Interactions Between Autophagy, Herpesvirus and Neurodegeneration in Alzheimer's Disease

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Introduction: Various microbes and viruses have been proposed to be involved in the pathogenesis of Alzheimer's Diseases (AD). Since microbes and viruses are detected in aging brains, it is not clear if their presence is a byproduct of AD pathology or a direct cause of it. Recently various publications considered the link between several herpesviruses and neurodegeneration in AD. Readhead et al. 2018 utilized multiomics data from post-mortem brain samples with and without neuropathological criteria for AD to construct biological networks and look for associations between viral load, viral activity and AD. This study reported strongest associations between human herpesviruses 6A and 7 with various features of AD. After viral replication and exit from the cell's nucleus, a secondary envelopment process by which HSV acquires its envelope, structurally resembles the process of autophagy. Thus, autophagy might have significant interactions with herpesviruses. Here we sought to determine associations between viral features, AD pathology and autophagy gene allelic variation.

Methods and Results: We prepared a comprehensive list of over 1000 autophagy-associated genes (ATG) from Tanpaku, PDB databases and genes we found in publications, as well as from an artificial-intelligence-based search for "dark ATG genes". We downloaded the R codes and datasets from Readhead et al. 2018 available on synapse.org. Using custom python codes we mined these digital datasets for ATG. We mined host RNA abundance in pre-AD, non-AD traits, and AD controls for ATG and found virtually all were down regulated in AD compared to controls. We mined quantitative trait loci (QTL) for correlations of host SNPs to viral load in preclinical and clinical AD and found many ATG SNPs associated with viral features. We found QTL of host genes to identify SNPs in ATG that correlated with cognition and Braak stage. We found a dozen genes associated with SNPs in ATG that associated with AD.

Conclusions: Results from mining different datasets with our comprehensive ATG list supported our initial hypothesis of a correlation between ATG expression and SNPs, viral load and progression of cognitive impairment and AD pathology. The integration of ATG in this project clarifies a potential role microbes and viruses may play in onset and progression of AD pathology.

Supported by NCRR and NCATS UL1TR001449.

"This project is supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences of the National Institutes of Health through Grant Number UL1TR001449."