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Signaling pathway revealed through which a promising anti-leukemia drug kills cancer cells

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Inhibiting a protein called BRD4 critical to the survival of acute myeloid leukemia (AML) cells has shown to be an effective therapeutic strategy. However, the mechanism that explains how the protein works has remained a mystery. Now, scientists at Cold Spring Harbor Laboratory (CSHL) have discovered the larger cancer-causing pathway that the protein fits into.

The discovery points to additional molecular targets for the development of drugs to treat AML as well as other cancers. The results appear online today in *Molecular Cell*.

In 2011, CSHL Associate Professor Christopher Vakoc and colleagues identified potential drug targets for AML—a relatively rare blood cell cancer—using a technology called RNA interference, in which RNA molecules are mobilized to inhibit gene expression. "We systematically went hunting for things required by leukemia cells to grow and thrive," says Vakoc.

Out of that approach came BRD4—a protein that affects epigenetic marks, chemical groups that attach to DNA at specific locations, influencing which genes are turned on and which are turned off. Leukemia cells were found to be extremely sensitive to perturbing the BRD4 protein. In a bit of serendipity, drugs to inhibit BRD4 had just been developed for other purposes. Vakoc and his colleagues tested

these drugs and found that one in particular, called JQ1, worked well against a mouse model of the most aggressive form of AML. "That disease was basically untreatable until we stumbled on BRD4 and the drug that targets it," says Vakoc.

In the past few years, several groups have reported similar therapeutic results in mice using JQ1 and closely related drugs. "It's been very satisfying to see that other groups have independently validated our findings," says Vakoc.

Due to the overwhelming evidence of their effectiveness in mice, inhibitors of BRD4 moved into clinical trials starting in 2013. Currently, there are 12 active clinical trials targeting BRD4 in leukemia and other cancers, including one sponsored by a company to which Vakoc has licensed JQ1. Last year, clinical trial findings presented at a conference indicated that an oral inhibitor of BRD4 similar to JQ1 had led to complete remission in some patients.

"Once we published the first paper in 2011, the main objective in our lab has been to understand why these drugs work," says Vakoc. "Knowing the mechanism of action of a drug is essential to making the drug better because there will likely be many generations of BRD4 inhibitors."

In the current study, the researchers discovered that BRD4 works very closely with an ensemble of proteins called transcription factors that also bind to DNA and very selectively control the activity of certain genes. The transcription factors that BRD4 associates with control blood formation and essentially give blood cells their identity. In leukemia, which Vakoc calls a disorder of mistaken blood identity, blood cells undergo genetic changes that prevent stem cells from maturing to white blood cells. "They try to be immortal by staying stem cells forever," says Vakoc.

The result is leukemia: an accumulation of immature cells with no useful function that crowd out viable blood cells in bone marrow, thereby decreasing the ability to fight infection and form blood clots in response to injury. Anemia eventually develops because the blood cannot sufficiently supply the body with oxygen.

The team has now discovered that the drug JQ1 can make leukemia cells shed their leukemia characteristics and mature, or differentiate, into normal white blood cells.

The team also identified an intermediary molecule called p300 between BRD4 and the leukemia-associated transcription factors. Active areas of research in Vakoc's lab include exploring other players in the pathway, particularly the molecules that BRD4 controls, and learning more about the transcription factors. "This new work is leading us to realize that transcription factors are the masters of the biological universe," Vakoc says. "Clearly they are driving the cancer phenotype."

In a related study from the Vakoc lab that was published April 25 in eLife, the team identified a way to target a protein called TRIM33 as a means of modulating the actions of a transcription factor called PU.1 in B-cell lymphoblastic leukemia, a cancer of blood cells that make antibodies. Although parallels exist between the activity of BRD4 and TRIM33, a major difference lies in the specificity of the proteins. TRIM33 is associated with a single transcription factor at a single binding site on the gene. In contrast, BRD4 is associated with many transcription factors at many binding sites throughout the gene.

"Our work raises a really provocative question," says Vakoc. "What if we target transcription factors directly? Would our therapies be more effective if we went to the source?"

Directly targeting transcription factors could be much more effective

than chemotherapy, he speculates. Chemotherapy makes all growing cells sick—cancer cells, but also cells in the gut, skin, and blood, among others. "There's no specificity as to which tissues are affected," says Vakoc. "Transcription factor targeting, on the other hand, would really zero in on one type of tissue."

More information: "BET bromodomain inhibition suppresses the functional output of hematopoietic transcription factors in acute myeloid leukemia," appears online May 14, 2015 in *Molecular Cell*. The authors are Jae-Seok Roe, Fatih Mercan, Keith Rivera, Darryl J. Pappin, and Christopher R. Vakoc. The paper can be viewed at: www.sciencedirect.com/science/journal/10972765

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