ALPHA-SYNUCLEIN IMPAIRS MACROAUTOPHAGY: IMPLICATIONS FOR PARKINSON’S DISEASE

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Introduction: The accumulation of ubiquitinated proteins, filamentous structures, and alpha-synuclein in the substantia nigra and Lewy bodies of Parkinson’s disease (PD) patients is indicative of a possible problem in protein and organelle degradation.

Aims: To address this possibility, we tested if known PD-associated multiplications of the alpha-synuclein gene affect macroautophagy, one of the main intracellular degradative pathways.

Results and methods: In this study we demonstrate that alpha-synuclein overexpression impairs macroautophagy in mammalian cells and in transgenic mice expressing multiple copies of alpha-synuclein. Our data show that alpha-synuclein compromises autophagy via Rab1a, a small GTPase that regulates ER-to-Golgi vesicular trafficking. Congruent with Rab1a impairment, we find that alpha-synuclein overexpression in mammalian cells impairs constitutive secretion and increases Golgi fragmentation. Overexpression of alpha-synuclein or knockdown of Rab1a caused mislocalization of the autophagy protein Atg9, decreased colocalization of Atg9 with LC3 (autophagosome marker) and decreased omegasome (autophagosome precursor) formation. The inhibition of autophagy by alpha-synuclein overexpression was specifically rescued by overexpression of Rab1a.

Conclusions: These findings are of interest, as an inhibition of autophagy by alpha-synuclein will likely have pleiotropic effects. In addition to the accumulation of aggregate-prone proteins, cells may not be effective in clearing dysfunctional mitochondria through autophagy, and may have increased susceptibility to certain apoptotic insults; all processes that have been implicated in PD and been shown to be compromised upon autophagy inhibition. Thus, autophagy inhibition caused by wildtype alpha-synuclein may provide a unifying mechanism for many of the disconnected cellular pathologies in Parkinson’s disease.