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Mucin glycosylating enzyme GALNT2 regulates the malignant character of hepatocellular carcinoma by modifying the EGF receptor

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ABSTRACT

Extracellular glycosylation is a critical determinant of malignant character. Here we report that N-acetylgalactosaminyltransferase 2 (GALNT2), the enzyme that mediates the initial step of mucin type-O glycosylation, is a critical mediator of malignant character in hepatocellular carcinoma (HCC) that acts by modifying the activity of the EGF receptor (EGFR). GALNT2 mRNA and protein were downregulated frequently in HCC tumors where these events were associated with vascular invasion and recurrence. Restoring GALNT2 expression in HCC cells suppressed EGF-induced cell growth, migration, and invasion in vitro and in vivo. Mechanistic investigations revealed that the status of the O-glycans attached to the EGFR was altered by GALNT2, changing EGFR responses after EGF binding. Inhibiting EGFR activity with erlotinib decreased the malignant characters caused by siRNA-mediated knockdown of GALNT2 in HCC cells, establishing the critical role of EGFR in mediating the effects of GALNT2 expression. Taken together, our results suggest that GALNT2 dysregulation contributes to the malignant behavior of HCC cells, and they provide novel insights into the significance of O-glycosylation in EGFR activity and HCC pathogenesis.

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