Poor recycling of BACE1 enzyme could promote Alzheimer's disease

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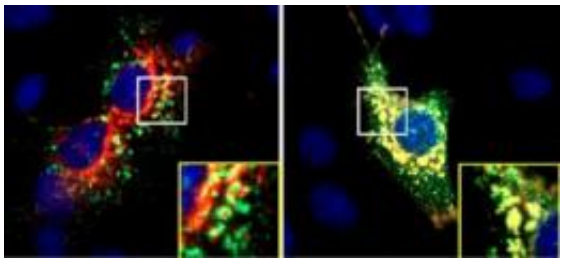

A study in the *Journal of Cell Biology* suggests that sluggish recycling of the BACE1 enzyme could promote Alzheimer's disease. Relative to control cells (left), cells short on the protein VPS35 (right) accumulate more BACE1 (red) in endosomes (green). BACE1 in endosomes appears yellow. Credit: Wen, L., et al. 2011. J. Cell Biol. http://dx.doi.org/10.1083/jcb.201105109

Sluggish recycling of a protein-slicing enzyme could promote Alzheimer's disease, according to a study published online on November 21 in The *Journal of Cell Biology*.

Abeta, the toxic protein that accumulates in the brains of Alzheimer's patients, is formed when enzymes cut up its parental protein, known as amyloid precursor protein. One of those enzymes is beta-secretase or BACE1. BACE1 cycles between the Golgi apparatus and the plasma membrane, traveling through endosomes on the way. A protein complex called the retromer helps transport proteins back from endosomes to the Golgi. Previous studies have found reduced levels of two retromer components, including the protein VPS35, in the brains of patients with Alzheimer's disease.

To find out whether VPS35 affects Alzheimer's disease progression, Wen-Cheng Xiong and colleagues crossed two mouse lines to create animals that are prone to many symptoms of the disease and generate half the normal amount of VPS35. The mice displayed Alzheimer's-like abnormalities earlier than their parental strains, and their brains accumulated more Abeta.

Cells lacking VPS35 carried extra BACE1 in their endosomes, consistent with a defect in retromer-mediated protein transport. BACE1 is more active in the acidic interior of endosomes than in the more basic surroundings of the Golgi apparatus. Thus, by leaving more BACE1 trapped in endosomes, the decline in VPS35 levels could enhance BACE1 activity and generate more Abeta. Although no VPS35 mutations have so far turned up in Alzheimer's patients, the protein's level in the brain dwindles in aging mice. The researchers suspect that certain Alzheimer's disease risk factors, such as oxidative stress, also diminish VPS35 levels in the brain.

More information: Wen, L., et al. 2011. *J. Cell Biol*. dx.doi.org/10.1083/jcb.201105109

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