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Study identifies biological mechanism that plays key role in early-onset dementia

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Using animal models, scientists at the Gladstone Institutes have discovered how a protein deficiency may be linked to frontotemporal dementia (FTD)—a form of early-onset dementia that is similar to Alzheimer's disease. These results lay the foundation for therapies that one day may benefit those who suffer from this and related diseases that wreak havoc on the brain.

As its name implies, FTD is a fatal disease that destroys cells, or neurons, that comprise the frontal and temporal lobes of the brain—as opposed to Alzheimer's which mainly affects brain's memory centers in the hippocampus. Early symptoms of FTD include personality changes, such as increased erratic or compulsive behavior. Patients later experience difficulties speaking and reading, and often suffer from long-term memory loss. FTD is usually diagnosed between the ages of 40 and 65, with death occurring within 2 to 10 years after diagnosis. No drug exists to slow, halt or reverse the progression of FTD.

A new study led by Gladstone Senior Investigator Robert V. Farese, Jr., MD, offers new hope in the fight against this and other related conditions. In the latest issue of the *Journal of Clinical Investigation*, available today online, Dr. Farese and his team show how a protein called progranulin prevents a class of cells called microglia from becoming "hyperactive." Without adequate progranulin to keep microglia in check, this hyperactivity becomes toxic, causing abnormally prolonged inflammation that destroys neurons over time—and leads to debilitating symptoms.

"We have known that a lack of progranulin is linked to neurodegenerative conditions such as FTD, but the exact mechanism behind that link remained unclear," said Dr. Farese, who is also a professor at the University of California, San Francisco (UCSF), with which Gladstone is affiliated. "Understanding the inflammatory process in the brain is critical if we are to develop better treatments not only for FTD, but for other forms of brain injury such as Parkinson's disease, Huntington's disease and multiple sclerosis (MS)—which are likely also linked to abnormal microglial activity."

Microglia—which are a type of immune cells that reside in the CNS—normally secrete progranulin. Early studies on traumatic CNS injury found that progranulin accumulates at the injury site alongside microglia, suggesting that both play a role in injury response. So, Dr. Farese and his team designed a series of experiments to decipher the nature of the relationship between progranulin and microglia. First, the team generated genetically modified mice that lack progranulin. They then monitored how the brains of these mice responded to toxins, comparing this reaction to a control group.

"As expected, the toxin destroys neurons in both sets of mice—but the progranulin-deficient mice lost twice as many neurons as the control group," said Lauren Herl Martens, a Gladstone and UCSF graduate student and the study's lead author. "This showed us that progranulin is crucial for neuron survival. We then wanted to see whether a lack of progranulin itself would injure these cells—even in the absence of toxins."

In a petri dish, the researchers artificially prevented microglia from secreting progranulin and monitored how these modified microglia interacted with neurons. They observed that a significantly greater number of neurons died in the presence of the progranulin-deficient microglia when compared to unmodified microglia. Other experiments

revealed the process' underlying mechanism. Microglia are the CNS's first line of defense. When the microglia sense toxins or injury, they trigger protective inflammation—which can become toxic to neurons if left unchecked. Dr. Farese's team discovered that progranulin works by tempering the microglia's response, thereby minimizing inflammation. Without progranulin, the microglia are unrestricted—and induce prolonged and excessive inflammation that leads to neuron damage—and can contribute to the vast array of symptoms that afflict sufferers FTD and other fatal forms of brain disease.

"However, we found that boosting progranulin levels in microglia reduced inflammation—keeping neurons alive and healthy in cell culture," explained Dr. Farese. "Our next step is to determine if this method could also work in live animals. We believe this to be a therapeutic strategy that could, for example, halt the progression of FTD. More broadly, our findings about progranulin and inflammation could have therapeutic implications for devastating neurodegenerative diseases such as Alzheimer's, Parkinson's and MS."

Provided by Gladstone Institutes

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