Huntington’s disease protein extends its reach

The mutant protein that causes Huntington’s disease doesn’t just wreak havoc inside the nucleus. It also makes trouble in the cytoplasm, as Wang et al. show.

The symptoms of Huntington’s disease—which include personality changes and jerky movements—stem from damage triggered by a version of the protein huntingtin that sports extra copies of the amino acid glutamine. The abnormal protein forms globs in the nuclei of brain cells and stifles transcription of necessary genes. Smaller clumps of huntingtin also lurk in the cytoplasm, but researchers weren’t sure whether these could injure neurons.

To find out, Wang et al. produced an intracellular antibody, or intrabody, that preferentially targeted mutant huntingtin in the cytoplasm. In rat brain cells that produce mutant huntingtin, nuclei break up and neurites—extensions that connect to neighboring cells—deteriorate. But both of these defects were less common when the authors engineered the cells to produce the intrabody.

The researchers then scaled up from cells to whole animals and asked whether the intrabody eased symptoms in mice that make mutant huntingtin. The team injected a virus carrying the intrabody gene into the striatum, a brain area devastated in the disease. Compared with controls, the injected animals had less difficulty walking and were better able to keep their balance on a slowly revolving rod. However, their life span didn’t increase, possibly because the intrabody protects only one of the brain regions injured by faulty huntingtin.

Intrabody-making cells harbored less mutant huntingtin in neurites than did control cells, the team found. The intrabody appears to promote attachment of ubiquitin molecules that spur destruction of the rogue molecules.

Because symptoms are less severe when the intrabody ties up mutant protein in the cytoplasm, the researchers conclude that nonnuclear huntingtin is responsible for some ill effects of the disease. How cytoplasmic huntingtin causes harm remains uncertain, however.

Wang, C.-E., et al. 2008. J. Cell Biol. doi:10.1083/jcb.200710158.

Slow synapses in schizophrenia?

The hallucinations, delusions, and confused thinking of schizophrenia might result from sluggish synapses, as Chen et al. reveal. The team found that neurotransmitter release slowed in mice missing a protein that’s also scarce in many schizophrenia patients.

Scientists have long suspected that synaptic transmission is faulty in schizophrenia. Clues to the mechanism might come from schizophrenia susceptibility genes, one of which codes for the synaptic protein dysbindin. Although scientists haven’t identified any dysbindin mutants in schizophrenia patients, lower levels of the protein in two brain areas, the hippocampus and the prefrontal cortex, might produce the disease’s symptoms. Chen et al. tested mutant mice that lack dysbindin (known as “sandy” mice) to determine how loss of the protein alters synaptic transmission.

Transmission across the synapse involves the release of neurotransmitter vesicles. The researchers first asked whether vesicle release in general was affected in sandy mice, by studying the animal’s adrenal gland cells—commonly used models for vesicle dynamics. Applying a technique called amperometry, which detects discharge of individual vesicles, the team found that although vesicles were larger than normal in sandy mice, vesicle release took longer and the odds of a particular vesicle unloading its contents were lower.

The researchers then saw a similar pattern in hippocampal neurons from sandy mice: larger vesicles but tardy release.

Neurotransmitter vesicles poised for release line up on the presynaptic side of the neuron. But neurons from sandy mice showed fewer of these vesicles than did control cells. The changes Chen et al. identified could impair a neuron’s ability to relay a message. The next step is to determine whether synapses in schizophrenia patients show similar changes.

Chen, X.-W., et al. 2008. J. Cell Biol. doi:10.1083/jcb.200711021.