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Fragile X protein may play role in Alzheimer's disease

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A brain afflicted by severe Alzheimer's disease is a sad sight, a wreck of tangled neural connections and organic rubble as the lingering evidence of a fierce internal battle.

A new study has now uncovered an unexpected link between this devastating neural degeneration and a protein whose absence causes a different neurological disease - the inherited mental retardation disorder called fragile X syndrome. In the Feb. 13 issue of the journal *Public Library of Science Biology*, University of Wisconsin-Madison researchers report that, in mice, the fragile X mental retardation protein may regulate the material responsible for the plaques and cell death seen in the brains of Alzheimer's patients. If similar research can be confirmed in humans, it offers a glimmer of hope for developing a treatment for Alzheimer's disease.

The telltale plaques of Alzheimer's disease contain remnants of dying cells and clumps of a small, sticky scrap of a protein called beta-amyloid. When the gummy protein builds up in the brain, it can band together and wreak havoc inside neurons, damaging and ultimately killing them.

No one knows what triggers toxic beta-amyloid accumulation in the brain, but the sticky bits are made when the larger amyloid precursor protein is chopped up by enzymes, says Jim Malter, a pathologist in the UW-Madison School of Medicine and Public Health and senior author of the new study. Scientists have long hoped to prevent or treat

Alzheimer's disease by keeping the amyloid precursor protein in check: less precursor should mean less of the dangerous pieces, which in turn should mean less cell death.

The current study pinpoints the fragile X mental retardation protein as an important player in this control. Malter and colleague Cara Westmark found that it normally restricts production of the full-length amyloid precursor in mice, releasing the protein's synthesis template only when the nerve cell is stimulated. By linking protein synthesis to neural activity, this regulation helps the brain cement useful connections while ignoring or eliminating worthless ones.

However, Malter and Westmark found that mice lacking the fragile X protein lost this level of control over the amyloid precursor and, subsequently, had much higher levels of the toxic beta-amyloid in their brains.

Links between developmental disabilities and degenerative disease do make sense, Malter says. Mental retardation and cognitive decline can reflect similar underlying problems, such as difficulties forming or maintaining correct neural pathways. Malter explains that the amyloid precursor protein was already known to be important at the sites of connections between neural cells and unusually high levels have been reported in patients with other developmental disorders, including autism and Down's syndrome.

While the new finding does not mean that the fragile X protein is directly involved in Alzheimer's disease, Malter says the result highlights a possible target for therapy. "Right now, there are no good drugs for Alzheimer's disease," he says. "The idea of reducing beta-amyloid seems sound in terms of treatment."

Rather than target the fragile X protein itself, Malter envisions using

drugs to block a cell-surface receptor, a gateway to the cell that kicks off the fragile X protein's response to neural stimulation. In fact, he says, several drugs targeting the receptor already exist, originally developed decades ago as anti-anxiety treatments. He plans to start testing these compounds in mice to see if they can reduce build-up of the toxic protein.

If such drugs are effective against dangerous protein accumulation, they might be used for patients in the early stages of Alzheimer's to prevent disease progression. Though unlikely to reverse existing Alzheimer's symptoms, Malter says, "Keeping people at the same place would be a victory."

Source: by Jill Sakai, University of Wisconsin-Madison