Study links normal function of protein, not its build up inside cells, to death of neurons

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A study led by St. Jude Children's Research Hospital investigators links the muscle weakness and other symptoms of a rare neurodegenerative disease to a misstep in functioning of a normal protein, rather than its build-up inside cells. The finding offers insight into the mechanism driving common nervous system disorders like Parkinson's and Alzheimer's diseases.

The work advances understanding of how the inherited mistake at the heart of spinobulbar muscular atrophy (SBMA) leads to the death of neurons in the brain and spinal cord. Investigators showed that the underlying mutation caused an amplification of the protein's normal function. The work appears in the September 23 online edition of the scientific journal *Neuron*.

"The idea that toxicity is mediated by the native, or normal, function of the protein itself is a departure from conventional wisdom. This research adds to growing evidence the principle applies very broadly in other neurodegenerative disorders, including Alzheimer's and Parkinson's diseases," said J. Paul Taylor, M.D., Ph.D., an associate member in the St. Jude Department of Developmental Neurobiology and the paper's senior author.

The current neurodegenerative disease model links the disorders to a toxic build-up of improperly folded proteins inside cells. Taylor said: "Our findings suggest the focus on protein aggregation inside cells may be misplaced." Developing therapies that target the normal protein

function will likely be easier and more effective, he added.

Medications are already available to block the androgen receptor (AR) protein, which is mutated in SBMA. Work is now underway in Taylor's laboratory to identify drugs that more selectively block AR functioning.

SBMA belongs to a family of eight disorders, including Huntington's disease, which stem from an overabundance of the same small, repeated sequence of DNA known as a trinucleotide. Such repetitions are common throughout the genome, but problems arise when they occur too frequently. That is what happens in the estimated 1 in 50,000 males with SBMA.

In the case of SBMA, the repeated sequence occurs in the gene for the androgen receptor. The repeated nucleotide sequence CAG is protein-production shorthand for an amino acid called glutamine. The resulting androgen receptor (AR) protein includes surplus glutamine.

After earlier work by other investigators showed that blocking testosterone prevented male mice with the SBMA mutation from developing the disease, Taylor and his colleagues set out to track what happened inside cells after the hormone bound to the mutated AR protein.

Working in a Drosophila fruit fly model of the disease, the scientists identified a small region of the AR protein, known as the AF-2 domain, which played a pivotal role.

Using a variety of techniques, researchers demonstrated they could rescue the cells by preventing certain members of a family of proteins called coregulators from binding to the AF-2 domain. Coregulators partner with AR and other transcription factors to regulate gene expression.

"In this study, we showed the ability of the mutant protein to interact with the normal binding partners is an essential step in the cascade of degeneration. By blocking it, we block degeneration," Taylor said. He added that the AF-2 domain is far from the mutated region of the AR protein. "That would be unexpected if the mechanism of toxicity were related to the protein aggregating," he explained.

Meanwhile, investigators are still studying why the protein's change in function is so deadly to cells. Taylor noted that research into inherited diseases like SBMA has historically provided important clues into the mechanisms at work in other more common neurodegenerative disorders, including Alzheimer's.

The findings also hold hope that treating or preventing SBMA by selectively disrupting AF-2 binding will soon be possible, Taylor said. "Selectively blocking the hormone will be key if we hope to prevent the side effects associated with androgen ablation in males," he said. The side effects include bone thinning, infertility or blocked sexual maturation.

The study also suggests the need to begin treatment earlier. If the damage to motor neurons begins with the hormone surge of puberty rather than the accumulation of mis-folded proteins, therapies must begin in childhood, Taylor said.

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