Researchers gain better understanding of mechanism behind tau spreading in the brain

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Researchers at Mount Sinai School of Medicine have gained insight into the mechanism by which a pathological brain protein called tau contributes to the progression of Alzheimer's disease (AD) and other neurodegenerative disorders. This finding, published in the most recent issue of the *Journal of Biological Chemistry,* may provide the basis for future investigations on how to prevent tau from damaging brain circuits involved in cognitive function.

Previous studies have shown that the abnormal folding, or misfolding, and buildup of tau are key neuropathological features of many neurodegenerative disorders, including AD. Some research has demonstrated that AD-type tau neuropathology spreads in the brain, seemingly moving from one brain cell to another.

A research group led by Giulio Maria Pasinetti, MD, PhD, Saunders Family Chair in Neurology at Mount Sinai School of Medicine, explored whether misfolded tau released by neurons from the human brain – also known as paired helical filaments (PHFs) – could actually be taken up by surrounding cells and promote the spread of tau neuropathology. The evidence was gathered by treating human neuronal cell lines with human Alzheimer's disease-derived PHFs. The researchers found that not only did the cells in fact internalize the human PHFs, the abnormal tau then propagated its abnormal state to the native, normal tau protein in the cells.

"While these findings are potentially important for possibly opening new

therapeutic avenues in Alzheimer's disease, they also shed light on a new therapeutic target for a wide variety of disorders sharing pathological features with Alzheimer's disease, for which there are currently no cures," said Dr. Pasinetti. "Such diseases include Progressive Supranuclear Palsy, frontotemporal dementia, and other devastating neurodegenerative disorders in which misfolded tau forms aggregates in the brain."

Next the researchers treated the same cell lines with a grape-seed extract enriched in polyphenols, which are natural compounds found in grapes, fruits, and vegetables, based on 2011 research showing the efficacy of this extract in preventing the progression of AD in mice. Dr. Pasinetti's group found that a subfraction of this natural grape-seed extract enriched in polyphenols was able to prevent the cell-to-cell spread of tau pathology in the same human neuronal cell lines.

"Pathology in neurodegenerative disorders is thought to be initiated decades before disease onset," said Dr. Pasinetti. "While further research is needed in humans, we hypothesize that this grape-derived compound may be a promising therapy for not only treating but preventing neurodegenerative disorders involving tau neuropathology."

Dr. Pasinetti and Jun Wang, PhD, Assistant Professor of Neurology at Mount Sinai, are named inventors of a pending application filed by Mount Sinai School of Medicine titled "Methods Preventing Neurodegenerative Disease" related to the use of grape-seed extracts for the treatment of neurodegenerative diseases and may benefit financially from this patent.

Provided by The Mount Sinai Hospital