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Studies demonstrate link among Alzheimer's disease, Down syndrome and atherosclerosis

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Nearly 20 years ago Huntington Potter kicked up a storm of controversy with the idea that Down syndrome and Alzheimer's were the same disease. Now the evidence is in: He was right.

And that's not all. Down syndrome, artery-clogging cardiovascular disease, and possibly even diabetes, appear to share a common disease mechanism with Alzheimer's disease,

Dr. Potter and colleagues at the Florida Alzheimer's Disease Research Center, USF Health Byrd Alzheimer's Institute, recently reported.

The researchers' two papers - one in *Molecular Biology of the Cell* and the other in PLoS ONE -- implicate the Alzheimer's-associated protein beta amyloid (amyloid protein), which damages the microtubule transport system responsible for moving chromosomes, proteins and other cargo around inside cells. Both studies were done in mice and humans cell cultures modeling Alzheimer's disease. Together, the laboratory discoveries suggest that protecting the microtubule network from this amyloid damage might be an effective way to prevent or even reverse Alzheimer's disease and associated disorders.

The first paper, by Antoneta Granic and colleagues published online Dec. 23 in Molecular Biology of the Cell, provides the mechanism behind previous work by Dr. Potter's laboratory showing that all Alzheimer's disease patients harbor some cells with three copies of chromosome 21, known as trisomy 21, instead of the usual two. Trisomy

21 is a characteristic shared by all the cells in people with the birth defect Down syndrome as well. This earlier work demonstrated that Alzheimer's disease could be considered a late onset form of Down syndrome.

By age 30 to 40, all people with Down syndrome develop the same brain pathology seen in Alzheimer's disease, including a nerve-killing buildup of sticky amyloid protein clumps. This contributes to accelerated nerve cell loss and dementia.

With the study reported in MBC, Dr. Potter and his colleagues now show that the Alzheimer's-associated amyloid protein is the culprit that interferes with the microtubule transport system inside cells. The microtubules are responsible for segregating newly duplicated chromosomes as cells divide.

"Beta amyloid basically creates potholes in the protein highways that move cargo, including chromosomes, around inside cells," said Dr. Potter, who holds the Eric Pfeiffer Endowed Chair for Research on Alzheimer's Disease.

When the microtubule network is disrupted, chromosomes can be incorrectly transported as cells divide and the result is new cells with the wrong number of chromosomes and an abnormal assortment of genes. For example, Down syndrome cells contain three copies of the beta amyloid gene on chromosome 21 - leading to more accumulation of the "bad" amyloid protein over a lifetime, Dr. Potter says. "Alzheimer's disease probably is caused in part from the continuous development of new trisomy 21 nerve cells, which amplify the disease process by producing extra beta amyloid."

The second paper by lead author Jose Abisambra and colleagues, published Dec. 31 in the online journal *PLoS ONE,* describes another

consequence of the damaged microtubule network caused by the amyloid protein.

Many Alzheimer's disease patients also commonly develop vascular diseases and diabetes. Whether this coincidence is bad luck or due to shared disease processes is intensely debated. Research teams have investigated the role that low-density lipoprotein (LDL), the bad cholesterol that causes atherosclerosis, cardiovascular disease and stroke, may play in the development of Alzheimer's with mixed results. However, the USF group focused on the amyloid protein's potential effects on LDL metabolism. The receptor needed to detect and use LDL is among the proteins transported by the microtubules.

As previously reported by their colleagues in the MBC paper, the second USF team found that the amyloid protein inflicts damage to the microtubule network. As a consequence, the receptor needed to pull LDL circulating throughout the bloodstream into the body's cells has trouble getting to the cell surface to retrieve this bad cholesterol. This interference with LDL metabolism may allow bad cholesterol to build up in into plaques that choke off blood supply to the brain and heart in people with Alzheimer's, Dr. Potter said.

Similarly, other key proteins - including insulin receptors and receptors for brain signaling molecules -- are also likely locked inside cells when the transport system is damaged by amyloid or other factors. "The insulin receptors are needed to get blood sugar inside the cell where it can be used for energy. The nerve cell signaling receptors help promote memory and learning," Dr. Potter said. "So, if these receptors are unable to function properly, it may lead to diabetes and problems with learning and memory."

"We're beginning to understand how conditions like cardiovascular disease and diabetes may manifest some of the same underlying disease

processes as Alzheimer's disease," he said, "rather than being independent diseases that just happen to develop in the same patient."

More information: Journal articles cited:

1. "Alzheimer Ab Peptide Induces Chromosome Mis-segregation and Aneuploidy, including Trisomy 21; Requirement for Tau and APP," Antoneta Granic, Jaya Padmanabhan, Michelle Norden, and Huntington Potter. *Molecular Biology of the Cell*, Dec. 23, 2009.

2. "LDLR Expression and Localization Are Altered in Mouse and Human Cell Culture Models of Alzheimer's Disease," Jose Abisambra, Tina Fiorella, Jaya Padmanabhan, Peter Neame, Inge Wefes, and Huntington Potter, *PLoS ONE*, Volume 5, Issue 1. (January 2010).

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