DEPLETION OF ENDOGENOUS KIF5B AMELIORATES TAU HYPERPHOSPHORYLATION, AGGREGATION AND MEMORY IMPAIRMENT IN MODELS OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is the most prevalent form of dementia, which leads to an impairment of many cognitive functions and memory loss. Dysregulation of axonal transport is linked to the pathogenesis of several neurodegenerative diseases including AD and tauopathies, but the specific contributions of each fast axonal transport motor such as kinesin-I to the underlying mechanisms of AD and tauopathies have not been clarified. The kinesin-1 motor transports several cargos crucial for neuronal development and functioning. Kinesin 1 (or KIF5) can form a complex with cargo in the presence or absence of light chains. In mammals, three Kif5 genes have been identified: Kif5a, Kif5b, and Kif5c. Abundant expression of kinesin-1 family genes has been shown to accelerate neuronal dysregulation in AD patients. Despite the normal neuronal function of kinesin-1, the dysfunction of these motor proteins leading to neurodegenerative diseases is not fully understood. Hence we hypothesize that the Kinesin 1 (Kif5B) motor domain protein interacts with tau leading to AD or Tauopathies, and how the reduction of kinesin-1 would be neuroprotective in AD despite kinesin-1's functional significance in normal neurons. To investigate the role of Kif5B on tau phosphorylation and aggregation, we reduced the levels of KIF5B in both cell and mouse of tau. Surprisingly, Kif5B siRNA knockdown reduced the phosphorylation of tau at PHF-1 and CP13 phosphoepitopes without influencing the levels of total tau in SHSY5Y-P301L Tau cells. In order to establish that our in vitro observations also stand in vivo, we crossed the heterozygous knock out Kif5B mice with the homozygous P301S Tau mice. The heterozygous Kif5B (+/-) and P301S Tau mice were born in the expected proportion and did not show changes in body weight. To check the memory reconsolidation and retention in in P301S+/_ and P301S+/- Kif5B+/- along with their approximate control Wt type mice, a contextual fear conditioning test was performed. The 2-day training with pre-shock, 24-hour context and 24-hour cue-tone assessments results clearly demonstrated that P301S+/- Kif5B+/- groups exhibited a prolonged freezing time with improved memory function in the hippocampus when compared with the P301S+/- mice. In an immunohistochemical analysis of brain slices, P301S-Tau;Kif5B+/- always showed qualitatively fewer AT8-positive neurons compared with P301S-Tau; Kif5B1+/+. In Western blotting analysis, we also found that the level of insoluble Tau at various phosphoepitopes AT8, AT180, AT100, PHF-1 were significantly reduced in the brain of P301S-Tau/Kif5B+/- mice. In contrast, the P301STau heterozygous mice show abundant accumulation of phospho Tau species which are clear signs of neurofibrillary tangles. It is interesting to note that KIF5B reduction promoted autophagy which is in part responsible for the reduction of Tau. In nutshell, we demonstrate the molecular interaction between KIF5B and Tau in the process of tau phosphorylation and deregulation thus may expand our knowledge on the pathogenesis of AD and other tauopathies

BIOGRAPHY:

Dr. D.Siva Sundara Kumar is presently an associate professor and head in the Department of Microbiology, School of Life Sciences, Central University of Tamil Nadu, India. Prior to this he served at the Hong kong Baptist University, Hong Kong, as Research Assistant Professor (2012-2017). He has been involved with teaching and research activities in HKBU in the area of cell biology, neurodegenerative diseases, microbiology etc. In order to extend his expertise in the neuroprotective strategies for treating neurodegenerative diseases, he was pleased to accept a postdoctoral fellow position in Hong Kong Baptist University (HKBU) (2006-2012). He is interested to understand the molecular mechanisms of Alzheimer's disease and Parkinson's disease and developing druggable targets for drug discovery using in vitro and in vivo approaches. These interests led him to use appropriate assay models to screen several natural small molecules. In addition to research, he has contributed to lab management and supervised PhD students, postdoctoral fellows, and senior research assistants on neurodegenerative diseases related research topics. His experience with outstanding mentors has made him realize the impact good teachers can make on students' lives. He has published 42 papers in peer reviewed journals (H-index: 20) and obtained 4 international patents. He has visited more than 14 foreign countries which includes USA, UK, South Africa, Belgium, Australia, Germany, France, Finland, China, etc., to present papers and lectures.