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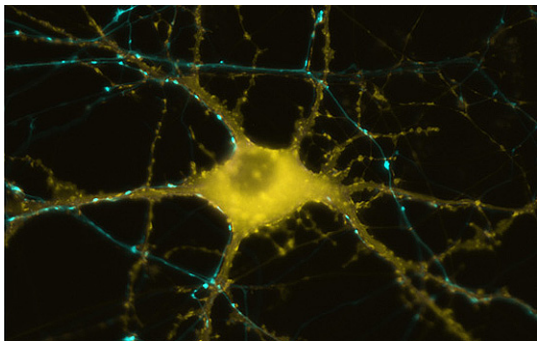
Two Proteins Offer a "Clearer" Way to Treat Huntington's Disease

Pair helps remove and prevent misfolding of proteins that cause neurodegeneration

In a paper published in the July 11 online issue of *Science Translational Medicine*, researchers at the University of California, San Diego School of Medicine have identified two key regulatory proteins critical to clearing away misfolded proteins that accumulate and cause the progressive, deadly neurodegeneration of Huntington's disease (HD).



A human neuron. UC San Diego scientists have identified a pair of proteins that help clear away other misfolded proteins responsible for the progressive degeneration of brain cells in Huntington's disease.

The findings explain a fundamental aspect of how HD wreaks havoc within cells and provides "clear, therapeutic opportunities," said principal investigator Albert R. La Spada, MD, PhD, professor of cellular and molecular medicine, chief of the Division of Genetics in the Department of Pediatrics and associate director of the Institute for Genomic Medicine at UC San Diego.

"We think the implications are significant," said La Spada. "It's a lead we can vigorously pursue, not just for Huntington's disease, but also for similar neurodegenerative conditions like Parkinson's disease and maybe even Alzheimer's disease."

In HD, an inherited mutation in the huntingtin (htt) gene results in misfolded htt proteins accumulating in certain central nervous system cells, leading to progressive deterioration of involuntary movement control, cognitive decline and psychological problems. More than 30,000 Americans have HD. There are no effective treatments currently to either cure the disease or slow its progression.

La Spada and colleagues focused on a protein called PGC-1alpha, which helps regulate the creation and operation of mitochondria, the tiny organelles that generate the fuel required for every cell to function.

“It’s all about energy,” La Spada said. “Neurons have a constant, high demand for it. They’re always on the edge for maintaining adequate levels of energy production. PGC-1alpha regulates the function of transcription factors that promote the creation of mitochondria and allow them to run at full capacity.”

Previous studies by La Spada and others discovered that the mutant form of the htt gene interfered with normal levels and functioning of PGC-1alpha. “This study confirms that,” La Spada said. More surprising was the discovery that elevated levels of PGC-1alpha in a mouse model of HD virtually eliminated the problematic misfolded proteins.

Specifically, PGC-1alpha influenced expression of another protein vital to autophagy – the process in which healthy cells degrade and recycle old, unneeded or dangerous parts and products, including oxidative, damaging molecules generated by metabolism. For neurons, which must last a lifetime, the self-renewal is essential to survival.

“Mitochondria get beat up and need to be recycled,” La Spada said. “PGC-1alpha drives this pathway through another protein called transcription factor EB or TFEB. We were unaware of this connection before, because TFEB is a relatively new player, though clearly emerging as a leading actor. We discovered that even without PGC-1alpha induction, TFEB can prevent htt aggregation and neurotoxicity.”

In their experiments, HD mice crossbred with mice that produced greater levels of PGC-1alpha showed dramatic improvement. Production of misfolded proteins was essentially eliminated and the mice behaved normally. “Degeneration of brain cells is prevented. Neurons don’t die,” said La Spada.

PGC-1alpha and TFEB provide two new therapeutic targets for Huntington’s disease, according to La Spada. “If you can induce the bioenergetics and protein quality control pathways of nervous system cells to function properly, by activating the PGC-1alpha pathway and promoting greater TFEB function, you stand a good chance of maintaining neural function for an extended period of time. If we could achieve the level of increased function necessary to eliminate misfolded proteins, we might nip the disease process in the bud. That would go a long way toward treating this devastating condition.”

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