Spherical TDP-43 Oligomers Likely Play a Key Role in the Mechanism of Neurodegenerative Diseases

Dr. Yun-Ru (Ruby) Chen, Assistant Research Fellow at the Genomics Research Center, and her colleagues recently discovered that the mechanism of neurodegenerative diseases that are caused by the protein TDP-43 is likely linked to the generation of toxic TDP-43 amyloid oligomers. These soluble aggregates are one of the likely causes of nerve cell degeneration and death. The research was published in the top journal *Nature Communications* on September 12, 2014.

TDP-43 is a major disease-causing protein in frontotemporal lobar dementia (FTLD) and amyotrophic lateral sclerosis (ALS), and abnormalities in TDP-43 leading to formation of TDP-43 inclusions also occur in a subset of Alzheimer's' patients and some other neurodegenerative diseases. FTLD with tau and α-synuclein negative but ubiquitin-positive inclusions (FTLD-TDP) is a major subtype of FTLD. FTLD is the second most prevalent cortical dementia occurring before the age of 65 years. ALS is a neurodegenerative disease characterized by progressive loss of motor neurons followed by weakness and muscular wasting, which ultimately results in paralysis and death.

Amyloids are defined as proteins that are prone to aggregate into amyloid fibrils composed of specific cross-β structures, which can be probed by Thioflavin-T (ThT) and Congo Red staining. They have been associated with the pathology of more than 20 serious human diseases including Alzheimer's, Parkinson's, and Huntington's diseases. Among which amyloid-β (Aβ) oligomer is considered the major culprit in Alzheimer's disease. Although TDP-43 is found in the form of inclusion bodies (aggregates) in the neurons of disease patients, TDP-43 inclusion bodies have not been classified as amyloids as the pathologic amyloid staining results have not been conclusive.

Dr. Chen and collaborators discovered that full-length TDP-43 readily forms spherical oligomers. The oligomers react with amyloid oligomer-specific antibody showing that TDP-43 shares common properties of amyloids. The TDP-43 oligomers are conformational and functionally distinct from native TDP-43 and are neurotoxic. Interestingly, the oligomers can convert Alzheimer's amyloid-β (Aβ) to form Aβ oligomers rather than fibrils. The result implicates a potential role of TDP-43 oligomers in Alzheimer's disease.

The team further proved that these TDP-43 oligomers exist in the FTLD-TDP patients by a specific conformational-dependent TDP-43 antibody and confirmed their result by immunoprecipitation and immunolabelling under electron microscope. They also found that such oligomers are present in the forebrain of transgenic TDP-43 mice and increase with age. Overall, the results demonstrated that a possible disease mechanism of TDP-43 proteinopathies is linked to the generation of toxic amyloid oligomers.

The full article is entitled “Full-length TDP-43 forms toxic amyloid oligomers that are present in frontotemporal lobar dementia-TDP patients” and is available at the Nature Communications website at:
http://www.nature.com/ncomms/2014/140912/ncomms5824/full/ncomms5824.html

The full list of authors is: Yu-Sheng Fang, Kuen-Jer Tsai, Yu-Jen Chang, Patricia Kao, Rima Woods, Pan-Hsien Kuo, Cheng-Chun Wu, Jhih-Ying Liao, Shih-Chieh Chou, Vinson Lin, Lee-Way Jin, Hanna S. Yuan, Irene H. Cheng, Pang-Hsien Tu, and Yun-Ru Chen