Scientists encourage cells to make a meal of Huntington's disease

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Scientists have developed a novel strategy for tackling neurodegenerative diseases such as Huntington's disease: encouraging an individual's own cells to "eat" the malformed proteins that lead to the disease.

Huntington's disease is one of a number of degenerative diseases marked by clumps of malformed protein in brain cells. Symptoms include abnormal movements, psychiatric disturbances like depression and a form of dementia. The gene responsible for the disease was discovered in 1993, leading to a better understanding of the condition and to improved predictive genetic testing, but it has yet to lead to any treatments that slow the neurodegeneration in Huntington's patients.

Professor David Rubinsztein, a Wellcome Trust Senior Clinical Fellow at the University of Cambridge, has been studying the molecular biology underlying Huntington's and other neurodegenerative diseases. Huntington's occurs when a protein known as huntingtin builds up in the brain cells of patients, mainly in neurons in the basal ganglia and in the cerebral cortex. Normally, cells dispose of or recycle their waste material, including unwanted or mis-folded proteins, through a process known as autophagy, or "self-eating".

"We have shown that stimulating autophagy in the cells – in other words, encouraging the cells to eat the malformed huntingtin proteins – can be an effective way of preventing them from building up," says Professor Rubinsztein. "This appears to stall the onset of Huntington's-like symptoms in fruit fly and mice, and we hope it will do the same in

humans."

Autophagy can be induced in mouse and fly models by administering the drug rapamycin, an antibiotic used as an immunosuppressant for transplant patients. However, administered over the long term, the drug has some side effects and Rubinsztein and colleagues are aiming to find safer ways of inducing autophagy long term.

Now, Professor Rubinsztein, together with Professor Stuart Schreiber's lab at the Broad Institute of Harvard/MIT, Boston in the US, and Dr Cahir O'Kane's group in the Department of Genetics at the University of Cambridge have found a way of identifying novel "small molecules" capable of inducing autophagy. The research is published today in the journal *Nature Chemical Biology*.

The screening process involves identifying small molecules that enhance or suppress the ability of rapamycin to slow the growth of yeast, though the selected molecules have no effects on yeast growth by themselves. Yeast is a single-celled organism and therefore less complex to study for initial screening purposes.

Three of the molecules that enhanced the growth-suppressing effects of rapamycin in yeast were also found to induce autophagy by themselves in mammalian cells independent of the action of rapamycin. These molecules enhanced the ability of the cells to dispose of mutant huntingtin in cell and fruit fly models and protect against its toxic effects.

"These compounds appear to be promising candidates for drug development," says Professor Rubinsztein. "However, even if one of the candidates does prove to be successful, it will be a number of years off becoming available as a treatment. In order for such drugs to be useful candidates in humans, we will need to be able to get them into right

places in the right concentrations, and with minimal toxicity. These are some of the issues we need to look at now."

Source: Wellcome Trust