

TDP-43 dysregulation promotes pathological tau accumulation and spread

Sarah M. Waldherr¹, Vaishnavi S. Jadhav^{1,2}, Aaron Long^{1,2}, and Nicole F. Liachko^{1,2}

¹ GRECC, Veterans Affairs Puget Sound Health Care System, Seattle, WA 98108, USA.

² University of Washington, Seattle, WA 98195, USA.

Alzheimer's disease (AD) is defined by the presence of amyloid beta (A β) and tau aggregates in the brain. However, up to half of AD patients also accumulate TDP-43 aggregates as a secondary pathology (LATE-AD). Clinically, LATE-AD patients have more severe cognitive impairment, more rapid cognitive decline, worse brain atrophy, and a shorter disease course. In these patients, TDP-43 dysfunction may synergize with neurodegenerative processes in AD, worsening disease. Using *C. elegans* models of mixed pathology, we have found that TDP-43 specifically synergizes with tau but not A β , resulting in enhanced neuronal dysfunction, selective neurodegeneration, and increased accumulation of pathological tau. To extend our results into a mammalian system, we have created two new mouse models of tau and TDP-43 co-pathology: one that uses dual transgene driven constitutive expression of tau and TDP-43 throughout the nervous system, and a second that combines constitutive transgenic expression of tau with adeno-associated virus (AAV) driven expression of TDP-43. Constitutive co-expression of tau and TDP-43 leads to mild neurological deficits, but no enhancement of pathologies up to 18 months of age. However, AAV-driven expression of TDP-43 in the adult brain promotes increased phosphorylated tau that spreads beyond the site of injection. Our data suggest additional "hits" may be needed to potentiate sustained co-pathology in an adult mouse brain, and also implicate astrocytes promoting neuroprotection against co-morbid tau and TDP-43.

Sponsored By: NIH R01AG066729 and VA ISRM I01BX005762

Presenter Name and contact information:

Nicole Liachko, Ph.D., Associate Professor

Department of Medicine, Division of Gerontology and Geriatric Medicine

University of Washington

Seattle, WA, USA

Email: nliachko@uw.edu