Stressed, toxic, zombie cells seen for first time in Alzheimer's

August 22 2018

Miranda Orr, Ph.D., of UT Health San Antonio, led research showing cell stress called senescence is present in Alzheimer's disease and is linked to tau protein tangles in the brain disorder. Credit: UT Health San Antonio

A type of cellular stress known to be involved in cancer and aging has now been implicated, for the first time, in Alzheimer's disease. UT Health San Antonio faculty researchers reported the discovery Monday [August 20, 2018] in the journal *Aging Cell.*

The team found that the stress, called cellular senescence, is associated with harmful tau protein tangles that are a hallmark of 20 human brain diseases, including Alzheimer's and traumatic brain injury. The researchers identified senescent cells in postmortem brain tissue from Alzheimer's patients and then found them in postmortem tissue from another brain disease, progressive supranuclear palsy.

Cellular senescence allows the stressed cell to survive, but the cell may become like a zombie, functioning abnormally and secreting substances that kill cells around it. "When cells enter this stage, they change their genetic programming and become pro-inflammatory and toxic," said study senior author Miranda E. Orr, Ph.D., VA research health scientist at the South Texas Veterans Health Care System, faculty member of the Sam and Ann Barshop Institute for Longevity and Aging Studies, and instructor of pharmacology at UT Health San Antonio. "Their existence means the death of surrounding tissue."

Improvements in brain structure and function

The team confirmed the discovery in four types of mice that model Alzheimer's disease. The researchers then used a combination of drugs to clear senescent cells from the brains of middle-aged Alzheimer's mice. The drugs are dasatinib, a chemotherapy medication that is U.S. Food and Drug Administration-approved to treat leukemia, and quercetin, a natural flavonoid compound found in fruits, vegetables and some beverages such as tea.

After three months of treatment, the findings were exciting. "The mice were 20 months old and had advanced brain disease when we started the therapy," Dr. Orr said. "After clearing the senescent cells, we saw improvements in brain structure and function. This was observed on brain MRI studies (magnetic resonance imaging) and postmortem histology studies of cell structure. The treatment seems to have stopped the disease in its tracks."

"The fact we were able to treat very old mice and see improvement gives us hope that this treatment might work in human patients even after they exhibit symptoms of a brain disease," said Nicolas Musi, M.D., study first author, who is Professor of Medicine and Director of the Sam and Ann Barshop Institute at UT Health San Antonio. He also directs the VA-sponsored Geriatric Research, Education and Clinical Center (GRECC) in the South Texas Veterans Health Care System.

Typically, in testing an intervention in Alzheimer's

mice, the therapy only works if mice are treated before the disease starts, Dr. Musi said.

Tau protein accumulation is responsible

In Alzheimer's disease, patient brain tissue accumulates tau protein tangles as well as another protein deposit called amyloid beta plaques. The team found that tau accumulation was responsible for cell senescence. Researchers compared Alzheimer's mice that had only tau tangles with mice that had only amyloid beta plaques. Senescence was identified only in the mice with tau tangles.

In other studies to confirm this, reducing tau genetically also reduced senescence. The reverse also held true. Increasing tau genetically increased senescence.

Importantly, the drug combination reduced not only cell senescence but also tau tangles in the Alzheimer's mice. This is a drug treatment that does not specifically target tau, but it effectively reduced the tangle pathology, Dr. Orr said.

"When we looked at their brains three months later, we found that the brains had deteriorated less than mice that received placebo control treatment," she said. "We don't think brain cells actually grew back, but there was less loss of neurons, less brain ventricle enlargement, improved cerebral blood flow and a decrease in the tau tangles. These drugs were able to clear the tau pathology."

Potentially a therapy to be tested in humans

"This is the first of what we anticipate will be many studies to better understand this process," Dr. Musi said. "Because these drugs are approved for other uses in humans, we think a logical next step would be to start pilot studies in people."

The drugs specifically target—and therefore only kill—the senescent cells. Because the drugs have a short half-life, they are cleared quickly by the body and no side effects were observed.

Dasatinib is an oral medication. The mice were treated with the combination every other week. "So in the three months of treatment, they only received the drug six times," Dr. Orr said. "The drug goes in, does its job and is cleared. Senescent cells come back with time, but we expect that it would be possible to take the drug again and be cleared out again. That's a huge benefit—it wouldn't be a drug that people would have to take every day."

Dosage and frequency in humans would need to be determined in clinical trials, she said.

Next, the researchers will study whether cell senescence is present in traumatic brain injury. TBI is a brain injury that develops tau protein accumulation and is a significant cause of disability in both military and non-military settings, Dr. Orr said.

More information: Nicolas Musi et al, Tau protein aggregation is associated with cellular senescence in the brain, *Aging Cell* (2018). DOI: 10.1111/acel.12840

Provided by University of Texas Health Science Center at San Antonio