Study pinpoints and plugs mechanism of AML cancer cell escape

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A study published this week in the journal *Leukemia* identifies a mechanism that acute myeloid leukemia (AML) cells use to evade chemotherapy – and details how to close this escape route.

"Introducing chemotherapy to cells is like putting a curve in front of a speeding car," says Christopher Porter, MD, investigator at the University of Colorado Cancer Center and assistant professor of pediatrics at the University of Colorado School of Medicine. "Cells that can put on the brakes make it around the corner and cells that can't speed off the track."

Porter and colleagues collaborated with James DeGregori, PhD, CU Cancer Center investigator and professor of biochemistry and molecular genetics at the CU School of Medicine to define a molecular braking process that AML cells use to survive the curves of chemotherapy. They also showed that when this molecular brake is removed, AML cells (but not their healthy neighbors) die on the corners.

The discovery of this escape route and how to plug it provides hope for survival for a greater proportion of the estimated 12,950 people diagnosed with AML every year in the United States.

The group's findings rely on the relatively new technique of functional genomic screening of AML cells, accomplished by the CU Cancer Center Functional Genomics Shared Resource at the University of Colorado Boulder.

Using techniques they developed, the group turned off a different gene in each of a population of AML cells all at once. Then they hit all cells with chemotherapy traditionally used for AML. The goal: to see which genes, when turned off, would make the cells especially susceptible to chemo.

In this study, which generated over 30 million data points, cells that lacked a gene to make something called WEE1 died in disproportionate numbers. When you turn off WEE1, cancer cells die.

"WEE1 is the brakes," Porter says. "With chemotherapy we introduce DNA damage in cancer cells – we push them toward the curve hopefully at a greater rate than healthy cells. If WEE1 is there, cancer cells can round the curve. Without it, they flip."

Hidden in Porter's words is an element that makes this an especially exciting finding: AML cells may be more dependent than are healthy cells on WEE1. And so when you inhibit WEE1, you strip the brakes from cancer cells but not their healthy neighbors, killing AML cells but leaving healthy cells able to corner on rails.

"I'm optimistic that this will eventually lead to a therapeutic regimen that allows us to target AML cells that have escaped conventional therapies," Porter says.

Porter calls the team's initial results combining a drug that inhibits WEE1 with chemotherapy in mouse models of AML, "extremely promising."

"In light of these data, we are already early in the clinical trial planning process," Porter says.