APC and oncogenic KRAS are synergistic in enhancing Wnt signaling in intestinal tumor formation and progression.

BACKGROUND & AIMS: Synchronous activation of the Wnt signaling pathway, mostly because of loss of function of the APC tumor suppressor, and of the oncogenic KRAS-signaling pathway is very frequent in colorectal cancer and is associated with poor prognosis. METHODS: We have generated a compound transgenic mouse model, KRAS(V12G)/Apc(+/-1638N), to recapitulate the human disease and compared it with single transgenic littermates. RESULTS: Compound mutant mice are characterized by a 10-fold increase in tumor multiplicity and by accelerated tumor progression, resulting in strongly enhanced morbidity and mortality. Tumors from compound mutant mice proliferate faster and show decreased levels of apoptosis. Several lines of evidence indicate that the observed increase in tumor multiplicity and malignant transformation is caused by the synergistic activation of Wnt signaling in cells with oncogenic KRAS and loss-of-function Apc mutations. Activated KRAS is known to induce tyrosine phosphorylation of beta-catenin, leading to its release from E-cadherin at the adherens junction. This results in an increased beta-catenin pool in the cytoplasm, its subsequent translocation to the nucleus, and the transcriptional activation of Wnt downstream target genes. Accordingly, intestinal tumors
from KRAS(V12G)/Apc(+/1638N) mice show a significant increase in cells with nuclear accumulation of beta-catenin when compared with Apc(+/1638N) animals. Moreover, Apc/KRAS-mutant embryonic stem cells show a significantly enhanced beta-catenin/T-cell factor-mediated transcriptional activation, accompanied by increased beta-catenin nuclear localization. CONCLUSIONS: This KRAS-induced increase in Wnt/beta-catenin signaling may enhance the plasticity and self-renewal capacity of the tumor, thus resulting in the drastically augmented tumor multiplicity and malignant behavior in compound mutant animals.