CHIP facilitates the degradation of aberrant PHF-tau species by regulating the Hsp90/chaperone complex

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ABSTRACT

One of the primary pathological components of Alzheimer's disease (AD) is the formation of neurofibrillary tangle (NFT) structures composed of hyper-phosphorylated tau (PHF-tau) arranged into paired helical filaments (PHF). Posttranslational modification such as this, disrupt its function of tubulin polymerization and facilitate its pathogenicity. Therefore, expediting the removal of these abnormal PHF-tau species is a highly relevant therapeutic stratagem. Here we demonstrate that select PHF-tau species are clients of the heat shock protein 90 (Hsp90) chaperone machine. The removal of these species was facilitated by a novel blood brain barrier permeable Hsp90 inhibitor. A central component for this Hsp90 degradative system, CHIP, an ubiquitin ligase that has been shown to bind and ubiquitinate PHF-tau, facilitated the proteasome-dependent degradation of PHF-tau following Hsp90 inhibition. Indeed, CHIP -/- mice, which had robust cerebral PHF-tau accumulation, also had altered levels of other constitutive chaperones, further suggesting the critical role for CHIP in controlling protein turnover. Other accessory chaperones that constitute the protein degradation complex such as Hop and Bag-1 also prevented Hsp90-mediated removal of PHF-tau; however the re-folding co-chaperone, P23, antagonized the degradation of PHF-tau, perhaps in an effort to restore functionality. Finally we demonstrated that peripheral administration of this novel Hsp90 inhibitor promoted the selective degradation of certain PHF-tau species in a progressive mouse model of tau accumulation, further suggesting the central role that the Hsp90 complex may play in the pathogenesis of tauopathies.

CONCLUSION

These findings demonstrate that select aberrant phospho-tau species are targeted for degradation by the Hsp90/CHIP chaperone complex, and CHIP in particular seems to be the checkpoint of the complex, deciding upon degradation if dephosphorylation and re-folding efforts by P23 and Pin1 are unsuccessful. The KXGS motif that is extremely conserved for the MAPT sequence also seems to be a major recognition sequence for CHIP, suggesting that phosphorylation of this serine residue could antagonize CHIP binding, protecting PS262/S356 tau from degradation. In addition, CHIP is essential for maintaining the balance of major chaperones and co-chaperones involved in the Hsp70/Hsp90 system. Perhaps most impressive from these studies was the finding that short term peripheral in vivo administration of a novel Hsp90 inhibitor was able to significantly reduce aberrant phospho-tau species in the brains of aged transgenic mice humanized for the tau gene. These findings coupled with the co-localization of several key chaperones with tau pathology in human AD cases suggests that the Hsp90 system is critical for the proper degradation of phospho-tau species, which based upon data from CHIP-/- mice is continually being turned over. Thus chronic minor perturbations in the chaperone system could lead to aggregation over time. Therefore, treatment with Hsp90 inhibitors to enhance Hsp90/CHIP-mediated phospho-tau degradation may provide clinical benefit for sufferers of tauopathies including AD.

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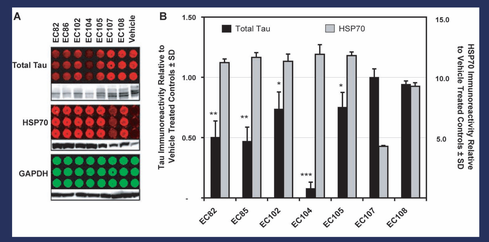
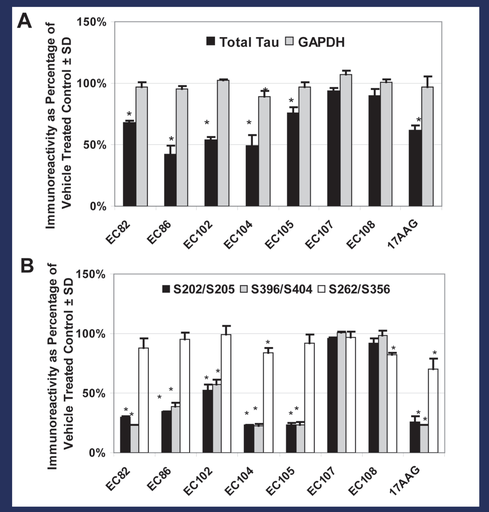
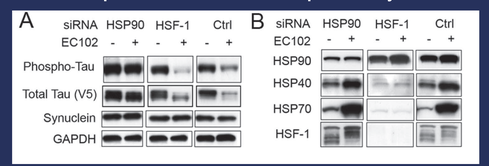
1. Development of novel In-Cell Western assays allowed for the quantitative assessment of reductions in pathogenic tau-species elicited by a panel of low molecular weight HSP90 inhibitors



