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Blocking immune cell action increases Alzheimer's-associated protein deposits

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The immune system's response against amyloid-beta, the protein that forms plaques in the brains of patients with Alzheimer's disease, appears to protect the brain from damage in early stages of the devastating neurological disorder. A report from Massachusetts General Hospital (MGH) researchers finds that lack of a protein required for recruitment of the brain's primary immune cell led to increased amyloid-beta deposits and earlier death in a mouse model of Alzheimer's disease. The paper will appear in the journal Nature Medicine and has received early online release.

"Our results provide in vivo evidence that the brain's immune system plays a protective role in early Alzheimer's disease by mediating the clearance of amyloid-beta," says Joseph El Khoury, MD, of the MGH Center for Immunology and Inflammatory Diseases, the paper's lead author. "This new connection between immune cell function and this debilitating disease suggests potential new therapeutic strategies."

While it has been known that the immune system reacts against amyloid-beta in the brain, the relation of that response to the pathology of Alzheimer's disease has not been clear. Within the brain and central nervous system, the inflammatory process is controlled by immune cells called microglia, known to accumulate around amyloid-beta plaques. Some evidence has suggested that microglia break down and remove amyloid-beta, but the cells also release factors that could contribute to neurodegeneration. The current study was designed to clarify the role of microglia in Alzheimer's and identify factors involved in the immune

cells' accumulation at amyloid plaques.

The research team focused on a molecule called CCR2, a receptor on the surface of microglia and other immune cells that is known to help direct them from the bloodstream to sites of inflammation within the brain. Since CCR2 is known to bind chemokines, proteins that attract immune cells and are elevated in brains affected by Alzheimer's, the receptor could be important for the movement of microglia to the site of amyloid-beta deposits. To test that possibility, the investigators used a mouse model of Alzheimer's disease and generated strains in which one or both copies of the CCR2 gene had been deleted.

They found that mice lacking CCR2 had significantly more amyloid-beta in their brains than did the Alzheimer's-model mice that retained the molecule. These deposits were primarily found in small blood vessels – similar to a condition called cerebral amyloid angiopathy, which is associated with an increased risk of cerebral hemorrhage. In addition, CCR2-deficient mice had significantly shortened life spans. By 130 days of age, 85 percent of mice in which both copies of the CCR2 gene had been deleted had died, as had 60 percent of those with one copy. This compares with 30 percent of the Alzheimer's-model mice with two copies of CCR2 and only 1 percent of normal mice.

Analysis of levels of several enzymes known to either promote or break down amyloid-beta deposits revealed that a lack of CCR2 appears to reduce clearance of the toxic protein from the brain. Other tests suggest that CCR2 is required for microglia to migrate to sites of amyloid deposition but that its absence does not interfere with the cells' activity once they encounter amyloid-beta.

"By showing that microglia have a protective role in helping remove amyloid-beta from the brain, our findings suggest that enhancing the accumulation of these cells may be beneficial to patients with early-stage

Alzheimer's disease," says Andrew Luster, MD, PhD, director of the MGH Center for Immunology and Inflammatory Diseases and senior author of the report.

The researchers also note that drugs that block CCR2 are currently being tested for chronic inflammatory diseases, and this study's results suggest that such agents could increase the risk of Alzheimer's in some individuals. Luster is a professor of Medicine at Harvard Medical School, where El Khoury is an assistant professor of Medicine.

Source: Massachusetts General Hospital