Microtubule-dependent autophagy is required for cellular clearance of aggregated Huntingtin

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CNS neurons are endowed with the ability to recover from cytotoxic insults associated with the accumulation of proteinaceous polyglutamine aggregates in Huntington's disease, but the cellular mechanism underlying this phenomenon is unknown. Here we show that autophagy is essential for the elimination of aggregated forms of mutant huntingtin. Autophagy is considered a highly regulated but non-selective pathway by which cytoplasmic constituents are degraded in lysosomes in response to nutrient deprivation. Our data show that autophagy is induced in response to impaired activity of the ubiquitin proteasome system. Autophagins, molecular determinants of autophagic vacuole formation, are recruited to aggresomes, pericentriolar cytoplasmic inclusion bodies that form when the capacity of the ubiquitin proteasome system is exceeded. Inhibition of autophagy with RNA interference demonstrates that this pathway is essential for cells to eliminate aggregated huntingtin. Recruitment of autophagins to aggresomes and aggregate clearance both require an intact microtubule cytoskeleton, suggesting that retrograde transport on microtubules is a mechanism used by cells to increase the efficiency and selectivity of this degradation pathway. Thus, autophagy is key component of the cellular defense against protein aggregation.

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