A new molecular zip code, and a new drug target for Huntington's disease

August 20 2007

McMaster University researchers have first insight into how Huntington's disease (HD) is triggered. The research will be published online in the British Journal, Human Molecular Genetics, on Monday, August 20.

"These are exciting results by the McMaster team," said Dr. Rémi Quirion, Scientific Director at the Canadian Institutes of Health Research, Institute of Neuroscience, Mental Health and Addiction. Even if the huntingtin protein has been known for almost 20 years, the cause of Huntington's disease is still not clear. Data reported here shed new lights on this aspect and possibly leading to new therapeutic potential in the future."

Ray Truant, professor in the Department of Biochemistry and Biomedical Sciences, has been studying the biological role of the huntingtin protein and the sequences in the protein that tell it where to go within a brain cell.

Huntington disease (HD) is a neurological disorder resulting from degeneration of brain cells. The degeneration causes uncontrolled limb movements and loss of intellectual faculties, eventually leading to death. There is no treatment. HD is a familial disease, passed from parent to child through a mutation in the normal gene. The disorder is estimated to affect about one in every 10,000 persons.

Truant and PhD candidate graduate student, Randy Singh Atwal, have

discovered a small protein sequence in huntingtin that allows it to locate to the part of the cell critical for protein quality control. Similar findings have been seen to be very important for other neurodegenerative diseases such as Parkinson's and Alzheimer's diseases.

Huntingtin protein is essential for normal development in all mammals, and is found in all cells, yet its function was unknown. It appears that huntingtin is crucial for a brain cell's response to stress, and moves from the endoplasmic reticulum into the nucleus, the control centre of the cell. When mutant huntingtin is expressed however, it enters the nucleus as it should in response to stress, but it cannot exit properly, piling up in the nucleus and leading to brain cell death in HD.

"What is important to Huntington disease research is that in the learning of the basic cell biology of this protein, we have also uncovered a new drug target for the disease," says Atwal.

Atwal additionally found that huntingtin can be sent to the nucleus by protein modifying enzymes called kinases, and he has determined the three-dimensional shape of this sequence.

Truant and Atwal's work indicates that if mutant huntingtin is prevented from entering the nucleus, it cannot kill a brain cell. This means that a kinase inhibitor drug may be effective for Huntington's disease. Kinase inhibitors form the largest number of successful new generation drugs that are coming to market for a plethora of diseases including stroke, arthritis and cancer.

"This is most exciting to us, because we immediately have all the tools and support in hand at McMaster to quickly hunt this kinase down, and find potential new drugs for Huntington's disease in ways that are similar or better than a large pharmaceutical company", says Truant. Truant's lab is also collaborating in the US with the Cure Huntington's Disease

Initiative (CHDI) a novel, non-profit virtual pharmaceutical company focused on HD.

A large portion of this work was completed in the new McMaster biophotonics facility, and additional research will be done in McMaster's unique high throughput screening lab and other new labs being established at the University.

"We can actually watch huntingtin protein move inside of a single live brain cell in real time in response to stress, and we can watch mutant huntingtin kill that cell, even over days," says Truant. "Using molecular tools, computer software and sophisticated laser microscopy techniques which we've been developing at McMaster over the last seven years, researchers can now use these methods to hopefully watch a drug stop this from happening."

Truant's laboratory is supported by grants from the United States High Q Foundation, the Canadian Institutes of Health Research, the Huntington Society of Canada and the Canada Foundation for Innovation.

"This discovery reflects Dr. Truant's growing contribution to the international campaign to create a world free from Huntington disease," says Don Lamont, CEO & Executive Director of the Huntington Society of Canada – Canada's only organization focused on research, education and support in the HD field.

"Our families live on a 'tightrope' waiting for an effective treatment or a cure for HD", says Lamont. "The discovery provides hope for the Huntington community – most of all, hope that their children will not have to suffer the devastation of this inherited disease."

Source: McMaster University