Nobel winner ties mental illness to immune defect

May 27 2010

The mice shown here both had a mutant gene named Hoxb8 that originated in bone marrow and caused the mice to groom themselves pathologically, pulling out their hair. The mouse on the left displays hair loss on its chest and flank. After receiving a bone marrow transplant from a normal mouse three months earlier, the mouse at right fully recovered from the pathological grooming mutation and regrew its lost hair. University of Utah geneticist and Nobel Laureate Mario Capecchi says the study is the first to show and direct cause-and-effect link between an immune system defect and a psychiatric disorder. Credit: Shau-Kwaun Chen, University of Utah

A Nobel Prize-winning University of Utah geneticist discovered that bone marrow transplants cure mutant mice who pull out their hair compulsively. The study provides the first cause-and-effect link between immune system cells and mental illness, and points toward eventual new psychiatric treatments.

"We're showing there is a direct relationship between a psychiatric disorder and the immune system, specifically cells named microglia that

are derived from bone marrow" and are found in the brain, says Mario Capecchi, a distinguished professor of human genetics at the University of Utah School of Medicine. "There's been an inference. But nobody has previously made a direct connection between the two."

The findings - published in the Friday, May 28 issue of the journal *Cell* - should inspire researchers "to think about potential new immune-based therapies for psychiatric disorders," says Capecchi, a 2007 Nobel laureate in physiology or medicine.

Capecchi and colleagues showed that pathological grooming and hair-pulling in mice - a disorder similar to trichotillomania (trick-o-til-o-MAY-nee-ah) in humans - is caused by a mutant Hoxb8 gene that results in defective microglia, which are immune system cells that originate in bone marrow and migrate from blood to the brain. Microglia defend the brain and spinal cord, attacking and engulfing infectious agents.

Mice with pathological grooming appear to groom normally, but do so too often and for too long, leading to hair removal and self-inflicted skin wounds. The disease of pulling out head or body hair is common in humans; studies in seven international communities found trichotillomania affecting 1.9 to 2.5 of every 100 people.

In the key experiment, geneticist Shau-Kwaun Chen, Capecchi and colleagues transplanted bone marrow from normal mice into 10 mice that had a mutant Hoxb8 gene and compulsively pulled out their own chest, stomach and side fur. As the transplant took hold during ensuing months, grooming behavior became normal, four mice recovered completely and the other six showed extensive hair growth and healing of wounds.

"A lot of people are going to find it amazing," says Capecchi. "That's the surprise: bone marrow can correct a behavioral defect."

Nevertheless, "I'm not proposing we should do bone marrow transplants for any psychiatric disorder" in humans, he says. Bone marrow transplants are expensive, and the risks and complications are so severe they generally are used only to treat life-threatening illnesses, including certain cancers and disabling autoimmune diseases such as lupus.

Capecchi says that mice with the mutant gene that causes pathological grooming now can be used to study the surprising connections between the immune system's microglia cells and mental illness - and ultimately to produce new treatments.

"We think it's a very good model for obsessive-compulsive disorder," he says.

The researchers also transplanted bone marrow into normal mice from Hoxb8 mutant, hair-pulling mice. The normal mice started pulling out their hair compulsively. Normal mice transplanted with normal bone marrow kept grooming normally, while mutant mice implanted with mutant bone marrow exhibited severe grooming and self-mutilation. Half died, probably due to difficulty re-establishing mutant bone marrow.

Capecchi and colleagues also proved that reduced sensitivity to pain among mutant Hoxb8 mice is not the cause of the animals' compulsive grooming and hair removal, as some researchers had believed.

Mutant Microglia from Marrow Link Immunity and Mental Disorder

Capecchi says previous studies have linked the immune system and psychiatric disorders, but not in a cause-and-effect manner.

"If you look at people who are depressed, often you find their immune system isn't working normally," Capecchi says. And studies have shown that genes that confer a higher rate of depression, schizophrenia, obsessive-compulsive disorder, bipolar disorder and autism also "have something to do with the immune system," he adds.

The new findings "provide direct evidence for an association between neuropsychiatric diseases and dysfunction of the immune system or of the blood-forming system," says Capecchi.

Hox genes orchestrate embryo development. Hoxb8 is responsible for maintaining "myeloid progenitor cells," including those that give rise to monocytes, which are white blood cells that move from the circulatory system to the brain and become microglia.

