

# 9<sup>th</sup> Global Neuroscience Conference

November 21-22, 2016 Melbourne, Australia

## Autophagy dysregulation in amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is an adult-onset devastating neurodegenerative disease resulted from the selective death of motor neurons (MNs) associated with abnormal protein aggregation in the spinal cord and brain. We have demonstrated that autophagy impairment may underlie the pathogenesis of ALS. Mutations in the genes encoding SOD1, TDP-43, OPTN and VCP can cause misfolding proteins and autophagy induction. It is still under debate whether autophagy has a protective or detrimental role in ALS. We have found that the macroautophagy is specifically activated in the MNs of SOD-1 mouse model of ALS at early stages. In addition, we have demonstrated that mTOR-dependent autophagy enhancer rapamycin treatment in the ALS animal model causes accumulation of AVs, but fails to reduce the level of mutant SOD1 aggregates, suggesting the abnormal autophagic flux in ALS. In addition, rapamycin treatment results in severe mitochondrial impairment, higher Bax levels and greater caspase-3 activation. On the contrast, application of mTOR independent autophagic enhancer trehalose prolongs the motor neuron survival and ameliorates autophagic flux defect in the ALS model. Recently, a study of whole exome sequencing in 2,874 ALS patients vs. 6,405 controls identified TANK-Binding Kinase 1 (TBK1) as an ALS gene. TBK1 is known to bind to and phosphorylate a number of proteins involved in innate immunity and autophagy, including optineurin (OPTN) and p62 (SQSTM1/sequestosome). These observations reveal a key role of the autophagic pathway in ALS, which may provide useful information designing to target on autophagy for the potential therapeutic intervention of this devastating disease.

### Biography

Weidong Le, MD, PhD is a Neurologist/Scientist with a major research interest in neurodegenerative disorders including Parkinson's disease, Alzheimer's disease and ALS. He graduated from Shanghai 2nd Medical University with a Doctoral degree in 1988, and received Post-doctoral Training at Dr. Stanley Appel's Laboratory from 1989-1991. He was promoted to Professor of Neurology in 2005 at Baylor College of Medicine; and since 2013, he is appointed as the Director of Center for Translational Research on Neurological Diseases and Vice President of 1st Affiliated Hospital, Dalian Medical University. He is a Full Affiliate Member of Houston Methodist Research Institute. He has published over 200 SCI papers in peer reviewed journals and 7 scientific books, and serves as Board Member or Associate Editor for 8 international journals.

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