SYNTHETIC LETHAL INTERACTION OF COMBINED BCL-XL AND MEK INHIBITION PROMOTES TUMOR REGRESSIONS IN KRAS-MUTANT CANCER MODELS

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Although KRAS is the most commonly mutated oncogene in human cancer, KRAS has proven difficult to target pharmacologically, and no effective therapies exist for KRAS-mutant cancers. Recently, there has been evidence that targeted therapy combinations inhibiting multiple downstream effectors of KRAS may be a promising approach for KRAS-mutant cancers. We developed a pooled shRNA-drug screen strategy to identify genes that, when inhibited, cooperate with MEK inhibitors to kill KRAS-mutant cancer cells. The anti-apoptotic BH3 family gene BCL-XL emerged as a top hit through this approach. ABT-263 (navitoclax), a chemical inhibitor that blocks the ability of BCL-XL to bind and inhibit pro-apoptotic proteins, in combination with a MEK inhibitor led to dramatic apoptosis in the vast majority of KRAS-mutant cell lines tested from different tissue types. Mechanistic studies revealed that MEK inhibition led to marked induction of the pro-apoptotic protein BIM in KRAS-mutant cancer cells, but that BIM remained bound and inhibited by BCL-XL. Pharmacologic inhibition of BCL-XL with ABT-263 disrupted this inhibitory complex, allowing BIM to trigger apoptosis. Epithelial differentiation and E-cadherin expression correlated with increased sensitivity to this inhibitor combination across a panel of 30 KRAS-mutant cell lines, while epithelial-to-mesenchymal transition (EMT) correlated with resistance. This combination also caused marked in vivo tumor regressions in three independent KRAS-mutant xenografts and in established lung tumors in two genetically-engineered KRAS-driven lung cancer mouse models. These data support combined BCL-XL/MEK inhibition as a promising therapeutic approach for evaluation in future clinical trials for patients with KRAS-mutant cancers.