How neuronal activity leads to Alzheimer's protein cleavage

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Amyloid precursor protein (APP), whose cleavage product, amyloid-b (Ab), builds up into fibrous plaques in the brains of Alzheimer's disease patients, jumps from one specialized membrane microdomain to another to be cleaved, report Sakurai et al in the *Journal of Cell Biology*.

Although there is no definitive evidence that Ab plaques are the direct cause of Alzheimer's disease, there is much circumstantial evidence to support this. And working on this hypothesis, scientists are investigating just how the plaques form and what might be done to stop or reverse their formation.

APP, a protein of unknown function, is membrane associated and concentrates at the neuronal synapse. Certain factors such as high cellular cholesterol and increased neuronal or synaptic activity are known to drive APP cleavage, and Sakurai and colleagues' paper pulls these two modes of Ab regulation together.

APP associates with membrane microdomains high in cholesterols (lipid rafts). These lipid rafts can also contain the enzyme necessary for APP cleavage, BACE. Synaptic activity is known to involve a very different type of membrane microdomain high in an excytosis-promoting factor called syntaxin. Sakurai et al. now show that although APP preferentially associates with syntaxin microdomains, upon neuronal stimulation APP instead associates with microdomains that contain BACE.

It's unclear why APP should be associated with syntaxin, though it might

suggest a role for APP in vesicle trafficking and exocytosis. Also unclear is why neuronal activity should cause APP to jump from syntaxin domains to BACE domains. What is clear, however, is that the process is an active one, requiring a kinase called cdk5. Furthermore, treating neurons with a cdk5 inhibitor called roscovitine, which is currently in trials for cancer treatment, reduced APP's association with BACE microdomains and reduced APP cleavage.

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