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The selective targeting of cell survival pathways in acute myeloid leukemia

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Abstract

Oncogenic activation of cell survival programs is a classical hallmark of cancer, allowing malignant cells to evade cytotoxic therapies. Although the concept of targeting cell survival in cancer has long been proposed, it has not yet proven clinically successful for the majority of cancers including acute myeloid leukemia (AML). We have identified a novel tyrosine kinase independent signaling mechanism by which diverse growth factor receptors regulate cell survival but not other cellular responses such as proliferation. We show that this "survival only" response is regulated via non-canonical growth factor receptor pathways that, remarkably, require the *protein* kinase activity of phosphoinositol 3-kinase (PI3K) but not its lipid kinase activity. The protein kinase activity of PI3K is constitutively activated in >80% of primary human AML patient samples and selective targeting of this novel PI3K pathway either pharmacologically or by RNAi results in the rapid induction of apoptosis. We therefore screened compound libraries for drugs that target "survival-only" pathways and have identified the kinase inhibitor, PIK-75, that is a potent inducer of apoptosis across a panel of 44 genetically diverse primary AML cases (mean IC50=395nM) at concentrations which did not affect the viability of non-transformed human bone marrow progenitors (p=0.0074). PIK-75 represents a first-in-class compound that blocks survival signalling in AML cells through *dual* inhibition of PI3K and the transcriptional kinase, cyclin dependent kinase 9 (Cdk9)(Kd<10nM), thereby transiently blocking RNA Polymerase II-mediated transcription leading to the rapid loss of the prosurvival protein, Mcl-1. Our studies reveal a previously unrecognized alliance between PI3K and Cdk9 in promoting oncogenic survival signals and we show that the simultaneous inhibition of PI3K and Cdk9 is highly synergistic not only AML cells (combination index <0.2), but tumor cells derived from multiple myeloma, breast cancer and brain cancer. Importantly, PIK-75 treatment is well tolerated in mice, results in the significant reduction of leukemic loads in mice engrafted with human AML cells (p=0.0059), and significantly increases their median survival (p=0005). Thus, our studies identify a novel lead compound that selectively targets two distinct and independent regulators of survival in AML. With the limited clinical efficacy reported so far for many kinase inhibitors, further investigation of dual PI3K and Cdk9 inhibitors is warranted.