The Wnt/β-Catenin and Ras-ERK Pahtway Interact in Cellular Transformaton

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The extracellular signal regulated kinase (ERK) and Wnt/β-catenin pathways are major transforming pathways involved in cellular transformation. However, the relationship between the Wnt/b-catenin and ERK signaling pathways is poorly understood. Several studies have pointed to interaction between the b-catenin/Wnt and the Ras-ERK pathways without clarifying the mechanism involved. We investigated interaction between Wnt/b-catenin and ERK pathways thoroughly by measuring an effect of APC on the ERK pathway. Overexpression of the negative regulator of Wnt/b-catenin pathway, adenomatous polyposis coli (APC), reduced the activation of ERK pathway induced by transfection with oncogenic *ras*, indicating that APC antagonizes the Ras-induced ERK pathway activation that is responsible for proliferation and malignant transformation. ERK activity was increased by Cre-virus-induced *APC* knock out in primary $APC^{flox/flox}$ mouse embryonic fibroblasts, indicating that APC inhibits ERK activity. ERK activity was increased by overexpression and decreased by knock down of β-catenin. The activation of Raf-1, MEK, and ERK kinases by b-catenin was reducedby co-expression of APC. These results indicate that APC inhibits the ERK pathway by an action on b-catenin. Ras-induced activation of the ERK pathway was reduced by the dominant negative form of Tcf-4, indicating that the ERK pathway regulation by APC/b-catenin signaling is, at least, partly caused by effects on β-catenin/Tcf-4-mediated gene expression. GTP loading was reduced by APC overexperession in cells retaining mutated *RAS* as well as wild-type *RAS*. The reduction of GTP-loading of mutated *ras* by APC accomplished not by GTP hydrolysis but by regulation of protein level and that identified by monitoring Ras protein level. APC strongly inhibits proliferation and transformation by Ras, indicating a potential role for APC in regulation of Ras-induced tumor progression. APC in tumor progression caused by Ras activation has been identified along with a potential for APC use as a therapeutic agent in cancers caused by Ras.