

11<sup>th</sup> International Conference on

# Alzheimers Disease & Dementia

May 24-25, 2018 | Vienna, Austria

## Neuropathophysiology cross-talk between Alzheimer's and Parkinson's disease

Li Zeng<sup>1,5</sup>, Zhongcan Chen<sup>1</sup>, Wei Zhang<sup>1</sup>, Ling Ling Chua<sup>1</sup>, Chou Chai<sup>1</sup>, Rong Li<sup>2</sup>, Lin Lin<sup>3,4</sup>, Zhen Cao<sup>1</sup>, Dario C Angeles<sup>1</sup>, Lawrence W Stanton<sup>3</sup>, Jianhe Peng<sup>2</sup>, Zhi Dong Zhou<sup>1,5</sup>, Kah Leong Lim<sup>1,4,5</sup> and Eng King Tan<sup>1,5</sup>

<sup>1</sup>National Neuroscience Institute, Singapore

<sup>2</sup>The Experimental Therapeutics Centre (ETC)—A\*STAR, Singapore

<sup>3</sup>Genome Institute of Singapore (GIS)—A\*STAR, Singapore

<sup>4</sup>National University of Singapore, Singapore

<sup>5</sup>DUKE-NUS Medical School, Singapore

**Background:** Leucine-rich repeat kinase 2 (LRRK2) mutations are the most common genetic cause of familial and sporadic Parkinson's disease (PD). Amyloid precursor protein (APP) is an important molecule in Alzheimer's disease (AD). Although recent research revealed that there might be common pathophysiological and genetic links between these two diseases, little is known about the potential biological interplay between LRRK2 and APP.

**Materials & Methods:** Here, we used LRRK2 G2019S mouse models and induced pluripotent stem cell (iPSC)-derived neurons from PD patients to investigate the potential pathophysiological interplay between LRRK2 and APP in PD.

**Results:** We demonstrate here that LRRK2 interacts with APP and LC/MS/MS analysis revealed LRRK2 phosphorylates APP at threonine-668 (T668). This in turn stimulates the production of the APP intracellular domain (AICD) and enhances AICD nuclear translocation, which is associated with the dopaminergic neuron loss in aging LRRK2 G2019S mutant mice. Importantly, we found that the expression of AICD exacerbates LRRK2 G2019S-induced neurotoxicity, whereas phospho-mutant AICD (T668A) has no effect on LRRK2 G2019S-induced neuronal loss in vitro and in LRRK2 G2019S mutant mice. Moreover, dopaminergic neurons generated from LRRK2 G2019S patient-derived induced pluripotent stem cells exhibit significantly elevated phospho-APP T668 levels relative to their counterparts derived from healthy individuals. The level of T668-phosphorylated APP is also significantly increased in LRRK2 G2019S post-mortem human brain tissues. Treatment with LRRK2 inhibitors reduces phosphorylation at T668 in LRRK2 G2019S patient's dopaminergic neurons and in LRRK2 G2019S mutant mice.

**Discussion:** APP and LRRK2 are physically and functionally linked, suggesting a shared pathway between the two most common neurodegenerative diseases that may help explain their overlapping pathology, especially in advanced stages of the respective disease.

**Conclusions:** APP is a substrate of LRRK2, and its phosphorylation promotes AICD function and neurotoxicity in PD.

### Biography

Li Zeng is currently working as Senior Research Scientist and Principal Investigator at Neural Stem Cells Research Laboratory at National Neuroscience Institute, Singapore. He has published more than 25 papers in reputed journals and has been serving as an Editorial Board Member of *repute*.

Li\_Zeng@nni.com.sg

### Notes: