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Authors
Lee, J-HS
Tang, S
Ortiz, V
et al.

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Abstract B45: Vertical inhibition of the PI3K pathway potently sensitizes diffuse large B cell lymphoma to BCL-2 antagonism

Jong-Hoon Scott Lee, Sarah Tang, Veronica Ortiz and David A. Fruman

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Abstract

The PI3K/AKT/mTOR axis is one of the most commonly mutated pathways in cancer, where aberrant activation promotes cell growth, proliferation, and survival. However, selective inhibitors targeting PI3K/AKT/mTOR have been hindered by their inability to effectively induce cell death in certain cancers. With the introduction of inhibitors that directly inhibit key pro-survival factors such as BCL-2 and BCL-XL (ABT-263 and ABT-199), the potential to achieve cancer cell death using combinations of targeted inhibitors has become a realizable goal. Here we show that selective inhibition of key components in the PI3K pathway (PI3K, AKT, or mTOR) potently sensitized a panel of DLBCL cell lines to ABT-263-induced apoptosis. While the degree of sensitization varied according to which PI3K pathway component was targeted, dual inhibition of both PI3K and mTOR consistently elicited the most potent sensitization across several cell lines. Previous work in other cancer types has linked the potency of this combination to the capacity of PI3K pathway inhibitors to reduce MCL-1 in an mTORC1-dependent manner. However, we found that this was not the case for DLBCL. For example, ABT-263 resistance induced by over-expression of MCL-1 was overcome when cells were co-treated with a dual-PI3K/mTOR inhibitor NVP-BEZ235 despite maintained expression of MCL-1. Instead, inhibition of the PI3K pathway led to a general increase in mitochondrial priming as measured by BH3 profiling. This occurred through distinct effects from both AKT and mTORC1 on the abundance of multiple BCL-2 family proteins at the mitochondria including reductions in the pro-survival proteins BCL-2, MCL-1, and BCL-XL as well as increases in Bim and Bad. In addition to these direct effects on BCL-2 family proteins, we found that inhibition of the PI3K pathway reduced expression of cancer-relevant proteins c-Myc and eIF4G as determined by reverse phase protein array. Thus, this project highlights the broad effects of dual-PI3K/mTOR inhibitors that sensitize DLBCL to apoptosis, and suggests that inhibition of the PI3K pathway has distinct effects on cell survival signaling among different cancer cell types.
