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Tumor suppressor WWOX limits neurodegeneration and Zfra mitigates the symptoms of Alzheimer's disease

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Substantial evidence reveals that tumor suppressor WW domain-containing oxidoreductase (known as WWOX, FOR or WOX1) blocks the progression of Alzheimer's disease (AD). We have first demonstrated that WWOX binds tau and tau-hyperphosphorylating enzymes GSK3 β , ERK and JNK1 and thereby inhibits tau hyperphosphorylation. In addition, WWOX promotes neuronal differentiation. Unfortunately, WWOX is frequently down-regulated in the AD hippocampi. And this down-regulation results in spontaneous aggregation of TIAF1 and TRAPPC6A Δ which leads to caspase activation, tau aggregation, APP degradation, formation of amyloid β and plaques in humans and in Wwox gene knockout mice. When WWOX protein is lost due to alteration of WWOX/Wwox gene such as missense or nonsense mutation and deletion, this leads to ataxia, epilepsy, dementia, neurodegeneration, diseases associated with HDL lipid metabolism and early death in humans, mice and rats. Our studies revealed that significant up-regulation of proteins which are involved in neurodegeneration is found in the cortex and hippocampus of Wwox gene knockout mice. These proteins include; GSK3 Δ , ERK, pERK, JNK1, pJNK1, TIAF1, pS35-TIAF1, TRAPPC6A Δ , pS37-TRAPPC6A Δ , α -synuclein, C9orf72, TDP-43 and others. Notably, a zinc finger-like peptide Zfra is able to ameliorate the symptoms of AD in the triple transgenic mice including neuronal death and memory and learning capabilities suggesting its potential use in therapy for AD.

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