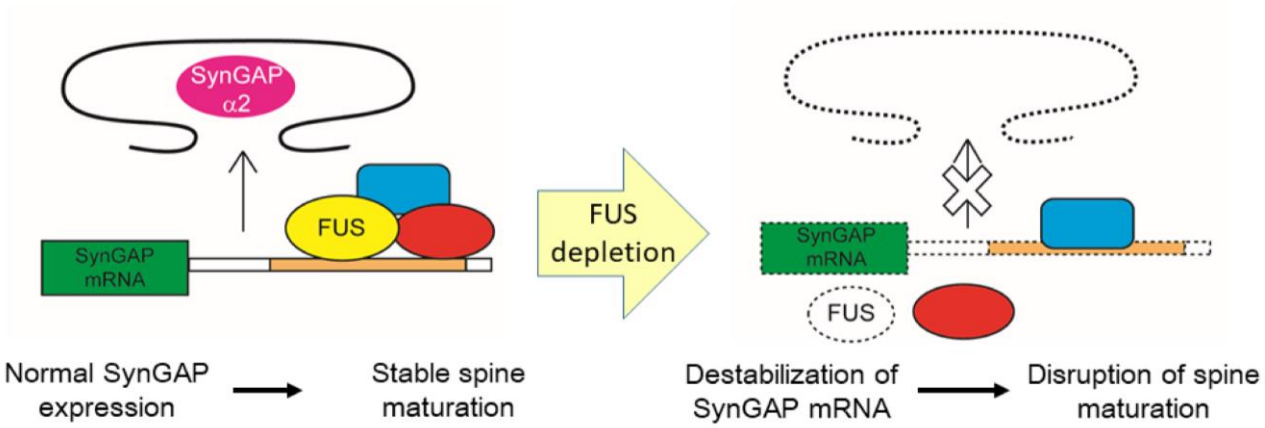

Figure 2: The graphical summary of the findings

Publication

Yokoi S, Udagawa T, Fujioka Y, Honda D, Okado H, Watanabe H, Katsuno M, Ishigaki S, Sobue G. 3'UTR length-dependent control of SynGAP isoform α2 mRNA by FUS and ELAV-like proteins promotes dendritic spine maturation and cognitive function. Cell Reports, 2017, in press.

DOI : http://dx.doi.org/10.1016/j.celrep.2017.08.100

Japanese ver.

https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Cell_R_20170927.pdf