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## The Role of Uridine-Cytidine Kinase 2 in the Development of Hepatocellular Carcinoma

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**Background and Objectives:** Hepatocellular Carcinoma (HCC) is the most common primary malignancy of the liver and is the third most common cause of cancer-related death in the world. There are limited options for effective treatment of advanced HCC. We investigated the role of uridine-cytidine kinase 2 (UCK2) in the development of HCC and its potential as a target for treatment.

**Methods:** Gene expression data from 377 patients in the TCGA HCC Project and protein expression data from 156 HCCs arrayed on tissue microarrays were analyzed for associations with survival and other clinical characteristics. In *in vitro* studies, we studied the functional consequences of forced expression of UCK2 in Huh7 and SNU387 cells, which have low endogenous expression of UCK2, and in Hep3B cells, which have high expression of UCK2. We also explored the mechanisms by which UCK2 promotes HCC tumorigenesis.

**Results:** mRNA expression of UCK2 was associated with both overall survival and disease free survival of HCC patients, while protein expression was only associated with overall survival. In *in vitro* studies, overexpression of UCK2 promoted proliferation and migration of Huh7 and SNU387 cell lines, while knockdown of UCK2 suppressed the proliferation and migration of the Hep3B cell line. UCK2 activated an EGFR-AKT-mTOR signaling axis at least in part through up-regulating the expression of EGFR. In turn, UCK2 was up-regulated by TGF $\beta$ 1 through Smad2/Smad3 dependent demethylation.

**Conclusion:** UCK2 enhances HCC tumorigenesis by mediating crosstalk between the TGF $\beta$  and EGFR signaling pathways.