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A critical role of the SUMO pathway in KRAS-driven oncogenesis

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The SUMOylation pathway modulates the activity of many cellular proteins and plays an important role in cellular stress protection. Through a genome-wide shRNA synthetic lethal screen against the KRAS oncogene, we identified the SUMO E2 ligase Ubc9 to be critical for KRAS-driven transformation in colorectal cancer cells. Strikingly, shRNA depletion of Ubc9 severely impairs clonogenic and anchorage-independent growth of KRAS mutant cells *in vitro* and attenuates tumor growth in xenograft models. SILAC mass-spectrometry reveals that the SUMOylation of multiple proteins are elevated in KRAS mutant cells. In particular, SUMOylation of the transcriptional repressor KAP1 is selectively elevated in KRAS mutant cells under anchorage independent conditions and functionally repress p21 upregulation. Our findings suggest a model where the SUMOylation pathway relieves the oncogenic stress associated with KRAS transformation. shRNA-rescue experiments using Ubc9 mutants indicate that KRAS-driven transformation requires Ubc9 enzymatic activity, thus Ubc9 inhibitor could be potentially useful at treating KRAS mutant colorectal cancer.

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