Medical researchers ID potential new drug target that could stop debilitating effects of MS

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Medical researchers at the University of Alberta have discovered a potential new drug target for Multiple Sclerosis that could prevent physical disability associated with the disease, once a new drug is developed.

In the first phase of MS, those with the condition have lots of inflammation of their brain cells, resulting in continuous cycles of inflammation attacks followed by recovery periods. In the second phase of the disease, the inflammation isn't as severe, but this is the stage where physical disability sets in due to the effects from substantial numbers of brain cells being killed in the first phase of the disease.

When immune cells become active due to inflammation, they can pass through the blood-brain barrier and enter the central nervous system. Some of these activated immune cells secrete a molecule, known as granzyme B, that can get inside neurons and wreak havoc – ultimately causing brain cell death. Granzyme B is found in MS brain lesions – especially in the early stages of inflammation. This molecule can get into brain cells through a "gatekeeper," known as receptor M6PR.

Researchers with the Faculty of Medicine & Dentistry discovered in lab experiments that if they prevent this granzyme B from entering neurons, "we can also prevent the killing of neurons," says principal investigator Fabrizio Giuliani, whose work was recently published in the peer-

reviewed publication, *The Journal of Immunology*.

"It is this loss of brain cells, in the long-term, which induces disability in those with MS," he says. "This is a new drug target for MS that is specific for the neurodegenerative processes following inflammation."

Giuliani, a researcher in the Division of Neurology and a practising neurologist, noted this latest research builds on previous findings by his colleagues within the faculty. Medical researcher and co-author Chris Bleackley made an earlier discovery about how granzyme B enters target cells through the receptor M6PR. Another faculty researcher discovered that the M6PR receptor is found mostly in neurons.

"We were just connecting the dots and said: 'OK, if this receptor is expressed in neurons specifically and not expressed in other cells, is it possible that this is the mechanism that allows this granzyme B to get into human neurons and start killing brain cells? What we found out is yes, this death receptor allows this specific molecule to get in. If you block the receptor, you also block the neurotoxic effect in neurons. This is an excellent example of collaboration with other researchers and translational research."

Many existing MS treatments primarily target brain inflammation, which is very effective in the first phase of the disease but not as helpful once patients reach the second phase. Giuliani says what is needed are new medications that can either repair inflamed brain cells or prevent brain degeneration in the first place. This newly discovered drug target could open the door to new medications that do just that – prevent brain cell death in the early stages of the disease.

Giuliani adds that with this drug target, only a specific function of a cell would be blocked, not multiple functions of a cell. Many medications currently on the market block multiple functions of a specific type of

cell. "We are blocking a specific function, not multiple pathways and eventually this strategy could reduce the side effects of new drugs," he notes.

Giuliani and his fellow researchers are continuing their work in this area.

Provided by University of Alberta