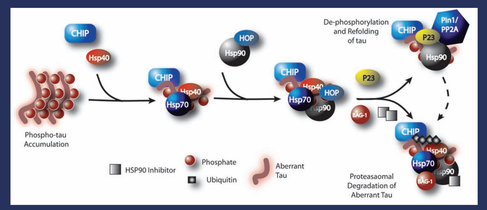
2. Disease-associated phospho-tau species were preferentially reduced following HSP90 inhibition, while total tau levels were only proportionally decreased



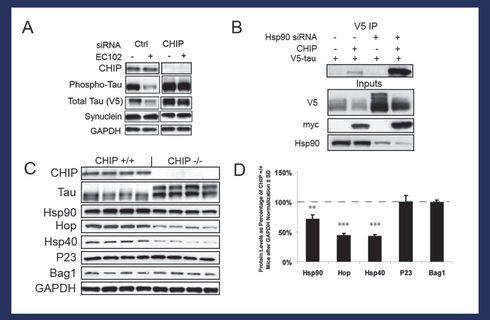
3. Hsp90 inhibition promotes the degradation of tau via an Hsp90-dependent mechanism rather than by de novo transcription of other heat shock proteins by HSF1



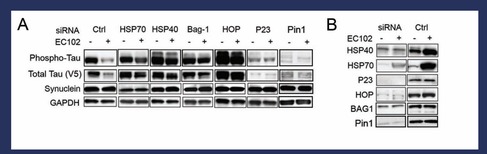
4. Proposed mechanism of Hsp90 inhibitor-mediated phospho-tau degradation



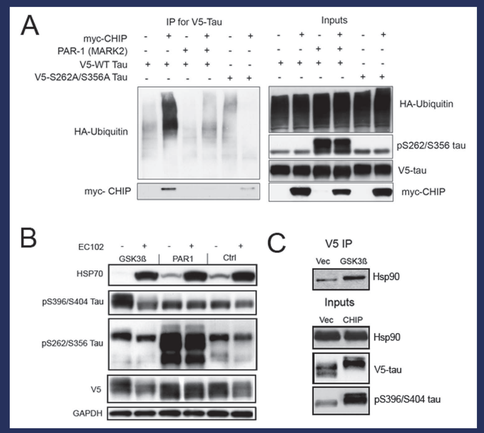
5. The unique co-chaperone CHIP is essential for Hsp90 inhibitor-mediated PHF tau degradation and regulates the levels of other chaperones, including Hsp90 itself



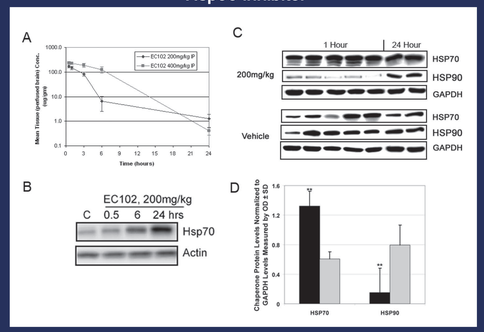
6. Several components of the cytosolic chaperone system are required to facilitate the degradation of aberrant tau species by Hsp90 inhibitors



7. Phosphorylation at S262/S356 prevents ubiquitination and degradation of tau by either CHIP or Hsp90 inhibition, but does not abolish CHIP/Hsp90 binding, further implicating ubiquitination of PHF-tau by CHIP as a necessary component for Hsp90-mediated degradation



8. EC102 crosses the blood brain barrier and acts as a bona-fide Hsp90 inhibitor



9. Acute peripheral in vivo administration of EC102 reduces selective phospho-tau species in humanized tau mice without affecting other Hsp90 client proteins