Leucemia linfocítica crônica É importante inibir a via PI3-kinase

PI3-kinase regulates survival of chronic lymphocytic leukemia B-cells by preventing caspase 8 activation.


Source

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Abstract

Studies to investigate signal transduction pathways that support viability and prevent apoptosis of chronic lymphocytic leukemia cells (CLL) were initiated as a result of microarray cDNA analyses which revealed expression of genes whose products regulate cell cycle progression. Immunoblots revealed translation of several genes including caspases, cyclin D1, and the PI3-kinase dependent, survival kinase, Akt. Akt was found to be activated. Inhibition of PI3-kinase with specific inhibitor, LY294002, led to the induction of apoptosis that was caspase 8 dependent, but independent of Akt as LY294002 did not depress a high basal level of Akt activity found in CLL cells. Phosphorylation of Akt was maintained, enzymatic activity undiminished, and phosphorylation of substrates sustained. Caspases, however were activated, PARP cleaved and DNA fragmented. Caspase inhibitors revealed that initiator caspase 8 was required for classic apoptosis when PI3-kinase was inhibited, and specific activity assays demonstrated its early activation. GSK-3beta a kinase regulated via PI3-kinase dependent, down-stream kinases, was responsible for regulating cyclin D1 levels in CLL cells, but neither GSK-3beta nor calpain was responsible for induction of apoptosis, or activation of executioner caspase 3, following LY294002 treatment. PI3-kinase mediated protection against caspase activation in CLL B-cells therefore is not mediated through classic Akt survival pathways. The data further support the hypothesis that signal transducing, membrane associated receptors triggered by extrinsic factors, maintain CLL leukemic B-cell survival in vivo by preventing caspase activation.

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