Stony Brook University
The Graduate School

Doctoral Defense Announcement

Abstract

Regulation of transposable elements by the ALS/FTD associated gene TDP-43

By

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TAR DNA Binding Protein 43 (TDP-43) pathology, in the form of ubiquitinated, hyperphosphorylated aggregates within the cytoplasm of neurons, is present in several neurodegenerative diseases. Amyotrophic lateral sclerosis and frontotemporal dementia are two examples where TDP-43 proteinopathies are a hallmark of the disease, with 95% and 45% of patients showing TDP-43 cytoplasmic inclusions on autopsy, respectively. A nuclear protein under normal conditions, TDP-43 plays roles throughout the RNA life cycle. Recent work has also shown a role for TDP-43 in regulating transposable elements (TEs). TEs make up ~45% of the human genome, and cells devote enormous resources to keep TEs suppressed. How TDP-43 regulates TEs is poorly understood. To this end, my dissertation work attempts to link known transcriptional regulatory mechanisms for TEs with TDP-43 interacting partners that help mediate TE silencing. I profiled transcriptomic and epigenomic alterations in TE loci following CRISPR mediated knock down of TDP-43 protein. As a positive control, I also manipulated global DNA methylation levels, using a chemical inhibitor of DNA methyltransferases, 5-azacytidine. I found that TDP-43 loss, in the context of 5-azaytidine treatment, led to both substantial and significant alterations in the transcriptomes and epigenomes of all major classes of TEs. Looking at correlated gene expression changes, I found that TDP-43 also regulates the expression of a large class of TE transcriptional regulators, the KRAB-Zinc finger protein family (KZFP). KZFPs are known to work together with the KZFP associated protein 1 (KAP1/TRIM28), and the SETDB1 complex to coordinate deposition of H3K9me3 histone marks at TE loci. Moreover, TDP-43 immunoprecipitation based proteomics profiles show direct interactions between TDP-43 and KAP1. Together, our results suggest that TDP-43: directly interacts with KAP1 protein, transcriptionally regulates KAP1's KZFP partners, and contributes to altered H3K9me3 marks at TE loci. While KAP1, the KZFPs, and SETDB1 are known regulators of TE expression, this protein complex has not previously been associated with TDP-43 function.

Date: April 30th, 2024 **Program**: Genetics
Time: 12:00pm **Dissertation Advisor**: Dr. Molly Gale-Hammell
Place: Hershey Building, East Wing, Cold Spring Harbor Laboratory
To attend virtually, contact the Program Director at martha.furie@stonybrook.edu