MedicalXpress

Scientists uncover potential target for treating common form of early-onset dementia

September 21 2011

No cure exists for frontotemporal dementia, which strikes between the ages of 40 and 64 and accounts for at least one in four cases of early-onset dementia. Caused by the death of cells in the front and sides of the brain, the disease can lead to dramatic changes in a patient's personality and behavior, including the loss of the ability to communicate.

Now UCLA scientists have discovered that a key signaling pathway plays an important role in the brain disorder and may offer a potential target for treatment. The journal *Neuron* publishes the findings in its Sept. 22 edition.

"A family history exists for nearly half of the frontotemporal dementia patients we see, suggesting a genetic component for the disease," explained Dr. Daniel Geschwind, who holds the Gordon and Virginia MacDonald Distinguished Chair in Human Genetics, and is a professor of neurology at the David Geffen School of Medicine at UCLA and a professor of psychiatry at the Semel Institute for Neuroscience and Human Behavior at UCLA. "Our goal was to reveal what happens on a molecular level that causes the neuron death leading to this devastating disease."

Earlier studies had linked the brain disorder with a mutation in the gene for a protein called granulin that regulates cell growth and survival. Previous research showed that the gene mutation reduced the amount of

granulin by half.

"Until now, little has been known about granulin's function in the brain," said Geschwind. "We wanted to explore whether a granulin shortage kick-starts the cell death that precedes dementia. We also were searching for naturally occurring protective responses that we could target to help alleviate the disease's symptoms."

Geschwind and his colleagues examined granulin's role from three fronts: in cell culture, in a gene-knockout mouse model and in post-mortem brain tissue from dementia patients.

"Cell death is easy to observe in brain tissue removed from patients after their death," said Geschwind. "We pursued two other approaches to determine the mechanism behind brain-cell survival and uncover how early it occurs in the disease."

The UCLA team performed a genetic analysis of granulin-deficient neurons made from human brain stem cells. The scientists used a powerful technique that allowed them to see the entire genome and search for networks of highly correlated genes.

"We discovered that a drop in granulin sabotaged brain cells' survival and boosted activity of Wnt, a major signaling pathway," said Geschwind. "Within this pathway, we identified a major increase in a specific receptor that Wnt binds to on the cell surface. This change occurred early in the disease process in both living mice and culture."

The scientists found that Wnt signaling through the receptor FZD2 was heightened in granulin-deficient mice. They demonstrated that reducing the receptor resulted in greater cell death while increasing it promoted neuron survival.

"We believe that Wnt boosts FZD2 to help protect brain-cell survival during the early stages of dementia," said Geschwind. "Our findings suggest that increasing this receptor and other parts of the Wnt pathway may provide a new drug target to treat this disease."

Provided by University of California - Los Angeles