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UBQLN2 regulation of α-synuclein in synucleinopathies

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Abstract

Background: The protein quality control protein ubiquilin-2 (UBQLN2) is implicated in synucleinopathies due to its accumulation in Lewy body diseases. However, little is known about how it may interact with and clear α-synuclein (α-syn). This study aimed to define the role of UBQLN2 in handling α-syn.

Method: To evaluate whether UBQLN2 regulates α-syn, we measured levels of α-synuclein in HEK-293 cells transiently expressing or deleted of UBQLN2. To evaluate whether UBQLN2 regulates α-syn clearance in the nervous system *in vivo*, we used western blot to measure total α-syn or phosphorylated human α-syn (pS129) levels in multiple transgenic mouse lines including: UBQLN2 overexpressing mice (Ub2-hi), UBQLN2 knock-out mice (Ub2-KO), and A53T α-syn mice crossed to either Ub2-hi or Ub2-KO mice. To assess changes in UBQLN2 solubility in synucleinopathies we measured levels of UBQLN2 by Western blot in PBS-soluble versus sarkosyl-soluble brain lysates from PD and LBD human brains and from A53T mouse brains.

Result: *In vitro*, UBQLN2 significantly decreased levels of soluble α-syn. *In vivo*, endogenous insoluble α-syn levels are decreased in Ub2-hi mice, while total endogenous α-syn levels are significantly increased in Ub2-KO mice. Total α-syn and pS129 levels were unchanged in A53TxUb2-hi mice versus A53T controls, but were significantly increased in A53TxUb2-KO mice. Solubility studies revealed increased insoluble UBQLN2 levels in human LBD and mouse A53T brains.

Conclusion: While UBQLN2 is known to colocalize with a-syn in disease, our results support a functional role for UBQLN2 in regulating α-syn levels. Further, we show that UBQLN2 solubility is altered in synucleinopathies. In disease, a change in UBQLN2 solubility may indicate a loss of its ability to handle a-syn, contributing to a-syn toxicity. Ongoing studies seek to elucidate the mechanism by which UBQLN2 handles, and potentially clears, α-syn.