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Stem cells and leukemia battle for marrow microenvironment

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Learning how leukemia takes over privileged "niches" within the bone marrow is helping researchers develop treatment strategies that could protect healthy blood-forming stem cells and improve the outcomes of bone marrow transplantation for leukemia and other types of cancer.

In a paper in the journal *Science*, available early online Dec. 19, 2008, researchers from the University of Chicago Medical Center show that by blocking one of the chemical signals that leukemic cells release, they could help prevent the cells that mature to become red and white blood cells from being shut down by the cancerous invader.

"We found an approach, in our mouse model, that could help protect the cells that give rise to healthy blood cells, and improve their accessibility for use in autologous transplantation," said study author Dorothy Sipkins, MD, PhD, assistant professor of medicine at the University of Chicago Medical Center. "The next step is to confirm this in human studies."

Sipkins and colleagues study the molecular characteristics of tissue microenvironments, or "niches," within the bone marrow where normal, healthy bone marrow stem cells divide and mature. From these niches, the stem cells produce all the different types of blood cells involved in transporting oxygen from the lungs to the rest of the body, fighting off infections and controlling blood clotting.

In patients with leukemia, however, these stem cells lose their powers. Part of the problem is that they are being crowded out by the rapid

multiplication and spread of diseased cells as they take over the bone marrow, but this isn't always the explanation.

Sipkins and colleagues have shown that the process is far more complicated, and focused, than simply overcrowding. Using sophisticated microscopy tools, they developed systems to monitor the movements of leukemia cells and hematopoietic progenitor cells (HPCs)--a group of cells that includes stem cells as well as more differentiated, though still primitive, progenitor cells that give rise to the various kinds of blood cells--as they struggled for these coveted niche sites.

One of the first actions of cancer cells, they found, is to settle into these niches, taking over the specialized supportive environments that HPCs need to perform their crucial role.

Within days of taking over a niche, leukemia cells began releasing a chemical signal, called stem cell factor (SCF), which attracts normal stem cells back to sites near their now-captive niche. Within one month, the leukemic cells could induce HPCs to leave even tumor-free niches and migrate to malignant sites.

But when the HPCs arrive, other signals released by leukemic cells interfere with the production of healthy new blood cells. As their microenvironments were taken over, the number of HPCs declined. HPCs also stopped responding to drugs designed to coax them out of the bone marrow and into the blood stream, where they could be harvested and used for transplantation.

Sipkins' team was able to blunt this effect by blocking the release of stem cell factor by tumor cells. When the researchers inhibited stem cell factor, the number of HPCs went back up, as did their ability to migrate out of the bone marrow.

"Our data suggest that therapeutic targeting of SCF may increase the hematopoietic reserve and improve outcomes for bone marrow transplantation and autologous stem cell harvest in the setting of hematopoietic malignancy," the authors conclude.

"This is not a cure for leukemia," Sipkins said, "but it's one more tool. We like to hit cancer from all sides. This approach could potentially boost the immune system's response to the cancer by protecting the HPCs that are the source of mature immune cells. It could also maintain the patient's ability to tolerate treatment and to remain active."

"If human stem cells respond in the same way as mouse cells do, it could buy us time to apply other therapies," Sipkins added. "By preserving the activity of HPCs and potentially boosting the immune system, the body's own weapon again leukemia, we support the patient and take away one of the disease's weapons."

It could also make transplantation an option for more patients, enabling physicians to collect stem cells from the peripheral blood, which could be banked for bone marrow "rescue," a technique that restores the patient's marrow after it was damaged by high-dose chemotherapy targeted at the leukemia."

Source: University of Chicago Medical Center