Molecular control of autophagy activation in Parkinson’s disease: activation of “pathological autophagy”? 

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Autophagy is typically regarded as a homeostatic process that is essential for cell survival. Through the formation of autophagosomes, damaged organelles and cytoplasmic content are sequestered and transported to the lysosomes for degradation. Deregulation of the autophagic pathways has recently been linked to the pathophysiology of neurodegenerative diseases including Parkinson’s, Alzheimer’s and Huntington’s disease, but the precise contribution of this deregulation remain incompletely understood. Using two mechanistically distinct models of Parkinson’s disease, we have identified two molecules, Cdk5 and endophilin B1, that are required for the aberrant activation of autophagy in these models. Phosphorylation of endophilin B1 by Cdk5 is elevated in Parkinson’s disease models, and suppressing this phosphorylation markedly reduces autophagy activation in the afflicted neurons, but not in control neurons. More importantly, inhibition of autophagy or attenuation of this crosstalk significantly limits neuronal loss in these Parkinson’s disease models, suggesting that autophagy activation may also contribute to neurodegeneration, and that Cdk5 and endophilin B1 are crucial mediators of the aberrant autophagy activation. In addition, since inhibition of Cdk5 and endophilin B1 crosstalk has negligible effects on basal autophagy in control neurons, our findings suggest that this pathway may be selectively associated with “pathological autophagy” that is activated during the disease states.

Bibliography