Truncated Tau Induces Mitochondrial Transport Failure Through the Impairment of TRAK2 Protein and Bioenergetics Decline in Neuronal Cells

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Mitochondria are highly specialized organelles essential for the synapse, and their impairment contributes to the neurodegeneration in Alzheimer?s disease (AD). Previously, we studied the role of caspase-3?cleaved tau in mitochondrial dysfunction in AD. In neurons, the presence of this AD-relevant tau form induced mitochondrial fragmentation with a concomitant reduction in the expression of Opa1, a mitochondrial fission regulator. More importantly, we showed that caspase-cleaved tau affects mitochondrial transport, decreasing the number of moving mitochondria in the neuronal processes without affecting their velocity rate. However, the molecular mechanisms involved in these events are unknown. We studied the possible role of motor proteins (kinesin 1 and dynein) and mitochondrial protein adaptors (RhoT1/T2, syntaphilin, and TRAK2) in the mitochondrial transport failure induced by caspase-cleaved tau. We expressed green fluorescent protein (GFP), GFP-full-length, and GPF-caspase-3?cleaved tau proteins in rat hippocampal neurons and immortalized cortical neurons (CN 1.4) and analyzed the expression and localization of these proteins involved in mitochondrial transport regulation. We observed that hippocampal neurons expressing caspase-cleaved tau showed a significant accumulation of a mitochondrial population in the soma. These changes were accompanied by evident mitochondrial bioenergetic deficits, including depolarization, oxidative stress, and a significant reduction in ATP production. More critically, caspase-cleaved tau significantly decreased the expression of TRAK2 in immortalized and primary hippocampal neurons without affecting RhoT1/T2 and syntaphilin levels. Also, when we analyzed the expression of motor proteins?Kinesin 1 (KIF5) and Dynein?we did not detect changes

in their expression, localization, and binding to the mitochondria. Interestingly, the expression of truncated tau significantly increases the association of TRAK2 with mitochondria compared with neuronal cells expressing full-length tau. Altogether these results indicate that caspase-cleaved tau may affect mitochondrial transport through the increase of TRAK2?mitochondria binding and reduction of ATP production available for the process of movement of these organelles. These observations are novel and represent a set of exciting findings whereby tau pathology could affect mitochondrial distribution in neurons, an event that may contribute to synaptic failure observed in AD.

kinesin

mitochondria

tau

TRAK2/Milton

transport

truncated tau

adenosine triphosphatase

caspase

caspase 3

dynein adenosine triphosphatase

green fluorescent protein

hypochlorite sodium

kinesin 1

kinesin 5A

lipofectamine

membrane protein

mitochondrial protein

outer membrane protein

Rho factor

RhoT1 protein

RhoT2 protein

superoxide

syntaphilin

tau protein

TRAK2 protein

unclassified drug

animal cell

animal experiment

Article

bioenergy

cell structure

cell transport

controlled study

depolarization

epifluorescence microscopy

genetic transfection

hippocampal neuronal culture

immunofluorescence

mitochondrial membrane potential

mitochondrial permeability

mitochondrion

mRNA expression level

nerve cell

nonhuman

oxidative stress

protein expression

protein localization

protein phosphorylation

protein processing

rat

real time polymerase chain reaction

retrovirus infection

Western blotting