Bone Marrow Transplants Arrest Pathology in Mouse Model of Rett Syndrome

BY JAMIE TALAN

Evidence from an animal model of Rett syndrome suggest that microglia may be involved in the pathophysiology of the disease and that bone marrow transplantation could prove to be a successful treatment in patients.

In experiments with Rett animal models, Jonathan Kipnis, PhD, associate professor of cellular and molecular neuroimmunology, Noël C. Derecki, and colleagues at the University of Virginia, found that symptoms of the disease — stunted growth, tremor, gait disturbances, and breathing problems — were improved following wild-type bone marrow transplantation. The findings were published in the March 18 online edition of *Nature*.

Rett syndrome, an X-linked disorder caused by defects in the *methyl-CpG-binding protein 2* (*MECP2*) gene, occurs almost exclusively in girls. The disorder is fatal in boys, resulting in miscarriage, stillbirth, or early death, but girls with the disorder live, on average, to their mid-40s. The girls may develop normally at first and then between six to 18 months, develop mild to severe symptoms, including apraxia, motor, and breathing problems, as well as intellectual disabilities and learning difficulties.

DR. ALEKSANDRA DJUKIC said the investigators treated the animals with bone marrow transplantation before symptoms developed, but they need to repeat the studies in animals that already have signs of the disease to see if it's possible to reverse the symptoms.

The mutant *MECP2* gene is expressed in many tissues and scientists have long considered that the illness is caused by neuronal dysfunction. More recent studies by Gail Mandel, PhD, a Howard Hughes Investigator at Oregon Health & Science University, and others have implicated glia, specifically astrocytes, in a murine model of the disease.

Building on the work by Dr. Mandel and others, the study authors speculated that microglia may also play a role in Rett syndrome. Microglia clean up normal cellular debris in the brain through the process of phagocytosis, they explained. Dr. Kipnis and his team discovered that when microglia lack properly functioning *MECP2*, they are unable to perform this crucial duty efficiently. Because microglia are derived from immune progenitor cells, they theorized that it would be possible to replace them via a bone marrow transplant.

The investigators administered radiation treatment in male mice with the mutation, followed by healthy bone marrow. As the migration and repopulation of new microglia occurred, the Rett mice began to grow instead of fail. The symptoms characteristic of the condition were improved; the animals were bigger, problems with apnea disappeared, anxiety was reduced and gait improved. And the animals with the healthy bone marrow lived up to one year.

The researchers are repeating the studies with female mice that live out a normal lifespan but suffer from the same problems in addition to cognitive deficits.

They also have established a genetic variant of bone marrow transplantation by crossing an existing Rett model with a mouse that drives expression of the target protein in myeloid cells. The resulting mice retained the normal gene in their myeloid cells (macrophages and microglia), but not in other cells. These animals are now 38 weeks.

"We express wild-type protein in the microglia and although the neurons are still sick, the wild-type microglia allow them to better function, probably by creating a healthy environment," said Dr. Kipnis.

"Our results do not claim that neurodegeneration underlies the pathology of the disease," the scientists said. "Rather, they suggest that *MECP2*-null microglia, deficient in phagocytic function, may be unable to keep pace in clearing debris left behind from the normal process of neural cell death or membrane shedding."

The findings suggest that agents that boost phagocytosis might be therapeutic for Rett syndrome. "A lot more work needs to be done," Dr. Kipnis added. "We are now trying to understand what exactly microglia are doing in the Rett brain. If we prove that debris accumulation due to microglia inability to clear them is indeed one of the underlying mechanisms of Rett, then this may change the field's perception of the pathophysiology of Rett syndrome."

THE INVESTIGATORS BEHIND THE RESEARCH: (left to right) Dr. Jonathan Kipnis; Jim Cronk; Dr. Noël Derecki.

EXPERTS COMMENT

"This is a really remarkable result," said Ben Barres, MD, PhD, professor of neurobiology and developmental biology at Stanford University. "It is completely unexpected and it suggests that microglia have very important roles in neural function that we do not begin to understand."

Dr. Mandel added that the new finding shows that neurological diseases are complex from the point of view of cell types and mechanisms involved. "The implications are that therapies are going to have to take this complexity into account and it may be that there will be no one target that can be easily fixed."

There have been hints from other diseases that glia are involved in the neuropathology and Dr. Mandel's group decided to revisit the issue in a more directed way, with more experiments and different antibodies. That microglia are involved is interesting, she said, "because they are not derived embryologically from the brain, but from blood." Plus, she added, "they demonstrated a significant role in recovery of symptoms."

She said it is too early to know whether replacing the brain with healthy microglia would help children with Rett syndrome. "But there is obviously interest in using bone marrow treatments."

Aleksandra Djukic, MD, PhD, director of the Tri-State Rett Center and associate professor of neurology and pediatrics at the Children's Hospital at Montefiore Medical Center in New York, agreed. "The results from the bone marrow transplantation are encouraging," she said. "That they found the immune system has a role in Rett syndrome helps us in understanding the nature of this disease."

Dr. Djukic noted that she has several Rett patients with severe immunodeficiency and had believed that this was related to their disease. This offers the first proof that she might be right.

Dr. Kipnis and his colleagues treated the animals with bone marrow transplantation before symptoms developed, she said, but they need to repeat the studies in animals that already have signs of the disease to see if it's possible to reverse the symptoms.

"I do believe that treating Rett is not beyond our reach," Dr. Djukic said. She has assembled a team of 20 physicians from all fields of medicine to work with the Rett girls and keep their bodies and minds as healthy as possible for when those experimental treatment trials do come along. "Our clinic is preparing to do such a clinical trial in anticipation of the completion of these studies. It feels closer than ever." •

REFERENCES:

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