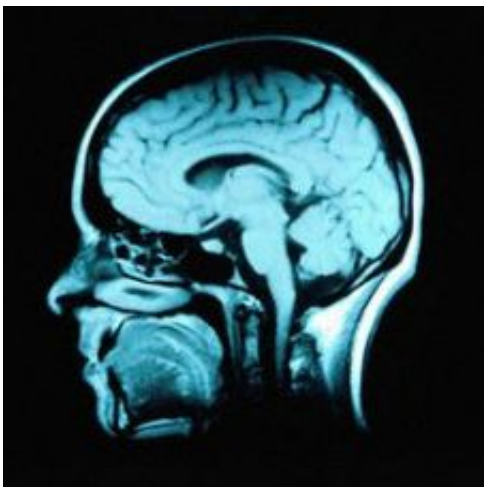
MedicalXpress

Protein clusters implicated in neurodegenerative diseases actually serve to protect brain cells

April 23 2014



People diagnosed with Huntington's disease, most in their mid-thirties and forties, face a devastating prognosis: complete mental, physical, and behavioral decline within two decades. "Mutant" protein clusters, long blamed for the progression of the genetic disease, have been the primary focus of therapies in development by pharmaceutical companies. But according to new research from Prof. Gerardo Lederkremer and Dr. Julia Leitman of Tel Aviv University's Department of Cell Research and Immunology, in collaboration with Prof. Ulrich Hartl of the Max Planck Institute for Biochemistry, these drugs may not only be

ineffective—they may pose a serious threat to patients.

In two ground-breaking studies, published in the journals *PLOS ONE* and *Nature Communications*, Prof. Lederkremer and his team demonstrated that protein clusters are not the cause of toxicity in Huntington's disease. On the contrary, these aggregates actually serve as a defense mechanism for "stressed" brain cells. Conducted on tissue cultures using cutting-edge microscopic technology, their studies identified a different causative agent—the "stress response" of affected brain cells.

"The upsetting implication for therapy of this disease is that drugs being developed to interfere with the formation of protein aggregates may in fact be detrimental," said Prof. Lederkremer. "The identification of the new cause will hopefully lead to the development of new therapeutic approaches. This may hold true for other neurodegenerative diseases as well."

Starting from genetic scratch

Prof. Lederkremer and his team chose to examine the effect of protein aggregates in the pathology of Huntington's disease because its genetic cause is well-known, unlike those of other neurodegenerative diseases, such as Parkinson's, whose origins remain less clear.

"What we found in this study—a surprise, although we suspected it—was that damage to the cells, the cell 'stress' that leads to death of cells, appeared well before the protein aggregates did," said Prof. Lederkremer. "And even more surprising, when the aggregates finally appeared, the stress was reduced, in some cases even stopping. The actual process of forming an aggregate was protective, isolating and segregating the problematic proteins. This explains why in autopsies of people who died of Huntington's and other diseases like Alzheimer's or old age, the protein aggregates in the brains were all quite similar,

reflecting no specific disease link."

By interfering with the stress response of brain cells, rather than the formation of protein clusters, scientists may be able to slow, or even halt, the progression of neurodegenerative diseases. According to Prof. Lederkremer, this research paves the way for a revolutionary new direction for pharmaceutical research to treat Huntington's, Alzheimer's, Parkinson's, and other neurodegenerative diseases.

Response to stress

"The practical consequences are that several companies are already in advanced stages of development of drugs inhibiting this form of protein aggregate, interfering with the body's natural process to protect the brain," said Prof. Lederkremer. "But the drugs should be focused on another area altogether, and the protein aggregates, a protective resource for the brain, should be left intact."

Samples of brain cells from mouse models afflicted with Huntington's disease were examined using "live cell imaging," the study of live cells through time-lapse microscopy. Prof. Lederkremer and his team were thus able to identify a compound that modified brain cells' response to stress, promoting their survival.

"Our approach was to interfere with the stress response instead of the formation of the protein aggregates, and the lab succeeded in identifying a compound that altered the response, rescuing affected cells from death," said Prof. Lederkremer. "Our findings are most encouraging for the development of a therapy for this devastating disease, which is presently incurable."

Provided by Tel Aviv University