CHIP facilitates the aggregation of toxic phophorylated tau species

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ABSTRACT

Accumulation of the microtubule associated protein tau into neurofibrillary lesions is a pathological consequence of several neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease. Hereditary mutations in the MAPT gene were shown to promote the formation of structurally distinct tau aggregates in patients that had a parkinsonian-like clinical presentation. Whether tau aggregates themselves or the soluble intermediate species that precede their aggregation are neurotoxic entities in these disorders has yet to be resolved; however, recent in vivo evidence supports the latter. We hypothesized that depletion of CHIP, a tau ubiquitin ligase, would lead to an increase in abnormal tau. Here, we show that deletion of CHIP in mice leads to the accumulation of non-aggregated, ubiquitin-negative, hyper-phosphorylated tau species. CHIP-/- mice also have increased neuronal caspase-3 levels and activity, as well as caspase-cleaved tau immunoreactivity. Over-expression of mutant (P301L) human tau in CHIP -/- mice is insufficient to promote either argyrophilic or "pre-tangle" structures, despite marked phospho-tau accumulation throughout the brain. These observations are supported in post-developmental studies using RNA interference for CHIP (chn-1) in C. elegans and cell culture systems. Our results demonstrate that CHIP is a primary component in the ubiquitin-dependent degradation of tau. We also show that hyper-phosphorylation and caspase-3 cleavage of tau both occur prior to aggregate formation. Based on these findings, we propose that poly-ubiquitnation of tau by CHIP may facilitate the formation of insoluble filamentous tau lesions.

CONCLUSION

Neither hyper-phosphorylation nor caspase-3 cleavage of tau, alone or in combination, are sufficient to induce aggregation of tau in the absence of CHIP, indicating that CHIP may function to not only facilitate proteasomal degradation of phospho-tau species, but that NFTs may actually be a protective mechanism of the neuron while an intermediate(s) are the cause of cognitive impairment and neurodegeneration in tauopathies. This also demonstrates that hyper-phosphorylation and caspase-3-mediated tau cleavage are occurring prior to aggregation, and that perhaps their effects on soluble tau species are the primary neurotoxic events in the pathogenic cascade. The CHIP-/- mice also demonstrate that tau phosphorylation may be a much more dynamic process than currently thought. The accumulation of endogenous phospho-tau in the CHIP-/- mice suggests that tau phosphorylation is an ongoing process under normal conditions and deletion of CHIP results in its accumulation. Thus wildtype mice with an intact repertoire of degradative components are able to prevent tau accumulation, but not aggregation, while the CHIP-/- mice accumulate massive amounts of non-aggregated, ubiquitin-negative, phospho-tau. Therefore a very delicate balance must be maintained between de novo synthesis, phosphorylation, microtubule binding, and degradation of tau for proper neuronal function. Certainly there would be redundancies in place to compensate for the loss of one of these critical factors involved, a phenomenon that may account for the CHIP-/- mice that lack a degenerate phenotype. In summary, CHIP reduces the accumulation of phospho-tau species within the brain, but may promote its sequestration into aggregates under diseased conditions.

FUNDING

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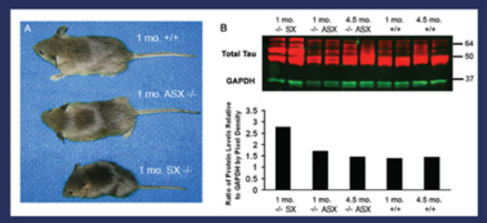
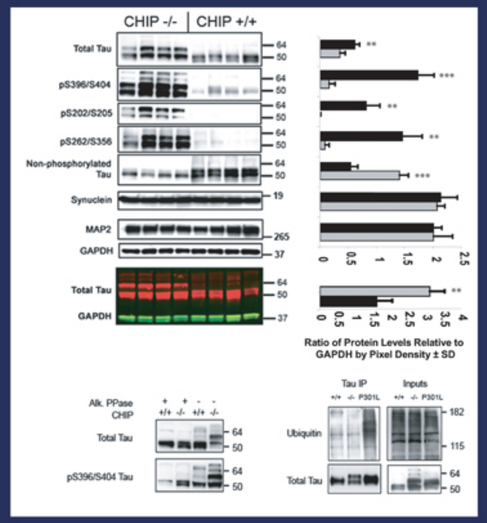
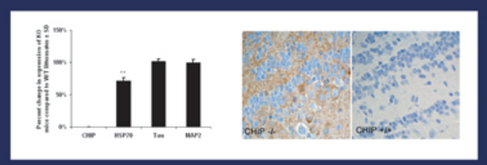
A large subset of CHIP-/- mice demonstrates P30-35 morbidity and marked accumulationof cerebral phospho-tau levels.



