

## Unsaturated Fatty Acids Stimulate Tumor Growth through Stabilization of $\beta$ -catenin

Some cancer cells exhibit elevated levels of free fatty acids as well as high levels of  $\beta$ -catenin, a transcriptional co-activator that promotes their growth. Here we link these two phenomena by showing that unsaturated fatty acids inhibit degradation of  $\beta$ -catenin. Unsaturated fatty acids bind to the UAS domain of Fas-associated factor 1 (FAF1), a protein known to bind  $\beta$ -catenin, accelerating its degradation. Fatty acid binding disrupts the FAF1/  $\beta$ -catenin complex, preventing proteasomal degradation of ubiquitinated  $\beta$ -catenin. This mechanism for stabilization of  $\beta$ -catenin differs from that of Wnt signaling, which blocks ubiquitination of  $\beta$ -catenin. In clear cell renal cell carcinoma (ccRCC) cells, unsaturated fatty acids stimulated cell proliferation through stabilization of  $\beta$ -catenin. In tissues from biopsies of human ccRCC, elevated levels of unsaturated fatty acids correlated with increased levels of  $\beta$ -catenin. Thus, targeting FAF1 may be an effective approach to treat cancers that exhibit elevated fatty acids and  $\beta$ -catenin.