Shanté P. Williams
PhD Candidate

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“The Role of Glycogen Synthase Kinase-3 Inhibitors in Brain Tumor Migration and Invasion”

12/15/2010
BRT 115
10:00am
VITA

12/20/1982 ............................ Born – Charlotte, NC

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COMMITTEE MEMBERS

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AWARDS AND HONORS

2009  
AACR Minority Scholar in Cancer Research

2008-2010  
Research Supplement to Promote Diversity in Health Related Research
RECENT PUBLICATIONS


ABSTRACT

Glioblastoma multiforme is the most common and severe form of malignant brain cancer accounting for 23% of all primary brain tumors. A hallmark of malignant brain tumors is the ability to infiltrate into the surrounding tissue, leading to subsequent tumor re-growth after surgery. Currently there are no anti-invasive therapies targeting migrating tumor cells or the signaling pathways responsible for the migratory process. Recently published data shows that pharmacological inhibitors of GSK-3 (glycogen synthase kinase-3), lithium chloride, AR-A014418 and SB415286, are effective in blocking glioma cell migration. GSK-3 is a serine/threonine protein kinase that plays a role in numerous signaling pathways and biological processes including insulin, growth factor, and nutrient signaling, cell fate specification during embryonic development, cell polarity in astrocytes, as well as an emerging role in cell motility. GSK-3 regulation is complex – in growth factor signaling GSK-3 is inactivated by phosphorylation and in Wnt signaling GSK-3 is inactivated by altered protein interactions leading to the stabilization of β-catenin, and the transcription of Wnt responsive genes. This work reports on a class of GSK-3 inhibitors, the indirubins, and their effects on both Glioblastoma cell migration. Indirubins potently blocked both glioblastoma migration and invasion. In gliomas indirubins inhibited GSK-3 to a greater extent than lithium as assessed by β-catenin TCF/LEF luciferase reporter assays and were effective at much lower concentrations than other GSK-3 inhibitors so far tested. When examined in animal xenograft models,treatment with 6-bromo-indirubin acetoxime (BIA) led to decreased tumor proliferation in both flank and intracranial tumors and an increase in survival. Histological examination of tumors showed a substantial decrease in blood vessel density in tumors in the flank and the brain (50% and 30% respectively), and a 40% reduction invasion of the brain. Finally, this study shows that indirubins block motility of endothelial cells...
in vitro, and also cause increased production of anti-angiogenic proteins. This data suggests that GSK-3 inhibitors may not only inhibit invasion of tumor cells, but also block angiogenesis, providing a new treatment paradigm for invasive gliomas.

Finally, the highly migratory nature of glioma cells highlights the need to identify the genes altered in glioma migration. A novel in vitro glioma migration model has recently been described in which synthetic polymers of polycaprolactone promoted glioma cell motility when in an aligned configuration. Using this novel model, a large number of alterations were identified in the transcriptome of migrating cells. These included upregulation of known pro-motility genes, as well as EGF ligands (HB-EGF) and various cytokines including IL-11. These changes suggested that STAT3 may be a common downstream mediator of these transcriptional alterations. Knocking-down STAT3 activation using various STAT3 inhibitors slowed migration on aligned fibers. These data describe a novel pathway involved in glioma migration and suggest further targets for pharmacologic intervention.

**RECENT ABSTRACTS AND PRESENTATION**


**Williams S, Nowicki MO, Godlewski J, Chiocca EA, Lawler S.** Indirubins Block Glioma Migration through GSK-3 Inhibition and the Stabilization of β-Catenin. American Association for Cancer Research 2009


**Williams S, Nowicki MO, Godlewski J, Chiocca EA, Lawler S.** Anti-glioma effects of protein kinase inhibitors that simultaneously block invasion and proliferation. Society for Neurooncology 2007