Abstract

Glioblastoma multiforme (GBM) is the most aggressive primary brain malignancy, with a median overall survival of approximately 14.6 months despite standard multimodal therapy. ORAI1-mediated store-operated calcium entry (SOCE) is aberrantly elevated in GBM and sustains pro-proliferative and anti-apoptotic signaling, making it a compelling therapeutic target. This study investigated the transcriptional signaling pathways modulated by MPT786, a novel Synta66-derived ORAI1/CRAC channel inhibitor, in A172 GBM cells. Following treatment at concentration of 10μM for 24 hours, RNA sequencing and cross-platform pathway enrichment analysis using IPA, KEGG, and Gene Ontology identified p53 Signaling as the most significantly enriched pathway (IPA $-\log p = 9.65$; z-score = 1.667). A curated set of 72 pathway-associated genes was subjected to CGGA survival analysis, ORAI1 co-expression correlation, GEPIA2 tumor-versus-normal comparative analysis, and univariate Cox proportional hazards regression. The top ten ORAI1-correlated genes (CDK2, AURKA, AURKB, CASP2, CHEK2, BAX, HIC1, STEAP3, DDB2, CHEK1) encompassed cell-cycle kinases, DNA damage checkpoint mediators, and p53 effectors, all exhibiting significant positive associations with adverse prognosis in glioma patients. A proposed mechanistic pathway illustrates how ORAI1 inhibition suppress glioblastoma progression by reducing intracellular Ca^{2+} signaling, thereby stabilizing p53 to induce G1/S and G2/M cell cycle arrest, impair DNA damage repair, and activate the intrinsic mitochondrial apoptotic pathway, ultimately reducing glioblastoma cell survival and proliferation. These findings position MPT786 as a mechanistically distinct anti-GBM agent and provide a foundational transcriptomic rationale for further preclinical and translational investigation of ORAI1-targeted therapy.

Keywords: glioblastoma; ORAI1 inhibitor; store-operated calcium entry; p53 signaling; CRAC channel inhibition