Constitutive activation of Akt contributes to the pathogenesis and survival of mantle cell lymphoma.

Abstract:

To determine whether the PI3K/Akt signaling pathway is involved in the pathogenesis of mantle cell lymphoma (MCL), we investigated the phosphorylation status of Akt and multiple downstream targets in primary MCL cases and cell lines. Akt was phosphorylated in 12 of 12 aggressive blastoid MCL variants and in 4 of 4 MCL cell lines. In contrast, phosphorylated Akt was present in only 5 of 16 typical MCL, 3 at comparable levels to the blastoid cases, and 2 at low levels. The presence of p-Akt was accompanied by the phosphorylation of p27(kip1), FRKHL-1, MDM2, Bad, mTOR, and p70S6K. Inhibition of the PI3K/Akt pathway in the MCL cell lines abrogated or reduced the phosphorylation of Akt, p27(kip1), FRKHL-1, MDM2, Bad, mTOR, GSK-3beta, IkappaB, and led to cell-cycle arrest and apoptosis. Six MCL cases (5 with activated Akt and 1 with inactive Akt) and 3 of 4 cell lines showed loss of PTEN expression. PIK3CA mutations were not detected. We conclude that constitutive activation of the PI3K/Akt pathway contributes to the pathogenesis of MCL and preferentially occurs in blastoid variants. One possible mechanism of activation is loss of PTEN expression. These data suggest that PI3K/Akt inhibitors may be effective in the treatment of Akt-activated MCL.