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11th International Conference on
CANCER STEM CELLS AND ONCOLOGY RESEARCH

June 11-13, 2018 | Dublin, Ireland

THERAPEUTIC STRESS INDUCED CELLULAR PLASTICITY: A POSSIBLE NEW MECHANISMS OF THERAPEUTIC RESISTANCE IN GLIOBLASTOMA

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Glioma stem cells (GSCs), a rare population of cancer cells capable of self-renewal, are known to underlie therapeutic resistance in glioblastoma (GBM), the most common and aggressive adult primary brain tumor. Previously, we have shown that the anti-glioma chemotherapy temozolomide (TMZ) initiates remarkable plasticity in glioma cells and promotes the conversion of differentiated glioma cells to therapy resistant GSCs. Our initial investigation indicated that Polycomb group protein EZH2 is critical for this therapy-induced cellular plasticity. Genome-wide chromatin immunoprecipitation (ChIP) in parallel with DNA sequencing analysis (ChIP-seq) revealed 1449 distinct regions enriched for EZH2 binding, specifically at the promoter regions of several key genes including PTPRT, CDK5R2, and Siglec6. Gene expression microarray analysis showed that this binding decreased cognate gene expression in an effort to activate the master transcription factor STAT3, a key molecular factor in promoting the GSC niche. To further investigate this plasticity-based adaptation, we next performed histone 3 lysine 27 acetylation (H3K27ac) enrichment analysis in order to mark the transcriptionally active chromatin state on a genome wide scale before and after exposure to TMZ. A significant number of distal H3K27ac peaks were detected only after chemo- (n = 452) and radiotherapy (n= 1029), indicating that H3K27ac was modified by anti-glioma therapies in a locus-specific manner. Furthermore, a *de novo* motif analysis identified the homeobox TF binding motif (p=0.025) enriched within the H3K27ac peak surrounding sequences during therapy. By combining the transcriptome analysis from patientderived xenograft models and GBM patient data (TCGA) with the H3K27ac enriched marks, we have identified several novel homeobox transcription factors, which may contribute to therapyinduced cellular plasticity and adaptation response. These findings provide new insight into the molecular mechanisms by which epigenetic plasticity regulates the GSC niche and may improve our understanding of how GBM cells resist current treatment modalities.

BIOGRAPHY

Atique U Ahmed is currently appointed as Assistant Professor of Cancer Biology and member of the Lurie Comprehensive Cancer Center, Northwestern University, Chicago IL USA. He received his PhD in Molecular Medicine from Mayo Graduate School, USA. He has over 60 publications that have been cited over 2500 times, and his/her publication H-index is 31 and has been American Cancer Society Scholar.

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