Huntington's disease discovery provides new hope for treatment

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Australian scientists have identified the behaviour of the mutant protein 'huntingtin' which leads to the fatal Huntington's disease providing potential targets to treat the disease, a University of Melbourne study reveals.

Huntington's disease is a genetic disease with no cure, characterized by a steady decline in motor control and the dysfunction and death of brain cells. The cause of the disease has long baffled scientists.

Symptoms tend to first appear when the person is in their thirties or forties. The most common symptom is jerky movements of the arms and legs. A person with Huntington's disease may also have difficulties with speech, swallowing and concentration.

Using state of the art technology, Dr Danny Hatters and his colleagues at the University of Melbourne's Department of Biochemistry and Molecular Biology at the Bio 21 Institute observed how human mutant 'huntingtin' proteins form into large clumps, which kills brain cells and leads to progressed Huntington's disease.

"Steps prior to the clustering of the mutated proteins were thought to damage cells, but these steps were not clearly detectable under a microscope," Dr Hatters says.

"Understanding this process and finding the right target to block the ultimate death of the brain cells has been extremely difficult to

determine," he says.

The technology called analytical ultracentrifugation and the methodology the researchers developed enabled them to visualize this process in much greater detail.

"What we have shown and are the first to show, is that mutated huntingtin protein forms three different sized clusters in the damaged cells," he says.

"This discovery will help to develop a targeted treatment that shuts down the key processes causing the clusters to form and for the disease to progress."

While researchers previously thought that small clusters of the mutant protein kept accumulating over time until they overwhelmed and killed the brain cells, Dr Hatters' team found that these clusters were static, which means they form in a more unpredictable manner than previously thought.

The discovery reveals the clusters place a steady stress on cells over time rather than steadily building up over time to some critical "toxic" level as previously thought.

"Why it takes so long for the cells to die in human disease is not known - however it could be that cells eventually cannot compensate anymore from the process where toxicity is built up to form one cluster called oligomers," he says.

"The real key of our work is that we now have direct targets in the critical steps in the process of cell toxicity and death and to gauge any therapeutic effects of drugs on these targets. We can also measure how this alleviates cellular toxicity and brain cell death.'

"Importantly our research techniques could have application in assisting to find drug targets for other neurodegenerative diseases where toxic clusters of proteins play a role in the progression of the disease, such as for Parkinson's disease."

More information: The research is published in the current issue of the Journal of Biological Chemistry.

Provided by University of Melbourne