Discovery offers hope for treating leukemia relapse post-transplant

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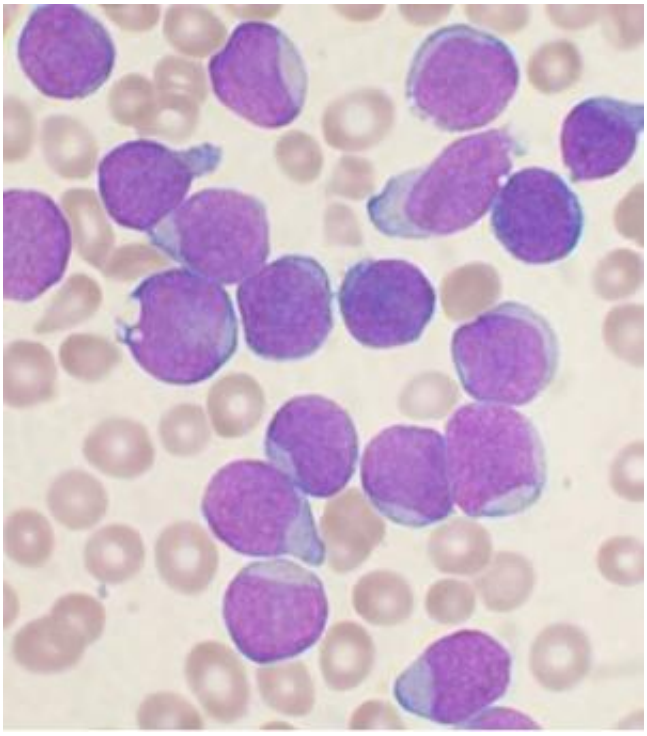

A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

Targeting exhausted immune cells may change the prognosis for patients with acute myeloid leukemia (AML) relapse after a stem cell transplant, according to Penn State College of Medicine researchers.

There is currently no effective treatment for this stage of leukemia, and

patients have only a 5 percent chance of survival over five years.

AML is a fast-moving cancer of the blood and bone marrow. In patients with AML, the bone marrow produces abnormal white or red blood cells or platelets. Powerful rounds of chemotherapy can damage bone marrow, so many patients are given an infusion of blood-forming stem cells from a donor to restore it. These donor cells also help fight off any remaining leukemia cells, a phenomenon known as the graft-versus-leukemia (GVL) effect.

However, in some transplant patients, GVL fails and the cancer returns. These patients often can't tolerate more chemotherapy, and they typically have less than a year to live.

After seeing many of her patients succumb to this, Hong Zheng, assistant professor of medicine, decided to investigate why some relapsed while others didn't. Comparing the blood of patients who relapsed to patients who didn't led her to exhausted T cells.

T cells are a major player in the GVL effect. They send out cytokines, killer compounds that can directly or indirectly eradicate leukemia cells. But over time, fighting off invaders can tire out T cells, causing "T cell exhaustion."

Zheng's team found that relapse patients had significantly elevated levels of PD-1hiTIM-3+ cells, which are markers of T cell exhaustion. Their T cells also produced fewer cytokines, bolstering the idea that these immune-system soldiers weren't functioning up to par. They reported their findings in *Blood Cancer Journal*.

These results could lead to new treatments sooner rather than later. There is currently a PD-1 antibody on the market that blocks T cell exhaustion in patients with solid tumors, like lung cancer and melanoma.

Zheng is planning a clinical trial to see if it could work for post-stem-cell transplant AML relapse patients as well.

She also believes the PD-1hiTIM-3+ cells could be used to diagnose relapses earlier than is currently possible. Catching relapses sooner opens the door to treatments, such as an infusion of donor T cells, which alone do not work once leukemia cells take over.

"Two months before we were able to clinically diagnose relapse in these patients, we found these markers elevated in them," Zheng says. "If we can have an early diagnostic marker, we will potentially be able to improve clinical outcome significantly."

Zheng is currently investigating the trigger for T cell exhaustion in AML stem cell transplant recipients.

"The hypothesis is that when you have chronic antigen stimulation, the T cell can get exhausted," she says. "We think that residual leukemia in our patients is the chronic stimulator that causes this."

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