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Blood-related genetic mechanisms found important in Parkinson's disease

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What does the genetics of blood cells have to do with brain cells related to Parkinson's disease? From an unusual collaboration of neurologists and a pharmacologist comes the surprising answer: Genetic mechanisms at play in blood cells also control a gene and protein that cause Parkinson's disease.

The finding, by scientists from the University of Wisconsin School of Medicine and Public Health (SMPH), Harvard University-affiliated Brigham and Women's Hospital and the University of Ottawa, may lead to new treatments for the neurological disorder that affects as many as 1.5 million Americans.

The study is published in the *Proceedings of the National Academy of Sciences Online Early Edition* the week of July 21-25, 2008.

Patients with Parkinson's disease (PD) have elevated levels of the protein called alpha-synuclein in their brains. As the protein clumps, or aggregates, the resulting toxicity causes the death of neurons that produce the brain chemical dopamine. Consequently, nerves and muscles that control movement and coordination are destroyed.

The researchers discovered that the activity of three genes that control the synthesis of heme, the major component of hemoglobin that allows red blood cells to carry oxygen, precisely matched the activity of the alpha-synuclein gene, suggesting a common switch controlling both.

The scientists then found that a protein called GATA-1, which turns on the blood-related genes, was also a major switch for alpha-synuclein expression, and that it induced a significant increase in alpha-synuclein protein. Finally, they demonstrated that a related protein — GATA-2 — was expressed in PD-vulnerable brain cells and directly controlled alpha-synuclein production.

"Very little was known previously about what turns on alpha-synuclein in brain cells and causes variations in its expression," says Emery Bresnick, a UW-Madison professor of pharmacology who is an expert on GATA factors and their functions in blood. "Understanding how GATA factors work in the brain may provide fundamental insights into the biology of Parkinson's disease."

The new knowledge also may allow scientists to design therapies that keep alpha-synuclein levels within the normal range.

"Simply lowering alpha-synuclein levels by 40 percent may be enough to treat some forms of Parkinson's disease," says Dr. Clemens Scherzer of Harvard. "So far, researchers have focused on ways to get rid of too much 'bad' alpha-synuclein in Parkinson patients' brains. Now we will be able to tackle the problem from the production site, and search for new therapies that lower alpha-synuclein production up front."

Scherzer and Dr. Michael Schlossmacher, now at Ottawa, had independently analyzed the blood of PD patients and controls in a search for genes that were active in the disease. They both were surprised to notice large amounts of alpha-synuclein in the blood. To understand what it was doing there, Scherzer's group used gene chip data to see whether any of the thousands of genes active in blood were linked to alpha-synuclein. They found a gene expression pattern composed of alpha-synuclein and the heme genes, one of which Bresnick had previously shown to be a direct GATA-1 target gene.

The neurologists contacted Bresnick. The UW group rapidly determined that GATA-1 directly activated the alpha-synuclein gene, and that finding led the collaborators to discover that GATA-2 is expressed in regions of the brain that are relevant to PD.

"We all were excited because we realized that GATA-2 was active in the relevant brain regions, and so there could be a connection," says Bresnick. Together the researchers set out to examine whether common mechanisms activated alpha-synuclein transcription in both the blood and nerve cells.

The studies showed that GATA-1 and GATA-2 proteins find the alpha-synuclein gene, stick to it and then directly control it.

"This is not an indirect pathway; it is direct regulation of the gene," says Bresnick. "This directness provides the simplest scenario for creating a therapeutic strategy."

Bresnick, Schlossmacher and Scherzer are working with geneticists to see if possible abnormalities in the GATA-2 gene may exist in PD patients, stimulating more production of alpha-syinuclein.

"The discovery of the link between GATA proteins and the alpha-synuclein gene is like finding a long-sought-after molecular switch," says Schlossmacher. "We were very fortunate to find in Emery Bresnick's team the ideal partner in this endeavor."

The family of GATA factors consists of six members, and some of them, beyond GATA-2, may also be influencing alpha-synuclein expression in the brain, adds Schlossmacher.

"Identifying these would further add to the complexity of regulating the production of the 'bad player' in Parkinson's disease," he says.

Says Bresnick, "The $10 million question will be does deregulation of the GATA mechanism in humans lead to alpha-synuclein overproduction and Parkinson's disease."

Source: University of Wisconsin-Madison