Aberrant TDP-43–Translational Machinery Interactions Trigger Neurodegeneration

Ju Gao[1], Fan Tang[2], Mao Ding[1], Siyue, Qin[1], Jiawei Xu[1], Devanshi Shukla[1], Evelyn Guerrero[1], Jingjing Liang[3], Pan Li[2] and Xinglong Wang[1]

[1]Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, Tucson, AZ, USA.[2]Department of Psychiatry and Behavioral Sciences, Division of Neurobiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.[3]Department of Pharmacy Practice and Science, College of Pharmacy, University of Arizona, Tucson, AZ, USA.

TDP-43 (TAR DNA-binding protein 43) proteinopathy, characterized by the cytoplasmic accumulation and aggregation of ubiquitinated, phosphorylated, and truncated TDP-43 species along with its nuclear depletion, is a hallmark of several neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). While significant progress has been made in understanding the mechanisms of TDP-43 mislocalization and aggregation, the upstream triggers of these pathological processes remain elusive. Here, we demonstrate that disruption of TDP-43's interactions with translation-related proteins is a key driver of its pathological mislocalization, post-translational modification, and aggregation. Our previous data indicate that TDP-43 interacts with translation-related proteins through a small N-terminal motif, referred to as the translation-related protein binding motif (TBM). To investigate the functional consequences of this disruption, we generated a mouse model in which the interaction between TDP-43 and translation-related proteins is selectively impaired by deleting the TBM. These mice recapitulated hallmark features of TDP-43 proteinopathy, including progressive cytoplasmic mislocalization, phosphorylation, and aggregation of TDP-43, accompanied by age-dependent neuronal loss and gliosis. Single-nucleus RNA sequencing (snRNA-seq) analysis of these mice revealed distinct transcriptomic alterations in both neurons and glial cells. These changes prominently affected pathways involved in chromatin remodeling, RNA splicing, protein translation, and mitochondrial function—molecular processes that are consistently implicated in TDP-43–related neurodegenerative diseases. Together, our findings highlight the central role of TDP-43's interactions with translation-related proteins in maintaining cellular homeostasis and underscore their disruption as an early and critical trigger of TDP-43 proteinopathy in ALS and FTLD.

Sponsored By: grant from NIH 7RF1AG065342

Presenter Name and contact information:
Ju Gao, M.D., Assistant Research Professor
Department of Pharmacology & Toxicology
University of Arizona College of Pharmacy
Tucson, Arizona, USA
Email: jugao@arizona.edu