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Apoptosis induced by GSK inhibitors in mutant KRas tumors

Mutant KRas, contributing to human oncogenesis, confers resistance to therapy in cancers such as pancreatic, colon, and lung. Currently there are no approved therapies that directly target mutant KRas. However, mutant KRas-driven cancers may gain dependencies through other pathways. Usually c-Myc overexpression is associated with tumorigenesis, but c-Myc can also induce apoptosis. This paper explored a new way that inhibiting phosphorylation of GSK3 substrates c-Myc and β-catenin induced apoptosis in mutant KRas-dependent tumors.

GSK3 suppression upregulates β-catenin and c-Myc to abrogate KRas-dependent tumors

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Abstract

Mutant KRas is a significant driver of human oncogenesis and confers resistance to therapy, underscoring the need to develop approaches that disable mutant KRas-driven tumors. Because targeting KRas directly has proven difficult, identifying vulnerabilities specific for mutant KRas tumors is an important alternative approach. Here we show that glycogen synthase kinase 3 (GSK3) is required for the in vitro and in vivo growth and survival of human mutant KRas-dependent tumors but is dispensable for mutant KRas-independent tumors. Further, inhibiting phosphorylation of GSK3 substrates c-Myc on T58 and β-catenin on S33/ S37/T41 and their subsequent upregulation contribute to the antitumor activity of GSK3 inhibition. Importantly, GSK3 blockade inhibits the in vivo growth of G12D, G12V, and G12C mutant KRas primary and metastatic patient-derived xenografts from pancreatic cancer patients who progressed on chemo- and radiation therapies. This discovery opens new avenues to target mutant KRas-dependent cancers.