Therapy exploits 'addiction' of leukemia cells

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A new study describes a therapeutic approach to halting cancer progression by exploiting a previously unrecognized "addiction" of leukemia cells to specific signaling molecules. The research, published by Cell Press online on April 16th in the journal *Cancer Cell*, identifies non-classical oncogenes critical for tumor development and survival, and describes a potentially less toxic strategy that selectively targets these molecules.

Many cancers are associated with the loss of function of the PTEN tumor suppressor gene, including T-cell acute lymphoblastic leukemia (T-ALL). Loss of PTEN leads to unbridled activation of the PI3K/Akt signaling pathway that drives tumor growth and survival. "We know that there are multiple types of PI3K molecules, designated PI3K?, ?, ?, or ?, the unrestricted activities of which could contribute to these processes," explains senior study author, Dr. Thomas Diacovo, from Columbia University Medical Center. "However, what role, if any, distinct PI3K subtypes play in the pathogenesis of T-ALL was unknown."

Using a mouse model of T-ALL, Dr. Diacovo and colleagues found that in the absence of PTEN, the unrestricted activity of either PI3K? or PI3K? was sufficient to support cancer progression and that deletion of both subtypes was required to impair the development of T-ALL. "We found that these two molecules act as a kind of bottleneck in the progression of T-ALL and that the cancer cells can become addicted to these two specific signaling molecules," says Dr. Diacovo. The researchers went on to show that dual inhibition of both PI3K subtypes was necessary to prolong survival of mice with T-ALL and to promote the death of human tumor cells.

"Our work represents a significant advancement in the understanding of the dynamic interplay that exists between PTEN and specific PI3K subtypes in regulating both normal and abnormal T cell development, as well as in sustaining tumor proliferation and survival," concludes Dr. Diacovo. "By pinpointing these therapeutic targets, it may be possible to limit the toxicity that is associated with current T-ALL therapies and to avoid the potential global impact that less selective inhibition of the PI3K/Akt signaling pathway may have on cancer patients."

More information: Subramaniam et al.: "Targeting non-classical oncogenes for therapy in T-ALL." *Cancer Cell* April 17, 2012/ DOI:10.1016/j.ccr.2012.02.029

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