ABSTRACT

Glioblastoma (GBM) or the high grade glioma is the most aggressive type of brain tumors resulting in maximum morbidity and mortality. The Ubiquitin-Proteasome System (UPS) is a key regulator of protein homeostasis, playing a crucial role in eliminating misfolded proteins and maintaining cellular health. UPS dysregulation is implicated in various CNS malignancies, including GBM. This study explores the multifaceted functions of the UPS, particularly its roles in cell cycle control, DNA damage response, apoptosis, and cellular stress regulation, with a focus on its involvement in the central nervous system (CNS). We have investigated the oncogenic potential of PSMC2, a 19S proteasome complex member, which is upregulated in GBM and promotes tumor progression by enhancing epithelial-to-mesenchymal transition (EMT). Through in vitro and in vivo experiments, we demonstrate that targeting PSMC2 inhibits GBM cell proliferation and induces apoptosis, highlighting its potential as a therapeutic target. Furthermore, our research reveals the interaction between PSMC2 and the AKT/GSK3β/β-catenin axis, which drives EMT, and the critical role of PTEN regulation in this process. Additionally, we have shown that temozolomide resistance in GBM, linking it to heightened proteasome activity that suppresses endoplasic reticulum (ER) stress and autophagy. Inhibiting PSMC2 reactivates pro-death autophagy and restores sensitivity to temozolomide.

We further explore the upstream regulators of PSMC2 and identified NRF1 (also known as NFE2L1) as a key transcription factor. NRF1 is cleaved from the ER membrane by the protease DNA damage inducible 1 homolog 2 (DDI2), allowing its release and subsequent localization to the nucleus. This mechanism prompted us to screen for drug candidates that could inhibit DDI2 activity, thereby suppressing PSMC2 expression. Molecular docking and simulation studies highlighted Alvimopan as a promising DDI2 inhibitor, offering a novel approach to target the UPS in GBM. This discovery emphasizes the potential of UPS-targeted therapies in CNS malignancies and opens new avenues for drug development.