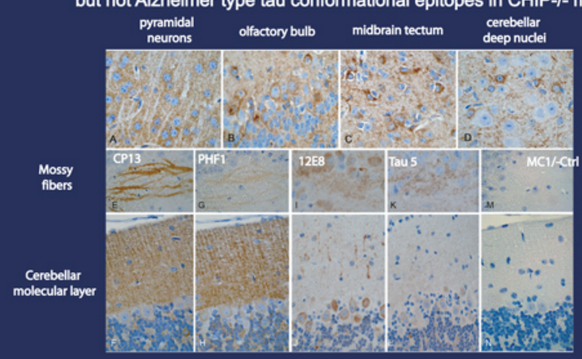
CHIP-/- mice develop marked accumulation of soluble phosphorylated tau species.



Tau mRNA expression is unaltered in CHIP-/- mice despite robust accumulation of phospho-tau speceis

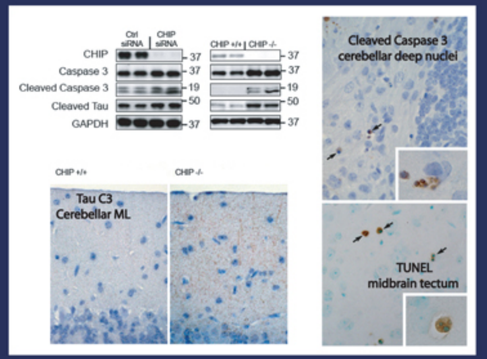


Presynaptic and perikaryal accumulation of phospho-tau, but not Alzheimer type tau conformational epitopes in CHIP-/- mice

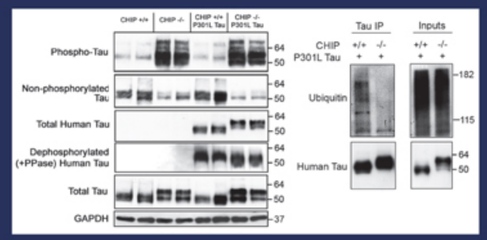


RNAi for CHIP and the C. elegans ortholog chn-1 promotes accumulation of abnormally phosphorylated tau in both a mouse neuroblastoma cell line and a transgenic nematode line

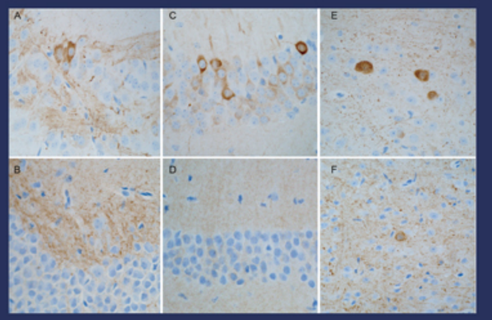
Caspase-3 activation is increased in CHIP-/- mice and is associated with increased apoptosis and elevated levels of caspase-3-cleavage of tau



CHIP deficient mice over-expressing a mutant form of human tau, convert all human tau into a higher molecular weight species but still fail to accumulate insoluble tau species



Human tau fails to form pre-tangles in JNPL3 mice on the CHIP-/- background



Presynaptic accumulation of human tau in CHT mice