NEURODEGENERATIVE DISEASE

Attacking Huntington's from the inside out

Huntingtin (HTT), the protein that is mutated in Huntington's disease (HD), tends to form inclusions within the neuronal nucleus and cytoplasm. Although nuclear HTT is known to contribute to the disease process, little is known about the relative contribution of cytoplasmic HTT to the pathogenesis. Li and colleagues now show that inhibiting mutant HTT accumulation in neuronal processes (the neuropil) can reduce its toxicity and lead to specific improvements in neurological function.

To investigate the effects of interfering with mutant HTT accumulation, the authors generated an intrabody — an antibody that is expressed within the target cell — that selectively binds to human mutant HTT. When they transfected cell lines expressing mutant human HTT with the intrabody, levels of cell death were reduced. Furthermore, in cultured rat cortical neurons, the intrabody prevented the changes in cell morphology that normally follow expression of mutant HTT.

Next the authors tested the intrabody in two transgenic mouse strains — R6/2 and N171-82Q — that are used as models of HD. An adenoviral vector encoding the intrabody was microinjected into the striatum of the mice at an early stage of the disease pathology. Several weeks later, the authors observed a decrease in the number of HTT aggregates in the neuropil close to the injection site. Nuclear aggregation was affected to a much lesser extent, suggesting that the antibody specifically interferes with cytoplasmic mutant HTT. The reduction in neuropil aggregation was associated with a gain in motor function.

The intrabody might alter the levels of HTT aggregates in the neuropil by redistributing the aggregates within the cytoplasm, or by promoting their degradation. When the authors examined striatal synaptosomal preparations obtained from treated and control N171-82Q mice, they observed an increase in the level of HTT cleavage products in the synaptosomes of the treated mice, indicative of an increase in degradation. Furthermore, when the intrabody was co-expressed in a cell line expressing mutant HTT, there was an increase in HTT degradation products and a decrease in the half-life of the mutant protein. This was accompanied by an increase in the levels of protein ubiquitylation, suggesting that it is this mechanism that underlies the effects of the intrabody on mutant HTT degradation.

This study demonstrates the usefulness of intrabodies as a research tool and as a potential future therapeutic approach. The results suggest that cytoplasmic HTT accumulation has a role in the pathogenesis of HD and could be a worthwhile therapeutic target; however, the expression of the intrabody in the limited brain region did not alter overall survival in the mouse models of HD, indicating that other mechanisms and brain regions are also important.

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ORIGINAL RESEARCH PAPER Wang, C.-E. *et al.* Suppression of neuropil aggregates and neurological symptoms by an intracellular antibody implicates the cytoplasmic toxicity of mutant huntingtin. *J. Cell Biol.* **181**, 803–816 (2008)