# Dismantling Malignant Brain Tumor Protections: Novel Role of POLK in Protecting GBM-derived Cells from Replication Catastrophe

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Glial cells provide structure and metabolic support for neurons. Glioblastomas (GBM) are malignant tumors of glial cells. To improve their survival, cancerous cells have elevated levels of proteins that resolve replication stress and repair DNA damage. Studies found that human DNA polymerase kappa (hpol ?) was overexpressed in glioblastomas; this increase is thought to play a role in tumor survival because the mechanism bypasses DNA lesions and protects tumor cells from DNA breakage and replication catastrophe (RC). In order to study the role of hpol ? in replication dynamics, glioblastoma-derived T98G cells without a functional Polk gene (GBM-POLKKO) were compared to wild-type cells. To study cells under stress, all cells were treated with an inhibitor of the Kinase Rad3-related (ATR) kinase, a regulator of replication stress response (RSR). ATR inhibition is known to induce RC in cells experiencing stress. To determine if hpol ? prevents RC, the changes in RSR proteins, replication fork dynamics, and markers of RC were measured using immunofluorescence microscopy and DNA fiber spreading. Between 13.7% more cells entered RC after being treated with ATR inhibitor and hydroxyurea (HU) in either GBM-POLKKO or GBM-WT cells compared to untreated control cells. New origins and stalled forks increased meaning that the cell was more likely in RC in GBM-POLKKO or in cells treated with ARTi. The results of this study suggests that inhibiting ATR and decreasing hpol ? function could be new potential treatments for patients.

**Awards Won:**