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ACTIVATION OF DOPAMINE RECEPTOR 2 INCREASES TUMORGENECITY AND ALTERS METABOLISM IN GLIOBLASTOMA IN SUB-TYPE DEPENDENT MANNER

Seamus Caragher, Jack Shireman, Cheol Hong Park, Mei Huang, Jason Miska, Herbert Meltzer, Maijic Lesniak and **Atique Ahmed**
Northwestern University, USA

Of all cancers, glioblastoma (GBM) remains one of the least treatable. Evidence indicates cellular plasticity—GBM cells' ability to adopt various expression profiles and functional attributes—is a key factor in this aggressive phenotype. This process includes the ability of differentiated GBM cells to attain a glioma-intiating cell (GIC) phenotype, characterized by heightened therapy-resistance and elevated self-renewal capacity. A variety of factors in the microenvironment have been shown to influence this process, including hypoxia, acidity, and therapeutic stress. Therefore, a better understanding of the mechanisms governing this conversion is needed. Developmental neurobiology suggests that dopamine, a monoamine neurotransmitter, may represent one such factor. Dopamine signaling influences differentiation of brain progenitor cells, highly similar to GICs. We set out to investigate how dopamine influences cellular plasticity in GBM. First, we analyzed epigenetic regulation of the five dopamine receptors (DRDs) in patient derived xenograft (PDX) cells. We found that therapy induces increased acetylation of H3K27 in the DRD2 promoter. Western blots and FACS confirmed increased DRD2 protein. Next, we performed neurosphere assays in the presence of a specific DRD2 agonist. Agonist treated classical PDX cells increased in sphere-forming capacity, while proneural PDX showed no change. Blocking DRD2 attenuated neurosphere-formation. To determine what pathways drive this DRD2 activated plasticity, we performed bioinformatics analysis of human GBM samples. DRD2 expression correlated positively with hypoxia inducible factor (HIF) signaling. Agonist treatment of PDX cells induced HIF protein, despite normoxic conditions. Microarray analysis of HIF genes confirmed subtype-dependent alterations in gene expression following DRD2 activation. Finally, we examined how these gene expression changes influence metabolism, a key functional output of HIF signaling. Seahorse analysis revealed classical GBM cells augment glycolytic rate following DRD2 activation, while proneural GBM cells decrease their consumption of glucose. In summary, these data highlight the contribution of CNS-specific molecules to cellular plasticity of GBM cells and provide evidence for functional differences in genetically defined tumor subpopulations.

BIOGRAPHY

Seamus Caragher earned his B.S. in Neurobiology, summa cum laude and Phi Beta Kappa, from Georgetown University in 2016. He then worked in the laboratory of Atique Ahmed, PhD at the Lurie Cancer Center of Northwestern University, focusing on cellular plasticity and the influence of the brain microenvironment in glioblastoma. He is currently pursuing an MSc in Cancer Sciences at the University of Glasgow as a British Marshall Scholar.

seamuscaragher@gmail.com