Results: C1GALT1 was overexpressed in HNSCC tumors and predicts poor survivals. C1GALT1 overexpression enhanced whereas C1GALT1 knockdown/knockout suppressed cell viability, migration, and invasion in HNSCC cells. Mechanistically, C1GALT1 modulated O-glycosylation of EGFR and enhanced EGF-EGFR binding affinity, leading to increased EGFR signaling and malignant phenotypes. Using mass spectrometry, we identified five O-glycopeptides on EGFR, among which four are within the ligand binding domain. Itraconazole, a C1GALT1 inhibitor, directly bound to C1GALT1 and changed O-glycans on cell surfaces and EGFR. Targeting C1GALT1 with CRISPR/Cas9, shRNA, or itraconazole was able to significantly suppress tumor growth in NOD/SCID mice.

Conclusions: Our findings indicate C1GALT1 as an attractive therapeutic target for HNSCC.

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