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Grant title: Regulatory role of HNK-1 capped branched O-Man glycan for glioma activation

Abstract

Gliomas are the most prevalent primary tumor of the CNS. Despite advances in imaging technologies, neurosurgical techniques, and radiotherapy, the median survival of patients with glioblastoma, the highest-grade glioma, is only 15 months(3). Several groups have reported that protein tyrosine phosphatase receptor Z (PTPRZ) is highly expressed in glioblastoma, and its soluble cleaved form (sPTPRZ) is detected at high concentrations in the cerebrospinal fluid (CSF) of glioma patients, indicating that CSF sPTPRZ might be a diagnostic marker for glioma. Furthermore, targeting PTPRZ attenuates tumor growth in mice. PTPRZ is abundant in gliomas. PTPRZ is modified with diverse glycan, including the PTPRZ-unique human natural killer-1 (HNK-1) capped O-Man core M2 glycans. However, the regulation and function of these unique glycans are unclear. Using CRISPR genome-editing technology we first demonstrated that disruption of the PTPRZ gene in human glioma LN-229 cells resulted in profoundly reduced tumor growth in xenografted mice, confirming the potential of PTPRZ as a therapeutic target for glioma. Furthermore, multiple glycan analyses revealed that PTPRZ derived from glioma patients and from xenografted glioma expressed abundant levels of HNK-1 capped O-Man glycans via extrinsic signals. Finally, since deficiency of O-Man core M2 branching enzyme N-acetylglucosaminyltransferase IX (GnT-IX) was reported to reduce PTPRZ protein levels, we disrupted the GnT-IX gene in LN-229 cells and found a significant reduction of glioma growth both *in vitro* and in the xenograft model. These results suggest that the PTPR glycosylation enzyme GnT-IX may represent a promising therapeutic target for glioma.