Novel pathway in Bcr-Abl signal transduction involves Akt-independent, PLC-gamma1-driven activation of mTOR/p70S6-kinase pathway.

In chronic myeloid leukemia, activation of the phosphoinositide 3-kinase (PI3K)/Akt pathway is crucial for survival and proliferation of leukemic cells. Essential downstream molecules involve mammalian target of rapamycin (mTOR) and S6-kinase. Here, we present a comprehensive analysis of the molecular events involved in activation of these key signaling pathways. We provide evidence for a previously unrecognized phospholipase C-gamma1 (PLC-gamma1)-controlled mechanism of mTOR/p70S6-kinase activation, which operates in parallel to the classical Akt-dependent machinery. Short-term imatinib treatment of Bcr-Abl-positive cells caused dephosphorylation of p70S6-K and S6-protein without inactivation of Akt. Suppression of Akt activity alone did not affect phosphorylation of p70-S6K and S6. These results suggested the existence of an alternative mechanism for mTOR/p70S6-K activation. In Bcr-Abl-expressing cells, we detected strong PLC-gamma1 activation, which was suppressed by imatinib. Pharmacological inhibition and siRNA knockdown of PLC-gamma1 blocked p70S6-K and S6 phosphorylation. By inhibiting the Ca-signaling, CaMK and PKCs we demonstrated participation of these molecules in the pathway. Suppression of PLC-gamma1 led to...
inhibition of cell proliferation and enhanced apoptosis. The novel pathway proved to be essential for survival and proliferation of leukemic cells and almost complete cell death was observed upon combined PLC-gamma1 and Bcr-Abl inhibition. The pivotal role of PLC-gamma1 was further confirmed in a mouse leukemogenesis model.