Abstract

In malignant B cells, signalling pathways emanating from the B cell receptor (BCR) are activated and involved in pathogenesis. Consequently, BCR associated kinases (BAK), e.g. Bruton tyrosine kinase (BTK) and phosphatidylinositol-3-kinase δ (PI3Kδ), constitute suitable targets for the therapy of B cell malignancies. For gaining new insights into the anti-lymphoma mechanisms of PI3K inhibitors, we sought to quantitatively evaluate the isoform-selective contributions to their potency against malignant B cell growth.

Here we show for the first time that overexpression of the p110δ_E1021K mutation in BaF3 cells leads to p110δ-dependent growth and we exploit this growth in a systematic approach to characterize PI3K inhibitors with regard to their isoform specific potency based on cellular cytotoxicity assessment.

Results of this assessment confirmed isoform specific biochemical inhibitor potencies against p110δ. Pan-class I and dual specific PI3K/mTOR inhibitors often showed lower potencies against p110δ.

With the resistance hotspot mutation I777M at the binding pocket of p110δ, we reconstituted cellular growth and intracellular p110δ activity by phosphorylation of AKT in the presence of p110δ specific inhibitors. This resistance is observed only with certain inhibitors, e.g. 10-fold resistance against idelalisib. Additionally, the gain-of-function mediated by the I777M mutation observed via increased AKT phosphorylation, was in agreement with pronounced structural changes suggested by molecular dynamic simulations.