Role of WWOX and Parkin in Parkinson disease

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Tumor suppressor WWOX is a recently defined risk factor for Alzheimer's disease. Indeed, loss of WWOX in newborns leads to development of severe neural disease, metabolic disorders and early death. To determine the role of WWOX in Parkinson disease (PD), we showed that when rats were exposed to 1-methyl-4-phenylpyridinium (MPP+) neurotoxin. WWOX is upregulated and activated via phosphorylated at Tyr33. PD-associated protein, Parkin, physically binds WWOX, as determined by yeast two-hybrid system and Förster resonance energy transfer (FRET) analysis. By co-immunoprecipitation, endogenous WWOX physically binds Parkin. FRET analysis also showed that Y33R-WWOX mutant and dnWWOX for blocking Y33 phosphorylation abrogated WWOX interaction with Parkin. Functionally, transiently overexpressed WWOX and/or Parkin induced apoptosis in SK-N-SH neuroblastoma. To narrow down the specific region(s) that mediates apoptosis, transiently overexpressed WW domain and Parkin induce apoptosis in an additive manner. FRET analysis revealed that post treatment with MPP+ for 16 hr, there was an enhanced binding of WWOX with Parkin in SK-N-SH cells. Further, MPP+ significantly up-regulated Parkin, pY33-WWOX, and p-ERK, along with complex formation of WWOX and Parkin, in which 17b-estradiol (E2) dissociated WWOX from Parkin. Triple-protein signaling analysis revealed that MPP+ initiated the WWOX/Tau/Parkin signaling, which drove the cells to death in vitro. MPTP induced rapid dopaminergic neuron loss in substantia nigra in Wwox wild type, rather than in heterozygous mice. Together, the WWOX/Tau/Parkin signaling contributes to the pathogenesis of PD and E2 blocks the effect, suggesting that the neuroprotective effect of E2 in MPP+-induced neuronal death.

Biography

Nan-Shan Chang is currently the Professor of the Molecular Medicine Institute, National Cheng Kung University (NCKU) in Taiwan. Dr. Chang is most noted for his discovery of tumor suppressor WWOX in 2000. Key Awards: Breast cancer and neurofibromatosis research awards from the Department of Defense, USA, in 2008 and 2010; Distinguished Professor Award 2010 to present from NCKU (4 times); Distinguished Scientist Award 2011 from the Society of Experimental Biology & Medicine, USA.

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