MOLECULAR NEURODEGENERATION

LECTURE PRESENTATION Open Access

Mechanisms and models of TDP-43 proteinopathies

Leonard Petrucelli

From 2011 International Conference on Molecular Neurodegeneration
Shanghai, China. 22-24 September 2011

Background

Abnormal distribution, modification and aggregation of transactivation response DNA-binding protein 43 (TDP-43) are the hallmarks of multiple neurodegenerative diseases, especially frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) and amyotrophic lateral sclerosis (ALS).

Results

To explore the pathogenic properties of mutant forms of TDP-43, we generated and characterized two mouse lines expressing human TDP-43 carrying the M337V mutation (hTDP-43_{M337V}). We found hTDP-43_{M337V} was expressed primarily in the nuclei of neurons in the brain and spinal cord, intranuclear and cytoplasmic phosphorylated TDP-43 aggregates were frequently detected, and the levels of TDP-43 LMW products of ~25 kDa and ~35 kDa species were also increased. Overexpression of hTDP-43_{M337V} dramatically down regulated the levels of mouse TDP-43 (mTDP-43) protein and RNA, indicating TDP-43 levels are tightly controlled in mammalian systems. TDP-43_{M337V} mice displayed reactive gliosis, widespread ubiquitination, chromatolysis, gait abnormalities, and early lethality. Abnormal cytoplasmic mitochondrial aggregates and abnormal phosphorylated tau were also detected in the mice.

Conclusion

While overexpression of hTDP-43 in wild-type TDP-43 and TDP-43_{M337V} mouse models produces similar phenotypes, our results suggest that overexpression of the hTDP-43_{M337V} can cause neuronal dysfunction due to its effect on a number of cell organelles and proteins, such as mitochondria and TDP-43, that are critical for neuronal activity.

Mayo Clinic Jacksonville, USA

Published: 7 February 2012

doi:10.1186/1750-1326-7-S1-L19
Cite this article as: Petrucelli: Mechanisms and models of TDP-43 proteinopathies. *Molecular Neurodegeneration* 2012 **7**(Suppl 1):L19.