Scientists identify promising new target to combat Alzheimer's disease

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Sometimes the more a person tries to fix a seemingly minor problem, the worse things become. Cells are no different, it turns out, though attempting to compensate for what begins as a minor deficiency or dysfunction can be dire. In the case of Alzheimer's disease, Lewis Katz School of Medicine at Temple University (LKSOM) researchers now

show that mitochondrial calcium transport remodeling—what appears to be an attempt by cells to compensate for flagging energy production and metabolic dysfunction—while initially beneficial, ultimately becomes maladaptive, fueling declines in mitochondrial function, memory, and learning.

The new research, published online in the journal *Nature Communications*, is the first to link maladaptive changes in calcium transport by mitochondria—the energy-generating powerhouses of cells—to the progression of Alzheimer's disease.

"Amyloid-beta deposition and tau pathology are considered the major contributors to Alzheimer's disease and, as a result, they have been the main focus of therapeutic development," explained John W. Elrod, Ph.D., Associate Professor in the Center for Translational Medicine at LKSOM and senior investigator on the new study. "Large clinical trials targeting these pathways have universally failed, however."

Altered calcium regulation and metabolic dysfunction have been suspected of contributing to neuronal dysfunction and Alzheimer's development. "But up to now, no one has investigated the impact of altered calcium transport into and out of the mitochondria on the progression of Alzheimer's disease," Dr. Elrod noted. "Our current study provides a missing link between these two hypotheses of Alzheimer's pathogenesis."

Calcium transport into mitochondria plays an important part in many cellular functions and requires the involvement of multiple proteins to be carried out effectively. Among the key regulators of this process is a protein known as NCLX, which previously was discovered by Dr. Elrod's laboratory to mediate calcium efflux from heart cells. NCLX expression is also important in mitochondrial calcium efflux in neurons.

In their new study, Dr. Elrod and colleagues examined the role of mitochondrial calcium uptake by neurons in Alzheimer's disease. To do so, the team used a mouse model of familial Alzheimer's disease in which animals harbored three gene mutations that give rise to age-progressive pathology comparable to Alzheimer's progression in human patients.

As mice carrying the three mutations aged, the researchers observed a steady reduction in NCLX expression. This reduction was accompanied by decreases in the expression of proteins that limit mitochondrial calcium uptake, resulting in damaging calcium overload. NCLX loss was further linked to increases in the production of cell-damaging oxidants.

To better understand the physiological relevance of NCLX loss, Dr. Elrod's team next completely eliminated NCLX expression in the forebrain of Alzheimer's disease mice. In tests for memory and cognitive function, the animals exhibited significant impairments. Analyses of brain tissue from these mice showed that NCLX reduction and the consequent loss of calcium efflux from mitochondria accelerated the development of amyloid beta and tau pathology. When NCLX expression was restored, levels of harmful protein aggregates declined, neuronal mitochondrial calcium homeostasis was reestablished, and mice were rescued from cognitive decline.

"Our findings indicate that maladaptive remodeling of pathways to compensate for abnormalities in calcium regulation, which perhaps are meant to maintain energy production in cells, lead to neuronal dysfunction and Alzheimer's pathology," Dr. Elrod said. "Moreover, our data suggest that amyloid beta and tau pathology actually lie downstream of mitochondrial dysfunction in the progression of Alzheimer's disease, which opens up a new therapeutic angle."

Dr. Elrod and colleagues plan next to carry out a more detailed

investigation of metabolic dysfunction that arises before Alzheimer's disease pathology emerges.

More information: Pooja Jadiya et al, Impaired mitochondrial calcium efflux contributes to disease progression in models of Alzheimer's disease, *Nature Communications* (2019). DOI: 10.1038/s41467-019-11813-6

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