It was surprising that the new study identified mutant microglia cells that originate in bone marrow as the cause of compulsive hair-pulling in mice. Researchers expected to find the mutant Hoxb8 in brain nerve cells that control grooming.

It is the first study to suggest "there is a connection between microglia and behavior - and a direct connection," Capecchi says.

Capecchi says nerve cells or neurons represent only about 10 percent of the brain, and the rest is made of various glial cells, including microglia. There are two kinds of microglia in the brain. Sixty percent are "resident" microglia that form in an embryo's brain even before the blood circulation system develops. The second kind of microglia in the brain - 40 percent of the total - originates in bone marrow, and then moves to the brain, circumventing the blood-brain barrier.

The geneticists believed the mutant microglia originated in bone marrow because they did not find them among the resident microglia present in

the mouse brain at birth, but instead saw microglia with mutant Hoxb8 first migrate into the mouse brain two days after birth. To identify the cells in the brain with active mutant Hoxb8 genes, the researchers used a method that attached a fluorescent yellow-green label to such cells.

Pathological Grooming is Different than Scratching an Itchy Rump

Capecchi first reported in 2002 that mice with mutant Hoxb8 genes displayed compulsive grooming and pulling out the hair on their chest, stomach and sides. Over the years, some researchers attributed this to reduced pain sensitivity also observed in mutant Hoxb8 mice, apparently due to nerve damage in the spinal cord. The idea was that reduced sensitivity to pain would make mice scratch more in response to an itch. In the new study, the Utah geneticists concluded that compulsive grooming and reduced sensitivity to pain were due to separate malfunctions of the Hoxb8 gene; the bone marrow transplants that cured hair-pulling did not restore the loss of pain sensitivity.

Also, mutating Hoxb8 genes in microglia from bone marrow made the mice groom pathologically but didn't make them insensitive to pain. Mutating Hoxb8 in the spinal cord resulted in reduced sensitivity to pain, but not compulsive grooming.

Finally, in earlier studies of mice insensitive to pain due to mutant Hoxb8, the mice used paws to scratch too much and cause hair loss and wounds on their rumps, near the tail. But mice in the Utah study used their teeth to remove hair on their chest, stomach and sides. They followed a normal head-to-rear grooming pattern, but did it excessively.

To be Determined: How Mutant Microglia Cause Hair-Pulling

How do mutant immune cells from bone marrow cause pathological grooming?

All we know now is that there are 15 percent fewer microglia in the brain when Hoxb8 is mutant, Capecchi says. "In the next wave of experiments, we can ask how microglia affect behavior. We anticipate it has to affect neural circuitry in some way."

He speculates ways mutant microglia might trigger pathological grooming: The microglia could make cytokines that activate or inhibit nerve activity, and thus influence behavior. Because microglia have long extensions that "feel" the synapses that connect nerve cells, they might be involved in controlling nerve-signal transmissions, he says.

For now, "we have no idea which will be right," Capecchi says.

In Capecchi's 2002 study of mice with compulsive grooming, the researchers recorded the number and duration of each mouse's grooming sessions using a video recorder, which was very labor intensive to analyze. So in the new study, the mouse cages were placed on sensitive vibration-detecting platforms capable of distinguishing mouse vibration from different activities such as eating, drinking, grooming, climbing, sitting still, walking and scratching. They tested the method's accuracy by using a video camera to double check what the mice were doing at times.

The result: Mice with the mutant Hoxb8 gene spent about twice as much time grooming as their normal littermates.

The new study was funded by the Howard Hughes Medical Institute and the National Institutes of Health. Capecchi is senior author. The first author is Chen, who recently completed a Ph.D. in human genetics. They conducted the study with human genetics postdoctoral fellows Petr

Tvrdik, Erik Peden and Sen Wu; Gerald Spangrude, an internal medicine professor; and Scott Cho, a graduate student in Spangrude's lab.

Capecchi shared the 2007 Nobel Prize in Physiology or Medicine for developing "gene targeting" in mice, a method of knocking genes out of action to see what goes wrong and thus learn each gene's normal function.

More information: Chen et al.: “Hematopoietic Origin of Pathological Grooming in Hoxb8 Mutant Mice.” Publishing in Cell 141, 775-785, May 28, 2010. DOI 10.1016/j.cell.2010.03.055

Provided by University of Utah