Immune cells of the brain renew hopes for curing Alzheimer's disease

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A new experimental study carried out in mice shows that microglia, immune cells of the brain, might play a key role in protecting the brain from Alzheimer's disease (AD). It is long believed that toxic sticky protein deposits in the brain called amyloid beta (Aβ) are responsible for loss of memory in AD patients. Earlier studies have shown that microglia can remove Aβ protein from the brain and therefore be vital for successful therapy. Interestingly, the doctoral thesis of Mr Lakshman Kumar Puli, MPharm (Pharmacology), indicates that microglia may play a significant role irrespective of their capacity to remove brain Aβ deposits.

These Aβ deposits initiate inflammation inside the brain. It is not clearly known if this inflammation is good or bad. Harmful brain inflammation fires up microglia, which may interfere with the normal functioning of brain cells or even kill them. However, according to this new study, stopping harmful activation of microglia is feasible even without the removal of Aβ protein from the brain.

Mr Puli's doctoral thesis titled "Experimental Immunomodulation in Alzheimer's disease" utilizes two different approaches to suppress harmful activation of microglia. Firstly, genetically modified mice with Alzheimer's disease when treated with polyclonal human intravenous immunoglobulins (IVIG) suppressed harmful activation of microglia and, surprisingly, also promoted the survival of newly born neurons in the hippocampus of the brain, which is regarded as the seat of memory. This is the first experimental study to suggest that IVIG can promote the

survival of newly born neurons in the hippocampus.

IVIG is currently in the final phase clinical trials in AD patients. In humans, IVIG has been reported to have stopped the progression of AD in a small number of patients for a remarkable period of three years. The mechanism remains unknown, but Mr Puli's experimental work suggests that IVIG might promote the clinical benefits in AD patients by suppressing harmful activation of microglia and enhancing the survival of newly born neurons in the brain.

"These studies have revealed some very important new mechanisms by which treatment with naturally occurring human antibodies can potentially benefit persons with Alzheimer's disease and other age related disorders," says Dr Norman Relkin (Weill Cornell Memory Disorders Program, New York, USA), who is leading the Gammaglobulin Alzheimer Partnership (GAP) Phase 3 Study of IVIG for Alzheimer's disease.

In the second approach, Mr Puli and his fellow researchers used a novel genetically modified mouse that lacks the key gene responsible for brain inflammation. Removal of this Nfkb1 gene greatly suppressed activation of microglia irrespective of its capacity to remove Aβ protein from the brain. However, in this study it was not clear if such a suppression is good or bad. Both these experiments clearly indicate that microglia can be influenced in a way which is beneficial for AD patients.

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