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## Defending against the Enemy Within

### ***The ability of some types of brain cells to clear mutant proteins better than others offers hints about how Huntington's disease works***

By Anna Lisa Lucido, PhD, and Anne D. Holden, PhD

The human brain is powerful, but it is also fragile. It is encased in many protective layers, including the skull and, underneath, the membrane-thin layers that regulate the brain's fluid, ion and energy balance. However, these layers can't protect the brain from the enemies within—the toxic proteins that build up in the brain over time due to age, various environmental insults, and genetic factors. This toxic buildup has long been viewed as the major contributor to neurodegenerative disease symptoms.

Huntington's disease is an all-too-perfect example of this phenomenon. A devastating and inherited neurodegenerative disorder, Huntington's is characterized by the buildup of a mutant form of an otherwise normal protein called huntingtin. Scientists have long known that mutant huntingtin accumulates in neurons and causes them to die. But, the finer details—how long the toxic proteins live in cells, whether and how neurons fight back, and how long after this buildup do neurons begin to die—were difficult to answer. Equally challenging to understand has been why neurons in certain regions of the brain suffer the consequences of mutant huntingtin buildup while others are spared—given that all cells of the brain can express it. To answer these questions, researchers would have to follow the same neurons over hours, days and even weeks—much longer than most types of laboratory equipment and cellular models allow.

But now, scientists at the Gladstone Institutes—using methods that track single neurons over time with exceptional precision—have discovered that the progression of the disease is not due to the buildup of toxic proteins themselves, but rather to an individual neurons' ability to clear them. Importantly, the research team also identified a therapeutic target that boosted this ability, which ultimately could protect the brain against Huntington's deadly effects.

In the latest issue of *Nature Chemical Biology*, researchers in the laboratory of Gladstone Investigator [Steve Finkbeiner, MD, PhD](#), describe how a newly developed technology allowed them to see—for the first time—how individual neurons fight back against the buildup of toxic proteins over time. Focusing their efforts in a cellular model of Huntington's disease, the team observed how different types of neurons in the brain each responded to this toxic buildup with different degrees of success, offering clues as to why the disease causes neurons in one region to die, while neurons in another are spared.

“Huntington’s is a progressive neurodegenerative disease that, as a result of the toxic buildup of mutant huntingtin protein in the brain, causes horrible motor and cognitive deficits,” explained Dr. Finkbeiner. “A long-standing mystery among researchers was the underlying process by which the buildup of the mutant huntingtin protein caused cells to degrade and die, but the technology available made it virtually impossible to see and monitor this process over time at the cellular level. In this study, we employed a method called optical pulse-labeling, or OPL, which allowed us to see how the mutant huntingtin ravaged the brain—neuron by neuron.”

Using neurons extracted from rodent models of Huntington’s, the research team employed the OPL method, which monitored the speed and efficiency with which different types of neurons were able to clear the mutant huntingtin. The faster a cell could clear out the toxic buildup, the longer the neuron survived, and vice versa.

Surprisingly, the research team began to notice significant differences in the ability of different types of neurons to clear mutant huntingtin. Neurons located in the striatum—the region of the brain primarily affected by Huntington’s disease, involved in muscle movement—were particularly susceptible to buildup, while neurons found in other regions, such as the cerebellum, were less so. And when they tracked those striatal neurons carrying a heavy load of mutant huntingtin that wasn’t being cleared, they found that they were much more likely to die than the neurons better at clearing it.

All cells depend on two main pathways to clear excess proteins: the ubiquitin-proteasome system (UPS) and autophagy. Although their mechanisms are distinct, their goal is the same: to literally gobble up excess proteins—autophagy translates as “to eat oneself”—and ensure that they are efficiently degraded, so that they do not interfere with normal cellular activity.

The research team found that, indeed, striatal neurons were especially sensitive to disturbances in autophagy. When autophagy was perturbed, the neuron’s efficiency at clearing mutant huntingtin was decreased. Conversely, when they boosted the activity of Nrf2, a protein that helps to accelerate protein clearance, they were able to prolong cell survival.

“If we could develop drugs that boost Nrf2 production in the neurons most susceptible to Huntington’s, we might extend their survival, thereby staving off the worst effects of the disease,” said former Gladstone Postdoctoral Fellow Andrey Tsvetkov, PhD, the study’s lead author. “Importantly, these results also demonstrate that the brain has evolved powerful coping mechanisms, like autophagy, against diseases such as Huntington’s. The fact that people don’t start experiencing symptoms of Huntington’s until the fourth or fifth decade of their lives—even though the mutant huntingtin is present at birth—is further evidence of the brain’s ability to stave off the effects of the disease.”

Toxic protein buildup is a prominent feature of many neurodegenerative diseases. In Alzheimer's disease, it's the accumulation of tau and amyloid-beta that leads to the formation of "tangles" and "plaques" in neurons. In Parkinson's patients, "Lewy bodies", which are large protein inclusions, are present in neurons of the substantia nigra, another region of the brain important in motor movement. Advanced Huntington's patients also have "inclusion bodies" filled with mutant huntingtin in their striatal neurons.

At one time, these toxic protein aggregates were thought to be one enemy within that caused neurons to die. But, as work from Dr. Finkbeiner's group, among others, has shown, these large protein aggregates may actually be an important way for neurons to cope with all the toxic proteins they have trouble clearing, a trouble that increases with age and the accumulation of environmental insults, and is influenced by genetics. Therefore, despite the very distinct signs and symptoms of these diseases, there may be common challenges in dealing with the underlying offenders, with certain cell types having more trouble dealing with the buildup than others.

"These results are critical not only for informing us as to underlying mechanisms behind neurodegenerative diseases such as Huntington's, but also to remind researchers that focusing only on the disease-causing protein—and not how individual cells respond to it—is only one side of the coin," said Dr. Finkbeiner. "To truly understand a complex disease like Huntington's, we must also look to the brain's naturally evolved defense mechanisms, which as we've shown here could represent an entirely new therapeutic strategy."