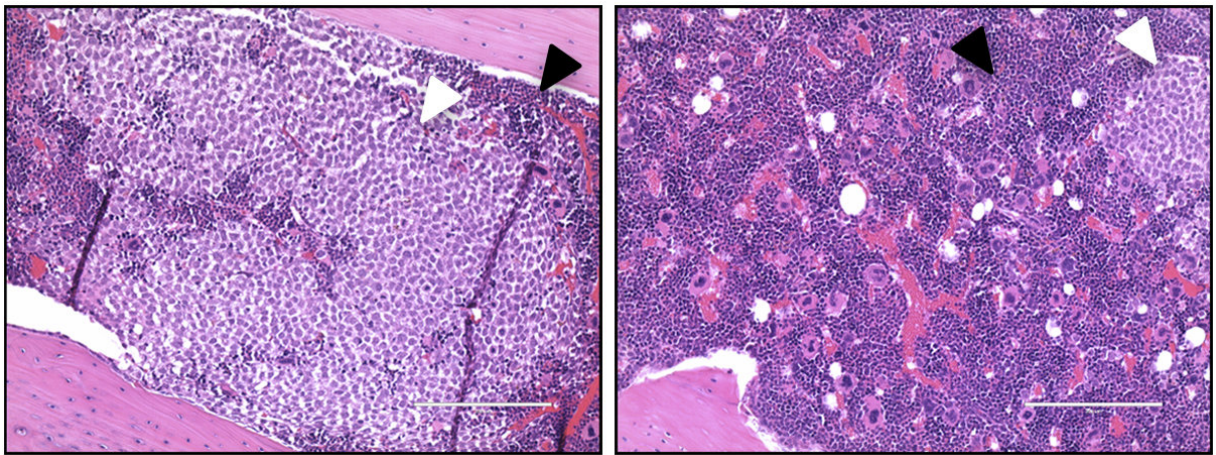


Single surface protein boosts multiple oncogenic pathways in acute myeloid leukemia

May 17 2018



In the femur of a control mouse (left), AML cells (white arrowhead) have displaced most of the normal bone marrow cells (black arrowhead). But the situation is reversed upon treatment with antibodies targeting IL1RAP (right). Credit: Mitchell et al., 2018

Researchers from the Albert Einstein College of Medicine in New York have discovered that a signaling protein elevated in patients with acute myeloid leukemia (AML) plays a much wider role in the disease than previously thought. The study, which will be published May 17 in the *Journal of Experimental Medicine*, raises hopes that current efforts to target this signaling protein could be a successful strategy to treat AML

and other blood cancers.

AML is driven by [leukemic stem cells](#) that differentiate abnormally and proliferate excessively, eventually displacing normal, healthy [blood stem cells](#) from the bone marrow. Leukemic stem [cells](#) are usually resistant to traditional chemotherapies, and so researchers are trying to develop new, more targeted approaches to eliminate these crucial cells.

One possible target is a protein called interleukin-1 receptor accessory protein (IL1RAP), which is often highly expressed on the surface of leukemic stem cells but largely absent from normal blood stem cells. But whether leukemic stem cells require IL1RAP to survive and proliferate—and therefore whether inhibiting IL1RAP could be a successful way to treat AML—is unclear.

A team of researchers led by Ulrich Steidl at the Albert Einstein College of Medicine found that antibodies, small hairpin RNAs, or genetic deletion targeting IL1RAP induce the death of AML cells, including leukemic stem cells, isolated from patients. The effects were seen in the absence of immune effector cells, indicating that AML cells intrinsically depend on IL1RAP. In contrast, antibodies targeting IL1RAP had no effect on the growth and survival of normal blood cells. Antibody treatment also inhibited the proliferation of AML cells in mice without causing any negative side effects.

As its name suggests, IL1RAP works in conjunction with the interleukin-1 receptor to promote an inflammatory signaling pathway that could play a key role in the development of AML. But Steidl and colleagues found that IL1RAP also enhances the activity of two other membrane receptor proteins, FLT3 and c-KIT, that are known to stimulate the proliferation of leukemic stem cells when activated by their ligands. IL1RAP antibodies inhibited the ability of these ligands to induce the proliferation of AML cells.

"Our findings show that IL1RAP can amplify multiple key pathways in AML, demonstrating a much broader role for this protein in disease pathogenesis than previously appreciated," Steidl explains.

Researchers are currently developing ways to prompt a patient's own immune cells to selectively recognize and kill IL1RAP-expressing cancer cells, but AML patients generally have defective immune systems. This new research suggests that directly targeting IL1RAP with antibodies or specific drug molecules could be even more effective at killing AML cells. The findings also suggest that IL1RAP-directed immunotherapies could be even more promising than currently assumed. Because AML cells functionally depend on IL1RAP, they cannot simply down-regulate the [protein](#) to escape immunotherapy and are therefore less likely to develop therapeutic resistance.

"Importantly, as IL1RAP is also overexpressed in the stem cells of chronic myeloid leukemia and high-risk myelodysplastic syndromes, there is significant therapeutic potential in further developing IL1RAP-directed targeting strategies," Steidl says.

More information: Mitchell et al., 2018. *J. Exp. Med.*
[jem.rupress.org/cgi/doi/10.1084/jem.20180147](https://doi.org/10.1084/jem.20180147)

Provided by Rockefeller University Press

Citation: Single surface protein boosts multiple oncogenic pathways in acute myeloid leukemia (2018, May 17) retrieved 20 April 2024 from <https://medicalxpress.com/news/2018-05-surface-protein-boosts-multiple-oncogenic.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.