News Release

Title

Elucidation of the function of RNA binding protein, FUS, which is associated with neurodegenerative diseases.

Key Points

- **Binding of FUS downstream or upstream of polyadenylation signal leads to up- or down-regulation, respectively, of the generation of an alternative short transcript.**
- **Position-specific regulation of mRNA lengths by FUS is operational in two-thirds of transcripts in neuronal cells, with enrichment in genes involved in synaptic activities.**
- **Aberration of mRNA length may be a key event in neurodegeneration.**

Summary

Professor Kinji Ohno, Associate Professor Akio Masuda at Neurogenetics and his collaborator Professor Gen Sobue at Neurology in Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.) revealed that position-specific binding of FUS to nascent RNA regulates mRNA length.

FUS is a multi-functional RNA binding protein, which is associated with amyotrophic lateral sclerosis (ALS) and fronto-temporal lobar degeneration (FTLD). In this study, we globally analyzed FUS-mediated transcriptions and RNA processing in neuronal cells using six different next generation sequencing techniques. We found that binding of FUS in the interior portion of nascent RNA results in the stalling of RNA polymerase II (RNAP II) and premature termination of transcription. We also demonstrated that FUS interacts with CPSF160. When FUS binds downstream of the polyadenylation signal (PAS) of an alternative polyadenylation (APA) site, FUS promotes binding of CPSF160 to PAS-containing RNA and facilitates polyadenylation. In contrast, we observed that when FUS binds upstream of the PAS of an APA site, polyadenylation is not induced. Thus, binding of FUS downstream or upstream of PAS leads to up- or down-regulation, respectively, of the generation of an alternative short transcript. Our analysis revealed that position-specific regulation of mRNA lengths by FUS is operational in two-thirds of transcripts in neuronal cells, with enrichment in genes involved in synaptic activities. This work was published online in *Genes & Development* in May 15, 2015.

Research Background

FUS, originally identified as a fusion protein caused by a chromosomal translocation inhuman liposarcomas, has multiple functions including transcriptional regulation, nucleocytoplasmic shuttling, pre-mRNA splicing, miRNA processing, formation of stress granules, and RNA transport. Mutations in *FUS* have been identified in familial ALS as well as FTLD, however, it remains elusive how aberrations of these RNA binding proteins are linked to the neurodegeneration observed in ALS and FTLD.

Research Results

In this study, we comprehensively analyzed signatures of FUS in RNA-processing in neuronal cells using next generation sequencing technologies. ChIP-seq of RNAP II demonstrated that FUS stalls RNAP II and prematurely terminates transcription. When FUS binds downstream of a PAS, FUS enhances polyadenylation by recruiting CPSF160 and upregulates the alternative short transcript. In contrast, when FUS binds upstream of a PAS, polyadenylation is not activated and the RNAP II-suppressing effect of FUS leads to downregulation of the alternative short transcript. Thus, binding of FUS downstream or upstream of PAS leads to up- or down-regulation, respectively, of the generation of an alternative short transcript. CAGE-seq and PolyA-seq revealed that position-specific regulation of mRNA lengths by FUS is operational in two-thirds of transcripts in neuronal cells, with enrichment in genes involved in synaptic activities.

Research Summary and Future Perspective

Our findings suggest that position-specific binding of FUS to RNA is crucial for regulation of mRNA length, especially in genes involved in synaptic activities. Aberration of mRNA length may be a key event in neurodegeneration in ALS and FTLD.

<Article>

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Position-specific binding of FUS to nascent RNA regulates mRNA length.

