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Titel des Beitrags: APC inactivation associates with abnormal mitosis completion and concomitant BUB1B/MAD2L1 up-regulation.

Abstract: BACKGROUND & AIMS: Chromosomal instability, a hallmark of most colorectal cancers, has been related to altered chromosome segregation and the consequent deficit in genetic integrity. A role for the tumor suppressor gene APC has been proposed in colorectal cancer that leads to compromised chromosome segregation even though the molecular mechanism is not yet understood. Here, we tackled the genetic basis for the contribution of APC to chromosomal instability in familial adenomatous polyposis and sporadic colorectal cancer.

METHODS: We have used video-microscopy of primary cultures and molecular genetic methods to address these issues in human samples and in genetically defined mouse models that either recapitulate the familial adenomatous polyposis syndrome (Apc(1638N)), or develop tumors in the absence of APC mutations (pwellin-KRASV12G).

RESULTS: Mutations in APC were associated with an increased incidence in cell cycle defects during the completion of cytokinesis. Transcriptome analysis performed on mouse models indicated a significant up-regulation of genes that regulate accurate mitosis. Notably, we identified up-regulated expression of BUB1B and MAD2L1, 2 genes that
are involved in the mitotic checkpoint, but have so far not been implicated in chromosomal instability induced by APC loss of function. In vitro modulation of APC expression suggested a causal association for this upregulation, which was consistently found in sporadic and familial adenomatous polyposis lesions, as an early event in colorectal tumorigenesis. CONCLUSIONS: In addition to the known function of APC during correct spindle assembly and positioning, we propose a concomitant involvement of APC in the surveillance mechanism of accurate mitosis.