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Regulation of the Coxsackie and Adenovirus Receptor (CAR) by the Ras/MAPK signal transduction pathway. M. Anders[1], R. X. Ding[1], E. M. Lipner[1], A. Balmain[1], F. McCormick[1], W.M. Korn[1,2]
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The recently identified human Coxsackie and Adenovirus receptor (CAR) represents the primary cellular site of adenovirus attachment during infection. As genetically modified adenoviruses have been devised as anti-cancer agents, information about the molecular mechanisms regulating CAR expression is needed for further development of this therapeutic modality. Here, we investigated the possibility that the Ras/MAPK signal transduction pathway regulates expression of CAR in human cancer cells. To test this hypothesis, cancer cells were treated with specific pharmacological inhibitors of Ras/MAPK signaling. Upon inhibition of Ras/MAPK signaling, up-regulation of CAR protein expression was observed in human colorectal and murine skin cancer cells. In parallel, increases of CAR mRNA expression levels were observed, indicating that CAR expression is, at least in part, transcriptionally regulated. MEK inhibition also restored preferential expression of CAR at the cell surface. In treated cells, adenovirus uptake was enhanced, resulting in increased transgene expression in the case of non-replicating adenovirus vectors and enhanced cytopathic effect induced by a replication-selective adenovirus (ONYX-015). Our study demonstrates that Ras/MAPK signaling negatively regulates expression of CAR in cancer cells, resulting in an impaired uptake of adenovirus by malignant cells. We conclude that pharmacological receptor restoration in cancer cells by inhibition of Ras/MAPK signaling could lead to an improved efficacy of adenovirus based cancer therapies.