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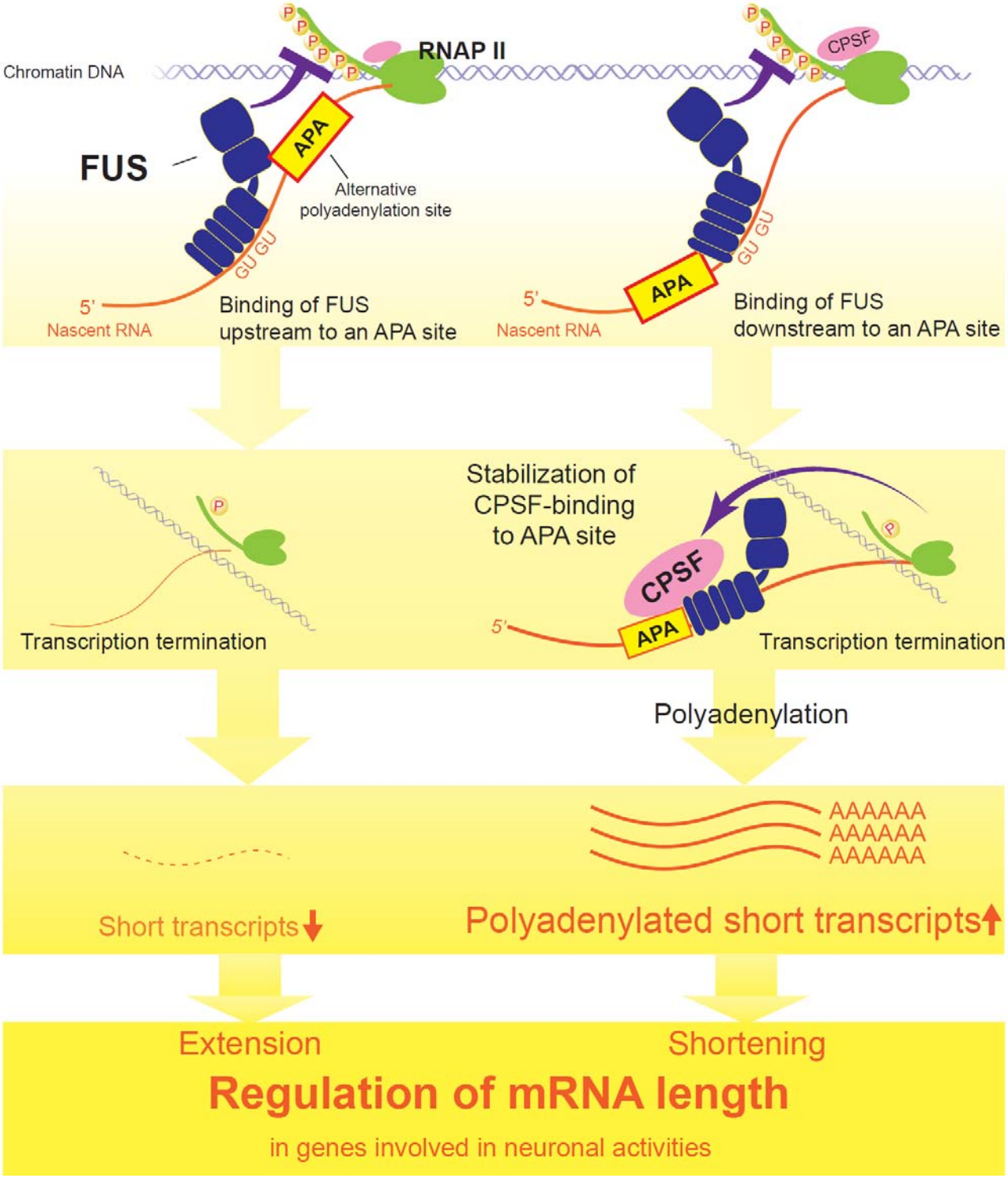
Japanese ver.

http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material_/nu_medical/_res/topix/2015/fus_20150515jp.pdf


Chromatin DNA
RNAP II
FUS
APA
Alternative polyadenylation site
GU GU
5'
Nascent RNA
Binding of FUS upstream to an APA site
CPSF
APA
Binding of FUS downstream to an APA site
Transcription termination
Stabilization of CPSF-binding to APA site
CPSF
APA
Transcription termination
Polyadenylation
AAAAAA
AAAAAA
AAAAAA
Short transcripts
Polyadenylated short transcripts
Extension
Shortening
Regulation of mRNA length
in genes involved in neuronal activities