News Release

Title

Altered tau isoform ratio caused by loss of FUS and SFPQ function leads to FTLD-like phenotypes

Key Points

- The nuclear interaction between FUS and SFPQ is affected by disease mutations.
- FUS/SFPQ regulate tau isoforms by altering skipping of *Mapt* exon 10.
- Silencing of FUS or SFPQ in adult mice exhibits the FTLD-like phenotypes which is rescued by co-silencing of 4R-T.

Summary

Fused in sarcoma (FUS) and splicing factor, proline- and glutamine-rich (SFPQ) are RNA binding proteins that regulate RNA metabolism. We found that alternative splicing of the Mapt gene at exon 10, which generates 4-repeat tau (4R-T) and 3-repeat tau (3R-T), is regulated by interactions between FUS and SFPQ in the nuclei of neurons. Hippocampus-specific FUS- or SFPQ-knockdown mice exhibit frontotemporal lobar degeneration (FTLD)-like behaviors, reduced adult neurogenesis, accumulation of phosphorylated tau, and hippocampal atrophy with neuronal loss through an increased 4R-T/3R-T ratio. Normalization of this increased ratio by 4R-T specific silencing resulted in recovery of the normal phenotype. These findings suggest a biological link among FUS/SFPQ, tau isoform alteration, and phenotypic expression, which may function in the early pathomechanism of FTLD.

Research Background

Frontotemporal lobar degeneration (FTLD) is a pathological process that has been characterized by personality changes, abnormal behaviors, language impairment, and progressive dementia. The genetic and pathological similarities in fused in sarcoma (FUS), transactive response (TAR) DNA-binding protein 43 (TDP-43), and C9orf72 in relation to FTLD and amyotrophic lateral sclerosis (ALS) have recently lead to the recognition that the two conditions represent points on a spectrum of a single disease entity. Additionally, FTLD has also been classified as a tauopathy, characterized by an accumulation of phosphorylated microtubule-associated protein tau (tau) in affected neurons.

Research Results

FUS and SFPQ comprise the intranuclear complex that regulates alternative splicing of the *Mapt* gene at exon 10. Hippocampus-specific FUS- or SFPQ-knockdown mice exhibit frontotemporal lobar degeneration (FTLD)-like behaviors, reduced adult neurogenesis, accumulation of

phosphorylated tau, and hippocampal atrophy with neuronal loss through an increased 4R-T/3R-T ratio. Normalization of this increased ratio by 4R-T specific silencing resulted in recovery of the normal phenotype.

Research Summary and Future Perspective

These findings suggest that a biological link between FUS/SFPQ and the regulation of 4R-T/3R-T isoforms is involved in the early phase phenotypic expression of FTLD. The FUS and SFPQ-silenced mice that we generated are expected to be useful disease models for the development of therapeutics for FTLD.

Publication

Ishigaki S, Fujioka Y, Okada Y, Riku Y, Udagawa T, Honda D, Yokoi S, Endo K, Ikenaka K, Takagi S, Iguchi Y, Sahara N, Takashima A, Okano H, Yoshida M, Warita H, Aoki M, Watanabe H, Okado H, Katsuno M, Sobue G. Altered tau isoform ratio caused by loss of FUS and SFPQ function leads to FTLD-like phenotypes. *Cell Reports*, published online on Jan.31.

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