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Researchers discover drug target and genetic pathway for graft-versus-host disease

Published on November 30, 2015 at 7:16 AM

A Seattle Children's Research Institute lab has discovered a genetic pathway that can be targeted with existing drugs to prevent graft-versus-host disease (GVHD), a common and deadly complication of bone marrow transplants. The results of their work were published in the journal Science Translational Medicine.

In patients with GVHD, newly transplanted T cells from the bone marrow graft attack the transplant recipient's body. Over 10,000 people in the United States receive bone marrow transplants each year for leukemia, other non-malignant blood conditions and autoimmune diseases. About 50-70 percent of bone marrow transplant patients will acquire GVHD. Of those who develop the most severe form, up to half will die.

"This is a mysterious disease that has perplexed doctors who treat bone marrow transplant patients for decades," said Dr. Leslie Kean, a pediatric cancer specialist at Seattle Children's Research Institute and lead study author. "We can cure patients of leukemia and other diseases with bone marrow transplants, but many of those patients get GVHD. In extreme cases, those patients end up with severe complications, chronic and painful side effects, and may even die of GVHD."

The disease can affect any part of the body, but the most common and severe damage is to liver, skin and gastrointestinal tissues.

"This condition is one of the main reasons that many bone marrow transplant patients endure long hospital stays after their diseases are cured," said Kean, who wears a bracelet around her badge from a pediatric patient cured of leukemia one year ago, but is still in the hospital due to complications from GVHD. "This finding is exciting because the drug we studied is in advanced clinical trials, so we are hopeful that bone marrow transplant recipients will benefit from this research in the near future."

The pathway Kean and her team studied is Aurora Kinase A, a well-known genetic target for cancer researchers. Aurora kinase A proteins are important for cell division and proliferation in human cells. Defects in the Aurora Kinase A gene can cause cells to over-proliferate and lead to cancers. The drug Kean's lab worked with is very similar to one that is produced by Takeda and is in phase III clinical trials for pediatric and adult cancers. The drug inhibits the Aurora Kinase A signaling pathway, causing cells to stop dividing.

"This study represents the very best of team science: hypothesis-driven, collaborative across multiple institutions, and immediately relevant to clinical patient care," said Dr. Ned Waller, Professor of Medicine, Pathology and Hematology/Oncology at Emory University and a collaborator on the study. "New approaches to understand the immunology of graft-versus-host disease and limit its impact are urgently needed to improve the quality of life for our patients and increase their long term cancer-free survival."

Kean and her lab are designing a clinical trial they hope to launch in 2016 to apply this new strategy so that patients undergoing bone marrow transplantation may have access to Aurora Kinase A inhibitors.

Source:
Seattle Children's Hospital
