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Ubiquilin-2 exacerbates tau toxicity *in vivo*

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Abstract

Background: Ubiquilin-2 (UBQLN2) is a protein quality control protein involved primarily in shuttling ubiquitinated substrates to the proteasome for degradation and by modulating autophagy. UBQLN2 has been implicated in neurodegenerative disease due to its accumulation in neuropathological deposits and its potential role in regulating protein dyshomeostasis common across different neurodegenerative disorders. The relationship of UBQLN2 to one of the most common aggregating proteins in disease, tau, is unknown.

Method: To evaluate whether UBQLN2 regulates tau clearance, we assessed levels of tau in human embryonic kidney-293 cells with and without UBQLN2. To determine whether UBQLN2 acts on tau *in vivo*, P301S tau transgenic mice were crossed with UBQLN2 transgenic and knockout mice and brain levels of tau were assessed at 3, 6 and 9 months of age. To define changes in UBQLN2 in human disease, we measured levels of soluble and insoluble UBQLN2 in human tauopathy brain tissue.

Result: Co-expressed UBQLN2 markedly lowered levels of tau in a cellular model. Conversely, siRNA knockdown of UBQLN2 significantly elevated levels of tau. Surprisingly, a UBQLN2 mutant incapable of binding ubiquitin was more effective at lowering tau than wildtype UBQLN2, suggesting that ubiquitin-independent pathways may allow UBQLN2 to "handle" tau. In contrast, wildtype UBQLN2 overexpression *in vivo* did not alter total levels of tau at 3, 6 or 9 months of age. However, UBQLN2 overexpression specifically increased phosphorylated tau while UBQLN2 knockout decreased phosphorylated tau at 9 months. Furthermore, UBQLN2 overexpression increased premature hindlimb paralysis and fatality. The possibility that UBQLN2 also undergoes alterations in disease was evidenced by the fact that UBQLN2 solubility is decreased in human brains with tau pathology.

Conclusion: Our findings highlight a new role for UBQLN2 in altering tau in the brain. Collectively, our results suggest that while on a rapid time scale UBQLN2 can decrease tau levels, long-term expression of UBQLN2 *in vivo* exacerbates tau toxicity. Ongoing research will determine how changing UBQLN2 levels alters components of proteostasis pathways to affect tau toxicity and whether ubiquitin-independent processes may compete with UBQLN2's function as a ubiquitin-proteasome shuttle factor to yield differential effects on tau toxicity.