Compensatory PI3-kinase/Akt/mTor activation regulates imatinib resistance development.

BCR/ABL-kinase mutations frequently mediate clinical resistance to the selective tyrosine kinase inhibitor Imatinib mesylate (IM, Gleevec). However, mechanisms that promote survival of BCR/ABL-positive cells before clinically overt IM resistance occurs have poorly been defined so far. Here, we demonstrate that IM-treatment activated the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTor)-pathway in BCR/ABL-positive LAMA-cells and primary leukemia cells in vitro, as well as in a chronic phase CML patient in vivo. In fact, PI3K/Akt-activation critically mediated survival during the early phase of IM resistance development before manifestation of BCR/ABL-dependent strong IM resistance such as through a kinase mutation. Accordingly, inhibition of IM-induced Akt activation using mTor inhibitors and Akt-specific siRNA effectively antagonized development of incipient IM-resistance in vitro. In contrast, IM-resistant chronic myeloid leukemia (CML) patients with BCR/ABL kinase mutations (n=15), and IM-refractory BCR/ABL-positive acute lymphatic leukemia patients (n=2) displayed inconsistent and kinase mutation-independent autonomous patterns of Akt-pathway activation, and mTor-inhibition overcame IM resistance only if Akt was strongly activated. Together, an IM-induced compensatory Akt/mTor...
activation may represent a novel mechanism for the persistence of BCR/ABL-positive cells in IM-treated patients. Treatment with mTor inhibitors may thus be particularly effective in IM-sensitive patients, whereas Akt-pathway activation variably contributes to clinically overt IM resistance.