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The role of therapeutic stress induced cellular plasticity in promoting therapeutic resistance in glioblastoma

Glioblastoma (GBM) is the most common and one of the most lethal brain tumors in adults. Previously, we have shown that anti-glioma chemotherapy Temozolomide (TMZ) initiates plasticity in glioma cells by promoting the conversion of differentiated glioma cells to therapy resistant Glioma Stem-like Cells (GS-lCs). Our initial investigation indicated that the Polycomb Repressor Complex 2 (PRC2) group protein EZH2 is critical for this therapy-induced cellular plasticity. Genome-wide Chromatin Immunoprecipitation (ChIP) in parallel with DNA sequencing analyses (ChIP-seq) revealed 1449 distinct regions enriched for EZH2 binding, specifically at the promoter regions of several genes including *PTPRT, CDK5R2*, and *SIGLEC6*, which work together to activate *STAT3*, a master transcription factor that is key in promoting the GS-lC niche. Recent reports have also demonstrated that the oncogenic activity of EZH2 is independent of PRC2. Consequently, we investigated if the non-canonical function of EZH2 is involved in chemo resistance in GBM by performing RNA seq analysis in GBM cells treated with TMZ (+/-EZH2) inhibitor. *ARL13B*, a member of the ADP-ribosylation factor-like protein family responsible for cilia maintenance, was the only gene whose expression was significantly down regulated in the presence of EZH2 inhibitors (6-fold, $p<0.05$, FDR=0.05). In the GBM patient database, *ARL13B* expression negatively correlates with time to recurrence. The shRNA-mediated knockdown of *ARL13B* in the Patient-derived Xenograft (PDX) model of GBM significantly impaired the ability of cells to form an orthotropic tumor in three different GBM subtypes. Most importantly, knocking down *ARL13B* significantly sensitized PDXs to TMZ therapy. These results suggest that a novel EZH2-*ARL13B* axis contributes to chemo resistance in GBM by promoting cellular plasticity regulated therapeutic adaptation.

Biography

Atique Ahmed is currently working as the Assistant Professor of Cancer Biology and Member of the Lurie Comprehensive Cancer Center, Northwestern University, USA. He has completed his PhD in Molecular Medicine from Mayo Graduate School, USA. He has over 66 publications that have been cited over 3400 times, and his publication H-index is 34 and has been the recipient of American Cancer Society Research Scholar Grant as well as his research is funded by the National Institute of Health, USA.

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