MedicalXpress

Mini-molecule governs severity of acute graft vs. host disease, study finds

March 12 2012

Researchers have identified a molecule that helps control the severity of graft-versus-host disease, a life-threatening complication for many leukemia patients who receive a bone-marrow transplant.

The study, led by researchers with the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James), used an animal model and tissues from human patients to show that high levels, or over-expression, of a molecule called microRNA-155 (miR-155) controls the severity of acute graft-versus-host disease (GVHD).

Reducing or blocking miR-155 expression, on the other hand, decreased acute GVHD severity and increased survival, a finding that suggests a new strategy for treating the condition.

Acute GVHD occurs in 35 to 45 percent of leukemia patients overall who receive a blood stem-cell transplant from another person, a procedure called allogeneic stem-cell transplantation. Severe acute GVHD has a poor prognosis: about 25 percent of patients survive grade III GVHD and about 5 percent survive grade IV disease.

The findings are published in the journal *Blood*.

"Currently, acute GVHD is treated with high doses of steroids, which further increase the patient's already high risk for infections, and they block the ability of the donor immune cells to fight the leukemia," says

principal investigator and hematologist Dr. Ramiro Garzon, assistant professor of internal medicine and a leukemia specialist.

"What is needed is a way to block acute GVHD without inhibiting the ability of transplanted cells to fight leukemia, and these findings suggest how that might be done."

GVHD arises when immune cells from the donor attack the healthy tissue of the recipient. For this study, Garzon and his colleagues used an animal model of GVHD to learn if miR-155 played a role in the disease. Donor animals were engineered to either over-express or under-express miR-155 in their T cells, the main type of immune cell involved in GVHD.

The researchers first learned that donor T cells removed from recipient animals with GVHD had levels miR-155 that were up to 6.5-fold greater than in controls. Additional experiments showed the following:

- When recipient animals are given T cells that are deficient in miR-155, GVHD severity is much less and overall survival is significantly greater.
- When recipient animals are given T cells that over-express miR-155, GVHD develops rapidly and survival is short.
- Blocking miR-155 in donor cells decreases the severity of clinical GVHD, increases survival and does not diminish the cells' ability to destroy leukemia cells.

Finally, Garzon and his colleagues examined five large-bowel biopsies of GVHD patients, and inflammatory T cells from all five showed high levels of miR-155. "This suggests that the relationship between miR-155 and graft-versus-host disease is relevant in humans, also," Garzon says.

Provided by The Ohio State University