Deadly complication of stem cell transplants reduced in mice

September 27 2012, by Julia Evangelou Strait

(Medical Xpress)—Studying leukemia in mice, researchers at Washington University School of Medicine in St. Louis have reduced a life-threatening complication of stem cell transplants, the only curative treatment when leukemia returns.

About 50 percent of leukemia patients who receive stem cells from another person develop graft-versus-host disease, a condition where donor immune cells attack the patient's own body. The main organs affected are the skin, liver and gut. Now, the scientists have shown they can redirect donor immune cells away from these vital organs. Steering immune cells away from healthy tissue also leaves more of them available for their intended purpose – killing cancer cells.

"This is the first example of reducing graft-versus-host disease not by killing the T- cells, but simply by altering how they circulate and traffic," says John F. DiPersio, MD, PhD, the Virginia E. and Sam J. Golman Professor of Medicine. "Donor T-cells do good things in terms of eliminating the recipient's leukemia, but they can also attack normal tissues leading to death in a number of patients. The goal is to minimize graft-versus-host disease, while maintaining the therapeutic graft-versus-leukemia effect."

The study is now available online in *Blood*.

Working with mice, Jaebok Choi, PhD, research assistant professor of medicine, showed that eliminating or blocking a particular protein – the

interferon gamma receptor – on donor T-cells makes them unable to migrate to critical organs such as the intestines but still leaves them completely capable of killing leukemia cells.

"The fact that blocking the interferon gamma receptor can redirect donor T-cells away from the gastrointestinal tract, at least in mice, is very exciting because graft-versus-host disease in the gut results in most of the deaths after stem cell transplant," DiPersio says. "People can tolerate graft-versus-host disease of the skin. But in the GI tract, it causes relentless diarrhea and severe infections due to gut bacteria leaking into the blood, which can result in severe toxicity, reduction in the quality of life or even death in some patients."

Long known to be involved in inflammation, the roles of interferon gamma, its receptor and their downstream signaling molecules are just beginning to be described in the context of graft-versus-host disease, says DiPersio, who treats patients at Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine.

The cascade begins when interferon gamma activates its receptor. The interferon gamma receptor then activates molecules known as JAK kinases, followed by STAT, and finally CXCR3. CXCR3 mediates the trafficking of donor T-cells to the GI tract and other target organs.

Since deleting the interferon gamma receptor from donor T-cells directs them away from target organs, the researchers asked whether they could produce the same beneficial effects by inhibiting some of the receptor's downstream signaling molecules. Indeed, Choi also found that knocking out CXCR3 reduces graft-versus- host disease, but not completely.

"There are probably additional downstream targets of interferon gamma receptor signaling other than JAKs, STATs and CXCR3 that are responsible for T-cell trafficking to the GI tract and other target organs,"

DiPersio says. "We're trying to figure out what those are."

To move their findings closer to possible use in humans, Choi and DiPersio also showed that they could mimic the protective effect of deleting the interferon gamma receptor with existing drugs that block JAK kinases. In this case, they tested two JAK inhibitors, one of which is currently approved by the U.S. Food and Drug Administration to treat myelofibrosis, a pre-leukemic condition in which the bone marrow is replaced with fibrous tissue.

While they showed that JAK inhibitors are effective in redirecting donor T-cells away from target organs and reducing graft-versus-host disease in mice with leukemia, they have not yet tested whether these drugs also preserve the desired anti-leukemia effect.

"The proof-of-principle behind these experiments is the exciting part," DiPersio says. "If you can change where the T-cells go as opposed to killing them, you prevent the life-threatening complications and maintain the clinical benefit of the transplant."

More information: Choi J, Ziga ED, Ritchey J, Collins L, Prior JL, Cooper ML, Piwnica-Worms D, DiPersio JF. INF gamma receptor signaling mediates alloreactive T cell trafficking and GvHD. *Blood*. Online Sept. 12, 2012.

Provided by Washington University School of Medicine