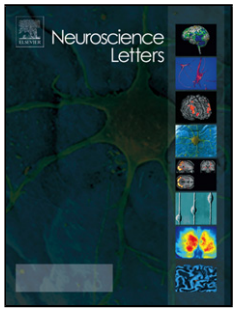

Title: TDP-43 interacts with mitochondrial proteins critical for mitophagy and mitochondrial dynamics

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TDP-43 interacts with mitochondrial proteins critical for mitophagy and mitochondrial dynamics

Stephani A. Davis[1,2], Sheed Itaman[1], Christopher M. Khalid-Janney[1], Justin A. Sherard[1], James A. Dowell[3], Nigel J. Cairns[4], Michael A. Gitcho[1,2,*]

[1]From the Department of Biological Sciences
[2]Delaware Center for Neuroscience Research, Delaware State University, Dover, DE 19901
[3]Wisconsin Institutes for Discovery, Madison, WI 53715
[4]Department of Neurology, Washington University School of Medicine, St. Louis, MO 63110

To whom correspondence should be addressed: Michael A. Gitcho, Ph.D., Delaware State University, Delaware Center for Neuroscience Research, 1200 North DuPont Highway, Dover, DE 19901, USA, Tel: (302) 857-6835, Fax: (302) 857-6512, email: mgitcho@desu.edu

Highlights

- Mitochondrial dysfunction is evident in age-related neurodegenerative diseases (Parkinson's disease, ALS, AD, and Huntington disease).
- TDP-43 is a major pathological protein in FTD, ALS, and AD and interacts with several mitochondrial proteins.
- TDP-43 interacts with and regulates MFN2 and PHB2, thus affects mitochondrial dynamics and mitophagy.
- We observed no increase in full-length TDP-43 in mitochondria in APP/PSEN1 mice, however there was a decrease in a 30kDa C-terminal TDP-43 fragment.
- Overexpression of the mitochondrial processing peptidase alpha subunit, PMPCA, increased 27kDa N-terminal TDP-43 expression.
- These observations expand our understanding of mitochondrial dynamics and may provide novel insights into the role TDP-43 plays in mitochondrial dysfunction.

ABSTRACT

Transactive response DNA-binding protein of 43kDa (TDP-43) functions as a heterogeneous nuclear ribonucleoprotein and is the major pathological protein in frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis/motor neuron disease (ALS/MND). TDP-43 pathology may also be present as a comorbidity in approximately 20 to 50% of sporadic Alzheimer's disease cases. In a mouse model of MND, full-length TDP-43 increases association with the mitochondria and blocking the TDP-43/mitochondria interaction ameliorates motor dysfunction. Utilizing a proteomics screen, several mitochondrial TDP-43-interacting partners were identified, including voltage-gated anion channel 1 (VDAC1) and prohibitin 2 (PHB2), a crucial mitophagy receptor. Overexpression of TDP-43 led to an increase in PHB2 whereas TDP-43 knockdown reduced PHB2 expression in cells treated with carbonyl cyanide m-chlorophenylhydrazone (CCCP), an inducer of mitophagy. These results suggest that TDP-43