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Huntington's disease (HD) is a genetic neurodegenerative disorder that has a late onset, usually in individuals in their 40s. In 1872, George Huntington first recognized the disorder in patients who had physical symptoms such as uncoordinated, jerky movements and stiffness or slow movement. Almost all individuals diagnosed with HD exhibit many of these physical symptoms, and many of them exhibit cognitive decline and psychiatric symptoms including anxiety, depression, and aggression. If many of the physical and psychiatric symptoms are evident in individuals younger than 20, then the condition is known as Juvenile HD.

It is currently known that HD is caused by a mutation in a single gene called the huntingtin gene (HTT). The mutated HTT gene codes for mutated proteins with abnormally long repeats of an amino acid called glutamine (abbv: Q). In many neurons, the defective "polyQ-expanded" protein is misfolded and clumps together, thereby damaging and killing these cells. However, very little is known about the mechanism that causes these cells to be damaged and die.

Martin Duennwald, a principal scientist at Boston Biomedical Research Institute in Watertown, Massachusetts, has been using rat cells that model neurons and mouse striatal cells, brain regions involved heavily in HD. When these cells have been generated with polyQ-expanded fragments, they quickly showed problems with proteins that had been marked for degradation in the endoplasmic reticulum (ER), an organelle used in folding proteins. These proteins were not tagged for degradation in areas of the cell outside of the ER. Also, even though there are many mechanisms in the cell that help misfolded proteins refold with the help of a class of proteins called chaperone proteins, polyQ-expanded proteins don't elicit a response for chaperone proteins. Thus, the cell is not able to alter protein folding in mutated proteins, and the low protein quality may be able to cause cell damage and death.

Duennwald then went on to uncover the basis for this breakdown: The polyQ-expanded fragments glom onto the key VCP/Npl4/Ufd1 protein complex that aids in the transport and degradation of the proteins that flunk quality control in the ER. However, when he genetically modified cells to overexpress two crucial proteins in the protein complex, the toxic effect dropped.

These interesting findings may be useful in finding a treatment for the disease. By targeting the cell's protein quality control mechanisms, researchers may be able to provide novel and effective treatment options for individuals with HD or other illnesses with polyQ-expanded proteins.