

C1GALT1 enhances proliferation of hepatocellular carcinoma cells via modulating MET glycosylation and dimerization

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Abstract

Altered glycosylation is a hallmark of cancer. The core 1 β 1,3-galactosyltransferase (C1GALT1) controls the formation of mucin-type O-glycans, far overlooked and underestimated in cancer. Here we report that C1GALT1 mRNA and protein are frequently overexpressed in hepatocellular carcinoma (HCC) tumors compared with non-tumor liver tissues, where it correlates with advanced tumor stage, metastasis and poor survival. Enforced expression of C1GALT1 was sufficient to enhance cell proliferation, whereas RNAi-mediated silencing of C1GALT1 was sufficient to suppress cell proliferation *in vitro* and *in vivo*. Notably, C1GALT1 attenuation also suppressed hepatocyte growth factor (HGF)-mediated phosphorylation of the MET kinase in HCC cells, whereas enforced expression of C1GALT1 enhanced MET phosphorylation. MET blockade with PHA665752 inhibited C1GALT1-enhanced cell viability. In support of these results, we found that the expression level of phospho-MET and C1GALT1 were associated in primary HCC tissues. Mechanistic investigations showed that MET was decorated with O-glycans, as revealed by binding to *Vicia villosa* agglutinin (VVA) and peanut agglutinin (PNA). Moreover, C1GALT1 modified the O-glycosylation of MET, enhancing its HGF-induced dimerization and activation. Together, our results indicate that C1GALT1 overexpression in HCC activates HGF signaling via modulation of MET O-glycosylation and dimerization, providing new insights into how O-glycosylation drives HCC pathogenesis.

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