Study illuminates role of cancer drug decitabine in repairing damaged cells

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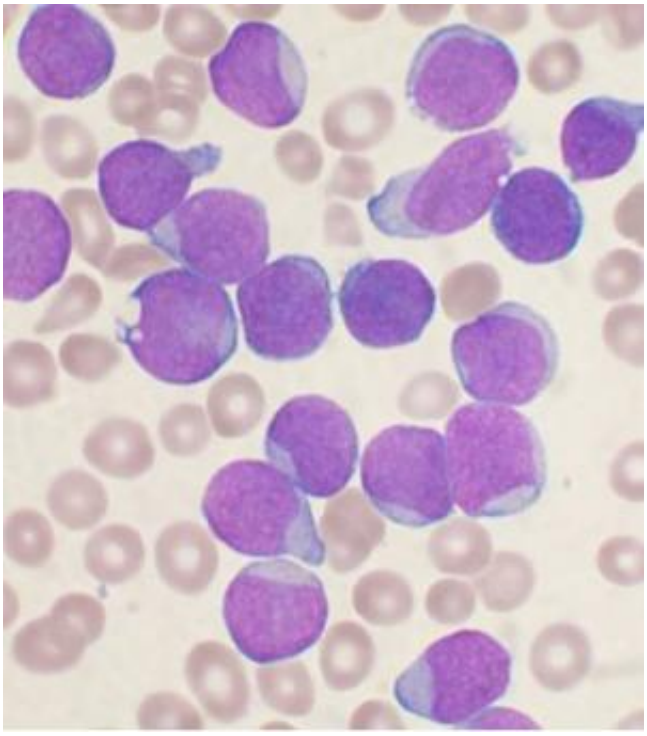

A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

A Purdue University study sheds light on how cell damage is reversed by the cancer drug decitabine and identifies a potential biomarker that could indicate a patient's stage of cancer and response to treatment.

A team led by Joseph Irudayaraj, professor of agricultural and biological

engineering, showed that decitabine combats some of the effects of cancer by taking the place of the nucleotide cytosine at specific locations on a replicating DNA strand. By mimicking cytosine, the drug helps "tame" cancerous cells by turning on tumor suppressor genes and turning off oncogenes, genes that can cause a normal cell to become cancerous.

The team also found that decitabine causes an unexpected boost in the amount of a molecule known as 5-hydroxymethylcytosine, or 5hmC. Because many types of cancer cause 5hmC levels to plummet, an uptick in 5hmC could be a sign that cancer treatments are working.

"We think that the expression of 5hmC could be used as a biomarker to define the stage or the aggressiveness of cancer and to possibly indicate the effectiveness of cancer treatment," Irudayaraj said. "This could help us monitor the clinical success of patients receiving decitabine."

Historically, cancer has been linked to mutations and errors in the genome. But in the last few decades, research has shown that cancer also has significant impacts on the epigenome, the collection of chemical compounds that direct which genes are expressed and when. While each cell in your body contains your entire genetic code, an epigenetic process called methylation determines how a cell functions - for example, activating the necessary genes to differentiate a skin cell from an eye cell.

Cancer, however, can hijack the methylation patterns passed down from cell to cell, switching off genes that suppress the formation of tumors and activating genes that instruct the cell to rapidly divide without differentiating. Tumors can result - masses of cells that perform no useful functions in the body.

Decitabine, one of the first epigenetic drugs, helps reverse the altered methylation patterns in cancerous cells, but its precise mode of action

has not been known. Using a combination of models, Irudayaraj and his fellow researchers hypothesized that decitabine is taking the place of cytosine at strategic positions on replicating strands of DNA in cancer cells.

When an enzyme tries to add a methyl group to silence decitabine - following the cancer-dictated patterns - the drug traps it in place, preventing methylation. This triggers another group of enzymes to transform a methylated cytosine on the parent DNA strand into 5hmC, a molecule whose biological function is not yet known.

The research team confirmed the increase in 5hmC levels in decitabine-treated leukemia cells.

Basudev Chowdhury, a postdoctoral researcher in the department of medicinal chemistry and molecular pharmacology and first author of the study, described the role of decitabine as a text editor that restores meaning to a garbled sentence and compared conventional chemotherapy - which destroys cancer cells - with a delete button.

"Think of nucleotides as the alphabet with which our cells compose messages," said Chowdhury, who conducted the research as a doctoral student in Irudayaraj's lab. "Epigenetics helps translate those messages into actions such as the production of proteins. But cancer can jumble the messages, making them nonsensical. Decitabine helps revise the messages so they can be understood."

More information: The paper was published in *Nature Scientific Reports* on Wednesday (April 22) and is available at www.nature.com/srep/2015/15040 … /full/srep09281.html

Provided by Purdue University