

DVL Inhibits the YAP1 Bypass Mechanism of KRAS Inactivation

Eltayib, Amal (School: Iowa City High School)

Yes-associated protein 1 (YAP1) is a transcriptional coactivator known for driving oncogenesis. YAP1 is able to revive the gene expression of transcription factor FOS following the downregulation of Kirsten rat sarcoma virus (KRAS), a proto-oncogene that transcribes for FOS. As a result, YAP1 bypasses KRAS inhibition. As Dishevelled (DVL) has been shown to reduce oncogenic YAP1 nuclear activity via cytoplasmic translocation, the goal of this study was to elucidate the effects of DVL on this bypass mechanism through a computational analysis of 631 samples of primary colorectal adenocarcinoma. In this study, mRNA sequencing data was collected to construct a transcriptomic profile compiled of 20,533 genes across 8,889,923 gene expression points to identify molecular effectors of YAP1. Samples were dichotomized into mutated and non-mutated KRAS samples, and RNA expression data was analyzed to examine the DVL's effects on the bypass mechanism. In order to validate these results, protein-protein interaction screens were used to isolate DVL, YAP1, and KRAS protein interaction levels. Marker gene identification of the transcriptomic profile revealed that DVL statistically significantly ($p < 0.05$) affected YAP1 expression. Further investigation into RNA expression data demonstrated that DVL inhibited the bypass mechanism by significantly lowering KRAS abundance ($p = 7.268 \times 10^{-6}$). Protein-protein interaction screens also validated DVL as a molecular effector of YAP1. This study presents statistically significant evidence supporting the DVL-mediated inhibition of this bypass mechanism. Identifying DVL as an inhibitor of YAP1's oncogenic activity has many implications as a possible therapeutic target in KRAS mutant cells.