Therapy targets leukemia stem cells

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New research takes aim at stubborn cancer stem cells that are thought to be responsible for treatment resistance and relapse. The study, published by Cell Press in the February 14 issue of the journal *Cancer Cell*, provides insight into mechanisms associated with the survival of leukemia stem cells and identifies a potential therapeutic target that is specific for these dangerously persistent cells.

Chronic myelogenous leukemia (CML) is a cancer of the white blood cells for which tyrosine kinase inhibitors are currently the first line of therapy. These drugs prolong survival, but disease recurrence is often seen after drug treatment is stopped. "Tyrosine kinase inhibitors do not eliminate leukemia stem cells, which remain a potential source of cancer recurrence," explains senior coauthor Dr. Ravi Bhatia from the City of Hope National Medical Center in Duarte, California. "CML patients need to take tyrosine kinase inhibitor treatment indefinitely, which carries a significant risk of toxicity, lack of compliance, drug resistance, relapse, and associated expense."

Strategies targeting leukemia stem cells are necessary to achieve a cure. Previous work has implicated the enzyme sirtuin 1 (SIRT1) in protecting stem cells from stress and in playing a role in leukemia, as well as other types of cancer. In the current study, Dr. Bhatia, coauthor Dr. WenYong Chen, first author Ling Li, and their colleagues investigated whether SIRT1 was involved in the survival and growth of CML stem cells. The researchers discovered that SIRT1 was overexpressed in CML stem cells and that inhibition of SIRT1selectively reduced the survival and growth of CML stem cells. Importantly, SIRT1 inhibition was associated with activation of the p53 tumor suppressor.

Taken together, the results reveal a specific mechanism that supports the survival of leukemia stem cells. "Our findings are important because they show that SIRT1-mediated inactivation of p53 contributes to CML leukemia stem cell survival and resistance to treatment with tyrosine kinase inhibitors," concludes Dr. Chen. "We suggest that SIRT1 inhibition is an attractive approach to selectively target leukemia stem cells that resist elimination by current treatments."

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