Role and therapeutic targeting of T-type calcium channels in glioblastoma

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Glioblastoma (GBM) is the most common and most deadly primary malignant brain tumor. Glioblastoma stem cells (GSCs) have been implicated in tumor initiation, recurrence and resistance to therapy. We investigated the expression, function, mechanism of action and therapeutic targeting of Cav3.2 T-type calcium channel in GBM and GSCs. We found that Cav3.2 is highly expressed in the majority of human GBM specimens and all GCSs. TCGA and REMBRANDT data analyses revealed that 11% of GBM tumors have upregulated Cav3.2 and that overexpression is associated with worse prognosis. Furthermore, treatment of cells with the Cav3.2 inhibitor Mibefradil or Cav3.2 gene silencing inhibited GSC growth and survival, induced GSC differentiation and sensitized the cells to temozolomide (TMZ) chemotherapy. We also discovered that Cav3.2 upregulation in GBM cells constitutes a mechanism of resistance of these cells to pharmacological therapies that target receptor tyrosine kinases. To investigate the mechanism of action of Cav3.2 in GBM, we performed proteomic and transcriptomic screenings of Mibefradil-treated GSCs using reverse phase protein arrays and RNA-seq, followed by functional rescue experiments. Inhibition of Cav3.2 significantly altered multiple cancer regulatory signaling molecules as well as the transcription of oncogenes and tumor suppressors. Among other, Cav3.2 inhibition suppressed GSC growth through inhibition of pro-survival pathways such as AKT/mTOR, whilst inducing apoptosis through upregulation of survivin, BAX and cleavage of caspase 9 and PARP. Cav3.2 inhibition also led to increase in the expression of tumor suppressors such as TNFRSF14 and HSD17B14 along with a decrease in the expression of oncogenes such as PDGFA, PDGFB and TGFB1. We also assessed the therapeutic effects of Mibefradil in a GSC-based GBM animal model. Oral administration of Mibefradil significantly inhibited tumor growth, prolonged animal survival and sensitized tumors to inhibition by TMZ and radiation. Our findings represent a first comprehensive characterization of Cav3.2 in GBM and show that Cav3.2 inhibition with the repurposed FDA-approved drug Mibefradil is a new promising strategy for GBM therapy.