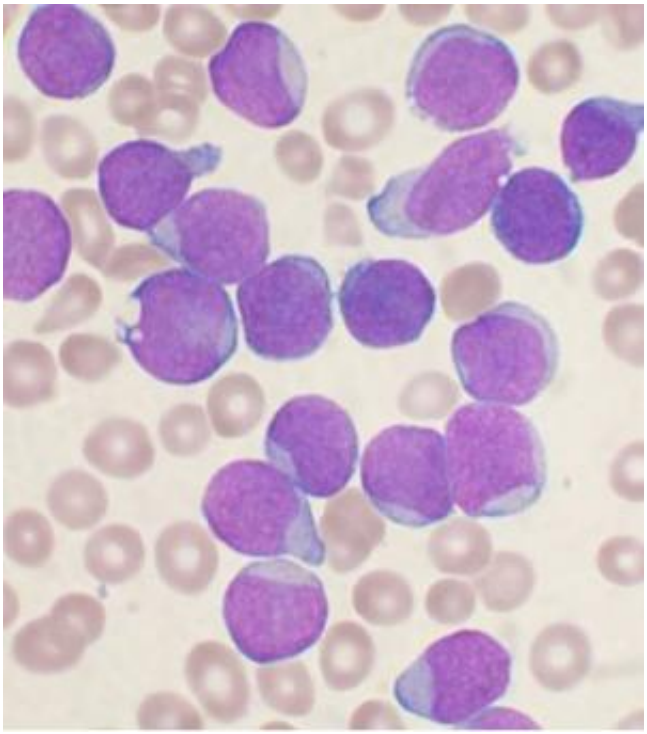
Prostaglandin E1 inhibits leukemia stem cells

September 25 2017



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

Two drugs, already approved for safe use in people, may be able to improve therapy for chronic myeloid leukemia (CML), a blood cancer that affects myeloid cells, according to results from a University of Iowa study in mice.

CML is a relatively common cancer. The American Cancer Society estimates that in 2017 there will be about 8,950 new cases and about

1,080 people will die of the disease.

In its initial, chronic stage, CML is relatively easy to treat. Drugs called tyrosine kinase inhibitors (TKIs) are generally successful at controlling the cancer. However, patients need to continue the expensive treatment for their lifetime. In some cases, even with that treatment, the cancer can progress to a more advanced stage that is no longer controlled.

One reason for this, explains Hai-Hui (Howard) Xue, MD, PhD, UI professor of microbiology and immunology, is that there are two kinds of tumor cells—bulk leukemia cells that can be killed by TKI drugs, and a subset of cells called leukemia stem cells, which are resistant to TKIs and to chemotherapy.

"A successful treatment is expected to kill the bulk leukemia cells and at the same time get rid of the leukemic stem cells. Potentially, that could lead to a cure," says Xue, who is senior author of the study published in the September issue of the journal *Cell Stem Cell* as the cover story.

With that goal in mind, Xue and his team joined forces with Chen Zhao, MD, PhD, UI assistant professor of pathology, and used their understanding of CML genetics to look for small molecules or drug compounds that might be able to eradicate the leukemia stem cells.

Focusing on two proteins known as transcription factors, the researchers showed that genetically removing the two transcription factors, Tcf1 and Lef1, in mice is sufficient to prevent leukemia stem cells from persisting. Importantly, this genetic alteration did not affect normal hematopoietic (blood) stem cells.

Next the researchers used an informatics method called connectivity maps to identify drugs or small molecules that can replicate the gene expression pattern that occurs when the two transcription factors are

removed. This screening test identified a drug called prostaglandin E1 (PGE1).

The team tested a combination of PGE1 and the TKI drug called imatinib in a mouse model of CML. The mice lived longer than control mice; 30 percent lived longer than 80 days compared to mice treated with only imatinib, all of which died within 60 days.

The team also looked at a different mouse model of CML, where human CML cells were transplanted into an immunocompromised mouse. When the mice received no treatment or were treated with imatinib alone, the human leukemia stem cells propagated and grew to relatively large numbers. In contrast, when the animals were treated with a combination of imatinib and PGE1, those numbers were greatly reduced, and mice did not develop leukemia.

"The results are a pleasant surprise," says Xue who also is a member of Holden Comprehensive Cancer Center at the UI. "We do these kinds of genetic studies all the time—looking at transcription factors and what they do. This is a good opportunity to connect what we do at the bench to something that could be useful clinically."

Investigating how the PGE1 works to suppress the leukemia stem cells, the team found that the effect relies on a critical interaction between PGE1 and its receptor EP4. They then tested the effect of a second drug molecule called misoprostol, which also interacts with EP4, and showed that misoprostol also has the ability to combine with TKI and significantly reduce the number of leukemia stem cells.

Both PGE1 and misoprostol are currently approved by the FDA for use in people. PGE1 is an injectable drug that is used to treat erectile dysfunction. Misoprostol is a pill that is used to treat ulcers.

"We would like to be able to test these compounds in a clinical trial," Xue says. "If we could show that the combination of TKI with PGE1, or misoprostol, can eliminate both the bulk tumor cells and the stem cells that keep the tumor going, that could potentially eliminate the cancer to the point where a patient would no longer need to depend on TKI."

More information: Fengyin Li et al, Prostaglandin E1 and Its Analog Misoprostol Inhibit Human CML Stem Cell Self-Renewal via EP4 Receptor Activation and Repression of AP-1, *Cell Stem Cell* (2017). DOI: 10.1016/j.stem.2017.08.001

Provided by University of Iowa