News Release

Title

Disease-developing mechanism of Fronto-temporal lober degenetion by depletion of RNA-binding protein FUS.

Key Points

○ Depletion of RNA-binding protein FUS, a causative factor of fronto-temporal lober degeneration (FTLD) and amyotrophic lateral sclerosis (ALS) in the mouse hippocampus induces FTLD-like behavioral abnormalities

○ Synaptic dysfunction is the major cause of behavioral abnormalities upon FUS depletion

○ Introduction of synaptic glutamate receptor subunit GluA1 ameliorates behavioral abnormalities and synaptic dysfunction caused by FUS depletion

Summary

A group of researchers, headed by Prof. Gen Sobue, Department of Neurology, Nagoya University Graduate School Medicine (Dean: Masahide Takahashi, M.D., Ph.D.), revealed one of the disease-developing mechanism of fronto-temporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS) caused by depletion of RNA-binding protein FUS. This work was published online in *Nature Communications* on May 13th, 2015.

FTLD and ALS are devastating neurodegenerative diseases, both caused by mutations in genes related to RNA metabolism. One such gene is the RNA-binding protein FUS. Although extensive studies have been made to identify disease-developing mechanism by FUS, little is known about which RNA(s) is responsible for the pathophysiology and which event is the actual cause of the disease. To date, no treatment has been developed for these diseases.

FTLD patients display typical psychiatric abnormalities, such as dysinhibition, disturbance in personality, and social interaction deficit. Many psychiatric syndromes are caused by malfunctioning of synapses where neurons communicate with one another. Thus the researchers set out to investigate synaptic gene expression, synaptic transmission and behavioral phenotypes using FUS-depleted mice and neuron cultures. They found that FUS depletion reduced the level of one of the synaptic glutamate receptor subunit GluA1, inhibits synaptic transmission, and induces FTLD-like behavioral abnormalities in the mice. Moreover they demonstrated that introduction of GluA1 gene in the FUS-depleted mice brain ameliorates these defects.

These findings suggest that FTLD pathophysiology might be initiated by synaptic dysfunction. It would be interesting to see if ALS, another devastating neurodegenerative disease caused by mutations in FUS gene, has similar disease-developing mechanism. These findings could be useful in the future for the diagnosis or the treatment of these neurodegenerative diseases.

Research Background

Fronto-temporal lobar degeneration (FTLD) is a second frequent dementia after Alzheimer's disease, characterized by disturbance in personality and social interaction deficit. Amyotrophic lateral sclerosis (ALS) is a severe motor impairment caused by muscle weakness due to muscular atrophy. To date no treatment has been developed for these devastating progressive neurodegenerative diseases.

FTLD and ALS are apparently two different diseases. However, it is becoming obvious that these diseases are on the same spectrum of disorders, sharing the same disease-causing factors including FUS and another RNA-binding protein TDP-43. A number of studies have suggested that aberrant RNA metabolism caused by the loss of these RNA-binding proteins inhibits normal neuronal functions and affects disease symptoms. However, till now little is known about which RNA(s) is responsible for the symptoms and what event is the initial cause of the diseases.

Research Results

In this study, the researchers specifically investigated an RNA-binding protein FUS, one of the causative genes of FTLD and FUS. In terms of biological aspects, they focus on neuronal subcellular structure, called 'synapse', where neurons communicate with one another, because FTLD patients display many psychiatric symptoms that are often caused by synaptic malfunctioning.

They set out to investigate synaptic gene expression using FUS-depleted neuron cultures and found that FUS depletion reduced one of the synaptic glutamate receptors, GluA1. Moreover they demonstrated that FUS actually bound to the mRNA, a template for protein synthesis, produced from GluA1 gene and stabilized it, thus maintaining proper GluA1 protein level.

In parallel, they created the mouse model in which FUS level is reduced in the brain. These FUS-depleted mice displayed behavioral abnormalities such as hyperactivity, disinhibition, and social interaction deficit, reminiscent to FTLD patients. In accordance to the results in the culture model, GluA1 protein level was decreased in the FUS-depleted mice and synaptic function was inhibited as well. Finally, the researchers demonstrated that introduction of GluA1 gene in the brain of FUS-depleted mice ameliorated synaptic and behavioral abnormalities.

Thus, this study first demonstrated that FUS depletion in the brain results in FTLD-like behavioral abnormalities and found the underlying mechanism by which FUS regulates synaptic functions via the control of synaptic glutamate receptor expression.

Research Summary and Future Perspective

This study shed new light on disease-developing mechanism of FTLD and suggested that synaptic dysfunction might be one of the key events for the development of neurodegenerative

diseases. It would be important to investigate whether ALS, another devastating neurodegenerative disease caused by FUS mutations, is also caused by the similar mechanism because ALS has defects in 'neuromuscular junction', a structure connecting neuron to muscle cell, which is comparable to 'synapse'. These findings could be useful in future for the diagnosis or the treatment of these neurodegenerative diseases.

Article

Udagawa T, Fujioka Y, Tanaka M, Honda D, Yokoi S, Riku Y, Ibi D, Nagai T, Yamada K, Watanabe H, Katsuno M, Inada T, Ohno K, Sokabe M, Okado H, Ishigaki S, Sobue G. FUS regulates AMPA receptor function and FTLD/ALS-associated behaviour via GluA1 mRNA stabilization. *Nature Communications* 2015; 6; 7098 .

Japanese ver.

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